PREFACE OF 2020 PUBLICATIONS

Discovery and the pursuit of knowledge are cornerstones of any thriving human civilization, without which technological innovations would never materialize and the human race would be rendered stagnant. Like a chain reaction that propagates and grows, the pursuit of knowledge itself creates new tools, which can be used to pursue new knowledge, which again leads to the development of new technologies that enable new discoveries, and so forth and so on. In Qatar, the seed to set off this chain reaction was planted over 25 years ago, in the establishment of Qatar Foundation with the vision to create an ecosystem where research, innovation, discovery and education come together for the singular purpose of unlocking human potential and creating life-changing knowledge.

Sidra Medicine, like many other institutes in the QF portfolio, was designed to the highest standards to achieve its goals of providing world-class healthcare to Qatar's women and children. True to its mission, Sidra Medicine follows an academic medical center model, where education and research are integral parts of the patient's journey, and the practice of precision medicine derives from bringing research technologies closer to patient care. Such technologies allow physicians to diagnose diseases that would otherwise remain idiopathic by standard of care workups, and to design personalized therapies for patients who would otherwise have suffered from the limitations of one-size-fits-all medicine.

This interaction of clinicians, researchers, residents, students and fellows gives birth to an ecosystem of discovery and translation unique in the region. Such 'bench to bedside' approach transforms Sidra Medicine's Research Branch from a peripheral function serving strictly academic purposes, to an integral arm of the personalized medicine experience for each patient. In the process, the knowledge created by Sidra's community is published in some of the highest impact journals in the world. Together, Sidra clinicians and scientists published nearly 300 papers in 2020. Importantly, Sidra Medicine was also awarded 18 national grants during this period, demonstrating the growing recognition of the importance of academic medical centers for translational discovery. This volume compiles publications that demonstrate Sidra's contribution to studying a wide range of conditions, including: rare diseases, immunological disorders, issues related to maternal-child health and the novel corona virus, impressing how quick our scientific community are in facing such global challenges.

Despite the pandemic, science never stops; if anything, Sidra demonstrated its resilience and importance for society. We trust this collection of papers is a demonstration of the high caliber of science that is produced by Sidra, and will continue to grow stronger in the coming years.

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Research Branch, 2020

سدرة للطب
Sidra Medicine

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SCIENTIFIC REPORTS
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Genome-wide association study identifies novel risk variants from *RPS6KA1*, *CADPS*, *VARS*, and *DHX58* for fasting plasma glucose in Arab population

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Consanguineous populations of the Arabian Peninsula, which has seen an uncontrolled rise in type 2 diabetes incidence, are underrepresented in global studies on diabetes genetics. We performed a genome-wide association study on the quantitative trait of fasting plasma glucose (FPG) in unrelated Arab individuals from Kuwait (discovery-cohort:n = 1,353; replication-cohort:n = 1,196). Genome-wide genotyping in discovery phase was performed for 632,375 markers from Illumina HumanOmniExpress Beadchip; and top-associating markers were replicated using candidate genotyping. Genetic models based on additive and recessive transmission modes were used in statistical tests for associations in discovery phase, replication phase, and meta-analysis that combines data from both the phases. A genome-wide significant association with high FPG was found at rs1002487 (*RPS6KA1*) (p-discovery = 1.64E-08, p-replication = 3.71E-04, p-combined = 5.72E-11; β-discovery = 8.315; β-replication = 3.442; β-combined = 6.551). Further, three suggestive associations (p-values < 8.2E-06) with high FPG were observed at rs487321 (*CADPS*), rs707927 (*VARS* and 2Kb upstream of *VWA7*), and rs12600570 (*DHX58*); the first two markers reached genome-wide significance in the combined analysis (p-combined = 1.83E-12 and 3.07E-09, respectively). Significant interactions of diabetes traits (serum triglycerides, FPG, and glycated hemoglobin) with homeostatic model assessment of insulin resistance were identified for genotypes heterozygous or homozygous for the risk allele. Literature reports support the involvement of these gene loci in type 2 diabetes etiology.

A large number of genome-wide association studies have been conducted in various populations (mostly on Europeans, Americans, and East Asians), resulting in the identification of more than 100 loci conferring susceptibility to type 2 diabetes mellitus[1–4]. Meta-analysis and genotype imputations from diverse ethnic populations help identify novel markers and causal loci. However, despite the observed high prevalence of type 2 diabetes in Arab countries[5,6], their populations were not included in global studies.

The Arabian Peninsula is at the nexus of Africa, Europe, and Asia; and has been assumed to be an early human migration route out of Africa. Consanguineous marriage (especially among first or second cousins) is an established practice among the Arabian Peninsula population. Consanguinity results in increased homozygosity, and accumulation of deleterious recessive alleles in the gene pool, creating the potential for certain variants to become

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PLOS ONE

RESEARCH ARTICLE

PR3 levels are impaired in plasma and PBMCs from Arabs with cardiovascular diseases

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Abstract

Cardiovascular disease (CVD) risks persist in patients despite treatment. CVD susceptibility also varies with sex and ethnicity and is not entirely explained by conventional CVD risk factors. The aim of the present study was to identify novel CVD candidate markers in circulating Peripheral blood mononuclear cells (PBMCs) and plasma from Arab obese subjects with and without CVD using proteomic approaches. Human adults with confirmed CVD (n = 208) and matched non-CVD controls (n = 152) living in Kuwait were examined in the present cross-sectional study. Anthropometric and classical biochemical parameters were determined. We employed a shotgun proteomic profiling approach on PBMCs isolated from a subset of the groups (n = 4, each), and differentially expressed proteins selected between the two groups were validated at the mRNA level using RT-PCR (n = 6, each). Plasma levels of selected proteins from the proteomics profiling: Proteinase-3 (PR3), Annexin-A3 (ANX3), Defensin (DEFA1), and Matrix Metalloproteinase-9 (MMP9), were measured in the entire cohort using human enzyme-linked immunosorbent assay kits and were subsequently correlated with various clinical parameters. Out of the 1407 we identified and quantified from the proteomics profiling, 47 proteins were dysregulated with at least twofold change between the two subject groups. Among the differentially expressed proteins, 11 were confirmed at the mRNA levels. CVD influenced the levels of the shortlisted proteins (MMP9, PR3, ANX3, and DEFA1) in the PBMCs and plasma differentially. Despite the decreased levels of both protein and mRNA in PBMCs, PR3 circulating levels increased significantly in patients with CVD and were influenced by neither diabetes nor statin treatment. No significant changes were; however, observed in the DEFA1, MMP9, and ANX3 levels in plasma. Multivariate logistic regression analysis revealed that only PR3 was independently associated with CVD. Our results suggest that the dysregulation of PR3 levels in plasma and PBMCs reflects underlying residual CVD risks even in the treated population. More prospective and larger studies are required to establish the role of PR3 in CVD progression.

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REVIEW ARTICLE

Exploring Dysregulated Signaling Pathways in Cancer

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Abstract: Cancer cell biology takes advantage of identifying diverse cellular signaling pathways that are disrupted in cancer. Signaling pathways are an important means of communication from the exterior of cell to intracellular mediators, as well as intracellular interactions that govern diverse cellular processes. Oncogenic mutations or abnormal expression of signaling components disrupt the regulatory networks that govern cell function, thus enabling tumor cells to undergo dysregulated mitogenesis, to resist apoptosis, and to promote invasion to neighboring tissues. Unraveling of dysregulated signaling pathways may advance the understanding of tumor pathophysiology and lead to the improvement of targeted tumor therapy. In this review article, different signaling pathways and how their dysregulation contributes to the development of tumors have been discussed.

Keywords: Angiogenesis, apoptosis, cell invasion, cell proliferation, drug targets, metastasis, signaling pathways, tumor microenvironment.

1. INTRODUCTION

Cancer is a disease affecting millions of people worldwide. Cancer cells have the ability to abnormally divide and grow as a result of alteration or mutation in specific genes. The common signaling pathways and processes underlying cancer are now easily understood due to the advanced DNA sequencing over the past few years [1]. The genes and pathways altered, varies across different individuals and different types of tumor. There must be a complete understanding of all these dysregulated cancer pathways in order to identify and broaden therapeutic options [2]. The cell signaling systems that control the fate of the cell are disrupted by oncogenic mutations which contribute towards the malignant behavior of the tumor cells. The development of a malignant tumor depends on the acquired traits of cancer cells, which are known as "Hallmarks of cancer". There are ten major hallmarks of cancer: sustained proliferative signals, replicating immortality, evading growth suppression, resisting cell death, activating invasion & metastasis, inducing angiogenesis, tumor-promoting inflammation, avoiding immune destruction, genomic instability & mutation, and deregulated cellular energetics [3].

Many studies have shown that solid tumors are highly complex eco-system infiltrated with many immune cells, endothelial cells, cancer-associated fibroblasts (CAFs), endocrine cells entangled in the extracellular matrix (ECM) proteins which together make the Tumor Microenvironment (TME). This TME, by secreting various growth factors, immune-suppressive factors recruit tumor-promoting macrophages, inflammatory cells, cancer-associated fibroblasts [4], help escape immune recognition [5], and provide a permissive environment for tumor progression, metastasis and development of resistance to therapy [6]. In addition, the accumulation of genetic and epigenetic alterations during the cancer progression results in the clonal selection of cells with more aggressive phenotypes. As the tumor size increases, its core loses access to the oxygen and nutrients that promote the formation of new blood vessels called angiogenesis as a compensatory mechanism to obtain more oxygen and nutrients, thus allowing cancer cells to enter the blood circulation to establish distant metastasis. Recent high throughput genomic data has identified a trove of mutations that result in the deregulation of many signal transduction pathways promoting cellular characteristics favoring carcinogenesis. In this review, the deregulated pathways imparting proliferative, survival, and invading advantages to various tumors have been comprehensively described [7].

2. SIGNALING PATHWAYS

Many signaling pathways are interconnected with each other and form complex networks. The activation of these cellular pathways by various external and internal cues and their integration lead to the execution of various cellular functions controlling cell growth, motility, cell architecture & polarity, differentiation, programmed cell death, protein synthesis, *etc*. [8] (Fig. **1**). While these signaling pathways are precisely controlled in normal cells, the deregulation of these pathways results in uncontrolled proliferation and development of cancers. The most common genetically/epigenetically altered signaling pathways in various cancers are discussed below [2].

2.1. ErbB/EGFR Signaling Pathway

The ErbB family, including ErbB-1/EGFR, HER2/neu/ErbB-2, HER3/ErbB-3 and HER4/ErbB-4 is a family of receptor tyrosine kinases that modulate numerous signal transducers and activate many intracellular pathways [9]. While mutations and alternative splicing play an important role in protein function, expression, and their stability, mutated and truncated EGFR (EGFRvIII) has been shown to play an important role in the development, progression, metastasis and therapeutic resistance of many cancers including

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ORIGINAL RESEARCH ARTICLE

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Functional characterization of human myosin-binding protein C3 variants associated with hypertrophic cardiomyopathy reveals exon-specific cardiac phenotypes in zebrafish model

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Abstract

Myosin-binding protein C 3 (*MYBPC3*) variants are the most common cause of hypertrophic cardiomyopathy (HCM). HCM is a complex cardiac disorder due to its significant genetic and clinical heterogeneity. *MYBPC3* variants genotype–phenotype associations remain poorly understood. We investigated the impact of two novel human *MYBPC3* splice-site variants: *V1*: c.654+2_654+4dupTGG targeting exon 5 using morpholino MOe5i5; and *V2*: c.772+1G>A targeting exon 6 using MOe6i6; located within C1 domain of cMyBP-C protein, known to be critical in regulating sarcomere structure and contractility. Zebrafish MOe5i5 and MOe6i6 morphants recapitulated typical characteristics of human HCM with cardiac phenotypes of varying severity, including reduced cardiomyocyte count, thickened ventricular myocardial wall, a drastic reduction in heart rate, stroke volume, and cardiac output. Analysis of all cardiac morphological and functional parameters demonstrated that *V2* cardiac phenotype was more severe than *V1*. Coinjection with synthetic human *MYBPC3* messenger RNA (mRNA) partially rescued disparate cardiac phenotypes in each zebrafish morphant. While human *MYBPC3* mRNA partially restored the decreased heart rate in *V1* morphants and displayed increased percentages of ejection fraction, fractional shortening, and area change, it failed to revert the *V1* ventricular myocardial thickness. These results suggest a possible *V1* impact on cardiac contractility. In contrast, attempts to rescue *V2* morphants only restored the ventricular myocardial wall hypertrophy phenotype but had no significant effect on impaired heart rate, suggesting a potential *V2* impact on the cardiac structure. Our study provides evidence of an association between *MYBPC3* exon-specific cardiac phenotypes in the zebrafish model providing important insights into how these genetic variants contribute to HCM disease.

KEYWORDS

hypertrophic cardiomyopathy, myosin-binding protein C3, splice site variants, ventricle, zebrafish

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***MicroRNA*, 2020, *9*, 1-8** **1**

REVIEW ARTICLE

Updates on the Current Technologies for microRNA Profiling

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Abstract: MicroRNAs are RNA molecules of ~22 nt length that regulate gene expression post-transcriptionally. The role of miRNAs has been reported in many cellular processes including apoptosis, cell differentiation, development and proliferation. The dysregulated expression of miRNAs has been proposed as a biomarker for the diagnosis, onset and prognosis of human diseases. The utility of miRNA profiles to identify and discriminate patients from healthy individuals is highly dependent on the sensitivity and specificity of the technologies used for their detection and the quantity and quality of starting material. In this review, we present an update of the current technologies for the extraction, QC assessment and detection of miRNAs with special focus to the most recent methods, discussing their advantages as well as their shortcomings.

Keywords: Microarray, miRNA, PCR, quality control, sequencing, technologies.

1. INTRODUCTION

MicroRNAs (miRNAs) are short non-coding RNA molecules that regulate mRNA expression by post-transcriptional silencing of target genes [1]. Silencing is obtained by a combination of translational repression and mRNA destabilization [2, 3]. Positioned up-stream of gene expression regulatory cascades, miRNA presence in tissues and fluids together with their remarkable stability make miRNAs good biomarkers for several diseases. In fact, miRNA identity and expression levels are often used to discriminate disease state and to distinguish diseased from healthy individuals [4, 5]. In the recent years, along with the revolutionary progress in genomics, the miRNA field has experienced rapid growth especially with regard to the technologies associated with miRNA isolation, detection and analysis. The expression levels of miRNAs can be influenced by the way the RNA is extracted and processed. Indeed, studies have often reported inconsistencies in miRNA expression results.

When assessing miRNA profiling, it is of paramount importance to choose the appropriate methods for miRNA isolation, detection, and data analysis and also being aware of the advantages and shortcomings of the different technologies. This paper is meant to provide the readers with an overview of the current technologies for miRNA isolation, QC, detection, and data analysis and will not discuss miRNA biology as this topic has been discussed elsewhere [1-4, 6-9].

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2. MIRNA EXTRACTION

When performing studies on miRNA profiling, it is of paramount importance to carefully choose the optimal methods for miRNA extraction in order to ensure consistent results. Initial efforts should also be spent to optimize and standardize extraction protocols [10-12]. Several starting materials can be used for miRNA extraction including tissues, cells and body fluids [13, 14]. Obviously, yield and purity of miRNA can vary largely depending on the type and quantity of starting material used. As an example, blood, cells and human tissues represent a good source of miRNAs, whereas body fluids give lower yield as compared to cells and tissues. When handling serum and plasma, generally a larger amount of starting material is required that exceeds the input volume recommended from commercially available kits [15]. MiRNA fraction is generally isolated together with total RNA. Nevertheless, selective isolation of miRNAs has also been proposed recently [10].

The initial methods for RNA extraction used phenol-chloroform and involved an RNA precipitation step. TRIzol reagent (Thermo Fisher Scientific, Waltham, MA, USA) is often employed for RNA extraction. TRIzol is a monophasic solution of phenol and guanidine isothiocyanate, which maintains the integrity of the RNA due to highly effective inhibition of RNase activity while disrupting cells and dissolving cell components during sample homogenization. An advantage in using TRIzol consists in the possibility to perform concurrent isolation of DNA and proteins from the same sample. Following homogenization through TRIzol, chloroform is added and the homogenate separates into three phases: i. a clear upper aqueous layer containing RNA, ii. an

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Review

Claudin-1, A Double-Edged Sword in Cancer

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Abstract: Claudins, a group of membrane proteins involved in the formation of tight junctions, are mainly found in endothelial or epithelial cells. These proteins have attracted much attention in recent years and have been implicated and studied in a multitude of diseases. Claudins not only regulate paracellular transepithelial/transendothelial transport but are also critical for cell growth and differentiation. Not only tissue-specific but the differential expression in malignant tumors is also the focus of claudin-related research. In addition to up- or down-regulation, claudin proteins also undergo delocalization, which plays a vital role in tumor invasion and aggressiveness. Claudin (CLDN)-1 is the most-studied claudin in cancers and to date, its role as either a tumor promoter or suppressor (or both) is not established. In some cancers, lower expression of CLDN-1 is shown to be associated with cancer progression and invasion, while in others, loss of CLDN-1 improves the patient survival. Another topic of discussion regarding the significance of CLDN-1 is its localization (nuclear or cytoplasmic vs perijunctional) in diseased states. This article reviews the evidence regarding CLDN-1 in cancers either as a tumor promoter or suppressor from the literature and we also review the literature regarding the pattern of CLDN-1 distribution in different cancers, focusing on whether this localization is associated with tumor aggressiveness. Furthermore, we utilized expression data from The Cancer Genome Atlas (TCGA) to investigate the association between CLDN-1 expression and overall survival (OS) in different cancer types. We also used TCGA data to compare CLDN-1 expression in normal and tumor tissues. Additionally, a pathway interaction analysis was performed to investigate the interaction of CLDN-1 with other proteins and as a future therapeutic target.

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ARTICLES

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^{1}H magnetic resonance spectroscopy of ^{2}H-to-^{1}H exchange quantifies the dynamics of cellular metabolism in vivo

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Quantitative mapping of the in vivo dynamics of cellular metabolism via non-invasive imaging contributes to our understanding of the initiation and progression of diseases associated with dysregulated metabolic processes. Current methods for imaging cellular metabolism are limited by low sensitivities, costs or the use of specialized hardware. Here, we introduce a method that captures the turnover of cellular metabolites by quantifying signal reductions in proton magnetic resonance spectroscopy (MRS) resulting from the replacement of ^{1}H with ^{2}H. The method, which we termed quantitative exchanged-label turnover MRS, only requires deuterium-labelled glucose and standard magnetic resonance imaging scanners, and with a single acquisition provides steady-state information and metabolic rates for several metabolites. We used the method to monitor glutamate, glutamine, γ-aminobutyric acid and lactate in the brains of unaffected and glioma-bearing rats following the administration of $^{2}H_2$-labelled glucose and $^{2}H_3$-labelled acetate. Quantitative exchanged-label turnover MRS should broaden the applications of routine ^{1}H MRS.

Cellular metabolism is maintained by a network of biochemical reactions that are essential for normal tissue function[1]. These reactions form larger metabolic pathways that exist under tight regulatory control to help balance metabolic fluctuations experienced by the cell. Therefore, it is not surprising that abnormal metabolism is a hallmark of several pathologies, including neurodegeneration and cancer[1,2]. Probing of the kinetics of metabolic pathways in vivo plays a key role in studying disease mechanisms, identifying new treatment strategies and developing biomarkers of treatment response. To date, several non-invasive techniques have been established to monitor the relationship between cellular function and metabolism[3].

Positron emission tomography (PET) using the glucose (Glc) analogue 2-^{18}F-fluoro-2-deoxy-D-glucose is a widely utilized clinical tool that provides high-resolution maps of Glc uptake in cancer, neurodegeneration and cardiac diseases[4–6]. However, PET also requires the use of radioactive 2-^{18}F-fluoro-2-deoxy-D-glucose and does not readily provide information on tissue metabolic activity beyond the initial step of glycolytic metabolism[7]. Conventional magnetic resonance imaging (MRI) provides outstanding anatomical information without exposure to ionizing radiation, but only offers limited insight with regard to metabolism[8]. Chemical exchange saturation transfer MRI offers enhanced detection sensitivity for a variety of metabolites, but is limited in its ability to measure dynamic changes in metabolite turnover[9,10]. Proton magnetic resonance spectroscopy (^{1}H MRS) is a gold standard for detecting and quantifying several endogenous tissue metabolites in a single acquisition, but it is not capable of tracking metabolic fluxes and pathways[11]. ^{13}C MRS in combination with administration of ^{13}C-labelled substrates has been used to study metabolic pathways in both preclinical and clinical settings[12–14], but its low sensitivity has limited its routine use in human studies. The advent of dynamic nuclear polarization combined with ^{13}C MRS has provided a strong boost to the sensitivity of this technique[15,16]. However, this approach is hindered by the short in vivo half-life of hyperpolarized ^{13}C in addition to the requirement of onsite polarizers and ^{13}C hardware.

Recently, ^{2}H MRS—also referred to as deuterium MRS (DMRS)—has been evaluated for its potential to assess tissue metabolic kinetics following administration of deuterated subtrates[17]. Preliminary studies have shown the utility of DMRS based deuterium metabolic imaging in the detection of human glioblastoma and hepatocellular carcinomas[18]. However, DMRS has low sensitivity relative to ^{1}H MRS and still requires specialized hardware for use on clinical scanners. Deuterated substrates have also been utilized in combination with stimulated Raman scattering imaging for spectral tracing of deuterium (STRIDE) to measure the metabolic dynamics of newly synthesized cellular macromolecules including DNA, proteins, lipids and glycogen[19]. Although this approach provides high-resolution, biochemically informative images of Glc anabolic utilization, it is mostly restricted to superficial tissue measurements and requires prolonged exposure (~10 d) to deuterated substrates.

Here, we present a method—quantitative exchanged-label turnover MRS (QELT, or simply qMRS)—that increases the sensitivity of magnetic resonance-based metabolic mapping without the requirement for specialized hardware. Similar to DMRS, qMRS relies on the administration of deuterium-labelled substrates to track the production of downstream metabolites. However, instead of ^{2}H-based detection of these metabolites, we performed ^{1}H MRS. Since ^{2}H is invisible on ^{1}H MRS, replacement of ^{1}H with ^{2}H leads to an overall reduction in ^{1}H MRS signal for the corresponding metabolites.

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Generation of a human induced pluripotent stem cell line (QBRIi009-A) from a patient with a heterozygous deletion of *FOXA2*

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A B S T R A C T

FOXA2 is a transcription factor, playing an important role during development. We established an induced pluripotent stem cell (iPSC) line, QBRIi009-A, using non-integrating Sendai virus from a 4-year-old boy, displaying a complex clinical phenotype. Molecular karyotyping and cytogenetics confirmed a *de novo* proximal 20p11.2 deletion with a reciprocal translocation between the short arm of chromosome 6 and 20. The deleted region (~969 kb) contains only one gene, *FOXA2*. The generated hiPSC line was fully characterized for its pluripotency and its genetic identity. This iPSC line provides a useful model to study FOXA2 role during human development and in disease pathogenesis.

Resource Table

Unique stem cell line identifier	QBRIi009-A
Alternative name(s) of stem cell line	FOXA2$^{+/-}$ iPSCs
Institution	Qatar Biomedical research institute QBRI, Hamad Bin Khalifa University, Qatar Foundation, Qatar.
Contact information of distributor	Essam M. Abdelalim. E-mail: emohamed@hbku.edu.qa
Type of cell line	iPSC
Origin	human
Additional origin info	Age: 4 years old Sex: Male Ethnicity: Bangali
Cell Source	Blood
Clonality	Clonal
Method of reprogramming	Integration-free Sendai virus vector for delivery of OCT3/4, SOX2, c-MYC and KLF4
Genetic Modification	YES
Type of Modification	Hereditary
Associated disease	Multiple syndromic features, growth hormone deficiency and central hypothyroidism
Gene/locus	Gene: FOXA2 Locus: chr20: 22,561,642 - 22,566,101 Deletion: chromosome 20 at bands p11.22 to p11.21
Method of modification	N/A
Name of transgene or resistance	N/A
Inducible/constitutive system	N/A
Date archived/stock date	Date cell line archived or deposited in repository
Cell line repository/bank	N/A
Ethical approval	Blood samples were obtained from Sidra Medicine hospital with full informed consent. The protocol was approved by the Institutional Review Board (IRB) of Sidra Medicine (no. 1702007608) and QBRI (no. 2018-002)

1. Resource utility

Our iPSC line was generated from a patient with a heterozygous deletion of chromosome 20 at bands p11.22 to p11.21, encompassing only *FOXA2* gene. This iPSC line offers an *in vitro* model to investigate the role of FOXA2 during human development and in the disease development.

2. Resource details

Previous studies reported that 20p11.2 proximal deletions, overlapping *FOXA2* displays multiple phenotypic abnormalities, including developmental delay, panhypopituitarism, heterotaxy and neurodevelopmental abnormalities (Dines et al., 2019; Dayem-Quere et al., 2013). *FOXA2* mutations are associated with hypopituitarism,

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ORIGINAL ARTICLE

Fatal Cytomegalovirus Infection in an Adult with Inherited NOS2 Deficiency

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ABSTRACT

BACKGROUND

Cytomegalovirus (CMV) can cause severe disease in children and adults with a variety of inherited or acquired T-cell immunodeficiencies, who are prone to multiple infections. It can also rarely cause disease in otherwise healthy persons. The pathogenesis of idiopathic CMV disease is unknown. Inbred mice that lack the gene encoding nitric oxide synthase 2 (*Nos2*) are susceptible to the related murine CMV infection.

METHODS

We studied a previously healthy 51-year-old man from Iran who after acute CMV infection had an onset of progressive CMV disease that led to his death 29 months later. We hypothesized that the patient may have had a novel type of inborn error of immunity. Thus, we performed whole-exome sequencing and tested candidate mutant alleles experimentally.

RESULTS

We found a homozygous frameshift mutation in *NOS2* encoding a truncated NOS2 protein that did not produce nitric oxide, which determined that the patient had autosomal recessive NOS2 deficiency. Moreover, all *NOS2* variants that we found in homozygosity in public databases encoded functional proteins, as did all other variants with an allele frequency greater than 0.001.

CONCLUSIONS

These findings suggest that inherited NOS2 deficiency was clinically silent in this patient until lethal infection with CMV. Moreover, NOS2 appeared to be redundant for control of other pathogens in this patient. (Funded by the National Center for Advancing Translational Sciences and others.)

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Dr. Mahdaviani, Ms. Neehus, and Mr. Hum and Drs. Marr, Jouanguy, Bustamante, Abel, Boisson-Dupuis, and Béziat contributed equally to this article.

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Keratinocytes derived from patient-specific induced pluripotent stem cells recapitulate the genetic signature of psoriasis disease

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Running Title: A patient-specific iPSC model of psoriasis

Abstract

Psoriasis is characterized by hyperproliferation and defective differentiation of keratinocytes (KCs). Patients with psoriasis are at a high risk of developing diabetes and cardiovascular diseases. The debate on the genetic origin of psoriasis pathogenesis remains unresolved due to lack of suitable *in vitro* human models mimicking the disease phenotypes. Here, we provide the first human induced pluripotent stem cell (iPSC) model for psoriasis carrying the genetic signature of the patients. iPSCs were generated from patients with psoriasis (PsO-iPSCs) and healthy donors (Ctr-iPSCs) and were efficiently differentiated into mature KCs. RNA sequencing of KCs derived from Ctr-iPSCs and PsO-iPSCs identified 361 commonly upregulated and 412 commonly downregulated genes. KCs derived from PsO-iPSCs showed dysregulated transcripts associated with psoriasis and KC differentiation, such as *HLA-C*, *KLF4*, chemokines, type I interferon (IFN)-inducible genes, solute carrier family, *IVL, DSG1, and HLA-DQA1* as well as transcripts associated with insulin resistance, such as *IRS2*, *GDF15*, *GLUT10*, and *GLUT14*. Our data suggests that the KC abnormalities are the main driver triggering psoriasis pathology and highlights the substantial contribution of genetic predisposition in the development of psoriasis and insulin resistance.

Key words: Induced pluripotent stem cells, psoriasis phenotypes, genetic predisposition, keratinocytes, insulin resistance, skin disorder, transcriptome profiling.

Genomics of Autism

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Abstract Autism spectrum disorder (ASD) is a heterogeneous condition affecting >1% of all children, characterized by impaired social interactions, repetitive behavior and a widely variable spectrum of comorbidities. These comorbidities may include developmental delay, gastrointestinal problems, cardiac disorders, immune and autoimmune dysregulation, neurological manifestations (e.g., epilepsy, intellectual disability), and other clinical features. This wide phenotypic heterogeneity is difficult to predict and manifests across a wide range of ages and with a high degree of difference in severity, making disease management and prediction of a successful intervention very difficult. Recently, advances in genomics and other molecular technologies have enabled the study of ASD on a molecular level, illuminating genes and pathways whose perturbations help explain the clinical variability among patients, and whose impairments provide possible opportunities for better treatment options. In fact, there are now >1000 genes that have been linked to ASD through genetic studies of more than 10,000 patients and their families. This chapter discusses these discoveries and in the context of recent developments in genomics and bioinformatics, while also examining the trajectory of gene discovery efforts over the past few decades, as both better ascertainment and global attention have been given to this highly vulnerable patient population.

Keywords Autism · Genomics · Next-generation sequencing · NGS · Copy number variations · Chromosomal abnormalities · Exome sequencing · Genome sequencing · Bioinformatics

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Original Article

ORIGINAL ARTICLE

Glucagon-like peptide-1 receptor and sarcoglycan delta genetic variants can affect cardiovascular risk in chronic kidney disease patients under hemodialysis

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ABSTRACT

Background. Chronic kidney disease (CKD) patients under hemodialysis show a higher risk of cardiovascular (CV) mortality and morbidity than the general population. This study aims to identify genetic markers that could explain the increased CV risk in hemodialysis.

Methods. A total of 245 CKD patients under hemodialysis were recruited and followed up for 5 years to record CV events. Genetic analysis was performed using single-nucleotide polymorphisms (SNPs) genotyping by Infinium Expanded Multi-Ethnic Genotyping Array (Illumina, San Diego, CA, USA) comparing patients with and without a history of CV events [161 cardiovascular diseases (CVDs) and 84 no CVDs]. The fixation index (Fst) measure was used to identify the most differentiated SNPs, and gene ontology analysis [Protein Analysis THrough Evolutionary Relationships (PANTHER) and Ingenuity Pathway Analysis (IPA)] was applied to define the biological/pathological roles of the associated SNPs. Partitioning tree analysis interrogated the genotype–phenotype relationship between discovered genetic variants and CV phenotypes. Cox regression analysis measured the effect of these SNPs on new CV events during the follow-up (FU).

Results. Fst analysis identified 3218 SNPs that were significantly different between CVD and no CVD. Gene ontology analysis identified two of these SNPs as involved in cardiovascular disease pathways (Ingenuity Pathway) and heart development (Panther) and belonging to 2 different genes: Glucagon-like peptide-1 receptor (*GLP1R*) and Sarcoglycan delta (*SGCD*). The phenotype–genotype analysis found a higher percentage of CVD patients carrying the *GLP1R* rs10305445 allele A ($P = 0.03$)

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REVIEW
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Reverting Immune Suppression to Enhance Cancer Immunotherapy

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Tumors employ strategies to escape immune control. The principle aim of most cancer immunotherapies is to restore effective immune surveillance. Among the different processes regulating immune escape, tumor microenvironment-associated soluble factors, and/or cell surface-bound molecules are mostly responsible for dysfunctional activity of tumor-specific $CD8^{+}$T cells. These dynamic immunosuppressive networks prevent tumor rejection at several levels, limiting also the success of immunotherapies. Nevertheless, the recent clinical development of immune checkpoint inhibitors or of molecules modulating cellular targets and immunosuppressive enzymes highlights the great potential of approaches based on the selective disruption of immunosuppressive networks. Currently, the administration of different categories of immunotherapy in combination regimens is the ultimate modality for impacting the survival of cancer patients. With the advent of immune checkpoint inhibitors, designed to mount an effective antitumor immune response, profound changes occurred in cancer immunotherapy: from a global stimulation of the immune system to a specific targeting of an immune component. This review will specifically highlight the players, the mechanisms limiting an efficient antitumor response and the current immunotherapy modalities tailored to target immune suppressive pathways. We also discuss the ongoing challenges encountered by these strategies and provide suggestions for circumventing hurdles to new immunotherapeutic approaches, including the use of relevant biomarkers in the optimization of immunotherapy regimens and the identification of patients who can benefit from defined immune-based approaches.

Keywords: immunotherapy, immunosuppression, tumor escape, soluble factors, tumor microenvironment, immune checkpoint inhibitors, immunosuppressive enzymes

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Cancer growth and progression is controlled by the immune cells infiltrating the tumor microenvironment (TME). Several reports provide clear evidence that activation of an antitumor immune response in the host results in tumor regression and translates into better clinical outcomes in animal and human cancers (1, 2). However, more often than not, the interactions between the immunological players and the tumor cells in the TME lead to immune evasion contributing to tumor progression (3). Importantly, the immune selection inadvertently favors the emergence of tumors with reduced immunogenicity. The stromal compartment is required to create a permissive environment for the extravasation and spread of genetically and epigenetically altered tumor cells (4), and maintain the inactivation of various components of the immune system, preventing their

cancers

MDPI

Review

Non-Coding RNAs as Regulators and Markers for Targeting of Breast Cancer and Cancer Stem Cells

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Abstract: Breast cancer is regarded as a heterogeneous and complicated disease that remains the prime focus in the domain of public health concern. Next-generation sequencing technologies provided a new perspective dimension to non-coding RNAs, which were initially considered to be transcriptional noise or a product generated from erroneous transcription. Even though understanding of biological and molecular functions of noncoding RNA remains enigmatic, researchers have established the pivotal role of these RNAs in governing a plethora of biological phenomena that includes cancer-associated cellular processes such as proliferation, invasion, migration, apoptosis, and stemness. In addition to this, the transmission of microRNAs and long non-coding RNAs was identified as a source of communication to breast cancer cells either locally or systemically. The present review provides in-depth information with an aim at discovering the fundamental potential of non-coding RNAs, by providing knowledge of biogenesis and functional roles of micro RNA and long non-coding RNAs in breast cancer and breast cancer stem cells, as either oncogenic drivers or tumor suppressors. Furthermore, non-coding RNAs and their potential role as diagnostic and therapeutic moieties have also been summarized.

Keywords: breast cancer stem cells; biogenesis; long non-coding RNA; microRNA; targets

1. Introduction

Breast cancer (BC) is the most common form of cancer among women and accounts for 11.6% of cancer incidences and 6.6% of cancer-associated deaths worldwide [1]. The high incidence and death rates in BC are linked to various factors, among which the most common being its heterogeneous

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Full Length Article

Brain microstructural changes support cognitive deficits in HIV uninfected children born to HIV infected mothers

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ABSTRACT

Introduction: Antiretroviral therapy (ART) is considered the most effective way to prevent perinatal transmission of human immunodeficiency virus (HIV). However, there is little knowledge about the effect of ART on the brain of HIV uninfected children born to HIV infected mothers (HUC). The current study evaluated the brain's microstructural integrity, and cognitive function in HUC compared to healthy children born to normal mothers (CHNM) and HIV infected children born to HIV infected mothers (HIC) to investigate the effect of in-utero exposure of ART on cerebral gray and white matter.

Materials and methods: Forty nine HIC, 12 HUC and 18 CHNM underwent neuropsychological (NP) assessment and a brain MRI. Diffusion tensor imaging (DTI) data was used to generate fractional anisotropy (FA) and mean diffusivity (MD) maps. Voxel wise comparison for FA and MD was performed between three groups using an analysis of covariance (ANCOVA) including age and sex as covariates, and correction for multiple comparisons (false discovery rate (FDR), $p < 0.05$ with minimum extended cluster size, 150 voxels). NP test scores were also compared between three groups using ANOVA with Post Hoc Bonferroni multiple comparison corrections ($p < 0.05$). Significantly changed FA and MD values in different brain regions in HIC and HUC compared to CHNM were used for correlation analysis with NP test scores using Pearson's correlation.

Results: HIC and HUC groups showed significantly decreased NP test scores in various domain compared to CHNM. Significantly lower NP test scores was observed in HIC than those of HUC. HIC showed decreased FA and increased MD in multiple brain sites as compared to both CHNM and HUC. Decreased FA along with both increased and decreased MD in different brain regions was present in HUC compared to CHNM. Both positive and negative correlation of altered FA and MD values from different brain regions in HIC and HUC with NP test scores was observed.

Conclusion: The presence of brain tissue changes and neurocognitive function deficit in absence of HIV infection in HUC indicates that ART may have a detrimental impact on the developing brain. The findings of the current study underscore the need for screening of ART exposed children for neurodevelopment and cognitive abnormalities at an early stage and call for access to early interventions, and nutritional and care programs.

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MICROBIOLOGY SOCIETY

Sequencing of serially passaged measles virus affirms its genomic stability and reveals a nonrandom distribution of consensus mutations

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Abstract

Oncolytic virotherapy is an emerging treatment option for numerous cancers, with several virus families currently being evaluated in clinical trials. More specifically, vaccine-strain measles virus has arisen as a promising candidate for the treatment of different tumour types in several early clinical trials. Replicating viruses, and especially RNA viruses without proofreading polymerases, can rapidly adapt to varying environments by selecting quasispecies with advantageous genetic mutations. Subsequently, these genetic alterations could potentially weaken the safety profile of virotherapy. In this study, we demonstrate that, following an extended period of virus replication in producer or cancer cell lines, the quasispecies consensus sequence of vaccine strain-derived measles virus accrues a remarkably small number of mutations throughout the nonsegmented negative-stranded RNA genome. Interestingly, we detected a nonrandom distribution of genetic alterations within the genome, with an overall decreasing frequency of mutations from the 3′ genome start to its 5′ end. Comparing the serially passaged viruses to the parental virus on producer cells, we found that the acquired consensus mutations did not drastically change viral replication kinetics or cytolytic potency. Collectively, our data corroborate the genomic stability and excellent safety profile of oncolytic measles virus, thus supporting its continued development and clinical translation as a promising viro-immunotherapeutic.

INTRODUCTION

Measles virus (MeV) is a member of the family *Paramyxoviridae* and harbours a single-stranded RNA genome of negative polarity [1]. Individual virions are enveloped, pleomorphic particles of variable size, which may contain a single or multiple copies of the nonsegmented, polyhexameric viral RNA genome packaged in a helical nucleocapsid [2–4]. The latter typically comprises 15894 nucleotides and is organized into six genes encoding six structural and two nonstructural proteins [5]. Human-pathogenic wild-type strains of MeV utilize CD150/SLAMF1 as a cellular receptor to infect a variety of immune cell subtypes (including macrophages, dendritic cells, activated or memory B and T cells) and nectin-4/PVRL4 on the basal side of polarized airway epithelial cells to exit the host via the respiratory route [6–9].

Measles is still a major global cause of morbidity and mortality [10], leading to an estimated 110000 deaths in 2017 [11]. Recently, an alarming rise in the number of measles cases has been observed, which is linked to a global increase in vaccine hesitancy [12]. Consequentially, the number of severe, and sometimes fatal, complications of wild-type MeV infections [such as acute encephalitis and subacute sclerosing

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Keywords: measles virus; serial passaging; genomic stability; mutations; sequencing; viral quasispecies.
Abbreviations: ADAR1, Adenosine Deaminase Acting on RNA 1; ATU, Additional Transcription Unit; CIU, Cell Infectious Units; CMV, Cytomegalovirus; DMEM, Dulbecco's Modified Eagle's Medium; DNA, Deoxyribonucleic Acid; DPBS, Dulbecco's Phosphate-Buffered Saline; EGFP, Enhanced Green Fluorescent Protein; MeV, Measles Virus; m.o.i., Multiplicity of Infection; ORF, Open Reading Frame; OV, Oncolytic Virus; PCR, Polymerase Chain Reaction; RNA, Ribonucleic Acid; RT-PCR, Reverse Transcription Polymerase Chain Reaction; UTR, Untranslated Region.
Sequence information: Reference viral genomic sequence has been deposited in the NCBI GenBank database, accession number MN822013.
Five supplementary figures and three supplementary tables are available with the online version of this article.

frontiers in Neurology

REVIEW
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C_2H_2-Type Zinc Finger Proteins in Brain Development, Neurodevelopmental, and Other Neuropsychiatric Disorders: Systematic Literature-Based Analysis

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Neurodevelopmental disorders (NDDs) are multifaceted pathologic conditions manifested with intellectual disability, autistic features, psychiatric problems, motor dysfunction, and/or genetic/chromosomal abnormalities. They are associated with skewed neurogenesis and brain development, in part through dysfunction of the neural stem cells (NSCs) where abnormal transcriptional regulation on key genes play significant roles. Recent accumulated evidence highlights C_2H_2-type zinc finger proteins (C_2H_2-ZNFs), the largest transcription factor family in humans, as important targets for the pathologic processes associated with NDDs. In this review, we identified their significant accumulation (74 C_2H_2-ZNFs: ∼10% of all human member proteins) in brain physiology and pathology. Specifically, we discuss their physiologic contribution to brain development, particularly focusing on their actions in NSCs. We then explain their pathologic implications in various forms of NDDs, such as morphological brain abnormalities, intellectual disabilities, and psychiatric disorders. We found an important tendency that poly-ZNFs and KRAB-ZNFs tend to be involved in the diseases that compromise gross brain structure and human-specific higher-order functions, respectively. This may be consistent with their characteristic appearance in the course of species evolution and corresponding contribution to these brain activities.

Keywords: brain development, structural abnormality, KRAB domain, mutation, neural stem cells, transcriptional regulation

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INTRODUCTION

Neurodevelopmental disorders (NDDs) are multifaceted pathologic conditions caused by skewed development of the central nervous system (CNS) and subsequent morphological and/or functional abnormalities (1). Manifestations associated with NDDs include, but are not limited to, neuropsychiatric problems, cognitive impairment, motor dysfunctions, language/speech abnormalities, and affective deficits (2). Intellectual disability (ID), autism spectrum disorders (ASDs), motor diseases including developmental coordination disorder, communication, speech and language disorders, attention-deficit/hyperactivity disorder (ADHD), and various genetic disorders, such as Down syndrome and fragile-X syndrome, all fall into the NDD entity (1).

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Lab resource: Stem Cell Line

Derivation of a human induced pluripotent stem cell line (QBRIi007-A) from a patient carrying a homozygous intronic mutation (c.613-7T>*G*) in the *SLC2A2* gene

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A B S T R A C T

Fanconi Bickel Syndrome (FBS) is an autosomal recessive disease resulting from mutations in the *SLC2A2* gene, encoding the GLUT2. FBS patients develop diabetes mellitus. Using non-integrating Sendai virus, we generated an induced pluripotent stem cell (iPSC) line, QBRIi007-A, carrying the c.613-7 *T>G* homozygous mutation in intron 5 of the *SLC2A2* gene from a 19-year-old female with FBS and diabetes. The iPSC line was characterized for pluripotency, differentiation potential, genomic integrity, and genetic identity. This iPSC line provides a useful cell model to understand the role of GLUT2 in the disease development and to discover new drug candidates.

Resource Table

Unique stem cell line identifier	QBRIi007-A
Alternative name(s) of stem cell line	GLUT2 Mut-int iPSCs
Institution	Qatar Biomedical research institute (QBRI), Hamad Bin Khalifa University (HBKU), Qatar Foundation, Doha, Qatar
Contact information of distributor	Essam M. Abdelalim (emohamed@hbku.edu.qa)
Type of cell line	iPSC
Origin	Human
Additional origin info	Age: 19 years old Sex: Female Ethnicity: Pakistan
Cell source	Blood
Clonality	Clonal
Method of reprogramming	Integration-free Sendai virus vector contain OCT3/4, SOX2, c-MYC and KLF4
Genetic modification	YES
Type of modification	Hereditary
Associated disease	Fanconi Bickel Syndrome and diabetes mellitus
Gene/locus	Gene: *SLC2A2* Locus: 3q26.2 Mutation: c.613-7 *T>G*: IVS5-7 *T>G* in intron 5
Method of modification	N/A
Name of transgene or resistance	N/A
Inducible/constitutive system	N/A
Date archived/stock date	August 2019
Cell line repository/bank	N/A
Ethical approval	Blood samples were obtained from Sidra Medicine hospital with full informed consent. The protocol was approved by the Institutional Review Board (IRB) of Sidra Medicine (no. 1702007608) and QBRI (no. 2018-002)

1. Resource utility

Our iPSC line is derived from a patient with FBS and diabetes due to a homozygous mutation in *SLC2A2* gene. This iPSC line provides an *in vitro* model for investigating the role of GLUT2 in the pathogenesis of FBS and diabetes. Also, it can be used to develop new therapies.

2. Resource details

The *SLC2A2* gene encodes GLUT2, a low affinity facilitative glucose transporter, is expressed in pancreatic beta cells, liver, kidney and intestine (Thorens *et al.*, 1990). Several *SLC2A2* genetic defects and

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ARTICLE

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Somatic mosaicism and common genetic variation contribute to the risk of very-early-onset inflammatory bowel disease

Eva Gonçalves Serra et al.#

Very-early-onset inflammatory bowel disease (VEO-IBD) is a heterogeneous phenotype associated with a spectrum of rare Mendelian disorders. Here, we perform whole-exome-sequencing and genome-wide genotyping in 145 patients (median age-at-diagnosis of 3.5 years), in whom no Mendelian disorders were clinically suspected. In five patients we detect a primary immunodeficiency or enteropathy, with clinical consequences (*XIAP, CYBA, SH2D1A, PCSK1*). We also present a case study of a VEO-IBD patient with a mosaic de novo, pathogenic allele in *CYBB*. The mutation is present in ~70% of phagocytes and sufficient to result in defective bacterial handling but not life-threatening infections. Finally, we show that VEO-IBD patients have, on average, higher IBD polygenic risk scores than population controls (99 patients and 18,780 controls; $P < 4 \times 10^{-10}$), and replicate this finding in an independent cohort of VEO-IBD cases and controls (117 patients and 2,603 controls; $P < 5 \times 10^{-10}$). This discovery indicates that a polygenic component operates in VEO-IBD pathogenesis.

#A full list of authors and their affiliations appears at the end of the paper.

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FULL PAPER

Magnetic Resonance in Medicine

Single-Voxel ^{1}H MR spectroscopy of cerebral nicotinamide adenine dinucleotide (NAD^{+}) in humans at 7T using a 32-channel volume coil

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Purpose: Reliable monitoring of tissue nicotinamide adenine dinucleotide (NAD^{+}) concentration may provide insights on its roles in normal and pathological aging. In the present study, we report a ^{1}H MRS pulse sequence for the in vivo, localized ^{1}H MRS detection of NAD^{+} from the human brain.

Methods: Studies were carried out on a 7T Siemens MRI scanner using a 32-channel product volume coil. The pulse sequence consisted of a spectrally selective low bandwidth E-BURP-1 90° pulse. PRESS localization was achieved using optimized Shinnar-Le Roux 180° pulses and overlapping gradients were used to minimize the TE. The reproducibility of NAD^{+} quantification was measured in 11 healthy volunteers. The association of cerebral NAD^{+} with age was assessed in 16 healthy subjects 26–78 years old.

Results: Spectra acquired from a voxel placed in subjects' occipital lobe consisted of downfield peaks from the H_2, H_4, and H_6 protons of the nicotinamide moiety of NAD^{+} between 8.9–9.35 ppm. The mean ± SD within-session and between-session coefficients of variation were found to be 6.14 ± 2.03% and 6.09 ± 3.20%, respectively. In healthy volunteers, an age-dependent decline of the NAD^{+} levels in the brain was also observed ($\beta = -1.24$ μM/y, SE = 0.21, $P < 0.001$).

Conclusion: We demonstrated the feasibility and robustness of a newly developed ^{1}H MRS technique to measure localized cerebral NAD^{+} at 7T MRI using a

Tumor Microenvironment pp 149-172 | Cite as

The Biology of Immune-Active Cancers and Their Regulatory Mechanisms

Authors Authors and affiliations

Davide Bedognetti, Alessandra Cesano, Francesco M. Marincola, Ena Wang

Chapter
First Online: 26 March 2020

Part of the Cancer Treatment and Research book series (CTAR, volume 180)

Abstract

The development of cancer results from the evolutionary balance between the proliferating aptitude of cancer cells and the response of the host's tissues. Some cancers are characterized by genetic instability dependent upon impaired DNA repair mechanisms that lead to the chaotic disruption of multiple cellular functions often in excess of the cancer survival needs and may exert broad effects on surrounding tissues, some beneficial and some detrimental to cancer growth. Among them, inflammatory processes that accompany wound healing may initiate a reaction of the host against the neo-formation. This is possibly triggered by the release by dying cancer cells of molecules known as ***Damage-Associated Molecular Patterns*** **(DAMPs)** following a process termed ***Immunogenic Cell Death*** **(ICD)** that initiates an immune response through innate and adaptive mechanisms. Indeed, analysis of large cancer data sets has shown that ICD is strictly associated with the activation of other immune effector or immune-regulatory pathways. Here, we will describe how immune activation and compensatory immune-regulatory mechanisms balance anti-cancer immune surveillance and the roles that innate and adaptive immunity play including the weight that neo-epitopes may exert as initiators and sculptors of high-affinity memory and effector immune responses against cancer. We will discuss the evolutionary basis for the existence of immune checkpoints and how several theories raised to explain cancer resistance to immunotherapy represent a facet of a similar evolutionary phenomenon that we described in the *Theory of Everything*. We will show how the biology of immunogenicity and counterbalancing immune regulation is widespread across cancers independent of their ontogenesis while subtle idiosyncratic differences are discernible among them. Finally, we will suggest that overcoming immune resistance implies distinct approaches relevant to the immune context of individual cancers.

Tumor Microenvironment pp 3-50 | Cite as

Functional In Vivo Imaging of Tumors

Authors Authors and affiliations

Mohammad Haris, Sabah Nisar, Sheema Hashem, Ajaz A. Bhat, Santosh Yadav, Muralitharan Shanmugakonar, Hamda Al-Naemi, Puneet Bagga, Shahab Uddin, Ravinder Reddy

Chapter
First Online: 26 March 2020

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Part of the Cancer Treatment and Research book series (CTAR, volume 180)

Abstract

Noninvasive imaging of functional and molecular changes in cancer has become an indispensable tool for studying cancer in vivo. Targeting the functional and molecular changes in cancer imaging provides a platform for the in vivo analysis of the mechanisms such as gene expression, signal transduction, biochemical reactions, regulatory pathways, cell trafficking, and drug action underlying cancer noninvasively. The main focus of imaging in cancer is the development of new contrast methods/molecular probes for the early diagnosis and the precise evaluation of therapy response. In clinical setup, imaging modalities facilitate screening, prediction, staging, biopsy and therapy guidance, therapy response, therapy planning, and prognosis of cancer. In this book chapter, we review different established and emerging in vivo imaging modalities and their applications in monitoring functional, molecular, and metabolic changes in cancer.

Keywords

Biomedical imaging Optical imaging Positron emission tomography Magnetic resonance imaging Magnetic resonance spectroscopy Hyperpolarization Chemical exchange saturation transfer

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A New Humanized Mouse Model Mimics Humans in Lacking α-Gal Epitopes and Secreting Anti-Gal Antibodies

Fayez M. Saleh,*,† Partha K. Chandra,‡ Dong Lin,§ James E. Robinson,¶ Reza Izadpanah,§ Debasis Mondal,‡,‖ Christian Bollensdorff,# Eckhard U. Alt,§ Quan Zhu, Wayne A. Marasco,** Stephen E. Braun,*,‡ and Ussama M. Abdel-Motal#,****

Mice have been used as accepted tools for investigating complex human diseases and new drug therapies because of their shared genetics and anatomical characteristics with humans. However, the tissues in mice are different from humans in that human cells have a natural mutation in the α1,3 galactosyltransferase (α1,3GT) gene and lack α-Gal epitopes on glycosylated proteins, whereas mice and other nonprimate mammals express this epitope. The lack of α-Gal epitopes in humans results in the loss of immune tolerance to this epitope and production of abundant natural anti-Gal Abs. These natural anti-Gal Abs can be used as an adjuvant to enhance processing of vaccine epitopes to APCs. However, wild-type mice and all existing humanized mouse models cannot be used to test the efficacy of vaccines expressing α-Gal epitopes because they express α-Gal epitopes and lack anti-Gal Abs. Therefore, in an effort to bridge the gap between the mouse models and humans, we developed a new humanized mouse model that mimics humans in that it lacks α-Gal epitopes and secretes human anti-Gal Abs. The new humanized mouse model (Hu-NSG/α-Gal^{null}) is designed to be used for preclinical evaluations of viral and tumor vaccines based on α-Gal epitopes, human-specific immune responses, xenotransplantation studies, and in vivo biomaterials evaluation. To our knowledge, our new Hu-NSG/α-Gal^{null} is the first available humanized mouse model with such features. ***The Journal of Immunology*****, 2020, 204: 000–000.**

The α-Gal epitope is a carbohydrate epitope that is synthesized by the α1,3 galactosyltransferases (α1,3GT) enzyme within the Golgi of the cell (1). Humans have a natural mutation in the α1,3GT gene, and therefore they do not express the enzyme or terminal α-Gal epitopes on glycoproteins (2). In addition, the loss of α-Gal epitopes leads to the loss of immune tolerance in humans and results in production of abundant natural anti-Gal Abs (2). In contrast, mice have an intact α1,3GT gene and active α1,3GT enzyme, therefore they express α-Gal epitopes and lack anti-Gal Abs (3).

Studies in animal models have shown that disrupting or knocking out the α1,3GT gene resulted in complete absence of α-Gal epitopes (4–6). The α1,3GT knockout (GTKO) mice lack the α-Gal epitope by targeted disruption of the α1,3GT gene with the neomycin resistance gene (7). In pigs, disruption of the α1,3GT gene locus, mediated by a pPL657 vector (5), results in an inactive enzyme and lack of the α-Gal epitope. Importantly, the production of anti-Gal Abs was demonstrated in both models (8). Despite the fact that these animals allow for analysis of anti-Gal Abs in mediating enhanced immunogenicity, they are limited to analysis of murine or pig immune responses and cannot be used for HIV-1 studies because they cannot be infected with HIV-1 virus.

Therefore, in an effort to develop a mouse model that is suitable for evaluating human immune responses, produces anti-Gal Abs, and can be infected with HIV-1 virus, this study generated a humanized mouse model that carries the features of both the GTKO (7) and NOD.Cg-*Prkdc*^{scid}*IL2Rγ*$^{tm1Wjl/SzJ}$ strain, which is commonly known as NOD SCID γc$^{-/-}$ (NSG) (9, 10) mice. The NSG mouse combines the features of the NOD/ShiLtJ background with several deficiencies in innate immunity, the SCID, and an IL-2 receptor γ-chain (IL-2Rγ) knockout (9). As a result, the NSG mice lack mature T cells, B cells, functional NK cells, and are also deficient in cytokine signaling. This strain is among the most immunodeficient described to date (11, 12) and permits the most efficient engraftment of normal human CD34$^+$ hematopoietic stem cells (HSCs) (10–13), resulting in long-term reconstitution and differentiation of a functional human immune system with human T cells, B cells, and dendritic cells (11) as well as sustained HIV infection (14, 15).

It is well documented that the most effective way to enhance poorly immunogenic proteins, such as tumor-associated Ags, is by forming an immune complex with their corresponding IgG Ab,

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Abbreviations used in this article: α1,3GT, α1,3 galactosyltransferase; GTKO, 1,3GT knockout; HSC, hematopoietic stem cell; IL-2Rγ, IL-2 receptor γ-chain; NSG, NOD SCID γc$^{-/-}$; PB, peripheral blood; SNP, single nucleotide polymorphism; SWBC, sheep whole blood lysate.

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Inherited human IFN-γ deficiency underlies mycobacterial disease

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Mendelian susceptibility to mycobacterial disease (MSMD) is characterized by a selective predisposition to clinical disease caused by the Bacille Calmette-Guérin (BCG) vaccine and environmental mycobacteria. The known genetic etiologies of MSMD are inborn errors of IFN-γ immunity due to mutations of 15 genes controlling the production of or response to IFN-γ. Since the first MSMD-causing mutations were reported in 1996, biallelic mutations in the genes encoding IFN-γ receptor 1 (IFN-γR1) and IFN-γR2 have been reported in many patients of diverse ancestries. Surprisingly, mutations of the gene encoding the IFN-γ cytokine itself have not been reported, raising the remote possibility that there might be other agonists of the IFN-γ receptor. We describe 2 Lebanese cousins with MSMD, living in Kuwait, who are both homozygous for a small deletion within the *IFNG* gene (c.354_357del), causing a frameshift that generates a premature stop codon (p.T119Ifs4*). The mutant allele is loss of expression and loss of function. We also show that the patients' herpesvirus Saimiri–immortalized T lymphocytes did not produce IFN-γ, a phenotype that can be rescued by retrotransduction with WT *IFNG* cDNA. The blood T and NK lymphocytes from these patients also failed to produce and secrete detectable amounts of IFN-γ. Finally, we show that human *IFNG* has evolved under stronger negative selection than *IFNGR1* or *IFNGR2*, suggesting that it is less tolerant to heterozygous deleterious mutations than *IFNGR1* or *IFNGR2*. This may account for the rarity of patients with autosomal-recessive, complete IFN-γ deficiency relative to patients with complete IFN-γR1 and IFN-γR2 deficiencies.

Introduction

Mendelian susceptibility to mycobacterial disease (MSMD) (OMIM #209950) is characterized by a predisposition to severe disease caused by weakly virulent mycobacteria, including *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) vaccines and environmental mycobacteria (1, 2). Patients are typically otherwise healthy, normally resistant to most other microbes, and have no overt hematological or immunological abnormalities in routine tests. Nevertheless, some patients can suffer from infections due to more virulent mycobacteria, such as *Mycobacterium tuberculosis* (3). Moreover, extraintestinal, nontyphoidal salmonellosis has also been documented in approximately half of the patients (2, 4–6). Other infections caused by intramacrophagic bacteria, fungi, and parasites occur more rarely (2, 7). In particular, chronic mucocutaneous candidiasis can be seen in patients with specific genetic etiologies (8). MSMD was first described in the 1950s, with various clinical manifestations ranging from recurrent localized disease to progressive disseminated infections (9–11). The clinical outcome and response to treatment also vary considerably from patient to patient. The overall prevalence of MSMD has been estimated at approximately 1 of 50,000 births, and cases have been diagnosed or reported in almost all

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Molecular Cancer

REVIEW Open Access

Role of non-coding RNA networks in leukemia progression, metastasis and drug resistance

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Abstract

Early-stage detection of leukemia is a critical determinant for successful treatment of the disease and can increase the survival rate of leukemia patients. The factors limiting the current screening approaches to leukemia include low sensitivity and specificity, high costs, and a low participation rate. An approach based on novel and innovative biomarkers with high accuracy from peripheral blood offers a comfortable and appealing alternative to patients, potentially leading to a higher participation rate.

Recently, non-coding RNAs due to their involvement in vital oncogenic processes such as differentiation, proliferation, migration, angiogenesis and apoptosis have attracted much attention as potential diagnostic and prognostic biomarkers in leukemia. Emerging lines of evidence have shown that the mutational spectrum and dysregulated expression of non-coding RNA genes are closely associated with the development and progression of various cancers, including leukemia. In this review, we highlight the expression and functional roles of different types of non-coding RNAs in leukemia and discuss their potential clinical applications as diagnostic or prognostic biomarkers and therapeutic targets.

Keywords: Cancer, Circular RNAs, Chromatin, Drug resistance, Epigenetics, Gene regulation, Long non-coding RNAs, MicroRNAs, Metastasis, Signaling pathways

Introduction

Leukemia is a class of blood cancers characterized by an oligoclonal expansion of hematopoietic cells that infiltrate the bone marrow and can also invade the blood and other extramedullary tissues [1]. The proliferation of leukemic cells causes the expulsion of the normal hematopoietic cells and the loss of their functions, leading to severe symptoms, including thrombocytopenia, anemia, and immunodeficiency. Hematological cancers are ranked as the 11th common type of cancer and the 10th common cause of cancer-related death. More than 350,000 new leukemia cases and 265,000 leukemia deaths were estimated to have occurred in 2012 [2]. In the United States, leukemia accounts for approximately 4% of cancer-derived mortalities and 3.5% of all cancer cases. The incidence, mortality, and survival of leukemia depends on the diagnosis, prognosis, as well as natural history of neoplasms arising from the malignant transformation of hemopoietic stem cells or progenitor cells in the bone marrow [3].

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RESEARCH Open Access

Profiling the Salivary microbiome of the Qatari population

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Abstract

Background: The role of the human microbiome in human health and disease has been studied in various body sites. However, compared to the gut microbiome, where most of the research focus is, the salivary microbiome still bears a vast amount of information that needs to be revealed. This study aims to characterize the salivary microbiome composition in the Qatari population, and to explore specific microbial signatures that can be associated with various lifestyles and different oral conditions.

Materials and methods: We characterized the salivary microbiome of 997 Qatari adults using high-throughput sequencing of the V1–V3 region of the 16S rRNA gene.

Results: In this study, we have characterized the salivary microbiome of 997 Qatari participants. Our data show that *Bacteroidetes*, *Firmicutes*, *Actinobacteria* and *Proteobacteria* are the common phyla isolated from the saliva samples, with Bacteroidetes being the most predominant phylum. *Bacteroidetes* was also more predominant in males versus females in the study cohort, although differences in the microbial diversity were not statistically significant. We also show that, a lower diversity of the salivary microbiome is observed in the elderly participants, with *Prevotella* and *Treponema* being the most significant genera. In participants with oral conditions such as mouth ulcers, bleeding or painful gum, our data show that *Prevotella* and *Capnocytophaga* are the most dominant genera as compared to the controls. Similar patterns were observed in participants with various smoking habits as compared to the non-smoking participants. Our data show that *Streptococcus* and *Neisseria* are more dominant among denture users, as compared to the non-denture users. Our data also show that, abnormal oral conditions are associated with a reduced microbial diversity and microbial richness. Moreover, in this study we show that frequent coffee drinkers have higher microbial diversity compared to the non-drinkers, indicating that coffee may cause changes to the salivary microbiome. Furthermore, tea drinkers show higher microbial richness as compared to the non-tea drinkers.

Conclusion: This is the first study to assess the salivary microbiome in an Arab population, and one of the largest population-based studies aiming to the characterize the salivary microbiome composition and its association with age, oral health, denture use, smoking and coffee-tea consumption.

Keywords: 16S rRNA gene sequencing, Saliva, Dysbiosis, Qatari, Oral health, Qatar Biobank

Background

The human microbiota is the collection of a wide array of microorganisms such as bacteria, archaea, fungi and viruses that inhabit various body sites including skin, saliva and the gut [1]. The microbiome, defined as the collection of microbiota and their genes, plays an important role in human health and disease [2]. The development in

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BMC Research Notes

RESEARCH NOTE Open Access

Influence of storage conditions of small volumes of blood on immune transcriptomic profiles

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Abstract

Objective: Transcriptome analysis of human whole blood is used to discover biomarkers of diseases and to assess phenotypic traits. Here we have collected small volumes of blood in Tempus solution and tested whether different storage conditions have an impact on transcriptomic profiling. Fifty µl of blood were collected in 100µl of Tempus solutions, freezed at − 20 °C for 1 day and eventually thawed, stored and processed under five different conditions: (i) − 20 °C for 1 week; (ii) +4 °C for 1 week; (iii) room temperature for 1 week; (iv) room temperature for 1 day, − 20 °C for 1 day, room temperature until testing at day 7, (v) − 20 °C for 1 week, RNA was isolated and stored in GenTegra solution. We used 272 immune transcript specific assays to test the expression profiling using qPCR based Fluidigm BioMark HD dynamic array.

Results: RNA yield ranged between 0.17 and 1.39µg. Except for one sample, RIN values were > 7. Using Principal Component Analysis, we saw that the storage conditions did not drive sample distribution. The condition that showed larger variability was the RT-FR-RT (room temperature–freezing–room temperature), suggesting that freezing–thawing cycles may have a worse effect on data reproducibility than keeping the samples at room temperature.

Keywords: Storage, Blood, Trancriptome, QPCR, Immune profiling, Tempus, GenTegra

Introduction

The genomic revolution of the last decade and the parallel increase of international collaborations have led to an unprecedented need for transferring biological samples across institutes worldwide. Emerging technologies offer the opportunity to transfer samples at room temperature with the advantage of reducing the logistic challenges associated with sample shipment as well as the carbon footprint associated with portable freezers [1].

Projects aiming at biomarker discovery often employ transcriptional profiling of whole blood [2–5]. Peripheral blood is perhaps the most practical tissue to profile gene expression of the human immune system due to its accessibility, allowing large-scale and non-invasive sampling [6, 7]. Recently, finger-stick blood collection systems have allowed a less invasive and quicker collection of peripheral blood that does not necessarily require medical infrastructures [8–11]. Small volumes of blood are more prone to thaw when compared to blood collected by venipuncture. Often, samples collected in a given place need to be transferred to a second place before processing. Blood samples are generally freezed for storage or shipment to other institutes. Fluctuations in temperature have a high impact on sample performance [12] and

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Review Article

Paracrine Mechanisms of Mesenchymal Stromal Cells in Angiogenesis

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The role of the mesenchymal stromal cell- (MSC-) derived secretome is becoming increasingly intriguing from a clinical perspective due to its ability to stimulate endogenous tissue repair processes as well as its effective regulation of the immune system, mimicking the therapeutic effects produced by the MSCs. The secretome is a composite product secreted by MSC *in vitro* (in conditioned medium) and *in vivo* (in the extracellular milieu), consisting of a protein soluble fraction (mostly growth factors and cytokines) and a vesicular component, extracellular vesicles (EVs), which transfer proteins, lipids, and genetic material. MSC-derived secretome differs based on the tissue from which the MSCs are isolated and under specific conditions (e.g., preconditioning or priming) suggesting that clinical applications should be tailored by choosing the tissue of origin and a priming regimen to specifically correct a given pathology. MSC-derived secretome mediates beneficial angiogenic effects in a variety of tissue injury-related diseases. This supports the current effort to develop cell-free therapeutic products that bring both clinical benefits (reduced immunogenicity, persistence *in vivo*, and no genotoxicity associated with long-term cell cultures) and manufacturing advantages (reduced costs, availability of large quantities of off-the-shelf products, and lower regulatory burden). In the present review, we aim to give a comprehensive picture of the numerous components of the secretome produced by MSCs derived from the most common tissue sources for clinical use (e.g., AT, BM, and CB). We focus on the factors involved in the complex regulation of angiogenic processes.

1. Introduction

Mesenchymal stromal cells (MSCs) were described for the first time in 1970 by Alexander Friedenstein as a "population of bone marrow stromal cells capable of mesodermal differentiation and trophic support of hematopoiesis" [1, 2]. Mesenchyme is derived from Greek, meaning "middle" (meso) "infusion," and it refers to the ability of mesenchymatous cells to spread and migrate in early embryonic development between the ectodermal and endodermal layers [3]. MSCs are pluripotent, self-renewing, spindle-shaped cells found in several adult and perinatal tissues. To differentiate MSCs from other morphologically similar cells, the International Society for Cellular Therapy (ISCT) defined the minimal set of criteria by which MSCs are identified: adherence to plastic under normal cell culture conditions; differentiation capability into multiple cell lineages including, and not limited to, adipocytes, osteocytes, and chondrocytes; positive expression of CD105, CD73, and CD90 surface markers; and lack of expression of CD45, CD14, CD19, and CD34 and a minimal expression of HLA-DR [4]. MSCs can be derived from bone marrow (BM), adipose tissue (AT), and other adult tissues such as dental pulp and dermal tissues. MSCs can also be isolated from perinatal tissues such as cord blood (CB), placenta, and amniotic fluid and membrane (AM), as well as umbilical cord Wharton's jelly (WJ) [5–7].

MSCs possess therapeutic properties demonstrated both *in vitro* and *in vivo*, with evidence pointing to anti-

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Analysis of Toll-Like Receptor-2 and 4 Expressions in Peripheral Monocyte Subsets in Patients with Type 1 Diabetes Mellitus

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ABSTRACT

Background: Dysfunction of the peripheral blood monocytes in the form of changes in their proportion, cytokines or pattern-recognition receptors (PRR) expressions may be involved in the pathogenesis of type 1 diabetes mellitus (T1DM). Our aim is to analyze the three monocyte subsets; classical, non-classical and intermediate monocytes and their expression of Toll-like receptors 2 (TLR-2) and 4 (TLR-4) in T1DM patients.
Methods: The peripheral blood monocytes of 20 T1DM patients were analyzed by Flow cytometry to measure their count and TLR-2 and TLR-4 expression.
Results: T1DM patients had more non-classical and intermediate monocytes, whereas classical monocytes were comparable between patients and control (20 healthy volunteers). Classical, non-classical and intermediate monocytes had no significant correlations with hemoglobin (Hb) A1C in controls, while all subsets showed positive correlations with HbA1C in T1DM. TLR-2 and TLR-4 expression were significantly increased in classical monocytes in patients, especially those with diabetic ketoacidosis (DKA), and both of them showed positive correlations with the duration of T1DM. The expression of TLR-2 inside non-classical monocytes showed a negative correlation with LDL cholesterol and TLR-4/TLR-2 ratio showed positive correlations with the duration of T1DM and negative correlations with total cholesterol. The expression of TLR-2 inside intermediate monocytes showed positive correlations with the duration of T1DM and TLR-4/TLR-2 ratio showed negative correlations with the duration of T1DM
Conclusions: The observed changes in both proportions and TLR-2 and TLR-4 expression of monocyte subsets can raise the possible role in the pathogenesis of early stages of T1DM and DKA.

Abbreviations APC: allophycocyanin; CBC: complete blood picture; DKA: diabetic acidosis; DM: diabetes mellitus; FITC: fluorescein isothiocyanate; FSC: forward scatter; Hb: haemoglobin; MFI: mean channel fluorescence intensity; PE: phycoerythrin; PRR: pattern-recognition receptors; SPSS: statistical package for the social sciences; SSC: side scatter; T1DM: Type1DM; TLRs: toll-like receptors

KEYWORDS
FACS analysis; type 1 diabetes; monocytes; toll-like receptor-2; toll-like receptor-4

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/iimm.

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REVIEW

Therapeutic Effects of Curcumol in Several Diseases; An Overview

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ABSTRACT

Curcumae Rhizoma, also known as *Ezhu* is a traditional Chinese medicine that has been used for many centuries against several diseases. The rhizome of the plant is composed of curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin), and essential volatile oils including curcumol, curdione, and germacrone. While curcuminoids have been extensively studied for their antimicrobial, antioxidant, anti-inflammatory and anticancer properties, the therapeutic efficacy of curcumol is still emerging. Recent studies have shown anticancer properties of curcumol against multiple solid tumors such as breast, colorectal, head and neck, and lung adenocarcinomas. The underlying anti-tumor mechanisms revealed inhibition of several signaling pathways (NF-κB, MAPK, PI-3K/AKT, and GSK-3β) associated with cell proliferation, survival, anti-apoptosis, invasion and metastasis. Besides curcumol, extracts from the *Curcumae Rhizoma* roots possess many other terpenoids such as β-elemene, δ-elemene, germacrone, furanodiene and furanodienone with known anticancer properties. In this review, we comprehensively focused on the composition of *Curcumae Rhizoma* essential oils, their structure, isolation and therapeutic uses of curcumol to aid in the improvement and development of novel drugs with minimal cytotoxicity, enhanced efficacy, and less cost.

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KEYWORDS
Antioxidant; apoptosis; cancer prevention; dietary intervention; oxidative stress; transcription factors

Introduction

The global acceptance of traditional medicines has prevailed for centuries, and there has been an increasing interest in phytochemicals derived from medicinal plants as a potential source for therapeutic applications against multiple chronic diseases including cancer, diabetes, cardiovascular and neurodegenerative disorders (1–4). Also, phytochemicals produced from these plants are helpful to the environment and agriculture due to their extensive biological and chemical properties (5). Importantly, medicinal plants, unlike pharmacological drugs are found to have less harmful effects and are easily accessible and affordable (6).

Zingiberaceae which is commonly known as a ginger family is spread throughout the tropical areas of Asia, Africa, and America. They consist of 1300 species of flowering plants that are divided into perennial herbs with tuberous rhizomes (7). *Curcumae longa (C. longa)* is a perennial herb and a member of the *Zingiberaceae* family, used in the production of many complex compounds essential in food preparation such as spices, seasoning and flavoring agents. They are also used in cosmetic and pharmaceutical industries as therapeutic pharmacological agents (8). Essential oils and phenolic pigments are the main components of *Curcuma* plants (9). Besides, the roots of *C. longa* contain a variety of pigments that provide color and flavor to the food (10,11) and are also an essential ingredient of curry powder in Asian cuisines (12). For thousands of years, *Curcumae Rhizoma* (*Zingiberaceae* family) has been traditionally used to treat blood stasis (13) and in alleviating pain (14). However, recent studies have shown it to possess many nontoxic polyphenolic derivatives such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin that have a strong therapeutic potential against many cancers (15), while *Curcumae Radix* and the dry root tubers of *Curcuma wenyujin*, *Curcuma phaeocaulis*, and *Curcuma kwangsiensis,* which are collectively known as zedoary in the Chinese Pharmacopeia (16,17) are used in the treatment of rheumatic

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Toward High-Dimensional Single-Cell Analysis of Graphene Oxide Biological Impact: Tracking on Immune Cells by Single-Cell Mass Cytometry

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Considering the potential exposure to graphene, the most investigated nanomaterial, the assessment of the impact on human health has become an urgent need. The deep understanding of nanomaterial safety is today possible by high-throughput single-cell technologies. Single-cell mass cytometry (cytometry by time-of flight, CyTOF) shows an unparalleled ability to phenotypically and functionally profile complex cellular systems, in particular related to the immune system, as recently also proved for graphene impact. The next challenge is to track the graphene distribution at the single-cell level. Therefore, graphene oxide (GO) is functionalized with $AgInS_2$ nanocrystals (GO–In), allowing to trace GO immune–cell interactions via the indium (^{115}In) channel. Indium is specifically chosen to avoid overlaps with the commercial panels (>30 immune markers). As a proof of concept, the GO–In CyTOF tracking is performed at the single-cell level on blood immune subpopulations, showing the GO interaction with monocytes and B cells, therefore guiding future immune studies. The proposed approach can be applied not only to the immune safety assessment of the multitude of graphene physical and chemical parameters, but also for graphene applications in neuroscience. Moreover, this approach can be translated to other 2D emerging materials and will likely advance the understanding of their toxicology.

Graphene, a single layer of hexagonally arranged carbon atoms, is considered the most versatile material available to mankind: the thinnest, the strongest, the lightest, extremely flexible, highly electrically and thermally conductive material,[1,2] a versatile entity for multiple functionalization. Due to its unique combination of superior properties, graphene is the starting platform for new disruptive technologies across a wide range of fields [3,4] Various graphene-based technologies have now transformed into commercial products, in sports goods, automotive coatings, conductive inks, touch screens and several others.[5] The massive production and use of graphene materials will increase exponentially over the coming years. On the other hand, an ever-growing literature is related to the explorations of graphene materials for new diagnostic and therapeutic strategies.[6–9] The graphene material exposure, due to the different applications, might open possible threats

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ORIGINAL ARTICLE

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Haploinsufficiency of the *FOXA2* associated with a complex clinical phenotype

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Abstract

Background: There are few reports describing the proximal deletions of the short arm of chromosome 20, making it difficult to predict the likely consequences of these deletions. Most previously reported cases have described the association of 20p11.2 deletions with Alagille syndrome, while there are others that include phenotypes such as panhypopituitarism, craniofacial dysmorphism, polysplenia, autism, and Hirschsprung disease.

Methods: Molecular karyotyping, cytogenetics, and DNA sequencing were undertaken in a child to study the genetic basis of a complex phenotype consisting of craniofacial dysmorphism, ocular abnormalities, ectopic inguinal testes, polysplenia, growth hormone deficiency, central hypothyroidism, and gastrointestinal system anomalies.

Results: We report the smallest described de novo proximal 20p11.2 deletion, which deletes only the *FOXA2* leading to the above complex phenotype.

Conclusions: Haploinsufficiency of the *FOXA2* only gene is associated with a multisystem disorder.

KEYWORDS

20p11.2 deletion, *FOXA2*, growth hormone deficiency, haploinsufficiency, hypothyroidism

1 | INTRODUCTION

The forkhead box A (FOXA) transcription factor plays an important role in multiple stages of life, from early development to endoderm formation, regulation of genes involved in growth and proliferation, fertility, organogenesis and differentiation, metabolism, homeostasis, and the immune system (Friedman & Kaestner, 2006; Kaestner, 2010; Kelleher et al., 2017). *FOXA2* expression occurs in the primitive streak and in the node of the embryo, which are both crucial for gastrulation. *FOXA2* expression is also active in the anterior axial mesoderm, definitive endoderm formation, as well as ectoderm-derived neural tissues and endoderm-derived tissues (pancreas, liver, thyroid, prostate, and lung) in early development and adulthood (Besnard, Wert, Hull, & Whitsett, 2004; Friedman & Kaestner, 2006; Kaestner, 2000).

β-cell-specific *FOXA2*-knockout mice exhibit severe hyperinsulinemic hypoglycemia and hypoglucagonemia phenotype due to an increased insulin to glucagon ratio (3–4 fold), and die shortly after birth due to inhibition of notochord and endoderm formation (Gao et al., 2010; Lantz et al., 2004; Sund et al., 2001). The phenotypic outcome is likely due to the role that *FOXA2* plays in regulating the expression of genes in pancreatic β-cells that are important in glucose sensing and insulin secretion, including

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Review

Graphene and other 2D materials: a multidisciplinary analysis to uncover the hidden potential as cancer theranostics

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Abstract

Cancer represents one of the main causes of death in the world; hence the development of more specific approaches for its diagnosis and treatment is urgently needed in clinical practice. Here we aim at providing a comprehensive review on the use of 2-dimensional materials (2DMs) in cancer theranostics. In particular, we focus on graphene-related materials (GRMs), graphene hybrids, and graphdiyne (GDY), as well as other emerging 2DMs, such as MXene, tungsten disulfide (WS2), molybdenum disulfide (MoS2), hexagonal boron nitride (h-BN), black phosphorus (BP), silicene, antimonene (AM), germanene, biotite (black mica), metal organic frameworks (MOFs), and others. The results reported in the scientific literature in the last ten years (>200 papers) are dissected here with respect to the wide variety of combinations of imaging methodologies and therapeutic approaches, including drug/gene delivery, photothermal/photodynamic therapy, sonodynamic therapy, and immunotherapy. We provide a unique multidisciplinary approach in discussing the literature, which also includes a detailed section on the characterization methods used to analyze the material properties, highlighting the merits and limitations of the different approaches. The aim of this review is to show the strong potential of 2DMs for use as cancer theranostics, as well as to highlight issues that prevent the clinical translation of these materials. Overall, we hope to shed light on the hidden potential of the vast panorama of new and emerging 2DMs as clinical cancer theranostics.

Key words: 2D materials, cancer theranostics, future perspectives, graphene, nanomedicine.

1. Introduction

Graphene, a single layer of graphite, is undoubtedly the most famous 2-dimensional material (2DM), due to its outstanding properties that can be exploited in various applications, ranging from electronics to composites and biomedical applications [1–3]. Moreover, an entire family of graphene-related

Journal for ImmunoTherapy of Cancer

Oncogenic states dictate the prognostic and predictive connotations of intratumoral immune response

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ABSTRACT

Background An immune active cancer phenotype typified by a T helper 1 (Th-1) immune response has been associated with increased responsiveness to immunotherapy and favorable prognosis in some but not all cancer types. The reason of this differential prognostic connotation remains unknown.

Methods To explore the contextual prognostic value of cancer immune phenotypes, we applied a multimodal pan-cancer analysis among 31 different histologies (9282 patients), encompassing immune and oncogenic transcriptomic analysis, mutational and neoantigen load and copy number variations.

Results We demonstrated that the favorable prognostic connotation conferred by the presence of a Th-1 immune response was abolished in tumors displaying specific tumor-cell intrinsic attributes such as high transforming growth factor-beta (TGF-β) signaling and low proliferation capacity. This observation was independent of mutation rate. We validated this observation in the context of immune checkpoint inhibition. WNT-β catenin, barrier molecules, Notch, hedgehog, mismatch repair, telomerase activity and AMPK signaling were the pathways most coherently associated with an immune silent phenotype together with mutations of driver genes including *IDH1/2, FOXA2, HDAC3, PSIP1, MAP3K1, KRAS, NRAS, EGFR, FGFR3, WNT5A* and *IRF7*.

Conclusions This is the first systematic study demonstrating that the prognostic and predictive role of a bona fide favorable intratumoral immune response is dependent on the disposition of specific oncogenic pathways. This information could be used to refine stratification algorithms and prioritize hierarchically relevant targets for combination therapies.

BACKGROUND

Evidence of the effects of antitumoral immunity on cancer progression has accumulated over the last decades. The identification of tumor immune escape mechanisms, most importantly the characterization of immune checkpoints, led to major advances in immunotherapy. Immune checkpoint inhibitors have dramatically improved clinical outcome for a subset of patients across multiple cancer types. Despite this progress, the majority of tumors (60%–80%) still fail to respond.[1 2] Understanding the relationship between tumor cell and the immune system is critical to develop more effective therapeutic strategies.

A pre-existing intratumoral antitumor immune response has been associated with favorable outcome and responsiveness to immunotherapy.[3] However, multiple studies have reported differences in the association between measures of intratumoral immune activity and survival across different cancer types.[4–8] In breast cancer, a positive association between survival and density of tumor infiltrating lymphocytes, as estimated by transcriptomic data, was restricted to tumors displaying a high mutational load or an aggressive/high proliferative phenotype.[9–11] Proposed transcriptome-based immunological classifications range from a measure of cytolytic activity by mean expression of *GZMA* and *PRF1* genes,[12] to reflections of immune cell infiltration by cell-specific transcriptional profiles,[10 13] or gene signatures reflecting molecular components of an active antitumor immune response, including major histocompatibility complex, costimulatory or immunomodulatory molecules.[4 14 15] Reported prognostic and predictive signatures typically show overlapping genes or genes involved in conserved immunologic processes.[3 16–19] We termed these mechanisms as the Immunologic Constant of Rejection (ICR).[3 14 20–22] The ICR signature incorporates interferon-stimulated genes driven by transcription factors *IRF1* and *STAT1*, *CCR5* and *CXCR3* ligands, immune

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RESEARCH Open Access

CSF total and oligomeric α-Synuclein along with TNF-α as risk biomarkers for Parkinson's disease: a study in *LRRK2* mutation carriers

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Abstract

Background: Asymptomatic carriers of leucine-rich repeat kinase 2 (*LRRK2*) gene mutations constitute an ideal population for discovering prodromal biomarkers of Parkinson's disease (PD). In this study, we aim to identify CSF candidate risk biomarkers of PD in individuals with *LRRK2* mutation carriers.

Methods: We measured the levels of CSF total- (t-), oligomeric (o-) and phosphorylated S129 (pS129-) α-syn, total-tau (tTau), phosphorylated threonine 181 tau (pTau), amyloid-beta 40 (Aβ-40), amyloid-beta-42 (Aβ-42) and 40 inflammatory chemokines in symptomatic ($n = 23$) and asymptomatic ($n = 51$) *LRRK2* mutation carriers, subjects with a clinical diagnosis of PD ($n = 60$) and age-matched healthy controls ($n = 34$). General linear models corrected for age and gender were performed to assess differences in CSF biomarkers between the groups. Markers that varied significantly between the groups were then analyzed using backward-elimination logistic regression analysis to identify an ideal biomarkers panel of prodromal PD.

Results: Discriminant function analysis revealed low levels of CSF t-α-syn, high levels of CSF o-α-syn and TNF-α best discriminated asymptomatic *LRRK2* mutation carriers from both symptomatic PD and healthy controls. Assessing the discriminative power using receiver operating curve analysis, an area under the curve > 0.80 was generated.

Conclusions: The current study suggests that CSF t-, o-α-syn and TNF-α are candidate risk biomarkers for the detection of PD at the prodromal stage. Our findings also highlight the dynamic interrelationships between CSF proteins and the importance of using a biomarkers' panel approach for an accurate and timely diagnosis of PD.

Keywords: Parkinson's disease, *LRRK2* mutation carriers, Alpha-synuclein oligomers, Biomarkers, Inflammatory markers

Background

Our understanding of the genetic basis of Parkinson's disease (PD) has increased tremendously over the past 20 years. Mutations in the gene encoding alpha-synuclein (α-syn) were the first to be associated with genetic PD. Another monogenic causative factor in PD patients is *leucine-rich repeat kinase 2* (*LRRK2*), of which more than 100 variants have been identified [1]. Asymptomatic carriers of *LRRK2* mutations constitute an ideal population for identifying predictive biomarkers of PD for several reasons: 1) a high risk of conversion to PD, 2) dopaminergic neuronal loss demonstrated by positron emission tomography (PET) scanning, and 3) similarity of the clinical phenotype of LRRK2-associated PD to that of patients with sporadic PD (sPD). While the exact involvement of LRRK2 in PD pathogenesis remains only partially

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Differential Responsiveness to BRAF Inhibitors of Melanoma Cell Lines BRAF V600e-Mutated

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Background

Melanoma is an aggressive neoplasm characterized by a complex etiology. Several molecular alterations occur during melanoma progression. The most commonly mutated pathway is the mitogen-activated protein kinases (MAPK)/ERK cascade. The activation of the MAPK/ERK signaling occurs either through gain-of-function mutations in BRAF and NRAS gene or through autocrine growth factor stimulation. Documented mutations have been found in the kinase domain of BRAF gene encoded by exon 11 and 15 with a frequency of 50–70%. The majority of these mutations affect one critical amino acid, resulting in the V600E substitution which account for more than 90% of all BRAF mutations. Given the high incidence of BRAF V600E mutation in melanoma, patient management is based on the use of specific inhibitors when patients carry BRAF V600E mutation.

By comparing RNA-seq and DNA Sanger sequencing data, we found that among 15 melanoma cell lines 3 were discordant in the mutation detection (BRAF V600E at DNA level/Sanger sequencing and BRAF WT on RNA-seq). We initially postulated that those cell lines may express only the WT allele at the RNA level although mutated at the DNA level. A more careful analysis showed that these cell lines express very low level of BRAF RNA and the expression may be in favor of the WT allele.

Given the low BRAF V600E RNA expression, we tested in this study whether the three discordant cell lines may respond differently to BRAF-specific inhibitors compared to the concordant BRAF WT and BRAF V600E control cell lines.

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Clinical, immunological, and genetic features in patients with Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) and IPEX-like Syndrome

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Running Head: Characteristic of patients with IPEX and IPEX-like Syndromes

Conflicts of Interest: The authors declare that they have no conflict of interest.

Abstract

Background: Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) syndrome is a rare inborn error of immunity caused by mutations in the forkhead box P3 (*FOXP3*) gene.

Objective: In this study, we conducted a systematic review of IPEX and IPEX-like patients to delineate differences in these two major groups.

Methods: The literature search was performed in PubMed, Web of Science and Scopus databases and demographic, clinical, immunologic, and molecular data were compared between IPEX (n= 312) and IPEX-like (n= 98) groups.

Results: A total of 459 patients were reported in 148 eligible articles. Major clinical differences between IPEX and IPEX-like patients were observed in rates of pneumonia (11% vs. 31%, $p<0.001$), bronchiectasis (0.3% vs. 14%, $p<0.001$), diarrhea (56% vs. 42%, $p=0.020$), and organomegaly (10% vs. 23%, $p=0.001$), respectively. Eosinophilia (95% vs. 100%), low regulatory T cell count (68% vs. 50%), and elevated IgE (87% vs. 61%) were the most prominent laboratory findings in IPEX and IPEX-like patients, respectively. In IPEX group, a lower mortality rate was observed among patients receiving HSCT (24%) compared to other patients (43%), $p=0.008$, however, in IPEX-like group it was not significant ($p=0.189$).

Conclusions: Patients with IPEX syndrome generally suffer from enteropathy, autoimmunity, dermatitis, eosinophilia, and elevated serum IgE. Despite similarities in their clinical presentations, patients with IPEX-like syndrome are more likely to present CVID-like phenotype such as respiratory tract infections, bronchiectasis, and organomegaly. HSCT is currently the only curative therapy for both IPEX and IPEX-like syndrome and may result in favorable outcome.

Keywords: Immunodysregulation, Polyendocrinopathy, and Enteropathy, X-Linked, IPEX, IPEX-like, Autoimmunity, FOXP3

frontiers in Immunology

SYSTEMATIC REVIEW
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Clinical, Immunological, and Genetic Features in 49 Patients With ZAP-70 Deficiency: A Systematic Review

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Background: Zeta-Chain Associated Protein Kinase 70 kDa (ZAP-70) deficiency is a rare combined immunodeficiency (CID) caused by recessive homozygous/compound heterozygous loss-of-function mutations in the *ZAP70* gene. Patients with ZAP-70 deficiency present with a variety of clinical manifestations, particularly recurrent respiratory infections and cutaneous involvements. Therefore, a systematic review of ZAP-70 deficiency is helpful to achieve a comprehensive view of this disease.

Methods: We searched PubMed, Web of Science, and Scopus databases for all reported ZAP-70 deficient patients and screened against the described eligibility criteria. A total of 49 ZAP-70 deficient patients were identified from 33 articles. For all patients, demographic, clinical, immunologic, and molecular data were collected.

Results: ZAP-70 deficient patients have been reported in the literature with a broad spectrum of clinical manifestations including recurrent respiratory infections (81.8%), cutaneous involvement (57.9%), lymphoproliferation (32.4%), autoimmunity (19.4%), enteropathy (18.4%), and increased risk of malignancies (8.1%). The predominant immunologic phenotype was low CD8+ T cell counts (97.9%). Immunologic profiling showed defective antibody production (57%) and decreased lymphocyte responses to mitogenic stimuli such as phytohemagglutinin (PHA) (95%). Mutations of the *ZAP70* gene were located throughout the gene, and there was no mutational hotspot. However, most of the mutations were located in the kinase domain. Hematopoietic stem cell transplantation (HSCT) was applied as the major curative treatment in 25 (51%) of the patients, 18 patients survived transplantation, while two patients died and three required a second transplant in order to achieve full remission.

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Identifying Novel Mutations in Iranian Patients with LPS-responsive Beige-like Anchor Protein (LRBA) Deficiency

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ABSTRACT

LPS-responsive beige-like anchor protein (LRBA) deficiency is a monogenic primary immunodeficiency characterized by a heterogeneous spectrum of clinical manifestations associated with immune dysregulation. In this study, we reported clinical, immunologic, and genetic evaluation of two Iranian patients from unrelated families, both suffering from recurrent respiratory tract infections, failure to thrive, interstitial lung disease, autoimmune cytopenia, and hypogammaglobulinemia. Pulmonary abscess in one patient and persistent enteropathy in another were also observed. Further investigations revealed causative mutations in the exon (c.2166_2766del) and intron (c.4730–3 T > G) of the *LRBA* gene. These results may provide further elucidation of the clinical phenotypes and responsible genetic factors of LRBA deficiency.

KEYWORDS

LPS-responsive beige-like anchor protein deficiency; LRBA; immune dysregulation; autoimmunity; enteropathy

Introduction

LPS-responsive and beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency caused by biallelic mutations in the *LRBA* gene leading to regulatory T cell defects and immune dysregulation (Azizi et al. 2018c). LRBA deficiency is characterized by a broad spectrum of clinical manifestations, predominantly including recurrent respiratory or gastrointestinal tract infections, autoimmunity, lymphoproliferative disorders, enteropathy, and allergic symptoms (Alkhairy et al. 2015; Gamez-Diaz et al. 2016).

The most frequent laboratory findings include hypogammaglobulinemia, normal T cell counts, diminished numbers of regulatory T cells (Tregs) and natural killer cells, and B-cell

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Supplemental data for this article can be accessed here.

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Article type : Original Article

Corneal nerve loss in children with Type 1 diabetes mellitus without retinopathy or microalbuminuria

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Abstract

Introduction/Aim

Corneal confocal microscopy is a rapid, non-invasive ophthalmic technique to identify sub-clinical neuropathy. The aim of this study was to quantify corneal nerve morphology in children with type 1 diabetes mellitus compared to age-matched healthy controls using corneal confocal microscopy.

Method

Twenty participants with type 1 diabetes mellitus (age 14±2 years, diabetes duration 4.08±2.91 years, glycated hemoglobin 9.3±2.1%) without retinopathy or microalbuminuria and 20 healthy controls were recruited from outpatient clinics. Corneal confocal microscopy was undertaken and corneal nerve fiber density (no./mm^2), corneal nerve branch density (no./mm^2), corneal nerve fiber length (mm/mm^2), corneal nerve fiber tortuosity and inferior whorl length (mm/mm^2) were quantified manually.

Results

Corneal nerve fiber density (22.73±8.84 vs. 32.92±8.59; *P*<0.001), corneal nerve branch density (26.19±14.64 vs. 47.34±20.01; *P*<0.001), corneal nerve fiber length (13.26±4.06 vs. 19.52±4.54; *P*<0.001) and inferior whorl length (15.50±5.48 vs. 23.42±3.94; *P*<0.0001) were significantly

lower, whilst corneal nerve fiber tortuosity (14.88±5.28 vs. 13.52±3.01; *P*=0.323) did not differ between children with type 1 diabetes mellitus and controls. Glycated hemoglobin correlated with corneal nerve fiber tortuosity (*P*<0.006) and aspartate aminotransferase correlated with corneal nerve fiber density (*P*=0.039), corneal nerve branch density (*P*=0.003), and corneal nerve fiber length (*P*=0.037).

Conclusion

Corneal confocal microscopy identifies significant sub-clinical corneal nerve loss, especially in the inferior whorl of children with type 1 diabetes mellitus without retinopathy or microalbuminuria.

Keywords: Type 1 diabetes mellitus, child, small fiber neuropathy

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PERSPECTIVE

Toward Nanotechnology-Enabled Approaches against the COVID-19 Pandemic

Carsten Weiss,*,# Marie Carriere,*,# Laura Fusco,# Ilaria Capua, Jose Angel Regla-Nava, Matteo Pasquali, James A. Scott, Flavia Vitale, Mehmet Altay Unal, Cecilia Mattevi, Davide Bedognetti, Arben Merkoçi, Ennio Tasciotti, Açelya Yilmazer, Yury Gogotsi, Francesco Stellacci, and Lucia Gemma Delogu*

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ABSTRACT: **The COVID-19 outbreak has fueled a global demand for effective diagnosis and treatment as well as mitigation of the spread of infection, all through large-scale approaches such as specific alternative antiviral methods and classical disinfection protocols. Based on an abundance of engineered materials identifiable by their useful physicochemical properties through versatile chemical functionalization, nanotechnology offers a number of approaches to cope with this emergency. Here, through a multidisciplinary Perspective encompassing diverse fields such as virology, biology, medicine, engineering, chemistry, materials science, and computational science, we outline how nanotechnology-based strategies can support the fight against COVID-19, as well as infectious diseases in general, including future pandemics. Considering what we know so far about the life cycle of the virus, we envision key steps where nanotechnology could counter the disease. First, nanoparticles (NPs) can offer alternative methods to classical disinfection protocols used in healthcare settings, thanks to their intrinsic antipathogenic properties and/or their ability to inactivate viruses, bacteria, fungi, or yeasts either photothermally or *via* photocatalysis-induced reactive oxygen species (ROS) generation. Nanotechnology tools to inactivate SARS-CoV-2 in patients could also be explored. In this case, nanomaterials could be used to deliver drugs to the pulmonary system to inhibit interaction between angiotensin-converting enzyme 2 (ACE2) receptors and viral S protein. Moreover, the concept of "nanoimmunity by design" can help us to design materials for immune modulation, either stimulating or suppressing the immune response, which would find applications in the context of vaccine development for SARS-CoV-2 or in counteracting the cytokine storm, respectively. In addition to disease prevention and therapeutic potential, nanotechnology has important roles in diagnostics, with potential to support the development of simple, fast, and cost-effective nanotechnology-based assays to monitor the presence of SARS-CoV-2 and related biomarkers. In summary, nanotechnology is critical in counteracting COVID-19 and will be vital when preparing for future pandemics.**

COVID-19: SETTING THE SCENE FOR NANOTECHNOLOGY

Through millions of years of evolution, viruses have gained a variety of molecular mechanisms for entry into cells; long-term survival within cells; and activation, inhibition, or modification of the host defense mechanisms at all levels.[1] Their ability to transfer genes with high efficiency inspired the development of noninfectious recombinant viral vectors for gene-therapy applications, beginning in 1990.[2−4] Efforts were then underway to improve the safety of viral vectors, including developing nonviral drug-delivery systems inspired by the natural capabilities of viruses. Researchers in the field of nanomedicine have designed a variety of nanosystems that can mimic the gene-transfer capacity and high infectivity of viral vectors. By learning the molecular mechanisms behind these vectors, nanomedicine and biomedical researchers have developed delivery systems used in different fields, including cancer therapy and regenerative medicine.[5,6] However, nanotechnology is not only inspired by virology to develop novel delivery tools but also at the forefront in combatting dangerous viruses.

Nanotechnology is not only inspired by virology to develop novel delivery tools but also at the forefront in combatting dangerous viruses.

Differential regulation of the immune system in a *brain-liver-fats* organ network during short term fasting

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ABSTRACT

Background: Different fasting regimens are known to promote health, mitigate chronic immunological disorders, and improve age-related pathophysiological parameters in animals and humans. Indeed, several clinical trials are currently ongoing using fasting as a potential therapy for a wide range of conditions. Fasting alters metabolism by acting as a reset for energy homeostasis, but the molecular mechanisms underlying the beneficial effects of short-term fasting (STF) are still not well understood, particularly at the systems or multi-organ level.

Methods: We performed RNA-sequencing in nine different organs from mice fed *ad libitum* (0 hours), or subjected to five different times of fasting (2-22 hours). We applied a combination of multivariate analysis, differential expression analysis, gene ontology and network analysis for an in-depth understanding of the multi-organ transcriptome. We utilized literature mining solutions, LitLab™ and Gene Retriever™, to identify the biological and biochemical terms significantly associated with our experimental gene set which provide additional support and meaning to the experimentally derived gene and protein data.

Results: We cataloged the transcriptional dynamics within and between organs during STF and discovered differential temporal effects of STF among organs. Using gene ontology enrichment analysis, we identified an organ network sharing 37 common biological pathways perturbed by STF. This network incorporates the brain, liver, interscapular brown adipose tissue, and posterior-subcutaneous white adipose tissue, hence we named it the *brain-liver-fats* organ network. Using Reactome pathways analysis, we identified the immune system, dominated by T cell regulation processes, as a central and prominent target of systemic modulations during STF in this organ network. The changes we identified in specific immune components point to the priming of adaptive immunity and parallel the fine-tuning of innate immune signaling.

Conclusions: Our study provides a comprehensive multi-organ transcriptomic profiling of mice subjected to multiple periods of STF and adds new insights into the molecular modulators involved in the systemic immuno-transcriptomic changes that occur during short-term energy loss.

Biological and clinical significance of T helper 17 cell deficiency: insight into monogenic defects.

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Review

Abstract

Summary

T helper 17 (Th17) are a $CD4^+$ T subpopulation cells which are involved in the host protection against microbes such as extracellular and intracellular bacteria, parasites, fungi, and viruses. Monogenic defects including those mutations in some genes such as the signal transducer and activator of transcription (STAT)1 and 3, dedicator of cytokinesis 8 (DOCK8), autoimmune regulator (AIRE), and interleukin 17 receptor A (IL-17RA) can lead to impairment in Th17 cell development and function along with the concomitant increased risk for chronic mucocutaneous candidiasis (CMC). The immunologic abnormalities in these patients include low frequency of Th17 cells; defective cutaneous or in vitro T cell response to Candida species, and/or autoantibodies against relevant cytokines. This review outlines the biological characteristics and functionality of Th17 cells, as well as the clinical features of individuals with genetic defects associated with Th17 deficiency.

More than smell – COVID-19 is associated with severe impairment of smell, taste, and chemesthesis

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Abstract

Recent anecdotal and scientific reports have provided evidence of a link between COVID-19 and chemosensory impairments such as anosmia. However, these reports have downplayed or failed to distinguish potential effects on taste, ignored chemesthesis, and generally lacked quantitative measurements. Here, we report the development, implementation and initial results of a multi-lingual, international questionnaire to assess self-reported quantity and quality of perception in three distinct chemosensory modalities (smell, taste, and chemesthesis) before and during COVID-19. In the first 11 days after questionnaire launch, 4039 participants (2913 women, 1118 men, 8 other, ages 19-79) reported a COVID-19 diagnosis either via laboratory tests or clinical assessment. Importantly, smell, taste and chemesthetic function were each significantly reduced compared to their status before the disease. Difference scores (maximum possible change ±100) revealed a mean reduction of smell (-79.7 ± 28.7, mean ± SD), taste (-69.0 ± 32.6), and chemesthetic (-37.3 ± 36.2) function during COVID-19. Qualitative changes in olfactory ability (parosmia and phantosmia) were relatively rare and correlated with smell loss. Importantly, perceived nasal obstruction did not account for smell loss. Furthermore, chemosensory impairments were similar between participants in the laboratory test and clinical assessment groups. These results show that COVID-19-associated chemosensory impairment is not limited to smell, but also affects taste and chemesthesis. The multimodal impact of COVID-19 and lack of perceived nasal obstruction suggest that SARS-CoV-2 infection may disrupt sensory-neural mechanisms.

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PELVIS

Diagnostic performance of multi-parametric MRI to differentiate benign sex cord stromal tumors from malignant (non-stromal and stromal) testicular neoplasms

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Abstract

Purpose Testicular stromal tumors are uncommon, although mostly benign. The purpose of this study is to assess the role of multi-parametric MRI in differentiating benign testicular stromal tumors from malignant testicular neoplasms (non-stromal and stromal).

Methods A single-center retrospective study comparing benign stromal tumors (STs) to malignant testicular neoplasms (MTNs) was conducted. MR imaging assessment included tumor size, T2- and T1-weighted signal intensity, T2- and T1-weighted texture pattern, diffusion restriction, presence of hemorrhage and/or necrosis, and measurement of apparent diffusion coefficient and dynamic contrast enhancement (DCE). Inter-observer agreement was assessed using Cohen's kappa and Bland–Altman and data were compared using independent *t*-tests or χ^2. Receiver operating characteristic curve analysis was used to test models incorporating various imaging features.

Results Radical orchiectomy and histopathology revealed 20 testicular neoplasms: seven STs (35%) and thirteen MTNs (65%). MTNs were significantly larger in size than STs (5.1 ± 2.36 cm vs. 1.27 ± 0.56 cm; p-value < 0.001). STs demonstrated more hypointense T2W signal (85.7% vs. 46.2%; p-value < 0.09), less T2W heterogeneous texture (14.3% vs. 61.5%; p-value < 0.04), and less diffusion restriction (16.7% vs. 83.3%; p-value < 0.01) in comparison to MTNs. STs demonstrated mainly homogenous post-contrast enhancement pattern (71.4% vs. 7.7%; p-value < 0.004), while MTNs showed primarily heterogeneous enhancement pattern (77% vs. 14.3%; p-value < 0.02). STs revealed greater corrected venous phase enhancement (STs: 0.59 ± 0.29; MTNs: 0.25 ± 0.25; p-value < 0.03). STs showed higher ADC values, though the difference was not statistically significant (p-value < 0.25). A model combining T2W, DWI, and DCE features showed the best overall diagnostic accuracy with area under ROC curve of 0.99 and confidence interval ranging from 0.94 to 1.

Conclusion Multi-parametric MRI can potentially differentiate benign stromal tumors from malignant testicular neoplasms, which can help to avoid radical orchiectomy. However, future studies using larger sample sizes are needed to validate our results.

Keywords Testicular neoplasms · Stromal tumor · Malignant testicular neoplasm · Magnetic resonance imaging · Orchiectomy

Introduction

Testicular cancer accounts for approximately 1% of all malignant tumors in males and is the most common tumor encountered in young men aged 15–35 years [1–4]. The most common type of testicular carcinomas are germ cell tumors (GCTs), representing 95% of primary neoplasms split evenly between classic seminomas and non-seminomatous germ cell tumors [5]. Sex cord stromal tumors (STs) represent the remaining 5% of primary testicular tumors [6] and originate from the testicular interstitium, which is derived from mesenchymal cells. These tumors are relatively rare but they are mostly (> 90%) benign.

Imaging is essential for the diagnosis of testicular neoplasms. However, differentiation between various testicular

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ORIGINAL ARTICLE

Three Copies of Four Interferon Receptor Genes Underlie a Mild Type I Interferonopathy in Down Syndrome

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Abstract

Down syndrome (DS) is characterized by the occurrence of three copies of human chromosome 21 (HSA21). HSA21 contains a cluster of four interferon receptor (IFN-R) genes: *IFNAR1*, *IFNAR2*, *IFNGR2*, and *IL10RB*. DS patients often develop mucocutaneous infections and autoimmune diseases, mimicking patients with heterozygous gain-of-function (GOF) *STAT1* mutations, which enhance cellular responses to three types of interferon (IFN). A gene dosage effect at these four loci may contribute to the infectious and autoimmune manifestations observed in individuals with DS. We report high levels of IFN-αR1, IFN-αR2, and IFN-γR2 expression on the surface of monocytes and EBV-transformed-B (EBV-B) cells from studying 45 DS patients. Total and phosphorylated STAT1 (STAT1 and pSTAT1) levels were constitutively high in unstimulated and IFN-α- and IFN-γ-stimulated monocytes from DS patients but lower than those in patients with GOF *STAT1* mutations. Following stimulation with IFN-α or -γ, but not with IL-6 or IL-21, pSTAT1 and IFN-γ activation factor (GAF) DNA-binding activities were significantly higher in the EBV-B cells of DS patients than in controls. These responses resemble the dysregulated responses observed in patients with *STAT1* GOF mutations. Concentrations of plasma type I IFNs were high in 12% of the DS patients tested (1.8% in the healthy controls). Levels of type I IFNs, IFN-Rs, and STAT1 were similar in DS patients with and without recurrent skin infections. We performed a genome-wide transcriptomic analysis based on principal component analysis and interferon modules on circulating monocytes. We found that DS monocytes had levels of both IFN-α- and IFN-γ-inducible ISGs intermediate to those of monocytes from healthy controls and from patients with GOF *STAT1* mutations. Unlike patients with GOF *STAT1* mutations, patients with DS had normal circulating Th17 counts and a high proportion of terminally differentiated $CD8^+$ T cells with low levels of STAT1 expression. We conclude a mild interferonopathy in Down syndrome leads to an incomplete penetrance at both cellular and clinical level, which is not correlate with recurrent skin bacterial or fungal infections. The constitutive upregulation of type I and type II IFN-R, at least in monocytes of DS patients, may contribute to the autoimmune diseases observed in these individuals.

Keywords Down syndrome · interferonopathy · interferon receptors · JAK-STAT

Introduction

Down syndrome (DS), or trisomy 21, was the first human disease attributed to a chromosomal abnormality and was even the first human genetic disease to be deciphered at the molecular level [1]. In the absence of medical intervention, it is the most common genetic cause of intellectual disability, with an incidence of about 1/700 newborns, and there were about 206,000 people with DS living in the USA in 2010 [2]. Infectious diseases have been reported to be one of the major

Stuart G Tangye, Stéphanie Boisson-Dupuis and Anne Puel contributed equally to this work.

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Editorial

HLA-G: A New Immune Checkpoint in Cancer?

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Abstract: Human leukocyte antigen G (HLA-G), known as a central protein in providing immune tolerance to the fetus in pregnant women, is also studied for a possible role in tumor development. Many studies have claimed HLA-G as a new immune checkpoint in cancer. Therefore, HLA-G and its receptors might be targets for immune checkpoint blockade in cancer immunotherapy. In order to substantiate that HLA-G is indeed an immune checkpoint in cancer, two important questions need to be answered: (1) To what extent is HLA-G expressed in the tumor by cancer cells? and (2) What is the function of HLA-G in cancer immune evasion? In this review, we discuss these questions. We agree that HLA-G is a potentially new immune checkpoint in cancer, but additional evidence is required to show the extent of intra-tumor and inter-tumor expression. These studies should focus on tumor expression patterns of the seven different HLA-G isoforms and of the receptors for HLA-G. Furthermore, specific roles for the different HLA-G isoforms should be established.

Keywords: HLA-G; immunotherapy; immune checkpoint; cancer

1. Introduction

Human leukocyte antigen G (HLA-G) is known as a central protein in providing immune tolerance to the fetus in pregnant women [1,2]. Because of its immune-inhibiting function, it is also studied for its role in tumor development, where it may function as an immune checkpoint. Several immune checkpoints have been identified, which, among others, include programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), of which their ligands (programmed death ligand-1 and -2 (PD-L1/PD-L2) and B7, respectively) can be expressed by tumor cells to escape recognition by the immune system [3]. Blocking the interaction between the molecules involved in immune checkpoint signaling using monoclonal antibodies has led to remarkable therapeutic success in cancer [4]. Many studies have claimed HLA-G as a new immune checkpoint in cancer [5]. Therefore, HLA-G and its receptors might be targets for immune checkpoint blockade in cancer immunotherapy. In order to substantiate that HLA-G is indeed an immune checkpoint in cancer, two important questions need to be answered: (1) To what extent is HLA-G expressed in the tumor by cancer cells? and (2) What is the function of HLA-G in cancer immune evasion? Here, we discuss evidence for possible answers to these two questions. Finally, we propose future directions for research on the role of HLA-G in cancer.

2. HLA-G

The HLA-G gene is located on chromosome 6 at region 6p21.3, within the class I gene cluster of the major histocompatibility complex (MHC). As a result of alternative RNA splicing, seven isoforms can be formed, comprising four membrane-bound isoforms (HLA-G1, G2, G3, and G4), and three secreted

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Review

Genetic and Neuroimaging Approaches to Understanding Post-Traumatic Stress Disorder

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Abstract: Post-traumatic stress disorder (PTSD) is a highly disabling condition, increasingly recognized as both a disorder of mental health and social burden, but also as an anxiety disorder characterized by fear, stress, and negative alterations in mood. PTSD is associated with structural, metabolic, and molecular changes in several brain regions and the neural circuitry. Brain areas implicated in the traumatic stress response include the amygdala, hippocampus, and prefrontal cortex, which play an essential role in memory function. Abnormalities in these brain areas are hypothesized to underlie symptoms of PTSD and other stress-related psychiatric disorders. Conventional methods of studying PTSD have proven to be insufficient for diagnosis, measurement of treatment efficacy, and monitoring disease progression, and currently, there is no diagnostic biomarker available for PTSD. A deep understanding of cutting-edge neuroimaging genetic approaches is necessary for the development of novel therapeutics and biomarkers to better diagnose and treat the disorder. A current goal is to understand the gene pathways that are associated with PTSD, and how those genes act on the fear/stress circuitry to mediate risk vs. resilience for PTSD. This review article explains the rationale and practical utility of neuroimaging genetics in PTSD and how the resulting information can aid the diagnosis and clinical management of patients with PTSD.

Keywords: PTSD; neuroimaging; PET; MRI; imaging genetics

1. Background

Post-traumatic stress disorder (PTSD) is a psychological illness that can arise after a person experiences one or more traumatic events such as military combat, physical trauma due to injury, or other accidents such as domestic violence, rape, childhood trauma, neglect, or abuse. The disorder is characterized by feelings of panic, anxiety, fearfulness, and negative alterations in mood. Symptoms include distress and panic attacks, and the involuntary re-experiencing of the trauma during flashbacks

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METHODOLOGY Open Access

A literature-based approach for curating gene signatures in multifaceted diseases

Mathieu Garand*, Manoj Kumar, Susie Shih Yin Huang and Souhaila Al Khodor*

Abstract

Background and aims: The task of identifying a representative and yet manageable target gene list for assessing the pathogenesis of complicated and multifaceted diseases is challenging. Using Inflammatory Bowel Disease (IBD) as an example, we conceived a bioinformatic approach to identify novel genes associated with the various disease subtypes, in combination with known clinical control genes.

Methods: From the available literature, we used Acumenta Literature Lab™ (LitLab), network analyses, and LitLab Gene Retriever to assemble a gene pool that has a high likelihood of representing immunity-related subtype-specific signatures of IBD.

Results: We generated six relevant gene lists and 21 intersections that contain genes with unique literature associations to Crohn's Disease (n = 60), Ulcerative Colitis (n = 17), and unclassified (n = 45) subtypes of IBD. From this gene pool, we then filtered and constructed, using network analysis, a final list of 142 genes that are the most representative of the disease and its subtypes.

Conclusions: In this paper, we present the bioinformatic construction of a gene panel that putatively contains subtype signatures of IBD, a multifactorial disease. These gene signatures will be tested as biomarkers to classify patients with IBD, which has been a clinically challenging task. Such approach to diagnose and monitor complicated disease pathogenesis is a stepping-stone towards personalized care.

Background

Inflammatory Bowel Disease (IBD) is an inflammatory disorder of the gastrointestinal tract (GIT), resulting from the complex interactions between host (genetic, immune responses) and environment (external factors, microbiota) [1]. IBD is characterized by repeated alternating cycles of clinical relapse and remission, and in the absence of adequate treatments, a chronic inflammation leading to irreversible intestinal damages [2]. IBD is classified into three major subtypes [3]: Ulcerative Colitis (UC), which primarily affects the colon, Crohn's Disease (CD), which affects various GIT sites [4], and a third subtype where histology assessments do not categorize to either UC or CD. The latter subtype is defined as "Inflammatory Bowel Disease, type unclassified" (IBDU) [5, 6].

A rapid increase in global incidences of UC and CD was observed after World War II, particularly in industrialized countries (www.crohnscolitisfoundation.org). Currently, IBD affects around 5 million people worldwide and is expected to increase steadily over the next decade [7]. Classifying IBD patients has been challenging due to disease heterogeneity and its various atypical phenotypes [8]. Although the mechanisms underlying IBD pathogenesis are not fully understood, an overactive mucosal immune response and a dysbiotic gut microbiome are commonly observed among IBD patients [9, 10]. Endoscopy and colonoscopy are the current methods used for differentiating CD and UC but they carry the risks of bowel perforation and infections. Non-invasive routine laboratory investigations, on the other hand, cannot

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REVIEW

Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications

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Abstract

Purpose Although genetic predisposition and exposure to dietary gluten are considered necessary triggers for the development of coeliac disease, alterations in the gut microbial composition may also contribute towards the pathogenesis of coeliac disease. This review aims to provide an overview of the available data on the potential mechanisms through which the gut microbiota plays a role in the causation of coeliac disease and to discuss the potential therapeutic strategies that could diminish the consequences of microbial dysbiosis.

Method A search of the literature was performed using the PubMed, Embase, and JSTOR databases; relevant articles were included.

Results Recent studies in patients with coeliac disease have reported an increase in the relative amounts of gram negative bacterial genera such as *Bacteroides*, *Prevotella*, and *Escherichia*, and reduced amounts of protective anti-inflammatory bacteria such as *Bifidobacteria* and *Lactobacilli*. Dysbiotic microbiota may lead to a dysregulated immune response that may contribute to the pathogenesis of coeliac disease. In infancy, antibiotic use and certain infant feeding practices may lead to alterations in the developing gut microbiota to influence the immune maturation process and predispose to coeliac disease.

Conclusion The induction of the intestinal immune system and gluten intolerance may be influenced by the relative abundance of certain microbiota. Factors such as infant feeding practices, diet, antibiotics, and infections, may be involved in the development of coeliac disease due to their influence on gut microbial composition. The efficacy of potential modulators of the gut microbiota such as probiotics, prebiotics, and fecal microbial transplant as adjunctive treatments to gluten-free diet in coeliac disease is unproven and requires further investigation.

Keywords Coeliac disease · Microbiota · Metagenomics · Dysbiosis

Introduction

Coeliac disease is an autoimmune disorder triggered by the ingestion of gluten in genetically susceptible people [1]. The disorder is characterized by a mucosal disease of the proximal small bowel as a result of a T-cell mediated destruction of mucosal epithelial cells. It is generally acknowledged that coeliac disease affects about 1% of the population with an increasing prevalence [2] that varies between countries [3]. Patients with coeliac disease develop a permanent loss of immune tolerance to gluten [4, 5], a protein found in cereals such as wheat, rye, and barley. Upon ingestion, gluten can cause a pathological injury characterized by progressive degrees of inflammation and loss of villi in the proximal small bowel leading to the development of gastrointestinal malabsorption along with extra-gastrointestinal manifestations [3].

Coeliac disease is a multifactorial disease, characterized by a complex interplay of genetic and environmental factors. While genetic factors (such as the presence of Human Leukocytic Antigen—mainly HLA-DQ2 or HLA DQ-8) and exposure to dietary gluten are considered to be necessary triggers, they are not sufficient for disease development [6]. Additional factors such as infant feeding practices, the amount of gluten ingested, the age at which gluten is

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Translational Psychiatry

REVIEW ARTICLE Open Access

Genetics of structural and functional brain changes in autism spectrum disorder

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Abstract

Autism spectrum disorder (ASD) is a neurological and developmental disorder characterized by social impairment and restricted interactive and communicative behaviors. It may occur as an isolated disorder or in the context of other neurological, psychiatric, developmental, and genetic disorders. Due to rapid developments in genomics and imaging technologies, imaging genetics studies of ASD have evolved in the last few years. Increased risk for ASD diagnosis is found to be related to many specific single-nucleotide polymorphisms, and the study of genetic mechanisms and noninvasive imaging has opened various approaches that can help diagnose ASD at the nascent level. Identifying risk genes related to structural and functional changes in the brain of ASD patients provide a better understanding of the disease's neuropsychiatry and can help identify targets for therapeutic intervention that could be useful for the clinical management of ASD patients.

Introduction

Autism spectrum disorder (ASD) is a neurological and developmental disorder consisting of a wide range of symptoms and disability that develop in early childhood and persists throughout life. The common symptoms of ASD include limited activities, lower engagement and communication, talking and learning problems, and repetitive behavior. According to the World Health Organization, the global burden of ASD is continuously growing, with a current prevalence rate of 1 in 160 children. Reported prevalence rates vary widely from country to country though. Recent data from the Centers for Disease Control and Prevention showed that about 1 in 68 children in the United States had been identified with some form of ASD, with more than 3 million people affected[1]. A recent study estimated prevalence of ASD in the United States in 2014–2016 was 2.47% among adolescents and children[2]. While in the United Kingdom, the annual prevalence rate for children aged 8 years between 2004 and 2010 was 3.8/1000 for boys and 0.8/1000 for girls[3]. Recent studies have shown that the pooled ASD prevalence estimate in Asia is 0.36%, including data from nine countries (China, Korea, India, Bangladesh, Lebanon, Iran, Israel, Nepal and Sri Lanka)[4]. The prevalence of ASD in the Middle East region was documented to be 1.4 per 10,000 children in Oman[5], 4.3 per 10,000 children in Bahrain[6], 1/167 in Saudi Arabia[7], and a recent study reported ASD prevalence to be 1.14 % in children aged 6–11 years in Qatar[8].

ASD incidence is 4–5 times greater in males than in females[9]. The exact cause of ASD remains unclear; however, it is thought that both genetic and environmental factors play essential roles. The effect of ASD on society is enormous and multifaceted as it affects not only the child but also the siblings and parents and significantly disturbs the functioning of family routine life. Individuals with ASD are very likely to encounter the criminal justice system, mostly due to a lack of knowledge of their social and communication difficulties. There are also financial pressures associated with the recovery and decreased opportunities for jobs. Various studies have focused on

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ARTICLE

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Blood genome expression profiles in infants with congenital cytomegalovirus infection

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Congenital CMV infection (cCMVi) affects 0.5–1% of all live births worldwide, making it the leading cause of sensorineural hearing loss (SNHL) in childhood. The majority of infants with cCMVi have normal hearing at birth, but are at risk of developing late-onset SNHL. Currently, we lack reliable biomarkers to predict the development of SNHL in these infants. Here, we evaluate blood transcriptional profiles in 80 infants with cCMVi (49 symptomatic, 31 asymptomatic), enrolled in the first 3 weeks of life, and followed for 3 years to assess emergence of late-onset SNHL. The biosignatures of symptomatic and asymptomatic cCMVi are indistinguishable, suggesting that immune responses of infants with asymptomatic and symptomatic cCMVi are not different. Random forest analyses of initial samples in infants with cCMVi, irrespective of their clinical classification, identify a 16-gene classifier signature associated with the development of SNHL with 92% accuracy, suggesting its potential value as a biomarker.

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Review

Cytokine-Mediated Dysregulation of Signaling Pathways in the Pathogenesis of Multiple Myeloma

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Abstract: Multiple myeloma (MM) is a hematologic disorder of B lymphocytes characterized by the accumulation of malignant plasma cells (PCs) in the bone marrow. The altered plasma cells overproduce abnormal monoclonal immunoglobulins and also stimulate osteoclasts. The host's immune system and microenvironment are of paramount importance in the growth of PCs and, thus, in the pathogenesis of the disease. The interaction of MM cells with the bone marrow (BM) microenvironment through soluble factors and cell adhesion molecules causes pathogenesis of the disease through activation of multiple signaling pathways, including NF-κβ, PI3K/AKT and JAK/STAT. These activated pathways play a critical role in the inhibition of apoptosis, sustained proliferation, survival and migration of MM cells. Besides, these pathways also participate in developing resistance against the chemotherapeutic drugs in MM. The imbalance between inflammatory and anti-inflammatory cytokines in MM leads to an increased level of pro-inflammatory cytokines, which in turn play a significant role in dysregulation of signaling pathways and proliferation of MM cells; however, the association appears to be inadequate and needs more research. In this review, we are highlighting the recent findings on the roles of various cytokines and growth factors in the pathogenesis of MM and the potential therapeutic utility of aberrantly activated signaling pathways to manage the MM disease.

Keywords: multiple myeloma; hematological malignancies; signal transduction; proliferation; cytokines

1. Introduction

Multiple myeloma (MM) is an ailment of the plasma cells (PCs) characterized by the uncontrolled proliferation of long-lived monoclonal PCs. These PCs accumulate in the bone marrow, which causes impairment of bone strength and weakness of the immune system [1]. MM is the second most prevailing hematological malignancy after non-Hodgkin lymphoma, responsible for approximately 20% of deaths caused by hematological malignancies [2]. The disease is less common in women than men, and despite substantial improvement over the past decade in cancer therapeutics, myeloma cases

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IMMUNOLOGY REVIEW ARTICLE

Annexin A3 in sepsis: novel perspectives from an exploration of public transcriptome data

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Summary

According to publicly available transcriptome datasets, the abundance of Annexin A3 (ANXA3) is robustly increased during the course of sepsis; however, no studies have examined the biological significance or clinical relevance of ANXA3 in this pathology. Here we explored this interpretation gap and identified possible directions for future research. Based on reference transcriptome datasets, we found that ANXA3 expression is restricted to neutrophils, is upregulated *in vitro* after exposure to plasma obtained from septic patients, and is associated with adverse clinical outcomes. Secondly, an increase in ANXA3 transcript abundance was also observed *in vivo*, in the blood of septic patients in multiple independent studies. ANXA3 is known to mediate calcium-dependent granules–phagosome fusion in support of microbicidal activity in neutrophils. More recent work has also shown that ANXA3 enhances proliferation and survival of tumour cells via a Caspase-3-dependent mechanism. And this same molecule is also known to play a critical role in regulation of apoptotic events in neutrophils. Thus, we posit that during sepsis ANXA3 might either play a beneficial role, by facilitating microbial clearance and resolution of the infection; or a detrimental role, by prolonging neutrophil survival, which is known to contribute to sepsis-mediated organ damage.

Keywords: annexin; bacteremia; cell proliferation; endotoxemia; immunity; inflammation; neutrophil; sepsis; transcriptome.

Introduction

This review article intends to explore a possible role for Annexin A3 (ANXA3) in the immunopathology of sepsis. Before attempting to do so by bringing forward original experimental evidence, the wealth of publicly available transcriptomic data can be leveraged to: (i) determine if changes in abundance of ANXA3 measured in earlier transcriptome profiling studies are robust; (ii) draw inferences regarding the potential biological significance or clinical relevance of such changes; and (iii) identify paths for future investigations.

A hands-on workshop held at Sidra Medicine (Qatar) focused on the discovery of novel candidate genes implicated in the pathogenesis of sepsis. Public omics data were used as a source of training material for target selection and gene-centric reductionist investigations *in silico*. The approach was described in a recent review ('collective omics data' training module 1 or COD1).[1]

Annexin A3 (ANXA3) was selected among a pool of candidates on the basis of: (i) its expression being increased *in vitro* in neutrophils exposed to plasma from a septic patient for 6 hr (GEO dataset GSE49755);[2] and (ii) the apparent lack of literature addressing the role of ANXA3 in sepsis (the selection process is described in more details in Ref. [1]).

Annexins are calcium-binding proteins: they bind negatively charged phospholipid membranes in a calcium-dependent manner. These proteins are characterized by a conserved 'core domain' consisting of Ca^{2+}-binding

Abbreviations: ANXA3, Annexin A3; COD, collective omics data; GEO, Gene Expression Omnibus; PBMCs, peripheral mononuclear cells

Child's Nervous System
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ORIGINAL ARTICLE

Presenting symptoms and time to diagnosis for Pediatric Central Nervous System Tumors in Qatar: a report from Pediatric Neuro-Oncology Service in Qatar

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Abstract

Introduction There are no previous published reports on primary pediatric tumors of the central nervous system (CNS) in Qatar. We undertook this retrospective cohort study to review the diagnosis of CNS tumors in children in Qatar to analyze the presentation characteristics including symptoms, referral pathways, and time to diagnosis.

Methods All children registered with Pediatric Neuro-Oncology service (PNOS) were included in the study. Data from the time of diagnosis (October 2007 to February 2020) were reviewed retrospectively. Presenting symptoms were recorded and pre-diagnosis symptom interval (PSI) was calculated from the onset of the first symptom to the date of diagnostic imaging.

Results Of the 61 children registered with PNOS during the study period, 51 were included in the final analysis. Ten children were excluded because they were either diagnosed outside Qatar ($n = 7$) or were asymptomatic at the time of diagnosis ($n = 3$). The median age was 45 (range 1–171) months. Common tumor types included low-grade glioma (LGG) (47.1%) and medulloblastoma/primitive neuro-ectodermal tumors (PNET) (23.5%). Nine children had an underlying neurocutaneous syndrome. Thirty-eight patients (74.5%) had at least one previous contact with healthcare (HC) professional, but 27 (52%) were still diagnosed through the emergency department (ED). Presenting symptoms included headache, vomiting (36.2%), oculo-visual symptoms (20.6%), motor weakness (18.9%), seizures, ataxia (17.2% each), irritability, cranial nerve palsies (12% each), and endocrine symptoms (10.3%). Median PSI was 28 days (range 1–845 days) for all CNS tumors. Longest PSI was seen with germ cell tumors (median 146 days), supratentorial location (39 days), and age above 3 years (30 days). Tumor characteristics of biological behavior (high-grade tumor) and location (infratentorial) were significantly associated with shorter PSI, as were presenting symptoms of ataxia, head tilt, and altered consciousness.

Conclusions Although overall diagnostic times were acceptable, some tumor types were diagnosed after a significant delay. The awareness campaign, such as the "HeadSmart" campaign in the United Kingdom (UK), can improve diagnostic times in Qatar. Further research is required to better understand the reasons for the delay.

Keywords Child · Brain · Delay in diagnosis

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Introduction

Primary CNS tumors are the largest group of solid tumors occurring in children [1–3]. They are also associated with the highest rate of cancer-related deaths in children [2, 4, 5]. The overall incidence of cancer and brain tumors in 0–14-year-old children follows the same pattern in Qatar, as elsewhere [6, 7]. Establishing the diagnosis of a CNS tumor is the crucial first step before treatment can be initiated. A delay in making a diagnosis can result in tumor progression, development of hydrocephalus, and even tentorial herniation in rare instances. If the diagnosis is delayed to the point that emergency neurosurgical intervention is required, it can lead to

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Cell type specific novel lncRNAs and circRNAs in the BLUEPRINT haematopoietic transcriptomes atlas

by Luigi Grassi, Osagie G. Izuogu, Natasha A.N. Jorge, Denis Seyres, Mariona Bustamante, Frances Burden, Samantha Farrow, Neda Farahi, Fergal J. Martin, Adam Frankish, Jonathan M. Mudge, Myrto Kostadima, Romina Petersen, John J. Lambourne, Sophia Rowlston, Enca Martin-Rendon, Laura Clarke, Kate Downes, Xavier Estivill, Paul Flicek, Joost H.A. Martens, Marie-Laure Yaspo, Hendrik G. Stunnenberg, Willem H. Ouwehand, Fabio Passetti, Ernest Turro, and Mattia Frontini

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Cell type specific novel lncRNAs and circRNAs in the BLUEPRINT haematopoietic transcriptomes atlas.

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Abstract

Transcriptional profiling of hematopoietic cell subpopulations has helped characterize the developmental stages of the hematopoietic system and the molecular bases of malignant and non-malignant blood diseases for the past three decades. Previously, only the genes targeted by expression microarrays could be profiled genome wide. High-throughput RNA sequencing (RNA-seq), however,

encompasses a broader repertoire of RNA molecules, without restriction to previously annotated genes. We analysed the BLUEPRINT consortium RNA- seq data for mature hematopoietic cell types. The data comprised 90 total RNA-seq samples, each composed of one of 27 cell types, and 32 small RNA-seq samples, each composed of one of 11 cell types. We estimated gene and isoform expression levels for each cell type using existing annotations from Ensembl. We then used guided transcriptome assembly to discover unannotated transcripts. We identified hundreds of novel non-coding RNA genes and showed that the majority have cell type dependent expression. We also characterized the expression of circular RNAs and found that these are also cell type specific. These analyses refine the active transcriptional landscape of mature hematopoietic cells, highlight abundant genes and transcriptional isoforms for each blood cell type, and provide a valuable resource for researchers of hematological development and diseases. Finally, we made the data accessible via a web-based interface: https://blueprint.haem.cam.ac.uk/bloodatlas/.

Introduction

Knowledge of the transcriptional programs underpinning the diverse functions of hematopoietic cells is essential for understanding how and when these functions are performed and for resolving the molecular bases of hematological diseases. Thanks to its accessibility, blood is the tissue of choice for the implementation of novel assays in primary samples. Indeed, several studies aiming to characterize gene expression profiles have been performed on increasingly purified primary hematopoietic cell populations in the post genome era[1-3]. These studies used expression arrays and thus required prior specification of the sequences to be interrogated. The probed sequences were often derived from the analysis of a very limited number of tissues and cell types[4], despite the early discovery that transcription is widespread throughout the human genome[5]. The introduction of high-throughput nucleic acid sequencing technologies[6] has improved the assembly of the human genome and the annotation of transcriptomes therein, and it has enabled a more comprehensive analysis of gene expression using transcriptomic assembly approaches[7]. The BLUEPRINT consortium[8] was established to characterize the epigenetic state and transcriptional profile of different types of hematopoietic cell. Reference datasets for DNA methylation, histone modifications and gene expression were generated using state-of-the-art technologies from highly purified cell populations, in accordance with quality standards set by the International Human Epigenome Consortium[9]. RNA-seq data from over 270 samples encompassing 55 cell types have been made publicly available (http://dcc.blueprint-epigenome.eu), a subset of which has been described previously[10, 11]. Here, we present the analysis of 90 total RNA samples obtained from cord and adult peripheral blood, each consisting of one of 27 mature cell types and 32 small RNA samples, each consisting of one of 11 mature cell types. We used a Bayesian differential expression analysis approach[12, 13] to determine changes in the expression levels of genes and transcripts at lineage commitment stages and to identify cell type specific transcriptional

Title: Sterol synthesis pathway inhibition as a target for cancer treatment

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Abstract:

Sterol synthesis is a highly complex and integrated pathway in mammals. In the present review, we briefly summarize the main steps of this pathway, especially concerning its main rate-limiting enzymes, HMG-CoA reductase (HMGCR) and squalene epoxidase (SQLE), in relation with cancer. We focus on studies reporting key findings linking cholesterol with cancer. The inhibition of HMGCR and SQLE to prevent and inhibit cancer are reviewed. Finally, a pan-cancer review of publicly available data on genomic aberrations in the main enzymes involved in sterol biosynthesis and their transcription factors is reported, providing hitherto unexplored findings that may be the subject of future research in cancer metabolomics and tumor targeted treatment.

Keywords: cholesterol, HMG-CoA reductase, genomic aberrations, squalene epoxidase

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ARTICLE

Willingness to participate in genome testing: a survey of public attitudes from Qatar

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Abstract

Genomics has the potential to revolutionize medical approaches to disease prevention, diagnosis, and treatment, but it does not come without challenges. The success of a national population-based genome program, like the Qatar Genome Program (QGP), depends on the willingness of citizens to donate samples and take up genomic testing services. This study explores public attitudes of the Qatari population toward genetic testing and toward participating in the QGP. A representative sample of 837 adult Qataris was surveyed in May 2016. Approximately 71% of respondents surveyed reported that they were willing to participate in the activities of the QGP. Willingness to participate was significantly associated with basic literacy in genetics, a family history of genetic diseases, and previous experience with genetic testing through premarital screening. Respondents cited the desire to know more about their health status as the principle motivation for participating, while lack of time and information were reported as the most important barriers. With QGP plans to ramp up the scale of its national operation toward more integration into clinical care settings, it is critical to understand public attitudes and their determinants. The results demonstrate public support but also identify the need for more education and individual counseling that not only provide information on the process, challenges, and benefits of genomic testing, but that also address concerns about information security.

Introduction

Precision health is a new paradigm that is increasing the use of genomic technologies for the assessment of susceptibility to major diseases as well as individual responses to therapeutic regimes [1, 2], thus, increasing the effectiveness of medical intervention. Increasingly, evidence is pointing to the influence of precision health on improved treatment and health outcomes for patients with breast [3], lung [4], and colorectal [5] cancers. Realizing this potential, and aided by the rapid evolution of sequencing technology, several countries have embarked on national projects to characterize the genomes of their own populations in preparation for large-scale implementation in clinical settings [1]. The State of Qatar in the Arabian Gulf is one of those countries. In late 2015, Qatar launched the pilot phase of the Qatar Genome Program (QGP), which is a population-based genome program aiming to sequence the whole genomes for a significant proportion of the Qatari population. The program has a comprehensive plan to facilitate the implementation of precision medicine involving drafting genomic

These authors contributed equally: Hanan F. Abdul Rahim and Said I. Ismail

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Article

PGAP3 Associated with Hyperphosphatasia with Mental Retardation Plays a Novel Role in Brain Morphogenesis and Neuronal Wiring at Early Development

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Abstract: Recessive mutations in Post-GPI attachment to proteins 3 (*PGAP3*) cause the rare neurological disorder hyperphosphatasia with mental retardation syndrome 4 type (HPMRS4). Here, we report a novel homozygous nonsense mutation in *PGAP3* (c.265C>T-p.Gln89*), in a 3-year-old boy with unique novel clinical features. These include decreased intrauterine fetal movements, dysgenesis of the corpus callosum, olfactory bulb agenesis, dysmorphic features, cleft palate, left ear constriction, global developmental delay, and hypotonia. The zebrafish functional modeling of PGAP3 loss resulted in HPMRS4-like features, including structural brain abnormalities, dysmorphic cranial and facial features, hypotonia, and seizure-like behavior. Remarkably, morphants displayed defective neural tube formation during the early stages of nervous system development, affecting brain morphogenesis. The significant aberrant midbrain and hindbrain formation demonstrated by separation of the left and right tectal ventricles, defects in the cerebellar corpus, and caudal hindbrain formation disrupted oligodendrocytes expression leading to shorter motor neurons axons. Assessment of zebrafish neuromuscular responses revealed epileptic-like movements at early development, followed by seizure-like behavior, loss of touch response, and hypotonia, mimicking the clinical phenotype human patients. Altogether, we report a novel pathogenic *PGAP3* variant associated with unique phenotypic hallmarks, which may be related to the gene's novel role in brain morphogenesis and neuronal wiring.

Keywords: hyperphosphatasia mental retardation syndrome 4 (HPMRS4); post-GPI attachment to proteins 3 (*PGAP3*); neurological disorder; human disease model; zebrafish; neural tube defect; whole genome sequencing

1. Introduction

Post-GPI attachment to the proteins 3 (*PGAP3*) gene, encoding a Glycosylphosphatidylinositol (GPI)-specific phospholipase, plays a critical role in the biosynthesis of GPI-anchored proteins (GPI-APs). It is

frontiers

Bioinspired scaffold action under the extreme physiological conditions of simulated space flights: osteogenesis enhancing under microgravity

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Keywords: stem cells; nanomaterials; scaffolds; microgravity; random positioning machine; bone; tissue regeneration; space biology.

Abstract

Prolonged exposure to microgravity (MG) during long-duration space flights is known to induce severe dysregulation of osteoblast functions connected to a significant bone loss, similar to the condition induced by osteoporosis. Hence, we here present MG as a promising model to challenge the effectiveness of new scaffolds designed for bone regeneration in counteracting bone loss.

To this end, we carried out an integrative study aimed to evaluate, in the extreme condition of Random Positioning Machine-simulated MG, the osteoinductive potential of nanocrystalline magnesium-doped hydroxyapatite/type I collagen composite scaffold (MHA/Coll), that we previously demonstrated to be an excellent tool for bone tissue engineering.

Initially, to test the osteo-inductivity properties of our bioinspired-scaffold, MHA/Coll structure was fully characterized under MG condition and compared to its static counterpart. Human bone marrow-derived mesenchymal stem cells were used to investigate the scaffold biocompatibility and ability to promote osteogenic differentiation after long-duration exposure to MG (up to 21 days). The results demonstrate that the nanostructure of MHA/Coll scaffold can alleviate MG-induced osteoblast dysfunction, promoting cell differentiation along the osteogenic lineage, with a consequent reduction in the expression of the surface markers CD29, CD44, and CD90. Moreover, these findings were corroborated by the ability of MHA/Coll to induce the expression of genes linked to osteogenesis, including alkaline phosphatase and osteocalcin. This study confirmed MHA/Coll capabilities in promoting osteogenesis even in extreme long-term condition of MG, suggesting MG as an effective challenging model to apply in future studies to validate the ability of advanced scaffolds to counteract bone loss, facilitating their application in translational Regenerative Medicine and Tissue Engineering.

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A modular framework for the development of targeted Covid-19 blood transcript profiling panels

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Abstract

Background: Covid-19 morbidity and mortality are associated with a dysregulated immune response. Tools are needed to enhance existing immune profiling capabilities in affected patients. Here we aimed to develop an approach to support the design of targeted blood transcriptome panels for profiling the immune response to SARS-CoV-2 infection.

Methods: We designed a pool of candidates based on a pre-existing and well-characterized repertoire of blood transcriptional modules. Available Covid-19 blood transcriptome data was also used to guide this process. Further selection steps relied on expert curation. Additionally, we developed several custom web applications to support the evaluation of candidates.

Results: As a proof of principle, we designed three targeted blood transcript panels, each with a different translational connotation: immunological relevance, therapeutic development relevance and SARS biology relevance.

Conclusion: Altogether the work presented here may contribute to the future expansion of immune profiling capabilities via targeted profiling of blood transcript abundance in Covid-19 patients.

Keywords: Blood transcriptomics, SARS-CoV-2, Covid-19, Immune monitoring

Background

Covid-19 is an infectious, respiratory disease caused by a newly discovered coronavirus: SARS-CoV-2. The course of infection vary widely, with most patients presenting mild symptoms. However, about 20% of patients develop severe disease and require hospitalization [1, 2]. The interaction between innate and adaptive immunity can lead to the development of neutralizing antibodies against SARS-CoV-2 antigens that might be associated with viral clearance and protection [3]. But immune factors are also believed to play an important role in the rapid clinical deterioration observed in some Covid-19 patients [4]. There is thus a need to develop new modalities that can improve the delineation of "immune trajectories" during SARS-CoV-2 infection.

Blood transcriptome profiling involves measuring the abundance of circulating leukocyte RNA on a genome-wide scale via RNA sequencing [5]. Processing of the samples and the raw sequencing data however, is time consuming and requires access to sophisticated

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Original article

Paradoxical association between blood modular interferon signatures and quality of life in patients with systemic lupus erythematosus

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Abstract

Objectives. Blood transcriptomic IFN signature is a hallmark of SLE. The impaired health-related quality of life (HRQOL) observed in SLE is poorly related to disease activity. The aim of this study was to test how IFN signatures were associated with HRQOL in SLE patients.

Methods. Among consecutive patients, blood transcriptomic profiles were analysed with a modular framework comprising 3 IFN modules: M1.2, M3.4 and M5.12. Disease activity was evaluated by the SLEDAI score, and HRQOL was assessed with the SF-36 questionnaire, which includes eight domains: physical function, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health (MH) and physical component summary and mental component summary scores.

Results. A total of 57 SLE patients were evaluated, among whom 27 (47%) were clinically quiescent, 30 (53%) were flaring, and 19 (33%) had active lupus nephritis. All SF-36 domains were altered in SLE patients compared with the general French population ($P < 0.0001$). In multivariate analysis, taking into account flares, age, ethnicity, smoking and renal severity, social functioning was independently associated with the IFN score ($P = 0.027$). Analyses restrained to quiescent patients ($n = 27$) yielded greater associations between social functioning and the three IFN modules, and between MH and M3.4. Considering all quiescent visits ($n = 51$), the IFN score was independently correlated with social functioning ($P = 0.022$) and MH ($P = 0.038$).

Conclusion. This unexpected paradoxical association between IFN signature and some specific HRQOL domains argues against a pivotal role of IFNs in the persistently altered HRQOL of SLE patients.

Key words: systemic lupus erythematosus, transcriptomic analysis, interferon; quality of life, SF-36

Rheumatology key messages

- Blood modular IFN signature is not associated with worse quality of life in SLE.
- Blood modular IFN signature is independently associated with better scores in some SF-36 domains.
- Persistent activation of IFN pathways does not explain the altered QOL in quiescent SLE patients.

Introduction

SLE is a chronic systemic autoimmune disease characterized by alternate periods of flares and clinical quiescence [1]. With major improvement in survival, health-related quality of life (HRQOL) has emerged as an important consideration in the evaluation and management of SLE patients, both in clinical routine and in therapeutic trials [2]. Although numerous reports have shown that HRQOL is severely impaired in SLE patients,

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Original article

Characterization of peripheral blood mononuclear cells gene expression profiles of pediatric *Staphylococcus aureus* persistent and non-carriers using a targeted assay

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ABSTRACT

Defects in innate immunity affect many different physiologic systems and several studies of patients with primary immunodeficiency disorders demonstrated the importance of innate immune system components in disease prevention or colonization of bacterial pathogens. To assess the role of the innate immune system on nasal colonization with *Staphylococcus aureus*, innate immune responses in pediatric *S. aureus* nasal persistent carriers (n = 14) and non-carriers (n = 15) were profiled by analyzing co-clustered gene sets (modules). We stimulated previously frozen peripheral blood mononuclear cells (PBMCs) from these subjects with i) a panel of TLR ligands, ii) live *S. aureus* (either a mixture of strains or stimulation with respective carriage isolates), or iii) heat-killed *S. aureus*. We found no difference in responses between carriers and non-carriers when PBMCs were stimulated with a panel of TLR ligands. However, PBMC gene expression profiles differed between persistent and non-*S. aureus* carriers following stimulation with either live or dead *S. aureus*. These observations suggest that individuals susceptible to persistent carriage with *S. aureus* may possess differences in their live/dead bacteria recognition pathway and that innate pathway signaling is different between persistent and non-carriers of *S. aureus*.

The spectrum of diseases resulting from *Staphylococcus aureus* infections includes serious skin infections, endocarditis, arthritis, osteomyelitis, and sepsis as a consequence of its ability to colonize a variety of different tissues and its ability to circumvent various immune surveillance systems [1,2]. Approximately 20–50% of adults and children nasal *S. aureus* carriers (persistent or intermittent carriers vs. non-carriers) based on the presence or absence of *S. aureus* in nasal cultures collected over time [3,4]. Nasal sampling over a defined time period allows classification of *S. aureus* carrier phenotypes as either persistent carriers (those testing positive ≥75% of the time), intermittent carriers (individuals <75% of the time) and non-carriers (negative for *S. aureus* over the sampling period) [5]. Although a genome-wide association study conducted by our group suggests that each carriage phenotype is in part shaped by host genetic profiles [6], characterization of antibody responses and *S. aureus* re-colonization studies suggest that the intermittent and non-carrier phenotypes are more similar to each other compared to persistent carriers [7,8].

A combination of environmental, genetic, and immune factors play roles in defining the respective *S. aureus* carriage phenotypes

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ORIGINAL ARTICLE

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Genome sequencing unveils mutational landscape of the familial Mediterranean fever: Potential implications of IL33/ST2 signalling

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Abstract

Familial Mediterranean fever (FMF) is the most common auto-inflammatory disease. It is transmitted as autosomal recessive trait with mutations in MEditerranean FeVer (*MEFV*) gene. Despite a typical clinical expression, many patients have either a single or no mutation in *MEFV*. The current work is aimed to revisit the genetic landscape of FMF disease using high-coverage whole genome sequencing. In atypical patients (carrying a single or no mutation in *MEFV*), we revealed many rare variants in genes associated with auto-inflammatory disorders, and more interestingly, we discovered a novel variant (a 2.1-Kb deletion) in exon 11 of *IL1RL1* gene, present only in patients. To validate and screen this patient-specific variant, a tandem of allele-specific PCR and quantitative real-time PCR was performed in 184 FMF patients and 218 healthy controls and we demonstrated that the novel deletion was absent in controls and was present in more than 19% of patients. This study sheds more light on the mutational landscape of FMF. Our discovery of a disease-specific variant in *IL1RL1* gene may constitute a novel genetic marker for FMF. This finding suggesting a potential role of the IL33/ST2 signalling in the disease pathogenicity highlights a new paradigm in FMF pathophysiology.

KEYWORDS

Familial Mediterranean Fever, *IL1RL1*, *MEFV*, Whole Genome Sequencing

1 | INTRODUCTION

Auto-inflammatory diseases (AIDs) are a distinct group of disorders characterized by an unprovoked systemic inflammation without the presence of high titre of autoantibodies nor antigen-specific T cells.[1,2] Most of the AIDs are monogenic and are caused by highly penetrant mutations in single genes encoding proteins involved in the innate immunity, but complex and polygenic AIDs with significant environmental influence have also been identified.[3]

Meenakshi Umar, Andre Megarbane and Jingxuan Shan contributed equally to this manuscript.

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Epigenetic and breast cancer therapy: Promising diagnostic and therapeutic applications

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ABSTRACT

The global burden of breast cancer (BC) is increasing significantly. This trend is caused by several factors such as late diagnosis, limited treatment options for certain BC subtypes, drug resistance which all lead to poor clinical outcomes. Recent research has reported the role of epigenetic alterations in the mechanism of BC pathogenesis and its hallmarks include drug resistance and stemness features. The understanding of these modifications and their significance in the management of BC carcinogenesis is challenging and requires further attention. Nevertheless, it promises to provide novel insight needed for utilizing these alterations as potential diagnostic, prognostic markers, predict treatment efficacy, as well as therapeutic agents. This highlights the importance of continuing research development to further advance the existing knowledge on epigenetics and BC carcinogenesis to overcome the current challenges. Hence, this review aims to shed light and discuss the current state of epigenetics research in the diagnosis and management of BC.

1. Introduction

Cancer is a significant global health concern. In 2018, an estimate of 18.1 million new individuals were diagnosed with cancer alongside 9.6 million mortalities [1]. By 2040, these numbers are expected to double, particularly in low and middle-income countries. Consequently, the burden of cancer on healthcare systems is likely to immensely increase worldwide [2]. This highlights the need for more research to further advance an early and rapid detection and management of this disease which serve as a key role of improving survival rates and patient-centered cancer care [3].

Breast Cancer (BC) is one of the most common diagnosed female cancers and leading cause of cancer death among women, accounting for an estimate of 627,000 (6.6 %) deaths worldwide [4]. Since 2008, BC incidence and mortality rates have increased globally by more than 20 % and 14 % respectively. The global BC burden is estimated to have risen to 2.1 million new cases in 2018 compared to nearly 1.7 million in 2012 [1,5].

The high incidence and death rates in BC are linked to various factors, among which the most common being its heterogeneous nature. The inter/intra-tumoral heterogeneity, usually affecting one anatomic site of the breast with phenotypic and molecular diversity, plays a key role in its histology and staging [6]. The molecular stratification of BC is primarily based on gene expression profiling; this also includes the

Abbreviations: MeCP2, Methyl-CpG-binding protein 2; H3, Histone 3; H4, Histone 4; TNBC, Triple negative breast cancer; ERα, Estrogen receptor α; PTEN, Phosphatase and tensin homolog; ERβ, Estrogen receptor beta; CAF, Cancer-associated fibroblasts; MMPs, Matrix metallopeptidases; TGF-β, Transforming growth factor-β; KMT2D, Lysine methyltransferase 2D; HDAC, Histone deacetylases; KDM7A, Lysine demethylase 7A; BCSCs, Breast cancer stem cells; ctDNA, Cell-free tumor DNA; LN, Lymph node.

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nutrients

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Brief Report

The Role of Polymorphisms in Vitamin D-Related Genes in Response to Vitamin D Supplementation

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Abstract: Background. Vitamin D deficiency represents a major healthcare problem. Vitamin D status is influenced by genetic and environmental determinants. Several observational studies have evaluated the association of single-nucleotide polymorphisms (SNPs) in vitamin D-related genes and vitamin D levels. Nevertheless, little is known about the role of these SNPs in the response to vitamin D supplementation. We conducted an interventional study to define the association between SNPs in vitamin D-related genes and the response to vitamin D supplementation in 100 self-reported healthy women of Arab ancestry for the majority. Methods. A total of 100 healthy female subjects received a weekly oral dose of 50,000 IU vitamin D for 12 weeks. Serum vitamin D concentration and metabolic profiles were measured at baseline and 12 weeks post-vitamin D supplementation. The genotypes of 37 SNPs selected from previously reported vitamin D-related genes have been assessed by Fluidigm genotyping assay. Results. Rs731236 (VDR gene) and rs7116978 (CYP2R1 gene) showed a significant association with vitamin D status. The rs731236 GG genotype and the rs7116978 CC genotype were associated with a "vitamin D sufficiency" state. Rs731236 GG and rs7116978 CC genotypes showed a higher response to vitamin D supplementation. Transcription factor binding site prediction analysis showed altered binding sites for transcription factors according to the different rs7116978 alleles. Interestingly, the 37 SNPs previously established to play a role in vitamin D-related pathways explained very little of the response to vitamin D supplementation in our cohort, suggesting the existence of alternative loci whose number and effect size need to be investigated in future studies. Conclusion. In this paper, we present novel data on vitamin D-related SNPs and response to vitamin D supplementation demonstrating the feasibility of applying functional genomic approaches in interventional studies to assess individual-level responses to vitamin D supplementation.

Keywords: vitamin D; polymorphisms; single-nucleotide polymorphism; SNP; 25-hydroxyvitamin D; 25(OH)D; vitamin D deficiency; blood

1. Introduction

Vitamin D plays an important role in the endocrine system, and it takes part in several biological processes such as blood pressure regulation, calcium and phosphate homeostasis, nerve conduction, skeletal development, erythropoiesis, and so forth. [1–3]. The active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)2D], regulates the expression of vitamin D-related genes involved in calcium transport and bone matrix protein [4,5]. Nevertheless, vitamin D deficiency has been well documented worldwide [6]. Several factors have been shown to contribute to vitamin D

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RESEARCH ARTICLE

STXBP6, reciprocally regulated with autophagy, reduces triple negative breast cancer aggressiveness

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Abstract

Background: Although autophagy plays a dual role in suppressing or promoting certain cancers, the nature of its involvement in breast cancers remains unclear. Here, we investigated the function of STXBP6, a protein regulating the autophagy-associated SNARE complex, in triple negative breast cancer (TNBC).

Results: We report that STXBP6 is profoundly downregulated in TNBC specimens in association with reduced overall patient survival. Notably, we found that *STXBP6* promoter was specifically hyper-methylated in TNBC specimens. Ectopic expression of *STXBP6* inhibited TNBC cell proliferation in cellular and mouse models. Mass spectrometric analysis revealed physical interactions of STXBP6 with a number of autophagy-related proteins including SNX27, a molecule involved in endocytosis of plasma membrane receptors and protein trafficking. Overexpression of *STXBP6* elicited autophagy through inhibition of mTORC1 signaling. Reciprocally, induction of autophagy rescued *STXBP6* expression by inhibiting EZH2 and altering *STXBP6* methylation. The mutual regulation between STXBP6 and autophagy was replicated in luminal breast cancer cells only when estrogen receptor (ER) activation was abrogated. Ectopic expression of *STXBP6* significantly reduced TNBC cells' migratory ability in vitro and tumor metastasis in vivo.

Conclusions: Our results unveil a role of STXBP6 in TNBC that highlights a new paradigm in autophagy regulation. Our results significantly enhance the understanding of the mechanisms of TNBC aggressiveness, which might help in designing novel therapies targeting TNBC.

Chapter 11

Functional Genome Profiling to Understand Cancer Immune Responsiveness

Ena Wang, Davide Bedognetti, and Francesco M. Marincola

Abstract

It has been almost two decades since we first proposed the use of minimally invasive serial biopsies to dissect the biology underlining cancer immune responsiveness (CIR) by looking for predictors of response, understanding mechanisms of action (MOA) of therapeutics and documenting strategies adopted by tumor cells to escape immune recognition. This approach led to the first description in 2002 of predictors of CIR, the characterization of the pharmacodynamics of several immune therapeutics, and the geneses of immune escape under immunological pressure prompted by successful treatment. The presumption was straightforward; study CIR where it occurs: the target organ. Since then, a large number of studies corroborated these early observations adding sophistication and accuracy to the investigations. Here, we summarize the history of functional genomic profiling as a discovery and validation tool for immune oncology (IO) and new insights that could be derived by single novel technologies.

Key words Genomic profiling, Immune oncology (IO), Cancer immune responsiveness (CIR), Mechanisms of action (MOA)

Abbreviations

ACT	Adoptive cellular therapy
CCR	C-C motif chemokine receptor
CIR	Cancer immune responsiveness
DAMP	Damage associated molecular pattern
HMB1	High-mobility group box protein 1
ICD	Immunogenic cell death
ICR	Immunologic constant of rejection
ICT	Immune-checkpoint inhibitor therapy
IFN	Interferon
IO	Immune oncology
MHC	Major histocompatibility complex
MOA	Mechanism of action
TCGA	The Cancer Genome Atlas

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ORIGINAL INVESTIGATION

Genome-wide landscape establishes novel association signals for metabolic traits in the Arab population

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Abstract

While the Arabian population has a high prevalence of metabolic disorders, it has not been included in global studies that identify genetic risk loci for metabolic traits. Determining the transferability of such largely Euro-centric established risk loci is essential to transfer the research tools/resources, and drug targets generated by global studies to a broad range of ethnic populations. Further, consideration of populations such as Arabs, that are characterized by consanguinity and a high level of inbreeding, can lead to identification of novel risk loci. We imputed published GWAS data from two Kuwaiti Arab cohorts ($n = 1434$ and 1298) to the 1000 Genomes Project haplotypes and performed meta-analysis for associations with 13 metabolic traits. We compared the observed association signals with those established for metabolic traits. Our study highlighted 70 variants from 9 different genes, some of which have established links to metabolic disorders. By relaxing the genome-wide significance threshold, we identified 'novel' risk variants from 11 genes for metabolic traits. Many novel risk variant association signals were observed at or borderline to genome-wide significance. Furthermore, 349 previously established variants from 187 genes were validated in our study. Pleiotropic effect of risk variants on multiple metabolic traits were observed. Fine-mapping illuminated rs7838666/*CSMD1* rs1864163/*CETP* and rs112861901/[*INTS10,LPL*] as candidate causal variants influencing fasting plasma glucose and high-density lipoprotein levels. Computational functional analysis identified a variety of gene regulatory signals around several variants. This study enlarges the population ancestry diversity of available GWAS and elucidates new variants in an ethnic group burdened with metabolic disorders.

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Introduction

The post-oil era of the Arabian Peninsula has witnessed a substantial increase in the prevalence of metabolic trait-related disorders, such as obesity, dyslipidemia, hypertension, and type 2 diabetes mellitus (T2D), in its population. Despite the high prevalence of metabolic-related disorders in the Arabian Peninsula (Abuyassin and Laher 2015; Al Rasadi et al. 2016; Al Sifri et al. 2014; Channanath et al. 2013; Klautzer et al. 2014; Ng et al. 2014; Tailakh et al. 2014), there is a lack of convincingly identified genetic determinants for metabolic traits in people from this region. The global genome-wide association studies (GWAS) performed for metabolic diseases and traits overrepresent people of European ancestry (Mills and Rahal 2019). Only a few GWAS from the Arabian Peninsula are reported in the literature, including those on unrelated individuals from Saudi Arabia (Ram et al. 2017; Wakil et al. 2016) and Lebanon (Ghassibe-Sabbagh et al. 2014), on an extended family

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We are entering a post-cancer genomic era, standing at the precipice of translating genomic insight into therapy. However, it is not as simple as initially thought. For cancer, plasticity, adaptation, and evolution are the rules. Dissecting the complex and bidirectional interactions between oncogenic alterations, developmental lineages, and biochemical and tissue microenvironments (Bi et al., 2020) will be critical for developing more effective treatments for glioblastoma patients (Figure 1B). The physiologically relevant mouse models described here demonstrate high fidelity and potential critical predictive power, even in such a complex disease as glioblastoma, suggesting that they will have an important role in future target discovery, validation, and therapeutic testing. It is with great anticipation that we look forward to seeing how this powerful experimental system that leverages fundamental neuroscience insights and mouse genetics will yield actionable targets that are poised to make a difference for patients.

DECLARATION OF INTERESTS

P.S.M. is co-founder of Boundless Bio, Inc. and serves as a consultant.

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A Multi-layer Molecular Fresco of the Immune Diversity across Hematologic Malignancies

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Immune checkpoint blockade has limited activity in the large majority of hematologic malignancies. In this issue of *Cancer Cell*, Dufva et al. provide an immunologic portrait of these heterogenous diseases and identify key relationships between oncogenic states and immune response that can spur the development of more efficient immunotherapeutic approaches.

In the last few years, the enthusiasm for the effectiveness of immune checkpoint blockade (ICB) in a considerable proportion of patients affected by solid tumors (20%–40%) has boosted a prolific translational research aimed to identify determinants of immune responsiveness and increased therapeutic efficacy. Longitudinal studies in cancer metastases have provided evidence that immune selection molds the development of seeding metastatic clones (Angelova et al., 2018). Multi-omics studies of large collections of primary tumors and cohorts of patients treated with ICB have unveiled complex and unexpected relationships between cancer cells and their host's immune system, allowing the identification of prognostic and predictive biomarkers and the rational design of combination strategies (Bedognetti et al., 2019; Thorsson et al., 2018).

Such a sharp gain in our knowledge of the molecular mechanisms governing immune-mediated rejection in solid tumors has not been paralleled in hematologic malignancies (HMs), which include a vast spectrum of genetically heterogenous diseases. Immunotherapies based on monoclonal antibodies and chimeric

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REVIEW Open Access

Pathophysiology and treatment strategies for COVID-19

Manoj Kumar and Souhaila Al Khodor*

Abstract

The outbreak of Coronavirus disease of 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), has posed a serious health threat. The increasing number of COVID-19 cases around the world is overwhelming hospitals and pushing the global death toll to over 746,000, which has pushed the sprint to find new treatment options. In this article, we reviewed the SARS-CoV-2 pathophysiology, transmission, and potential treatment strategies.

Keywords: SARS-CoV-2, Pandemic, 2019 novel coronavirus, Viral inhibitor, ACE-2 receptor, Receptor binding protein

COVID19 pandemic background

Coronavirus Disease 2019 (COVID-19) caused by an infection with the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has caused one of the largest global outbreaks in recent years, and posed a serious threat to the global public health [1, 2]. Considering the rapidly increasing cases of COVID-19 and disease severity, the World Health Organization (WHO) declared a global health emergency on January 30, 2020 [3]. Despite implementing worldwide combined efforts to prevent SARS-CoV-2 further transmission by quarantining the infected persons and their family members, social distancing, and schools closure, the spreading of infection could not be contained; therefore, on March 11, 2020, the WHO declared COVID-19 a pandemic [3]. As of now, around 213 countries and territories outside of the Mainland China have reported SARS-CoV-2 infections [1, 4]. The massive impact of SARS-CoV-2 infection has been seen in the United States of America, Europe, and Asia. As of Aug 12th, 2020, the time of writing this review, SARS-CoV-2 has infected more than 20.54 million people worldwide and resulted in 746,151 deaths (Additional file 1: Figure S1A).

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The worldwide date indicates an exponential infection rate of SARS-CoV-2 cases after the first week of March-2020 (Additional file 1: Figure S1B). The mean primary reproduction number (R0) was estimated to range from 2.24 [95% confidence interval (CI) 1.96–2.55] to 3.58 (95% CI 2.89–4.39), and associated with two- to eight-fold increase in the reporting rate as compared to other viral infections (Additional file 1: Figure S1C) [5, 6]. The current statistics are showing that the epidemic doubling time is as low as 6.4 days [5], including potential asymptomatic transmissions. Although the situation is evolving and updated on daily basis, more data is required to confirm these estimations. This data indicates a high potential for the SARS-CoV-2 outbreak and warrants immediate therapeutic interventions.

Outbreaks of coronavirus

Seven Coronaviruses (CoV) of zoonotic origins have crossed the species barrier so far, to cause infections in humans, and three of them have caused a deadly infection in last two decades, including the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), and SARS-CoV-2 (Fig. 1) [7–9]. Among these, SARS-CoV originating from bats emerged in Guangdong, China in 2002, and resulted in the 2003 outbreak with about 10% case fatality rate (CFR) [10], while MERS-CoV originating

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RESEARCH ARTICLE

THE FASEB JOURNAL

Multiple signaling pathways converge on proapoptotic protein BAD to promote survival of melanocytes

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Abstract

Melanocyte survival is mediated by diverse signaling pathways. However, the molecular mechanisms they use and molecules that they target are incompletely understood. Here, we show that melanocyte survival is mediated by diverse, non-redundant signaling pathways, including ERK1/2, AKT, PKA, and PKC. Each of these pathways is exerting prosurvival effects by phosphorylating the BAD. While Ser112-BAD phosphorylation is regulated by pERK, pPKA and pPKC, Ser136 and Ser155 phosphorylation are exclusively controlled by pAKT and pPKA, respectively. Inhibition of these pathways individually resulted in only modest apoptosis; however, most significant apoptosis, as a result of BAD dephosphorylation, was seen when all pathways were inhibited concurrently. BAD phosphorylation was essential for survival of melanocytes as cells expressing phosphorylation-deficient BAD were not rescued by any of the identified pathway. Furthermore, melanocytes became insensitive to kinase inhibitor-induced apoptosis when BAD expression was knocked down by BAD-shRNA. Overexpression of BAD in melanocytes stimulated faster apoptosis in response to kinase inhibitors. Taken together, our results show that BAD is acting as a convergence point for diverse survival pathways in melanocytes. Understanding the molecular mechanisms of melanocyte survival provides fundamental new insights into physiological mechanisms involved in the development of various melanocyte pathologies such as melanoma and vitiligo.

KEYWORDS

AKT, apoptosis, MAPK, PKA, PKC

1 | INTRODUCTION

Skin is the largest organ of the body and interfaces with the environment. Melanocytes are located in the basal layer of the epidermis and they are unique in synthesizing melanin pigment. Melanocytes are exposed to various environmental and biochemical insults, such as pollutants, UV radiation, and endogenous reactive oxygen species such as hydrogen peroxide.[1,2] To sustain these cues, melanocytes deploy multicomponent signaling mechanisms that protect them from stressors.[3] Melanocyte survival and proliferation are controlled by a complex network of signaling mechanisms.

Abbreviations: AKT, protein kinase B; BAD, BCL2-associated agonist of cell death; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PKC, protein kinase C; shRNA, small hairpin RNA.

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BMC Medical Genetics

CASE REPORT Open Access

A de novo synonymous variant in *EFTUD2* disrupts normal splicing and causes mandibulofacial dysostosis with microcephaly: case report

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Abstract

Background: Mandibulofacial dysostosis with microcephaly (MFDM) is a rare autosomal dominant genetic disease characterized by intellectual and growth retardations, as well as major microcephaly, induced by missense and splice site variants or microdeletions in the *EFTUD2* gene.

Case presentation: Here, we investigate the case of a young girl with symptoms of MFDM and a normal karyotype. Whole-exome sequencing of the family was performed to identify genetic alterations responsible for this phenotype. We identified a de novo synonymous variant in the *EFTUD2* gene. We demonstrated that this synonymous variant disrupts the donor splice-site in intron 9 resulting in the skipping of exon 9 and a frameshift that leads to a premature stop codon.

Conclusions: We present the first case of MFDM caused by a synonymous variant disrupting the donor splice site, leading to exon skipping.

Keywords: *EFTUD2*, Mandibulofacial dysostosis with microcephaly, de novo, Synonymous splice variant, Exonic splice enhancer variant, Whole-exome sequencing, Case report

Background

Mandibulofacial dysostosis with microcephaly (MFDM) is a rare autosomal dominant disease characterized by malar and mandibular hypoplasia and microcephaly. Some of its main features include conductive hearing loss, intellectual disability, distinctive facial features and craniofacial malformations that may include characteristic external ear malformations, cleft palate, choanal atresia, and facial asymmetry. In some instances, one observes extracranial malformations such as esophageal atresia (~ 40%), congenital heart disease (~ 40%), and thumb abnormalities (~ 25%). Short stature is present in approximately one-third of individuals [1–4].

Its exact prevalence is unknown, but more than 80 cases have been described in the literature until now. MFDM is mostly caused by de novo variants in the *EFTUD2* gene (MIM# 603892) [5]. In some rarer instances, the MFDM is transmitted from a parent in an autosomal dominant manner (19% of the cases) or due to germline mosaicism (6% of the cases). *EFTUD2* encodes the U5-116kD, a highly conserved GTPase component of the major spliceosome complex that processes precursor mRNAs to produce mature mRNAs by

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PLOS ONE

RESEARCH ARTICLE

Corneal confocal microscopy demonstrates minimal evidence of distal neuropathy in children with celiac disease

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Abstract

Objectives

The aim of this study was to utilise corneal confocal microscopy to quantify corneal nerve morphology and establish the presence of sub-clinical small fibre damage and peripheral neuropathy in children with celiac disease.

Methods

This is a cross-sectional cohort study of twenty children with celiac disease and 20 healthy controls who underwent clinical and laboratory assessments and corneal confocal microscopy. Corneal nerve fiber density (no.mm^2), corneal nerve branch density (no.mm^2), corneal nerve fiber length (mm.mm^2), corneal nerve fiber tortuosity and inferior whorl length (mm.mm^2) were quantified manually.

Results

Corneal nerve fiber density (34.7±8.6 vs. 32.9±8.6; $P = 0.5$), corneal nerve branch density (47.2±24.5 vs. 47.3±20.0; $P = 0.1$) and corneal nerve fiber length (20.0±5.1 vs. 19.5±4.5; $P = 0.8$) did not differ between children with celiac disease and healthy controls. Corneal nerve fiber tortuosity (11.4±1.9 vs 13.5±3.0; $P = 0.01$) was significantly lower and inferior whorl length (20.0±5.5 vs 23.0±3.8; $P = 0.06$) showed a non-significant reduction in children with celiac disease compared to healthy controls. Inferior whorl length correlated significantly with corneal nerve fiber density (P = 0.005), corneal nerve branch density (P = 0.04), and corneal nerve fiber length (P = 0.002).

Herpes simplex encephalitis in a patient with a distinctive form of inherited IFNAR1 deficiency

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Inborn errors of TLR3-dependent IFN-α/β– and IFN-λ–mediated immunity in the CNS can underlie herpes simplex virus 1 (HSV-1) encephalitis (HSE). The respective contributions of IFN-α/β and IFN-λ are unknown. We report a child homozygous for a genomic deletion of the entire coding sequence and part of the 3′-UTR of the last exon of *IFNAR1*, who died of HSE at the age of 2 years. An older cousin died following vaccination against measles, mumps, and rubella at 12 months of age, and another 17-year-old cousin homozygous for the same variant has had other, less severe, viral illnesses. The encoded IFNAR1 protein is expressed on the cell surface but is truncated and cannot interact with the tyrosine kinase TYK2. The patient's fibroblasts and EBV-B cells did not respond to IFN-α2b or IFN-β, in terms of STAT1, STAT2, and STAT3 phosphorylation or the genome-wide induction of IFN-stimulated genes. The patient's fibroblasts were susceptible to viruses, including HSV-1, even in the presence of exogenous IFN-α2b or IFN-β. HSE is therefore a consequence of inherited complete IFNAR1 deficiency. This viral disease occurred in natural conditions, unlike those previously reported in other patients with IFNAR1 or IFNAR2 deficiency. This experiment of nature indicates that IFN-α/β are essential for anti–HSV-1 immunity in the CNS.

Introduction

Herpes simplex virus 1 (HSV-1) is an α-herpesvirus that infects about 75% of the general population by the age of 18 years (1, 2). Following primary infection, it typically establishes latency in trigeminal ganglia, whence it may occasionally reactivate, typically manifesting as labial mucocutaneous lesions. In about 1–2 per 10,000 infected individuals, HSV-1 can reach the brain via the olfactory bulb or trigeminal nerve, causing life-threatening herpes simplex encephalitis (HSE) of the forebrain or brainstem, respectively (3). HSE is the most common sporadic viral encephalitis affecting otherwise healthy humans, at least in Western countries. Its incidence peaks between the ages of 3 months and 6 years, earlier than would be predicted from age at primary infection alone (1). During HSE, the infection is restricted to the CNS, with the forebrain affected in about 95% of cases and the brainstem affected in the remaining approximately 5% of cases (1, 4). There are usually no mucocutaneous lesions, no detectable viremia, and no lesions of internal organs other than the brain. The advent of acyclovir treatment has decreased the mortality of HSE from about 75% to about 20% (5). However, 40%–60% of survivors suffer mild-to-severe (10%–20%) neurological sequelae (6–8). With the exception of the identification of the causal virus, the pathogenesis of HSE remained unexplained until 2006–2007,

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Title

Convalescent Plasma for the Treatment of Patients with Severe Coronavirus Disease 2019; a Preliminary Report

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Abstract

Background

The role of convalescent plasma therapy for patients with Coronavirus Disease 2019 (COVID-19) is unclear.

Methods

We retrospectively compared outcomes in a cohort of critical COVID-19 patients who received standard care (SC Group) and those who, in addition, received convalescent plasma (CP Group).

Results

Forty patients were included in each group. The median patient age was 53.5 years [interquartile range (IQR) 42–60.5], and the majority required invasive ventilation (69, 86.2%). Plasma was harvested from donors after a median of 37 days (IQR 31–46) from the first positive SARS-CoV-2 PCR result, and 26 days (IQR 21–32) after documented viral clearance; and was administered after a median of 10 days (IQR 9–10) from onset of symptoms and 2.5 days (IQR 2–4) from admission to ICU. The primary endpoint of improvement in respiratory support status within 28 days was achieved in 26 (65%) in the SC Group, and 31 (77.5%) in the CP Group (*P* 0.32). All-cause mortality at 28 days (12.5% *versus* 2.5%, *P* 0.22), and viral clearance (65% *versus* 55%, *P* 0.49) were not significantly different between the two groups. Convalescent plasma was not significantly associated with the primary endpoint (adjusted hazard ratio 0.87; 95% confidence interval 0.51-1.49, *P* 0.62). Adverse events were balanced between the two study groups.

Conclusion

In severe COVID-19, convalescent plasma therapy was not associated with clinical benefits. Randomized trials are required to confirm our findings.

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EDITORIAL Open Access

Translational cancer biology

Cristina Maccalli*

We are excited to announce the launch of a new section in the *Journal of Translational Medicine* entitled "*Translational Cancer Biology*". This section aims to provide a platform for the communication and dissemination of advances in cancer biology and their translational applications. Studies considered for publication include those dissecting the mechanisms of transformation, progression and metastatization, the biology of cancer stem cells and their immunological properties, the mechanisms undergoing the epithelial-to mesenchymal (EMT) transition and tumor dormancy, their relationship with immune functions and the mechanisms undergoing cancer resistance to therapies. This section is also dedicated to those investigations dedicated to the translational aspects and the development of novel therapies related to the aforementioned themes and the identification of patient's responsiveness and outcome to therapies.

Cancer is one of the leading causes of morbidity and mortality in the western world. The progress in understanding the oncogenic and pro-survival pathways as well as the immunological profile of cancer cells allowed to design novel targeted therapies and immunotherapy, leading to the improvement of the overall survival of cancer patients. Nevertheless, a significant proportion of cancer patients are unresponsive or develop resistance to therapies. Advances in genome sequencing allowed to show that tumor lesions results from heterogeneous mixture of genetically distinct subclones that arise through tumor evolution [1–3]. The unique driver mutations within each subclone can impact the cancer hallmarks differently, thereby contributing to functional heterogeneity. In addition, a variety of DNA mutations arise at different stage and dynamically along with tumor development and progression [4, 5]. These genetic variants together with epigenetic modifications drive the development of hierarchically organized neoplastic tissues comprising subpopulations of self-renewing cells with "stemness" properties that allow the long term maintenance of tumors. The evidence that rare cells within tumor lesions, cancer stem cells/cancer initiating cells (CSCs/CICs), represent a key component of tumor initiation and propagation was obtained initially in hematological malignancies [6, 7] and subsequently in solid tumors with different histological origins [8–11].

CSCs/CICs are endowed with the ability to modulate their proliferative status from quiescent to slow or fast cycling [12, 13] and with the resistance to therapeutic treatment, such as chemotherapy and radiotherapy [14–20]. These cells can survive and initiate the formation of local recurrence, and through migrating at distant site, of metastases, even many years after the initial clinical response to the treatments [19, 21–24]. One of the major factor influencing the phenotype, molecular properties and proliferative status of CSCs/CICs is represented by the "niche" or tumor microenvironment (TME) [25, 26]. The epithelial-to-mesenchymal transition (EMT) is a developmental program underlying the acquisition of mesenchymal properties by epithelial cells [27, 28]. EMT become re-activated in cancer cells, promoting cell migration, dissemination of cells and metastasis formation [29, 30] and is associated with the generation of CSCs/CICs [31, 32]. The identification of key signaling pathways underlying CSCs/CICs properties would more accurately provide insights for the clinical contribution and significance of these cells [33–36]. Epigenetic mechanisms, including DNA methylation, histone modifications, chromatin remodeling and changes in non-coding RNA, such as miRNAs, regulate the landscape of cells. The deregulation of these genomic make-up can increase stemness and self-renew,

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Generation of two human iPSC lines from patients with maturity-onset diabetes of the young type 2 (MODY2) and permanent neonatal diabetes due to mutations in the *GCK* gene

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A B S T R A C T

Heterozygous and homozygous mutations in the *glucokinase* (*GCK*) gene leads to maturity-onset diabetes of the young type 2 (MODY2) and permanent neonatal diabetes (PNDM), respectively. Here, we report the generation of two induced pluripotent stem cell (iPSC) lines, QBRIi010-A and QBRIi011-A, from patients with MODY2 and PNDM due to mutations in the *GCK* gene (c.437 T > C). The generated iPSC lines displayed pluripotency characteristics, were able to differentiate into the three germ layers, and showed normal karyotypes. These iPSC lines will serve as valuable human cell models for understanding diabetes pathogenesis and developing new therpaies for diabetes.

1. Resource Table

Unique stem cell lines identifier	QBRIi010-A QBRIi011-A
Alternative name(s) of stem cell line	*GCK*-MODY2 iPSCs (QBRIi010-A) *GCK*-PNDM iPSCs (QBRIi011-A)
Institution	Qatar Biomedical research institute (QBRI), Hamad Bin Khalifa University (HBKU), Qatar Foundation, Doha, Qatar
Contact information of distributor	Essam M. Abdelalim (emohamed@hbku.edu.qa)
Type of cell line	iPSC
Origin	human
Cell Source	Blood
Clonality	Clonal
Method of reprogramming	Integration-free Sendai virus vector contain OCT3/4, SOX2, c-MYC, and KLF4
Genetic Modification	YES
Type of Modification	Hereditary
Associated disease	Patient 1: (Maturity diabetes of the young type 2 (MODY2) Patient 2: Permanent neonatal diabetes mellitus (PNDM)
Gene/locus	Gene: *GCK* Locus: 7p13 Heterozygous mutation: c.437 T > C in exon 4 (Patient 1) Homozygous mutation: c.437 T > C in exon 4 (Patient 2)
Method of modification	N/A
Name of transgene or resistance	N/A
Inducible/constitutive system	N/A
Date archived/stock date	*Date cell line archived or deposited in repository*
Cell line repository/bank	N/A
Ethical approval	The protocol was approved by the Institutional Review Board (IRB) of Sidra Medicine (no. 1702007608) and QBRI (no. 2018–002)

2. Resource utility

We established two iPSC lines from patients with MODY2 and PNDM due to heterozygous and homozygous mutations in the *GCK* gene (c.437 T > C), respectively. These iPSC lines will serve as human cell models for elucidating underlying mechanism of *GCK*-associated diabetes and developing novel therapies for diabetes.

3. Resource details

Glucokinase (*GCK*) gene encodes an enzyme that phosphorylate

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Inborn errors of type I IFN immunity in patients with life-threatening COVID-19

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Clinical outcome upon infection with SARS-CoV-2 ranges from silent infection to lethal COVID-19. We have found an enrichment in rare variants predicted to be loss-of-function (LOF) at the 13 human loci known to govern TLR3- and IRF7-dependent type I interferon (IFN) immunity to influenza virus, in 659 patients with life-threatening COVID-19 pneumonia, relative to 534 subjects with asymptomatic or benign infection. By testing these and other rare variants at these 13 loci, we experimentally define LOF variants in 23 patients (3.5%), aged 17 to 77 years, underlying autosomal recessive or dominant deficiencies. We show that human fibroblasts with mutations affecting this pathway are vulnerable to SARS-CoV-2. Inborn errors of TLR3- and IRF7-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in patients with no prior severe infection.

frontiers in Pediatrics

ORIGINAL RESEARCH
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Successful Establishment of the First Neonatal Respiratory Extracorporeal Membrane Oxygenation (ECMO) Program in the Middle East, in Collaboration With Pediatric Services

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Background: Extracorporeal membrane oxygenation (ECMO) is a complex life-saving support for acute cardio-respiratory failure, unresponsive to medical treatment. Starting a new ECMO program requires synergizing different aspects of organizational infrastructures and appropriate extensive training of core team members to deliver the care successfully and safely.

Objectives: To describe the process of establishing a new neonatal ECMO program and to evaluate the program by benchmarking the ECMO respiratory outcomes and mechanical complications to the well-established Extracorporeal Life Support Organization (ELSO) registry data.

Materials and Methods: We reviewed the processes and steps involved in planning and setting up the new ECMO program. To assess the success of the ECMO implementation program, we retrospectively reviewed data of clinical outcomes and technical complications for the first 11 patients who have received ECMO therapy for respiratory indications since program activation (July 2018–May 2020). We analyzed mechanical complications as a tool to measure infrastructures and our effective training for the core team of ECMO specialists. We also looked at all clinical complications and benchmarked these numbers with the last 10 years of ELSO registry data (2009–2019) in the corresponding categories for comparison. Chi-square test was used to compare, and outcomes are presented in percentage; a p-value of <0.05 is considered significant.

Results: A total of 27 patients underwent ECMO in the hospital, out of which 11 (six neonatal and five pediatric) patients had acute respiratory failure treated with venovenous (VV) ECMO or veno-arterial (VA) ECMO over a 22-month period. We had a total of 3,360 h of ECMO run with a range from 1 day to 7 weeks on ECMO. Clinical outcomes and mechanical complications are comparable to ELSO registry data (no significant difference); there were no pump failure, oxygenator failure, or pump clots.

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Blood gene transcript signature profiling in pregnancies resulting in preterm birth: A systematic review

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ABSTRACT

Objective: To pursue a systematic review and summarise the current evidence for the potential of transcriptome molecular profiling in investigating the preterm phenotype.
Study design: We systematically reviewed the literature, using readily available electronic databases (i.e. PubMed/Medline, Embase, Scopus and Web of Science) from inception until March 2020 to identify investigations of maternal blood-derived RNA profiling in preterm birth (PTB). Studies were included if circulating coding or non-coding RNA was analysed in maternal blood during pregnancy and/or at delivery. Interventional trials were not included. The primary outcome was the availability of whole genome expression patterns evaluated in pregnancies resulting in preterm deliveries.
Results: A total of 35 articles were included in the final analysis. Most of the studies were conducted in high-income countries and published in the last decade. Apart from spontaneous PTB, a variety of phenotypes leading to preterm delivery were reported. Differences in sampling methods, target gene selection and laboratory protocols severely limited any quantitative comparisons. Most of the studies revealed that gene expression profiling during pregnancy has high potential for identifying women at risk of spontaneous and/or non-spontaneous PTB as early as in the first trimester.
Conclusion: Assessing maternal blood-derived transcriptional signatures for PTB risk in pregnant women holds promise as a screening approach. However, longitudinally followed, prospective pregnancy cohorts are lacking. These are relevant for identifying causes leading to PTB and whether prediction of spontaneous PTB or co-morbidities associated with PTB is achievable. More emphasis on widely employed standardised protocols is required to ensure comparability of results.

Contents

Abbreviations: ANC, antenatal care; DNA, deoxyribonucleic acid; EGA, estimated gestational age; FGR, fetal growth restriction; HIC, high-income country; LIC, low-income country; LMP, last menstrual period; MIC, middle-income country; miRNA, microRNA; mRNA, messenger RNA; NGS, next generation sequencing; PCR, polymerase chain reaction; PICo, Population phenomenon of Interest and Context; PPROM, preterm premature rupture of membranes; PROSPERO, Prospective Register of Systematic Reviews; PTB, preterm birth; PTL, preterm labour; PoA, proportion of agreement; RIN, RNA integrity number; RNA, Ribonucleic acid; SDG, Sustainable Development Goal; SGA, small for gestational age; sPTB, spontaneous preterm birth; sPTL, spontaneous preterm labour; WBC, white blood cells; WHO, World Health Organization.

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Article

Single-Cell Analyses Identify Brain Mural Cells Expressing CD19 as Potential Off-Tumor Targets for CAR-T Immunotherapies

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SUMMARY

CD19-directed immunotherapies are clinically effective for treating B cell malignancies but also cause a high incidence of neurotoxicity. A subset of patients treated with chimeric antigen receptor (CAR) T cells or bispecific T cell engager (BiTE) antibodies display severe neurotoxicity, including fatal cerebral edema associated with T cell infiltration into the brain. Here, we report that mural cells, which surround the endothelium and are critical for blood-brain-barrier integrity, express CD19. We identify *CD19* expression in brain mural cells using single-cell RNA sequencing data and confirm perivascular staining at the protein level. *CD19* expression in the brain begins early in development alongside the emergence of mural cell lineages and persists throughout adulthood across brain regions. Mouse mural cells demonstrate lower levels of *Cd19* expression, suggesting limitations in preclinical animal models of neurotoxicity. These data suggest an on-target mechanism for neurotoxicity in CD19-directed therapies and highlight the utility of human single-cell atlases for designing immunotherapies.

INTRODUCTION

CD19-targeting CAR-T cells have shown tremendous clinical efficacy in patients with B cell leukemia and lymphoma, including those who have relapsed after receiving traditional chemotherapy regimens (Brentjens et al., 2003; Kochenderfer et al., 2010; Porter et al., 2011; Brentjens et al., 2013; Grupp et al., 2013). For example, in a recent phase II study of 111 patients

BMJ Open

Cohort profile: molecular signature in pregnancy (MSP): longitudinal high-frequency sampling to characterise cross-omic trajectories in pregnancy in a resource-constrained setting

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ABSTRACT

Purpose A successful pregnancy relies on the interplay of various biological systems. Deviations from the norm within a system or intersystemic interactions may result in pregnancy-associated complications and adverse pregnancy outcomes. Systems biology approaches provide an avenue of unbiased, in-depth phenotyping in health and disease. The molecular signature in pregnancy (MSP) cohort was established to characterise longitudinal, cross-omic trajectories in pregnant women from a resource constrained setting. Downstream analysis will focus on characterising physiological perturbations in uneventful pregnancies, pregnancy-associated complications and adverse outcomes.

Participants First trimester pregnant women of Karen or Burman ethnicity were followed prospectively throughout pregnancy, at delivery and until 3 months post partum. Serial high-frequency sampling to assess whole blood transcriptomics and microbiome composition of the gut, vagina and oral cavity, in conjunction with assessment of gene expression and microbial colonisation of gestational tissue, was done for all cohort participants.

Findings to date 381 women with live born singletons averaged 16 (IQR 15–18) antenatal visits (13 094 biological samples were collected). At 5% (19/381) the preterm birth rate was low. Other adverse events such as maternal febrile illness 7.1% (27/381), gestational diabetes 13.1% (50/381), maternal anaemia 16.3% (62/381), maternal underweight 19.2% (73/381) and a neonate born small for gestational age 20.2% (77/381) were more often observed than preterm birth.

Future plans Results from the MSP cohort will enable in-depth characterisation of cross-omic molecular trajectories in pregnancies from a population in a resource-constrained setting. Moreover, pregnancy-associated complications and unfavourable pregnancy outcomes will be investigated at the same granular level, with a particular focus on population relevant needs such as effect of tropical infections on pregnancy. More detailed knowledge on multiomic perturbations will ideally result in the development of diagnostic tools and ultimately lead to targeted interventions that may disproportionally benefit pregnant women from this resource-limited population.

Trial registration number NCT02797327.

Strengths and limitations of this study

- The major strength is the prospective nature of the study and frequent follow-up, coupled with high-frequency sampling and thus, availability of detailed clinical information and a considerable number of biological samples.
- High-throughput analysis, in combination with clinical data, will enable investigation of a number of pregnancy-related physiological and pathological changes.
- Frequently populations from low-resource settings are disproportionally burdened by adverse birth outcomes that may be based on exposure to different communicable diseases; hence, including them in high-end clinical research, addresses a significant research gap and may result in improvements of limited relevance to high-income countries.
- Low numbers for some phenotypes (eg, preterm birth) may prove to be detrimental for the validity of observed differences; although the power will depend on the magnitude of observed differences in molecular signatures.
- In low-resource settings, complete biological sample sets are often difficult to obtain, which may downsize the richness of the data.

INTRODUCTION

A successful pregnancy relies on well-timed adaptations and the interplay of multiple maternal biological systems. These

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Article

Adult Diabetes and Prediabetes Prevalence in Kuwait: Data from the Cross-Sectional Kuwait Diabetes Epidemiology Program

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Abstract: Background: This study aimed to estimate the prevalence of diabetes and prediabetes in adults in Kuwait. Methods: The Kuwait Diabetes Epidemiology Program was a nationally representative, cross-sectional study of diabetes and obesity in Kuwait conducted between 2011 and 2014. The survey sampled 4937 adults in Kuwait aged 20 years or more and recorded participants' demographics, behaviours, medical history, physical measurements and blood biochemical measurements. Prediabetes was defined as fasting plasma glucose between 6.1 and 6.9 mmol/L or HbA1c between 6 and 6.4% (42–47 mmol/mol). Diabetes was defined as self-reported history with prescribed glucose-lowering medication or FPG ≥7mmol/L or HbA1c level ≥6.5% (≥48 mmol/mol). Results: The overall adjusted prevalence of diabetes was 19.1%. The overall adjusted prevalence of prediabetes was 13.5%. Diabetes prevalence was 5.4%, 14.2%, 38.7% and 64.8% in adults aged 20–29, 30–44, 45–59 and 60 years or more, respectively. Diabetes prevalence was 22.4% in men and 14.4% in women. Prediabetes prevalence was 14.8% in men and 11.5% in women. In Kuwaitis, diabetes and prediabetes prevalence was 21.8% and 11.1%, respectively, while prevalence in non-Kuwaitis was 18.2% for diabetes and 14.3% for prediabetes. Conclusion: These findings illustrate the severe public health challenge posed by diabetes in Kuwait.

Keywords: diabetes; prediabetes; prevalence; Kuwait; epidemiology

1. Introduction

The global prevalence of diabetes continues to rise. The prevalence of diabetes was estimated by the International Diabetes Federation (IDF) to be 9.3% in 2019, increased from 4.6% in 2000 in adults aged 20–79 years [1]. The age-adjusted prevalence of adult diabetes in the Middle East and North Africa (MENA) region, which includes Kuwait, was 12.2%, the highest estimated prevalence of all the IDF regions. Prevalence in the MENA region is expected to increase to 13.9% by 2045 [1].

Kuwait is a small country nestled between Iraq and Saudi Arabia on the Arabian Peninsula. The discovery of oil has transformed Kuwait into a wealthy country with a largely expatriate workforce, over two-thirds of which are men [2]. This economic transformation has led to rapid urbanisation, a sedentary lifestyle and lack of physical exercise, which has in turn led to a rise in noncommunicable diseases (NCDs). A recent World Health Organization (WHO) STEPS cross-sectional survey found

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Exploiting B Cell Receptor Stereotypy to design Tailored Immunotherapy in Chronic Lymphocytic Leukemia

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Running title: Immunotherapy for BcR stereotypy in CLL

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Abstract

Purpose: Approximately 30% of patients with chronic lymphocytic leukemia (CLL) can be grouped into subsets with stereotyped B cell receptor immunoglobulin (BcR IG) displaying remarkable similarity in the heavy complementarity-determining region 3 (VH CDR3). Here, we investigated whether the consensus VH CDR3 sequences from CLL stereotyped subsets can be exploited for immunotherapy approaches.

Experimental Design: Immunogenic epitopes from the consensus VH CDR3 sequence of the clinically aggressive subsets #1 and #2 and from Eμ-TCL1 mice, which spontaneously develop CLL with BcR IG stereotypy, were identified and used to generate specific HLA class I- and II-restricted T cells *in vitro*. T cell reactivity was assayed *in vitro* as IFN-γ production. Bone marrow derived-dendritic cells (BM-DC) loaded with the peptides were used as vaccination strategy to restrain leukemia development in the Eμ-TCL1 mouse model.

Results: These stereotyped epitopes were naturally processed and presented by CLL cells to the VH CDR3-specific T cells. Furthermore, we validated the efficacy of VH CDR3 peptide-based immunotherapy in the Eμ-TCL1 transplantable mouse model. Immunization of mice against defined VH CDR3 peptide epitopes, prior to the challenge with the corresponding leukemia cells, resulted in the control of CLL development in a significant fraction of mice, and increased overall survival.

Conclusions: Our data highlight the immunogenicity of stereotyped VH CDR3 sequences and support the feasibility and efficacy of their use for novel cancer vaccine in CLL. Such approach has the advantage to generate “off-the-shelf” therapeutic vaccines for relevant groups of patients belonging to stereotyped subsets.

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Research

RESEARCH

A map of tumor–host interactions in glioma at single-cell resolution

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ABSTRACT

Background: Single-cell RNA sequencing is the reference technique for characterizing the heterogeneity of the tumor microenvironment. The composition of the various cell types making up the microenvironment can significantly affect the way in which the immune system activates cancer rejection mechanisms. Understanding the cross-talk signals between immune cells and cancer cells is of fundamental importance for the identification of immuno-oncology therapeutic targets. **Results:** We present a novel method, single-cell Tumor–Host Interaction tool (scTHI), to identify significantly activated

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REVIEW
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Cancer Immunotherapy Using Chimeric Antigen Receptor Expressing T-Cells: Present and Future Needs of Clinical Cancer Centers

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Chimeric Antigen Receptor-T cells (CAR-T) are considered novel biological agents, designed to selectively attack cancer cells expressing specific antigens, with demonstrated clinical activity in patients affected with relapsed/refractory B-cell malignancies. In consideration of their complexity, the use of CAR-T requires dedicated clinical setting and health care practitioners with expertise in the selection, treatment, and management of toxicities and side effects. Such issue appears particularly important when contextualized in the rapid progress of CAR-T cell treatment, translating into a constant need of updating and evolution. Moreover, the clinical grade manufacturing of CAR-T cells is complex and implies articulated regulatory and organizational aspects. The main goal of this review is to summarize and provide an accurate analysis of the clinical, logistic, and regulatory requirements of CAR-T cell centers. Finally, we describe a new occupational figure called "CAR-T specialist" devoted to the establishment and coordination of the required facilities and regulatory landscape in the context of cancer centers.

Keywords: CAR-T cells, CAR-T process, CAR-T Unit, CAR-T Specialist, JACIE, GMP, ATMP

INTRODUCTION

The demonstration that the immune system can control tumor growth has been provided for the first time by Thomas and Burnet (1, 2). This evidence has been confirmed after several decades, demonstrating the prognostic role of immune cells infiltrating the tumor lesions (3–10). The crescent knowledge of cancer immunology and immunotherapy has allowed the development of novel biological agents that showed unprecedented clinical results (11). These results contributed to turn into reality the paradigm that patient's immune system represents effective "living drugs" against cancer cells. Among these, adoptive cell therapy (ACT) that implies the isolation and

Organ-specific Toxicity Evaluation of Stearamidopropyl Dimethylamine (SAPDMA) Surfactant Using Zebrafish Embryos

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Abstract

Surfactants are widely used in the industry of detergents, household products, and cosmetics. SAPDMA is a cationic surfactant that is used mostly in cosmetics, conditioning agents and has recently gained attention as a corrosion inhibitor in the sea pipelines industry. In this regard, literature concerning the ecotoxicological classification of SAPDMA on aquatic animals is lacking. This study aims to evaluate the potential ecotoxicity of SAPDMA using the aquatic zebrafish embryo model. The potential toxic effects of SAPDMA was assessed by different assays. This includes (i) mortality/survival assay to assess the median lethal concentration (LC_{50}); (ii) teratogenicity assay to assess the no observed effect concentration (NOEC); (iii) organ-specific toxicity assays including cardiotoxicity, neurotoxicity (using locomotion assay), hematopoietic toxicity (hemoglobin synthesis using o-dianisidine staining), hepatotoxicity (liver steatosis and yolk retention using Oil Red O (ORO) stain); (iv) cellular cytotoxicity (mitochondrial membrane potential) by measuring the accumulation of JC-1 dye into mitochondria. Exposure of embryos to SAPDMA caused mortality in a dose-dependent manner with a calculated LC_{50} of 2.3 mg/L. Thus, based on the LC_{50} value and according to the Fish and Wildlife Service (FWS) Acute Toxicity Rating Scale, SAPDMA is classified as “moderately toxic”. The No Observed Effect Concentration (NOEC) concerning a set of parameters including scoliosis, changes in body length, yolk, and eye sizes was 0.1 mg/L. At the same NOEC concentration (0.1 mg/L), no organ-specific toxicity was detected in fish treated with SAPDMA, except hepatomegaly with no associated liver dysfunctions. However, higher SAPDMA concentrations (0.8 mg/L) have dramatic effects on zebrafish organ development (eye, heart, and liver development). Our data recommend a re-evaluation of the SAPDMA

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Expression of NK cell receptor ligands in primary colorectal cancer tissue in relation to the phenotype of circulating NK- and NKT cells, and clinical outcome

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ABSTRACT

Introduction: Natural killer (NK) cells and natural killer T (NKT) cells are implicated in the development and progression of colorectal cancer (CRC). Tumor cells express NK cell receptor ligands that modulate their function. This study aimed to investigate the expression of such ligands in CRC in relation to the phenotype of circulating NK- and NKT cells, and clinical outcome.

Methods: Primary tumor tissues were analyzed for protein expression of NK cell ligands using immunohistochemistry with automated image analysis in a cohort of 78 CRC patients. For 24 of the 78 patients, RNA expression of NK cell ligands was analyzed in primary tumor tissue using RNA sequencing. Receptor expression on circulating NK- and NKT cells was previously measured by us in 71 of the 78 patients using flow cytometry.

Results: High Proliferating Cell Nuclear Antigen (PCNA) protein expression in the primary tumor associated with shorter disease-free survival (DFS) of CRC patients ($P = 0.026$). A trend was observed towards shorter DFS in CRC patients with above-median galectin-3 protein expression in the primary tumor ($P = 0.055$). High protein expression of galectin-3, CD1d, and human leukocyte antigen (HLA) class I, and high RNA expression of *UL16-binding protein (ULBP)-1, -2, and -5,* and *HLA-E* in the tumor tissue correlated with low expression of the corresponding receptors on circulating NK- or NKT cells ($P < 0.05$).

Conclusions: Galectin-3 and PCNA expression in the primary tumor may be prognostic biomarkers in CRC patients. Furthermore, our results suggest that NK cell receptor ligands expressed by tumor cells may modulate the phenotype of circulating NK- and NKT cells, and facilitate immune escape of metastasizing cells.

Abbreviations: ADCC, Antibody-dependent Cell-mediated Cytotoxicity; BAG6, BCL2-associated Athanogene 6; CC, Colon Cancer; CFP, Complement Factor P; CI, Confidence Interval; CLEC2A, C-type Lectin Domain Family 2 Member A; CLEC2D, C-type Lectin Domain Family 2 Member D; COAD, Colon Adenocarcinoma; CRC, Colorectal Cancer; DFS, Disease-free Survival; DNAM-1, DNAX Accessory Molecule-1; ECM, Extracellular Matrix; EMT, Epithelial-mesenchymal Transition; FFPE, Formalin-fixed Paraffin-embedded; H&E, Hematoxylin and Eosin; HLA, Human Leukocyte Antigen; HR, Hazard Ratio; IFN, Interferon; IHC, Immunohistochemistry; ILT2, Ig-like Transcript 2; KIR, Killer Cell Immunoglobulin-like Receptor; LGALS3, Galectin-3; LUMC, Leiden University Medical Center; MFI, Median Fluorescence Intensity; MIC, MHC Class I-related Chain; MSI, Multispectral Imaging; NCR, Natural Cytotoxicity Receptor; NID1, Nidogen-1; NK, Natural Killer; NKG2A, Natural Killer Group 2-A; NKG2C, Natural Killer Group 2-C; NKG2D, Natural Killer Group 2-D; NKT, Natural Killer T; OS, Overall Survival; PBMC, Peripheral Blood Mononuclear Cell; PCNA, Proliferating Cell Nuclear Antigen; PDGFD, Platelet-derived Growth Factor D; PVR, Poliovirus Receptor; SLAM, Signaling Lymphocytic Activation Molecule; TCGA, The Cancer Genome Atlas (TCGA); TCR, T Cell Receptor; TME, Tumor Microenvironment; TNM, Tumor Node Metastasis; ULBP, UL-16 Binding Protein; VIM, Vimentin.

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ARTICLE
Translational Therapeutics

A balance score between immune stimulatory and suppressive microenvironments identifies mediators of tumour immunity and predicts pan-cancer survival

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BACKGROUND: The balance between immune-stimulatory and immune-suppressive mechanisms in the tumour microenvironment is associated with tumour rejection and can predict the efficacy of immune checkpoint-inhibition therapies.
METHODS: We consider the observed differences between the transcriptional programmes associated with cancer types where the levels of immune infiltration predict a favourable prognosis versus those in which the immune infiltration predicts an unfavourable prognosis and defined a score named **M**ediators of **I**mmune **R**esponse **A**gainst **C**ancer in so**L**id micro**E**nvironments (MIRACLE). MIRACLE deconvolves T cell infiltration, from inhibitory mechanisms, such as TGFβ, EMT and PI3Kγ signatures.
RESULTS: Our score outperforms current state-of-the-art immune signatures as a predictive marker of survival in TCGA ($n = 9305$, HR: 0.043, p value: 6.7×10^{-36}). In a validation cohort ($n = 7623$), MIRACLE predicts better survival compared to other immune metrics (HR: 0.1985, p value: 2.73×10^{-38}). MIRACLE also predicts response to checkpoint-inhibitor therapies ($n = 333$). The tumour-intrinsic factors inversely associated with the reported score such as EGFR, PRKAR1A and MAP3K1 are frequently associated with immune-suppressive phenotypes.
CONCLUSIONS: The association of cancer outcome with the level of infiltrating immune cells is mediated by the balance of activatory and suppressive factors. MIRACLE accounts for this balance and predicts favourable cancer outcomes.

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BACKGROUND

The presence of an active immune microenvironment with a high density of activated T cells associates with favourable prognosis and responsiveness to immunotherapy.[1] Genetic factors preventing the development of a favourable immune milieu and/or responsiveness to immunotherapy include limited expression of neoantigens,[2,3] which is partially a function of mutational load, and high tumour aneuploidy. However, in the "immune-active" tumours, upregulation of pro-inflammatory signals is accompanied by the expression of interferon-gamma-inducible immune regulatory molecules like programmed death ligand-1 (PD-L1) and indoleamine 2,3-dioxygenase dioxygenase (IDO), whose levels correlate with response to anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA4) treatment. The expression of such molecules as well as of other immune-regulatory markers (e.g., FOXP3, CTLA4 and PD-1) characterise a *compensatory immune resistance*, reflecting the presence of counter-regulatory mechanisms that follow, rather than precede,[4,5] the recognition of tumour antigens by T cells and the subsequent amplification of the inflammatory response.[6,7] Correlative studies in humans and experimental models suggest that checkpoint inhibitors are less effective in tumours characterised by a primary immune suppression (also called as "primary immune ignorance"), including the ones with low mutational load,[1,8] or dominated by the genomic dysregulations of oncogenic pathways leading to T cell exclusion such as WNT/beta-catenin,[9–11] mitogen-activated protein kinase[6,7,12] and transforming growth factor-β (TGFβ) pathways[13–15] The dichotomy between "immune active" (associated with the displaying of compensatory immune resistance) and "immune silent" (typified by the presence of a primary immune suppression) might be useful to explain a general phenomenon but do not reflect the high level of inter-patient heterogeneity and do not take into account the contribution of antagonist signals involved in primary immune suppression. In fact, one of the major limitations of the transcriptomic studies performed so far is the use of gene signatures or modules that capture only a dominant process or a group of processes tightly interconnected or correlated among each other.

We speculate that the concurrent measurement of stimulatory and suppressive immunologic signals might better define the true immune state of the tumour–immune microenvironment and thus develop the **M**ediators of **I**mmune **R**esponse **A**gainst **C**ancer in

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cells

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Review

Reading between the (Genetic) Lines: How Epigenetics is Unlocking Novel Therapies for Type 1 Diabetes

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Abstract: Type 1 diabetes (T1D) is an autoimmune condition where the body's immune cells destroy their insulin-producing pancreatic beta cells leading to dysregulated glycaemia. Individuals with T1D control their blood glucose through exogenous insulin replacement therapy, often using multiple daily injections or pumps. However, failure to accurately mimic intrinsic glucose regulation results in glucose fluctuations and long-term complications impacting key organs such as the heart, kidneys, and/or the eyes. It is well established that genetic and environmental factors contribute to the initiation and progression of T1D, but recent studies show that epigenetic modifications are also important. Here, we discuss key epigenetic modifications associated with T1D pathogenesis and discuss how recent research is finding ways to harness epigenetic mechanisms to prevent, reverse, or manage T1D.

Keywords: chromatin; DNA methylation; epigenetics; histone modifications; metaboloepigenetics; miRNA; therapy; type 1 diabetes

1. Introduction

The hallmark of type 1 diabetes (T1D) is T cell-mediated autoimmune destruction of pancreatic beta cells, leading to insulin deficiency, elevated blood glucose concentrations, and life-long need for exogenous insulin therapy. Globally, the annual number of new cases of T1D is rising, and in the under-20 age group alone, numbers are fast approaching 100,000 (www.diabetesatlas.org). The incidence rate varies between countries and ranges from 6% in sub-Saharan Africa to 77% in some parts of Scandinavia [1]; altogether another five million people are expected to be diagnosed with T1D by 2050 [2], with profound implications for healthcare systems globally and the potential for a staggering socio-economic impact. Staying well with T1D requires normoglycemia to be achieved and maintained, but this goal is not currently achievable for many patients using existing treatment strategies [3]. Understanding the intrinsic and extrinsic factors underlying the development and progression of T1D is necessary for the development of novel intervention therapies that could delay or even prevent clinical progression in individuals susceptible to T1D or be used to treat/manage glycemic excursions in those worst affected.

Despite ongoing research, dissecting the etiology of T1D has proven a herculean task. Genetic studies have recognized more than 60 regions (loci) associated with or predisposing to T1D; the first and still strongest reported genetic association is with the human leukocyte antigen HLA region [4,5], while the second most significant T1D genetic association is with insulin gene promoter polymorphism [6]. Even so, only 5% or fewer of children bearing the high-risk HLA haplotypes and about 10% of those

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Coronavirus Disease 2019 (COVID-19): An Overview of the Immunopathology, Serological Diagnosis and Management

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Running Head: COVID-19 immunopathology and management

Abstract

SARS-CoV-2 is a novel human coronavirus responsible for the Coronavirus disease 2019 (COVID-19) pandemic. Pneumonia and acute respiratory distress syndrome are the major complications of COVID-19. SARS-CoV-2 infection can activate innate and adaptive immune responses and result in massive inflammatory responses later in the disease. These uncontrolled inflammatory responses may lead to local and systemic tissue damage. In patients with severe COVID-19, eosinopenia and lymphopenia with a severe reduction in the frequency of CD4+ and CD8+ T cells, B cells, and natural killer (NK) cells is a common feature. COVID-19 severity hinges on the development of cytokine storm characterized by elevated serum levels of pro-inflammatory cytokines. Moreover, IgG, IgM, and IgA specific antibodies against SARS-CoV-2 can be detected in most patients, along with the viral RNA, forming the basis for assays that aid in patient diagnosis. Elucidating the immunopathological outcomes due to COVID-19 could provide potential targets for immunotherapy and are important for choosing the best clinical management by consultants. Currently, along with standard supportive care, therapeutic approaches to COVID-19 treatment involve the use of antiviral agents that interfere with the SARS-CoV-2 lifecycle to prevent further viral replication and utilizing immunomodulators to dampen the immune system in order to prevent cytokine storm and tissue

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Original article

The influence of the prebiotic gum acacia on the intestinal microbiome composition in rats with experimental chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) is a globally common and important disease and there are evidence for a bidirectional relationship between microbiota and CKD. The aim of the study was to examine the influence of prebiotic – gum acacia (GA) on the intestinal microbiota in rats with adenine-induced CKD. Animals were randomly distributed into four equal groups (n = 6): control, adenine, GA and adenine + GA groups. CKD was induced by adenine (0.75% w/w) given in the diet daily for four weeks, and GA was administered in drinking water at a concentration of 15% w/v. The 16s rRNA analysis was performed on Illumina Miseq targeting V3-V4 region to characterize microbial composition. The abundance of Actinobacteria, Proteobacteria, Tenericutes and Verrucomicrobia bacteria was increased in adenine-induced CKD, and GA treatment successfully reversed those levels. Interestingly, alpha and beta diversity index were both reduced with GA treatment in rats with CKD. Short chain fatty acids (SCFAs) measurement and PICRUSt analysis have shown that GA treatment completely restored the depleted butyrate level and various perturbated functional pathways, respectively, in CKD rats. Taking together, our results suggest that GA supplementation has a beneficial role in treating CKD, through an increased production of butyrate, as well as its anti-inflammatory, antioxidant capacity and anti-nitrosative properties.

1. Introduction

The human gut microbiota is now known to have many metabolic, immunologic, protective and other functions that can impact human health [1]. It is also reported to encode the potential for the biosynthesis and transformation of compounds that are physiologically vital for both the microbes themselves and their host [2,3]. Microbial composition and abundance on or in the human body is also associated with the development and progression of a score of human and animal diseases and conditions [4,5].

Chronic kidney disease (CKD) is a common, globally important disease with an estimated prevalence of up to 16% [6]. CKD can progress to end-stage renal disease (ESRD), which can only be managed by renal transplantation or frequent dialysis, which are both costly and may not be readily available in many countries in the world [7].

It is established that the gut flora has a significant role in the pathogenesis and progression of CKD, and that CKD itself can influence the composition and abundance of gut microbes [8,9]. The former can have

Abbreviations: Ade, adenine; Ade+GA, adenine+gum acacia; AKI, acute kidney injury; ANOSIM, analysis of similarities; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; GA, gum acacia; g/d, grams per day; HD, hemodialysis; HP, high protein; IAA, indole acetic acid; IS, indoxyl sulfate; KEGG, Kyoto Encyclopedia of Genes and Genomes; LC, liquid chromatography; LDA, linear discriminant analysis; LEfSe, Linear discriminant analysis effect size; LPD, low protein diet; MS, mass spectrometry; NAG, *N*-acetyl- β-*D*-glucosaminidase; NGAL, Neutrophil gelatinase-associated lipocalin; OTU, operational taxonomic units; p-CS, p-cresol or p-cresyl sulfate; PD, peritoneal dialysis; PEAR, paired-end read merger; PICRUSt, Phylogenetic Investigation of Communities by Reconstruction of Unobserved States QIIME, Quantitative Insights Into Microbial Ecology; SCFA, short-chain fatty acid; SD, Sprague-Dawley; SEM, standard error of mean; TIF, tubulointerstitial fibrosis; w/v, weight/volume; UUO, Unilateral Ureteral Obstruction.

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Review

Molecular and Immune Biomarkers for Cutaneous Melanoma: Current Status and Future Prospects

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Simple Summary: The prognosis and treatment of metastatic melanoma have changed substantially since the advent of target therapy and immune checkpoint inhibitors. Thus, strategies must be developed to identify responder patients, reduce toxicities, and investigate target and immune based therapy ideal sequencing. To this aim, the determinants driving response, resistance, and adverse events, should be defined. In addition, novel oncogenic drivers should be discovered to provide new therapeutic targets. Current methods of detection, prognosis and monitoring of melanoma are based on clinical, morphological and histopathologic characteristics of the tumor. This review provides an update on prognostic and predictive biomarkers with a potential application in melanoma patients' clinical management.

Abstract: Advances in the genomic, molecular and immunological make-up of melanoma allowed the development of novel targeted therapy and of immunotherapy, leading to changes in the paradigm of therapeutic interventions and improvement of patients' overall survival. Nevertheless, the mechanisms regulating either the responsiveness or the resistance of melanoma patients to therapies are still mostly unknown. The development of either the combinations or of the sequential treatment of different agents has been investigated but without a strongly molecularly motivated rationale. The need for robust biomarkers to predict patients' responsiveness to defined therapies and for their stratification is still unmet. Progress in immunological assays and genomic techniques as long as improvement in designing and performing studies monitoring the expression of these markers along with the evolution of the disease allowed to identify candidate biomarkers. However, none of them achieved a definitive role in predicting patients' clinical outcomes. Along this line, the cross-talk of melanoma cells with tumor microenvironment plays an important role in the evolution of the disease and needs to be considered in light of the role of predictive biomarkers. The overview of the relationship between the molecular basis of melanoma and targeted therapies is provided in this review, highlighting the benefit for clinical responses and the limitations. Moreover, the role of different candidate biomarkers is described together with the technical approaches for their identification. The provided evidence shows that progress has been achieved in understanding the molecular basis of melanoma and in designing advanced therapeutic strategies. Nevertheless, the molecular determinants of melanoma and their role as biomarkers predicting patients' responsiveness to therapies warrant further investigation with the vision of developing more effective precision medicine.

Cell – ECM Interactions Play Multiple Essential Roles in Aortic Arch Development

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Running title: Integrin α5β1 and Fn1 in Arch Artery Formation

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ABSTRACT

***Rationale*:** Defects in the morphogenesis of the 4th pharyngeal arch arteries (PAAs) give rise to lethal birth defects. Understanding genes and mechanisms regulating PAA formation will provide important insights into the etiology and treatments for congenital heart disease.

***Objective*:** Cell-ECM interactions play essential roles in the morphogenesis of PAAs and their derivatives, the aortic arch artery (AAA) and its major branches; however, their specific functions are not well-understood. Previously, we demonstrated that integrin α5β1 and fibronectin (Fn1) expressed in the *Isl1* lineages regulate PAA formation. The objective of the current studies was to investigate cellular mechanisms by which integrin α5β1 and Fn1 regulate AAA morphogenesis.

***Methods and Results*:** Using temporal lineage tracing, whole-mount confocal imaging, and quantitative analysis of the second heart field (SHF) and endothelial cell (EC) dynamics, we show that the majority of PAA EC progenitors arise by E7.5 in the SHF and contribute to pharyngeal arch endothelium between E7.5 and E9.5. Consequently, SHF-derived ECs in the pharyngeal arches form a uniform plexus of small blood vessels, which remodels into the PAAs by 35 somites. The remodeling of the vascular plexus is orchestrated by signals dependent on the pharyngeal ECM microenvironment, extrinsic to the endothelium. Conditional ablation of integrin α5β1 or Fn1 in the *Isl1* lineages showed that signaling by the ECM regulates AAA morphogenesis at multiple steps: 1) accumulation of SHF-derived ECs in the pharyngeal arches, 2) remodeling of the uniform EC plexus in the 4th arches into the PAAs; and 3) differentiation of neural crest-derived cells adjacent to the PAA endothelium into vascular smooth muscle cells.

***Conclusions*:** PAA formation is a multi-step process entailing dynamic contribution of SHF-derived ECs to pharyngeal arches, the remodeling of endothelial plexus into the PAAs, and the remodeling of the PAAs into the AAA and its major branches. Cell-ECM interactions regulated by integrin α5β1 and Fn1 play essential roles at each of these developmental stages.

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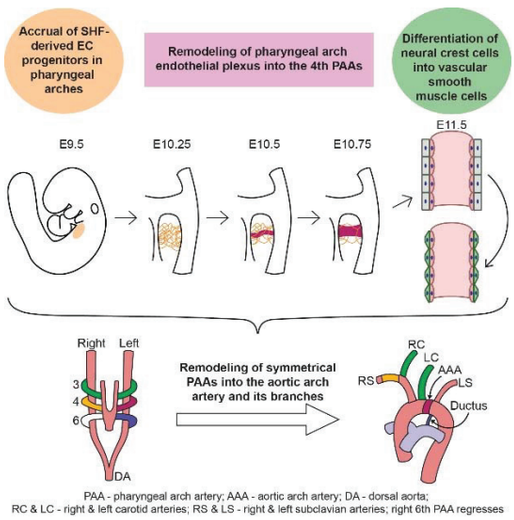
Key Words:
Integrin α5β1, fibronectin, second heart field, endothelial progenitor cells, pharyngeal arch arteries, aortic arch arteries, congenital, congenital heart disease, development, developmental biology, vasculogenesis.



frontiers in Immunology

ORIGINAL RESEARCH
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A Neutrophil-Driven Inflammatory Signature Characterizes the Blood Transcriptome Fingerprint of Psoriasis

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Transcriptome profiling approaches have been widely used to investigate the mechanisms underlying psoriasis pathogenesis. Most researchers have measured changes in transcript abundance in skin biopsies; relatively few have examined transcriptome changes in the blood. Although less relevant to the study of psoriasis pathogenesis, blood transcriptome profiles can be readily compared across various diseases. Here, we used a pre-established set of 382 transcriptional modules as a common framework to compare changes in blood transcript abundance in two independent public psoriasis datasets. We then compared the resulting "transcriptional fingerprints" to those obtained for a reference set of 16 pathological or physiological states. The perturbations in blood transcript abundance in psoriasis were relatively subtle compared to the changes we observed in other autoimmune and auto-inflammatory diseases. However, we did observe a consistent pattern of changes for a set of modules associated with neutrophil activation and inflammation; interestingly, this pattern resembled that observed in patients with Kawasaki disease. This similarity between the blood-transcriptome signatures in psoriasis and Kawasaki disease suggests that the immune mechanisms driving their pathogenesis might be partially shared.

Keywords: psoriasis, transcriptomics, blood, Kawasaki disease, systems biology

INTRODUCTION

Inflammation has an important role to play as part of the host defense against infection. However, prolonged or excessive inflammation can cause notable pathology (1–3). One example of such a pathology is psoriasis, which affects ~100 million individuals worldwide (4). This common, immune-mediated disease results in a unique skin barrier abnormality caused by excessive epidermal proliferation and inflammation (5, 6). Psoriasis pathogenesis is likely driven by many factors, including environmental triggers, genetic susceptibility, and even microbiome composition

Journal for ImmunoTherapy of Cancer

SITC cancer immunotherapy resource document: a compass in the land of biomarker discovery

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ABSTRACT

Since the publication of the Society for Immunotherapy of Cancer's (SITC) original cancer immunotherapy biomarkers resource document, there have been remarkable breakthroughs in cancer immunotherapy, in particular the development and approval of immune checkpoint inhibitors, engineered cellular therapies, and tumor vaccines to unleash antitumor immune activity. The most notable feature of these breakthroughs is the achievement of durable clinical responses in some patients, enabling long-term survival. These durable responses have been noted in tumor types that were not previously considered immunotherapy-sensitive, suggesting that all patients with cancer may have the potential to benefit from immunotherapy. However, a persistent challenge in the field is the fact that only a minority of patients respond to immunotherapy, especially those therapies that rely on endogenous immune activation such as checkpoint inhibitors and vaccination due to the complex and heterogeneous immune escape mechanisms which can develop in each patient. Therefore, the development of robust biomarkers for each immunotherapy strategy, enabling rational patient selection and the design of precise combination therapies, is key for the continued success and improvement of immunotherapy. In this document, we summarize and update established biomarkers, guidelines, and regulatory considerations for clinical immune biomarker development, discuss well-known and novel technologies for biomarker discovery and validation, and provide tools and resources that can be used by the biomarker research community to facilitate the continued development of immuno-oncology and aid in the goal of durable responses in all patients.

OVERVIEW

In the **Introduction to biomarkers for the immunotherapy of cancer** section, we introduce the cancer immunotherapy revolution from the standpoint of biomarkers and their roles in predicting clinical outcome or adverse events, as well as in quantifying antitumor immune responses. We discuss best practices for biomarker development, validation, and harmonization of data, and technical considerations for sample collection and reporting of data. Finally, we review recent biomarker discovery literature and regulatory considerations for developing diagnostics. These topics are divided into the following elements:

- Background.
- Recently approved cancer immunotherapies—a breakthrough.
- Biomarkers of immune response and clinical outcome in patients with cancer.
- Biomarkers of immune-related adverse events and correlation with clinical response.
- Quantifying the antitumor immune response.
- The development and validation of immunotherapy biomarkers.
- Data harmonization efforts for biomarker discovery.
- Sample collection: technical considerations for processing, storage, and shipment of tumor samples for immunological studies.
- Reporting of biomarker data in clinical trials and publications.
- Novel biomarker discovery: immunotherapy biomarker useful literature review.
- Regulatory agency guidelines for diagnostics.

In the **New and emerging technologies for biomarker discovery** section, we focus on technology platforms, especially those that are new and emerging, for use in biomarker discovery. These are grouped by the type of cellular target. First, we consider nucleic acid-based platforms, including genomic, microbiome, mitochondrial genome, epigenetic, transcriptomic (including single-cell),

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Article

Human T-bet Governs Innate and Innate-like Adaptive IFN-γ Immunity against Mycobacteria

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SUMMARY

Inborn errors of human interferon gamma (IFN-γ) immunity underlie mycobacterial disease. We report a patient with mycobacterial disease due to inherited deficiency of the transcription factor T-bet. The patient has extremely low counts of circulating *Mycobacterium*-reactive natural killer (NK), invariant NKT (iNKT), mucosal-associated invariant T (MAIT), and Vδ2$^+$ γδ T lymphocytes, and of *Mycobacterium*-non reactive classic T_H1 lymphocytes, with the residual populations of these cells also producing abnormally small amounts of IFN-γ. Other lymphocyte subsets develop normally but produce low levels of IFN-γ, with the exception of CD8$^+$ αβ T and non-classic CD4$^+$ αβ T_H1^* lymphocytes, which produce IFN-γ normally in response to mycobacterial antigens. Human T-bet deficiency thus underlies mycobacterial disease by preventing the development of innate (NK) and innate-like adaptive lymphocytes (iNKT, MAIT, and Vδ2$^+$ γδ T cells) and IFN-γ production by them, with mycobacterium-specific, IFN-γ-producing, purely adaptive CD8$^+$ αβ T, and CD4$^+$ αβ T_H1^* cells unable to compensate for this deficit.

INTRODUCTION

In the course of primary infection, life-threatening disease in otherwise healthy children, adolescents, and even adults, can result from monogenic inborn errors of immunity (IEI), which display genetic heterogeneity and physiological homogeneity (Casanova, 2015a, 2015b, 2020, 2021). Mendelian susceptibility to mycobacterial disease (MSMD) is characterized by a

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REVIEW Open Access

Non-invasive biomarkers for monitoring the immunotherapeutic response to cancer

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Abstract

Immunotherapy is an efficient way to cure cancer by modulating the patient's immune response. However, the immunotherapy response is heterogeneous and varies between individual patients and cancer subtypes, reinforcing the need for early benefit predictors. Evaluating the infiltration of immune cells in the tumor and changes in cell-intrinsic tumor characteristics provide potential response markers to treatment. However, this approach requires invasive sampling and may not be suitable for real-time monitoring of treatment response. The recent emergence of quantitative imaging biomarkers provides promising opportunities. In vivo imaging technologies that interrogate T cell responses, metabolic activities, and immune microenvironment could offer a powerful tool to monitor the cancer response to immunotherapy**.** Advances in imaging techniques to identify tumors' immunological characteristics can help stratify patients who are more likely to respond to immunotherapy. This review discusses the metabolic events that occur during T cell activation and differentiation, anti-cancer immunotherapy-induced T cell responses, focusing on non-invasive imaging techniques to monitor T cell metabolism in the search for novel biomarkers of response to cancer immunotherapy.

Keywords: Cancer metabolism, Immunotherapy, T cells, Tumor microenvironment, Imaging biomarkers

Introduction

Cancer immunotherapy has emerged as a treatment method for various cancers by targeting the mechanisms that govern the interplay between tumor microenvironment and immune cells. The general premise of immunotherapy for cancer is to stimulate, enhance, or improve the antitumor immune response of the host. Despite the advances in immunotherapy, only some patients showed a significant clinical benefit while the majority of patients depicted substantial side effects. Therefore, the immunotherapies must be targeted to the patients who are likely to benefit, suggesting an urgent need to identify biomarkers that can direct patient selection and help determine the response to treatment at an early stage. Non-invasive molecular imaging has become an essential diagnostic modality in cancer management. Because of molecular imaging's potential to test biological processes with high precision in vivo non-invasively at the whole-body level, it is of great importance to improve these technologies to direct treatment under many oncological conditions. Several immunotherapeutic techniques are employed in cancer therapy, including modulation of T cell activity through adoptive cell transfer (ACT), monoclonal antibodies (mAbs), checkpoint inhibitors, and cancer vaccines [1–3]. The common denominator for successfully implemented immunotherapies in the clinic is their ability to stimulate or increase cytotoxic T cells' infiltration into the tumor. Thus, in vivo imaging technologies that target T cell responses in patients are powerful tools for further development of immunotherapy. The following sections provide an overview of T cells' metabolism and

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Precision medicine in the era of artificial intelligence: implications in chronic disease management

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Abstract

Aberrant metabolism is the root cause of several serious health issues, creating a huge burden to health and leading to diminished life expectancy. A dysregulated metabolism induces the secretion of several molecules which in turn trigger the inflammatory pathway. Inflammation is the natural reaction of the immune system to a variety of stimuli, such as pathogens, damaged cells, and harmful substances. Metabolically triggered inflammation, also called metaflammation or low-grade chronic inflammation, is the consequence of a synergic interaction between the host and the exposome—a combination of environmental drivers, including diet, lifestyle, pollutants and other factors throughout the life span of an individual. Various levels of chronic inflammation are associated with several lifestyle-related diseases such as diabetes, obesity, metabolic associated fatty liver disease (MAFLD), cancers, cardiovascular disorders (CVDs), autoimmune diseases, and chronic lung diseases. Chronic diseases are a growing concern worldwide, placing a heavy burden on individuals, families, governments, and health-care systems. New strategies are needed to empower communities worldwide to prevent and treat these diseases. Precision medicine provides a model for the next generation of lifestyle modification. This will capitalize on the dynamic interaction between an individual's biology, lifestyle, behavior, and environment. The aim of precision medicine is to design and improve diagnosis, therapeutics and prognostication through the use of large complex datasets that incorporate individual gene, function, and environmental variations. The implementation of high-performance computing (HPC) and artificial intelligence (AI) can predict risks with greater accuracy based on available multidimensional clinical and biological datasets. AI-powered precision medicine provides clinicians with an opportunity to specifically tailor early interventions to each individual. In this article, we discuss the strengths and limitations of existing and evolving recent, data-driven technologies, such as AI, in preventing, treating and reversing lifestyle-related diseases.

Keywords: Exposome, Chronic inflammation, Chronic diseases, Precision medicine, Personalized treatment, Deep phenotyping, Big-data analytics, Machine leaning, Artificial intelligence

Introduction

The average lifespan of humans has more than doubled in the last two hundred years, largely due to modern medicine and public health initiatives. However, an extended lifespan is associated with increases in various types of diseases among which noncommunicable diseases (NCDs), also commonly referred to as chronic diseases. Recent evidence indicates that chronic inflammatory

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The potential role of vitamin D supplementation as a gut microbiota modifier in healthy individuals

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Vitamin D deficiency affects approximately 80% of individuals in some countries and has been linked with gut dysbiosis and inflammation. While the benefits of vitamin D supplementation on the gut microbiota have been studied in patients with chronic diseases, its effects on the microbiota of otherwise healthy individuals is unclear. Moreover, whether effects on the microbiota can explain some of the marked inter-individual variation in responsiveness to vitamin D supplementation is unknown. Here, we administered vitamin D to 80 otherwise healthy vitamin D-deficient women, measuring serum 25(OH) D levels in blood and characterizing their gut microbiota pre- and post-supplementation using 16S rRNA gene sequencing. Vitamin D supplementation significantly increased gut microbial diversity. Specifically, the *Bacteroidetes* to *Firmicutes* ratio increased, along with the abundance of the health-promoting probiotic taxa *Akkermansia* and *Bifidobacterium*. Significant variations in the two-dominant genera, *Bacteroides* and *Prevotella*, indicated a variation in enterotypes following supplementation. Comparing supplementation responders and non-responders we found more pronounced changes in abundance of major phyla in responders, and a significant decrease in *Bacteroides acidifaciens* in non-responders. Altogether, our study highlights the positive impact of vitamin D supplementation on the gut microbiota and the potential for the microbial gut signature to affect vitamin D response.

Vitamin D is a lipid-soluble vitamin that is absorbed from dietary sources or supplements in the proximal small intestine[1], and is essential for maintaining skeletal integrity and function[2], as well as for electrolyte reabsorption[3], and immune system regulation[4]. In some populations, sub-clinical vitamin D deficiency is common, affecting close to 40% of individuals in both the US[5] and Europe[6], as well as 80–85% of people living in Arab countries[7–10]. This is of particular concern given recent studies revealing the association between vitamin D deficiency and a multitude of diseases including cancer, cardiovascular diseases[11–13], diabetes, obesity[14,15] and inflammatory bowel disease (IBD)[16,17]. In diabetes[18] and IBD[19], vitamin D is intimately involved in the regulation of inflammation via a bidirectional relationship with the gut microbiota[20,21]. Studies also suggest that the amount of dietary vitamin D and its circulating levels may be involved in maintaining immune homeostasis in healthy individuals, partially via modulating the gut microbial composition[22]. However, it is currently unknown how supplementing otherwise-healthy vitamin D-deficient people affects their gut microbiota.

Several studies have assessed the impact of vitamin D supplementation on the microbiota composition, predominantly in disease states. For example, Kanhere et al. showed that weekly vitamin D supplementation modifies the gut and airway microbiota in patients with cystic fibrosis[23]. In another study, vitamin D3 supplementation of patients with multiple sclerosis increased abundance of the mucosal-integrity-promoting genus *Akkermansia* in the gut, as well as *Fecalibacterium* and *Coprococcus*; these latter two being the major butyrate producers of the Firmicutes phylum[24]. Similarly, in vitamin D-deficient pre-diabetic individuals, supplementation leading to increased serum 25(OH) D was inversely correlated with abundance of *Firmicutes* (genus *Ruminococcus*) and *Proteobacteria*, and positively correlated with *Bacteroidetes* abundance[22,25,26]. A randomized clinical trial in vitamin D-deficient overweight or obese adults also showed that increased levels of vitamin D were associated with greater abundance of bacteria from the genus *Coprococcus* and lower abundance of the genus *Ruminococcus*[27].

Studies examining the effect of vitamin D supplementation on the gut microbiota composition of healthy individuals are limited. In one study, increased relative abundance of *Bacteroidetes* and decreased *Proteobacteria*

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Recent Smell Loss Is the Best Predictor of COVID-19 Among Individuals With Recent Respiratory Symptoms

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Abstract

In a preregistered, cross-sectional study, we investigated whether olfactory loss is a reliable predictor of COVID-19 using a crowdsourced questionnaire in 23 languages to assess symptoms in individuals self-reporting recent respiratory illness. We quantified changes in chemosensory abilities during the course of the respiratory illness using 0–100 visual analog scales (VAS) for participants reporting a positive (C19+; *n* = 4148) or negative (C19–; *n* = 546) COVID-19 laboratory test outcome. Logistic regression models identified univariate and multivariate predictors of COVID-19

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Review

Exploring the Triple Interaction between the Host Genome, the Epigenome, and the Gut Microbiome in Type 1 Diabetes

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Abstract: Type 1 diabetes (T1D) is an auto-immune disorder characterized by a complex interaction between the host immune system and various environmental factors in genetically susceptible individuals. Genome-wide association studies (GWAS) identified different T1D risk and protection alleles, however, little is known about the environmental factors that can be linked to these alleles. Recent evidence indicated that, among those environmental factors, dysbiosis (imbalance) in the gut microbiota may play a role in the pathogenesis of T1D, affecting the integrity of the gut and leading to systemic inflammation and auto-destruction of the pancreatic β cells. Several studies have identified changes in the gut microbiome composition in humans and animal models comparing T1D subjects with controls. Those changes were characterized by a higher abundance of *Bacteroides* and a lower abundance of the butyrate-producing bacteria such as *Clostridium* clusters IV and XIVa. The mechanisms by which the dysbiotic bacteria and/or their metabolites interact with the genome and/or the epigenome of the host leading to destructive autoimmunity is still not clear. As T1D is a multifactorial disease, understanding the interaction between different environmental factors such as the gut microbiome, the genetic and the epigenetic determinants that are linked with the early appearance of autoantibodies can expand our knowledge about the disease pathogenesis. This review aims to provide insights into the interaction between the gut microbiome, susceptibility genes, epigenetic factors, and the immune system in the pathogenesis of T1D.

Keywords: microbial dysbiosis; intestinal permeability; immuno-regulation; short-chain fatty acid; virome; single nucleotide polymorphism; *HLA*; NOD mice

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1. Introduction

Type 1 diabetes (T1D) is an auto-immune disorder caused by a complex interaction between the host immune system and different environmental factors in genetically predisposed individuals [1–4]. Furthermore, it is well known that T1D exhibit gender-related differences in which males are more predisposed to T1D in populations with the highest incidence, whereas a female bias was observed in the lowest risk populations (non-European origin), due to various factors [5–8].

According to the recent report from the International Diabetes Federation (IDF), a total of 600,900 children and adolescents up to 14 years old have T1D [9]. The incidence of T1D in children is increasing worldwide, with strong indications of a geographical-specific increase, with the highest rates of T1D (>5 per 100,000) found in North Africa and America [9].

Recently, a substantial increase in T1D incidence was observed [10], suggesting that multiple contributing factors must be involved in this higher incidence. Those factors include genetic and epigenetics contributors, autoimmunity, viral infections, antibiotics-mediated dysbiosis, gut microbiome composition, and lifestyle factors such as nutrition and modern diet [2,11–15]. Although certain *HLA* risk alleles are known to increase the susceptibility to T1D in children at risk, only 5% or fewer of them actually develop T1D [16], highlighting the importance of the non-genetic modifiers, in addition to other environmental factors in T1D pathogenesis [12,17,18]. While the genetic predisposition is considered

Early Nutrition and risk of Type 1 Diabetes: the role of Gut Microbiota

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Keywords: T1D, early nutrition, gut microbiota, probiotics, prebiotics, postbiotics

17 **Abstract**

18 Type 1 diabetes (T1D) appears most frequently in childhood, with an alarming increasing incidence in
19 the last decades. Although the genetic predisposition is a major risk factor, it cannot solely explain the
20 complex etiology of T1D which is still not fully understood. In this paper, we reviewed the most recent
21 findings on the role of early nutrition and the involvement of the gut microbiota in the etiopathogenesis
22 of T1D. The main conclusions that are withdrawn from the current literature regarding alleviating the
23 risk of developing T1D through nutrition are the encouragement of long-term breast-feeding for at least
24 the first 6 months of life and the avoidance of early complementary foods and gluten introduction
25 (before 4 months of age) as well as cow milk introduction before 12 months of life. These detrimental
26 feeding habits create a gut microbiota dysbiotic state that can contribute to the onset of T1D in infancy.
27 Finally, we discussed the possibility to introduce probiotics, prebiotics and postbiotics in the prevention
28 of T1D.

29

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CLINICAL AND TRANSLATIONAL MEDICINE Open Access

WILEY

RESEARCH ARTICLE

Definition of erythroid cell-positive blood transcriptome phenotypes associated with severe respiratory syncytial virus infection

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Abstract

Biomarkers to assess the risk of developing severe respiratory syncytial virus (RSV) infection are needed. We conducted a meta-analysis of 490 unique profiles from six public RSV blood transcriptome datasets. A repertoire of 382 well-characterized transcriptional modules was used to define dominant host responses to RSV infection. The consolidated RSV cohort was stratified according to four traits: "interferon response" (IFN), "neutrophil-driven inflammation" (Infl), "cell cycle" (CC), and "erythrocytes" (Ery). We identified eight prevalent blood transcriptome phenotypes, of which three Ery+ phenotypes comprised higher proportions of patients requiring intensive care. This finding confirms on a larger scale data from one of our earlier reports describing an association between an erythrocyte signature and RSV disease severity. Further contextual interpretation made it possible to associate this signature with immunosuppressive states (late stage cancer, pharmacological immunosuppression), and with a population of fetal glycophorin A+ erythroid precursors. Furthermore, we posit that this erythrocyte cell signature may be linked to a population of immunosuppressive erythroid cells previously described in the literature, and that overabundance of this cell population in RSV patients may underlie progression to severe disease. These findings outline potential priority areas for biomarker development and investigations into the immune biology of RSV infection. The approach that we developed and employed here should also permit to delineate prevalent blood transcriptome phenotypes in other settings.

CLINICAL ARTICLE

Validation of a statistical toolkit based on the ten-group Robson Classification of cesarean delivery

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KEYWORDS

Cesarean delivery rate; Robson Classification; Ten-group Robson Classification; Toolkit; WHO statement on cesarean section rates; World Health Organization.

SYNOPSIS

The toolkit provided additional data for each Robson group, and successfully accommodated majority (94.8%) of the study cases ending up in Cesarean section.

ABSTRACT

Objective:

To assess the validity of a statistical toolkit based on the original ten-group Robson Classification of cesarean delivery.

Methods:

A retrospective pilot study at Al Wakra Hospital in Doha, Qatar, was conducted from June 1 to June 30, 2017, involving consecutive women undergoing cesarean delivery, using a three-stage approach. A Microsoft Excel-based toolkit was developed by dividing each of the 10 groups of the original Robson Classification into clinical groups and subgroups. A critical review of the toolkit was then undertaken by four independent physicians based on different potential clinical scenarios that could culminate in cesarean delivery in each Robson group. The toolkit was validated by populating it with the data of the cesarean deliveries of the women involved in the study.

Results:

The data from cesarean deliveries of 153 women were utilized in the pilot study. The toolkit catered for and successfully accommodated 94.8% of the cases without any need for change. The remaining 5.2% of cases required additional adjustments in the toolkit. The toolkit provided instant access to important data about the labor and delivery which could be used for audit and research purposes and ultimately for service improvement.

Conclusion:

The toolkit significantly improved the clinical efficacy of the Robson Classification as a potential statistical tool for comparison of local and international data.

1 INTRODUCTION

The 2010 world health report [1] showed that an estimated 6.2 million unnecessary cesarean deliveries were performed costing an estimated USD 2.32 billion as global excess cesarean delivery cost, against USD 432 million as global needed cesarean cost**.**

Rising cesarean delivery rate (CDR) is a major global issue [2, 3]. Whereas it may save the life of a mother and her baby if medically indicated, its overuse can have potentially negative implications for the mother, the baby and the service provider [4, 5]. A disparity in supply and demand between the resource-rich and resource-poor world further complicated the situation with the resource poor countries struggling to cope with the additional costs of otherwise medically un-necessary Cesarean sections. In order to devise a workable solution, uniform and valid data are required worldwide regarding CDR and its contributing factors.

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ORIGINAL ARTICLE: OUTCOMES

PEDIATRIC PULMONOLOGY WILEY

A comparison between high-flow nasal cannula and noninvasive ventilation in the management of infants and young children with acute bronchiolitis in the PICU

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Abstract

Background: Different modalities of noninvasive respiratory support have been recommended for the management of acute bronchiolitis in the pediatric intensive care unit (PICU). High-flow nasal cannula (HFNC) is among the new modalities that have been widely used in the last decade.

Methods: This is a retrospective study involving infants and young children between the ages of 1 month and 2 years during the respiratory season of 2016-2017 (October-May). We compared the failure rate of HFNC with the failure rates of bi-level positive airway pressure (BiPAP) vs continuous positive airway pressure (CPAP) in the management of acute bronchiolitis in the PICU. Failure was defined as a change to another respiratory support modality or endotracheal intubation and mechanical ventilation.

Results: One hundred thirty-seven patients met the inclusion criteria, of which 77 patients needed HFNC, 10 needed CPAP, and 50 were on BiPAP. Among baseline characteristics, there were significant variations in age among the three groups. HFNC had a higher failure rate compared with the other two noninvasive ventilation modalities (50.6% for HFNC [n = 39 out of 77] vs 0% for CPAP [n = 0 out of 10] vs 8% for BiPAP [n = 4 out of 50], $P < .01$). Among the 39 patients who failed HFNC, 90% were successfully shifted to BiPAP and weaned off later, whereas the other 4 were intubated and required mechanical ventilation. However, all four patients who failed BiPAP were intubated and mechanically ventilated. No respiratory complications or mortalities were reported in the three groups. No differences were observed among the three groups in terms of the lengths of PICU or hospital stays.

Conclusions: We observed a higher failure rate of HFNC compared with BiPAP or CPAP in the management of infants and children with acute bronchiolitis in the PICU. Further prospective randomized trials are recommended to confirm this finding.

KEYWORDS

bronchiolitis, high-flow nasal cannula, noninvasive ventilation, pediatric intensive care unit

Abbreviations: AAP, American Academy of Pediatrics; BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; HGH, Hamad General Hospital; NIV, noninvasive ventilation; PEEP, positive end expiratory pressure; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; RV, human rhinovirus; V-Q, ventilation perfusion.

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Trials

STUDY PROTOCOL Open Access

Acute severe paediatric asthma: study protocol for the development of a core outcome set, a Pediatric Emergency Reserarch Networks (PERN) study

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Abstract

Background: Acute severe childhood asthma is an infrequent, but potentially life-threatening emergency condition. There is a wide range of different approaches to this condition, with very little supporting evidence, leading to significant variation in practice. To improve knowledge in this area, there must first be consensus on how to conduct clinical trials, so that valid comparisons can be made between future studies. We have formed an international working group comprising paediatricians and emergency physicians from North America, Europe, Asia, the Middle East, Africa, South America, Central America, Australasia and the United Kingdom.

Methods/design: A 5-stage approach will be used: (1) a comprehensive list of outcomes relevant to stakeholders will be compiled through systematic reviews and qualitative interviews with patients, families, and clinicians; (2) Delphi methodology will be applied to reduce the comprehensive list to a core outcome set; (3) we will review current clinical practice guidelines, existing clinical trials, and literature on bedside assessment of asthma severity. We will then identify practice differences in tne clinical assessment of asthma severity, and determine whether further prospective work is needed to achieve agreement on inclusion criteria for clinical trials in acute paediatric asthma in the emergency department (ED) setting; (4) a retrospective chart review in Australia and New Zealand will identify the incidence of serious clinical complications such as intubation, ICU admission, and death in children hospitalized with acute severe asthma. Understanding the incidence of such outcomes will allow us to understand how common (and therefore how feasible) particular outcomes are in asthma in the ED setting; and finally (5) a meeting of the Pediatric Emergency Research Networks (PERN) asthma working group will be held, with invitation of other clinicians interested in acute asthma research, and patients/families. The group will be asked to achieve consensus on a core set of outcomes and to make recommendations for the conduct of clinical trials in acute
(Continued on next page)

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MDPI

Review

Claudin-1, A Double-Edged Sword in Cancer

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Abstract: Claudins, a group of membrane proteins involved in the formation of tight junctions, are mainly found in endothelial or epithelial cells. These proteins have attracted much attention in recent years and have been implicated and studied in a multitude of diseases. Claudins not only regulate paracellular transepithelial/transendothelial transport but are also critical for cell growth and differentiation. Not only tissue-specific but the differential expression in malignant tumors is also the focus of claudin-related research. In addition to up- or down-regulation, claudin proteins also undergo delocalization, which plays a vital role in tumor invasion and aggressiveness. Claudin (CLDN)-1 is the most-studied claudin in cancers and to date, its role as either a tumor promoter or suppressor (or both) is not established. In some cancers, lower expression of CLDN-1 is shown to be associated with cancer progression and invasion, while in others, loss of CLDN-1 improves the patient survival. Another topic of discussion regarding the significance of CLDN-1 is its localization (nuclear or cytoplasmic vs perijunctional) in diseased states. This article reviews the evidence regarding CLDN-1 in cancers either as a tumor promoter or suppressor from the literature and we also review the literature regarding the pattern of CLDN-1 distribution in different cancers, focusing on whether this localization is associated with tumor aggressiveness. Furthermore, we utilized expression data from The Cancer Genome Atlas (TCGA) to investigate the association between CLDN-1 expression and overall survival (OS) in different cancer types. We also used TCGA data to compare CLDN-1 expression in normal and tumor tissues. Additionally, a pathway interaction analysis was performed to investigate the interaction of CLDN-1 with other proteins and as a future therapeutic target.

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ORIGINAL ARTICLE

10-Day structured initiation protocol from multiple daily injection to hybrid closed-loop system in children and adolescents with type 1 diabetes

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Abstract

Aim The aim of this study was to evaluate the 10-day initiation protocol for MiniMed 670G hybrid closed-loop (HCL) system in individuals with type 1 diabetes on multiple daily injection (MDI) in achieving desirable glycemic control.

Methods An open-label single-arm, single-center, clinical investigation in children aged 7–18 years on MDI following a structured protocol: 2 days, HCL system assessment; 5 days, HCL system training (2-h sessions on 5 consecutive days with groups of 3–5 participants and families); 3 days, Manual Mode use of HCL system; 84 days, Auto Mode use of the HCL system, cumulating in 10 days from MDI to Auto Mode activation.

Results A total of 30 children (age 10.24 ± 2.6 years) were enrolled in the study, and all completed the planned 84 days on Auto Mode. The participants used the sensor for a median of 92% of the time and spent a median of 89% in Auto Mode. The mean HbA1c decreased from 8.2 ± 1.4% (66 ± 15.3 mmol/mol) at baseline to 6.7 ± 0.5% (50 ± 5.5 mmol/mol) at the end of the study ($p = 0.017$). Time in range (70–180 mg/dL) increased from 46.9 ± 18.5% at baseline to 75.6 ± 6.9% in Auto Mode ($p < 0.001$). This was achieved while spending 2.8% of the time below 70 mg/dL and without any severe hypoglycemia or DKA.

Conclusion Children and adolescents with type 1 diabetes on MDI therapy can successfully initiate the HCL system, using a concise structured 10-day protocol.

Keywords Hybrid closed-loop system · Multiple daily injection · Protocol · Type 1 diabetes

Introduction

Improving glycemic control in individuals with type 1 diabetes without increasing risk of hypoglycemia is a challenge for both individuals and health providers. Intensive insulin treatment in combination with regular self-monitoring of blood glucose (SMBG) is the standard of care for individuals with type 1 diabetes. Nevertheless, the majority of individuals fail to achieve optimal glycemic control with HbA1c below 7% (53 mmol/mol) [1]. Monitoring glucose levels from the interstitial fluid, either continuously with real-time continuous glucose monitoring (CGM) or intermittently, by scanned continuous glucose monitoring (isCGM), demonstrated better diabetes management for children and adolescents with diabetes [2].

Recent technological advances in diabetes treatment have integrated continuous subcutaneous insulin delivery (CSII) with CGM, where insulin delivery can be automated by sensor glucose (SG)-driven algorithms. Insulin delivery suspension when reaching a low glucose level [3, 4] or in prediction of a low glucose level [5, 6] has demonstrated significant reduction in hypoglycemia exposure.

Further development in technology of integrated closed-loop systems provides algorithm-derived automated adjustment of insulin delivery to address both hypoglycemia and hyperglycemia [7–11].

The first approved hybrid closed-loop (HCL) system [12] is the MiniMed 670G system (Medtronic Diabetes, Northridge, CA, USA) for children above 7 years old [13],

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Clinical Investigation

CLINICAL INVESTIGATION

A randomised double-blind dose–response study of weight-adjusted infusions of norepinephrine for preventing hypotension during combined spinal–epidural anaesthesia for Caesarean delivery

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†F. Fu and F. Xiao contributed equally to this study.

Abstract

Background: Norepinephrine infusion has been suggested as an effective method for preventing hypotension during spinal anaesthesia for Caesarean delivery. However, optimal dosing regimens for norepinephrine have not been well established. This study aimed to determine the dose–response characteristics of a weight-adjusted fixed-rate infusion of norepinephrine to prevent hypotension during neuraxial anaesthesia for Caesarean delivery.

Methods: In a double-blind, randomised controlled trial, 80 parturients having elective Caesarean delivery received a prophylactic norepinephrine infusion at 0.025 μg kg^{-1} min^{-1} (Group N1), 0.05 μg kg^{-1} min^{-1} (Group N2), 0.075 μg kg^{-1} min^{-1} (Group N3), or 0.10 μg kg^{-1} min^{-1} (Group N4), starting immediately after induction of combined spinal–epidural anaesthesia. The primary outcome was non-occurrence of hypotension, defined as a decrease in systolic arterial pressure ≥20% below baseline value or to ≤90 mm Hg, before delivery. Values for 50% effective dose (ED_{50}) and ED_{90} were calculated using probit regression.

Results: The incidence of hypotension was 11/20 (55%), 6/20 (30%), 2/20 (10%), and 1/20 (5%) in Groups N1, N2, N3, and N4, respectively ($P<0.0001$). The ED_{50} and ED_{90} (95% confidence interval) of norepinephrine infusions for preventing hypotension were 0.029 (−0.002 to 0.043) and 0.080 (0.065–0.116) μg kg^{-1} min^{-1}, respectively. The incidence of reactive hypertension increased with increasing norepinephrine dose ($P=0.002$). Other adverse effects were similar among groups.

Conclusions: Under the conditions of this study, an infusion of norepinephrine 0.08 μg kg^{-1} min^{-1} was effective for preventing hypotension in 90% of patients. This information should provide a guide for initiating norepinephrine infusions.

Clinical trial registration: ChiCTR1900022322 at the Chinese Clinical Trial Registry (http://www.chictr.org.cn/enindex.aspx).

Keywords: Caesarean delivery; hypotension; infusion; norepinephrine; obstetric anaesthesia; prevention; spinal anaesthesia

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Amputation Versus Limb Reconstruction for Fibula Hemimelia: A Meta-analysis

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Purpose: Fibula hemimelia is the most common congenital deficiency of long bones. Primary treatment options include amputation with prosthetic fitting or limb reconstruction. The aim of our study was to conduct a systematic review comparing amputation with limb reconstruction for fibula hemimelia.

Methods: MEDLINE, EMBASE, Web of Science, Elsevier Scopus, and the Cochrane Registry of Clinical Trials were searched from 1951 to 2019 for studies that evaluated amputation versus limb reconstruction for fibula hemimelia. Random effect models were utilized for the meta-analytic comparisons of amputation versus limb reconstruction for patient satisfaction and surgical complications. Descriptive, quantitative, and qualitative data were extracted.

Results: Seven retrospective cohort studies were eligible for the meta-analysis, with a total of 169 fibula hemimelia cases. Amputation resulted in an odds ratio of 6.8 (95% confidence interval: 2.4, 19.2) when compared with limb reconstruction in terms of patient satisfaction. Furthermore, limb reconstruction was found to have an odds ratio of 28 (95% confidence interval: 7.8, 100.3) for complications. The total surgical complication rates in the amputation and limb reconstruction groups were 0.2 and 1.2 complications per limb. The rate of surgical procedures per patient was 1.5 and 4.2 for amputation and limb reconstruction, respectively.

Conclusions: The cumulative evidence at present indicates better patient satisfaction with less surgical complications and less number of procedures with amputation for fibula hemimelia when compared with limb reconstruction. Absence of uniform protocols make it difficult to compare results accurately.

Level of Evidence: Level III—therapeutic.

Key Words: fibula, hemimelia, amputation, reconstruction, meta-analysis

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A.E.: data collection, manuscript preparation. A.F.A: statistical analysis, manuscript preparation. A.H. and J.E.H.: manuscript preparation. T.I.: study design, manuscript preparation.

J.E.H. (Consultant): Smith and Nephew, Orthofix, OrthoPaediatrics, OrthoSpin, Wishbone, NuVasive. The remaining authors declare no conflicts of interest.

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Fibula hemimelia consists of a spectrum of anomalies ranging from fibula shortening to complete absence of the fibula.[1] It is one of the most common congenital deficiency of long bones with an incidence of 7 to 20 per million live births.[2–5] The etiology is poorly understood. However, it is theorized to be a consequence of a vascular or mechanical insult to the extremity bud in utero.[6] The condition usually affects the entire limb and is not only limited to the fibula. It is associated with anteromedial tibial bowing, absent lateral rays of the foot, tarsal coalition, ball and socket ankle joint, cruciate ligament deficient knee, proximal femoral focal deficiency, and developmental dysplasia of the hip.[7,8]

Several classification systems have been proposed for fibula hemimelia. The Achterman and Kalamchi[1] classification focuses on the morphology of the fibula. The Birch classification takes into account whether the foot is reconstructable.[9] The Paley classification considers the foot and ankle deformities as the 2 important factors in determining treatment of fibula hemimelia.[10]

The treatment for fibula hemimelia either consists of amputation or limb reconstruction.[11] Amputation in the form of foot ablation and prosthetic fitting has been reported as a successful method in the treatment of fibula hemimelia.[1,12,13] Likewise, limb reconstruction procedures consisting of limb lengthening and deformity correction have obtained favorable results through external fixation, and foot and ankle reconstruction.[10,14–16] The literature has shown mixed results for which treatment is superior with regards to patient satisfaction. Studies seem to contradict other studies, with possible author bias. Amputation has been reported to have better satisfaction.[11,17] More recent reports have found no difference, which might be explained with the advancements in limb reconstruction techniques.[15,18] Therefore, the aim of this

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The learning curve for robotic-assisted pyeloplasty in children: Our initial experience from a single center

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Free PMC article

Abstract

Background: Robotic-assisted pyeloplasty surgery has become the preferred approach of ureteropelvic junction obstruction (UPJO) in pediatrics. However, to our knowledge, there is limited data on the learning curve for robotic-assisted pyeloplasty in children and no similar study from Saudi Arabia.

Aims: The objective of the study was to evaluate the progression of the surgical team performing robotic-assisted laparoscopic pyeloplasty (RALP) and to assess the feasibility of the RALP in children, since it is having been recently started in the Kingdom.

Settings and design: Retrospective charts and surgical videos review at the tertiary care centre.

Subjects and methods: After approval from the internal review board (IRB), we reviewed the surgical video recording of the RALP procedure of 15 patients presented with UPJO from January 2016 to October 2017. Statistical analysis was done for the variables includes dissection time, pyelotomy, anastomosis on both sides, and total surgery time and calculated in minutes. Renal ultrasound reviewed to assess any change in grade.

Results: Fifteen patients with UPJO underwent RALP. Of 15 cases, nine were primary and six cases as secondary UPJO. The median age was 8 (3-15) years. Out of 15 cases, 13 and 2 patients diagnosed as Society for Fetal Urology grades of 4 and 3, respectively. Total operative time was prolonged in secondary group as compared to primary pyeloplasty group (mean [standard deviation (SD)]: 166.3 [35.1], range: 125-223, $P = 0.0028$ versus mean (SD): 149.17 (30.4), range: (114-207), $P = 0.0008$). The success rate was 100% in primary and 84% in secondary cases. The median length of follow-up was 12.0 (7.0-18.0) and 10.0 (8.0-12.5) months in primary and secondary cases, respectively. The overall complication rate was 13% (2/15) (Clavien grade: 1-2).

Conclusions: The evaluation of the learning curve of RALP for this group of patients concluded that total operative time for RALP, performed by the pediatric urology team, steadily decreased with collective surgical experience.

Keywords: Learning curve; pediatric; pyeloplasty; robotics.

JAMA Pediatrics | Original Investigation

Sustained Inflation vs Standard Resuscitation for Preterm Infants
A Systematic Review and Meta-analysis

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IMPORTANCE Most preterm infants require respiratory support to establish lung aeration after birth. Intermittent positive pressure ventilation and continuous positive airway pressure are standard therapies. An initial sustained inflation (inflation time >5 seconds) is a widely practiced alternative strategy.

OBJECTIVE To conduct a systematic review and meta-analysis of sustained inflation vs intermittent positive pressure ventilation and continuous positive airway pressure for the prevention of hospital mortality and morbidity for preterm infants.

DATA SOURCES MEDLINE (through PubMed), Embase, the Cumulative Index of Nursing and Allied Health Literature, and the Cochrane Central Register of Controlled Trials were searched through June 24, 2019.

STUDY SELECTION Randomized clinical trials of preterm infants born at less than 37 weeks' gestation that compared sustained inflation (inflation time >5 seconds) vs standard resuscitation with either intermittent positive pressure ventilation or continuous positive airway pressure were included. Studies including other cointerventions were excluded.

DATA EXTRACTION AND SYNTHESIS Two reviewers assessed the risk of bias of included studies. Meta-analysis of pooled outcome data used a fixed-effects model specific to rarer events. Subgroups were based on gestational age and study design (rescue vs prophylactic sustained inflation).

MAIN OUTCOMES AND MEASURES Death before hospital discharge.

RESULTS Nine studies recruiting 1406 infants met inclusion criteria. Death before hospital discharge occurred in 85 of 736 infants (11.5%) treated with sustained inflation and 62 of 670 infants (9.3%) who received standard therapy for a risk difference of 3.6% (95% CI, −0.7% to 7.9%). Although analysis of the primary outcome identified important heterogeneity based on gestational age subgroups, the 95% CI for the risk difference included 0 for each individual gestational age subgroup. There was no difference in the primary outcome between subgroups based on study design. Sustained inflation was associated with increased risk of death in the first 2 days after birth (risk difference, 3.1%; 95% CI, 0.9%-5.3%). No differences in the risk of other secondary outcomes were identified. The quality-of-evidence assessment was low owing to risk of bias and imprecision.

CONCLUSIONS AND RELEVANCE There was no difference in the risk of the primary outcome of death before hospital discharge, and there was no evidence of efficacy for sustained inflation to prevent secondary outcomes. These findings do not support the routine use of sustained inflation for preterm infants after birth.

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Supplemental content

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Epidemiology and Infection

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Comparison of routine field epidemiology and whole genome sequencing to identify tuberculosis transmission in a remote setting

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Abstract

Yukon Territory (YT) is a remote region in northern Canada with ongoing spread of tuberculosis (TB). To explore the utility of whole genome sequencing (WGS) for TB surveillance and monitoring in a setting with detailed contact tracing and interview data, we used a mixed-methods approach. Our analysis included all culture-confirmed cases in YT (2005–2014) and incorporated data from 24-locus Mycobacterial Interspersed Repetitive Units-Variable Number of Tandem Repeats (MIRU-VNTR) genotyping, WGS and contact tracing. We compared field-based (contact investigation (CI) data + MIRU-VNTR) and genomic-based (WGS + MIRU-VNTR + basic case data) investigations to identify the most likely source of each person's TB and assessed the knowledge, attitudes and practices of programme personnel around genotyping and genomics using online, multiple-choice surveys ($n = 4$) and an in-person group interview ($n = 5$). Field- and genomics-based approaches agreed for 26 of 32 (81%) cases on likely location of TB acquisition. There was less agreement in the identification of specific source cases (13/22 or 59% of cases). Single-locus MIRU-VNTR variants and limited genetic diversity complicated the analysis. Qualitative data indicated that participants viewed genomic epidemiology as a useful tool to streamline investigations, particularly in differentiating latent TB reactivation from the recent transmission. Based on this, genomic data could be used to enhance CIs, focus resources, target interventions and aid in TB programme evaluation.

Introduction

Tuberculosis (TB) remains an important public health concern in Canada, particularly in Northern rural and remote areas where the endemic spread of TB is commonplace [1, 2]. Understanding the patterns of transmission in these settings is an integral part of developing evidence-based prevention and care strategies, and prioritizing public health resources. This includes understanding the burden of disease resulting from recent local transmission *vs.* reactivation of historic latent TB infection (LTBI), as well as understanding the nature of recent transmission. This latter point is critical for improving TB services in a region – understanding the clinical, demographic and/or epidemiological factors driving TB transmission is vital to developing informed prevention programmes, screening activities and contact investigations (CIs), and ultimately preventing the continued spread of TB.

Field-based epidemiologic investigation is used to identify both infected contacts, secondary active cases and possible sources of a given case, and for decades was the only means to detect transmission [3]. In recent years, a combination of field and molecular epidemiology has been used in many settings – contact data collected through patient interviews may reveal the potential links between cases, while genotyping techniques identify related *Mycobacterium tuberculosis* (*Mtb*) isolates and can help to confirm or refute a potential transmission event. Now, several studies have shown that whole genome sequencing (WGS) yields more accurate transmission reconstructions than the approaches based on genotypic data [4–8].

Despite global interest in WGS as a tool for understanding TB epidemiology and a continuously expanding dataset of publicly available *Mtb* genomes, there are gaps in our understanding of how useful this new technique is. There are technical questions around how consistent *Mtb* mutation rates are, particularly during latent infection *vs.* active disease [9, 10] and from human host to human host [11, 12], as well as around how to identify transmission-informative variants

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ESPR

Intracavitary contrast-enhanced ultrasonography in children: review with procedural recommendations and clinical applications from the European Society of Paediatric Radiology abdominal imaging task force

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Abstract

Contrast-enhanced ultrasonography (US) has become an important supplementary tool in many clinical applications in children. Contrast-enhanced voiding urosonography and intravenous US contrast agents have proved useful in routine clinical practice. Other applications of intracavitary contrast-enhanced US, particularly in children, have not been widely investigated but could serve as a practical and radiation-free problem-solver in several clinical settings. Intracavitary contrast-enhanced US is a real-time imaging modality similar to fluoroscopy with iodinated contrast agent. The US contrast agent solution is administered into physiological or non-physiological body cavities. There is no definitive list of established indications for intracavitary US contrast agent application. However, intracavitary contrast-enhanced US can be used for many clinical applications. It offers excellent real-time spatial resolution and allows for a more accurate delineation of the cavity anatomy, including the internal architecture of complex collections and possible communications within the cavity or with the surrounding structures through fistulous tracts. It can provide valuable information related to the insertion of catheters and tubes, and identify related complications such as confirming the position and patency of a catheter and

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TOPIC PAPER

Fertility and sexuality issues in congenital lifelong urology patients: male aspects

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Abstract

Purpose To review existing literature about fertility and sexuality of boys born with complex congenital genitourinary anomalies.

Methods A Pubmed review was performed in December 2018 to identify the most relevant original manuscripts regarding male complex congenital conditions affecting the urogenital system in male patients including spina bifida (SB), bladder exstrophy–epispadias complex (BEEC) and hypospadias. A comprehensive review was drafted exploring sexual dysfunction from a medical, psychosexual, surgical and reproductive point of view during transition from childhood (or adolescence) to adulthood.

Results About 75% of men with SB have erectile dysfunction (ED) (Gamé et al. in Urology 67(3):566–570, 2006; Diamond et al. in 58(4):434–435, 1986). Most SB patients have impaired sexual development mainly due to diminished self-esteem, dependence on caregivers and lack of privacy (Blum et al. in Pediatrics 88(2):280–285, 1991). Men with BEEC have fewer intimate relationships than women because of the greater difficulties with issues regarding their genitalia and sexual activities (Deans et al. in Am J Obstet Gynecol 206(6):496.e1–496.e6, 2012). However, a good quality of life is achievable with the effective use of coping strategies (Deng et al. in Transl Androl Urol 7:941, 2018; Rikken et al. in BMC Womens Health 18(1):163, 2018; Friedler et al. in Reprod Biomed Online 32(1):54–61, 2016). Chordee occurs in 25% of all hypospadias patients. More severe hypospadias is related to a greater risk for complications. The long-term sexual quality of life (QoL) in men who underwent hypospadias surgery is influenced by a lot of factors. Therefore, an interactive and dynamic biopsychosocial model of sexual QoL was proposed.

Conclusions The care of patients with congenital urologic conditions becomes a challenge especially in the period of 'transition'. The goal of follow-up is a holistic management viewed from a medical, psychosexual, surgical end reproductive point. All patients should be asked for specific urinary, fecal or sexual concerns.

Keywords Spina bifida · Bladder-exstrophy–epispadias complex · Hypospadias · Fertility · Sexuality

Abbreviations

AYA	Adolescents and young adults
BE	Bladder exstrophy
BEEC	Bladder exstrophy–epispadias complex
DSD	Disorders of sexual development
ED	Erectile dysfunction
SB	Spina bifida
VC	Ventral curvature

Introduction

As children with congenital urologic conditions reach adulthood, aspects of care such as in sexual and reproductive function will become more important. The period where the children evolve into adolescents and young adults (AYA) is a challenge for the patient and his/her caregiver and is called 'transition' [1]. Patients with congenital urologic conditions have a desire to be 'normal'. In many cases, 'normal' means

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Original Research

Outcome of patients with stage IV high-risk Wilms tumour treated according to the SIOP2001 protocol: A report of the SIOP Renal Tumour Study Group

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KEYWORDS
Wilms;
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TP53

Abstract ***Introduction:*** High-risk (HR) metastatic (stage IV) Wilms tumours (WTs) have a particular poor outcome.
Methods: Here, we report the results of HR (diffuse anaplastic [DA] or blastemal type [BT]) stage IV WT treated patients according to the HR arm in the SIOP2001 prospective study.
Results: From January 2002 to August 2014, 3559 patients with WT were included in the SIOP2001 trial. Among the 525 patients (15%) with metastatic WT, 74 (14%) had stage IV HR-WT. The median age at diagnosis was 5.5 years (range: 1.4–18.3). Thirty-four patients (47%) had BT-WT and 40 (53%) had DA-WT. Five-year event-free survival rates were 44 ± 17% and 28 ± 15% for BT-WT and DA-WT, respectively ($p = 0.09$). Five-year overall survival rates were 53 ± 17% and 29 ± 16% for BT-WT and DA-WT, respectively ($p = 0.03$). Metastatic complete response after preoperative treatment was significantly associated with outcome in univariate and multivariate analyses (hazards ratio = 0.3; $p = 0.01$). Postoperative radiotherapy of metastatic sites might also be beneficial. Forty-three of 74 patients experienced a relapse or progression predominantly in the lungs (80%). The median time to relapse/progression after diagnosis was 7.3 months (range: 1.6–33.3) and 4.9 months (range: 0.7–28.4) for BT-WT and DA-WT, respectively ($p = 0.67$). This is the first prospective evidence of inferior survival of stage IV BT-WT as compared with historical intermediate-risk WT. Survival of patients with stage IV DA-WT has not improved compared to the previous SIOP93-01 study.
Conclusion: These results call for new treatment approaches for patients with HR stage IV WT.

1. Introduction

The International Society of Pediatric Oncology (SIOP) strategy for Wilms tumour (WT) is tailored to the patient based on overall tumour stage at diagnosis (localised, metastatic (stage IV) or bilateral (stage V) disease), histological risk group and local stage of the primary tumour after preoperative chemotherapy and nephrectomy (stage I–III) and response to preoperative treatment of metastatic or bilateral disease [1]. With this approach, survival has risen to a current cure rate of more than 90% for patients with localised disease and intermediate-risk or low-risk (IR/LR) histology [2]. Stage IV disease occurs in 12–20% of patients at diagnosis [3–5]. The survival rates of stage IV patients reach 90% in case of IR/LR histology and metastatic complete response (m-CR) after preoperative chemotherapy and surgery. However, almost 20% of children with metastatic WT at diagnosis die [3]. The negative impact of diffuse anaplasia (DA) on survival has been widely demonstrated [6–9]. In patients with metastatic disease enrolled in the previous SIOP93-01 trial, DA-WT had been associated with a lower 5-year event-free survival (EFS) compared with IR/LR histology (33.3% vs 76.8%, $p < 0.001$; hazard ratio, 3.6; 95% confidence interval [CI], 1.7 to 7.6), thus being confirmed as one of the most important prognostic factors in WT [3]. The blastemal subtype (blastemal-type WT [BT-WT]) has been associated with poor outcome based on SIOP93-01 results [10,11] and therefore defined and treated as 'high-risk' (HR) histology in the prospective international SIOP2001 study [12]. A recent report showed improved survival for localised BT-WT as a consequence of intensified treatment [13]. We thus analysed whether this effect can also be documented in the stage IV cohort and present the outcome of patients with stage IV HR (DA- and BT-WT) WT treated according to the SIOP2001 protocol with an intensified postoperative schedule.

2. Patients and methods

2.1. Patients

Patients with metastatic BT- and DA-WT were prospectively included in the SIOP2001 study from 2002 to 2014. Clinical data were retrieved from the SIOP2001 database and through national coordinators and/or local centres. Written informed consent was obtained

cells

MDPI

Review

Urine as a Main Effector in Urological Tissue Engineering—A Double-Edged Sword

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Abstract: In order to reconstruct injured urinary tract tissues, biodegradable scaffolds with autologous seeded cells are explored in this work. However, when cells are obtained via biopsy from individuals who have damaged organs due to infection, congenital disorders, or cancer, this can result in unhealthy engineered cells and donor site morbidity. Thus, neo-organ construction through an alternative cell source might be useful. Significant advancements in the isolation and utilization of urine-derived stem cells have provided opportunities for this less invasive, limitless, and versatile source of cells to be employed in urologic tissue-engineered replacement. These cells have a high potential to differentiate into urothelial and smooth muscle cells. However, urinary tract reconstruction via tissue engineering is peculiar as it takes place in a milieu of urine that imposes certain risks on the implanted cells and scaffolds as a result of the highly cytotoxic nature of urine and its detrimental effect on both growth and differentiation of these cells. Both of these projections should be tackled thoughtfully when designing a suitable approach for repairing urinary tract defects and applying the needful precautions is vital.

Keywords: urethra; tissue engineering; cytotoxicity; urinary reconstruction; urothelial cells

1. Clinical Need

The urinary tract transports urine and stores it after kidney filtration. The urinary bladder is the principal reservoir for urine while both ureters and urethra play the role of passageways. The unique feature of bladder repetitive contraction and expansion, together with a sound barrier of urine and potency to bear the pressure of urine make the bladder a complex organ. On the other hand, urethra and ureters are less complex but are still under radial pressure and shear strain of fluid during the transit of urine. The walls of the lower urinary tract are lined by urothelium, a multilayered epithelial lining which protects stroma against urine leak [1,2].

Several congenital and acquired pathologies can affect the human urinary tract, such as hypospadias, strictures, fistulas, trauma, and cancer. As a result, various reconstructive approaches have been utilized to restore the function of the urinary tract in these circumstances. However, certain factors make this process very complicated for surgeons, including poor quality of local tissues, which would mandate extra tissues for replacement. Additional sources of tissues, among others, include genital skin [3], buccal mucosa [4], and lingual mucosa [5]. However, significant complications, donor site morbidity, and limited tissue quantities that can be obtained from these

Accuracy of cerebrospinal fluid ferritin for purulent meningitis

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ABSTRACT

Objective To evaluate the use of cerebrospinal fluid (CSF) ferritin levels in the diagnosis of purulent meningitis (PM).

Method We studied 81 children between 28 days and 12 years of age who presented with clinical suspicion of meningitis to the emergency department. CSF ferritin levels were measured and compared between diagnostic groups (PM, aseptic meningitis (AM) and no meningitis).

Results The median age was 24 (IQR 8–69) months. There were 32 patients with AM (39%), 23 with PM (28%) and 26 with no meningitis (32%). Median CSF ferritin was 4.2 ng/mL (IQR 3.0–6.5), 52.9 ng/mL (IQR 30.7–103 ng/mL) and 2.4 ng/mL (IQR 2–4), respectively. CSF ferritin was higher in children with PM compared with AM (p<0.001) or no meningitis (p<0.001). There was no difference between AM and no meningitis.

Conclusion CSF ferritin may be a useful biomarker to discriminate PM in children with clinical symptoms of this disease.

What is already known on this topic?

- Purulent meningitis is an important cause of mortality. Diagnosis through cerebrospinal fluid (CSF) may initially be difficult.
- The presumptive diagnosis by CSF analysis is limited and the result may be inconclusive in some cases.
- Ferritin is a promising biomarker increasingly studied in acute infectious diseases.

What this study adds?

- Ferritin levels are elevated in the CSF of children with purulent meningitis.
- CSF ferritin has a good discrimination for the diagnosis of purulent meningitis and may be useful as a screening or adjunctive test for meningitis.

INTRODUCTION

Purulent meningitis (PM) is an important cause of child morbidity and mortality. Early initiation of treatment is critical, but establishing a definitive diagnosis is difficult.[1 2] The gold standard test for the diagnosis of PM is bacterial culture of cerebrospinal fluid (CSF). However, sensitivity is usually low and it requires at least 24–48 hours for definitive results. Presumptive diagnosis is made using CSF analysis (cell count and differential, glucose and protein, and Gram stains), but accuracy of these tests is limited.[3 4] CSF is often inconclusive (or appears normal) in the more fulminant presentations of bacterial infections, as well as in more fragile population (eg, children with immunosuppression). Moreover, in underdeveloped or remote areas CSF analysis can take hours or days to be performed. A number of studies have evaluated performance of classic and new CSF markers of meningitis, but diagnosis accuracy for such devastating illness remains a concern for paediatricians.[3–5]

CSF ferritin has been studied as a possible meningitis biomarker that can be rapidly and inexpensively performed.[6–8] Ferritin is an acute phase reactant that acutely rises in serum in response to infection. If ferritin could be used as a diagnostic test for meningitis, commercially available point-of-care testing could be used for rapid diagnosis in remote areas.[9] In this study we aimed to evaluate CSF ferritin as a biomarker for the diagnosis of PM and tested performance of the cut-off ferritin values of commercially available point-of-care tests.

MATERIALS AND METHODS

We performed a cross-sectional study in two hospitals in Brazil, Hospital São Lucas da PUCRS and Hospital Universitário de Santa Maria, from 2005 to 2015. Inclusion criteria were children aged 28 days to 12 years admitted to emergency department with clinical suspicion of acute meningitis. Exclusion criteria were traumatic lumbar punctures (lumbar punctures with CSF containing more than 400 red cells x 10^6/L), malignancy, intracranial bleed, Guillain-Barré syndrome and mycobacterial or fungal infection, and previous use of antibiotics. We also excluded patients with screening for other sources of infection, with borderline cellular values in the CSF who were treated with antibiotics but had no clinical evolution compatible with meningitis.

Patients were classified into three groups according to their diagnosis: PM, aseptic meningitis (AM) and no meningitis. The classification as PM was: identification of a bacterium in the CSF and/or presence of leucocyte count >500 x 10^6/L with predominance of neutrophils, protein >100 mg/dL

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ORIGINAL RESEARCH

"Double-Lumen Valve-Controlled Intra-Operative Pyeloplasty Stent (VIPs)": A New Technology for Post-Pyeloplasty Stenting – Proof of Concept Study in a Preclinical Large Animal Model

This article was published in the following Dove Press journal:
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Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/T8AmXn1SMow

Background: Pyeloplasty is a common surgical operation with a high success rate. However, significant challenges are to be optimized in the design of stenting systems in order to improve perioperative monitoring of urine drainage and enhance patient and family comfort through easier post-operative care.

Materials and Methods: In a preliminary study in six pigs, handling, mechanical and functional features of this stent system were tested. In our main study, six double-lumen stents (230 mm long each) and 6F/9F external diameter were implanted through the ureteric walls of six domestic pigs to allow postoperative drainage and monitoring following ureter-oureterostomy. After a 7-day survival period, monitoring with intravenous antibiotic coverage, and pain control, contrast antegrade pyelogram, under valve control, and renal ultrasonography were conducted and stents explanted and the animals were then euthanized.

Results: The double-lumen valve-controlled stent supported the healing of the neo anastomoses and helped to monitor perioperative urine drainage and perianastomotic leakage accurately. It also guided a well-controlled more informative radiological contrast-supported imaging before removal of the stents that confirmed the healing of the neo anastomotic site and no leak formation. The double-lumen system demonstrated high feasibility regarding its insertion, functionality, and removal capacities. The excellent flexibility of the individual stents allowed exact anatomically controlled implantation.

Conclusion: The double-lumen valve-controlled stent system was studied in a porcine model, which demonstrated its feasibility. Preclinical experience revealed favorable results concerning stent implantation, operability and functionality, in the perioperative management of pyeloplasty or ureteric surgery.

Keywords: pyeloplasty, stent, double lumen, animal model

Introduction

Congenital ureteropelvic junction obstruction (UPJO) necessitates surgical pyeloplasty with the construction of a new pyelo-ureteric anastomosis. Since 1949, the Anderson-Hynes pyeloplasty has been considered the gold standard for the repair of UPJO. Debate remains over whether to divert urine post-operatively or not although pyeloplasty is considered as the gold standard for the correction of the UPJO,[1] and it was first described as a stent-less procedure with proven efficacy and a high success rate which exceeds 95%. Transanastomitic stenting was thought to prevent

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Lab resource: Stem Cell Line

Derivation of a human induced pluripotent stem cell line (QBRIi007-A) from a patient carrying a homozygous intronic mutation (c.613-7T>*G*) in the *SLC2A2* gene

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A B S T R A C T

Fanconi Bickel Syndrome (FBS) is an autosomal recessive disease resulting from mutations in the *SLC2A2* gene, encoding the GLUT2. FBS patients develop diabetes mellitus. Using non-integrating Sendai virus, we generated an induced pluripotent stem cell (iPSC) line, QBRIi007-A, carrying the c.613-7 *T>G* homozygous mutation in intron 5 of the *SLC2A2* gene from a 19-year-old female with FBS and diabetes. The iPSC line was characterized for pluripotency, differentiation potential, genomic integrity, and genetic identity. This iPSC line provides a useful cell model to understand the role of GLUT2 in the disease development and to discover new drug candidates.

Resource Table

Unique stem cell line identifier	QBRIi007-A
Alternative name(s) of stem cell line	GLUT2 Mut-int iPSCs
Institution	Qatar Biomedical research institute (QBRI), Hamad Bin Khalifa University (HBKU), Qatar Foundation, Doha, Qatar
Contact information of distributor	Essam M. Abdelalim (emohamed@hbku.edu.qa)
Type of cell line	iPSC
Origin	Human
Additional origin info	Age: 19 years old Sex: Female Ethnicity: Pakistan
Cell source	Blood
Clonality	Clonal
Method of reprogramming	Integration-free Sendai virus vector contain OCT3/4, SOX2, c-MYC and KLF4
Genetic modification	YES
Type of modification	Hereditary
Associated disease	Fanconi Bickel Syndrome and diabetes mellitus
Gene/locus	Gene: *SLC2A2* Locus: 3q26.2 Mutation: c.613-7 *T>G*: IVS5-7 *T>G* in intron 5
Method of modification	N/A
Name of transgene or resistance	N/A
Inducible/constitutive system	N/A
Date archived/stock date	August 2019
Cell line repository/bank	N/A
Ethical approval	Blood samples were obtained from Sidra Medicine hospital with full informed consent. The protocol was approved by the Institutional Review Board (IRB) of Sidra Medicine (no. 1702007608) and QBRI (no. 2018-002)

1. Resource utility

Our iPSC line is derived from a patient with FBS and diabetes due to a homozygous mutation in *SLC2A2* gene. This iPSC line provides an *in vitro* model for investigating the role of GLUT2 in the pathogenesis of FBS and diabetes. Also, it can be used to develop new therapies.

2. Resource details

The *SLC2A2* gene encodes GLUT2, a low affinity facilitative glucose transporter, is expressed in pancreatic beta cells, liver, kidney and intestine (Thorens *et al.*, 1990). Several *SLC2A2* genetic defects and

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Review Article

Obsessive-compulsive disorder in children and adolescents: epidemiology, diagnosis and management

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Obsessive-compulsive disorder (OCD) can be found in about 4% of the general population and is characterized by various compulsions and obsessions that interfere with the person's quality of life from a mild to severe degree. The following discussion reflects on current concepts in this condition, including its epidemiology and etiologic underpinnings (behavioral, neurological, immunological, gastroenterological, as well as genetic). The interplay of PANS and PANDAS are included in this review. In addition, the core concepts of OCD diagnosis, differential diagnosis, and co-morbidities are considered. It is stressed that the quality of life for persons with pediatric OCD as well as for family members can be quite limited and challenged. Thus, principles of management are presented as a guide to improve the quality of life for these persons as much as possible.

Keywords: Obsessions; compulsions; diagnosis; co-morbidities; quality of life; psychological therapy; selective serotonin reuptake inhibitors

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Introduction

The presence of obsessions and compulsions with or without the obsessive-compulsive disorder (OCD) has been observed and suggested in human beings for eons of time with considerable impact on human history as well as world religions ("religious scrupulosity") (1-5). Scrupulosity focusing on morality was noted in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR that identified it as a symptom of obsessive-compulsive personality disorder (6,7). Medical attention on obsessive-compulsive traits and disorder in children and adolescents—apart from that found in adults—gradually began in the 20th century and has continued into the 21st century as well (8-11). This discussion considers the current understanding of pediatric OCD with special focus on its epidemiology, etiology, diagnosis, differential diagnosis, co-morbidities, and management (12-15).

Overview

OCD is currently identified by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) as a condition with obsessions (repeating urges or ideas that are irrational, intrusive) combined with compulsions (behaviors) interfering with the person's quality of life and often in association with other neurodevelopmental or psychiatric

[Intervention Protocol]

Probiotics for maintenance of remission in ulcerative colitis

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Editorial group: Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group.
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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To assess the efficacy of probiotics for the maintenance of remission in UC.

2. To assess the occurrence of adverse events associated with the use of probiotics for maintaining remission in UC.

[Intervention Review]

Probiotics for induction of remission in ulcerative colitis

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ABSTRACT

Background

Ulcerative colitis is an inflammatory condition affecting the colon, with an annual incidence of approximately 10 to 20 per 100,000 people. The majority of people with ulcerative colitis can be put into remission, leaving a group who do not respond to first- or second-line therapies. There is a significant proportion of people who experience adverse effects with current therapies. Consequently, new alternatives for the treatment of ulcerative colitis are constantly being sought. Probiotics are live microbial feed supplements that may beneficially affect the host by improving intestinal microbial balance, enhancing gut barrier function and improving local immune response.

Objectives

To assess the efficacy of probiotics compared with placebo or standard medical treatment (5-aminosalicylates, sulphasalazine or corticosteroids) for the induction of remission in people with active ulcerative colitis.

Search methods

We searched CENTRAL, MEDLINE, Embase, and two other databases on 31 October 2019. We contacted authors of relevant studies and manufacturers of probiotics regarding ongoing or unpublished trials that may be relevant to the review, and we searched ClinicalTrials.gov. We also searched references of trials for any additional trials.

Selection criteria

Randomised controlled trials (RCTs) investigating the effectiveness of probiotics compared to standard treatments or placebo in the induction of remission of active ulcerative colitis. We considered both adults and children, with studies reporting outcomes of clinical, endoscopic, histologic or surgical remission as defined by study authors

Data collection and analysis

Two review authors independently conducted data extraction and 'Risk of bias' assessment of included studies. We analysed data using Review Manager 5. We expressed dichotomous and continuous outcomes as risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs). We assessed the certainty of the evidence using the GRADE methodology.

Main results

In this review, we included 14 studies (865 randomised participants) that met the inclusion criteria. Twelve of the studies looked at adult participants and two studies looked at paediatric participants with mild to moderate ulcerative colitis, the average age was between 12.5 and 47.7 years. The studies compared probiotics to placebo, probiotics to 5-ASA and a combination of probiotics plus 5-ASA compared to 5-ASA alone. Seven studies used a single probiotic strain and seven used a mixture of strains. The studies ranged from two weeks to 52 weeks. The risk of bias was high for all except two studies due to allocation concealment, blinding of participants, incomplete reports of outcome data and selective reporting. This led to GRADE ratings of the evidence ranging from moderate to very low.

DR. MOHAMMED YOUSUF KARIM (Orcid ID : 0000-0003-0912-1629)

Article type : Letter to the Editor

Increased awareness of hypogammaglobulinemia after B-cell targeting therapies

TITLE PAGE

Letter to the Editor

Regarding:

Md Yusof MY, Vital EM, McElvenny DM, Hensor EMA, Das S, Dass S, et al. Predicting severe infection and effects of hypogammaglobulinemia during therapy with rituximab in rheumatic and musculoskeletal diseases. Arthritis Rheumatol 2019;71:1812-23.

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BMC Microbiology

RESEARCH ARTICLE Open Access

Antibiotic resistance and virulence patterns of pathogenic *Escherichia coli* strains associated with acute gastroenteritis among children in Qatar

Nahla O. Eltai[1], Asmaa A. Al Thani[1,2], Sara H. Al Hadidi[1], Khalid Al Ansari[3,4] and Hadi M. Yassine[1,2*]

Abstract

Background: The treatment of *Enterobacteriaceae* family including diarrheagenic *E. coli* (DEC) has been increasingly complicated due to the emergence of resistant strains. Here we report on the phenotypic resistance profiles and ESBL genotype and virulence profiles of Enteroaggregative *E. coli* (EAEC) and Enteropathogenic *E. coli* (EPEC) isolated from children hospitalized with acute gastroenteritis in Qatar (AGE).

Results: *E. coli* were isolated and characterized from 76 diarrheagenic stool positive samples, collected from hospitalized children less than 10 years old. Isolates were tested for antibiotic susceptibility against eighteen clinically relevant antibiotics using E-test method. Conventional PCR was performed to detect genes encoding ESBL and virulence factors. Chi-square test was performed to compare the individual antibiotic resistance between EPEC and EAEC.

A significant percentage (73.7%) of isolates were resistant to at least one antibiotic. Overall, high resistance (70%) was reported to the first-line antibiotics such as ampicillin, tetracycline (46.4%), and sulfamethoxazole-trimethoprim (42.9%). Further, 39.5% of the isolates were multidrug resistant (MDR), with 22.4% being ESBL producers. On the other hand, all isolates were susceptible to carbapenem, fosfomycin, amikacin and colistin. The incidences of resistance to the 18 antibiotics between EPEC and EAEC were not significantly different by Pearson chi -square test ($P > 0.05$). Genetic analysis revealed that 88.23% of ESBL production was *bla* $_{\text{CTX-M-G1}}$ (*bla* $_{\text{CTX-M-15}}$, *bla* $_{\text{CTX-M-3}}$) - encoded. Several different combinations of virulence markers were observed, however, there was no specific trend among the isolates apart from absence of the bundle-forming pilus *(bfpA)* gene, which encodes the type IV fimbriae in EPEC adherence factor (EAF) plasmid (pEAF), among all EPEC (atypical). 15% of the EAEC strains were positive for a combination of *astA*, *aap* & *capU*, while 10% were positive for three different combinations. The *aap*, *aatA*, *capU* and *aggR* virulence genes showed the highest frequency of 65, 60, 55 and 55% respectively. Others genes, *east*, *astA*, and *aai*, showed frequencies of 35, 30 and 20% respectively.

(Continued on next page)

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BMC Infectious Diseases

CASE REPORT Open Access

Unusual accumulation of a wide array of antimicrobial resistance mechanisms in a patient with cytomegalovirus-associated hemophagocytic lymphohistiocytosis: a case report

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Abstract

Background: Infections with multidrug-resistant organisms (MDRO) pose a serious threat to patients with dysregulated immunity such as in hemophagocytic lymphohistiocytosis (HLH), but such infections have rarely been comprehensively characterized. Here, we present a fatal case of HLH secondary to cytomegalovirus (CMV) infection complicated by both anti-viral drug resistance and sepsis from multiple MDROs including pandrug-resistant superbug bacteria.

Case presentation: A previously healthy, six-year-old boy presented with a 45-day history of fever prior to a diagnosis of hemophagocytic lymphohistiocytosis and hemorrhagic colitis, both associated with CMV. On hospital admission, the patient was found to be colonized with multiple, multidrug-resistant (MDR) bacteria including vancomycin-resistant enterococci (VRE) and carbapenamase-producing organisms (CPO). He eventually developed respiratory, urine and bloodstream infections with highly drug-resistant, including pandrug-resistant bacteria, which could not be controlled by antibiotic treatment. Antiviral therapy also failed to contain his CMV infection and the patient succumbed to overwhelming bacterial and viral infection. Whole genome sequencing (WGS) of the MDR bacteria and metagenomic analysis of his blood sample revealed an unusual accumulation of a wide range of antimicrobial resistance mechanisms in a single patient, including antiviral resistance to ganciclovir, and resistance mechanisms to all currently available antibiotics.

Conclusions: The case highlights both the risk of acquiring MDR superbugs and the severity of these infections in HLH patients.

Keywords: Multidrug-resistant organism, Antiviral resistance, Cytomegalovirus, Hemophagocytic lymphohistiocytosis

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Pediatric Cardiology
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REVIEW ARTICLE

Tetralogy of Fallot Will be Treated Interventionally Within Two Decades

Muhammed Riyas K. Rahmath[1] · **Younes Boudjemline**[1]

Received: 26 November 2019 / Accepted: 17 January 2020

Abstract
Tetralogy of Fallot is considered a prototype congenital heart disease because of its embryological, anatomical, pathophysiological, and management aspects. Current management usually relies on a complete surgical repair that is electively performed between 3 and 6 months of age. With the advances of interventional cardiology especially in the fields of ventricular septal defect closure, stent, and pulmonary valve replacement, the question of complete repair of tetralogy of Fallot by interventional means can be discussed. Tetralogy of Fallot is a complex disease with multiple lesions, all individually amenable to transcatheter treatment. In this article, we will review current status of various aspects of tetralogy of Fallot focusing on interventional aspects, giving insights of what would be the ideal platform of a fully interventional repair.

Keywords Tetralogy of fallot · Transcatheter · Stent · Cardiac catheterization

Introduction

Tetralogy of Fallot is considered a prototype congenital heart disease because of its embryological, anatomical, pathophysiological, and management aspects. Understanding of pathophysiology and management of this disease have evolved over decades. Operated tetralogy of Fallot patients have become a major group of patients in adult congenital heart disease category [1–3]. Clinical spectrum of tetralogy of Fallot varying from severe cyanosis and ductus dependent pulmonary circulation to older patients with subtle cyanosis. Current management usually relies on a complete surgical repair that is electively performed between 3 and 6 months of age. This timing can be overwhelmed in situation where pulmonary blood is not sufficient to provide adequate oxygenation. Care of those patients may be more complicated requiring a multi-disciplinary approach involving cardiologists, interventionists, and cardiac surgeons. Patients with inadequate pulmonary blood flow usually have to go to palliative approach before being amenable to a complete repair. With the advances of interventional cardiology especially in the fields of ventricular septal defect closure, stent, and pulmonary valve replacement, the question of complete repair of tetralogy of Fallot by interventional means can be discussed. Tetralogy of Fallot is a complex disease with multiple lesions, all individually amenable to transcatheter treatment. In this article, we will review current status of various aspects of tetralogy of Fallot focusing on interventional aspects, giving insights of what would be the ideal platform of a fully interventional repair.

Anatomical Features of Tetralogy of Fallot

Fundamentally, tetralogy of Fallot is a monology as the hallmark lesion is a cephalad and anterior displacement of the infundibular septum resulting in both ventricular septal defect and right ventricular outflow tract obstruction (Fig. 1). However, tetralogy of Fallot represents a wide spectrum of diseases. There might be varying degree of aortic override and condition will be labeled as double outlet right ventricle if there is more than 50% of the aortic valve override to the right ventricle [4]. Obstruction to pulmonary flow in tetralogy of Fallot is usually sub-valvular but other lesions can be present. Pulmonary valve stenosis can rarely be the major cause of obstruction especially in infants. All types of lesions can be seen here from stenosis of a three leaflet valves to hypoplastic annulus with absent leaflets. In addition, stenosis of the pulmonary arteries can also be seen complicating management of those patients.

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GUEST EDITORIAL

New Horizons for Interventional Cardiology - A Plug for the Future

Damien Kenny[1] · Gareth Morgan[2] · Ziyad M. Hijazi[3]

Congenital interventional cardiology has changed greatly over the past twenty years moving from a predominantly diagnostic tool to a therapeutic one. Interventions have become more complex and a myriad of imaging platforms has evolved to optimize comprehension of 3-D anatomy, facilitate precision and decrease radiation exposure. Smaller older and more complicated could be the tag line for our specialty's development. The scope of procedural collaboration with surgeons has led to an atmosphere of co-dependence, moving us away from the paternalistic and often dictatorial systems of decision making and management of the past. This newer way of thinking is evident inside and outside the operating and interventional rooms in our clinics and multidisciplinary meetings and might be best described as hybrid thinking.

It is an exciting time to be involved in the field but rapid change brings its own challenges. In this special edition we are honored to have some of the greatest minds in congenital interventional cardiology share their thoughts on the future of our specialty. Rather than focus on specific interventions, in the earlier section of the edition we wanted to examine the impact of broader cultural and personal influences on the field. Culture is a buzz word in larger corporations but how is it influencing our field? Do we understand ourselves well enough to ensure our decision making for our patients is sound, both in the pre-procedural and intra-procedural realms? How are we protecting ourselves and our patients from increasingly complex interventions and ensuring we have appropriate data to reflect on whether we are moving in the right direction?

Congenital intervention is recognized by the wider cardiology community as a hotbed of innovation. However, low potential sales volumes deter industry from investing the money required to turn a brilliant idea into a product on our shelf. We need to work with regulators and industry partners to ensure that congenital patients are not disadvantaged by this; finding innovative ways to facilitate availability of much needed technology. We have excellent articles dealing with each of these topics that should be of great interest to readers.

In the second part of the edition, we look at more specific approaches, some of which have been evolving over decades without gaining widespread acceptance such as fetal interventions and MRI catheterization, and others which have evolved more rapidly such as hybrid interventions. We have included articles by our surgical colleagues to ensure we have a broader viewpoint on the direction of the specialty. Precision or personalized medicine is gaining widespread traction throughout healthcare but what does it mean for our patients, each with unique anatomy that would surely benefit from more bespoke devices and interventional approaches. Finally, we chose a common congenital defect, tetralogy of Fallot and invited renowned interventional and surgical commentators to discuss whether a purely interventional approach to treat this condition is achievable within the next twenty years.

The foundations of our specialty are steeped in problem solving and innovation. We hope this special edition outlines the challenges and solutions to continuing the tradition of providing the best, least invasive anatomically and physiologically corrective therapies for the current and future generations of very special patients we treat.

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BRIEF REPORT

Pediatric Dermatology WILEY

Recurrent sterile abscesses in a case of X-linked neutropenia

Abstract

Cutaneous manifestations are common in monogenic immune disorders, including both infectious and non-infectious etiologies. We report follow-up of a case initially published in *Pediatric Dermatology* in 2001 of a 13-year-old boy with a history of inflammatory skin lesions and neutropenia who developed neutrophilic dermatoses precipitated by G-CSF. Whole exome sequencing performed at 36 years of age revealed a gain-of-function mutation in the *WAS* gene, leading to a diagnosis of X-linked neutropenia. This case report provides closure on a decades-long diagnostic odyssey and underscores the importance of genetic sequencing in patients who present with unusual dermatologic findings.

1 | INTRODUCTION

Next-generation sequencing (NGS) is expanding the recognition of monogenic immune disorders in clinical medicine. These include conditions with severe skin manifestations of unknown etiology. Here, we provide an update on a patient previously reported in *Pediatric Dermatology*, who, 19 years after the initial report, has now received a genetic diagnosis.[1]

2 | CASE REPORT

The patient first presented at 5 years of age, when he was admitted for painful leg swelling and neutropenia. He was treated with IV antibiotics, incision and drainage, and the lesion took several weeks to heal. The patient was then admitted throughout childhood for recurrent sterile abscesses with protracted healing, often developing at sites of prior intravenous catheter insertion or mild tissue injury or infection (Figure 1A).

The patient received 3 courses of granulocyte-colony stimulating factor (G-CSF) during adolescence for neutropenia. However, treatment was followed by severe flares of sterile abscesses characterized by fever and multiple exquisitely tender nodules. Biopsy demonstrated panniculitis with a primarily neutrophilic infiltrate. Special stains and cultures were negative for bacteria, mycobacteria, and fungi. The case was reported in *Pediatric Dermatology* in 2001 as neutrophilic eruptions triggered by G-CSF, and further treatment with G-CSF has been avoided.[1]

Over the years, he continued experiencing recurrent sterile abscesses without a diagnosis, and at 36 years of age, he was re-evaluated, this time using now available NGS. Laboratory studies demonstrated chronic severe neutropenia (Table 1). Whole-exome sequencing identified a validated pathogenic mutation in the *WAS* gene (NM_000377.2:c.881T>C), which converts isoleucine to threonine (NP_000368.1:p.Ile294Thr) (Figure 1B).[2] This confers a gain-of-function phenotype and leads to the clinical condition X-linked neutropenia (XLN). Parental sequencing confirmed carrier status in the patient's mother, who has a history of low platelets and low to normal neutrophils without infections (Figure 1C). After a range of therapeutic trials, his sterile abscesses are now empirically treated with a broad-spectrum antibiotic and fluconazole, with or without dexamethasone.

3 | DISCUSSION

X-linked neutropenia is caused by activating mutations in the *WAS* gene, leading to enhanced actin polymerization and altered hematopoietic cell development and function.[3,4] The most prominent laboratory features are neutropenia and monocytopenia.[2] Unlike Wiskott-Aldrich syndrome and X-linked thrombocytopenia caused by loss-of-function *WAS* mutations, patients with XLN have mildly low or normal platelet counts without microplatelets.[2] XLN patients may suffer from infections, however, without clear correlation between neutrophil count and infection rate.[2] This discrepancy has been attributed to increased actin dynamics enhancing neutrophil migration and activity in tissues, thus compensating for reduced myelopoiesis.[5]

We report a case of XLN with severe neutropenia, and paradoxically, recurrent sterile abscesses that flared following treatment with G-CSF. This highlights that XLN patients can suffer from neutrophil-mediated inflammatory complications in tissue despite a paucity of neutrophils in peripheral blood, and that treatments aimed at enhancing neutrophil production and activity may have detrimental side effects. XLN should be considered in patients with sterile abscesses, in particular those with neutropenia or monocytopenia. Clinicians should apply NGS in cases of severe skin disease where a clinical diagnosis has been elusive and a genetic etiology is suspected, irrespective of the patient's age and phenotypic presentation.

cancers

MDPI

Review

Renal Tumors of Childhood—A Histopathologic Pattern-Based Diagnostic Approach

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Abstract: Renal tumors comprise approximately 7% of all malignant pediatric tumors. This is a highly heterogeneous group of tumors, each with its own therapeutic management, outcome, and association with germline predispositions. Histopathology is the key in establishing the correct diagnosis, and therefore pathologists with expertise in pediatric oncology are needed for dealing with these rare tumors. While each tumor shows different histologic features, they do have considerable overlap in cell type and histologic pattern, making the diagnosis difficult to establish, if based on routine histology alone. To this end, ancillary techniques, such as immunohistochemistry and molecular analysis, can be of great importance for the correct diagnosis, resulting in appropriate treatment. To use ancillary techniques cost-effectively, we propose a pattern-based approach and provide recommendations to aid in deciding which panel of antibodies, supplemented by molecular characterization of a subset of genes, are required.

Keywords: pediatric; oncology; renal tumors; immunohistochemistry; molecular analysis

1. Introduction

In Europe, each year about 1000 children are diagnosed with a renal tumor, thereby comprising approximately 7% of all pediatric malignant tumors. Approximately 90% of pediatric renal tumors comprise Wilms tumor (WT), the remainder consisting of clear cell sarcoma of the kidney (CCSK), malignant rhabdoid tumor of the kidney (MRTK), renal cell carcinoma (RCC), congenital mesoblastic nephroma (CMN), and other rare tumors (Table 1) [1]. They represent a very heterogeneous group, which includes a spectrum of tumors from those with low malignant potential (e.g., CMN) to highly

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ORIGINAL ARTICLE

A case of aberrant CD8 T cell–restricted IL-7 signaling with a Janus kinase 3 defect–associated atypical severe combined immunodeficiency

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Abstract

Severe combined immunodeficiency (SCID) disorders compromise lymphocyte numbers and/or function. One subset of SCID typically affects T cell and Natural Killer (NK) cell development in tandem ($T^-B^+NK^-$) due to mutations arising in the genes encoding the common γ chain or Janus Kinase 3 (JAK3). In rare circumstances, mutations in the *JAK3* gene have been reported to cause atypical SCID that selectively affects T cells ($T^-B^+NK^+$). Here we describe a case involving a female infant who was referred to our institution on day nine of life following an abnormal newborn screen result for T^-SCID. Immunological assessments revealed a $T^-B^+NK^+$ phenotype and molecular analyses, including whole exome sequencing, identified compound heterozygous JAK3 variants (R117C and E658K). Pre-transplant phosflow analyses revealed a persistent IL-7 signaling defect, based on phospho-STAT5 measurements, only in CD8 but not CD4 T cells. Intriguingly, phospho-STAT5 signals in response to IL-2 stimulation were not affected in either CD4 or CD8 T cells. The pre-transplant clinical course was unremarkable, and the patient received a cord-blood stem cell transplant on day 716 of life. Post-transplant monitoring revealed that despite normalization of lymphocyte counts, the CD8 T cell-restricted IL-7 signaling defect was still evident at day 627 post-transplant (phospho-STAT5 signal in CD8 T cells was > 60% reduced compared with CD4 T cells). The post-transplant clinical course has also been complicated by identification of autoimmune responses and likely GVHD-induced ichthyosis. To the best of our knowledge, this report represents the third case of JAK3-associated atypical SCID reported in the literature.

Keywords JAK3 · Atypical-SCID · IL-7 · IL-7R · pSTAT5 · CD8 T cells

Introduction

The underlying causes of congenital T cell deficiency are diverse and the molecular aberrations that underpin this phenotype are incompletely understood [1]. One well-known group of disorders that induce congenital T cell deficiency is severe combined immunodeficiency (SCID), and the specific features that currently define typical/classic and atypical/variant SCID ("leaky" SCID) have been previously established by the primary immune deficiency treatment consortium (PIDTC) [2]. Children born with T cell defects greatly benefit from early diagnosis and treatment, which usually involves life-saving curative approaches such as a stem cell transplant or gene therapy, in addition to other critical therapeutic interventions such as enzyme replacement, immunoglobulin infusions, stringent antibiotic prophylaxis, and avoidance of live vaccines [1, 3]. Newborn screening for

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Assessing *pulsus paradoxus* in severe exacerbations of asthma

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Normal breathing will cause fluctuations of left ventricular stroke volume and blood pressure due to changes in intrathoracic pressure during the breathing cycle. *Pulsus paradoxus* is defined as a decrease in systolic blood pressure of more than 10 mm Hg during inspiration. A severe exacerbation of asthma, tension pneumothorax or cardiac tamponade can result in pulsus paradoxus. We are all taught to look for pulsus paradoxus as a measure of severity, but we rarely perform this part of the examination because it is not easy to measure accurately; it is subjective with poor inter-rater reliability and is simply not practical. Even with a high-fidelity electronic stethoscope and audio video recording, manually measured pulsus paradoxus does not correlate with severity of acute asthma in children[1] because of poor inter-rater reliability.

Pulse oximetry is now routinely used in acute medicine. Can this bedside tool help us assess the severity of an asthma exacerbation? Krishnan S *et al* have examined 285 patients with exacerbations of their asthma and have assessed the role of pulse oximetry in evaluating the presence of pulsus paradoxus.[2] There are a number of criticisms of this paper, but it should make us refocus on this old sign. The research team trained triage nurses in the determination of presence of pulsus paradoxus. In this study, it was taken as qualitatively present if there was regular variation in the amplitude of the plethysmograph waveform in accordance with the breathing cycle of the patient. They did not measure the magnitude of it and they did not show the inter-rater reliability of the recognition of the sign. The treating physicians were not aware of the ongoing study, and their clinical decisions on treatment and disposition were not influenced by the pulsus paradoxus assessment. The primary outcomes were need for adjunct medications, supplementary ventilation and the need for admission to a paediatric high-dependency unit (PHDU) or a paediatric intensive care unit (PICU). The outcomes were compared with those children with pulsus paradoxus on admission and those with pulsus paradoxus after initial inhaled treatment. Those children who still had pulsus paradoxus after initial treatment were 12 times more likely to need extra medication, and nearly six times more likely to need supplementary ventilation and admission to PICU/PHDU.

This is a novel approach to assessing pulsus paradoxus and it looks promising, as a way of identifying those children in need of escalation of therapy and more intensive therapy. Identifying pulsus paradoxus by the triage nurse could also make the initial process of asthma severity assessment at presentation more efficient. There are wide confidence limits highlighting small numbers in the study, but certainly it suggests that pulsus paradoxus, when identified on pulse oximetry, may well have a role as a potential point of care tool. This could help assess response to initial treatment in children with moderate to severe exacerbations of asthma. It is interesting that the researchers looked at the utility of the presence of pulsus paradoxus after the initial treatment; it is recognised that severity assessment after 1 hour of treatment may be a better predictor of the need for admission to hospital and PICU than on initial assessment at presentation to the emergency department (ED).[3]

The Pleth Variability Index (PVI) is the ratio of the calculated difference in maximum and minimum amplitudes of the plethysmograph waveform and the maximum amplitude. The PVI is considered to be a proxy for pulsus paradoxus. In a single-centre prospective study of 117 children with an exacerbation of asthma, 48 patients were discharged home, 61 were admitted to the floor, and eight were admitted to the ICU. The median PVI for each of these groups was 0.27 (IQR 0.19–0.39) for discharges, 0.29 (IQR 0.20–0.44) for patients admitted to the floor and 0.56 (IQR 0.35–0.70) for patients admitted to the ICU. A Kruskal-Wallis test demonstrated a significant difference in the PVI between each of the groups ($p=0.0087$). Their conclusions were that PVI may be a useful tool in the triage of children who present to the ED with obstructive airway disease and that the oximeter plethysmograph waveform can be used as a continuous, objective measure of asthma exacerbation and response to treatment.[4]

Asthma severity scores have been developed and validated for use in research and do have a clinical role for assessing severity and prediction of need for admission and escalation of care. There are 36 asthma severity scores, but there remains concern about how well validated these scores are, what the changes in the score actually mean to the patient clinically and which score has the best performance. The Paediatric Respiratory Measure score and the Acute Asthma Intensity Research Score score are perhaps the best at defining the severity of an exacerbation and are most easy to use.[5] The use of accessory muscles, presence of wheezing, oxygen requirement, air entry, intercostal and subcostal recession, inspiratory to expiratory ratio and scalene muscle use have all been components of these scores. Though there are multiple asthma scores, pulsus paradoxus is not currently used in any score to assess the severity of asthma as part of a clinical prediction tool.[5]

We do not have a well-validated asthma severity score for the assessment of acute asthma and for using to predict the outcome of an attack and for research. Perhaps the measurement of pulsus paradoxus can be more reliably assessed by plethysmography oximetry either as a PVI calculation or something as simple as the visual recognition of it on the wave form. We need to have further studies to examine the intraobserver and interobserver reliability of the recognition of pulsus paradoxus on the waveform, ability to assess the magnitude of pulsus paradoxus, and further validation for its role in guiding asthma management and for research studies. Perhaps adding pulsus paradoxus into one of the better validated asthma severity scores may well improve the validity of the score and become a more useful tool for acute asthma research. Physiologically, pulsus paradoxus is not a dichotomous measure, but it is a continuous measure and incorporating it as such in future models might enhance its predictive value. Pulsus paradoxus may also be a useful parameter to include the use of the scores to assess the severity of asthma, need for early escalation of therapy and the need for PICU admission.

Contributors We have both contributed to the concept and the writing of this editorial. RM wrote the initial article after discussion with CP and then the article was completed and edited by CP.

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Title page

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Abstract

Mechanical ventilation is potentially live saving in neonatal patients with respiratory failure. The main purpose of mechanical ventilation is to ensure adequate gas exchange, including delivery of adequate oxygenation and enough ventilation for excretion of CO_2. The possibility to measure and deliver small flows and tidal volumes have allowed develop very sophisticated modes of assisted mechanical ventilation for the most immature neonates, such as volume targeted ventilation, which is used more and more by many clinicians. Use of mechanical ventilation requires a basic understanding of respiratory physiology and pathophysiology of the disease leading to respiratory failure. Understanding pulmonary mechanics, elastic and resistive forces (compliance and resistance), and its influence on the inspiratory and expiratory time constant, and the mechanisms of gas exchange are necessary to choose the best mode of ventilation and adequate ventilator settings to minimize lung injury. Considering the pathophysiology of the disease allows a physiology-based approach of these concepts in daily practice for decision making regarding the use of modes and settings of mechanical ventilation, with the ultimate aim of providing adequate gas exchange and minimising lung injury.

Keywords: Mechanical ventilation, Pulmonary mechanics, Dead space, Volume targeted ventilation, Lung injury

Intramuscular versus buccal midazolam for pediatric seizures: A randomized double blinded trial

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Short title: IM vs buccal midazolam for seizure

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Data Statement: Deidentified individual participant data (including data dictionaries, related documents) will not be made available.

Clinical Trial Registration: www.clinicaltrials.gov (identifier NCT02897856)

Abbrevations:

IM- Intramuscular

Versus- vs

CI- Confidence Interval

PEC- Pediatric Emergency Center

PICU- Pediatric Intensive Care Unit

SD- Standard Deviation

Word count: 2672

Abstract (word count 219)

Objective: We compared efficacy and safety of intramuscular to buccal midazolam as first line treatment for active seizures in children brought to the Emergency Department.

Study Design: In a double-blind, double-dummy randomized trial, patients with an active seizure lasting more than 5 minutes received blinded treatments on arrival. We employed deferred consent. The proportion of patients with cessation of seizure within 5 minutes of drug administration was the primary efficacy outcome; proportions needing additional medication to control seizure, duration of seizure activity, and side effects were secondary outcomes.

Results: We enrolled 150 children presenting with active seizure, age range 4.5–167.5 months. Cessation of seizure occurred in 61% of the intramuscular and 46% of the buccal treatment groups, (P= 0.07, difference 15.5%, 95% CI for the difference -1.0 to 32.0%). Proportions requiring additional anti-seizure treatment were 39% in the intramuscular and 51% in the buccal groups, respectively. Mean duration of seizure activity after administration of study medication was 15.9 minutes (SD 28.7) in the intramuscular and 17.8 minutes (SD 27.5) in the buccal group. One patient in the intramuscular group developed respiratory depression and hypotension; there were no side effects attributed to investigational treatment in the buccal group.

Conclusions: Efficacy and safety of intramuscular midazolam as first line treatment for pediatric seizures compare favorably to that of buccal midazolam.

Key words: seizure; midazolam; buccal; intramuscular; length of stay; cessation of seizure; status epilepticus

SPECIAL ARTICLE

Novel Coronavirus 2019 (2019-nCoV) Infection: Part I - Preparedness and Management in the Pediatric Intensive Care Unit in Resource-limited Settings

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First reported in China, the 2019 novel coronavirus has been spreading across the globe. Till 26 March, 2020, 416,686 cases have been diagnosed and 18,589 have died the world over. The coronavirus disease mainly starts with a respiratory illness and about 5-16% require intensive care management for acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Children account for about 1-2% of the total cases, and 6% of these fall under severe or critical category requiring pediatric intensive care unit (PICU) care. Diagnosis involves a combination of clinical and epidemiological features with laboratory confirmation. Preparedness strategies for managing this pandemic are the need of the hour, and involve setting up cohort ICUs with isolation rooms. Re-allocation of resources in managing this crisis involves careful planning, halting elective surgeries and training of healthcare workers. Strict adherence to infection control like personal protective equipment and disinfection is the key to contain the disease transmission. Although many therapies have been tried in various regions, there is a lack of strong evidence to recommend anti-virals or immunomodulatory drugs.

Keywords: *COVID-19, Guideline, Pandemic, SARI, Treatment.*

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The year 2020 started with the emergence of the 2019 novel corona virus (2019-nCoV) as a threat to the world; shortly afterwards the World Health Organization (WHO) declared it a pandemic. Having begun in China, globalization and travel led its spread all over the globe, overwhelming the healthcare resources and resulting in high mortality and morbidity. About 5% of adults, especially those with co-morbidities, were critically ill and required intensive care unit (ICU) care [1]. People of all ages were found to be susceptible but severe illness was rare in children [2]. Most of the experience of critical care management of pediatric patients with coronavirus disease 2019 (COVID-19) is derived from the affected children of present epidemic in China, as well as from the previous coronaviral outbreaks *viz.* Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). We write this review as a guidance statement for preparedness and managing children with suspected or confirmed COVID-19 requiring intensive care in a resource-limited setting like India.

BURDEN

Global: Till March 26, 2020, a total of 416,686 confirmed cases from 197 countries with 18,589 deaths have been reported by WHO. China has reported the maximum cases with a total of 81,869, followed by Italy with 69,176 cases. However, mortality is more in Italy with 6,820 (9.9%) deaths followed by China having 3,287 (4%) deaths. The United States of America has surpassed Spain and Germany over the last few days with 51,914 cases and 673 deaths [3].

Indian scenario: A total of 606 cases with 10 deaths have been reported from India as on March 26, 2020 as reported by the WHO. Among these cases, only one child from Kerala has been tested positive.

EPIDEMIOLOGY

The 2019-nCoV belongs to a group of enveloped positive-sense RNA viruses in the family, Coronaviridae with 4 genera *viz.,* alpha, beta, gamma and delta. Human coronaviruses (HCoV) belong to alpha and beta genus

SPECIAL ARTICLE

Novel Coronavirus 2019 (2019-nCoV) Infection: Part II - Respiratory Support in the Pediatric Intensive Care Unit in Resource-limited Settings

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The 2019-novel coronavirus predominantly affects the respiratory system with manifestations ranging from upper respiratory symptoms to full blown acute respiratory distress syndrome (ARDS). It is important to recognize the risk factors, categorize severity and provide early treatment. Use of high flow devices and non-invasive ventilation has been discouraged due to high chances of aerosol generation. Early intubation and mechanical ventilation areessential to prevent complications and worsening, especially in resource-limited settings with very few centers having expertise to manage critical cases. Hydrophobic viral filter in the ventilator circuit minimizes chances of transmission of virus. Strategies to manage ARDS in COVID-19 include low tidal volume ventilation with liberal sedation-analgesia. At the same time, prevention of transmission of the virus to healthcare workers is extremely important in the intensive care setting dealing with severe cases and requiring procedures generating aerosol. We, herein, provide guidance on non-invasive respiratory support, intubation and management of ARDS in a child with COVID-19.

Keywords: *2019- nCoV, Aerosol generation, ARDS, Management, Pandemic, SARI.*

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Novel coronavirus 2019 (2019-nCoV) infection has been declared a pandemic by the World Health Organization (WHO). We elaborated the epidemiology, preparedness of intensive care units, clinical course, intensive care needs and complication of patients with Coronavirus disease (COVID-19) in a previous article [1]. In this write-up, we will focus on the respiratory manifestations, progression and intensive care management of respiratory complications of COVID-19. As we learn more about the 2019-nCoV (novel coronavirus) and the impact this has had on the patients and health care workers (HCW) globally, the focus has shifted to safety of the HCW so that the patients can be treated appropriately and kept safe. This is based on the lessons learned from previous epidemics and mitigating steps to reduce risks to HCW. Most of the following suggestions are based on expert opinionon providing safe care in these challenging times.

RESPIRATORY DISEASE DUE TO 2019 NCOV INFECTION

Clinical Course

The most common presentation is short history of prodrome with myalgias, malaise, cough and low-grade fever. As per the case series from China, only 40-70% of the pediatric patients have fever as an initial presentation [2-4]. During the second week of illness, progression of the disease gradually leads to difficulty in breathing. Reports from China have suggested that it takes an average of 8 days for the development of dyspnea and 9 days for the onset of pneumonia/pneumonitis [5].

Investigations

CDC does not currently recommend chest radiography (CXR) or computed tomography (CT) to diagnose COVID-19 [6]. Viral testing remains the only specific method of diagnosis and has been discussed in detail in part-I [1]. Confirmation with the viral test is required, even if radiologic findings are suggestive of COVID-19 on CXR or CT scan [7].

Differential Diagnosis

The clinical presentation and findings on chest imaging in COVID-19 are not specific.The clinical presentation of COVID-19 overlaps with other infections like influenza, respiratory syncytial virus (RSV), adenovirus, human

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BASIC SCIENCE

WILEY

SCAI position statement on adult congenital cardiac interventional training, competencies and organizational recommendations

This document was endorsed by the Adult Congenital Heart Association (ACHA) in March 2020.

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KEYWORDS: congenital heart disease, adults, congenital heart disease, pediatrics, complications, pediatric catheterization/intervention

1 | BACKGROUND

Congenital heart disease (CHD) is the most common congenital anomaly and occurs in ~0.8% of all live births. Medical and surgical advancements over the past 80 years have resulted in markedly improved survival, and the majority of CHD patients are now surviving to reach adulthood. The number of adults with CHD (ACHD) in the United States now exceeds the number of pediatric patients.[1] This changing demographic trend towards adulthood was first recognized in the early 1970s, and several clinics specializing in ACHD were developed in the 1980s.[2] Over the past 40 years, there has been an incremental increase in the number of ACHD clinics and specialty centers, mostly based at large academic medical centers, and often staffed by both adult and pediatric cardiology specialists. Along with the rise in the number of ACHD patients, there has been a parallel increase in the volume and variety of transcatheter interventional procedures applicable to ACHD patients.

The definition of ACHD can be somewhat arbitrary depending on the various stakeholders managing CHD patients and the institutional culture and expertise. Most agree that age 18 years is the typical cut-off that separates pediatric from adult patients. However, some Children's hospitals will accept CHD patients as old as 26 years or even

older, especially if they have been cared for all of their lives in the same institution. Often, during the college age years (18–22 years), patients and their parents may prefer continued care with their pediatric cardiologist. Meanwhile, there are also adult cardiologists and hospitals willing to manage late adolescent CHD patients, especially those with adult weight ranges and those with comorbidities such as diabetes, hypertension and dyslipidemia. Issues of contraception, pregnancy planning and pregnancy management in young women with ACHD require special consideration and teams experienced in this area of ACHD, be they pediatric or adult specialists, are best suited to care for these patients. Models of "expert ACHD centers" that exist currently vary widely from collaboration between a free-standing children's hospital that collaborates with a partner adult hospital/s, to a children's hospital embedded within an adult medical center to adult hospitals with no affiliation with a Children's hospital but that have collaborative arrangements with pediatric cardiologists. While diversity of ACHD centers exists, it is clear that a team approach involving both pediatric and adult CHD experts and multispecialty collaborators is optimal for the best care of ACHD patients from adolescence through older adulthood.

The rapid rise in the number and complexity of transcatheter interventional procedures performed in this population has prompted the publication of consensus recommendations from stakeholder organizations regarding the delivery of ACHD interventional care, including recommendations within the ACC/AHA guidelines explicitly stating that interventional procedures should be performed at regional ACHD centers by qualified specialists with training and experience in ACHD interventional care and in laboratories with appropriate staffing and experience to fulfill this task.[3] The Adult Congenital Heart Association (ACHA) was founded as a national organization in the United States that includes patients and medical professionals and helps educate and empower ACHD patients and their families. In 2014, the ACHA developed an ACHD center accreditation process that includes a comprehensive list of staffing and care process requirements (https://www.achaheart.org/provider-support/accreditation-program/). The ACHA's accreditation steering committee attempted to establish certain well-defined quality measures for the delivery of ACHD care in the United States. This accreditation program has become a cornerstone for ensuring that comprehensive care centers for ACHD meet prespecified acceptable thresholds, including recommendations for the delivery of transcatheter interventional care. The ACHA Comprehensive Care Center requirements state that ACHD interventions should be performed by trained and experienced specialists at centers with adequate facilities and expertise to deliver such care. The availability of around the clock interventional and surgical coverage is critical, as is the participation of the ACHD team in the periprocedural care as well as long-term anticipatory planning of these patients.

Specialized training in ACHD has taken place at pioneering ACHD programs in the United States for over three decades. The early training programs did not include a uniform curriculum but relied on the age-old technique of a master clinician accepting to tutor and train willing apprentices who would then go on to establish grow new and established ACHD programs. These specialists came from both adult and pediatric cardiology backgrounds, hence, the majority of established ACHD programs in the United States currently include adult and pediatric cardiac specialists working collaboratively. Interventional ACHD procedures are currently performed by both pediatric and adult specialists at pediatric, adult, and combined hospital settings.[4] ACHD was certified as a unique sub-specialty by the American Board of Medical Specialties in 2012 and the American Board of Internal Medicine instituted a certifying examination that, thus far, has been given in 2015 and 2017; there are now over 300 physicians from pediatric and adult cardiology backgrounds certified as ACHD specialists in the United States. The Accreditation Council for Graduate Medical Education (ACGME) now certifies ACHD training programs for a 2-year fellowship in ACHD that can be offered after successful completion of fellowship training in adult or pediatric cardiology. Within the 2-year ACHD fellowship curriculum is a requirement for a minimum of 2 months of catheterization training and there are an additional 6 months that can be utilized for research and/or elective rotations.

In recognition of the need for specific recommendations regarding interventional training, an expert consensus statement from the Society for Cardiovascular Angiography and Interventions (SCAI) was published in 2010.[5,6] The authors appropriately highlighted that "training needs to be aligned with the goals and priorities of a "basic" or "advanced" level; moreover the training should be categorized into either "acquired" or "congenital" interventional cardiology. Moreover, the experts concluded that fellowship training in structural and congenital interventions is but "a foundation for a lifetime of learning and maturation, and very few trainees will master more than either the basics of a very select number of complex procedures during a 1- or even 2-year program." The experts recommended a minimum fellowship duration of one year but strongly encouraged ongoing mentorship and continued learning thereafter. This consensus document also highlighted the importance of integrated multidisciplinary care in partnership with established centers of excellence in ACHD. An additional expert consensus document from SCAI was published in 2014 focusing on interventional training in pediatric (and congenital) interventional cardiology.[7] This document was not specific to ACHD and was primarily focused on pediatric interventional training. The experts proposed case numbers of specific procedures and encouraged the utilization of a performance evaluation tool for ongoing trainee assessment. The duration of training can vary but the experts recommended at least 250 total cases be performed, 150 of which should be interventional procedures. ACHD-specific case numbers and case types were not stated.

2 | METHODOLOGY

Multidisciplinary stakeholders from the interventional and ACHD communities were invited to attend a roundtable meeting organized by SCAI at the 2018 SCAI Scientific Sessions. Attendees included

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ORIGINAL ARTICLE

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Haploinsufficiency of the *FOXA2* associated with a complex clinical phenotype

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Abstract

Background: There are few reports describing the proximal deletions of the short arm of chromosome 20, making it difficult to predict the likely consequences of these deletions. Most previously reported cases have described the association of 20p11.2 deletions with Alagille syndrome, while there are others that include phenotypes such as panhypopituitarism, craniofacial dysmorphism, polysplenia, autism, and Hirschsprung disease.

Methods: Molecular karyotyping, cytogenetics, and DNA sequencing were undertaken in a child to study the genetic basis of a complex phenotype consisting of craniofacial dysmorphism, ocular abnormalities, ectopic inguinal testes, polysplenia, growth hormone deficiency, central hypothyroidism, and gastrointestinal system anomalies.

Results: We report the smallest described de novo proximal 20p11.2 deletion, which deletes only the *FOXA2* leading to the above complex phenotype.

Conclusions: Haploinsufficiency of the *FOXA2* only gene is associated with a multisystem disorder.

KEYWORDS

20p11.2 deletion, *FOXA2*, growth hormone deficiency, haploinsufficiency, hypothyroidism

1 | INTRODUCTION

The forkhead box A (FOXA) transcription factor plays an important role in multiple stages of life, from early development to endoderm formation, regulation of genes involved in growth and proliferation, fertility, organogenesis and differentiation, metabolism, homeostasis, and the immune system (Friedman & Kaestner, 2006; Kaestner, 2010; Kelleher et al., 2017). *FOXA2* expression occurs in the primitive streak and in the node of the embryo, which are both crucial for gastrulation. *FOXA2* expression is also active in the anterior axial mesoderm, definitive endoderm formation, as well as ectoderm-derived neural tissues and endoderm-derived tissues (pancreas, liver, thyroid, prostate, and lung) in early development and adulthood (Besnard, Wert, Hull, & Whitsett, 2004; Friedman & Kaestner, 2006; Kaestner, 2000).

β-cell-specific *FOXA2*-knockout mice exhibit severe hyperinsulinemic hypoglycemia and hypoglucagonemia phenotype due to an increased insulin to glucagon ratio (3–4 fold), and die shortly after birth due to inhibition of notochord and endoderm formation (Gao et al., 2010; Lantz et al., 2004; Sund et al., 2001). The phenotypic outcome is likely due to the role that *FOXA2* plays in regulating the expression of genes in pancreatic β-cells that are important in glucose sensing and insulin secretion, including

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Molecular epidemiology of influenza, RSV, and other respiratory infections among children in Qatar: A six years report (2012–2017)

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ABSTRACT

Background: Studies on the etiology of respiratory infections among children in Qatar and surrounding countries are limited.
Objectives: To describe the prevalence and seasonality of RSV, influenza, and other respiratory pathogens among children in Qatar.
Methods: We retrospectively collected and analyzed data of 33,404 children (<15 years) presented with influenza-like illness from 2012 to 2017.
Results: At least one respiratory pathogen was detected in 26,138 (78%) of patients. Together, human rhinoviruses (HRV), respiratory syncytial virus (RSV), and influenza viruses comprised nearly two-thirds of all cases, affecting 24%, 19.7%, and 18.5%, respectively. A prevalence of 5-10% was recorded for adenovirus, parainfluenza viruses (PIVs), human bocavirus (HboV), and human coronaviruses (HCoVs). Human metapneumovirus (HMPV), enteroviruses, *M. pneumonia*, and parechovirus had prevalences below 5%. While RSV, influenza, and HMPV exhibited strong seasonal activity in the winter, HRV was active during low RSV and influenza circulation. The burden of RSV exceeds that of influenza among young age groups, whereas influenza correlated positively with age. Further, HRV, adenovirus, influenza, and RSV infection rates varied significantly between male and females.
Conclusion: This comprehensive multi-year study provides insights into the etiology of ILI among children in Qatar, which represents the Gulf region. Our results reinforce the significance of active surveillance of respiratory pathogens to improve infection prevention and control strategies, particularly among children.

1. Introduction

Acute Respiratory infections (ARIs) are the world's most common illnesses, causing a persistent public health concern in both developed and developing countries (Monto, 2002; World Health Organization, 2004). Respiratory infections are easily transmitted among individuals resulting in high morbidity and mortality rates particularly in children and the elderly (Goldstein et al., 2015; Walsh and Falsey, 2012; Bednarska et al., 2015). According to the WHO, respiratory infections were responsible for about a million deaths in children younger than four years old during 2017 (World Health Organization (WHO), 2017).

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JAMA Neurology | Special Communication

Proposal for Updated Nomenclature and Classification of Potential Causative Mechanism in Patent Foramen Ovale–Associated Stroke

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IMPORTANCE Recent epidemiologic and therapeutic advances have transformed understanding of the role of and therapeutic approach to patent foramen ovale (PFO) in ischemic stroke. Patent foramen ovale is likely responsible for approximately 5% of all ischemic strokes and 10% of those occurring in young and middle-aged adults.

OBSERVATIONS Randomized clinical trials have demonstrated that, to prevent recurrent ischemic stroke in patients with PFO and an otherwise-cryptogenic index ischemic stroke, PFO closure is superior to antiplatelet medical therapy alone; these trials have provided some evidence that, among medical therapy options, anticoagulants may be more effective than antiplatelet agents.

CONCLUSIONS AND RELEVANCE These new data indicate a need to update classification schemes of causative mechanisms in stroke, developed in an era in which an association between PFO and stroke was viewed as uncertain. We propose a revised general nomenclature and classification framework for PFO-associated stroke and detailed revisions for the 3 major stroke subtyping algorithms in wide use.

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Supplemental content

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Group Information: A complete list of the Patent Foramen Ovale Associated Stroke International Working Group authors appears at the end of the article.

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Stroke is the second leading cause of death worldwide and among the most common debilitating diseases. Overall, 70% of strokes are ischemic and carry a high long-term recurrence risk.[1,2] Ischemic stroke is a heterogeneous disorder because numerous mechanisms produce vascular occlusion and infarction. *Cryptogenic ischemic stroke* (CIS), the term used when no causative mechanism has been identified, accounted for 40% of all ischemic strokes a half-century ago; however, with diagnostic advances, especially imaging, the proportion has declined to 15% to 30%.[3,4] Cryptogenic ischemic stroke occurs more frequently in young and middle-aged patients (<60 years old) who have fewer risk factors for atherosclerotic disease.[3,4] The most frequent pattern of CIS is a nonlacunar infarct (superficial, large, deep, or combined superficial and deep).[5]

As a diagnosis of exclusion, rendered when adequate workup has failed to identify a defined causative mechanism of stroke, CIS is a conceptual entity that requires continuous curation and pruning. When scientific advances unveil new causative mechanisms of stroke, patients with those conditions should no longer be characterized as cryptogenic but rather placed in the appropriate defined causation category. The most common, broad, defined categories are large artery atherosclerosis, cardioembolism, small vessel disease, and other causes. Three detailed classification systems to assign patients among these categories have gained wide acceptance: (1) Trial of Org 10172 in Acute Stroke Treatment (TOAST); (2) Causative Classification of Stroke (CCS); and (3) atherosclerosis, small vessel, cardioembolism, and other dissection (ASCOD).[6-9] Also influential has been the embolic stroke of undetermined source (ESUS) construct for the preliminary classification of patients.[4]

The most frequent advance requiring alteration in cryptogenic stroke classification is recognition of new, uncommon causative mechanisms that fall within the motley supraordinate category termed *other*. Examples of newly recognized or more easily diagnosed causative mechanisms since the first promulgation of formal causative classification systems in 1993[6] include cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and reversible cerebral vasoconstriction syndrome.[10,11] Incorporation of these uncommon entities into diagnostic frameworks of causative mechanisms is straightforward; they become additional members of the category of other defined causative mechanisms of stroke. A less frequent and more challenging development mandating alteration to CIS classification is a change in status of a component entity within a defined category, such as cardioembolic stroke. When large-scale studies demonstrate a particular cardioembolic mechanism is more likely to be a genuine cause of stroke than was understood when classification systems were

An Orbital Abscess Secondary to Intraoral Impalement

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Abstract: Penetrating orbital trauma in the pediatric population is rare. Even more unusual is a secondary orbital infection following penetrating trauma. Here we present a highly unusual case of fulminant facial cellulitis with an orbital abscess in an otherwise healthy 3-year-old boy following a penetrating injury to the orbit from a point of entry on the gingiva-buccal sulcus, sustained during a fall while carrying a wooden lollipop stick. Examination of the retina revealed a focal injury at the inferior pole of the globe. The organisms cultured from pus sampled from the abscess and from the discharging intraoral wound revealed the same oral commensals while the MRI revealed a track in continuity with the orbital collection.

Key Words: *Atopobium parvulum*, *Granulicatella adiacens*, intraoral impalement, orbitotomy, periorbital abscess, periorbital cellulitis

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Penetrating orbital trauma in the pediatric population is rare. Even less common is a post-traumatic subperiosteal abscess within the orbital cavity. Severe orbital infections risk permanent damage to the adjacent globe and may even be life threatening.[1–3] As a high index of suspicion and appropriate radiological investigations are needed to make such a diagnosis, these patients typically present with facial and periorbital cellulitis but fail to improve on antibiotic therapy alone. The following clinical study documents a recent, highly unusual case. The case highlights the potential for low velocity penetrating trauma to result in a vision-threatening infection in the pediatric population. The case further demonstrates the invaluable contribution that prompt, definitive radiological investigation and surgical intervention made in achieving a satisfactory outcome.

CLINICAL REPORT

A 3-year-old boy with a history of an ectopic kidney and short stature receiving growth hormone supplementation presented to the emergency room with a 36 hours history of fever, left periorbital swelling and a laceration to the left gingiva-buccal sulcus (Fig. 1A). The only relevant history was of a fall while sucking on a lollipop. On examination by an emergency physician the small intraoral laceration and recent fall was thought to be incidental to the fever and a diagnosis of pre-septal cellulitis was made. An ophthalmology consult was conducted which was revealed chemosis only and, as his core temperature was recorded at 38.6°C, he was admitted for observation and intravenous antibiotics (clindamycin and ceftriaxone). Twelve hours later he was septic with a core temperature of 39°C. The facial swelling was notably worse and he exhibited proptosis (Fig. 1B). An ultrasound was requested which did not identify a facial collection. Overnight, his temperature increased to 39.8°C and the facial swelling continued to worsen. A diagnosis of periorbital necrotizing fasciitis was considered and an MRI scan, including turbo-spin echo diffusion weighted sequences was performed under general anesthetic. These studies confirmed the presence of an intra-orbital abscess tracking along the infero-medial quadrant of the orbital wall with evidence of tracking into the facial soft tissues inferiorly (Fig. 2A-D). The patient was taken immediately to the operating room. The penetrating intraoral wound was identified and microbiological samples were taken from pus expressing from the wound (Fig. 3A). The orbit was accessed using a transconjunctival approach. Entry into the orbit was met with the release of copious pus (Fig. 3B). Microbiological samples of the intraorbital pus were taken and a thorough washout was performed. The transconjunctival opening was closed. Intra-operative slit lamp examination revealed commotio retinae in the infero-temporal quadrant of the left eye but without puncture. The patient was returned to the ward and the antibiotics continued for a further week. Microbiological culture and sensitivity analysis revealed the presence of *Granulicatella adiacens* and *Atopobium parvulum*. After surgery, the symptoms of sepsis resolved and the swelling slowly settled. He was discharged 7 days following surgery. Out-patient follow up one week later confirmed the resolution of the infection.

DISCUSSION

The abscess identified in this case was a well circumscribed collection between the infero-medial wall of the orbit and the periorbita with moderate displacement of globe laterally and mild

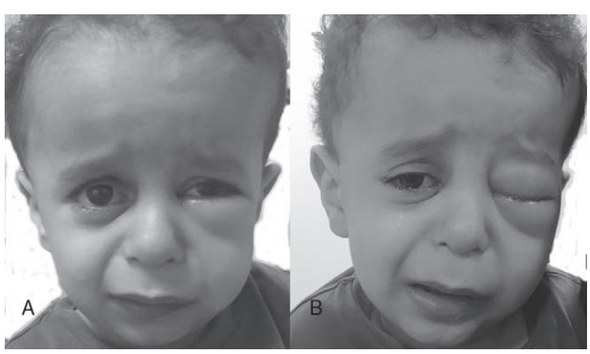

FIGURE 1. A: The appearance of the patient at presentation and, B: at re-examination 12 hours later.

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ORIGINAL STUDIES

WILEY

Preclinical comparative assessment of a dedicated pediatric poly-L-lactic-acid-based bioresorbable scaffold with a low-profile bare metal stent

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Abstract

Background: Polymer-based bioresorbable scaffolds (PBBS) have been assessed for coronary revascularization with mixed outcomes. Few studies have targeted pediatric-specific scaffolds. We sought to assess safety, efficacy, and short-term performance of a dedicated drug-free PBBS pediatric scaffold compared to a standard low-profile bare metal stent (BMS) in central and peripheral arteries of weaned piglets.

Methods: Forty-two devices (22 Elixir poly-L-lactic-acid-based pediatric bioresorbable scaffolds [BRS] [6 × 18 mm] and 20 control BMS Cook Formula 418 [6 × 20 mm]) were implanted in the descending aorta and pulmonary arteries (PAs) of 14 female Yucatan piglets. Quantitative measurements were collected on the day of device deployment and 30 and 90 days postimplantation to compare device patency and integrity.

Results: The BRS has a comparable safety profile to the BMS in the acute setting. Late lumen loss (LLL) and percent diameter stenosis (%DS) were not significantly different between BRS and BMS in the PA at 30 days. LLL and %DS were greater for BRS versus BMS in the aorta at 30 days postimplantation (LLL difference: 0.96 ± 0.26; %DS difference: 16.15 ± 4.51; $p < .05$). At 90 days, %DS in the aortic BRS was less, and PA BRS LLL was also less than BMS. Histomorphometric data showed greater intimal proliferation and area stenosis in the BRS at all time points and in all vessels.

Conclusions: A dedicated PBBS pediatric BRS has a favorable safety profile in the acute/subacute setting and demonstrates characteristics that are consistent with adult BRSs.

KEYWORDS

bioabsorbable devices/polymers, stent bioabsorbable, pediatric intervention, congenital heart disease, pediatrics, bare metal stent

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Research Note

Assessment of English language performance scores and academic performance in an English-based curriculum for pharmacy students with English as a second language

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ABSTRACT

Background: The primary objective was to determine if there is a relationship between English language performance and graduating grade point average (GPA) in pharmacy students with English as a second language (ESL).
Methods: Students graduating from a four-year pharmacy program in 2016–2018 were invited to participate in the study. We compared pharmacy students' pre-admission ESL scores to their cumulative GPA at graduation in each of the three graduating cohorts and also determined if these results held true for both genders. Correlation of GPA to individual mathematics, chemistry, and Chinese language scores were used as points of reference to compare the degree of correlation.
Results: There were 148 students screened for the study with 31 students not meeting the inclusion criteria and four students declining to participate. Statistical analyses show an overall weak correlation. There was a statistically significant stronger correlation between pre-admission ESL scores and cumulative graduating GPA ($r = 0.273$) as compared to the correlation of GPA with mathematics ($r = 0.187$), chemistry ($r = 0.181$), or Chinese language scores ($r = 0.059$). The results did not change when the study population was separated by gender as English score still had the strongest correlation as compared to the other subjects.
Conclusion: This study provides evidence that English language scores correlate more strongly with academic performance than mathematics, chemistry, or Chinese language scores in ESL pharmacy students. Also, this English language correlation is stronger for females than males.

Introduction

The diversity of students admitted into healthcare education programs and the international adoption of curriculums delivered predominantly in English are likely increasing alongside globalization.[1] English language skills difficulty has been identified as a main concern for English as a second language (ESL) students in a healthcare program.[2] Academic success is considered a strong indicator of postgraduate achievement.[3]

It is important to identify what attributes are predictors of student success when designing admission criteria for a program to

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ORIGINAL RESEARCH

The Impact of a Communication Skills Workshop on Doctors' Behavior Over Time

This article was published in the following Dove Press journal:
Advances in Medical Education and Practice

Carma L Bylund[1,2]
Kelsy-Ann Adams[1]
Tripiti Sinha[2]
Abdelhamid Afana[3]
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Purpose: Communication skills education is still relatively new in some non-Western countries. Further, most evaluation research on communication skills education examines only short-term results. In our communication skills program in Qatar, we aimed to: 1) assess the impact of the communication skills course on participant skills application; 2) assess the length of time since course completion associated with participant skills application; and 3) assess participant gender or clinical position associated with participant skills application.

Methods: Seven hundred and thirty-eight physicians completed a seven-module communication skills course. Participants reflected on what they learned in the course and how the course had impacted their behavior through a nine-item online survey that included a four-item Communication Workshop Impact Scale (CWIS), three open questions, and two demographic questions. To assess the effect of time since workshop on outcomes, we stratified the respondents into five groups based on how long ago they had completed the course.

Results: Three hundred and thirty-two physicians completed the survey. Participants reported agreement with the items on the CWIS: X=4.45 (range 1–5; SD=0.70). When asked which skill(s) they had been able to implement in their clinical practice, 235 gave a specific response, either a specific communication skill (eg, ask open questions), a higher-order category of skills (eg, questioning skills), or the name of one of the seven modules of the course. Only 28 participants listed the name of a skill or module name that they had not been able to implement. There was no evidence of difference in CWIS score based on time since course completion. There was no gender difference; however, residents had significantly lower CWIS scores than fellows (4.70 vs. 4.29, p<0.05).

Conclusion: Participants reported agreement with response items about the impact of the course on their skills application. Participant gender did not play a significant role, but residents had lower scores than did fellows. Furthermore, most physicians (92%) were able to name something specific that they had learned from the course and were currently implementing in their practice. Positive outcomes of the course did not seem to diminish over time. Future research should identify whether observable communication behavior matches the self-reported behavior.

Keywords: communication skills training, medical education, physician–patient communication

Introduction

Patient-centered communication in healthcare is important to improving patient outcomes, ensuring patient safety, and increasing the quality of healthcare internationally.[1–3] However, substantial research shows that communication in healthcare settings is often suboptimal (eg,[4]). Patients' misunderstandings, non-adherence, and dissatisfaction, as well as medical errors and malpractice suits, are often linked to poor communication.[5–7]

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The Journal of Rheumatology

Pilot study of the juvenile dermatomyositis consensus treatment plans: a CARRA Registry study

Kuan Liu, George Tomlinson, Ann M. Reed, Adam M. Huber, Olli Saarela, Sharon M. Bout-Tabaku, Megan Curran, Jeffrey A. Dvergsten, Barbara A. Eberhard, Lawrence K. Jung, Susan Kim, Sarah Ringold, Kelly A. Rouster-Steven, Melissa Tesher, Dawn M. Wahezi and Brian M. Feldman, for the CARRA Registry Investigators

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http://www.jrheum.org/content/early/2020/03/25/jrheum.190494

Abstract

Objectives: To determine the feasibility of comparing the Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans (CTPs) in treating new-onset, moderate juvenile dermatomyositis (JDM) using the CARRA registry, and to establish appropriate analytic methods to control for confounding by indication and missing data.

Methods: A pilot cohort of 39 JDM patients from the CARRA registry was studied. Patients were assigned by the treating physician, considering patient/family preferences, to one of three CTPs: methotrexate and prednisone (MP), intravenous methylprednisolone, methotrexate and prednisone (MMP) or intravenous methylprednisolone, methotrexate, prednisone and intravenous immunoglobulin (MMPI) .The primary outcome was the proportion of patients achieving moderate improvement at 6 months under each CTP. Statistical methods including multiple imputation and inverse probability of treatment weighting were used to handle missing data and confounding by indication.

Results: Patients received MP (n=13), MMP (n=18) and MMPI (n=8). Patients in all CTPs had significant improvement in disease activity. Of the 36 patients who remained in the pilot study at 6 months, 16 (44%) of them successfully achieved moderate improvement at 6 months (6/13, 46% for MP; 7/15, 47% for MMP; 3/8, 38% for MMPI).After correcting for confounding there were no statistically significant pairwise differences between the CTPs (p = 0.328-0.88).

Conclusion: We gained valuable experience and insight from the pilot study to guide the design and analysis of comparative effectiveness studies using the CARRA registry CTP approach. Our analytical methods can be adopted for future comparative effectiveness studies and applied to other rare disease observational studies.

Long-Term Fate of the Incised Urethral Plate in Snodgrass Procedure; A Real Concern Does Exist

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Key Words:
Hypospadias; Urethra, Histology; Acquired Chordee; Fibrosis; Incised Plate

Abstract

We present here a case of a patient post tabularized incised plate urethroplasty for distal hypospadias without chordee who developed urethral stenosis and acquired curvature along the territory of the incised plate necessitating a redo surgery. The histological analysis of the incised urethral plate revealed absence of smooth muscles, vessels and elastin fibers within the area of the incised plate which could explain the poor compliance of this segment and the development of the curvature. To our knowledge, this case is the first in humans displaying the long-term histological findings of healing post tabularized incised plate urethroplasty.

The Efficacy and Safety of Rapid Cycling Vagus Nerve Stimulation in Children with Intractable Epilepsy

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Manuscript: Word count – 2033, Table: 4, References: 21

Abstract:

Purpose: Vagus nerve stimulation (VNS) is an effective adjunctive therapy for drug-resistant epilepsy (DRE). Nevertheless, information is lacking regarding stimulation parameters optimization to improve efficacy. Our study examines the safety and efficacy of rapid duty cycle (RDC) VNS (off time ≤1.1 minute keeping duty cycle <50%) in pediatric cohort with intractable epilepsy.

Methods: Retrospective chart review of 50 patients (1-17 years) with drug-resistant epilepsy treated with VNS between 2010 and 2015 at a single pediatric epilepsy center. Safety and tolerability data were aggregated across all patient visits to determine frequency of adverse events between differing duty cycles. We also compared seizure reduction rates (SRRs) for each patient at (1) last regular duty cycle visit, (2) first rapid duty cycle visit, and (3) last recorded rapid duty cycle visit.

Results: RDC was well tolerated, with no adverse events reported in 96.6% of patient encounters. At the last visit prior to switching to RDC 45.5% of patients were showing response to VNS (SRRs ≥ 50%). This increased to 77.3% after switching to RDC and remained at 77.4% at the last RDC visit. Fifteen patients (34.1%) became responders to VNS after switching to rapid cycling, another 19 (43.2%) maintained their response with mostly improved SRRs. In only a few instances, responders became non-responders after switching to RDC.

Conclusions: RDC VNS is probably safe and well tolerated. It may also be more efficacious than regular cycling VNS in some patients. This study highlights the necessity of prospective, long-term, double-blinded studies for understanding the advantages of this VNS modality.

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REVIEW ARTICLE

History of WOFAPS (1963–2019)

Jose Boix-Ochoa[1] · **David Sigalet**[2,3]

Accepted: 5 March 2020 / Published online: 7 April 2020

Abstract
The formation of the World Federation of Associations of Pediatric Surgery (WOFAPS) was an important unifying force in the emergence of pediatric surgery as a distinct specialty. Beginning with the formation of several national societies in the early '60s, an early, multinational effort was created. This was in large part fostered by the International Pediatric Association (IPA), which lent logistical support from the medical pediatric community to the pediatric surgeons. In 2001, the mission of the Federation was formalized to focus on the development and education of surgeons serving children, in all parts of the world. This was articulated in the famous Kyoto Declaration of Pediatric Surgery: "Every infant and child who suffers from an illness or disease has the right to be treated in an environment devoted to their care by a pediatric medical or surgical specialist". This vision was unique at the time and foreshadowed the major increase in advocacy activity which has emerged in recent years. While the mission has evolved with time, the present organization continues to hold true to the guiding principles of the original founders and seeks to improve the quality of "Surgical Care for the child, no matter where they live". Education and collaboration across borders underpins the organization's endeavors.

Keywords Global surgery · Low and middle-income countries · Kyoto declaration of pediatric surgery · Teaching collaboration

Introduction

This article will present many historical details that have been drawn from lectures given by Professor Jose (Pepe) Boix-Ochoa over the years. The goal of these lectures, and this article, is to create awareness of both the challenges and successes incurred along the WOFAPS journey so that today's pediatric surgeons can incorporate this knowledge of the "past to build the present to ensure the future" as articulated by Pepe.

Today's WOFAPS has much to be proud of and the achievements are the result of efforts by many prominent pediatric surgeons. The journey began in early 1950 and 60s. Although the development of pediatric surgery as a distinct specialty was slow in its acceptance, the concept gained awareness when surgeons caring for children in developed countries like England, US, Canada, France, Argentina, Brazil, Australia and Japan recognized the need for a national organization as a forum for advancing the quality of pediatric surgical care. These national associations fostered development through debate and discussion of individual experiences inclusive of successes and challenges with like-minded surgeons, dealing with the unique needs of the pediatric patient. Unfortunately, in the rest of the world, the surgical care of children was still under the helm of adult surgeons, who had varying types of relationships with the corresponding pediatric medical community within that region. There was no international pediatric surgical organization, and consequently no unifying voice to develop international and universal educational and scientific guidelines for the surgical care of children at this time.

The founding of WOFAPS

In 1963 at the Paris Congress of the French Association, Prof. Pellerin (Hopital des Enfant, Paris) proposed the creation of the International Union of Pediatric Surgeons (IUPS) to provide support for pediatric surgeons in developing

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Systematic review with meta-analysis: the efficacy of tranexamic acid in upper gastrointestinal bleeding

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Summary

Background: Upper gastrointestinal bleeding is a common medical emergency associated with substantial mortality. Tranexamic acid may be effective for reducing mortality in upper gastrointestinal bleeding.

Aim: To examine the effects of tranexamic acid in upper gastrointestinal bleeding by systematic review and meta-analysis.

Methods: We searched PubMed, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL) and other relevant websites for randomised controlled trials investigating the effect of tranexamic acid published from inception to December 10, 2019. The primary outcome of interest was mortality. Estimates of effect were pooled with a random effects model. Quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.

Results: The search identified 1572 citations. Eleven trials comprising 2076 patients were eligible for inclusion. Of these, 10 trials (2013 patients) compared tranexamic acid with placebo. Risk of death was significantly reduced in patients who received tranexamic acid compared with those who received placebo (RR 0.59, 95% CI 0.43-0.82, P = 0.001) with no significant heterogeneity noted among studies (I^2 = 0%, P = 0.81). The GRADE assessment rated the quality of the evidence for mortality as moderate due to risk of bias. There were no statistically significant differences between tranexamic acid and placebo for the prevention of re-bleeding, need for surgical interventions, need for blood transfusions or frequency of thromboembolic events.

Conclusions: Moderate-quality evidence shows that tranexamic acid is superior to placebo for the reduction in mortality in patients with upper gastrointestinal bleeding. While our findings lend further support to the use of tranexamic acid for treating patients with upper gastrointestinal bleeding, additional higher-quality trials are needed.

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan. The Handling Editor for this article was Dr Colin Howden, and it was accepted for publication after full peer-review.

SEPSIS

BCG vaccination–induced emergency granulopoiesis provides rapid protection from neonatal sepsis

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Death from sepsis in the neonatal period remains a serious threat for millions. Within 3 days of administration, bacille Calmette-Guérin (BCG) vaccination can reduce mortality from neonatal sepsis in human newborns, but the underlying mechanism for this rapid protection is unknown. We found that BCG was also protective in a mouse model of neonatal polymicrobial sepsis, where it induced granulocyte colony-stimulating factor (G-CSF) within hours of administration. This was necessary and sufficient to drive emergency granulopoiesis (EG), resulting in a marked increase in neutrophils. This increase in neutrophils was directly and quantitatively responsible for protection from sepsis. Rapid induction of EG after BCG administration also occurred in three independent cohorts of human neonates.

INTRODUCTION

Neonatal death remains a serious threat, currently comprising nearly half of all under 5-year-old mortality (*1*). Among the causes of neonatal death, infections are prominent, leading to an estimated 1.6 million neonatal deaths every year (*2*, *3*). The most severe and overwhelming form of neonatal infection is sepsis, most commonly striking during the first few days of life (*4*–*6*). Although a microbial cause for neonatal sepsis is identified in only one-fifth of cases, the list of possibly causative pathogens is not only long but also varies between populations (*7*–*9*). This poses considerable difficulty in providing protection from neonatal sepsis through pathogen-specific vaccination. A pathogen-agnostic approach to broadly protect from neonatal sepsis is urgently needed.

Neonatal bacille Calmette-Guérin (BCG) vaccination can reduce overall neonatal mortality in addition to tuberculosis, variably referred to as BCG's beneficial heterologous, off-target, nonspecific, or pathogen-agnostic effect (*10*, *11*). In a meta-analysis of three randomized controlled trials comprising 6544 high-risk neonates in low-resource settings, BCG-Denmark administered shortly after birth reduced overall mortality in the first 28 days of life by 38% [95% confidence interval (CI), 17 to 54%] and the in-hospital sepsis case fatality by 54% (2 to 78%); of note, a 45% decrease in mortality was already detected in the first 3 days after BCG administration (*6*, *10*). The mechanisms for BCG's pathogen-agnostic protective effects have not been established but have been hypothesized to possibly involve cross-reactive T cells and/or activation of innate immunity (*12*, *13*). Given the substantial public health implications of neonatal infection and BCG's beneficial nonspecific effects, understanding the underlying mechanisms is extremely important (*14*–*17*).

RESULTS

BCG vaccination was protective against polymicrobial sepsis

To identify the mechanism of BCG's nonspecific effects, we tested BCG in a well-established murine neonatal sepsis model in which we subcutaneously administered 50 μl of BCG-Denmark (Statens Serum Institute) to neonatal mice [day of life (DOL) 4 to 5], followed 3 days later by intraperitoneally injected cecal slurry (CS) to induce polymicrobial sepsis (*18*–*23*). We found that BCG markedly improved survival in neonatal mice as it does in humans (Fig. 1A and data file S1). BCG-mediated protection was, however, time limited after neonatal vaccination, and it no longer conferred protection when challenge was delayed by 10 to 12 days (fig. S1A). BCG-induced protection was also dependent on the age of administration, such that mice vaccinated in the juvenile period (preweaning; DOL 17 to 18) were protected, whereas adult mice immunized at 6 weeks

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REVIEW ARTICLE

OPEN ACCESS

Adjuvants in IVF—evidence for what works and what does not work

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ABSTRACT

The field of assisted reproductive technology is shaped and changed constantly by advances in science and cutting-edge innovations. In a quest to maximise outcomes, add-on interventions are often adopted and utilised prematurely while the principles of evidence-based medicine seem to be less strictly adhered to. In this review we will attempt to summarise the latest evidence about some of the adjuvants.

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KEYWORDS
Adjuvant therapy; IVF

Introduction

Known also as treatment add-ons, adjuvants or adjuncts are additional, optional, treatment steps that may be offered on top of standard fertility treatments. The topic of add-ons has been heavily debated as many consider such treatments unfounded.

However, one has to agree that the very reason that this kind of treatments exists, and new innovative treatments keep emerging, is the challenge faced by the clinicians along with the frustration experienced by those trying to conceive.

When clinics start offering such treatments a Pandora's box opens, as the question then would be where one draws the line. Worldwide the *in vitro* fertilisation (IVF) industry is already worth billions of dollars and is booming so there seems to be no easy answer to this question.

As the debate regarding the provision of add-ons is ongoing, several regulatory bodies and professional learned societies have released guidance and statements urging the public to be cautious and to question the use of such treatment modalities. Among those bodies are the Royal College of Obstetricians and Gynaecologists (RCOG) and Human Fertilisation and Embryology Authority (HFEA) in the UK, and the Australian-based Victorian Assisted Reproductive Treatment Authority (VARTA). The issue of add-ons has been under the spotlight even by investigative undercover journalists who have condemned the practice of some private clinics.

Large randomised trials in IVF are very hard to pursue as patients are very keen to try novel or already established empirical therapies and therefore being randomised to a placebo arm is unappealing for them. For most of the add-ons presented in this publication, the available evidence is suboptimal, and better-designed studies are essential to give conclusive answers. We will therefore refrain from repeating the same argument separately for each treatment modality. We will also not elaborate on strategies used in order to improve success rates such as: freeze-all, routine use of ICSI for non-male factor infertility, preimplantation genetic testing for all cycles, continuous monitoring of the embryos (time lapse imaging), testing for endometrial receptivity or endometrial microbiome, and advanced sperm selection techniques such as intracytoplasmic morphologically selected sperm injection (IMSI), physiological ICSI (PICSI), and sperm head's birefringence. It is our belief that these do not strictly speaking constitute adjuvants to treatment, and the decision regarding their use may be influenced by other factors. Instead we will try to focus on what we consider as 'pure' add-ons to treatment.

IVF laboratory-related adjuvants

Embryo glue and adherence compounds

The idea of a using a substance that could facilitate blastocyst implantation originates in the early days of IVF. Fibrin sealants have failed to demonstrate significant improvement in clinical outcomes; however, lately the spotlight has been on a specific culture medium with added hyaluronan, marketed as EmbryoGlue. Hyaluronan is a glycoprotein which is well known to provide a high viscosity environment in the uterus. It has also been observed that the synthesis of intrauterine hyaluronan increases before implantation and goes back to near basal levels after. The latest Cochrane review of 3898 participants from 17 randomised control trials (RCTs) demonstrated moderate-quality evidence for an improvement in clinical pregnancy rates (CPR) and live birth rates (LBR), with an associated increase in multiple pregnancy rate, when transfer medium was supplemented with hyaluronan. The published evidence may be suggestive of a beneficial

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REVIEW

First Case of Rhinocerebral Mucormycosis Caused by *Lichtheimia ornata*, with a Review of *Lichtheimia* Infections

Junling Pan · Clement Tsui · Mengxing Li · Kun Xiao · G. Sybren de Hoog · Paul E. Verweij · Yu Cao · Hongguang Lu · Yanping Jiang

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Abstract

Background *Lichtheimia* species are emerging opportunistic fungal pathogens in the Mucorales, causing serious skin and respiratory infections in immunocompromised patients. Established agents are *Lichtheimia corymbifera* and *L. ramosa*, while *L. ornata* is a novel agent. Available data on a species-specific analysis of *Lichtheimia* infections are limited.

Methods The first case of a fatal rhino-orbital-cerebral infection in a hematopoietic stem cell transplantation recipient caused by *L. ornata* is reported; the agent was identified by sequencing the ITS ribosomal region. We reviewed the literature on mucormycosis due to *Lichtheimia* species between 2009 and 2018, with an analysis of risk factors and epidemiological and clinical data.

Results In addition to our *Lichtheimia ornata* case, 44 cases of human *Lichtheimia* were analyzed. *Lichtheimia* predominated in Europe (68.2%), followed by Asia (16%), and Africa (9%). The most common underlying condition was hematological malignancy (36.3%), followed by trauma/major surgery (27.3%), while diabetes mellitus was rare (11.4%). Site of infection was mostly skin and soft tissues (45.5%) and lung (25%), while relatively few cases were disseminated (13.6%) or rhinocerebral (11.4%). Mortality (36.4%) was mainly due to disseminated and rhinocerebral infections.

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Remdesivir in the treatment of Coronavirus Disease 2019 (COVID-19): A simplified summary

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Abstract

The pandemic of COVID-19 (Coronavirus Disease-2019) is an extremely contagious respiratory illness due to a novel coronavirus, SARS-CoV-2. Certain drugs have several protein targets and many illnesses share overlapping molecular paths. In such cases, reusing drugs for more than one objective and finding their novice uses can considerably decrease the time in finding new cures for unforeseen diseases .Remdesivir has been recently a strong candidate for the treatment of Covid-19. In this commentary, we have portrayed the structure of the coronavirus in a simple way as well as the site where remdesivir acts. We have also displayed the ongoing clinical trials, as well as a published study that was conducted on compassionate base.

The covid-19 pandemic might wean down by the end of summer 2020, but the risk of seasonality exists. Therefore, future disposal of agents such as remdesivir might be crucial for ensuring an efficient treatment, decrease mortality and allow early discharge.

Keywords: Remdesivir; Covid-19; treatment

Introduction

The pandemic of COVID-19 (Coronavirus Disease-2019) is an extremely contagious respiratory illness (Sarma et al., 2020; Elmezayen et al., 2020). Globally, scientists are attempting to study this novel virus, and to discover efficient management to control and prevent the illness

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Selection of Endogenous Control Reference Genes for Studies on Type 1 or Type 2 Endometrial Cancer

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A panel of 32 candidate reference genes was used to identify the most stable genes for gene normalisation in quantitative RT-PCR studies using endometrial biopsies obtained from women with endometrial cancer (type 1 or type 2) and without cancer (controls). RNA from the biopsies was isolated, examined for purity and quality, and then reverse transcribed into cDNA before being subjected to real-time qRT-PCR analysis in triplicate within the TaqMan gene Expression Assay kit. The most 'stable' endogenous control genes were then identified using the geNorm qbase + 2 and NormFinder software packages. PSMC4, PUM1 and IPO8 were identified as the best reference genes combination for type 1 endometrial cancer (grades 1, 2 and 3), whereas for type 2 endometrial cancer (serous and carcinosarcoma), UBC, MRPL19, PGK1 and PPIA were the best reference genes combination. We conclude that the use of these normaliser combinations should provide accurate interpretation of gene expression at the transcript level in endometrial cancer studies especially for types 1 and 2 cancers.

The use of biomarkers is the cornerstone of effective precision medicine[1,2]. RNA forms an excellent source of biomarkers to enable early disease detection, assessment of prognosis, monitoring patient response to therapy or selecting the right treatment for the right patient (personalised medicine). The gold standard method for studying biomarkers at the RNA level in the past decade has been measurement of microRNA in plasma[3] and in the past two decades measurement of messenger RNA (mRNA) in tissue biopsies[4,5]. The measurement of these moieties has occurred primarily through quantitative real time PCR (qRT-PCR) with microRNA- and gene-specific primers, respectively. Application of qRT-PCR to the study of transcript levels in many disease processes has increasingly replaced northern blotting because it is easy to use, fast, reproducible, highly sensitive, specific, and provides high sample throughput[6–9]. In particular, it has been used to identify and assess several molecular markers associated with the staging[10], initiation[11], progression[12], and metastatic potential[13] of endometrial cancer and recently in patient prognosis[14,15].

Elimination of sources of error in the qRT-PCR technique, such as differences in the quantity and quality of extracted mRNA, the presence of contaminating genomic or operator DNA, divergences in reverse transcription and PCR efficiencies must occur for the qRT-PCR to be valid[16–18]. To ensure uniformity and reproducibility of published data, the "Minimum Information for publication of Quantitative real time PCR Experiments" (MIQE) guidelines suggest that the choice of and number of reference genes should be an essential part of all qRT-PCR studies. Validation of this important step guarantees normalisation of resulting data[19]. This normalisation step, where an endogenous reference (housekeeping) gene compensates for any variations in sample or experimental conditions, is essential because all genes under test (both the genes of interest and the reference gene) are assessed under the same experimental conditions. A unified, single "best" reference gene is therefore unlikely to be found routinely, because almost all genes are modified under some conditions[20].

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Spontaneous Resolution of Congenital Hyperinsulinism With Octreotide Therapy

Hyperinsulinemic hypoglycemia is caused by dysregulated insulin secretion from the pancreatic β-cells. Congenital hyperinsulinism (CHI) is caused by genetic mutations in twelve known genes. Histologically, lesions can be focal or diffuse. Focal forms are often associated with paternal heterozygosity in *KCNJ11/ ABCC8* genes, whereas diffuse forms are seen in patients with maternal heterozygous, homozygous or compound heterozygous mutations. 18F-DOPA PET/CT imaging can precisely localize the lesion in focal forms, thereby facilitating cure by focal lesionectomy unlike diffuse form is mostly resistant to medical treatment and needs subtotal pancreatectomy [1].

We report the case of a term non-dysmorphic male baby (weight 2400 g) born to a non-consanguineous couple in Myanmar. He was born through meconium stained liquor with low Apgar scores, required resuscitation and was ventilated for ten days. Hypoglycemia (1.6 mmol/L) was noted at six hours of age, which required mini bolus followed by glucose infusion rate of 5.6 mg/kg/min. On day six, he developed seizures with hypoglycemia and GIR was gradually escalated to 19.5 mg/kg/min. Diagnosis of hyperinsulinemic hypoglycemia was made in the presence of detectable insulin (10.7 mU/L) with hypoglycemia (0.3 mmol/L) and hypoketonemia (0.3 mmol/L). Medical treatment was initiated with nifedipine while awaiting supply of diazoxide. Diazoxide was initiated at a dose of 5 mg/kg/day and was gradually increased to 15 mg/kg/day over a week with discontinuation of nifedipine. Subcutaneous octreotide (dose of 7.5 mcg/kg/day) was added as GIR continued to rise on diazoxide. With adequate response to octreotide, diazoxide was later discontinued.

DNA samples of the proband and parents were sent to UK for genetic study. A novel heterozygous *KCNJ11* missense variant, c.866G>C p. (Gly289Ala) was identified in the proband. Sequencing of the *ABCC8* gene was normal. Sanger sequencing of *KCNJ11* gene for the familial variant indicated heterozygous mutation in father whereas the mother was negative. The clinical significance of the *P*. (Gly289Ala) variant is uncertain. A focal lesion was suspected with the paternal mutation and 18F-DOPA PET/ CT scan was recommended.

DOPA PET/CT scan was unavailable in Myanmar and there was no funding source for overseas transfer. Treatment with octreotide was continued and GIR was successfully weaned off with feeding increments to achieve full feeds by six months of age. At nine months of age, octreotide dose was auto-tapered to 3 mcg/kg/day while maintaining normoglycemia and discontinued at 9.5 months of age. His glucose profile remained stable on follow-up but neurodevelopmental assessment at 22 months of age showed moderate mental and motor retardation. Vision and hearing tested normal. He is currently enrolled in an early intervention programme.

CHI is a heterogeneous disease caused by mutations in at least twelve known genes [1]. Loss-of-function mutations in K_{ATP} channel regulating genes constitute nearly 90% of cases of diazoxide-unresponsive CHI, of which *KCNJ11* is associated in 10% [2].

The index case had diazoxide-unresponsive CHI that detected a novel paternally inherited *KCNJ11* missense variant of uncertain significance at p. (Gly289Ala). A different missense variant at the same residue was previously reported by Mohnike, *et al*. [2] in a patient with diazoxide-responsive CHI, which was shown to have arisen *de novo* in the proband.

Similar spontaneous resolution has been reported at 1.6 and 1.9 year in patients with CHI [3,4]. DOPA tracer uptake may not correlate with the capacity of the pancreatic lesion to secrete insulin and the clinical remission of CHI could be a functional process without apoptosis of mutated β-cells [5]. This finding prompts long-term follow-up of our case to ensure optimal glucose regulation.

Most patients with K_{ATP} channel gene mutations do not respond to diazoxide treatment as it exerts its effects by keeping the channel open, preventing β-cell membrane depolarization and release of insulin. Octreotide reduces insulin secretion by inhibiting intracellular entry of calcium and by decreasing the insulin gene promoter activity [6]. These differences in the site action possibly explain the treatment response in the index case.

In summary, normoglycemia should be maintained to prevent brain injury with high GIR and/or high caloric enteral feeds in infants with CHI. Octreotide can be tried in diazoxide unresponsive patients and spontaneous resolution can be seen in CHI. Genetic studies help indicate the type of mutation. DOPA-PET scan confirms nature of lesion prior to surgery, which however remain poorly accessible in resource-limited settings.

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Platelets and Immature Neutrophils in Preterm Infants with Feeding Intolerance

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Abstract

Objective Feeding intolerance (FI) is a common presentation of necrotizing enterocolitis (NEC) and sepsis. NEC and sepsis are associated with hematological changes, but these changes alone are not reliable biomarkers for early diagnosis. This study examined whether the combination of hematological indices and FI can be used as an early diagnostic tool for NEC or sepsis.

Study Design This retrospective cohort study included infants born at <1,500 g or <30 weeks who had symptoms of FI. The exclusion criteria were congenital or chromosomal disorders, thrombocytopenia or platelet transfusion before the onset of FI, and history of bowel resection. We compared the hematological indices from infants with pathologic FI (due to NEC or sepsis) to infants with benign FI.

Results During the study period, 211 infants developed FI; 185 met the inclusion criteria. Infants with pathologic FI ($n = 90$, 37 cases with NEC and 53 with sepsis) had lower birth gestational age and weight compared with 95 infants with benign FI ($n = 95$). Pathologic FI was associated with lower platelet count (median 152×10^3/μL vs. 285×10^3/μL, $p < 0.001$) and higher immature-to-total neutrophil (I/T) ratio (median 0.23 vs. 0.04, $p < 0.001$) at the onset of FI. Pathologic FI was also associated with a decrease in baseline platelets compared with an increase in benign FI. For diagnosis of pathologic FI, a decrease ≥10% in platelets from baseline had a sensitivity and specificity of 0.64 and 0.73, respectively, I/T ratio ≥0.1 had a sensitivity and specificity of 0.71 and 0.78, respectively, and the combination of both parameters had a sensitivity and specificity of 0.50 and 0.97, respectively.

Conclusion FI caused by NEC or sepsis was associated with a decrease in platelets from baseline, and a lower platelet level and higher I/T ratio at the onset of FI. These findings can help clinicians in the management of preterm infants with FI.

Keywords
- prematurity
- necrotizing enterocolitis
- sepsis
- feeding intolerance
- platelets
- neutrophils

Key Points

- FI is a common presentation of NEC and sepsis in preterm infants.
- FI due to NEC or sepsis is associated with changes in platelets and I/T ratio.
- These changes could be useful as early markers for diagnosis.

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REVIEW

Congenital central pulmonary artery anomalies: Part 2

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Abstract
There is a broad spectrum of congenital anomalies of the central pulmonary arteries including abnormalities of development, origin, course and caliber. These anomalies incorporate simple lesions such as isolated pulmonary valve stenosis to very complex anomalies with many associated abnormalities. Part 1 and Part 2 of this review describe the range of anatomical variations that are encountered as well as important aspects of anatomy, physiology and surgical correction. The authors summarize and illustrate both well-recognized and more complex anomalies to provide a broad and comprehensive understanding of these lesions and their appearances on CT and MR imaging. In Part 2 the authors review abnormalities in development, origin and course of the central branch pulmonary arteries as well as abnormal pulmonary artery caliber.

Keywords Anomalies · Children · Computed tomography · Congenital · Magnetic resonance imaging · Pulmonary artery

Introduction

The classification of congenital pulmonary artery anomalies used is based on anomalous development or origin of the main pulmonary artery (MPA) (Part 1); and anomalous origin, development or course of the central branch pulmonary arteries (PAs), and abnormal PA caliber (Part 2) (Table 1). There is overlap among these categories and some entities fit into more than one; they are discussed in their "best fit" category and then referred to briefly elsewhere for completeness and clarity.

CME activity This article has been selected as the CME activity for the current month. Please visit the SPR website at www.pedrad.org on the Education page and follow the instructions to complete this CME activity.

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Anomalous origin, development or course of central branch pulmonary arteries

Pulmonary artery abnormality and ductus arteriosus [1, 2]

The bilateral ductus arteriosi are derived embryologically from the distal 6th aortic arches; the right-side ductus arteriosus typically disappears early in utero while the left ductus arteriosus persists; however, occasionally either one or both remain patent. Therefore both ductus arteriosi and their ligamentous remnants can be associated with pathology, much more commonly on the left than the right. The left ductus arteriosus is the normal in utero connection between the proximal descending aorta of a left aortic arch and proximal left pulmonary artery (LPA). The embryologic connection of the ductus arteriosus on the side opposite the definitive aortic arch is from the base of the ipsilateral innominate artery to the proximal branch PA on that side. In utero, the left ductus arteriosus normally diverts right ventricular output from the pulmonary circulation to the descending aorta. When there is reversed flow through the ductus prenatally, seen with significant right-side obstructive lesions, the ductus may be smaller and arise from the undersurface of the aortic arch with a more acute angle to the descending aorta (Fig. 1) [1, 2]. Increased oxygen and decreasing endogenous prostaglandin levels after birth lead to constriction of the smooth muscle wall of the ductus with typical physiological closure within 48 h of birth and anatomical closure within a few weeks [2, 3].

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Multidisciplinary team management and cesarean delivery for a Jordanian woman infected with SARS-COV-2: A case report

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ABSTRACT

The SARS-COV-2 virus appears to have originated in Hubei Province in China towards the end of 2019 and has spread worldwide. Currently, there is little literature on COVID-19, and even less on its effect on pregnant mothers and infants. At this time, there are no clear recommendations specific to pregnant women with COVID-19. We report the multidisciplinary team management of a cesarean delivery for a woman infected with SARS-COV-2, including her pre-delivery care, intraoperative considerations, and post-delivery recommendations for the mother and baby. We also discuss the currently available recommendations and guidelines on the management of such cases.

1. Introduction

The SARS-COV-2 virus appears to have originated in Wuhan, the capital of Hubei Province in China, towards the end of 2019. The World Health Organization declared the virus outbreak a pandemic on March 11, 2020 [1,2]. The COVID-19 virus is primarily transmitted between people through respiratory droplets and contact routes. However, other routes of transmission, including vertical transmission, are currently being studied [3,4].

There is little literature on COVID-19, and even less on its effect on pregnant mothers and infants. At this time, there are no clear recommendations specific to pregnant women with COVID-19. To the best of our knowledge, this is the first reported cesarean delivery for a woman infected with SARS-COV-2 in Jordan and the Arab world.

2. Case Presentation

A 30-year-old woman, gravida 4 para 3, was admitted at 36 weeks of gestation in March 2020 after her nasopharyngeal swab tests came back positive for SARS-COV-2 using a rapid PCR technique. She complained of mild dry cough, runny nose, episodes of chills and headache three days prior to admission. She had no shortness of breath, no chest pain, and no muscle ache.

On admission her vital signs were stable and she had no fever. Oxygen saturation in room air was 98%. Regarding this pregnancy, she mentioned having regular antenatal care.

She reported that she had attended a social event a few days prior to presentation. Two days later, she started to have symptoms. She initially thought they were not significant but she sought medical advice many days later when a person at the same event had tested positive for SARS-COV-2. Before admission to the hospital she was living with her 2 children and husband.

She was given hydroxychloroquine 400 mg twice daily for a total of 9 days. Her symptoms were mild. Her blood tests were unremarkable except for mild elevation of D-Dimer 0.65 micrograms/ml (0.1–0.5 micrograms/ml). An ultrasound scan showed appropriate baby growth for age, with average liquor and upper placenta. The mother reported good fetal movement. On the night of her second day of admission, she started to complain of abdominal pain. Upon assessment she was found to be in labor.

Her obstetric history included uncomplicated full-term vaginal delivery of her first daughter. Her second pregnancy was complicated by placental abruption and a cesarean section was done at 35 weeks of gestation. Her third pregnancy ended with a stillborn infant delivered vaginally and was complicated by severe postpartum hemorrhage requiring massive blood transfusion and surgical exploration under

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ORIGINAL RESEARCH
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Extraction and Detection of Avian Influenza Virus From Wetland Sediment Using Enrichment-Based Targeted Resequencing

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Early virus detection and characterization is key to successful avian influenza virus (AIV) surveillance for the health of humans as well as domestic poultry. We explored a novel sampling approach and molecular strategy using sediment from wetlands and outdoor waterbodies on poultry farms as a population-level proxy of AIV activity in waterfowls. RNA was extracted using the MoBio RNA PowerSoil Total RNA isolation kit with additional chloroform extraction steps to reduce PCR inhibition. AIV matrix protein (MP) gene was detected in 42/345 (12.2%) samples by RT-qPCR; an additional 64 (18.6%) samples showed evidence of amplification below the threshold and were categorized as "suspect positive." Enrichment-based targeted resequencing (TR) identified AIV sequences in 79/345 (22.9%) samples. TR probes were designed for MP, hemagglutinin (HA), and neuraminidase (NA), however PB2 and PA were also identified. Although RT-qPCR and TR only had fair-moderate agreement, RT-qPCR positivity was predictive of TR-positivity both when using only strictly positive RT-qPCR samples (OR = 11.29) and when coding suspect positives as positive (OR = 7.56). This indicates that RT-qPCR could be used as a screening tool to select samples for virus characterization by TR and that future studies should consider RT-qPCR suspect positives to be positive samples for subsequent resequencing when avoiding false negatives is the priority, for instance in a diagnostic test, and to consider suspect positives to be negative samples when cost efficiency over a large number of samples is the priority, for instance in a surveillance program. A total of 13 HA (H1-7, H9-13, H16) and 9 NA (N1-9) subtypes were identified, with a maximum of 8 HA and 8 NA subtypes detected in a single sample. The optimized RNA extraction and targeted resequencing methods provided increased virus detection and subtyping characterization that could be implemented in an AIV surveillance system.

Keywords: avian influenza virus, next generation sequencing, nucleic acid extraction, RT-qPCR, surveillance, sediment, waterfowl

Relationship between a single measurement at baseline of body mass index, glycated hemoglobin, and the risk of mortality and cardiovascular morbidity in type 2 diabetes mellitus

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Objective **This study aims to evaluate the relationship between a single measurement at baseline of body mass index (BMI), glycated hemoglobin (HbA1c) and subsequent clinical outcomes in patients with type 2 diabetes mellitus (T2DM).**

Method **Patients with T2DM were recruited from an outpatient diabetes clinic in a single large teaching hospital in Kingston upon Hull, UK. At baseline, demographics and HbA1c were recorded. Patients were categorized by BMI: normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (>30 kg/m^2). Multivariable Cox regression models that included demographic, risk factors, and comorbidities were separately constructed for all-cause, cardiovascular, cancer and sepsis-related mortality, using four groups of HbA1c (<6%, 6.0–6.9%, 7.0–7.9%, and >8%).**

Results **In total, 6220 patients with T2DM (median age 62 years, 54% male) were followed for a median of 10.6 years. HbA1c levels >8.0% were associated with increased risk of all-cause mortality and cardiovascular death. However, this increased risk was not consistent across the weight categories and reached statistical significance only in overweight patients (BMI 25–29.9 kg/m^2).**

Conclusions **In a large cohort of patients with T2DM elevated HbA1c levels at baseline did not consistently predict increased risk of all-cause and cardiovascular mortality across the different BMI categories.** ***Cardiovasc Endocrinol Metab*** **9: 177–182**

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Keywords: body mass index, obesity, obesity paradox, type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) and obesity are major causes of morbidity and mortality worldwide [1]. Obesity is a major risk factor for both diabetes and cardiovascular disease (CVD) [2,3].

The percentage of hemoglobin that is glycated in the blood (HbA1c) is routinely used in the diagnosis and monitoring of patients with diabetes. Large epidemiological studies in patients with T2DM suggest that having either a high or a low HbA1c is associated with increased all-cause mortality compared with HbA1c in the middle of the range [4,5]. A number of factors are known to affect HbA1c levels, mainly time since diagnosis of diabetes, cholesterol levels, and age [6,7].

The association between HbA1c and body weight is less clear and mainly affected by the interaction of different hypoglycemic treatment which can reduce HbA1c levels and cause either weight loss or gain [8]. Whether the relationship body weight and HbA1c affects clinical prognostic outcomes is unclear. To our knowledge, this association has never been fully explored, but only investigated in the context of interaction analysis between HbA1c and body mass index (BMI) to predict all-cause mortality [5,9]. In particular, van Munster *et al.* [9] demonstrated a significant interaction between HbA1c and BMI toward risk of mortality in a cohort of patients with T2DM. Similarly, Li *et al.* [5] in a subgroup analysis of their study demonstrated that higher HbA1c levels were associated

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ORIGINAL ARTICLE

Breast

Breast Reconstruction Combining Lipofilling and Prepectoral Prosthesis after Radiotherapy

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Background: Prosthetic reconstruction in previously irradiated breasts has been associated with a higher risk of complications. Here we describe the surgical and cosmetic outcome of our breast reconstruction process based on primary fat grafting combined with prosthetic placement.
Methods: In this multicenter retrospective study, 136 patients who underwent mastectomy and external chest wall radiotherapy between 2014 and 2018 were benefited from chest wall lipofilling and silicone implant placement were chosen. Patients were assessed for skin trophicity, thickness, and mobility and were allowed to undergo several lipofilling sessions before implant placement, if required. No patient had >3 lipofilling sessions. Cosmetic outcome was evaluated by the patient, surgeon, and nurse, using a Likert-type ordinal scale.
Results: We included 136 patients: 79 patients (58%) received only 1 session of lipofilling before implant placement, 33 (24.6%) had 2 sessions, and 24 (17.4%) had 3 sessions. The volume of the third lipofilling was significantly higher and the volume of the prosthesis of these patients was significantly lower than those of patients undergoing 1 or 2 lipofillings. Reconstruction failure rate was 2.2% (3 patients had explantation); however, all benefited from prosthesis reconstruction a year after the initial procedures. The average satisfaction score was 4.7 out of 5 as evaluated by patients, 4.8 out of 5 by surgeons, and 4.8 out of 5 by nurses.
Conclusions: Primary lipofilling combined with prosthesis placement after radiotherapy is a reconstructive method that yields a satisfactory cosmetic outcome with a low complication rate. Such minimally invasive breast reconstruction approach can be an alternative to flap-based reconstruction. *(Plast Reconstr Surg Glob Open 2020;8:e2659; doi: 10.1097/GOX.0000000000002659; Published online 26 May 2020.)*

INTRODUCTION

Delayed breast reconstruction after total mastectomy and radiotherapy is essentially based on a free or pedicled autologous flap.

When autologous flap-based reconstruction is contraindicated, or declined by patients refusing additional scars or invasive surgeries, a prosthetic-based reconstruction could represent an alternative. Unfortunately, prosthetic breast reconstruction after radiation is associated with a high rate of complications and usually results in poor cosmetic outcomes compared with patients without radiation (relative risk, 2.58).[1–3]

Since the work by Coleman[4] in the early 1990s, indications of autologous fat transfer (AFT) have considerably grown in the management of cosmetic sequelae after breast cancer surgery and particularly in the context of secondary breast reconstructions.[5–8] Prepectoral AFT before prosthesis placement has been associated to increased skin trophicity and vascularization and improved cosmetic results. AFT allows to fill defect areas, improves outlines and overall shape, and leads to increased skin flexibility.[8] The first evaluations of such approach show a significant improvement in the outcome of prosthetic reconstruction with reduced complications.[9,10]

In a recent meta-analysis of 21 studies analyzing 1,011 breast reconstructions in 834 patients, 2.84–4.66 sessions were required to complete reconstruction.[11]

The number of fat grafting sessions to complete breast reconstruction was significantly higher for irradiated compared with nonirradiated patients (4.27 versus 2.84; $P < 0.05$). The complication rate was mainly related to radiation therapy with 5.4% in the irradiated group compared

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Review Article

Nonpuerperal Uterine Inversion: What the Gynaecologists Need to Know?

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Introduction. Nonpuerperal uterine inversion (NPUI) is a rare clinical problem with diagnostic and surgical challenges. The objective of our study was to review the literature on NPUI and describe causative pathologies, diagnosis, and different surgical options available for treatment. *Materials and Methods*. A comprehensive literature review was carried out on MEDLINE and Google Scholar databases to look for NPUI using the term "non-puerperal uterine inversion," and further went through the cross-references of the published articles. Data are published case reports from 1911 to September 2018. Of the 153 published cases, 133 reports had adequate details of surgery for analysis. These reports were analyzed, concerning the clinical presentation, methods of diagnosis, and surgical treatment. *Results*. Mean age of the women was 46.3 years (standard deviation: 18, $N = 153$). Leiomyoma remained the commonest (56.2%) aetiology. While malignancies contributed to 32.02% of cases, 9.2% were idiopathic. High degree of clinical suspicion and identification of unique features on ultrasonography and magnetic resonance imaging enable prompt diagnosis. In cases of uncertainty, laparoscopy or biopsy of the mass was used to confirm the diagnosis. Hysterectomy or repositioning and repair of the uterus are the only treatment options available. The surgical methods implemented were analyzed in three aspects: route of surgical access, method of repositioning, and final surgical procedure undertaken. The majority (48.8%) had only abdominal access, while 27.1% had both abdominal and vaginal access. Haultain procedure was the most useful procedure for reposition (18.0%) of the uterus. The majority (39.7%) required abdominal hysterectomy with or without debulking of the tumour abdominally, while 15.0% had uterine repair after repositioning. We reviewed the different surgical techniques and described and proposed a treatment algorithm. *Conclusions*. Fibroids were the commonest cause for NPUI. Malignancies accounted for one-third of cases. A combined abdominal and vaginal approach, followed by hysterectomy or repair after repositioning, seems to be better for nonmalignant cases.

1. Introduction

Uterine inversion is a condition where the fundus of the uterus turns inside out and the latter prolapses through the cervix. Puerperal uterine inversion was the first uterine inversion type to be recognized, possibly due to its common occurrence. In Ayurveda, the ancient Hindu system of medicine, there is some evidence to suggest that uterine inversion was known to them. However, Hippocrates (460–370 B.C.) is credited as the first to recognize uterine inversion [1, 2].

Inversion of the uterus was classified by Jones in 1951 into two types: puerperal or obstetric and nonpuerperal or gynaecological [3]. While puerperal inversions are seen following delivery or miscarriages and may be acute or chronic, the nonpuerperal variety is mostly related to benign or malignant tumours associated with the uterine corpus. Nonpuerperal inversions present mostly as chronic cases, although Das has reported 8.6% of nonpuerperal inversion as a sudden onset [1].

Nonpuerperal uterine inversion (NPUI) is rare, and actual incidence is not known. Most of the published

Intellectual developmental disorder and autism spectrum disorder in the WPA next triennium mainstream

Both intellectual developmental disorder (IDD) and autism spectrum disorder (ASD) are included in the section of neurodevelopmental disorders of the ICD-11 and DSM-5. They represent meta-syndromic groups including many different clinical conditions characterized by cognitive and relational impairment. The guiding syndromic pattern involves maladaptive cognitive impairment in IDD and severe limitation and restriction of complex interpersonal interactions in ASD[1]. The two conditions often co-occur, and their differentiation may be difficult, especially in the context of increasing severity of cognitive impairment. About 30-40% of persons with ID have pervasive features of ASD, and about 80% of persons with ASD have lower intellectual functioning compared to the general population[2,3].

Both IDD and ASD are associated with a broad vulnerability to concomitant health issues, especially psychiatric disorders, with a prevalence five or more times higher than in the general population[4]. The identification of concomitant psychiatric disorders in persons with IDD and ASD requires a specific knowledge and expertise. The symptomatology can in fact be mixed, intermittent, atypical, masked, and range from poorly defined to extremely rigid. Even key elements of some syndromes, such as delusions, hallucinations or suicidal ideation, are often very hard to recognize, especially in persons with low or absent verbal communication skills, who may only be able to express themselves through changes in behaviour[5].

IDD and ASD impose an enormous burden on families and caregivers, require high service provision, and have high health and societal costs[6].

Despite the above evidence, IDD and ASD have often been overlooked as mental health issues by the majority of national and international organizations worldwide. Even in those countries where specific care programs are available, significant gaps are usually reported between awareness, planning and delivery of services, especially for persons with higher severity of impairment in communication, conceptual and adaptive skills. Specific training for psychiatrists and other mental health professionals is also often lacking, at every level within the clinical education system, including undergraduate, graduate and postgraduate training as well as professional continuing education.

Around one half of the persons with ID and low-functioning ASD receive psychotropic medication, and in one-third of cases drugs are prescribed to manage problem behaviours such as aggression or self-injury, in the absence of a diagnosed psychiatric disorder[7].

These vulnerabilities and shortage of services to address them seem to extend to persons with borderline intellectual functioning (BIF), who present an IQ below the average (between one and two standard deviations), but not enough to be comprised within the upper limit of IDD. According to research findings, at least one-eighth of the world population has BIF and shows, compared to people with higher IQ, greater social disadvantage, higher rates of psychiatric disorders and substance use, and more frequent use of psychopharmacological therapies and health services, including emergency ones[8,9].

To address the above-mentioned issues, to raise awareness, and to provide some initial solutions, the WPA has just launched a specific program within its proposed Action Plan 2021-2024. During the 19th World Congress of Psychiatry, held in Lisbon in August 2019, two interrelated working groups on IDD and ASD have been established, comprising experts with long-standing contributions to WPA activities in the field.

In the next triennium, these groups will produce a set of collaborative documents on policies, services, as well as education and training. Within these documents, the diagnosis of concomitant psychiatric disorders, and the relevant treatment and outcome measures, will occupy a central place.

The WPA Action Plan 2021-2024 aims to address the mental health needs of persons with IDD and ASD, develop strategies for the collaboration of psychiatrists with other health professionals, and promote partnerships for joint collaborative work in capacity building among medical students, young psychiatrists and allied professionals.

The overarching objective is to strengthen the care of persons with IDD and ASD worldwide and to fulfil their right to mental health care, in accordance to the United Nations Convention on the Rights of Persons with Disabilities.

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REVIEW

Current practice in atrial septal defect occlusion in children and adults

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ABSTRACT

Introduction: Atrial septal defect (ASD) is one of the most common congenital heart diseases (CHD) in children and adults. This group of malformations includes several types of atrial communications allowing shunting of blood between the systemic and the pulmonary circulations. Early diagnosis and treatment carries favorable outcomes. Patients diagnosed during adulthood often present with complications related to longstanding volume overload such as pulmonary artery hypertension (PAH), atrial dysrhythmias, and right (RV) and left (LV) ventricular dysfunction.

Area covered: This article intended to review all aspects of ASD; anatomy, pathophysiology, clinical presentation, natural history, and indication for treatment. Also, we covered the transcatheter therapy in detail, including the procedural aspect, available devices, and outcomes.

Expert opinion: There has been a remarkable improvement in the treatment strategy of ASD over the last few decades. Transcatheter closure of ASD is currently accepted as the treatment of choice in most patients with appropriately selected secundum ASDs. This review will focus on the most recent advances in diagnosis and treatment strategy of secundum ASD.

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KEYWORDS
Atrial septal defect; transcatheter closure; echocardiography; congenital heart disease; pulmonary hypertension; cardiac catheterization

1. Introduction

ASDs are the third most common type of CHD with an estimated incidence of 56 per 100,000 live births [1]. By definition, an ASD is a direct communication between the atrial cavities that allow shunting of blood. There are four types of ASD, including primum, secundum, sinus venosus (SV), and coronary sinus (CS) defects. Secundum ASD is located in the region of the fossa ovalis and considered a true defect of the atrial septum. The other three types of ASD represent interatrial communications that are located outside the area of the true atrial septum. Primum ASD represents persistence of the embryonic ostium primum, and in many cases, the oval fossa is well formed and intact. SV defects are located outside the confines of the true septum, superiorly or inferiorly and referred to as superior and inferior SV defects, respectively. The superior SV defect allows the orifice of the superior vena cava (SVC) to override the septum and drain into both atrial chambers and commonly associated with partial anomalous connection of the right superior pulmonary vein to the SVC. The inferior SV defect is similar to the superior type but related to the orifice of the inferior vena cava (IVC) and not uncommonly associated with partial anomalous connection of the right inferior pulmonary vein to the IVC. CS defects represent many morphologic variations of defects that allow interatrial communication. They are holes at the site of the CS orifice that allow direct interatrial communication or are located on the postero-inferior wall of the left atrium (LA) allowing passage of blood between the LA and the CS channel [2]. Secundum ASD accounts for 65% to 75% of all ASDs. Females compose 65% to 75% of patients with secundum ASD, but the sex distribution is equal for the other type of ASD [3].

ASD can present as isolated defects (the most common) or in association with other CHD such as pulmonary stenosis or mitral valve prolapse. Genetics play a role and there are associations of certain ASD types with particular syndromes. Skeletal abnormalities of the forearm and hand are associated with secundum ASD from mutations in TBX5 gene. Familial forms of secundum ASD have been associated with prolonged conduction times and GATA4 and NKX2.5. At the Royal Brompton Hospital in 250 consecutive cases undergoing secundum ASD closure, there was a 2% incidence of family history in 1 or more with close relatives [4].

Although many ASDs are diagnosed in childhood, a significant number first present during adulthood. It has been reported that 50% of ASD patients presented in adult life [4].

2. Pathophysiology

Usually, ASD results in a left-to-right (L-R) shunt. Both the direction and magnitude of blood flow through a small ASD are determined by the size of the defect and by the relative atrial pressures, which relate to the compliances of the left (LV) and right (RV) ventricles. In large ASD, both atrial pressures are relatively equalized and the shunt only depends on the ratio of the LV and RV compliances. Normally the RV compliance is

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Clinical and Genomic characteristics of LAMA2 Related congenital Muscular Dystrophy in a Patients' Cohort from Qatar. A population Specific Founder Variant

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Abstract

Congenital *LAMA2* related muscular dystrophy (LAMA2-RD), the most commonly recognized type of congenital muscular dystrophies, has been described in patients' cohorts from Europe and the UK but not from Middle-Eastern. This study aimed to reveal the prevalence, clinical and genomic characteristics of congenital LAMA2-RD in a patient's cohort of 17 families (21 patients) from the Gulf and Middle East.

Affected subjects exhibited the classic phenotype of generalized hypotonia, developmental delay, and progressive muscular weakness. Despite the homogeneous background of most of our patients, clinical variability was evident; however, none of our patients was able to achieve independent ambulation. The associated features of nephrocalcinosis, infantile-onset osteopenia, and cardiac arrest were first described in this study. *LAMA2* mutations constituted 48% of the genetic causes underlying congenital muscular dystrophies (CMDs) in our patients. We estimated a point prevalence of 0.8 in 100.000 for LAMA2-RD in Qatar, relatively higher compared to that described in Europe's studies. The founder mutation and high rate of consanguinity are potential contributors. This study identified five *LAMA2* truncating variants, two novel and three recurrent, of which the c.6488delA-frameshift that was found in 12 unrelated Qatari families, highlighting a founder mutation in Qatari patients. The two novel variants involved an acceptor splice site and N-terminus deletion that removes the *LAMA2* promoter, exon1, and part of intron1. The "residual" expression of LAMA2 transcript and protein associated with this large N-terminus deletion suggested an alternative promoter that, while seems to be activated, acts less efficiently.

Key words

Covid-19 induced superimposed bacterial infection

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Abstract

Viral respiratory infections are very common and they are frequently eliminated from the body without any detrimental consequences. Secondary serious bacterial infection has been an apprehension expressed by health care providers, and this fear has been exacerbated in the era of Covid-19. Several published studies have shown an association between Covid-19 illness and secondary bacterial infection. However, the proposed mechanism by which a virus can develop a secondary bacterial infection is not well delineated. The aim of this commentary is to update the current evidence of the risk of bacterial infection in patients with Covid-19. We present several clinical studies related to the topic as well as a brief review of the potential pathophysiology of secondary infections that could present with Covid-19.

Keywords: Covid-19; secondary bacterial infection; studies; pathogenesis

1. Introduction

Viral respiratory infections are very common and they are frequently eliminated from the body without any detrimental consequences. Secondary serious bacterial infection has been an apprehension expressed by health care providers (Hendaus et al., 2015). This fear has been recently exacerbated when clinicians face patients with Coronavirus Disease-2019 (Covi19) infection.

RESEARCH

The effects of empagliflozin vs metformin on endothelial microparticles in overweight/obese women with polycystic ovary syndrome

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Abstract

Context: Endothelial microparticles (EMPs) are novel, surrogate biomarkers of endothelial function and have been shown to be elevated in women with polycystic ovary syndrome (PCOS). It remains poorly understood how pharmacological options for managing PCOS affect EMP levels.

Objective: To characterise and compare the effects of empagliflozin vs metformin on the circulating levels of EMPs in overweight/obese women with PCOS.

Methods: This was a randomised, comparative, 12-week single-centre trial conducted at the Academic Diabetes, Endocrinology and Metabolism Research Centre, Hull, UK. This analysis includes data from 39 overweight/obese women with PCOS who completed the study and were randomised to empagliflozin (15 mg/day) (n = 19) or metformin (1500 mg/day) (n = 20). Blood samples were collected at baseline and 12 weeks after treatment and analysed for specific surface proteins (ICAM-1, VCAM-1, PECAM-1, E-selectin and endoglin) expressed by circulating EMPs using flow cytometry.

Results: In the empagliflozin group, ICAM-1 (P = 0.006), E-selectin (P = 0.016) and VCAM-1 (P = 0.001) EMPs increased significantly following 12 weeks of treatment, but no changes were seen in PECAM-1 (P = 0.93) or endoglin (P = 0.13) EMPs. In the metformin group, VCAM-1 EMPs (P < 0.001) increased significantly after 12 weeks of treatment, whereas all other EMPs remained unchanged. When data were expressed as percentage change from baseline in each group, no significant differences were seen between groups for any biomarker (P-values from 0.22 to 0.80).

Conclusions: Short-term administration of empagliflozin and metformin in overweight/obese women with PCOS appear to increase EMPs expressed by endothelial cells during their activation.

Key Words
- endothelial microparticles
- polycystic ovary syndrome
- SGLT2 inhibitors
- empagliflozin
- metformin

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Review

Transcatheter pulmonary valve replacement in pediatric patients

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Abstract

Introduction: Right ventricular outflow tract (RVOT) dysfunction is common among individuals with congenital heart disease (CHD). Surgical intervention often carries prohibitive risks due to the need for sequential pulmonary valve (PV) replacements throughout their life in the majority of cases. Transcatheter pulmonary valve replacement (tPVR) is one of the most exciting recent developments in the treatment of CHD and has evolved to become an attractive alternative to surgery in patients with RVOT dysfunction.

Areas covered: In this review, we examine the pathophysiology of RVOT dysfunction, indications for tPVR, and the procedural aspect. Advancements in clinical application and valve technology will also be covered.

Expert opinion: tPVR is widely accepted as an alternative to surgery to address RVOT dysfunction, but still significant numbers of patients with complex RVOT morphology deemed not suitable for tPVR, As the technology continues to evolve, new percutaneous valves will allow such complex RVOT patient to benefit from tPVR.

Keywords: Transcatheter pulmonary valve; Pulmonary regurgitation; Congenital Heart Disease; Tetralogy of Fallot

Poor Agreement but Good Predictive Value Between Automated and Manual QTc Intervals in Pediatric Emergency Department Electrocardiograms

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Objectives: QTc interval is significant because prolongation may lead to ventricular dysrhythmia. Computerized electrocardiogram machines typically measure QT interval length and, using an algorithm assessment of multiple leads, calculate a QTc value. Manual measurement of the QT interval used to calculate the QTc value is more time-consuming but potentially more accurate. In this study, we compare the automated QTc calculation with the QTc value calculated using manual QT measurements.

Methods: We prospectively obtained 350 resting 12-lead electrocardiograms (ECGs) in children aged 2 to 14 years in an academic pediatric emergency department. Manual measurement of the QT interval was performed and the QTc was calculated using the 2 most commonly used correction methods, Bazzet and Fridericia formulas. The paired values were used to perform a Bland-Altman analysis and create a receiver operating characteristic curve.

Results: Bland-Altman analysis determined that QT-automated and QTc-Bazett had an average difference of 3.8 milliseconds, with a standard deviation of 86 milliseconds (95% confidence interval = −161 to 176). An automated QTc value of 455 milliseconds was sensitive to detect manual QTc values of greater than 480 milliseconds.

Conclusions: In children with resting ECGs, there is a poor agreement between the automated QTc produced by a computerized electrocardiogram and the QTc value obtained using manual QT measurement. Statistically and clinically relevant discrepancy between the automated QTc and QTc values calculated after manual QT measurement was present. Automated QTc values may be used as a screening tool to detect prolonged QTc, but for accurate determination of QTc, manual measurement is necessary.

Key Words: QT, QTc, Bazett, Fridericia, torsades, ECG

(*Pediatr Emer Care* 2020;36: 286–290)

The primary relevance of the QT interval and associated QTc interval of an ECG is that prolongation of this interval may result in torsades de pointes and potentially death. In children, prolongation of the QT interval as a result of medication exposure and/or long QT syndrome is of concern.[1]

Most modern cardiograph machines are computerized, and they typically provide a QTc value produced by an algorithmic analysis of the QT interval in multiple leads. There is a modest amount of published literature comparing QT and QTc interval values that result from automated versus manual measurement. These typically are studies performed in adult volunteers.[2,3] Few pediatric studies of QT measurement exist, and none are in emergency or acute care settings. Neonatal studies[4] and several studies of pediatric QTc measurement from Japan, where routine screening for prolonged QTc is regularly carried out, have been published.[5]

Most studies on the topic show discrepancy between automated and manual QTc measurement. Expert panels on the topic of long QT syndrome recommend that QT intervals be measured manually.[6,7] We sought to compare automated QTc measurements (QTcA) with QTc values that were produced by manual measurement in pediatric emergency department patients.

METHODS

This institutional review board–approved prospective study was conducted in an academic pediatric emergency department with a census of 250,000/year. Electrocardiograms from children aged 2 to 14 years who were being treated in the ED were obtained. This was performed with a Phillips Pagewriter Tc70 Cardiograph (Phillips Healthcare, Cleveland, Ohio) producing a standard 12-lead ECG with 25.0 mm/s and 10 mm/mV.

After completing a 6-hour course on ECG interpretation in athletes, which includes specific focus on methods of QT interval measurement QTc calculation,[8] a pediatric emergency physician manually measured the QT and RR interval of each ECG. This was performed using digital calipers accurate to 0.01 mm (Mitutoyo Corporation, Tokyo, Japan). These intervals were measured as the preceding RR interval, and QT was from the first deflection of the Q wave until the terminus of the T wave. The T wave terminus, which is typically the only difficult aspect of the interval to measure and that area that leads to variability in measurement, was considered to be the shorter of the intervals defined by the return to the isoelectric line or the tangent of the steepest downward slope of the T wave intersecting with the isoelectric line. Intervals were preferentially measured in lead II if the tracing and T wave morphology was adequate. If not, the QRS was measured, followed by other limb leads with the tallest T waves.

For QTc calculation, the 2 most commonly used correction formulae were used. These were the Bazett formula, which uses the square root of the RR interval and is more broadly referred to in general medical practice but is known to overestimate QTc at higher heart rates, and Fridericia formula, which uses the cube root of the RR interval and may be more accurate but can overcorrect at slower heart rates. The QTcA value, QTc values obtained by manual measurement using Bazett correction (QTcB), and the similar value produced by Fridericia correction (QTcF) were compared using Stata 12.0 (Stata Corp, College Station, Tex) statistical software, a Bland-Altman analysis. Receiver operator characteristic curves were also produced to determine what QTcA value best predicts prolonged QTcB and QTcF values. The US Food and Drug Administration recommended significant values of QTc of 480 and 500 milliseconds were used.

Statistical reporting includes bias, standard deviation of bias, and 95% confidence interval, and for ROC curve, the

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Article type : Original Article

Corneal nerve loss in children with Type 1 diabetes mellitus without retinopathy or microalbuminuria

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Corneal nerve loss in children with Type 1 diabetes mellitus without retinopathy or microalbuminuria

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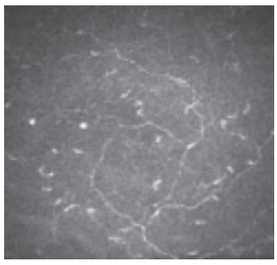

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Abstract

Introduction/Aim

Corneal confocal microscopy is a rapid, non-invasive ophthalmic technique to identify sub-clinical neuropathy. The aim of this study was to quantify corneal nerve morphology in children with type 1 diabetes mellitus compared to age-matched healthy controls using corneal confocal microscopy.

Method

Twenty participants with type 1 diabetes mellitus (age 14±2 years, diabetes duration 4.08±2.91 years, glycated hemoglobin 9.3±2.1%) without retinopathy or microalbuminuria and 20 healthy controls were recruited from outpatient clinics. Corneal confocal microscopy was undertaken and corneal nerve fiber density (no./mm^2), corneal nerve branch density (no./mm^2), corneal nerve fiber length (mm/mm^2), corneal nerve fiber tortuosity and inferior whorl length (mm/mm^2) were quantified manually.

Results

Corneal nerve fiber density (22.73±8.84 vs. 32.92±8.59; *P*<0.001), corneal nerve branch density (26.19±14.64 vs. 47.34±20.01; *P*<0.001), corneal nerve fiber length (13.26±4.06 vs. 19.52±4.54; *P*<0.001) and inferior whorl length (15.50±5.48 vs. 23.42±3.94; *P*<0.0001) were significantly

lower, whilst corneal nerve fiber tortuosity (14.88±5.28 vs. 13.52±3.01; *P*=0.323) did not differ between children with type 1 diabetes mellitus and controls. Glycated hemoglobin correlated with corneal nerve fiber tortuosity (*P*<0.006) and aspartate aminotransferase correlated with corneal nerve fiber density (*P*=0.039), corneal nerve branch density (*P*=0.003), and corneal nerve fiber length (*P*=0.037).

Conclusion

Corneal confocal microscopy identifies significant sub-clinical corneal nerve loss, especially in the inferior whorl of children with type 1 diabetes mellitus without retinopathy or microalbuminuria.

Keywords: Type 1 diabetes mellitus, child, small fiber neuropathy

Introduction

Type 1 Diabetes Mellitus (T1DM) affects over half a million children worldwide (1, 2). Diabetes is associated with chronic microvascular complications in adults which increases morbidity and all-cause mortality (3). Diabetes is the main cause of distal symmetric polyneuropathy (DSPN) (4-6). Adults with DSPN present with a combination of symptoms such as numbness, pain, and tingling in the feet (7). The American Diabetes Association endorses screening for distal symmetric polyneuropathy (DSPN) at diagnosis of T2DM, 5 years after the diagnosis of T1DM and annually thereafter (8). Children and adolescents with T1DM rarely complain of neuropathic symptoms. However, a study of children with T1DM showed reduced motor and sensory nerve conduction velocities (24%) and at least one neuropathic symptom (60%) or sign (58%) (9) and in another study symptomatic neuropathy was present in 13.5%, whilst 22.5% had neurophysiological evidence of neuropathy (10) and 18% had impaired vibrotactile sense (11). Furthermore, in one study 36% had >2 abnormal autonomic function tests and 18.8% had severe autonomic neuropathy (12). In a prospective study abnormal nerve conduction velocity (NCV) was found in 31.6% at baseline which increased to 63.2% after 5 years (13) and in another study over 10 years the prevalence of clinical neuropathy increased from 6.5% to 16.1%, whilst NCV abnormalities increased from 17.7% to 46.8% (14). Whilst, neurophysiologic assessments are highly sensitive they are not easily performed in children (15). Vibration perception threshold (VPT) and tactile perception threshold tests are easy to perform but lack sensitivity for the early detection of DSPN (16). There is a need for non-invasive sensitive screening tools for the early detection of neuropathy in children with diabetes.

Corneal confocal microscopy (CCM) is a rapid, non-invasive and well-tolerated technique to detect and quantify neuropathy in adults with T1DM (17-24). An early study found no significant changes in CCM parameters in children with T1DM (15). However, a more recent study has shown a significant reduction in corneal nerve fibre measures in young children with T1DM with and without diabetic retinopathy (25). The aim of this study was to quantify corneal nerve morphology in the central cornea and inferior whorl of children with T1DM compared to age-matched healthy controls using CCM.

Methods

Twenty participants with T1DM and 20 age-matched healthy controls underwent CCM. Patients with a history of any other cause of neuropathy, malignancy, deficiency of B12 or folate, chronic renal failure, liver failure, connective tissue or systemic disease (rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, systemic scleroderma, Raynaud Phenomenon), previous corneal trauma or systemic disease that affects the cornea, surgery and a history of or current contact lens wear were excluded from the study. All participants provided assent and parental informed consent and the research adhered to the tenets of Declaration of Helsinki and was approved by Sidra Medicine and Weill Cornell Medicine Research Ethics Committee.

Image selection and quantification

Six central sub basal nerve plexus (SBNP) images were selected from the central cornea and corneal nerve fiber density (CNFD), (no./mm^2) corneal nerve branch density (CNBD) (no./mm^2), corneal nerve fiber length (CNFL) (mm/mm^2), corneal nerve fiber tortuosity (CNFT) were quantified using manual CCMetrics. Six images centred on the inferior whorl and adjacent areas (upper right/left corner and lower right/left corners) were selected and the inferior whorl length (IWL) (mm/mm^2) was quantified utilizing the manual CNFL mode in CCMetrics (Figure 1) (26). The investigator was blind to the study group when performing CCM and analysing CCM images.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software Version 26 and $P<0.05$ was considered statistically significant. Normally distributed data were expressed as mean ± standard deviation and the means were compared using an independent sample t-test. Pearson correlation was undertaken to investigate the association between clinical parameters and corneal nerve fibre parameters. Graph prism version 8 was used to build dot plots.

Results

Twenty participants with T1DM and 20 healthy controls underwent CCM. Subjects with T1DM were slightly older ($P<0.02$) and taller ($P<0.02$) but had comparable weight and BMI. They also had a lower aspartate aminotransferase (AST) ($P<0.02$) but comparable bilirubin and alanine aminotransferase (ALT) (Table 1).

Only 4 (20%) of the patients met the American Diabetes Association (ADA) criteria (>10 yrs. of age and >5 yrs. of diabetes) to undergo screening for microvascular complications. Eight (40.0%)

underwent assessment for retinopathy and 11 (55.0%) underwent assessment for microalbuminuria of whom none had retinopathy or microalbuminuria.

CNFD (22.73±8.84 vs. 32.92±8.59; *P*=0.001), CNBD (26.19±14.64 vs. 47.34±20.01; *P*<0.001) and CNFL (13.26±4.06 vs. 19.52±4.54; *P*<0.001) were lower in patients with T1DM compared to healthy controls (Figure 2A-C). CNFT did not differ between groups (14.88±5.28 vs. 13.52±3.01; *P*=0.323) (Figure 3D). IWL was significantly lower in patients with T1DM (n=19) compared to controls (n=19) (15.50±5.48 vs. 23.42±3.94; *P*<0.0001) (Figure 3 A-C). CNFD, CNBD, CNFL and IWL were >2SD lower than the mean of controls in 15%, 10%, 30% and 50% of patients with T1DM.

Correlation between CCM parameters and clinical/laboratory measures

Age, height, BMI, 25(OH)D, bilirubin and ALT did not correlate with any CCM parameter (*P*>0.05). There was no correlation between duration of diabetes and CCM parameters (*P*>0.05) and only glycated hemoglobin (HbA_{1c}) correlated significantly with CNFT (*P*<0.006). AST correlated with BMI (P<0.01), CNFD (*P*=0.039), CNBD (*P*=0.003), and CNFL (*P*=0.037) (Table 2).

Discussion

In the present study there is evidence of significant corneal nerve loss in children with T1DM without retinopathy or microalbuminuria. It is critical to detect and prevent nerve damage at the earliest stage of diabetic neuropathy as improvement in glycaemic control and other risk factors such as obesity, hypertension, dyslipidaemia may prevent nerve degeneration and promote nerve regeneration (27, 28).

Previous studies in adults with T1DM have found a significant reduction in central CNFD, CNBD and CNFL compared to healthy controls (18, 29-35) and in T1DM patients without retinopathy or microalbuminuria (34). Corneal nerve loss has good diagnostic utility for both diabetic somatic and autonomic neuropathy (22). Furthermore, a lower CNFL is associated with the development of clinical diabetic neuropathy (31, 36, 37), and a more rapid reduction in CNFL predicts the development and progression of diabetic neuropathy (38). Significant improvements in CNFD, CNBD, and CNFL have been observed in T1DM patients after simultaneous pancreas and kidney transplantation (39, 40), omega-3 supplementation (41) and an improvement in multiple risk factors for diabetic neuropathy (42).

In the present study a significant reduction in central corneal nerve fibre parameters in young children with T1DM has been demonstrated, which is comparable with a previous study in children and young adolescents with T1DM (25). Established risk factors for diabetic neuropathy such as age, height, HbA_{1c} and BMI were not associated with the reduction in corneal nerve parameters, consistent with previous findings in adults with T1DM (35, 43). CNFT was not altered, in contrast with a study in adults with diabetes where nerve tortuosity was higher (44). A reduction in corneal nerves occurs, regardless of diabetes duration, in young patients with T1DM (35) and adults with T2DM (45).

The ADA has recommended initial screening for albuminuria and retinopathy in patients with T1DM aged over 10 years, after 3-5 years of diabetes (46). Whilst 20% of this cohort fulfilled the criteria for screening, none had microalbuminuria or retinopathy. Indeed, the significant corneal nerve loss in these children with T1DM without retinopathy or microalbuminuria agrees with previous findings in adults with T1DM (25, 34) and supports the thesis that neuropathy may precede retinopathy (47). It also argues for earlier screening of diabetic neuropathy in children with T1DM using CCM. AST was lower in our cohort with T1DM and

correlated with CNFD, CNBD, and CNFL. No relationship between AST and CCM has been observed in studies in adults with diabetes (21, 22, 30, 48). Whilst the association between body mass index and elevated AST is well established as a marker for liver injury in obese adults (49-52), in the present study AST was inversely correlated with BMI.

The inferior whorl is distal to the central nerves and may allow the identification of earlier nerve damage (26, 53). Studies in adults with T1DM and T2DM have shown a greater reduction in IWL (48, 54), especially in those with painful diabetic neuropathy (55, 56). This is the first study in children with T1DM showing a marked reduction in IWL, with 50% having a reduction >2SD lower than the mean in controls.

A limitation of the current study is the cross-sectional design, relatively small number of subjects studied and the lack of additional measures of diabetic neuropathy. Prospective studies are needed to assess progression of corneal nerve abnormalities in relation to other complications and risk factors for diabetic neuropathy.

Significant corneal nerve loss has been demonstrated in the central cornea and inferior whorl indicative of neuropathy in children with T1DM without microalbuminuria or retinopathy. This suggests that CCM could be used to screen for early sub-clinical neuropathy and to assess disease progression in children with T1DM.

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Disclosure

The authors have declared that no competing interests exist.

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Figure 1. Central corneal sub-basal nerve plexus and inferior whorl.

[Insert Figure 1]

(A) Schematic presentation of the sub-basal nerve plexus (SBNP) at the central and inferior whorl. (B) Nerve fibres at the central cornea, (C) tracing of the nerves using CCMetrics, (D) Nerve fibres at the inferior whorl (IW), (E) tracing of the IW using CCMetrics.

Figure 2. CCM parameters and images of the sub-basal plexus in children with T1DM and healthy controls.

[Insert figure 2]

(A) CNFD: Corneal nerve fiber density, (B) CNBD: corneal nerve branch density, (C) CNFL: corneal nerve fiber length, (D) CNFT: corneal nerve fiber tortuosity, (E) CCM image of corneal nerves in a healthy control, (F) CCM image of reduced corneal nerves in a child with T1DM.

Figure 3. Inferior whorl length and CCM images of the inferior whorl in children with T1DM and healthy controls.

[Insert figure 3]

(A) IWL (Inferior whorl length) in healthy controls and children with TIDM, (B) CCM image of IWL in a healthy control and (C) CCM image of IWL in a child with T1DM.

Table 1. Clinical and laboratory measures in patients with T1DM and controls.

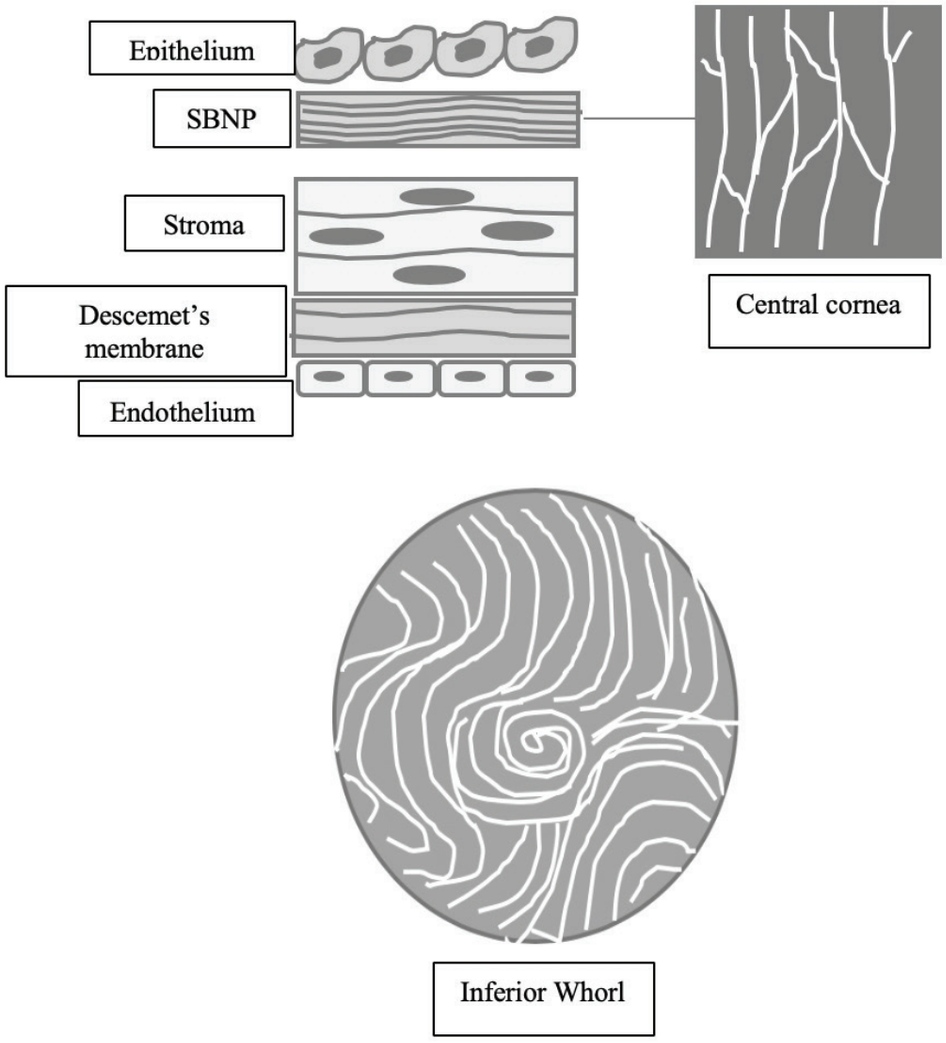
	Healthy (n=20)	T1DM (n=20)	*P*-value
Age	12.83±1.91	14.47±2.43	**0.02**
Duration of T1DM	-	4.08±2.91	N/A
Height (m)	1.45±0.13	1.54±0.09	**0.02**
Weight (kg)	47.87±18.63	51.65±13.46	0.467
BMI (Kg/m^2)	22.26±5.47	21.68±5.09	0.733
HbA$_{1c}$ (%)	-	9.3±2.1	N/A
Bilirubin (µmol/L)	10.54±5.4	13.22±5.92	0.206
AST (IU/L)	24.83±5.45	20.44±4.23	**0.02**
ALT (IU/L)	15.08±4.03	16.44±3.74	0.339
25(OH)D (ng/ml)	23.88±8.96	18.16±8.56	0.085
Microalbuminuria n (%)			
Yes	-	0	N/A
No	-	11 (55.0%)	
Diabetic retinopathy n (%)			
Yes	-	0	N/A
No	-	8 (40.0%)	

Data are presented as mean ± SD. BMI: Body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

Table 2. Correlations between CCM parameters and clinical and metabolic parameters.

	Age (years)	Duration of disease (years)	HbA_{1c} (%)	Height (m)	BMI (Kg/m^2)	25(OH)D (ng/ml)	Bilirubin (µmol/L)	AST (IU/L)	ALT (IU/L)
CNFD ($no./mm^2$)	-0.278 (0.235)	0.027 (0.915)	-0.300 (0.226)	-0.028 (0.907)	-0.396 (0.084)	0.072 (0.783)	-0.207 (0.41)	0.489 (**0.039**)	-0.121 (0.633)
CNBD ($no./mm^2$)	-0.144 (0.544)	0.108 (0.670)	0.221 (0.377)	0.040 (0.876)	-0.329 (0.157)	-0.002 (0.995)	0.033 (0.897)	0.666 (**0.003**)	0.129 (0.611)
CNFL (mm/mm^2)	-0.188 (0.428)	0.067 (0.791)	-0.036 (0.887)	0.053 (0.824)	-0.257 (0.275)	-0.099 (0.706)	-0.127 (0.615)	0.495 (**0.037**)	-0.013 (0.959)
CNFT (TC)	0.28 (0.231)	0.032 (0.899)	0.619 (**0.006**)	0.202 (0.392)	0.203 (0.39)	0.244 (0.344)	0.267 (0.284)	-0.165 (0.505)	-0.282 (0.256)
IWL (mm/mm^2)	0.195 (0.423)	0.029 (0.911)	-0.009 (0.974)	0.063 (0.798)	0.358 (0.133)	-0.380 (0.132)	-0.456 (0.066)	0.014 (0.957)	-0.001 (0.995)

CNFD: Corneal nerve fibre density, CNBD: corneal nerve branch density, CNFL: corneal nerve fiber length, CNFT: Corneal nerve fiber tortuosity, IWL: inferior whorl length, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase.



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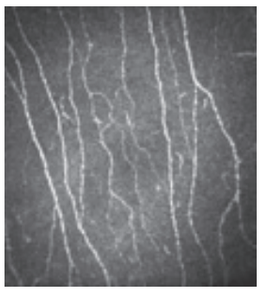

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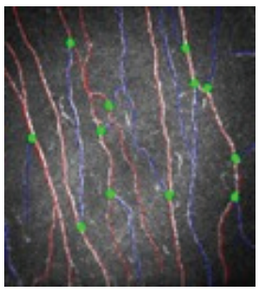

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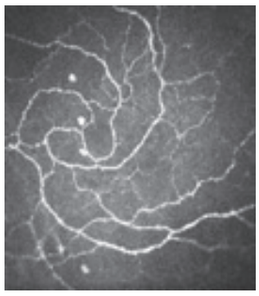

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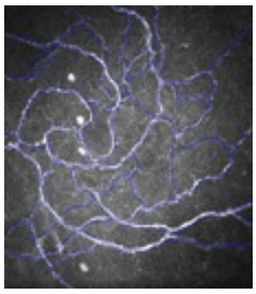

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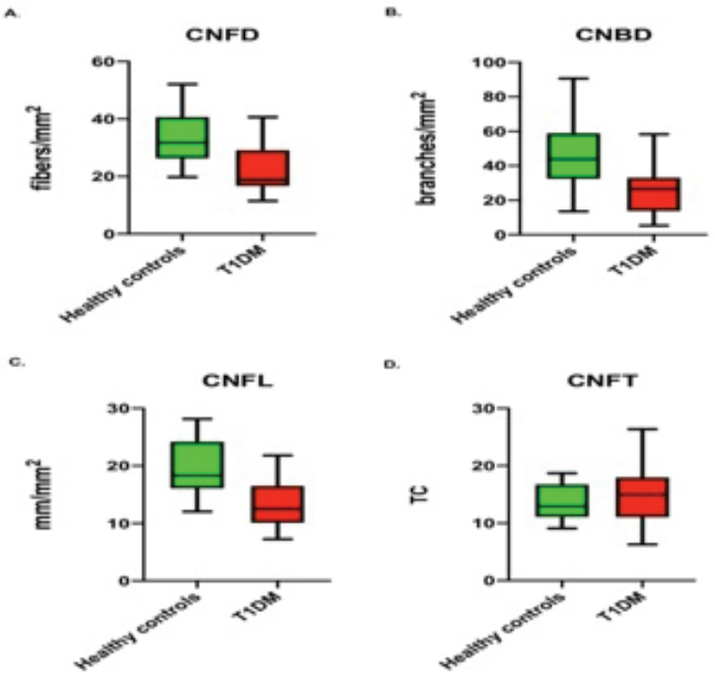

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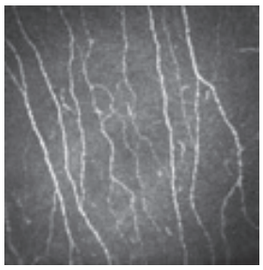

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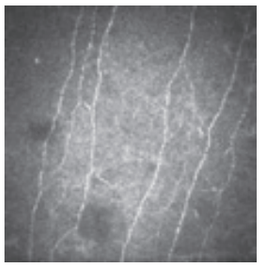

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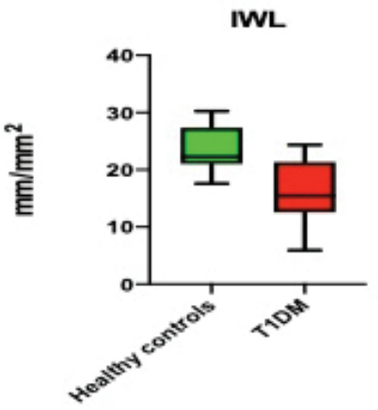

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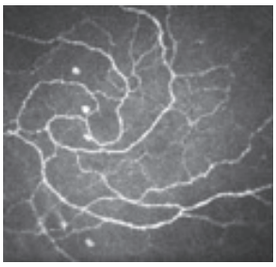

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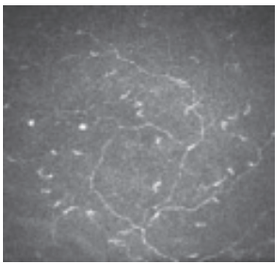

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AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Resource Announcements

GENOME SEQUENCES

Draft Genome Sequence of an Extended-Spectrum β-Lactamase-Producing *Klebsiella oxytoca* Strain Bearing *mcr-9* from Qatar

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ABSTRACT *Klebsiella oxytoca* is an opportunistic human pathogen causing nosocomial infection. We report the draft genome of an extended-spectrum β-lactamase-producing *K. oxytoca* isolate harboring an *mcr-9* gene, a recently discovered colistin resistance analog, from Qatar. The genome statistics, along with the sequence type and resistance mechanisms, are predicted for the assembled genome.

Colistin in combination with other agents is used for the treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria. The emergence of plasmid-mediated resistance to colistin due to lipid A-modifying enzymes encoded by 10 different *mcr* genes in *Enterobacterales* has endangered the last-resort treatment (1–3). One of the genes, *mcr-9*, has been recently described in *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., and *Salmonella enterica* serotype Typhimurium (4–9) from animals and humans. The increasing reports of novel *mcr* genes have become a great concern in many countries. Therefore, it is crucial to understand the molecular mechanisms of colistin resistance in Qatar.

Klebsiella oxytoca is an opportunistic pathogen associated with nosocomial infections (10, 11). It becomes a public health concern because of resistance to antimicrobials due to the presence of bla_{OXY}, $bla_{CTX\text{-}M}$, and bla_{SHV} genes (11). Here, we report the genome of *K. oxytoca* strain 18099069b harboring *mcr-9*, which was isolated from a rectal swab obtained from a child during admission to the intensive care unit to screen for extended-spectrum β-lactamase (ESBL)- and carbapenemase-producing *Enterobacteriaceae*. Swabs are routinely inoculated onto CHROMagar ESBL and CHROMagar mSuperCARBA (CHROMagar, France). Plates are incubated under aerobic conditions at 35 ± 2°C for 18 to 24 h, minimizing exposure to light. Suspicious colonies growing on the chromogenic agar plates after overnight incubation are identified using the matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) Biotyper system (Bruker, Bremen, Germany). In this case, MALDI-TOF mass spectrometric identification was performed on a single colony picked from the ESBL chromogenic plate onto the MALDI target plate. Antimicrobial susceptibility testing was performed using the Phoenix system (Becton, Dickinson, USA). The MIC for colistin was determined by broth microdilution (ComASP Colistin; Liofilchem, Italy). MICs were interpreted according to the CLSI breakpoints (12). Ethics approval for the study was obtained from the institutional review board of Sidra Medicine.

DNA was extracted using the NucliSENS easyMag platform (bioMérieux, France). DNA libraries were constructed with a Nextera XT kit (Illumina, CA) and sequenced on the Illumina MiSeq system with 2 × 300 cycles. The sequence data were trimmed using

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Paediatric procedural sedation in the emergency department: is ketamine safe?

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Procedural sedation and analgesia involve the use of one or more sedative and analgesic agents to relieve pain and anxiety and to control motor activity in patients undergoing diagnostic and therapeutic procedures.[1–4] Administration of effective procedural sedation can maximise patient comfort, thus leading to a higher frequency of procedural success and it is also often linked with increased parental satisfaction with the emergency department (ED) experience, even though the administration of sedation can be associated with increased length of stay.[1–4] Typical indications for procedural sedation include diagnostic imaging, fracture or dislocation reduction, wound care and repair of a laceration, incision and drainage of an abscess, lumbar puncture and placement of a central venous catheter.[1–4] This paper will discuss the safety profile of ketamine when used in procedural sedation and how to prevent or manage ketamine sedation-related adverse events.

KETAMINE: PHARMACOLOGY AND ACTIONS

Ketamine is N-methyl-D-aspartate receptor blocker, a dissociative agent chemically related to phencyclidine. It produces a trance-like cataleptic state of sensory isolation characterised by profound analgesia, sedation and amnesia while maintaining cardiovascular stability and preserving spontaneous respirations and airway reflexes.[4] Ketamine undergoes hepatic metabolism to norketamine, an active metabolite with one-third of the analgesic potency of ketamine. It has a short duration of action and can be administered intravenously, intramuscularly or intranasally. The intravenous route is highly preferred in procedural sedation using ketamine. The onset of action of ketamine is rapid (1–2 min), the duration is brief (10–15 min) and the recovery time is short (30–60 min). The initial dose is 1–1.5 mg/kg, and an additional 0.5 mg/kg doses can be administered within the next 4 min and titrated to effect. The dose given should achieve and maintain dissociation. This is an important concept. Other drugs used for sedation in the ED will demonstrate a dose-response continuum, which generally involve more drug to achieve deeper sedation but with concomitant depression of protective airway reflexes and cardiorespiratory status. Ketamine will produce a threshold of dissociation without that effect.[4]

The intramuscular route is typically limited to situations where intravenous access cannot be obtained or where severe aggressive behaviour prevents cooperation in obtaining intravenous access. The initial dosing is 4–6 mg/kg, with subsequent 2–4 mg/kg doses administered after 10 min as needed. The onset of action is delayed to about 10–15 min and clinically useful sedation lasts 30–40 min. The intranasal route can also be used in paediatric population where higher doses of up to 9 mg/kg have been used.[1–4]

KETAMINE: SEDATION-RELATED ADVERSE EVENTS

The primary disadvantage of ketamine is its adverse event profile. Respiratory events include hypersalivation, apnoea, laryngospasm, clinically apparent pulmonary aspiration and oxygen desaturation. Apnoea may require an intervention to stimulate or assist ventilation including vigorous tactile stimulation, application of bag mask with assisted ventilation or tracheal intubation.[4] Laryngospasm is a partial or complete upper airway obstruction with oxygen desaturation caused by involuntary and sustained closure of

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Full length article

Group B streptococcal disease in the mother and newborn—A review

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ABSTRACT

Group B Streptococcus, a common commensal in the gut of humans and in the lower genital tract in women, remains an important cause of neonatal mortality and morbidity. The incidence of early onset disease has fallen markedly in countries that test women for carriage at 35–37 weeks of pregnancy and then offer intrapartum prophylaxis with penicillin during labour. Countries that do not test, but instead employ a risk factor approach, have not seen a similar fall. There are concerns about the effect on the neonatal microbiome of widespread use of antibiotic prophylaxis during labour, but so far the effects seem minor and temporary. Vaccination against GBS would be acceptable to most women and GBS vaccines are in the early stages of development.

Tweetable abstract: Group B Strep is a key cause of infection, death and disability in young babies. Antibiotics given in labour remain the mainstay of prevention, until a vaccine is available.

What is group B Streptococcus (GBS)?

Antony Van Leeuwenhoek (1632–1723) was the first to identify microscopic one-celled organisms, which he called 'animalcules'. He described bacteria of the genus Selenomonas (crescent shaped bacteria from the human mouth) in 1676. The understanding of bacteria was greatly increased by the work of Louis Pasteur (1822–1895), but it was Robert Koch (1843–1910) who first linked specific microorganisms to particular diseases, such as tuberculosis, cholera and anthrax. A Viennese surgeon, Theodor Billroth (1829–1894) coined the term Streptococcus to describe a group of bacteria within the order Lactobacillales and phylum Firmicutes. Beta-haemolytic Streptococci are so-called because when they are cultured on blood agar (a growth medium made from algae and enriched with mammalian blood, usually from sheep or horses), the red blood cells are lysed and the haemoglobin the cells contained is denatured so that its red colour disappears. Group A beta-haemolytic Streptococci (characterised by possessing the Lancefield group A antigen, a carbohydrate structure found in the cell wall) tend to cause severe infections. An example is S.pyogenes, part of the skin microbiome in 2–17 % of individuals, which causes diseases such as rheumatic and scarlet fevers.

Group B beta-haemolytic Streptococci (GBS) are called S.agalactiae (Latin for "without milk") because they cause mastitis in cows [1]. It is a common bowel commensal in many animals including fish, cattle - and humans, in which it is present in 20–40 % of adults [2]. It can be divided into ten serotypes based on a serological reaction directed against the polysaccharide capsule [3] and which are thought to influence virulence and antibiotic resistance. The most frequently identified serotypes that cause invasive disease in neonates are III (60.6 %) and Ia (17.3 %), whereas type VI (32.7 %), Ib (19.4 %), and V (19.4 %) are the most common cause of invasive disease in adults. Serotype VI is the leading type that colonizes pregnant women (35.0 %) [4]. However, the differences are not currently thought to be sufficient to make them useful in clinical practice.

Clinical importance of GBS

Maternal infection – incidence

The clinical importance of group B Streptococcus is that, although it is commonly a commensal in the gut and vagina, it can

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Microbial Ecology
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SOIL MICROBIOLOGY

Changes in Bacterial and Fungal Microbiomes Associated with Tomatoes of Healthy and Infected by *Fusarium oxysporum* f. sp. *lycopersici*

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Abstract

Fusarium wilt of tomato caused by the pathogen *Fusarium oxysporum* f. sp. *lycopersici* (*Fol*) is one of the most devastating soilborne diseases of tomato. To evaluate whether microbial community composition associated with *Fol*-infected tomato is different from healthy tomato, we analyzed the tomato-associated microbes in both healthy and *Fol*-infected tomato plants at both the taxonomic and functional levels; both bacterial and fungal communities have been characterized from bulk soil, rhizosphere, rhizoplane, and endosphere of tomatoes using metabarcoding and metagenomics approaches. The microbial community (bacteria and fungi) composition of healthy tomato was significantly different from that of diseased tomato, despite similar soil physicochemical characteristics. Both fungal and bacterial diversities were significantly higher in the tomato plants that remained healthy than in those that became diseased; microbial diversities were also negatively correlated with the concentration of *Fol* pathogen. Network analysis revealed the microbial community of healthy tomato formed a larger and more complex network than that of diseased tomato, probably providing a more stable community beneficial to plant health. Our findings also suggested that healthy tomato contained significantly greater microbial consortia, including some well-known biocontrol agents (BCAs), and enriched more functional genes than diseased tomato. The microbial taxa enriched in healthy tomato plants are recognized as potential suppressors of *Fol* pathogen invasion.

Keywords *Fusarium oxysporum* · Tomato Fusarium wilt · Microbiome · Mycobiome · Metabarcoding · Shotgun metagenomics

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00248-020-01535-4) contains supplementary material, which is available to authorized users.

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Introduction

Tomato (*Solanum lycopersicum*) is one of the most widely cultivated vegetables worldwide, with a global annual yield of more than 177 million tons (FAO, http://www.fao.org/faostat). The production of tomato is often limited by diseases, especially the devastating soilborne disease Fusarium wilt, which is caused by the tomato-specific fungus *Fusarium oxysporum* f. sp. *lycopersici* (*Fol*) [1, 2]. This pathogen can infect tomato plants at all stages of growth and is one of the most devastating diseases of tomato [3]. Disease-resistant cultivars, chemical fungicides, biocontrol agents (BCAs), crop rotation, and soil fumigation are commonly used to manage Fusarium wilt [1, 2]. Crop rotation, however, is not favorable for greenhouse farmers who do not prefer growing less profitable cereals. Methyl bromide (for soil fumigation) is quite effective but has been phased out in the "Montreal Protocol," due to its considerable environmental

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Article type : Clinical Overview

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Clinical overview

Promoting attachment between parents and neonates despite the COVID-19 pandemic

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Abstract

Social distancing is the only option available during the COVID-19 pandemic until a vaccine is developed. However, this is having a major impact on human relationships and bonding between parents and neonates is a major concern. Separation during this health emergency could have lifelong consequences for offspring and there are even greater concerns if newborn infants are sick or vulnerable and need intensive care. We look at how bonding can be safely supported and maintained without risking infecting neonates, by comparing the international guidelines and proposing safe actions within those frameworks.

Key words: bonding, COVID-19, guidelines, pandemic, separation

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Dramatic decrease of laboratory-confirmed influenza A after school closure in response to COVID-19

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Keywords: influenza A; SARS-CoV-2; COVID-19; school closure; transmission.

Abbreviated title: Decrease of influenza A during COVID-19

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The novelty of the coronavirus disease 2019 (COVID-19) has led some researchers to use influenza models and changes in influenza activity to infer the impact of social distancing measures to mitigate the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1-2]. However, it has been argued that the effectiveness of school closure to reduce influenza transmission is not transferrable to the COVID-19 pandemic given the alleged lower attack rate in children compared with adults and the greater basic reproductive number of SARS-CoV-2 as opposed to influenza[3].

Sidra Medicine is the main referral centre for the pediatric population of Qatar with 76,694 pediatric emergency department (PED) visits in 2019. A proactive school closure was the first social distancing measure implemented by the State of Qatar on March 10. Table 1 shows a comparison of the molecular detection of respiratory viruses other than SARS-CoV-2 on nasopharyngeal swabs from our PED per 1000 emergency visits before school closure, between February 13 and March 14, assuming a maximum incubation period for influenza of 4 days, and after school closure, between March 15 and April 11. Notably, whereas the rate of laboratory-confirmed influenza A infections decreased more than 30-fold after school closure, rates of total respiratory pathogen tests and positive tests for other viruses, except for adenovirus, varied slightly. In fact, influenza A has not been detected by our laboratory since March 30. This dramatic decrease is unlikely to be related to seasonal variations as rates of laboratory-confirmed influenza A were similar during the same weeks in 2019 (RR, 1.3; 95% CI, 0.4-3.8, P=0.7), which was consistent with the typical transmission pattern in the northeastern coast of the Arabian Peninsula where influenza A circulates throughout the year with secondary peaks occurring usually in March[4]. Although the rates of common human coronaviruses (common HCoVs), including types 229E, HKU1, NL63 and OC43, did not change significantly before and after

Asthma Frequently asked questions

Magnesium Sulphate for Acute Asthma in children

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Key words: severe asthma attacks, Magnesium Sulphate, pharmacology.

Abstract

Most children who present to the emergency department with acute asthma, respond well to inhaled β_2-agonists (spacer or nebulizer), oxygen (if required) and systemic steroids. Guidelines across the world agree on this simple, straight forward evidenced based approach. In children with more severe asthma attacks and those who do not respond to initial treatment, the evidence base for the secondary level treatment is less clear. Many regimens exist for the next step. Intravenous Magnesium Sulphate ($MgSO_4$) is now used frequently in these situations and some centres are starting to use nebulized $MgSO_4$ as part of the initial maximal inhaled therapy options. This paper examines the role of $MgSO_4$ in acute asthma in children. It focusses on how $MgSO_4$ might work, what are the current recommendations for use and then what is the current evidence base to support its use. We have presented the evidence for the use of both nebulized and intravenous $MgSO_4$. At the end of the paper we have suggested future directions for research in this area. Our aim is to present a synthesis of the current role of $MgSO_4$ in the management of an acute asthma attack.

EFFECTS OF ISOLATION ON MOOD AND RELATIONSHIPS IN PREGNANT WOMEN DURING THE COVID-19 PANDEMIC

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Dear Editor,

We note that COVID-19 is a global public health emergency that has resulted in a significant psychological impact on the mental health of women during pregnancy[1]. There has been emerging evidence of further secondary morbidity associated with the pandemic with an in increase in domestic violence associated with the strategies implemented to slow its spread, namely social isolation and lockdown.[2] There is a known increased risk of domestic violence

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Original article

Relationship between inflammation and metabolic regulation of energy expenditure by GLP-1 in critically ill children

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SUMMARY

Background & aims: Critical illness is associated with derangement in the metabolic and inflammatory response. Previous investigators have highlighted the cross-link between feeding, inflammation and gut homeostasis. Glucagon like peptide-1 (GLP-1) is a gut derived hormone that plays an important role in the modulation of energy metabolism through appetite regulation and promotion of gastric motility. Growing evidence suggests that GLP-1 might influence energy expenditure. The aim of this study was to assess the relationship between inflammatory activation and metabolic regulation of energy expenditure by assessing cytokine release, levels of GLP-1 and energy expenditure in a cohort of critically ill children.
Method: This is a prospective study conducted in critically ill children. A blood sample was collected from each child during the first few days of critical illness, for the analysis of serum inflammatory cytokines (TNF-α, IL-10, IL-6 and IL-1β) and GLP-1 in 42 children. Indirect calorimetry (IC) measurements were performed concurrently in a subset of 21 children. The metabolic index was determined using the ratio of Measured Resting Energy Expenditure (MREE)/Predicted Resting Energy Expenditure (PREE) based on the Schofield equation. Correlation analysis was performed, followed by a stepwise linear regression analysis to assess factors affecting GLP-1 and the metabolic index.
Results: A total of 42 children (0–14 years) were included in this study. The regression analysis indicated that CRP, TNF-α, IL-6 and IL-1β statistically influenced GLP-1 concentrations ($p < 0.01$). Where IC measurements were performed ($N = 21$), GLP-1 showed a statistically significant association with the metabolic index ($p < 0.01$). No evidence of statistical association was recorded between the inflammatory mediators and the metabolic index. Overall the results showed that circulating GLP-1 was increased in response to inflammatory stimuli in critically ill children. GLP-1 contributed to the changes observed in MREE induced by critical illness in our cohort.
Conclusion: Energy expenditure is extremely variable in critically ill children, our study suggests that changes in GLP-1 might contribute to a significant amount of this variation. If confirmed in larger studies, GLP-1 could be used as a correction factor for REE predictive equations in critically ill children.

1. Introduction

Critical illness is associated with derangements in host metabolic and inflammatory responses [1]. As a result of close interrelationships between inflammatory, metabolic and endocrine homeostatic pathways, an acute insult to one may have implications on the normal functioning of the others [2]. Under physiological conditions, inflammatory cytokines have the capacity to regulate energy metabolism through suppression of appetite and modulation of stress hormones [3]. In critical illness, it is suggested that inflammatory cytokines can affect energy expenditure [2,3],

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Research Article

Comparison of Two Percutaneous Atrial Septal Defect Occluders for Device Healing and Nickel Release in a Chronic Porcine Model

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Aims. To investigate the healing process and nickel release of the Hyperion occluder (Comed BV, Netherlands), as compared to the Amplatzer septal occluder (ASO) (St. Jude Medical Inc., St. Paul, MN, USA) in a chronic swine model. *Background*. Some long-term complications occurring after percutaneous atrial septal defect (ASD) closure may be partially associated with an inappropriate healing of the device and increased nickel release. There is no direct comparative study of different occluders for healing and nickel release. *Methods*. After percutaneous ASD creation, 12 pigs were implanted with 15 mm Hyperion ($n = 6$) and 15 mm ASO ($n = 6$) devices. After 1 month ($n = 3$ for each device) and 3 months ($n = 3$ for each device) of follow-up, device explantation was performed and healing was assessed using histopathological workup. Systemic and tissular nickel release was performed. *Results*. Implantation was successful in 100% without complications. Device coverage was observed as early as 1 month after implantation and was almost complete after 3 months. A granulation tissue with a predominantly mononuclear inflammatory reaction was observed in contact with nitinol wires while an inflammatory reaction was seen in contact with textile fibers. We found no statistically significant difference between the 2 devices whether for histological grading scores or systemic nickel release, regardless to follow-up duration. *Conclusions*. In this preclinical study, we demonstrated that Amplatzer septal occluder and Hyperion occluder were not significantly different for device healing and nickel release processes.

1. Introduction

Transcatheter device occlusion of secundum atrial septal defects (ASD) has become the currently gold-standard treatment strategy for patients with suitable anatomy [1, 2]. The Amplatzer septal occluder (ASO) (St. Jude Medical Inc., St. Paul, MN, USA) has become the leading device worldwide for closing ASDs in the last two decades owing to its novel design, ease of use, and proven sustained efficacy. Long-term follow-up in both pediatric and adult ASD patients have shown favorable outcome with this device [3, 4]. However, although rare, device closure of ASD is also associated with some potentially serious complications including device thrombosis, device related endocarditis, or migraine headache [5, 6]. It has been suggested that those complications may be partially associated with (1) an

frontiers in Pediatrics

CASE REPORT
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A Novel *HNF4A* Mutation Causing Three Phenotypic Forms of Glucose Dysregulation in a Family

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Maturity-onset diabetes of the young (MODY) classically describes dominantly inherited forms of monogenic diabetes diagnosed before 25 years of age due to pancreatic β-cell dysfunction. In contrast, mutations in certain MODY genes can also present with transient or persistent hyperinsulinemic hypoglycemia in newborn infants, reflecting instead β-cell dysregulation. Of the MODY genes described to date, only hepatocyte nuclear factor-4-alpha (*HNF4A*; MODY1) and hepatocyte nuclear factor-1-alpha *(HNF1A*; MODY3) mutations may result in a biphasic phenotype of hypoglycemia in early life and hyperglycemia in later life. We report a family with a novel *HNF4A* mutation with diverse phenotypic presentations of glucose dysregulation. The proband was a term, appropriate-for-gestational age male infant with symptomatic hypoglycemia on day 3 of life needing high glucose infusion rate to maintain normoglycemia. He was born to a non-obese and non-diabetic mother. Glucose regulation was optimized using diazoxide upon confirmation of hyperinsulinism. Cascade genetic screening identified the same mutation in his father and elder sister, but mother was negative. Father was diagnosed with Type 1 diabetes at 15 years of age that required insulin therapy. Proband's elder sister, born at term appropriate for gestational age, presented with transient neonatal hypoglycemia needing parenteral glucose infusion for a week followed by spontaneous resolution. The paternal grandparents were negative for this mutation, confirming a paternal *de novo* mutation and autosomal dominant inheritance in this family. This pedigree suggests that the presence of early-onset paternal diabetes should prompt molecular testing in infants presenting in the newborn period with diazoxide-responsive hyperinsulinemic hypoglycemia, even in the absence of maternal diabetes and macrosomia.

Keywords: maturity-onset diabetes mellitus, hepatocyte nuclear factor 4-alpha, hepatocyte nuclear factor−1- alpha, hyperinsulinemic hypoglycemia of infancy, congenital hyperinsulinism, diazoxide

Original Article

Child abuse and neglect in a rapidly developing country: Parents' perspectives

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Abstract

Purpose: To identify parental awareness and knowledge regarding child abuse and neglect in the State of Qatar. **Methods:** A cross-sectional study using a questionnaire was conducted at Hamad Medical Corporation, the only tertiary pediatric hospital in the State of Qatar at the time of the study. Parents of children of all ages were offered a questionnaire that included demographic details, parental knowledge, and awareness of child abuse and neglect. **Results:** 300 questionnaires were completed (response rate = 95%). More than 70% of parents were older than 30 years of age, 60% of them were females, and 66% were college graduates. The majority of the participants stated their familiarity about child abuse, and 6% witnessed morbidity or mortality due to child abuse in the society. Despite the identified laws, only 50% of the parents were aware of laws restricting child abuse. In regards to children with special needs, only 16% of the participants agreed that disabled children are at a higher risk of abuse compared to healthy children, while 33% were neutral and 52% disagreed. In addition, one-fifth of the respondents stated that hitting is discipline, while 63% disagreed. Almost one-third of the respondents agreed that hitting hands and buttock or hitting with soft objects is acceptable form of discipline. Unexpectedly, one-quarter of participants stated that it is okay to hit a child as long as no damage incurs. As for verbal abuse, around one-third of parents stated that yelling is not a form of child abuse, and that yelling does not affect growth and development. Comparing both corporal and verbal abuse, approximately 70% of parents stated that yelling is less harmful than hitting. In terms of child neglect, around half of the respondents agreed with the statement "Leaving a child (<5 years) unattended at home is a form of neglect," while 42% were neutral. Finally, approximately 50% of the participants believed that it is okay to depend on nannies in assisting their children in eating and using the bathroom. **Conclusion:** Parents residing in the State of Qatar believe that they have a good knowledge regarding child abuse and neglect. However, this study shows many deficiencies in parental knowledge of child abuse and neglect. Parents' attitudes and perceptions are considered indispensable targets for community health intervention.

Keywords: Child abuse, parents, Qatar

Introduction

The Child Abuse Prevention and Treatment Act (CAPTA) has defined child abuse and neglect as "any recent act or failure to act on the part of a parent or caregiver that results in death, serious physical or emotional harm, sexual abuse, or exploitation, or an act or failure to act that presents an imminent risk of serious harm."[1] Abuse of a child's right to protection is a common issue and one of the paramount barriers to interfere in such a problem is the parental lack of knowledge on the use of positive attitudes as a way to discipline children.[2] The concept of child abuse and neglect (CAN) is a well-known issue globally. However,

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Title : UPPER LIB GRAFT (ULG) FOR REDO URETHROPLASTIES IN CHILDREN . A STEP BY STEP VIDEO

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UPPER LIB GRAFT (ULG) FOR REDO URETHROPLASTIES IN CHILDREN . A STEP BY STEP VIDEO

PURPOSE

Lower lip and cheek are commonly used sources of buccal mucosa grafts for urethroplasty. In recent years, aiming to improve the donor site morbidity, our preference changed to the use (ULG). The aim of this video is to illustrate the technical details of the ULG harvesting for children

MATERIAL AND METHODS

The inner surface of the upper lib is exposed by two stay sutures. The frenulum is spared, the mucosa to be harvested is marked and local submucosal infiltration is done with a solution of bupivacaine plus epinephrine. The edges are incised ant the submucosa plane created with a scissor. The graft is detached, defatted, and applied with quilting stitches over the recipient site with the standard technique. Hemostasis is secured and the donor site is left open.

RESULTS

From 2015 to 2018, 25 ULG harvests were done in 24 patients. Only one (5%) presented local pain associated to the procedure in the first 24 hours. After minimum 2 months after surgery, none of the patients presented perioral nubmness, difficulty with mouth opening, contraction of the donor site or changes in salivation.

CONCLUSIONS

ULG harvest is easy and a suitable alternative source of oral mucosa for urethroplasty in children.

Anxiety and Depression Scores in Maternity Healthcare Workers during the Covid-19 Pandemic

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Brief Communication

While Severe-Acute-Respiratory-Syndrome-CoronaVirus-2 (SARSCoV-2/Covid-19) causes physical morbidity for healthcare workers (HCWs)[1], Covid-19 also carries psychological morbidity for HCWs[2-3]. This morbidity translates to anxiety and depressive

Suruchi Mohan*, Rauf Ghani, Stephen Lindow and Tom Farrell

Antenatal survey of women's birthing choices in Qatar

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Abstract

Objectives: Attitudes towards labour care and women's choices for their preferred mode of delivery are documented in studies from the around the world, however less is known about women's birth choices in the Middle East. This study was designed with the aim of exploring beliefs and attitudes in this region.

Methods: Voluntary participation in an ethics-approved survey was offered to pregnant women attending the antenatal clinic at Sidra Medicine from August 2018 to January 2019 with no exclusion criteria.

Results: Of the 346 respondents, 58.1% were Arabic and the remainder expatriates. This group composition allowed comparison between women native and non-native to the Gulf region. Arabic and non-Arabic women differed significantly in previous birth experiences: the Arabs had had more doctor-led deliveries (45 vs. 34%), epidurals (56.6 vs. 45%) and episiotomies (65.7 vs. 54%). 70.2% of the respondents chose a normal delivery as their preferred birth mode though a smaller majority of the Arabic subgroup did (63.2 %). 60.4% preferred delivery by doctors and longer hospital stays (47.6), more so Arabic participants (64.7 and 68.6 %). Significantly less Arabs, would choose husbands as birth partners (51.2 vs. 86.2%) and more expressed a gender preference for doctors. Other group choices are presented.

Conclusions: Though women in this region made comparable choices about mode of delivery as their Western counterparts, they demonstrated an expectation of a culturally distinct and more medicalized approach to care in labour. The findings highlight the need for further studies to inform regional obstetric care and health education interventions as well as tailoring maternity care services.

Keywords: birth choices; survey; Qatar.

Introduction

Although birth is a natural process it can be subject to medical interventions at various stages. Many factors may influence women's views towards how they would prefer to labour and give birth and how they engage with interventions offered during the process [1]. Satisfaction with birth experience may have implications for the woman's emotional and mental health and may also influence on their decisions in future pregnancies [2]. Therefore, a knowledge of women's expectations and beliefs is critical to developing effective patient-centred maternity services.

While women's birth preferences, especially around maternal request Caesarean sections, have been explored in different parts of the world [3], this aspect remains relatively unexplored in Middle Eastern populations. Therefore, this study was designed with the aim of exploring these attitudes and beliefs in a Middle Eastern population.

Materials and methods

Ethics approval was sought and received from the local Ethics Committee.

A modified validated survey questionnaire [4] exploring pregnant women's background and birthing choices was selected and piloted (Survey questionnaire Appendix 1). The survey was carried out for a five-month period from August 2018 to January 2019 at Sidra Medicine, Qatar.

The antenatal clinic at Sidra Medicine, is a consultant-led service supported by midwifery/nursing staff and with imaging and full laboratory services. Voluntary participation in the survey was offered to pregnant women attending the clinic on their first visit.

The initial questions in the questionnaire were aimed at collecting demographic data. Events around previous births were then explored followed by plans for future pregnancies. This was followed by questions on the woman's preferences in the current pregnancy.

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SCIENTIFIC REPORTS
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OPEN

A metagenomics-based diagnostic approach for central nervous system infections in hospital acute care setting

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The etiology of central nervous system (CNS) infections such as meningitis and encephalitis remains unknown in a large proportion of cases partly because the diversity of pathogens that may cause CNS infections greatly outnumber available test methods. We developed a metagenomic next generation sequencing (mNGS)-based approach for broad-range detection of pathogens associated with CNS infections suitable for application in the acute care hospital setting. The analytical sensitivity of mNGS performed on an Illumina MiSeq was assessed using simulated cerebrospinal fluid (CSF) specimens (n = 9). mNGS data were then used as a training dataset to optimize a bioinformatics workflow based on the IDseq pipeline. For clinical validation, residual CSF specimens (n = 74) from patients with suspected CNS infections previously tested by culture and/or PCR, were analyzed by mNGS. In simulated specimens, the NGS reads aligned to pathogen genomes in IDseq were correlated to qPCR C_T values for the respective pathogens (R = 0.96; p < 0.0001), and the results were highly specific for the spiked pathogens. In clinical samples, the diagnostic accuracy, sensitivity and specificity of the mNGS with reference to conventional methods were 100%, 95% and 96%, respectively. The clinical application of mNGS holds promise to benefit patients with CNS infections of unknown etiology.

Central nervous system (CNS) infections such as meningitis and encephalitis are potentially life threatening diseases caused by a myriad of infectious pathogens. Besides high rates of mortality, meningitis and encephalitis are major causes of morbidity, and permanent disabilities such as brain damage, hearing loss, and learning disabilities can result from CNS infections[1–5]. A specific etiologic agent cannot be identified in 15–60% of cases of meningitis and up to 70% of encephalitis[6,7]. Clinical management of meningitis and encephalitis is highly dependent on early and rapid detection of underlying causes of the disease, so that appropriate antimicrobial or anti-viral therapy can be instituted in a timely manner. Specific diagnosis is also important to avoid unnecessary treatment and hospitalization of patients with self-limiting forms of viral meningitis to minimize potential harm and unnecessary cost to patients[6].

Current diagnostic test methods for CNS infections include CSF Gram staining, CSF cell count, glucose, and protein measurements and biomarkers such as procalcitonin (PCT) and lactate. These tests are generally performed to distinguish between bacterial versus viral infections, and they are not specific for any causative pathogens. Bacteriological culture or PCR testing to detect specific pathogens in cerebrospinal fluid (CSF) are currently the most important methods for the diagnosis of CNS infections. However, a large number pathogens known to cause meningitis and encephalitis cannot be routinely cultured, and most molecular tests are targeted to common pathogens only. A broad-range, unbiased method to identify all pathogens in CSF would markedly improve the management of patients who are critically ill with undiagnosed disease.

Advances in genomic approaches—particularly in sequencing technologies—are being applied in many research and clinical settings. For example, next generation sequencing (NGS) technology, which is capable of deciphering millions of DNA and RNA sequences in parallel, has shown promise for detecting pathogens in clinical samples[8]. In a recent online survey, with infectious diseases physicians, microbiologists and other associated

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Plasmid-mediated colistin resistance encoded by *mcr-1* gene in *Escherichia coli* co-carrying *bla*$_{\text{CTX-M-15}}$ and *bla*$_{\text{NDM-1}}$ genes in pediatric patients in Qatar

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Sir,

Colistin in combination with other agents is indicated as a last resort agent for the treatment of severe infections caused by multiple-drug resistant gram-negative bacteria, particularly those resistant to carbapenems. Worryingly, the recent emergence and global dissemination of the plasmid-mediated resistance gene *mcr-1*, which encodes a phosphoethanolamine transferase, threatens to render treatment with polymyxins ineffective [1]. This scenario has been further

Neonatal diabetes due to homozygous *INS* gene promoter mutations: highly variable phenotype, remission and early relapse during the first 3 years of life

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Conflict of interest: Nothing to disclose

Abstract

Neonatal diabetes mellitus (NDM) is a rare form of monogenic diabetes presenting within the first 6 months of life. INS gene promoter mutations have been shown to cause both remitting/relapsing and permanent NDM. We, herein, present three interesting patients with *INS* gene promoter mutations. Two cousins with an identical homozygous c.-331C>G mutation presented with NDM. The first cousin had non-remitting diabetes and still requires multi-dose insulin injections at the current age of 6.1 years. However, the other cousin's diabetes remitted at the age of 9 months, and she is still in remission at the age of 3-years with no medication or dietary intervention required (latest HbA1c was 4.9 %). The third patient had NDM also due to a homozygous *INS* promoter c.-331C>A mutation. Her diabetes remitted at the age of two-months and relapsed at the age of 2.6-years with severe diabetic ketoacidosis. Distinct clinical phenotype and relapse with severe DKA in one of the three cases suggest that *INS* promotor mutations can cause a heterogeneous phenotype and even cases exhibiting remission can relapse unpredictably. Therefore, as the age of relapse is unpredictable, close follow-up and family education on diabetes symptoms are essential for cases with remitting/relapsing diabetes due to INS gene mutations.

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BMC Pediatrics

RESEARCH ARTICLE Open Access

Global incidence of Necrotizing Enterocolitis: a systematic review and Meta-analysis

Amer Alsaied[1,2,3], Nazmul Islam[1] and Lukman Thalib[1*]

Abstract

Background: Necrotizing Enterocolitis (NEC) is a major cause of morbidity and mortality in the Neonatal Intensive Care Unit (NICU), yet the global incidence of NEC has not been systematically evaluated. We conducted a systematic review and meta-analysis of cohort studies reporting the incidence of NEC in infants with Very Low Birth Weight (VLBW).

Methods: The databases searched included PubMed, MEDLINE, the Cochrane Library, EMBASE and grey literature. Eligible studies were cohort or population-based studies of newborns including registry data reporting incidence of NEC. Incidence were pooled using Random Effect Models (REM), in the presence of substantial heterogeneity. Additional, bias adjusted Quality Effect Models (QEM) were used to get sensitivity estimates. Subgroup analysis and meta-regression were used to explore the sources of heterogeneity. Funnel plots as appropriate for ratio measures were used to assess publication bias.

Results: A systematic and comprehensive search of databases identified 27 cohort studies reporting the incidence of NEC. The number of neonate included in these studies was 574,692. Of this 39,965 developed NEC. There were substantial heterogeneity between studies (I^2 = 100%). The pooled estimate of NEC based on REM was 7.0% (95% CI: 6.0–8.0%). QEM based estimate (6.0%; 95% CI: 4.0–9.0%) were also similar. Funnel plots showed no evidence of publication bias. Although, NEC estimates are similar across various regions, some variation between high and low income countries were noted. Meta regression findings showed a statistically significant increase of NEC over time, quantified by the publication year.

Conclusion: Seven out of 100 of all VLBW infants in NICU are likely to develop NEC. However, there were considerable heterogeneity between studies. High quality studies assessing incidence of NEC along with associated risk factors are warranted.

Keywords: Necrotizing Enterocolitis, Incidence, Systematic review, Meta-analysis

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REVIEW

Role of the gut microbiota in the pathogenesis of coeliac disease and potential therapeutic implications

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Abstract

Purpose Although genetic predisposition and exposure to dietary gluten are considered necessary triggers for the development of coeliac disease, alterations in the gut microbial composition may also contribute towards the pathogenesis of coeliac disease. This review aims to provide an overview of the available data on the potential mechanisms through which the gut microbiota plays a role in the causation of coeliac disease and to discuss the potential therapeutic strategies that could diminish the consequences of microbial dysbiosis.

Method A search of the literature was performed using the PubMed, Embase, and JSTOR databases; relevant articles were included.

Results Recent studies in patients with coeliac disease have reported an increase in the relative amounts of gram negative bacterial genera such as *Bacteroides*, *Prevotella*, and *Escherichia*, and reduced amounts of protective anti-inflammatory bacteria such as *Bifidobacteria* and *Lactobacilli*. Dysbiotic microbiota may lead to a dysregulated immune response that may contribute to the pathogenesis of coeliac disease. In infancy, antibiotic use and certain infant feeding practices may lead to alterations in the developing gut microbiota to influence the immune maturation process and predispose to coeliac disease.

Conclusion The induction of the intestinal immune system and gluten intolerance may be influenced by the relative abundance of certain microbiota. Factors such as infant feeding practices, diet, antibiotics, and infections, may be involved in the development of coeliac disease due to their influence on gut microbial composition. The efficacy of potential modulators of the gut microbiota such as probiotics, prebiotics, and fecal microbial transplant as adjunctive treatments to gluten-free diet in coeliac disease is unproven and requires further investigation.

Keywords Coeliac disease · Microbiota · Metagenomics · Dysbiosis

Introduction

Coeliac disease is an autoimmune disorder triggered by the ingestion of gluten in genetically susceptible people [1]. The disorder is characterized by a mucosal disease of the proximal small bowel as a result of a T-cell mediated destruction of mucosal epithelial cells. It is generally acknowledged that coeliac disease affects about 1% of the population with an increasing prevalence [2] that varies between countries [3]. Patients with coeliac disease develop a permanent loss of immune tolerance to gluten [4, 5], a protein found in cereals such as wheat, rye, and barley. Upon ingestion, gluten can cause a pathological injury characterized by progressive degrees of inflammation and loss of villi in the proximal small bowel leading to the development of gastrointestinal malabsorption along with extra-gastrointestinal manifestations [3].

Coeliac disease is a multifactorial disease, characterized by a complex interplay of genetic and environmental factors. While genetic factors (such as the presence of Human Leukocytic Antigen—mainly HLA-DQ2 or HLA DQ-8) and exposure to dietary gluten are considered to be necessary triggers, they are not sufficient for disease development [6]. Additional factors such as infant feeding practices, the amount of gluten ingested, the age at which gluten is

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Translational Psychiatry

REVIEW ARTICLE Open Access

Genetics of structural and functional brain changes in autism spectrum disorder

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Abstract

Autism spectrum disorder (ASD) is a neurological and developmental disorder characterized by social impairment and restricted interactive and communicative behaviors. It may occur as an isolated disorder or in the context of other neurological, psychiatric, developmental, and genetic disorders. Due to rapid developments in genomics and imaging technologies, imaging genetics studies of ASD have evolved in the last few years. Increased risk for ASD diagnosis is found to be related to many specific single-nucleotide polymorphisms, and the study of genetic mechanisms and noninvasive imaging has opened various approaches that can help diagnose ASD at the nascent level. Identifying risk genes related to structural and functional changes in the brain of ASD patients provide a better understanding of the disease's neuropsychiatry and can help identify targets for therapeutic intervention that could be useful for the clinical management of ASD patients.

Introduction

Autism spectrum disorder (ASD) is a neurological and developmental disorder consisting of a wide range of symptoms and disability that develop in early childhood and persists throughout life. The common symptoms of ASD include limited activities, lower engagement and communication, talking and learning problems, and repetitive behavior. According to the World Health Organization, the global burden of ASD is continuously growing, with a current prevalence rate of 1 in 160 children. Reported prevalence rates vary widely from country to country though. Recent data from the Centers for Disease Control and Prevention showed that about 1 in 68 children in the United States had been identified with some form of ASD, with more than 3 million people affected[1]. A recent study estimated prevalence of ASD in the United States in 2014–2016 was 2.47% among adolescents and children[2]. While in the United Kingdom, the annual prevalence rate for children aged 8 years between 2004 and 2010 was 3.8/1000 for boys and 0.8/1000 for girls[3]. Recent studies have shown that the pooled ASD prevalence estimate in Asia is 0.36%, including data from nine countries (China, Korea, India, Bangladesh, Lebanon, Iran, Israel, Nepal and Sri Lanka)[4]. The prevalence of ASD in the Middle East region was documented to be 1.4 per 10,000 children in Oman[5], 4.3 per 10,000 children in Bahrain[6], 1/167 in Saudi Arabia[7], and a recent study reported ASD prevalence to be 1.14 % in children aged 6–11 years in Qatar[8].

ASD incidence is 4–5 times greater in males than in females[9]. The exact cause of ASD remains unclear; however, it is thought that both genetic and environmental factors play essential roles. The effect of ASD on society is enormous and multifaceted as it affects not only the child but also the siblings and parents and significantly disturbs the functioning of family routine life. Individuals with ASD are very likely to encounter the criminal justice system, mostly due to a lack of knowledge of their social and communication difficulties. There are also financial pressures associated with the recovery and decreased opportunities for jobs. Various studies have focused on

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Letter to the Editor

A novel *STING1* variant causes a recessive form of STING-associated vasculopathy with onset in infancy (SAVI)

To the Editor:

Stimulator of interferon response genes (STING) encoded by stimulator of interferon response cGAMP interactor 1 (*STING1*), previously known as transmembrane protein 173 (*TMEM173)* is an important pattern recognition receptor that detects microbial dinucleotides and functions as an adaptor molecule in the cytosolic DNA sensing pathway that binds 2'3'-cyclic GMP-AMP (cGAMP), which is generated when cytosolic DNA activates cyclic GMP-AMP synthase (cGAS).[1,2] STING activation stimulates the induction of type I interferons, which activate interferon responses. Gain-of-function (GOF) variants in *STING1* lead to autoactivation without ligand binding and cause a rare autoinflammatory disease named STING-associated vasculopathy with onset in infancy (SAVI) (Online Mendelian Inheritance in Man catalog no. 615934).[3,4] Patients with SAVI present in infancy with the following symptoms: recurrent fevers; cold-induced skin vasculitis that can progress to tissue loss and amputation of fingers and toes; and/or interstitial lung disease, which is the main cause of the mortality that often occurs before patients reach adulthood. So far, all reported cases of SAVI have been caused by autosomal dominant variants, with most of them occurring *de novo*.

We have identified 6 patients from 4 unrelated families, all of whom are of Arabic ethnicity and harbor pathogenic *STING1* variants that are disease causing only in homozygosity. The patients had clinical disease suggestive of SAVI and were enrolled into institutional review board–approved protocols, including the National Institutes of Health natural history protocol (NCT02974595).

Patient 1, the index patient, presented at 4 weeks of age with a cough and failure to thrive, as well as with a maculopapular violaceous rash with a livedoid appearance (Fig 1, *A* and *B*). A chest computed tomography scan showed diffuse bilateral parenchymal opacities. His lung disease progressed despite steroid therapy and short-term treatment with the JAK inhibitor tofacitinib, and he died of respiratory failure at 5 months of age. His older brother (patient 2) died at 18 months of age with chronic cough and failure to thrive. Although genetic testing was not performed, the clinical manifestations and similarities of patient 2 to those of his younger brother strongly suggest that he had SAVI. Patient 3 presented at 3 months of age with recurrent fever, erythematous rash, cough, and dyspnea, ultimately progressing to oxygen dependence. He had a chest computed tomography scan with results consistent with interstitial lung disease and a lung biopsy specimen that showed chronic interstitial pneumonitis with intraalveolar hemorrhage. He is currently taking the JAK inhibitor ruxolitinib. His brother, patient 4, had respiratory symptoms starting at the age of 6 months; he was diagnosed with SAVI at the age of 15 months and was initially treated with steroids, after which baricitinib (a selective JAK1/2 inhibitor) was added to his treatment regimen. Patient 5 presented at the age of 2 months with cough, tachypnea, and recurrent lung infections; she was diagnosed with chronic aspiration pneumonia and had a laryngeal cleft that was repaired at the age of 4.5 years. Because of her lung disease (Fig 1, *E*), she has required supplemental oxygen since the age of 7 months and bilevel positive airway pressure support while sleeping since the second year of life, when digital clubbing was noticed. She developed pulmonary hypertension by the age of 4 years. At the age of 5 she developed polyarthritis, an erythematous rash over the soles of her feet and clubbing. She began taking baricitinib at the age of 7 years; there was clinical improvement, but her oxygen dependence continued. Patient 6 presented at the age of 8 months with a history of persistent tachypnea and failure to thrive, polyarthritis, intermittent vasculitic rashes, and clubbing (Fig 1, *C* and *D*). All of the parents and siblings were asymptomatic with normal inflammatory markers. Additional clinical and laboratory information is available in Table E1 (in this article's Online Repository at www.jacionline.org).

Patients 1, 3, and 4 underwent targeted sequencing of *STING1*, whereas whole exome sequencing was performed on families 3 and 4. Sequencing of all patients revealed a homozygous *STING1* (NM_198282) variant c.841C>T, p.Arg281Trp, p.R281W (Fig 1, F). This variant was present in heterozygosity in only 2 of 282,822 alleles reported in gnomAD (gnomad.broadinstitute.org) and is predicted to be damaging by PolyPhen-2 and deleterious by the scale-invariant feature transform algorithm (SIFT), and it has a Combined Annotation-Dependent Depletion (CADD)-PHRED-scaled score of 26.4. This variant has not been reported previously in patients with SAVI (https://infevers.umai-montpellier.fr). All of the parents, as well as several of the unaffected siblings, were heterozygous carriers of this variant (Fig 1, *F*). A variant affecting the same amino acid residue but mutated to a glutamine (c.842G>A, p.Arg281Gln, p.R281Q) has previously been described to cause an autosomal dominant form of SAVI[5] (Fig 1, *G*).

A strikingly high interferon response gene signature and systemic inflammation in patients with SAVI has led to their designation as having an autoinflammatory interferonopathy.[6] A standardized interferon response gene score was elevated only in patients who were homozygous for the p.R281W variant and who had clinical disease, and not in the siblings and parents who were heterozygous carriers of the variant or in healthy controls (Fig 1, *H*).

Transfection of HEK293T cells with the *STING1* construct containing the R281W mutation led to activation of *IFNB1* luciferase reporter without ligand binding (see Fig E1 in this article's Online Repository at www.jacionline.org), indicating that p.R281W is a pathogenic GOF variant. The mutant remained responsive to cGAMP (see Fig E1), suggesting no effect on ligand binding.

Disease-causing SAVI variants[3] cluster in 2 areas. The cryoelectron microscopy structure model of STING[7] has mapped the class 1 variants, p.N154S, p.V155M, and p.V147L to the connector helix loop (Fig 1, *G*) which controls a cGAMP ligand–induced 180° rotation of the ligand-binding area of the STING dimer that induces polymerization and activation. The

Extracorporeal Life Support Organization (ELSO): 2020 Pediatric Respiratory ELSO Guideline

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Reviewers: Thomas V. Brogan, MD,¶ Mark Davidson, MD,‖ Graeme MacLaren, MBBS, FCCM,# Giles Peek, MD, FRCS CTh, FFICM**

Disclaimer: **This guideline describes prolonged extracorporeal life support (ECLS) and extracorporeal membrane oxygenation (ECMO), applicable to Pediatric respiratory failure. These guidelines describe useful and safe practice, prepared by ELSO and based on extensive experience and are considered consensus guidelines. These guidelines are not intended to define standard of care and are revised at regular intervals as new information, devices, medications, and techniques become available.**

PATIENT SELECTION

Indications (ELSO Red Book, 5th Edition Ch 19)[1]

Extracorporeal membrane oxygenation (ECMO) should be considered in patients in whom a reversible pathology is known or suspected, and in whom providing ECMO poses less risks than not providing extracorporeal support (Table 1).

Decisions should be made on an individual level based on knowledge of the patient's disease, institutional experience, expert consensus, and consultation.

ECMO support should be offered in all patients with acute severe respiratory failure who demonstrate progressive persistent failure despite optimized conventional therapies and maneuvers.[2]

ECMO should be considered when the risk of mortality reaches 50% and is strongly indicated when mortality risk approaches 80% with conventional therapy.[3] Earlier consideration may be indicated to minimize barotrauma and other morbidities from aggressive conventional therapies.

With the advent of lung protective ventilation strategies, the decision to offer ECMO may be made at an individual patient level in patients who have required 2 weeks or more of mechanical ventilation.

Contraindications (ELSO Red Book 5th Edition Ch 19)

Although there are few absolute contraindications, ECMO should not be employed when the patient has an overall poor prognosis or when there is high likelihood of survival with unacceptable disability (Table 2).

MODE OF SUPPORT

Rationale

Choosing between venovenous (V-V) and venoarterial (V-A) support in patient with respiratory failure may be challenging, and decisions should be made according to the support required to assure appropriate hemodynamic function at the time of cannulation.

If the patient requires minimal to modest inotropic/vasopressor support at the time of cannulation, it is always worthwhile to first-attempt V-V ECMO. Sometimes, providing adequate O_2 can improve hemodynamics such that V-A cannulation will not be required.

In some instances, there may initially be some hemodynamic instability warranting V-A ECMO. After initial clinical improvement, and if a long run is predicted given the underlying disease process, the patient may occasionally be converted to V-V ECMO.

Cannulation Variations

There are many ways in which to support a patient who requires ECMO for respiratory support and these vary according to local expertise, equipment availability, and patient properties. Some of the possibilities include:[4]

V-V support with two site cannulation using single lumen catheters
(dl)V-V support with one site cannulation using a double-lumen atrial catheter
(dl)V-V support with one site cannulation and a double-lumen, bicaval catheter
V-A support—venous drainage and arterial return
VV-A (venovenous arterial) when an additional drainage cannula is required to support flows
V-VA (venovenoarterial) where there is additional venous return either through a second venous cannula
(dl)V-VA (veno-venoarterial) where there is additional venous return via the return limb of a dual-lumen venous cannula

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CFTR modulator therapy for cystic fibrosis caused by the rare c.3700A>G mutation

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ABSTRACT

Background: The c.3700A>G mutation, a rare cystic fibrosis (CF)-causing CFTR mutation found mainly in the Middle East, produces full-length transcript encoding a missense mutation (I1234V-CFTR), and a cryptic splice site that deletes 6 amino acids in nucleotide binding domain 2 (I1234del-CFTR).

Methods: FRT cell models expressing I1234V-CFTR and I1234del-CFTR were generated. We also studied an I1234del-CFTR-expressing gene-edited human bronchial (16HBE14o-) cell model, and primary cultures of nasal epithelial cells from a c.3700A>G homozygous subject. To identify improved mutation-specific CFTR modulators, high-throughput screening was done using I1234del-CFTR-expressing FRT cells. Motivated by the in vitro findings, Trikafta was tested in two c.3700A>G homozygous CF subjects.

Results: FRT cells expressing full-length I1234V-CFTR had similar function to that of wildtype CFTR. I1234del-CFTR showed reduced activity, with modest activation seen with potentiators VX-770 and GLPG1837, correctors VX-809, VX-661 and VX-445, and low-temperature incubation. Screening identified novel arylsulfonyl-piperazine and spiropiperidine-quinazolinone correctors, which when used in combination with VX-445 increased current ~2-fold compared with the VX-661/VX-445 combination. The combination of VX-770 with arylsulfonamide-pyrrolopyridine, piperidine-pyridoindole or pyrazolo-quinoline potentiators gave 2–4-fold greater current than VX-770 alone. Combination potentiator (co-potentiator) efficacy was also seen in gene-edited I1234del-CFTR-expressing human bronchial epithelial cells. In two CF subjects homozygous for the c.3700A>G mutation, one subject had a 27 mmol/L decrease in sweat chloride and symptomatic improvement on Trikafta, and a second subject showed a small improvement in lung function.

Conclusions: These results support the potential benefit of CFTR modulators, including co-potentiators, for CF caused by the c.3700A>G mutation.

1. Introduction

Cystic fibrosis (CF) is caused by loss-of-function mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a cAMP-activated chloride channel expressed in the lungs, pancreas and other tissues [1, 2]. More than 2000 CFTR gene variants have been identified, with >300 associated with CF of varying severity [1, 3]. Although F508del is the most prevalent mutation in Europe and the US, there is considerable regional variability in many CFTR mutations [4]. The c.3700A>G mutation is a relatively common CF-causing mutation in the Middle East [5–8], present in nearly all CF subjects in Qatar and ~11% of CF subjects in Saudi Arabia. Clinically, the c.3700A>G mutation is associated with lung disease, lung infections, low bone mineral density, and late-onset pancreatic insufficiency, though disease severity is vari-

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[Intervention Review]

Probiotics for induction of remission in Crohn's disease

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ABSTRACT

Background

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract, in which the pathogenesis is believed to be partly influenced by the gut microbiome. Probiotics can be used to manipulate the microbiome and have therefore been considered as a potential therapy for CD. There is some evidence that probiotics benefit other gastrointestinal conditions, such as irritable bowel syndrome and ulcerative colitis, but their efficacy in CD is unclear. This is the first update of a Cochrane Review previously published in 2008.

Objectives

To assess the efficacy and safety of probiotics for the induction of remission in CD.

Search methods

The following electronic databases were searched: MEDLINE (from inception to 6 July 2020), Embase (from inception to 6 July 2020), the Cochrane Central Register of Controlled Trials (CENTRAL), The Cochrane IBD Review Group Specialised Trials Register, World Health Organization (WHO) International Clinical Trials Registry, and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) that compared probiotics with placebo or any other non-probiotic intervention for the induction of remission in CD were eligible for inclusion.

Data collection and analysis

Two review authors independently extracted data and assessed the methodological quality of included studies. The primary outcome was clinical remission. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes.

Main results

There were two studies that met criteria for inclusion. One study from Germany had 11 adult participants with mild-to-moderate CD, who were treated with a one-week course of corticosteroids and antibiotics (ciprofloxacin 500 mg twice daily and metronidazole 250 mg three times a day), followed by randomised assignment to *Lactobacillus rhamnosus* strain GG (two billion colony-forming units per day) or corn starch placebo. The other study from the United Kingdom (UK) had 35 adult participants with active CD (CDAI score of 150 to 450) randomised to receive a synbiotic treatment (comprised of freeze-dried *Bifidobacterium longum* and a commercial product) or placebo. The overall risk of bias was low in one study, whereas the other study had unclear risk of bias in relation to random sequence generation, allocation concealment, and blinding. There was no evidence of a difference between the use of probiotics and placebo for the induction of remission in CD (RR 1.06; 95% CI 0.65 to 1.71; 2 studies, 46 participants) after six months. There was no difference in adverse events

Pediatric RESEARCH www.nature.com/pr

REVIEW ARTICLE

A literature review of 2019 novel coronavirus (SARS-CoV2) infection in neonates and children

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At the time of writing, there are already millions of documented infections worldwide by the novel coronavirus 2019 (2019-nCoV or severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)), with hundreds of thousands of deaths. The great majority of fatal events have been recorded in adults older than 70 years; of them, a large proportion had comorbidities. Since data regarding the epidemiologic and clinical characteristics in neonates and children developing coronavirus disease 2019 (COVID-19) are scarce and originate mainly from one country (China), we reviewed all the current literature from 1 December 2019 to 7 May 2020 to provide useful information about SARS-CoV2 viral biology, epidemiology, diagnosis, clinical features, treatment, prevention, and hospital organization for clinicians dealing with this selected population.

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IMPACT:

- Children usually develop a mild form of COVID-19, rarely requiring high-intensity medical treatment in pediatric intensive care unit.
- Vertical transmission is unlikely, but not completely excluded.
- Children with confirmed or suspected COVID-19 must be isolated and healthcare workers should wear appropriate protective equipment.
- Some clinical features (higher incidence of fever, vomiting and diarrhea, and a longer incubation period) are more common in children than in adults, as well as some radiologic aspects (more patchy shadow opacities on CT scan images than ground-glass opacities).
- Supportive and symptomatic treatments (oxygen therapy and antibiotics for preventing/treating bacterial coinfections) are recommended in these patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic.[1] Since its first outbreak in Wuhan, in the Hubei province of China in early December 2019,[2] SARS-CoV2 has spread all over the world infecting millions of people and causing hundreds of thousands o deaths [case fatality rate (CFR): 6.25%, John Hopkins Coronavirus Resource Center, accessed 7 May 2020].[3]

Respiratory viral infections, in general, are more frequent and severe in children than in adults. SARS-CoV2, instead, showed a different scenario. Infection rates appear to be similar between children and adults; however, children develop a milder illness with a low CFR (<0.1%).[3–7] The reasons for this milder severity in childhood are not yet understood, and the actual epidemiologic and clinical data of infected neonates and children are not sufficient to solve these gaps. Thus, due to the scarcity of data on SARS-CoV2 in children, we aimed at evaluating the current literature available to provide useful information for clinicians dealing with this particular population.

SEARCH STRATEGY

References for this review were identified through searches on PubMED, Ovid MEDLINE, and EMBASE from 1 December 2019 to 7 May 2020, by two highly experienced librarians at Children's Hospital Bambino Gesù by using relevant terms related to 2019-nCoV, COVID-19, and SARS-CoV2 in neonates and children (Supplementary Material 1). Reference lists of the articles identified by this search strategy were also searched. Earlier reports were not excluded, especially if they were highly cited articles. Only articles published in English were included in this review. Three hundred and seventy-four papers were published in PubMed, 117 in Ovid MEDLINE, and 119 in EMBASE. Among them,

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CLINICAL INVESTIGATION

Norepinephrine or phenylephrine during spinal anaesthesia for Caesarean delivery: a randomised double-blind pragmatic non-inferiority study of neonatal outcome

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Abstract

Background: Norepinephrine is an effective vasopressor during spinal anaesthesia for Caesarean delivery. However, before it can be fully recommended, possible adverse effects on neonatal outcome should be excluded. We aimed to test the hypothesis that umbilical arterial cord pH is at least as good (non-inferior) when norepinephrine is used compared with phenylephrine for treatment of hypotension.

Methods: We enrolled 668 subjects having elective and non-elective Caesarean delivery under spinal or combined spinal–epidural anaesthesia in this randomised, double-blind, two-arm parallel, non-inferiority clinical trial. Arterial blood pressure was maintained using norepinephrine 6 μg ml^{-1} or phenylephrine 100 μg ml^{-1} according to the practice of the anaesthetist, either prophylactically or therapeutically, as an infusion or bolus. The primary outcome was umbilical arterial pH with a chosen non-inferiority margin of 0.01 units.

Results: Of 664 subjects (531 elective and 133 non-elective) who completed the study, umbilical arterial cord blood was analysed for 351 samples from 332 subjects in the norepinephrine group and 343 samples from 332 subjects in the phenylephrine group. Umbilical arterial pH was non-inferior in the norepinephrine group (mean, 7.289; 95% confidence interval [CI], 7.284–7.294) compared with the phenylephrine group (mean, 7.287; 95% CI, 7.281–7.292) (mean difference between groups, 0.002; 95% CI, −0.005 to 0.009; P=0.017). Subgroup analysis confirmed the non-inferiority of norepinephrine for elective cases but was inconclusive for non-elective cases.

Conclusions: Norepinephrine was non-inferior to phenylephrine for neonatal outcome assessed by umbilical arterial pH. These results provide high-quality evidence supporting the fetal safety of norepinephrine in obstetric anaesthesia.

Clinical trial registration: ChiCTR-IPR-15006235.

Keywords: Caesarean delivery; hypotension; norepinephrine; obstetric anaesthesia; phenylephrine; spinal anaesthesia

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ORIGINAL ARTICLE

Presenting symptoms and time to diagnosis for Pediatric Central Nervous System Tumors in Qatar: a report from Pediatric Neuro-Oncology Service in Qatar

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Abstract

Introduction There are no previous published reports on primary pediatric tumors of the central nervous system (CNS) in Qatar. We undertook this retrospective cohort study to review the diagnosis of CNS tumors in children in Qatar to analyze the presentation characteristics including symptoms, referral pathways, and time to diagnosis.

Methods All children registered with Pediatric Neuro-Oncology service (PNOS) were included in the study. Data from the time of diagnosis (October 2007 to February 2020) were reviewed retrospectively. Presenting symptoms were recorded and pre-diagnosis symptom interval (PSI) was calculated from the onset of the first symptom to the date of diagnostic imaging.

Results Of the 61 children registered with PNOS during the study period, 51 were included in the final analysis. Ten children were excluded because they were either diagnosed outside Qatar ($n = 7$) or were asymptomatic at the time of diagnosis ($n = 3$). The median age was 45 (range 1–171) months. Common tumor types included low-grade glioma (LGG) (47.1%) and medulloblastoma/primitive neuro-ectodermal tumors (PNET) (23.5%). Nine children had an underlying neurocutaneous syndrome. Thirty-eight patients (74.5%) had at least one previous contact with healthcare (HC) professional, but 27 (52%) were still diagnosed through the emergency department (ED). Presenting symptoms included headache, vomiting (36.2%), oculo-visual symptoms (20.6%), motor weakness (18.9%), seizures, ataxia (17.2% each), irritability, cranial nerve palsies (12% each), and endocrine symptoms (10.3%). Median PSI was 28 days (range 1–845 days) for all CNS tumors. Longest PSI was seen with germ cell tumors (median 146 days), supratentorial location (39 days), and age above 3 years (30 days). Tumor characteristics of biological behavior (high-grade tumor) and location (infratentorial) were significantly associated with shorter PSI, as were presenting symptoms of ataxia, head tilt, and altered consciousness.

Conclusions Although overall diagnostic times were acceptable, some tumor types were diagnosed after a significant delay. The awareness campaign, such as the "HeadSmart" campaign in the United Kingdom (UK), can improve diagnostic times in Qatar. Further research is required to better understand the reasons for the delay.

Keywords Child · Brain · Delay in diagnosis

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Introduction

Primary CNS tumors are the largest group of solid tumors occurring in children [1–3]. They are also associated with the highest rate of cancer-related deaths in children [2, 4, 5]. The overall incidence of cancer and brain tumors in 0–14-year-old children follows the same pattern in Qatar, as elsewhere [6, 7]. Establishing the diagnosis of a CNS tumor is the crucial first step before treatment can be initiated. A delay in making a diagnosis can result in tumor progression, development of hydrocephalus, and even tentorial herniation in rare instances. If the diagnosis is delayed to the point that emergency neurosurgical intervention is required, it can lead to

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Original Research

Procedural Interventions and Stabilization Times During Interfacility Neonatal Transport

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A B S T R A C T

Objective: Transport teams perform multiple procedural interventions during the stabilization of critically ill neonates. The setting of this study was a national cohort of interfacility neonatal transports from nontertiary centers.

Methods: A retrospective cohort study of neonatal transports having interventional procedures using the Canadian Neonatal Transport Network database during 2014 to 2016. Demographics and procedures associated with stabilization times ≤ 120 versus > 120 minutes were analyzed. Predictors of stabilization time were evaluated using multivariable logistic regression analysis.

Results: Among 3,350 neonatal transports analyzed, the 3 most frequently performed procedures were peripheral intravenous insertion, arterial blood gas sampling, and endotracheal tube insertion, with success rates of 85.2%, 89.1%, and 95.3%, respectively. The frequency of procedures varied across gestational age subgroups, and success rates were lower for umbilical arterial catheter insertions. After adjustment for confounders, more invasive procedures and a higher number of interventions were associated with longer stabilization times.

Conclusion: The type and frequency of procedures performed had a significant impact on stabilization time. Any procedures that are nonessential for stabilization at the nontertiary center, such as umbilical arterial catheter insertion, could be minimized to promote timely admission to tertiary centers. The demonstrated variations in procedural success among teams provide useful information for benchmarking and promote the sharing of training practices.

Pediatric critical care transport by specialized teams results in improved outcomes compared with transport by nonspecialized teams,[1] with decreased unplanned events such as airway-related events, cardiopulmonary arrest, sustained hypotension, and loss of crucial intravenous access and lower mortality rates.[2] The transport team is composed of trained health care professionals, including nurses, respiratory therapists, nurse practitioners (NPs), paramedics, or physicians,[3] who provide specialized skills for complex and high acuity patients. An appropriate stabilization before transport is essential to improve the clinical outcome of these babies, with interventions aimed at blood sugar and temperature control, airway and breathing control for oxygenation and ventilation, and blood pressure and hemodynamic stability.[4]

The term *stabilization time* refers to the time taken by the transport team to prepare a patient for transport, including performing any interventions necessary to achieve stabilization, and is measured

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ORIGINAL ARTICLE

Aortopulmonary Collaterals in Single Ventricle Physiology: Variation in Understanding Occlusion Practice Among Interventional Cardiologists

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Abstract
Although aortopulmonary collaterals (APCs) frequently develop in patients with single ventricle palliation, there is a lack of understanding of pathophysiology, natural history, and outcomes with no universal guidelines for management and interventional practice. We conducted a study to assess the views held by interventional congenital cardiologists regarding the hemodynamic impact of APCs in patients with single ventricle palliation, and their embolization practice. An electronic survey using the Pediatric Interventional Cardiology Symposium (PICS) mailing list was conducted between February and March 2019 with one reminder sent 2 weeks after initial invitation for participation. Of the 142 interventional cardiologist respondents, 95 (66.9%) reside in North America and 47 (33.1%) worldwide. We elected to exclude the data from interventionalists outside North America in this analysis as it was not representative of worldwide practice. Hypoxemia was considered to be the most common trigger for development of APCs by 56 (58.9%) respondents. After completion of total cavopulmonary connection, 30 (31.6%) respondents reported the APC burden stays the same while 31 (32.6%) feel it decreases. In evaluating the burden of APC flow, only 4 (4.2%) reported measuring oxygen saturation at different pulmonary artery segments, 21 (22.1%) perform segmental aortic angiograms, and 18 (19%) perform selective bilateral subclavian artery angiograms. A majority of respondents, 71 (74.7%), occlude the feeder vessel at different locations, while 10 (10.5%) occlude only the origin of the vessel. Our study demonstrates significant variation in the understanding of the cause and prognosis of APCs in patients with single ventricle palliation. Furthermore, there is variation in the approach for diagnosis and management among interventional cardiologists. Further studies are required to improve understanding of APCs and develop universal management guidelines.

Keywords Aortopulmonary collaterals · Hemodynamics · Intervention · Occlusion · Single ventricle physiology

Introduction

The development of aortopulmonary collaterals in patients with single ventricle palliation is common with an estimated prevalence of almost 85% [1]. Visualization of aortopulmonary collaterals is highly dependent on aortopulmonary collateral burden and angiogram injection technique [2, 3]. Due to the lack of understanding of the hemodynamic impact of aortopulmonary collaterals on single ventricle palliation, and short- and long-term postoperative outcomes, there is significant variation in the practice of managing aortopulmonary collaterals among congenital interventional cardiologists and centers across the world [4, 5]. Some studies have reported the presence of aortopulmonary collaterals does not influence the immediate outcome of total cavopulmonary

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ARTICLE

Willingness to participate in genome testing: a survey of public attitudes from Qatar

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Abstract

Genomics has the potential to revolutionize medical approaches to disease prevention, diagnosis, and treatment, but it does not come without challenges. The success of a national population-based genome program, like the Qatar Genome Program (QGP), depends on the willingness of citizens to donate samples and take up genomic testing services. This study explores public attitudes of the Qatari population toward genetic testing and toward participating in the QGP. A representative sample of 837 adult Qataris was surveyed in May 2016. Approximately 71% of respondents surveyed reported that they were willing to participate in the activities of the QGP. Willingness to participate was significantly associated with basic literacy in genetics, a family history of genetic diseases, and previous experience with genetic testing through premarital screening. Respondents cited the desire to know more about their health status as the principle motivation for participating, while lack of time and information were reported as the most important barriers. With QGP plans to ramp up the scale of its national operation toward more integration into clinical care settings, it is critical to understand public attitudes and their determinants. The results demonstrate public support but also identify the need for more education and individual counseling that not only provide information on the process, challenges, and benefits of genomic testing, but that also address concerns about information security.

These authors contributed equally: Hanan F. Abdul Rahim and Said I. Ismail

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Introduction

Precision health is a new paradigm that is increasing the use of genomic technologies for the assessment of susceptibility to major diseases as well as individual responses to therapeutic regimes [1, 2], thus, increasing the effectiveness of medical intervention. Increasingly, evidence is pointing to the influence of precision health on improved treatment and health outcomes for patients with breast [3], lung [4], and colorectal [5] cancers. Realizing this potential, and aided by the rapid evolution of sequencing technology, several countries have embarked on national projects to characterize the genomes of their own populations in preparation for large-scale implementation in clinical settings [1]. The State of Qatar in the Arabian Gulf is one of those countries. In late 2015, Qatar launched the pilot phase of the Qatar Genome Program (QGP), which is a population-based genome program aiming to sequence the whole genomes for a significant proportion of the Qatari population. The program has a comprehensive plan to facilitate the implementation of precision medicine involving drafting genomic

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MDPI

Article

PGAP3 Associated with Hyperphosphatasia with Mental Retardation Plays a Novel Role in Brain Morphogenesis and Neuronal Wiring at Early Development

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Abstract: Recessive mutations in Post-GPI attachment to proteins 3 (*PGAP3*) cause the rare neurological disorder hyperphosphatasia with mental retardation syndrome 4 type (HPMRS4). Here, we report a novel homozygous nonsense mutation in *PGAP3* (c.265C>T-p.Gln89*), in a 3-year-old boy with unique novel clinical features. These include decreased intrauterine fetal movements, dysgenesis of the corpus callosum, olfactory bulb agenesis, dysmorphic features, cleft palate, left ear constriction, global developmental delay, and hypotonia. The zebrafish functional modeling of PGAP3 loss resulted in HPMRS4-like features, including structural brain abnormalities, dysmorphic cranial and facial features, hypotonia, and seizure-like behavior. Remarkably, morphants displayed defective neural tube formation during the early stages of nervous system development, affecting brain morphogenesis. The significant aberrant midbrain and hindbrain formation demonstrated by separation of the left and right tectal ventricles, defects in the cerebellar corpus, and caudal hindbrain formation disrupted oligodendrocytes expression leading to shorter motor neurons axons. Assessment of zebrafish neuromuscular responses revealed epileptic-like movements at early development, followed by seizure-like behavior, loss of touch response, and hypotonia, mimicking the clinical phenotype human patients. Altogether, we report a novel pathogenic *PGAP3* variant associated with unique phenotypic hallmarks, which may be related to the gene's novel role in brain morphogenesis and neuronal wiring.

Keywords: hyperphosphatasia mental retardation syndrome 4 (HPMRS4); post-GPI attachment to proteins 3 (*PGAP3*); neurological disorder; human disease model; zebrafish; neural tube defect; whole genome sequencing

1. Introduction

Post-GPI attachment to the proteins 3 (*PGAP3*) gene, encoding a Glycosylphosphatidylinositol (GPI)-specific phospholipase, plays a critical role in the biosynthesis of GPI-anchored proteins (GPI-APs). It is

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Mainstem Bronchial Diameters and Dimensions in Infants and Children: A Systematic Review of the Literature.

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Anatomic measurements of the right (RMB) and left mainstem bronchi (LMB) in infants and children have been accomplished using various modalities. The objective of the present review was to determine whether enough data were available to provide standardized lower airway dimensions in the pediatric population. For the present study, 12 studies with data of the lower pediatric airway dimensions of 1,611 children published from 1923-2020 were reviewed and analyzed. The eligible criteria included studies measuring lower airway dimensions in the pediatric population. Various techniques were used for airway measurement, with computed tomography studies being most abundant. There was a progressive increase in the size of RMB and LMB with age, with a close approximation of the LMB-to-RMB ratio across all studies. In children younger than 1 year old, the RMB and LMB diameters were between 4 and 5 mm and 3 and 5 mm, respectively. Overall, there was significant variation in the methods and modality used to obtain measurements, and therefore it was difficult to establish standardized lower airway dimensions in the pediatric population. Additional homogeneous data with standardized measurement techniques and modalities across different pediatric age groups are needed to define these dimensions further. Such data may be helpful in designing airway equipment, lung isolation devices, and airway stents. Collapse

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Clinical report

Outcome associated with EPCAM founder mutation c.499dup in Qatar

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c.499dup mutation
Founder effect

ABSTRACT

Tufting enteropathy (TE) is a rare autosomal recessive congenital enteropathy that usually requires long-term parenteral nutrition (PN). In the Arabic Peninsula, four distinct EPCAM mutations have been identified to cause TE. As consanguineous marriages are socially favored, pre-marital and pre-conception testing has become a critical disease prevention strategy. This study aimed to identify the pathogenic EPCAM mutations causing TE in Qatari families and determine possible genotype-phenotype correlations. Twenty-two TE patients from seven multiplex families with TE were identified. Blood samples were collected from patients and first-degree relatives. Exons of the gene were amplified and sequenced. Retrospective chart review and/or family interviews were conducted to determine phenotypic characteristics of the disease. Sequence analysis revealed a single, previously described c.499dup mutation in exon 5 of all families tested, suggesting a founder effect. Of the 18 patients whose full clinical information was available, three patients (17%) were off PN with a good quality of life, without intestinal transplantation, and one (6%) was receiving partial PN. Our patients with TE were severely stunted compared to a similar group of patients receiving long-term PN for short bowel syndrome, suggesting that this could possibly be due to TE rather than secondary to inadequate nutrition. Our study identified the EPCAM mutation c.499dup as the genetic defect causing TE in all the participant Qatari families. This finding should facilitate early diagnosis of TE and genetic counseling. Furthermore, it should aid in the prevention of TE through pre-marital screening, antenatal diagnosis, and pre-implantation genetic diagnosis.

1. Introduction

Tufting enteropathy (TE), also known as intestinal epithelial dysplasia, is an autosomal recessive congenital enteropathy that presents with early-onset, severe intractable diarrhea, persistent villous atrophy, and specific histological abnormalities (Goulet et al., 1998). First described by Reifen et al. (1994) in 1994, its estimated prevalence is approximately one in 50,000–100,000 in Western Europe and higher in areas with high degree of consanguinity, including patients of Arabic origin (Goulet et al., 2007). It causes malabsorption, which usually requires long-term parenteral nutrition (PN). Intestinal transplantation has been performed in a few PN-dependent patients (Lacaille et al., 1998; Paramesh et al., 2003). However, favorable outcomes with definitive weaning from PN have been reported, suggesting genetic and pathophysiological differences across patients (Cameron and Barnes, 2003; Lemale et al., 2011). In 2008, Sivagnanam et al. identified the epithelial cell adhesion molecule (EPCAM) gene as the gene involved in TE (Sivagnanam et al., 2008). Since then, many other reports have described various mutations among different ethnic populations (Al-Mayouf et al., 2009; Sivagnanam et al., 2010a; Ko et al., 2010; Salomon et al., 2011; Salomon et al., 2014; d'Apolito et al., 2016; AlMahamed and Hammo, 2017; Schnell et al., 2013; Thoeni et al., 2014; Shakhnovich et al., 2017; Tang et al., 2018; Pathak et al., 2019). Another mutation, *SPINT2*, has also been identified as a cause of the syndromic

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Intra-tracheal delivery of AAV6 vectors results in sustained transduction in murine lungs without genomic integration

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ARTICLE INFO

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ABSTRACT

Despite the progress made in AAV-based gene therapy targeting different organ systems, lung-targeted gene therapy using AAV vectors has not been effective, mostly due to the poor transduction and un-sustained gene expression in airway epithelium. Furthermore, concerns over possible harmful insertional mutagenesis seen in other cell types, particularly hepatocytes, raised a question about AAV safety. In this study, we evaluate the long-term persistence of this vector in mouse lungs and any possible harmful integration of these vectors into the host genome. AAV6 vectors expressing reporter gene (firefly luciferase) were delivered to the lungs of C57BL/6 mice through intra-tracheal intubation. Despite the large variation among individual animals, most animals had high and sustained luciferase activity with a peak from 2 to 3 weeks post-transduction before a significant decline between 15 and 19 weeks post-transduction. More importantly, even after its decline, most animals maintained detectable luciferase expression for 150 days or more, which was confirmed by post-necropsy qPCR analysis of luciferase gene expression. At the termination point of experiments, an average of one copy of AAV expression cassette per mouse genome was detected. We also found that partial overlaps between the AAV6 expression cassette and the mouse genome were distributed broadly with no apparent systematic preference in any mouse chromosomal map location. In summary, our data suggest that AAV6 mediated long-term gene expression in the lungs with no evidence of genomic integration, and thus, any insertional mutagenesis.

1. Introduction

Lung-directed gene therapy is a potentially promising therapeutic option for genetically determined lung diseases such as Cystic Fibrosis (CF), α1-antitrypsin (α1-AT) deficiency, and for disease modification of non-genetically detriment pulmonary disorders such as chronic obstructive pulmonary disease (COPD), asthma and lung cancer. However, numerous previous attempts at preclinical and clinical gene therapy trials have failed to identify a reliable vector platform for gene transfer to overcome the lung's anatomical and natural defenses (van Haasteren et al., 2018; Guggino and Cebotaru, 2017; Sondhi et al., 2017; Alapati and Morrisey, 2017).

Non-viral vectors, in the form of chemically modified liposomes or encapsulated plasmid DNA or mRNA, can overcome the limitations of viral vectors such as vector size and immunogenicity. However, the relatively low efficiency of gene transfer and the transient therapeutic effect hinders the use of these vectors in clinical trials (Alton et al., 2015; Ramamoorth and Narvekar, 2015; Hill et al., 2016). On the other hand, viral vectors such as adenovirus or lentivirus can be more effective vehicles of gene transfer, but safety concerns related to their high immunogenicity, cytotoxicity and the high potential of harmful insertional mutagenesis in the host genome remain significant drawbacks for their use as well (Wold and Toth, 2013; Alton et al., 2017).

Adeno-associated viruses (AAV) are non-pathogenic parvovirus. Several different serotypes of AAV have been widely explored as a potentially safe and effective clinical-stage vector for gene therapy in a broad spectrum of genetic diseases ranging from Leber's congenital amaurosis to hemophilia B and muscular dystrophy (High and Aubourg, 2011; Mendell et al., 2012; Jacobson et al., 2015). Most recently, AAV-based treatment of rare eye disease and spinal muscular atrophy (SMA) in children became two novel gene therapy treatments ever approved by the US FDA (Smalley, 2017; Keeler and Flotte, 2019). However, similar successes of the AAV-based gene therapy of lung diseases, such as CF, α1-AT or COPD could not be achieved. One reason for this is the inability of previously tested AAV vector serotypes to transfer clinically sufficient levels of the therapeutic gene into the airway epithelial cells

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A modular framework for the development of targeted Covid-19 blood transcript profiling panels

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Abstract

Background: Covid-19 morbidity and mortality are associated with a dysregulated immune response. Tools are needed to enhance existing immune profiling capabilities in affected patients. Here we aimed to develop an approach to support the design of targeted blood transcriptome panels for profiling the immune response to SARS-CoV-2 infection.

Methods: We designed a pool of candidates based on a pre-existing and well-characterized repertoire of blood transcriptional modules. Available Covid-19 blood transcriptome data was also used to guide this process. Further selection steps relied on expert curation. Additionally, we developed several custom web applications to support the evaluation of candidates.

Results: As a proof of principle, we designed three targeted blood transcript panels, each with a different translational connotation: immunological relevance, therapeutic development relevance and SARS biology relevance.

Conclusion: Altogether the work presented here may contribute to the future expansion of immune profiling capabilities via targeted profiling of blood transcript abundance in Covid-19 patients.

Keywords: Blood transcriptomics, SARS-CoV-2, Covid-19, Immune monitoring

Background

Covid-19 is an infectious, respiratory disease caused by a newly discovered coronavirus: SARS-CoV-2. The course of infection vary widely, with most patients presenting mild symptoms. However, about 20% of patients develop severe disease and require hospitalization [1, 2]. The interaction between innate and adaptive immunity can lead to the development of neutralizing antibodies against SARS-CoV-2 antigens that might be associated with viral clearance and protection [3]. But immune factors are also believed to play an important role in the rapid clinical deterioration observed in some Covid-19 patients [4]. There is thus a need to develop new modalities that can improve the delineation of "immune trajectories" during SARS-CoV-2 infection.

Blood transcriptome profiling involves measuring the abundance of circulating leukocyte RNA on a genome-wide scale via RNA sequencing [5]. Processing of the samples and the raw sequencing data however, is time consuming and requires access to sophisticated

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ORIGINAL ARTICLE

Electrocardiogram interpretation among pediatricians: Assessing knowledge, attitudes, and practice

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ABSTRACT

Objectives : **This study assesses the competency of pediatricians in interpreting electrocardiograms (ECGs).**

Methods : **A cross-sectional study involving 125 pediatricians comprised of 71 general pediatricians, 15 pediatric cardiologists, and 39 other subspecialists recruited from all public hospitals and two specialty centers. Participants completed a questionnaire that included 10 ECGs and questions regarding backgrounds, attitudes, and practices. The ECGs were graded to obtain a knowledge score out of 30 points. Mann–Whitney U test and Kruskal-Wallis test with *post hoc* analysis and Bonferroni adjustment were used to compare groups.**

Results : **The mean knowledge score ranged from 47.7% to 69.7% among various pediatric specialties (P = 0.006). Age, increasing years of experience, confidence level, number of cardiology referrals, and perceived importance of having good ECG interpretation skills were significantly related to the knowledge score ($P \leq 0.05$). Accuracy was highest in identifying normal ECGs (76.8%), supraventricular tachycardia (64.8%), along with long QT interval (58.4%), and was lowest for right bundle branch block (RBBB) (10.4%), 2:1 atrioventricular conduction (10.4%), and atrial tachycardia (AT) (4.8%). Accuracy among pediatric cardiologists was highest for long QT interval (100%), normal ECG (80%), as well as Wolff-Parkinson-White syndrome (80%), and lowest for RBBB (13.3%) and AT (0%). Most pediatricians believe that ECGs are "useful" (78.4%) and that having good interpretation skill is "important" (80.6%).**

Conclusions : **Pediatricians recognize the importance of ECGs. However, their skill and level of accuracy at interpretation is suboptimal, including cardiologists, and may affect patient care. Thus, efforts should be made to improve ECG understanding to provide better service to patients.**

Keywords : Electrocardiogram, interpretation, pediatric cardiologists, pediatrician

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Transcatheter Interventions in Adult Congenital Heart Disease

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KEYWORDS

• Adult congenital heart disease • Transcatheter intervention • Pulmonary valve replacement
• VSD closure • ASD closure • Valvuloplasty

KEY POINTS

- Transcatheter interventions are replacing traditional surgical procedures for many types of native and operated congenital heart disease.
- Transcatheter interventions often require fluoroscopic and echocardiographic guidance.
- Transcatheter pulmonary valve replacement is now considered standard of care in patients with failing bioprosthetic valves and conduits.
- New self-expanding devices are undergoing human trials and will allow for transcatheter valve replacement of patients with large native right ventricular outflow tracts and pulmonary regurgitation.

BACKGROUND

The past 3 decades have witnessed an exponential growth of transcatheter interventions for congenital heart disease (CHD). Nowhere has this been more evident than in the adult CHD population, because survival into adulthood is now the norm for most forms of CHD.[1,2] In 1976 King and Mills published the first report of transcatheter device closure of an atrial septal defect (ASD).[3] Since that time, improvements in device design, catheterization technology, and procedural techniques have brought interventional cardiology to the forefront as a therapeutic intervention that may delay or obviate the need for surgery in CHD. Advances in noninvasive cardiovascular imaging have made diagnostic cardiac catheterization in a shrinking pool of patients. Transthoracic echocardiography with Doppler is now the noninvasive imaging work horse for congenital and structural cardiology and is cost effective and widely available. Cross-sectional imaging modalities such as computed tomography scans and MRI provide 3-dimensional volumetric data that are invaluable in the assessment of anatomy and function, especially in those with complex anatomy. The combination of echocardiography and cross-sectional imaging provides a powerful noninvasive armamentarium that is capable of accurately assessing most anatomic and physiologic types of CHD thus relegating diagnostic catheterization to a small subset of patients, typically those with single ventricle physiology, pulmonary hypertension, or those in whom noninvasive imaging results in confusing or contradictory findings. Because most hemodynamic determinations can be made by Doppler echocardiography and anatomic determinations can be made by computed tomography scans or MRI, diagnostic catheterizations are

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Mutations in *MYLPF* Cause a Novel Segmental Amyoplasia that Manifests as Distal Arthrogryposis

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We identified ten persons in six consanguineous families with distal arthrogryposis (DA) who had congenital contractures, scoliosis, and short stature. Exome sequencing revealed that each affected person was homozygous for one of two different rare variants (c.470G>T [p.Cys157Phe] or c.469T>C [p.Cys157Arg]) affecting the same residue of *myosin light chain, phosphorylatable, fast skeletal muscle* (*MYLPF*). In a seventh family, a c.487G>A (p.Gly163Ser) variant in *MYLPF* arose *de novo* in a father, who transmitted it to his son. In an eighth family comprised of seven individuals with dominantly inherited DA, a c.98C>T (p.Ala33Val) variant segregated in all four persons tested. Variants in *MYLPF* underlie both dominant and recessively inherited DA. Mylpf protein models suggest that the residues associated with dominant DA interact with myosin whereas the residues altered in families with recessive DA only indirectly impair this interaction. Pathological and histological exam of a foot amputated from an affected child revealed complete absence of skeletal muscle (i.e., segmental amyoplasia). To investigate the mechanism for this finding, we generated an animal model for partial MYLPF impairment by knocking out zebrafish *mylpfa*. The *mylpfa* mutant had reduced trunk contractile force and complete pectoral fin paralysis, demonstrating that *mylpf* impairment most severely affects limb movement. *mylpfa* mutant muscle weakness was most pronounced in an appendicular muscle and was explained by reduced myosin activity and fiber degeneration. Collectively, our findings demonstrate that partial loss of MYLPF function can lead to congenital contractures, likely as a result of degeneration of skeletal muscle in the distal limb.

Introduction

The distal arthrogryposes (DA) are a group of Mendelian conditions with overlapping phenotypic characteristics, shared genetic etiologies, and similar pathogenesis.[1] Clinically, the DAs are characterized by non-progressive congenital contractures of the limbs, most commonly affecting the hands, wrists, feet, and ankles. Congenital contractures of the face, ocular muscles, neck webbing, pterygia, short stature, and scoliosis are less frequent, variable findings that facilitate delineation among the most common DA conditions: DA1[2] (MIM: 108120), DA2A[3] (Freeman-Sheldon syndrome [MIM: 193700]), and DA2B[4] (Sheldon-Hall syndrome [MIM: 601680]). Variants in any one of sixteen different genes can underlie DA but the overwhelming majority of known pathogenic variants occur in just five genes: *TPM2* (MIM: 190990), *TNNI2* (MIM: 191043), *TNNT3* (MIM: 600692), *MYH3* (MIM: 160720), and *MYH8* (MIM: 160741).[5,6] Nevertheless, collectively pathogenic variants are identified in only ~60% of families diagnosed with a DA, so the precise genetic etiology remains unknown in nearly half of DA-affected families.

Most of the genes that underlie DA encode sarcomeric components of skeletal muscle fibers. Thus, genes encoding sarcomeric proteins have long been considered

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ORIGINAL ARTICLE

Intraspecific Diversity and Taxonomy of *Emmonsia crescens*

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Abstract *Emmonsia crescens* is known as an environmental pathogen causing adiaspiromycosis in small rodents. As the generic name *Emmonsia* is no longer available for this species, its taxonomic position is re-evaluated. The intraspecific variation of *Emmonsia crescens* was analyzed using molecular, morphological, and physiological data, and the relationship between frequency of adiaspiromycosis and body temperature of host animals was explored. A North American and a pan-global lineage could be discerned, each with subclusters at low genetic distance. European strains produced the classical type of very large adiaspores, while in the North American lineage adiaspores relatively small, resembling the broad-based budding cells of *Blastomyces*. Members of the closely related genus *Emergomyces* may exhibit large, broad-based in addition to small, narrow-based budding cells. We conclude that the morphology of the pathogenic phase in these fungi differs gradationally between species and even populations, and is therefore less suitable as a diagnostic criterion for generic delimitation. Two *Emmonsia* species are reclassified in *Emergomyces*.

Keywords Rodent · Multilocus analysis · Ecology · Onygenales · *Emmonsia* · Taxonomy

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Full Title - Efficacy of non-invasive respiratory support modes as post extubation respiratory support in preterm neonates: A Systematic Review and Network Meta-analysis.

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Author contributions

VVR, TB, DN, PB and KM were involved in the conception of the systematic review and data collection. VVR and TB did the analysis and interpretation of data. KM and VIO did the revision of the initial draft. AG gave intellectual inputs and approved the final version for submission.

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Category of research - Systematic review / Network meta-analysis

Impact statement -

- This network meta-analysis compares different non-invasive respiratory support (NRS) modalities for which direct evidence is not available and adds further indirect evidence to the existing pair-wise comparisons.

- The quality of evidence for different NRS comparisons across outcomes was very low to moderate (mostly low)

- The efficacy of NRS varies widely when analysed by device; Synchronized non-invasive positive pressure ventilation (S-NIPPV) appears to be the most effective modality for post-extubation support, Constant Flow CPAP (CF-CPAP) the least effective one.

ABSTRACT

Background: Multiple non-invasive respiratory support (NRS) modalities are used for post extubation support in preterm neonates. Seven NRS modalities were compared - Constant flow CPAP (CF-CPAP) [bubble CPAP; ventilator CPAP], Variable

flow CPAP (VF-CPAP), High flow nasal cannula (HFNC), Synchronized non-invasive positive pressure ventilation (S-NIPPV), Non-synchronized NIPPV (NS-NIPPV), Bilevel CPAP (BiPAP), non-invasive high frequency oscillation ventilation (nHFOV).

Design: Systematic review and network meta-analysis using the Bayesian random effects approach. MEDLINE, EMBASE, CENTRAL, WHO-ICTRP were searched.

Main outcome measure: Requirement of invasive mechanical ventilation within 7 days of extubation.

Results: 33 studies with 4080 preterm neonates were included. S-NIPPV, NS-NIPPV, nHFOV and VF-CPAP were more efficacious in preventing re-intubation than CF-CPAP [RR (95% CrI) - 0.22 (0.12, 0.35); 0.44 (0.27, 0.67); 0.42 (0.18, 0.81); 0.73 (0.52, 0.99)]. SUCRA value ranked S-NIPPV to be the best post extubation intervention (SUCRA - 0.98). S-NIPPV was more effective than NS-NIPPV, BiPAP, VF-CPAP and HFNC [RR (95% CrI) - 0.52 (0.24, 0.97); 0.32 (0.14, 0.64); 0.30 (0.16, 0.50); 0.24 (0.12, 0.41)]. NS-NIPPV resulted in lesser re-intubation compared to VF-CPAP and HFNC [RR (95% CrI) - 0.61 (0.36, 0.97); 0.49 (0.27, 0.80)]. BiPAP, VF-CPAP and HFNC had comparable efficacies. The overall quality of evidence was very low to moderate.

Conclusion: Results of this NMA indicate that S-NIPPV might be the most effective and CF-CPAP the least effective NRS modality for preventing extubation failure.

INTRODUCTION

Prolonged mechanical ventilation can be associated with significant morbidity in preterm neonates and the practice of early extubation to non-invasive respiratory support (NRS) has been the focus since the past decade[1-3]. NRS modalities that are widely used in neonatal care include continuous positive airway pressure (CPAP), high flow

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TITLE

Efficacy of non-invasive respiratory support modes for primary respiratory support in preterm neonates with Respiratory Distress Syndrome: Systematic review and network meta-analysis.

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Keywords

non invasive ventilation, CPAP, Bilevel CPAP, non invasive positive pressure ventilation, heated humidified high flow cannula, RDS

ABSTRACT

Objectives: To compare the efficacy of different non-invasive respiratory support modes for primary respiratory support of preterm infants with Respiratory Distress Syndrome (RDS).

Design: Systematic review and network meta-analysis using the Bayesian random effects approach. MEDLINE, EMBASE and CENTRAL were searched.

Interventions: HFNC (High Flow Nasal Cannula), CPAP (Continuous Positive Airway Pressure), BiPAP (Bilevel CPAP), NIPPV (Non Invasive Positive Pressure Ventilation).

Main outcome measures: Requirement of invasive mechanical ventilation, any treatment failure.

Results: 35 studies including 4078 neonates were included. NIPPV was more effective in decreasing the requirement of mechanical ventilation than CPAP {RR [95% Credible Interval (CrI)] - 0.60 (0.44, 0.77)}and HFNC [0.66 (0.43, 0.97)]. Surface under the cumulative ranking curve (SUCRA) for NIPPV, BiPAP, HFNC and CPAP were 0.95, 0.59, 0.32 and 0.13. For the outcome of treatment failure, both NIPPV and BiPAP were more efficacious compared to CPAP and HFNC {0.56 (0.44, 0.71) [NIPPV vs CPAP], 0.69 (0.51, 0.93) [BiPAP vs CPAP], 0.42 (0.30, 0.63) [NIPPV vs HFNC], 0.53 (0.35, 0.81) [BiPAP vs HFNC]}. The SUCRA for NIPPV, BiPAP, CPAP and HFNC were 0.96, 0.70, 0.32 and 0.01. NIPPV was associated with a reduced risk of air leak compared to BiPAP and CPAP [0.36 (0.16, 0.73); 0.54(0.30, 0.87), respectively]. NIPPV resulted in lesser incidence of BPD or mortality when compared to CPAP [0.74 (0.52, 0.98)]. Nasal injury was lesser with HFNC compared to CPAP [0.15 (0.01, 0.60)].

Conclusions: Most effective primary mode of non-invasive respiratory support in preterm neonates with RDS was NIPPV.

INTRODUCTION

The introduction of surfactant had a major impact in improving the outcomes of preterm neonates with RDS[1].There was a major shift in the practice of surfactant therapy in the last decade with studies showing better outcomes with early selective rescue treatment when

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Assessment of neonatal perfusion

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ARTICLE INFO

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ABSTRACT

Disorders of perfusion in newborn infants are frequently observed in neonatal intensive care units. The current assessment practices are primarily based on clinical signs. Significant technologic advances have opened new avenues for continuous assessment at the bedside. Combining these devices with functional echocardiography provides an in-depth understanding of perfusion and allows targeting therapy to the pathophysiology rather than monitoring and targeting blood pressure. This change in approach is guided by the fact that perfusion disorders can result from a number of causes and a single management approach might do more harm than good. This approach has the potential to improve long term outcomes but needs to be tested in well-designed trials.

1. Introduction

Assessment and management of neonatal perfusion is an integral part of neonatal intensive care. The routinely used clinical signs have a limitation because of low sensitivity during early periods of impaired perfusion and are deranged only when the newborn has progressed to a state of uncompensated or irreversible shock [1]. Over the years there have been key technologic advances that help complement the clinical examination with bedside assessment tools. There is now a potential for early diagnosis of neonatal perfusion impairment, which if timely managed, could reduce morbidity and mortality. There are, however, concerns that overzealous treatment could do more harm than good. The selection of assessment tools is governed by striking a balance between tests with high sensitivity but limited availability (such as functional echocardiography, MRI) with tests enabling continuous assessment but with only borderline sensitivity [such as near-infrared spectroscopy (NIRS)].

With better understanding of transitional circulation and the heterogeneity of neonatal hemodynamic problems, it is now clear that one size does not fit all. Clinicians have to understand the pathophysiology of the hemodynamic problems to objectively match the therapy to the cause rather than be guided by the traditional approaches to management using volume, inotropes and vasopressors. This requires an understanding of the physiologic concepts of hemodynamics and the pharmacodynamic properties of the pharmaceutical agents used for management.

Over the years we have been treating hypotension rather than impaired perfusion. Hypotension is a numerical or statistical value connoting a blood pressure that is more than two standard deviations from the mean. This may or may not represent a pathological state of shock, which is derangement of perfusion. It is a condition connoting circulatory failure, where tissues cannot be provided with adequate oxygen or nutrients. This change in concept is pivotal for appropriate management of hemodynamic disturbance and hence assessment of neonatal perfusion is important in day to day practice.

2. What is perfusion and why is it important?

Perfusion is the delivery of blood to the tissue capillary bed. This facilitates oxygen transport to the tissues (DO_2), which in turn is utilized for aerobic metabolism. In hypoxic or ischemic states, when the oxygen delivery falls below the critical level,anaerobic metabolism commences resulting in the production of lactic acid. To maintain oxygen delivery, the cardio-pulmonary system has to function effectively and the systemic vascular resistance should be maintained. The DO_2 is dependent upon the lungs, heart, vascular bed, and hemoglobin. Ventilation and diffusion of gases are often affected in respiratory disorders and could affect transitional circulation leading to pulmonary hypertension. The heart is a pump and systolic or diastolic dysfunction can lead to pump failure and states of shock. The vascular system is comprised of venous and arterial sides. The venous bed accounts for preload, and the arterioles maintain the systemic vascular resistance within the capillary bed

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[Overview of Reviews]

Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews

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ABSTRACT

Background

Asthma is an illness that commonly affects adults and children, and it serves as a common reason for children to attend emergency departments. An asthma exacerbation is characterised by acute or subacute worsening of shortness of breath, cough, wheezing, and chest tightness and may be triggered by viral respiratory infection, poor compliance with usual medication, a change in the weather, or exposure to allergens or irritants.

Most children with asthma have mild or moderate exacerbations and respond well to first-line therapy (inhaled short-acting beta-agonists and systemic corticosteroids). However, the best treatment for the small proportion of seriously ill children who do not respond to first-line therapy is not well understood. Currently, a large number of treatment options are available and there is wide variation in management.

Objectives

Main objective

- To summarise Cochrane Reviews with or without meta-analyses of randomised controlled trials on the efficacy and safety of second-line treatment for children with acute exacerbations of asthma (i.e. after first-line treatments, titrated oxygen delivery, and administration of intermittent inhaled short-acting beta$_2$-agonists and oral corticosteroids have been tried and have failed)

Secondary objectives

- To identify gaps in the current evidence base that will inform recommendations for future research and subsequent Cochrane Reviews

- To categorise information on reported outcome measures used in trials of escalation of treatment for acute exacerbations of asthma in children, and to make recommendations for development and reporting of standard outcomes in future trials and reviews

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C-reactive protein as a predictor of meningitis in early onset neonatal sepsis: a single unit experience

Naveed Ur Rehman Durrani, S. Dutta, N. Rochow, S. el Helou, Enas el Gouhary less • Published 2020 • Medicine • Journal of Perinatal Medicine

Abstract Objectives To determine whether there is a cut off value of serum C-reactive protein (CRP) associated with a higher risk of meningitis in suspected early onset sepsis (EOS) (onset birth to 7 days of life). Methods A retrospective cohort study on neonates admitted in neonatal intensive care unit at McMaster Children's Hospital from January 2010 to 2017 and had lumbar puncture (LP) and CRP for workup of EOS. Included subjects had either (a) non-traumatic LP or (b) traumatic LP with cerebral spinal fluid (CSF) polymerase chain reaction or gram stain or culture-positive or had received antimicrobials for 21 days. Excluded were CSF done for metabolic errors, before cytomegalovirus (CMV) treatment; from ventriculo-peritoneal (VP) shunts; missing data and contamination. Neonates were classified into definite and probable meningitis and on the range of CRP. We calculated sensitivity, specificity, and likelihood ratios for CRP values; and area under the receiver operating characteristic (AUROC) curve. Results Out of 609 CSF samples, 184 were eligible (28 cases of definite or probable meningitis and 156 controls). Sensitivity, specificity, predictive values, likelihood ratios, and AUROC were too low to be of clinical significance to predict meningitis in EOS. Conclusions Serum CRP values have poor discriminatory power to distinguish between subjects with and without meningitis, in symptomatic EOS. Collapse

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Clinical and Translational Allergy

RESEARCH Open Access

The association between airborne pollen monitoring and sensitization in the hot desert climate

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Abstract

Background: Pollen is a major cause of allergic respiratory diseases. In Qatar, data on the presence and prevalence of allergenic airborne types of pollen is quite limited.

Methods: The study aimed to determine and correlate the most frequently implicated airborne pollen detected by aerobiological monitoring samplers in respiratory allergy symptoms. An aerobiological survey was started on May 8, 2017. Airborne pollen was collected using two Hirst type seven-day recorder volumetric traps. Skin prick test in patients attending allergy clinics in Doha using commercial extracts was conducted.

Results: Twenty-five pollen types representing the native, as well as the introduced plants, with a relatively low daily mean concentration were observed from May 2017 to May 2019. The highest pollen concentrations were reached by Amaranthaceae (58.9%), followed by Poaceae (21.7%). SPT revealed a comparatively higher degree of sensitization to pollen. Among 940 patients, 204 were sensitized to pollen (54% female) with 135 (66.2%) and 114 (55.8%) to Amaranthaceae and Poaceae, respectively. Some patients had polysensitization. There was a statistically significant association between Amaranthaceae, and asthma ($r = 0.169$, $P = 0.016$) and allergic rhinitis ($r = 0.177$, $P = 0.012$).

Conclusions: This is the first study to monitor airborne pollen in the state of Qatar. The main pollen detected were Amaranthaceae and Poaceae. Pollen may represent a possible exacerbating factor in adult patients with allergic diseases such as asthma and allergic rhinitis.

Keywords: Qatar, Allergy, Aerobiology, Pollen, Skin prick test

Introduction

The prevalence of asthma and allergic rhinitis is high and increasing in western countries [1]. However, relatively little is known about the prevalence rate of allergic disorders in the Middle East and Arab Gulf countries. Specifically, the Qatari population has a high prevalence of diagnosed asthma (19.8%), allergic rhinitis (30.5%), and atopic dermatitis (22.5%) in children and adults [2].

Allergic diseases related to pollen are called pollinosis and include rhinitis, conjunctivitis, and asthma. During the last few decades, pollen has received increasing attention due to its strong allergenic potential, with severe impacts on human health [3]. There is a body of evidence suggesting that the prevalence of respiratory allergic reactions induced by pollen has been increasing in the most developed countries, especially in North America and Europe [3, 4].Understanding pollen emission dynamics is fundamental for the characterization of potential allergens that may be of greater health relevance in both natural and inhabited areas [5]. The allergenic content of the atmosphere varies according

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Segmental testicular infarction associated to torsion: First case report in childhood

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Abstract

Testicular torsion in children is not uncommon emergency problem which occur due to twist in the spermatic cord leading to ischemia or infarction to testicle.
Hemorrhagic infarction can occur following testicular torsion is globally, however, in extremely rare situation such infarction can be segmental.
Segmental testicular infarction (STI) was reported in an infant due to epididymitis and a newborn with STI in 1 testicle with complete infarction in the contralateral testicle due to birth trauma.
To best of our knowledge, our case of STI in a child associated to testicular torsion is the first described in the literature.

Key words:
Testicular Torsion , Pediatric , Testicular Segmental infarction , Ultrasound

Introduction

Testicular torsion in children accounts for 10-15% of acute scrotal conditions in children with an incidence of 3.8 per 100,000 pediatric patients (1,2,3). This condition is usually associated to deficiency of testicular fixation, allowing increased motility and torsion around the spermatic cord (4, 5). Herein, we report a rare case of segmental testicular infarction (STI) following torsion.

Case report

9-year-old boy presents with a 2-day history of progressive scrotal pain after minor trauma to genitalia while playing football. Gradual left scrotal swelling started on the second day without any other symptomatology. In the past 2 years he had similar episodes of pain when a Doppler ultrasound (US) was performed revealing increased left testicular flow that were generically labelled as orchitis. Physical

Plate Objective Scoring Tool (POST);

An Objective Methodology for the Assessment of Urethral Plate in Distal Hypospadias

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Keywords: hypospadias, risk factors, tubularized incised plate repair, urethral plate evaluation

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Plate Objective Scoring Tool (POST);
An Objective Methodology for the Assessment of Urethral Plate in Distal Hypospadias

Structured Summary

Background: Estimation of the quality of the urethral plate (UP) seems to be important when assessing postoperative outcomes of hypospadias repair, but its evaluation remains subjective. We developed an objective model aiming to standardize this assessment, proposing a methodology that could be adopted in future studies designed to evaluate outcomes in the treatment of hypospadias.

Objectives: To evaluate the inter and intra observer reliability of a method to assess the quality of the urethral plate (UP) in hypospadias (POST - Plate Objective Scoring System) based on elements of glans characteristics. The reliability of such scoring methodology was compared to an analog accepted tool: the Glanular-Meatal-Shaft (GMS) score. A secondary goal was to compare some characteristics of the UP in GMS score to POST values; aiming to find the threshold between favorable and unfavorable plates.

Methods: Data were prospectively obtained from prepubertal boys who underwent primary hypospadias repair between January 2018 and November 2019. Intrinsic elements of the glanular UP (A: distal midline mucocutaneous junction; B: Glanular knob where the mucosal edges of the UP's edge change direction; C: Glanular/coronal junction) were marked and the AB/BC ratio calculated. The “G” and “M” components of the GMS score were measured electronically three times by four different reviewers with variable pediatric urology experience and blinded to each

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Near-Infrared spectroscopy for perfusion assessment and neonatal management☆,☆☆

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A B S T R A C T

Term and preterm infants often present with adverse conditions after birth resulting in abnormal vital functions and severe organ failure, which are associated or sometimes caused by low oxygen and/or blood supply. Brain injury may lead to substantial mortality and morbidity often affecting long-term outcome. Standard monitoring techniques in the NICU focus on arterial oxygen supply and hemodynamics and include respiratory rate, heart rate, blood pressure and arterial oxygen saturation as measured by pulse oximetry but provide only limited information on end organ oxygen delivery. Near-Infrared Spectroscopy can bridge this gap by displaying continuous measurements of tissue oxygen saturation, providing information on the balance of oxygen delivery and consumption in organs of interest. Future techniques using multi-wavelength devices may provide additional information on oxidative metabolism in real time adding important information.

1. Introduction

The prognosis for Very Low birthweight infants (VLBWI) has improved over the past two decades [1,2], but short-term and long-term morbidity, especially among Extremely Low birth Weight Infants (ELBWI) remains high [1,2]. There seems to be considerable variation in survival without neurodevelopmental impairment comparing different cohorts, even after adjustment for co-variables when comparing perinatal centers [1,2]. Respiratory and cardiovascular events, especially hypoxia, oxidative injury, inflammation, gut complications, sepsis, and shock are key factors in the pathogenesis of diseases leading to death or adverse neurodevelopmental outcomes. Many strategies used for treatment of adverse conditions are not evidence-based and vary among institutions, which may explain part of the variability in outcomes. One of the most commonly observed conditions is arterial hypotension, where the assessment and treatment continues to be extremely controversial within the neonatal community. Traditional clinical hemodynamic monitoring includes pulse oximetry (SpO_2), heart rate (HR), blood pressure (BP), capillary refill, and urine output. Additional tools including functional echocardiography, Near-Infrared Spectroscopy (NIRS), non-invasive cardiac output (CO) monitoring, and amplitude-integrated EEG (aEEG) have been suggested to provide more insight into the pathophysiology of critically ill neonates [3]. The most vulnerable organ exposed to adverse hemodynamic conditions during transition and early life in critically ill infants is probably the brain, and comprehensive hemodynamic monitoring including NIRS is considered the next logical step towards monitoring systemic and regional blood flow and oxygenation. With unchanged arterial oxygen saturation and thus SpO_2 and unchanged metabolic rate, changes in regional tissue oxygen saturation are usually caused by changes in organ perfusion. Therefore, monitoring of regional tissue oxygen saturation provides additional information on the balance of oxygen delivery and consumption and thus indirectly on tissue perfusion and oxygen supply.

2. NIRS techniques and basic assumptions about oxygen delivery/blood flow

2.1. Techniques

NIRS was introduced in the 1980s. It uses light in the near-infrared range (650–1000 nm), which can pass well through skin and skull structures, and fiberoptic devices or optodes, which measure transmitted/reflected light. Tissue is composed of different substances and the absorption spectra of different tissues are well-known for the wavelengths used, such as for oxygenated (HbO_2) or deoxygenated hemoglobin (HbR). The absorption spectra of hemoglobin changes when it becomes oxygenated/deoxygenated.

Different techniques have been used, and the continuous wave method is probably most commonly used in neonates. Since the true optical distance (so called pathlength) is usually not known, only

☆ This work is attributed to Sidra Medicine, Doha, Qatar and to Children's Hospital, Ulm University, Germany.
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Successful Initiation of Hybrid Closed-Loop System Using Virtual Pump Training Program in a Teenager With Type 1 Diabetes Previously Treated with Multiple Daily Injections

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Abstract

Due to the coronavirus disease 2019 restrictions in providing diabetes services, we have developed an innovative pump training program, which consisted of technical session, pump training, one in-person practical session, and four consecutive online sessions (Skype Meet Now).

A 13-year-old female patient with a 4-year history of type 1 diabetes (T1D) on multiple daily injections (MDI) with glycated hemoglobin 8.9%; 74 mmol/mol) initiated Minimed 670G system using the program. Time in range (70-180 mg/dL) of 39% and sensor glucose (SG) of 214±91 mg/dL (MDI with continuous glucose monitoring) increased to 69% in the first 2 weeks and reached 86% and SG of 140±40 mg/dL in the first month of auto mode initiation, without severe hypoglycemia or hyperglycemia. Virtual pump training program can be an effective tool to initiate a hybrid closed-loop system and to improve glycemic control in people with T1D on MDI.

Keywords

closed-loop systems, COVID-19, diabetes education, type 1 diabetes, virtual training

Introduction

Training, education, and support are the most important factors[1] in achieving success with continuous subcutaneous insulin delivery (CSII) in people with type 1 diabetes (T1D), where CSII training is traditionally delivered in person by either individual or group sessions.

The ongoing coronavirus disease 2019 (COVID-19) pandemic has prompted many diabetes health providers to search for and implement alternative approaches to deliver diabetes services.

T1D is a uniquely suited to a telemedicine approach, as many diabetes devices (CSII, continuous glucose monitoring [CGM], Bluetooth insulin pens, and glucometers) can be uploaded via the internet to a cloud-specific database. Different software applications exist which enable health providers to review the aggregated device data. Telemedicine as an innovative approach in T1D management appeared to have comparable efficacy on glycemic control with standard (in person) clinic visits.[2] Telemedicine can be also used safely and effectively for new-onset T1D training and education for both pediatric and adult patients and their families.[3]

Due to the COVID-19 restrictions in providing regular diabetes services at Sidra Medicine in Qatar, the traditional training and education, a 10-day initiation protocol[4] for hybrid closed-loop (HCL) system in patients previously treated with multiple daily injections (MDI) was postponed, as the service was not considered critical in the current situation. In an attempt to continue to support CSII initiation, the diabetes team developed an innovative "virtual pump training program," based on the previous initiation protocol for the HCL system,[4] using video conferencing Skype "Meet Now" (Skype Communications S.a.r.l., Palo Alto, CA, USA).

HCL training, insulin start in manual mode, the transition to auto mode, and follow-up visits were performed online, using Skype.

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SCAI THINK TANK PROCEEDING

WILEY

Hot topics in interventional cardiology: Proceedings from the society for cardiovascular angiography and interventions 2020 think tank

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Abstract

The society for cardiovascular angiography and interventions (SCAI) think tank is a collaborative venture that brings together interventional cardiologists, administrative partners, and select members of the cardiovascular industry community for high-level field-wide discussions. The 2020 think tank was organized into four parallel sessions reflective of the field of interventional cardiology: (a) coronary intervention, (b) endovascular medicine, (c) structural heart disease, and (d) congenital heart disease (CHD). Each session was moderated by a senior content expert and co-moderated by a member of SCAI's emerging leader mentorship program. This document presents the proceedings to the wider cardiovascular community in order to enhance participation in this discussion, create additional dialogue from a broader base, and thereby aid SCAI and the industry community in developing specific action items to move these areas forward.

KEYWORDS
congenital heart disease, coronary artery disease, pediatrics, peripheral arterial disease, structural heart disease intervention

1 | INTRODUCTION

Held annually since 2012, the society for cardiovascular angiography and interventions (SCAI) think tank is a collaborative venture that brings together interventional cardiologists, administrative partners, and select members of the cardiovascular industry community for high-level field-wide discussions. During the SCAI 2020 scientific sessions, relevant topics in interventional cardiology were debated with the goals of defining the current state of the field, identifying challenges, and proposing potential near-term solutions. Topics were determined by nomination, and solidified through a voting process ultimately vetted by SCAI leadership and the industry relations committee. The 2020 think tank was organized into four parallel sessions reflective of the field of interventional cardiology: (a) coronary intervention, (b) endovascular medicine, (c) structural heart disease (SHD), and (d) congenital heart disease (CHD). Each session was moderated by a senior content expert and co-moderated by a member of SCAI's emerging leader mentorship program. This document presents the proceedings to the wider cardiovascular community in order to enhance participation in this discussion, create additional dialogue from a broader base, and thereby aid SCAI and the industry community in developing specific action items to move these areas forward.

2 | CORONARY: SCAI ROLE IN INCREASING ADOPTION OF PHYSIOLOGY/IMAGING

Data has shown that physiology/imaging guided PCI produces better long-term outcomes. Adoption rates of this technology in many areas outside the US are much higher. What role should SCAI play in increasing the adoption of physiology/imaging assessments for percutaneous coronary intervention (PCI) when it comes to reimbursement, clinical guidance, and education?

Although coronary angiography (CA) results alone can guide the decision to perform a PCI, fractional flow reserve (FFR) and resting pressure indices such as instantaneous wave-free ratio (iFR) are invasive physiological indices measured to assess the functional significance of a coronary artery stenosis. Studies have shown that FFR-guided PCI improves clinical outcomes compared with CA-guided treatment, supporting current guideline recommendations for FFR-guided PCI.[1] Despite this, penetration of FFR and iFR remains low. Since the implementation of appropriate use criteria and metrics for PCI, the use of FFR/iFR has significantly increased in patients with stable ischemic heart disease, with the latest data from the veterans administration indicating an 18.5% utilization overall in diagnostic catheterization and 75% usage rate in intermediate lesions undergoing PCI.[2]

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are intravascular imaging modalities primarily used to characterize lesion morphology, quantify plaque burden, guide stent sizing, assess stent expansion, and identify procedural complications. IVUS-guided PCI was associated with a 33% relative risk reduction for cardiovascular death compared to CA alone.[3] Despite extensive and widely disseminated evidence supporting the benefits of imaging, the utilization varies from 5% in Europe, 7%–15% in the US, and 80%–90% in Japan.[4] This correlates with reimbursement differences. In Europe there is no additional reimbursement for imaging (additional costs are not covered) compared to Japan where separate reimbursement for imaging is granted even for diagnostic cases. In the US reimbursement is limited to a small additional physician payment, with no

RESEARCH ARTICLE

REVISED Refinement of the critical genomic region for congenital hyperinsulinism in the Chromosome 9p deletion syndrome [version 2; peer review: 3 approved with reservations]

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Abstract

Background: Large contiguous gene deletions at the distal end of the short arm of chromosome 9 result in the complex multi-organ condition chromosome 9p deletion syndrome. A range of clinical features can result from these deletions with the most common being facial dysmorphisms and neurological impairment. Congenital hyperinsulinism is a rarely reported feature of the syndrome with the genetic mechanism for the dysregulated insulin secretion being

Open Peer Review

Reviewer Status ? ? ?

	Invited Reviewers		
	1	**2**	**3**
version 2 (revision) 04 Aug 2020			

PLOS NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

Emerging *Cryptococcus gattii* species complex infections in Guangxi, southern China

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Abstract

The emergence and spread of cryptococcosis caused by the *Cryptococcus gattii* species complex has become a major public concern worldwide. *C. deuterogattii* (VGIIa) outbreaks in the Pacific Northwest region demonstrate the expansion of this fungal infection to temperate climate regions. However, infections due to the *C. gattii* species complex in China have rarely been reported. In this study, we studied eleven clinical strains of the *C. gattii* species complex isolated from Guangxi, southern China. The genetic identity and variability of these isolates were analyzed via multi-locus sequence typing (MLST), and the phylogenetic relationships among these isolates and global isolates were evaluated. The mating type, physiological features and antifungal susceptibilities of these isolates were also characterized. Among the eleven isolates, six belonged to *C. deuterogattii*, while five belonged to *C. gattii sensu stricto*. The *C. deuterogattii* strains from Guangxi, southern China were genetically variable and clustered with different clinical isolates from Brazil. All strains were *MAT*α, and three *C. deuterogattii* isolates (GX0104, GX0105 and GX0147) were able to undergo sexual reproduction. Moreover, most strains had capsule and were capable of melanin production when compared to the outbreak strain from Canada. Most isolates were susceptible to antifungal drugs; yet one of eleven immunocompetent patients died of cryptococcal meningitis caused by *C. deuterogattii* (GX0147). Our study indicated that the highly pathogenic *C. deuterogattii* may be emerging in southern China, and effective nationwide surveillance of *C. gattii* species complex infection is necessary.

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ORIGINAL ARTICLE

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A founder RAB27A variant causes Griscelli syndrome type 2 with phenotypic heterogeneity in Qatari families

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Abstract

Griscelli syndrome type 2 (GS2) is a rare autosomal recessive disorder caused by pathogenic variants in the *RAB27A* gene and characterized by partial albinism, immunodeficiency, and occasional hematological and neurological involvement. We reviewed and analyzed the medical records of 12 individuals with GS2 from six families belonging to a highly consanguineous Qatari tribe and with a recurrent pathogenic variant in the RAB27A gene (NM_004580.4: c.244C > T, p.Arg82Cys). Detailed demographic, clinical, and molecular data were collected. Cutaneous manifestations were the most common presentation (42%), followed by neurological abnormalities (33%) and immunodeficiency (25%). The most severe manifestation was HLH (33%). Among the 12 patients, three patients (25%) underwent HSCT, and four (33%) died. The cause of death in all four patients was deemed HLH, providing evidence for this complication's fatal nature. Interestingly, two affected patients (16%) were asymptomatic. This report highlights the broad spectrum of clinical presentations of GS2 associated with a founder variant in the *RAB27A* gene (c.244C > T, p.Arg82Cys). Early suspicion of GS2 among Qatari patients with cutaneous manifestations, neurological findings, immunodeficiency, and HLH would shorten the diagnostic odyssey, guide early and appropriate treatment, and prevent fatal outcomes.

KEYWORDS

founder effect, GS2, HLH, Qatari, *RAB27A*

1 | INTRODUCTION

Griscelli syndrome (GS) is a rare autosomal recessive disorder first described in 1978 as a disorder of partial albinism associated with immunodeficiency (Griscelli et al., 1978). Symptoms of GS overlap

Abbreviations: DD, developmental delay; GS2, Griscelli syndrome type 2; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; ID, intellectual disability.

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RESEARCH ARTICLE

STXBP6, reciprocally regulated with autophagy, reduces triple negative breast cancer aggressiveness

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Abstract

Background: Although autophagy plays a dual role in suppressing or promoting certain cancers, the nature of its involvement in breast cancers remains unclear. Here, we investigated the function of STXBP6, a protein regulating the autophagy-associated SNARE complex, in triple negative breast cancer (TNBC).

Results: We report that STXBP6 is profoundly downregulated in TNBC specimens in association with reduced overall patient survival. Notably, we found that *STXBP6* promoter was specifically hyper-methylated in TNBC specimens. Ectopic expression of *STXBP6* inhibited TNBC cell proliferation in cellular and mouse models. Mass spectrometric analysis revealed physical interactions of STXBP6 with a number of autophagy-related proteins including SNX27, a molecule involved in endocytosis of plasma membrane receptors and protein trafficking. Overexpression of *STXBP6* elicited autophagy through inhibition of mTORC1 signaling. Reciprocally, induction of autophagy rescued *STXBP6* expression by inhibiting EZH2 and altering *STXBP6* methylation. The mutual regulation between STXBP6 and autophagy was replicated in luminal breast cancer cells only when estrogen receptor (ER) activation was abrogated. Ectopic expression of *STXBP6* significantly reduced TNBC cells' migratory ability in vitro and tumor metastasis in vivo.

Conclusions: Our results unveil a role of STXBP6 in TNBC that highlights a new paradigm in autophagy regulation. Our results significantly enhance the understanding of the mechanisms of TNBC aggressiveness, which might help in designing novel therapies targeting TNBC.

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Review

Fanconi–Bickel Syndrome: A Review of the Mechanisms that Lead to Dysglycaemia

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Abstract: Accumulation of glycogen in the kidney and liver is the main feature of Fanconi–Bickel Syndrome (FBS), a rare disorder of carbohydrate metabolism inherited in an autosomal recessive manner due to *SLC2A2* gene mutations. Missense, nonsense, frame-shift (fs), in-frame indels, splice site, and compound heterozygous variants have all been identified in *SLC2A2* gene of FBS cases. Approximately 144 FBS cases with 70 different *SLC2A2* gene variants have been reported so far. *SLC2A2* encodes for glucose transporter 2 (GLUT2) a low affinity facilitative transporter of glucose mainly expressed in tissues playing important roles in glucose homeostasis, such as renal tubular cells, enterocytes, pancreatic β-cells, hepatocytes and discrete regions of the brain. Dysfunctional mutations and decreased GLUT2 expression leads to dysglycaemia (fasting hypoglycemia, postprandial hyperglycemia, glucose intolerance, and rarely diabetes mellitus), hepatomegaly, galactose intolerance, rickets, and poor growth. The molecular mechanisms of dysglycaemia in FBS are still not clearly understood. In this review, we discuss the physiological roles of GLUT2 and the pathophysiology of mutants, highlight all of the previously reported *SLC2A2* mutations associated with dysglycaemia, and review the potential molecular mechanisms leading to dysglycaemia and diabetes mellitus in FBS patients.

Keywords: Fanconi–Bickel Syndrome (FBS); *SLC2A2* mutation; GLUT2 dysfunction; dysglycaemia; liver; pancreatic β cell; cAMP; insulin secretion; birth weight; hepatomegaly

1. Introduction

Fanconi–Bickel syndrome (OMIM# 227810), a carbohydrate metabolism disorder due to glucose transporter 2 (GLUT2) transporter defect was first described by Fanconi and Bickel in 1949 [1]. In 1987, Fanconi–Bickel Syndrome (FBS) was identified as a defect in a sodium glucose secondary active transporter responsible for galactose and glucose transport in many tissues, including kidney and liver [2]. Studies in 1989, using Xenopus oocytes injected with human liver type glucose transporter synthetic mRNA construct, identified the role of the plasma membrane glucose transporter in sensing glucose, uptake of glucose, and its possible role in non-insulin-dependent diabetes mellitus [3]. In 1994, a study in Xenopus oocytes proved that a highly conserved GLUT2 missense mutation in one allele of the gene (substituted Val197 to Ile197) leads to GLUT2 dysfunction, and might be expected to play an important role in pathogenicity of non-insulin dependent diabetes mellitus [4,5]. Then in 1997, Santer et. al. (1997) for first time described the role of GLUT2 (*SLC2A2*) gene mutations in three FBS affected families, that includes the original patient reported by Fanconi and Bickel in 1949 [6].

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Full length article

Bacterial vaginosis in pregnancy – *a storm in the cup of tea*

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ABSTRACT

Human vaginal microbiota is dominated by *Lactobacillus spp* both in the non-pregnant and pregnant state. Bacterial vaginosis (BV) is an imbalance of vaginal microbiota caused by a reduction in the normal lactobacillary bacteria, and a heavy over-growth of mixed anaerobic bacteria. Various clinical (Amsel's Criteria), laboratory (Nugent's score) and molecular diagnostic method (quantitative PCR) are used for diagnosis. BV in pregnancy is associated with increased risk of preterm birth, low birth weight, chorioamnionitis and postpartum endometritis, apart from bothersome vaginal discharge. Antibiotic treatment with metronidazole or clindamycin are effective in eradicating bacterial vaginosis and safe to use in pregnancy. Treatment of bacterial vaginosis has not been shown to improve obstetric outcomes in women at low risk of preterm birth, but may reduce the risk of preterm birth and low birth weight in women at increased risk of preterm birth. Routine screening and treatment is not recommended in low risk women. Test for cure should be performed after treatment. Further research is required on other treatment modalities such as probiotic therapy and microbiota transplantation.

Background

There is increasing interest in human microbiota and their influence on health and diseases. The vaginal microbiota is unique and undergoes major compositional changes from birth to puberty and menopause [1,2]. Sex steroids appear to play an important role in the changes in composition and stability of vaginal microbiota [3–6]. Vaginal microbiota are known to undergo changes in pregnancy. Some studies also show changes in vaginal microbiota with menstruation, sexual intercourse, use of intrauterine contraceptive devices, contraceptive pills, medroxyprogesterone acetate injection, cervical caps and spermicidal creams [4,7–9] and it can also vary between different ethnic population [10]. Bacterial vaginosis is an imbalance of vaginal flora caused by a reduction in the normal lactobacillary bacteria, and a heavy over-growth of mixed anaerobic bacteria. In spite of a large number of studies, there remains a gap in the full understanding of the composition and dynamics of vaginal microbiota and their influence on physiology in both health and diseases.

Developments in molecular techniques of cloning and sequencing of 16S rRNA genes have helped to identify taxa that are not cultured in the vaginal microbiota [11].In healthy asymptomatic, non-pregnant women of reproductive age, vaginal microbiota can be classified into six types of community states. Types I to IV are dominated by *Lactobacillus spp.* commonly one of the four types, which include *L. crispatus, L. iners, L. jensenii and L. gasseri* [12–14], while types V and VI are composed of less numbers of *lactobacilli* and dominated by different anaerobic bacteria which include *Prevotella, Megasphaera, Gardnerella vaginalis, Sneathia and Atopobium vaginae, Dialister, Peptoniphilus, Eggerthela, Aerococcus, Finegoldia and Mobiluncus.* [11,15,16]. Although, these can be found in otherwise healthy asymptomatic women, they are more often associated with bacterial vaginosis. In the lower vagina, the microbiota may be contaminated by other genera of bacteria, such as *Streptococcus agalactiae*, *Staphylococcus epidermidis* and *Escherichia coli* that are typically observed in skin and the gastrointestinal tract [17–19].

The human vaginal microbiota plays an important role in preventing vaginal infections such as bacterial vaginosis (BV), viral infections and sexually transmitted diseases [16,20]. *Lactobacillus spp.* is thought to protect the genital tract from non-indigenous bacteria and maintain a healthy state by maintaining the vagina pH at less than 4.5 through the production of lactic acid [21]. Estrogen helps to release glycogen into the vaginal environment where it is broken down to glucose and maltose by alpha-amylase present in the vaginal epithelium. Lactobacilli use these carbohydrates to produce lactic acid by fermentation. Lactic acid in turn keeps the vaginal pH below 4.5, which is detrimental to pathogenic bacteria [22,23]. However, the protective action of vaginal microbiota appears to be more complex and might be regulated by host innate

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Review

Illustrative Case Series and Narrative Review of Therapeutic Failure of Immunotherapy for Allergic Rhinitis

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Abstract

This is a series of 4 cases (3 therapeutic failure and 1 early relapse) in adult patients treated with allergen immunotherapy (AIT) for allergic rhinitis (AR) in our immunotherapy clinic, which treats 110 new patients per year. AIT includes both subcutaneous and sublingual routes. The current national/international AIT recommendations and the literature have been searched to identify guidance for the optimal management of therapeutic failure of AIT in AR. There is scant information available to support clinicians when treatment failure and/or intolerable side effects occur. The importance is highlighted for developing the guidance and evidence base for the benefit of this patient subgroup. The potential strategies that clinicians have proposed are discussed in this article, though it is acknowledged that these are mostly not evidence-based.

Keywords

allergen, side effects, tolerability, desensitization, grass pollen

Introduction

Allergen immunotherapy (AIT) is a globally used superior treatment for allergic rhinitis (AR) and remains the only curative treatment. AIT includes both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). In addition to curative potential, AR may influence subsequent development of asthma in children with AR.[1,2] AIT is indicated for moderate/severe AR, when symptom control has not been achieved with allergen avoidance and/or pharmacological methods, and there is evidence of specific immunoglobulin E (IgE) to clinically relevant allergens.[3–6] Treatment is usually carried out for at least 3 years (can be 3–5 years, dependent on the duration of the maintenance period).[5–8] While there is greater experience with SCIT, it is well recognized that both SCIT and SLIT are effective in the treatment of AR.[9–12] Detailed systematic reviews and meta-analyses, including a limited number of studies directly comparing efficacy between SCIT and SLIT, concluded no major difference.[11–13]

However, even with careful patient selection, treatment failure may still occur. In our clinical practice, we observe a very small percentage of therapeutic failures with AIT. We have considered therapeutic failure as either inadequate symptomatic response or intolerable side effects, which are both well recognized.[14,15] This is a series of 4 cases (3 therapeutic failure and 1 early relapse) encountered in our AIT clinic, where patients are treated using either SCIT or SLIT protocols, depending on clinical evaluation and patient preference. All patients provided informed consent to be included. Assessment according to the National Health Service Health Research Authority definitions indicated that Research Ethics Committee approval was not required

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Review

Interventions for escalation of therapy for acute exacerbations of asthma in children: An overview of Cochrane reviews

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WHY DO WE NEED AN OVERVIEW?

Most children with asthma have mild or moderate exacerbations and respond well to first-line therapy (inhaled short-acting beta-agonists (SABAs) and systemic corticosteroids). However, the best treatment for the small proportion of children who are seriously ill and do not respond to first-line therapy is poorly understood.

Currently, a large number of treatment options are available, and there is wide variation in practice. A prospective study in the United Kingdom (UK) and Ireland found wide variation in the prevalence of intravenous treatment for acute paediatric asthma, ranging from 0% to 19.4% [1]. Recently, a registry study from the United States of America found that intravenous (IV) magnesium was given to children with acute asthma in 5.1–15.6% of visits [2].

In this paper, we provide a brief summary of all the evidence available from current Cochrane reviews, detailed results for one primary outcome (length of stay), a summary of other important outcomes, and suggest directions for future research.

OBJECTIVES

(1) To summarise the efficacy and safety of treatment for acute exacerbations of asthma in children who are unresponsive to standard first-line therapy;

(2) To identify evidence gaps and inconsistency in outcome measures to guide future research efforts.

METHODS

We searched the Cochrane Database of Systematic Reviews to identify systematic reviews that assessed interventions for children with acute exacerbations of asthma. We assessed the risk of bias in each systematic review, and extracted summary data for our primary and secondary outcomes according to Cochrane methodology [3]. Our outcomes included length of stay, hospital admission, intensive care unit admission, and adverse effects.

We assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [4].

MAIN RESULTS

We identified 13 reviews that reported results for children alone (Table 1) [5]. The reviews included a total of 67 trials. Most outcomes, particularly for parenteral treatment, included 1–3 trials, and less than 100 participants. The total number of children in each review ranged from 40 to 2630. Four out of 13 reviews were at high risk of bias due to concerns with identification and selection of studies.

WHICH INTERVENTIONS REDUCE LENGTH OF STAY?

Two reviews reported emergency department length of stay as an outcome, while six reported hospital length of stay. Neither continuous vs. intermittent SABA administration nor IV

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Using clinical cases to restore basic science Immunology knowledge in physicians and senior medical students

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Abstract:

The majority of medical students and many physicians find basic science immunology confusing and the teaching of immunology to be uninteresting. Physicians undergoing training in a range of disciplines treat patients with immunological disease, including Allergy/Immunology and Rheumatology. It is essential for senior medical students and physicians to understand the pathology of immune diseases and the pharmacology of immune interventions. In order to optimise this learning, underlying concepts of basic immunology need to be revised, or sometimes learnt for the first time. Teachers may need to overcome baseline attitudinal negativity. Medical students and postgraduates are more able to relate to basic immunology if approached through a clinical route. Case presentations and case-based discussions are a familiar format for medical students and physicians, though typically they are utilised to enhance understanding of clinical presentation, investigation, and treatment. Hence, they may be more receptive to "difficult" immunology concepts when presented in a familiar teaching framework. Although there is data supporting case-based learning for basic immunology in medical students, there is little data in physicians. Extrapolating from the medical student literature, I devised a programme of clinical cases for physicians whereby understanding the immunopathological basis of the condition and/or its immunological treatment was employed as a platform to appreciate the basic science immunology in more depth. A variety of cases were selected to illustrate different immunological topics. The sessions were small group, and highly interactive in nature. As this programme has only recently been introduced, formal evaluation has yet to be concluded.

Keywords:

Postgraduate, education, Rheumatology, immunodeficiency, interactive, case-based learning

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Epidemiology of Irritable Hip in Western Scotland: A Follow-Up Study

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Abstract

Background

A ‘limping child’ commonly presents to the emergency department (ED). In the absence of trauma, many are diagnosed with irritable hip (IH). The aetiology of IH is not well understood and there may be geographical and seasonal variations. We previously established one year (2016) epidemiological data of IH presenting to the Royal Hospital for Children (RHCG) ED in Glasgow, Scotland. The sentinel findings in that year were (i) an age distribution shift to younger (peak at two years of age), (ii) no marked association with social class, and (iii) a spring preponderance. We sought to strengthen or refute these findings by repeating our study to obtain comparative data for 2017.

Methods

We performed a retrospective analysis of all children discharged from the RHCG ED from January to December 2017. Relevant discharge codes were determined, and patient records screened. Patients without a discharge code had their presenting complaint and medical record screened. These data were compared to that of the previously published study from the same ED (2016).

Results

Several findings were consistent with the conclusions of the 2016 study. The incidence was similar with 362 and 354 cases diagnosed in 2017 and 2016 respectively. The boy-girl ratio was consistent across both data-sets, 2:1 and 1.9:1 respectively. The mean age of presentation was similar (3.3 vs 3.5 years) across both years, with the same medians (three years) and peaks (two years). There was no overt difference in incidence or correlation to social deprivation. However, in 2016, a spring preponderance was seen whereas there was an autumn preponderance in 2017. Pooling data from the two cohorts, 93% (n=668) of patients were managed exclusively by ED physicians, with 70% (n=504) not requiring any further follow-up. The majority of patients who required follow-up were seen in ED clinics (169/212, 79.7%). No patient initially diagnosed as IH was found to have septic arthritis (SA).

Conclusion

In this follow-up study, we again found (i) a younger age profile than other studies, and (ii) no overt association with social deprivation. The major difference between the previous (2016) and current (2017) study was the apparent seasonal peaks: spring (2016), and autumn (2017). This difference does not negate the 'antecedent infection' hypothesis, but any aetiological proposal should be capable of accounting for this discrepancy. Additionally, our studies highlight that the majority of these patients can be managed in the ED alone.

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Introduction

Irritable hip (IH) is a common, time-limited benign condition that is often seen in the paediatric emergency departments (ED) [1]. Its most common presenting symptom is a limp though patients can complain of pain, restricted range of motion and/or a low grade fever [2-4].

IH is classically seen as a diagnosis of exclusion, ensuring that more serious conditions such as septic arthritis (SA), osteomyelitis, bone tumours, leukaemia, Perthes disease, slipped capital femoral epiphysis (SCFE) and traumatic injury are ruled out [5]. However, after a sufficient history and examination, investigations in these patients can be selective and not all patients require a complete laboratory or radiological work-up [6].

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ORIGINAL ARTICLE

Thoracic imaging of coronavirus disease 2019 (COVID-19) in children: a series of 91 cases

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Abstract

Background Pulmonary infection with SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2; COVID-19) has rapidly spread worldwide to become a global pandemic.

Objective To collect paediatric COVID-19 cases worldwide and to summarize both clinical and imaging findings in children who tested positive on polymerase chain reaction testing for SARS-CoV-2.

Materials and methods Data were collected by completion of a standardised case report form submitted to the office of the European Society of Paediatric Radiology from March 12 to April 8, 2020. Chest imaging findings in children younger than 18 years old who tested positive on polymerase chain reaction testing for SARS-CoV-2 were included. Representative imaging studies were evaluated by multiple senior paediatric radiologists from this group with expertise in paediatric chest imaging.

Results Ninety-one children were included (49 males; median age: 6.1 years, interquartile range: 1.0 to 13.0 years, range: 9 days–17 years). Most had mild symptoms, mostly fever and cough, and one-third had coexisting medical conditions. Eleven percent of children presented with severe symptoms and required intensive unit care. Chest radiographs were available in 89% of patients and 10% of them were normal. Abnormal chest radiographs showed mainly perihilar bronchial wall thickening (58%) and/or airspace consolidation (35%). Computed tomography (CT) scans were available in 26% of cases, with the most common abnormality being ground glass opacities (88%) and/or airspace consolidation (58%). Tree in bud opacities were seen in 6 of 24 CTs (25%). Lung ultrasound and chest magnetic resonance imaging were rarely utilized.

Conclusion It seems unnecessary to perform chest imaging in children to diagnose COVID-19. Chest radiography can be used in symptomatic children to assess airway infection or pneumonia. CT should be reserved for when there is clinical concern to assess for possible complications, especially in children with coexisting medical conditions.

Keywords Children · Computed tomography · Coronavirus · COVID-19 · Imaging · Lower respiratory tract infection · Pneumonitis · Radiography

Introduction

Since the outbreak in China in December 2019, pulmonary infection with the novel SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2; causing COVID-19) has rapidly spread worldwide to become a global pandemic threatening the capacity of numerous national health care systems. Although COVID-19 predominantly affects adults, there have been reports of paediatric patients. The largest paediatric epidemiological report of COVID-19 in children by Dong et al. [1] found that children of all ages were susceptible to SARS-CoV-2 infection, but clinical manifestations were

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Original Paper

Perfusion

A case series of transcatheter Potts Shunt creation in a pediatric population affected with refractory pulmonary artery hypertension: focus on the role of ECMO

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1–6

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Abstract

Purpose: Patients with suprasystemic idiopathic pulmonary hypertension (S-PAH) have a poor prognosis. Therapeutic options are limited. Reverse Potts shunt creation modifies physiology transforming patients with PAH into Eisenmenger physiology with a better outcome. Percutaneous transcatheter stent secured aortopulmonary connection (transcatheter Potts Shunt, TPS) is a feasible very high-risk procedural option in such patients. We report our experience with patients undergoing TPS at our institution requiring extracorporeal membrane oxygenation (ECMO) support.

Methods: A prospective observational study of patients with drug-refractory PAH, worsening NYHA class, and right ventricular failure undergoing TPS. Two patients required rescue ECMO for cardiac arrest during the procedure. Subsequently, "standby ECMO" was available in all the following cases and elective support was provided in patients with extremely poor conditions.

Results: Ten pediatric patients, underwent TPS at our institution. Two patients were rescued by ECMO after cardiac arrest during the shunt creation. This occurred as a result of the acute loading of the left ventricle (LV) after retrograde aortic arch filling through the Potts shunt. Following this, another two patients underwent elective ECMO after the uneventful induction of anesthesia. They all died postoperatively despite a successful TPS procedure. The causes of death were not related to the use of ECMO, but the complication of severe PAH. Six patients with successful TPS did not require ECMO and survived.

Conclusions: TPS is a pioneering procedure offering the opportunity to treat high-risk idiopathic drug-refractory PAH patients. Acute LV failure is a complication of TPS in patients with S-PAH. Elective ECMO, an option to avoid circulatory arrest and acute profound hypoxia secondary to exclusive right-to left shunt systemic perfusion by Potts shunt and LV dysfunction with resulting pulmonary edema, may be used at the early stage of the learning curve, but it does not influence the prognosis of these patients which remains poor.

Keywords

pulmonary hypertension; ECMO; children; reversed Potts shunt; cath lab

Introduction

Supra systemic pulmonary arterial hypertension (PAH) often leads to right ventricular (RV) failure due to chronically elevated afterload. When untreated, idiopathic PAH results in death within 2-3 years following the diagnosis in adults and within the first 1 year of diagnosis in children.[1–3] There are limited therapeutic options. The first line treatment is medical therapy, which includes phosphodiesterase-5 inhibitors, endothelin receptor antagonists and prostacyclin analogues. Despite maxi-

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Inhaled nitric oxide (iNO) for preventing prematurity-related bronchopulmonary dysplasia (BPD): 7-year follow-up of the European Union Nitric Oxide (EUNO) trial

Contribution to journal › Article › peer-review

Anne Greenough, Fabrice Decobert, David Field, Mikko Hallman, Helmut D. Hummler, Baldvin Jonsson, Manuel Sánchez Luna, Bart Van Overmeire, Virgilio P. Carnielli, Jim L. Potenziano, Jean Christophe Mercier

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Abstract

Most studies of inhaled nitric oxide (iNO) for prevention of bronchopulmonary dysplasia (BPD) in premature infants have focused on short-term mortality and morbidity. Our aim was to determine the long-term effects of iNO. A 7-year follow-up was undertaken of infants entered into a multicenter, double-blind, randomized, placebo-controlled trial of iNO for prevention of BPD in premature infants born between 24 and 28 weeks plus six days of gestation. At 7 years, survival and hospital admissions since the 2-year follow-up, home oxygen therapy in the past year, therapies used in the previous month and growth assessments were determined. Questionnaires were used to compare general health, well-being, and quality of life. A total of 305 children were assessed. No deaths were reported. Rates of hospitalization for respiratory problems (6.6 vs. 10.5%, iNO and placebo group, respectively) and use of respiratory medications (6.6 vs. 9.2%) were similar. Two patients who received iNO and one who received placebo had received home oxygen therapy. There were no significant differences in any questionnaire-documented health outcomes. iNO for prevention of BPD in very premature infants with respiratory distress did not result in long-term benefits or adverse long-term sequelae. In the light of current evidence, routine use of iNO cannot be recommended for prevention of BPD in preterm infants.

Clinical characteristics and long-term follow-up of patients with diabetes due to *PTF1A* enhancer mutations

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Abstract

Context: Biallelic mutations in the *PTF1A* enhancer are the commonest cause of isolated pancreatic agenesis. These patients do not have severe neurological features associated with loss-of-function *PTF1A* mutations. Their clinical phenotype and disease progression have not been well characterised.

Objective: To evaluate phenotype and genotype characteristics and long-term follow-up of patients with *PTF1A* enhancer mutations.

Setting: Twelve tertiary paediatric endocrine referral centres.

Patients: 30 patients with diabetes caused by *PTF1A* enhancer mutations. Median follow-up duration was 4 years.

Main Outcome Measures: Presenting and follow-up clinical (birthweight, gestational age, symptoms, auxology) and biochemical (pancreatic endocrine and exocrine functions, liver function, glycated haemoglobin) characteristics, pancreas imaging, genetic analysis.

Results: Five different homozygous mutations affecting conserved nucleotides in the *PTF1A* distal enhancer were identified. The commonest was the Chr10:g.23508437A>G mutation (n=18). Two patients were homozygous for the novel Chr10:g.23508336A>G mutation.

Birthweight was often low (median SDS=-3.4). The majority of patients presented with diabetes soon after birth (median age of diagnosis:5 days). Only 2/30 presented after 6 months of age. All patients had exocrine pancreatic insufficiency. Five had developmental delay (4 mild) on long term follow-up. Previously undescribed common features in our cohort were: transiently elevated ferritin level (n=12/12 tested), anaemia (19/25) and cholestasis (14/24). Postnatal growth was impaired (median height SDS:-2.35, median BMI SDS:-0.52 SDS) with 20/29 (69%) cases having growth retardation.

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Effects of fasting during Ramadan on seizure control and quality of life in patients with epilepsy

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ABSTRACT

Background: During Ramadan, the ninth month of the lunar Islamic calendar, adult Muslims are obliged to fast, which involves refraining from taking any food, beverages, or oral medications from dawn to sunset. Fasting's effect on seizure control is not fully understood, and a few observational studies have provided inconclusive results. This study aimed to investigate the effect of fasting during Ramadan on seizure control and quality of life in adult patients with epilepsy.

Methods: This was a prospective observational study over a 3-month period (one month before fasting, the fasting month, and one month after fasting). We recruited adult patients with active epilepsy who were able to fast during the month of Ramadan. The primary outcome measures were as follows: 1) seizure control and 2) quality of life score using the Arabic version of the Ferrans and Powers Quality of Life Index (QLI). Changes in anticonvulsant medications were not allowed during the study period. We used a seizure log provided to participants to record the number of seizures during the 3-month period. Quality of life was scored at the end of each month of the study period.

Results: Thirty-seven patients were studied (59% males). The mean age was 30 years (range, 14–51 years), and mean age at epilepsy onset was 13 years (range, 0.5–35 years). On average, patients were on three antiepileptic medications at baseline (range: 2–5). A total of 1576 seizures were reported during the 3-month follow-up, where seizures prior to fasting represented 35.5% of all seizures. Multilinear regression analysis revealed a significant decline of seizures by 21% during the fasting month compared with baseline (adjusted coefficient = 0.79, $p < 0.01$, 95% confidence interval (CI); 0.61–0.98, $R2 = 0.81$) and by 29% during post fasting compared with baseline (adjusted coefficient = 0.71, $p < 0.01$, 95% CI; 0.53–0.90, $R2 = 0.79$). No significant change was found in the QLI scores calculated during the three months of the study period.

Conclusion: Fasting during Ramadan might have a positive impact on seizure control in patients with epilepsy, which continued during the month following fasting, whereas the quality of life scores were not affected by fasting.

1. Introduction

Fasting during Ramadan, the ninth month of the lunar Islamic calendar, requires adult Muslims to refrain from taking any food, beverages, or oral medications from dawn to sunset. The total hours of fasting depend on the geographic location and the season, as the daytime is longer in the summer and shorter in the winter. The average length of fasting was around 15 h per day in Saudi Arabia, when this study was conducted. Alterations in the timing of antiepileptic drugs (AEDs), disturbances in the circadian pattern of sleep, or even sleep deprivation are expected during Ramadan [1]. These changes in the daily routine are known risk factors for worsening seizure control [2,3]. However, diet control is one of the oldest and most common forms of treatment for many diseases. Epilepsy is no exception; physicians have treated epilepsy through changes and restrictions in diet for centuries. The use of fasting in the treatment of epilepsy can be traced back to the era of

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ORIGINAL ARTICLE

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Insights from healthcare academics on facilitating interprofessional education activities

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ABSTRACT

Facilitators are of paramount importance to the success of interprofessional education (IPE) activities; hence, it is crucial to explore their perspectives and experiences in delivering IPE in Qatar. Using an exploratory case study approach, semi-structured interviews were conducted, in 2018, among faculty members, who had facilitated at least one IPE activity in Qatar, from healthcare professional education programs at Qatar University Colleges of Pharmacy, Medicine, and Health Sciences, Weill Cornell Medicine in Qatar, the University of Calgary in Qatar, and the College of North Atlantic. Interviews were recorded and transcribed verbatim. Inductive thematic content analysis was implemented. Twenty-one interviews were conducted with the following professions represented: medicine (n = 6), pharmacy (n = 5), nursing (n = 4), biomedical science (n = 3), respiratory theory (n = 2) and public health (n = 1). Four main themes emerged from the interviews: drivers to facilitator involvement that included interest and commitment to IPE and awareness of collaborative practice benefits; facilitator participation which was based on facilitator attributes and preparedness and readiness for IPE facilitation; the organizational support in terms of dedicated structure for IPE and IPE design and delivery and; student participation in terms of group dynamics and student engagement. Some key recommendations include having a dedicated unit for IPE, scheduling protected time for IPE, and organizing facilitators' training and debriefing workshops. The facilitators valued and appreciated IPE in preparing students for future collaborative practice. These findings can inform the development of quality and sustainable IPE activities in the future.

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Qualitative method; interprofessional education; facilitation; faculty development; interprofessional research; interviews

Introduction

The World Health Organization (WHO)'s "Global Strategy on Human Resources for Health: Workforce 2030" recognizes the importance of interprofessional education (IPE) and collaborative practice (CP) as part of transformative strategies to scale up health worker education to improve long-term care for older patients, and enhance both the capacity and satisfaction of healthcare workers. This is expected to lead to better team performance and the delivery of cost-effective patient-centred care (World Health Organization, 2016). The strategy recommends that educational institutions need to adapt their strategies to align them with transformative educational needs which calls for the promotion of IPE and CP. IPE is defined as a pedagogical strategy of which interaction among a group of healthcare students coming from two or more health professions in order to learn with, from and about each other to promote a culture of collaboration that can be translated into practice settings (Buring, Bhushan, Brazeau et al., 2009; CAIPE, 2002).

Due to the significant impact of such an educational approach on improving the quality of care, IPE has received increased attention worldwide in the past 20 years and it is well established in some western countries such as Canada, United States, United Kingdom, and Australia. Similarly, the concept of IPE is emerging in the Middle Eastern countries with an increasing number of health professional degree programs aiming to maintain high standards of education through meeting international accreditation standards (Awan et al., 2018; El-Awaisi et al., 2017; Zeeni et al., 2016). Many accrediting bodies of the medical and healthcare programmes require evidence of IPE incorporation into curricula, which is an important element in driving IPE forward and in expediting the healthcare faculty's positive shift toward this educational transformation (Barker et al., 2005; El-Awaisi et al., 2016; Olenick & Allen, 2013; Thistlethwaite, 2015; Wilby et al., 2015).

To be most effective, it is recognized that IPE should be embedded in the early stages of undergraduate curricula (Harden, 2015). Early immersion enabling these students to prevent negative stereotyping, understand their professional role and valuing the role of other health professionals (Lapkin et al., 2012; Lawlis et al., 2016). However, from the perspective of program developers, IPE preparation and delivery should not be underestimated. Planning and developing an IPE activity requires an extensive amount of time and resources, reportedly requiring three times the preparation of a traditional course content delivery (Buring, Bhushan, Broeseker et al., 2009). In preparation for an IPE event, simply recruiting facilitators may not lead to a worthwhile IPE experience. Even experienced facilitators may not be equipped with the necessary knowledge and skills to facilitate IPE effectively (Egan-Lee, Baker, et al., 2011a). This could be due to a lack of exposure to IPE and IPC concepts in their training and/or in their work environment (Anderson et al., 2009; Buring, Bhushan, Broeseker et al., 2009; Hall & Zierler, 2015). A key

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Generation of two human iPSC lines from patients with maturity-onset diabetes of the young type 2 (MODY2) and permanent neonatal diabetes due to mutations in the *GCK* gene

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A B S T R A C T

Heterozygous and homozygous mutations in the *glucokinase* (*GCK*) gene leads to maturity-onset diabetes of the young type 2 (MODY2) and permanent neonatal diabetes (PNDM), respectively. Here, we report the generation of two induced pluripotent stem cell (iPSC) lines, QBRIi010-A and QBRIi011-A, from patients with MODY2 and PNDM due to mutations in the *GCK* gene (c.437 T > C). The generated iPSC lines displayed pluripotency characteristics, were able to differentiate into the three germ layers, and showed normal karyotypes. These iPSC lines will serve as valuable human cell models for understanding diabetes pathogenesis and developing new therpaies for diabetes.

1. Resource Table

Unique stem cell lines identifier	QBRIi010-A QBRIi011-A
Alternative name(s) of stem cell line	*GCK*-MODY2 iPSCs (QBRIi010-A) *GCK*-PNDM iPSCs (QBRIi011-A)
Institution	Qatar Biomedical research institute (QBRI), Hamad Bin Khalifa University (HBKU), Qatar Foundation, Doha, Qatar
Contact information of distributor	Essam M. Abdelalim (emohamed@hbku.edu.qa)
Type of cell line	iPSC
Origin	human
Cell Source	Blood
Clonality	Clonal
Method of reprogramming	Integration-free Sendai virus vector contain OCT3/4, SOX2, c-MYC, and KLF4
Genetic Modification	YES
Type of Modification	Hereditary
Associated disease	Patient 1: (Maturity diabetes of the young type 2 (MODY2) Patient 2: Permanent neonatal diabetes mellitus (PNDM)
Gene/locus	Gene: *GCK* Locus: 7p13 Heterozygous mutation: c.437 T > C in exon 4 (Patient 1) Homozygous mutation: c.437 T > C in exon 4 (Patient 2)
Method of modification	N/A
Name of transgene or resistance	N/A
Inducible/constitutive system	N/A
Date archived/stock date	*Date cell line archived or deposited in repository*
Cell line repository/bank	N/A
Ethical approval	The protocol was approved by the Institutional Review Board (IRB) of Sidra Medicine (no. 1702007608) and QBRI (no. 2018–002)

2. Resource utility

We established two iPSC lines from patients with MODY2 and PNDM due to heterozygous and homozygous mutations in the *GCK* gene (c.437 T > C), respectively. These iPSC lines will serve as human cell models for elucidating underlying mechanism of *GCK*-associated diabetes and developing novel therapies for diabetes.

3. Resource details

Glucokinase (*GCK*) gene encodes an enzyme that phosphorylate

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Identification of Three Novel and One Known Mutation in the *WFS1* Gene in Four Unrelated Turkish Families: The Role of Homozygosity Mapping in the Early Diagnosis

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What is already known on this topic?

Wolfram syndrome 1 (WS1) is a clinically heterogeneous disease with variable manifestations and progression pattern depending on the underlying molecular genetic aetiology. Patients may present with incomplete phenotype, but the disease has a progressive nature with a negative impact of poor glycaemic control. Identification of molecular genetic aetiology provides early diagnostic confirmation and thereby an opportunity to detect and manage the subtle symptoms more appropriately.

What this study adds?

Our study expands the mutation database of WFS1 with three novel variants and provides further insights into the genotype and phenotype association. We used homozygosity mapping as an adjunctive tool, which contributed to early detection of molecular genetic etiology in cases that presented with incomplete WS1 phenotype.

Abstract

Objective: Bi-allelic mutations in the *wolframin* gene *(WFS1)* cause Wolfram syndrome 1 (WS1 or DIDMOAD) characterized by non-autoimmune diabetes mellitus, optic atrophy, diabetes insipidus, sensorineural deafness, urinary tract abnormalities, and neuropsychiatric disorders. Patients presenting with an incomplete phenotype of WS1 were evaluated using homozygosity mapping and subsequent whole-exome sequencing.

Methods: Four unrelated consanguineous Turkish families, including seven affected children, and their unaffected parents and siblings were evaluated. Homozygosity mapping was performed, followed by whole-exome sequencing of *WFS1*. Mutations were classified according to results of "*in silico*" analyses, protein prediction, and functional consequences.

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Full length article

Intestinal parasitic infections in pregnancy – A review

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ABSTRACT

Intestinal parasitic infections are widespread worldwide and with increased global travel and transport of food, these are not entirely limited to traditionally endemic areas. The prevalence of parasitic infections in endemic areas among pregnant women ranges from 24 to 70 % with approximately 10 % of women having multiple parasites. Pregnancy with its increased nutritional demands and altered immunological defenses is an especially vulnerable time for acquiring parasitic infections, which may be associated with adverse outcomes such as anaemia, which in some cases may even contribute to mortality. The presence of a helminthic infections during pregnancy may also cause immunological effects that can contribute to maternal morbidity and mortality as well as affecting the maternal immune response and immune system function in the baby after birth. Mass administration of anthelminthic drug therapy has been applied in endemic areas but there is inconclusive evidence of its benefit in improving pregnancy outcomes, however, no safety concerns have been highlighted with the use of the recommended drugs for parasitic infections.

Introduction

The World Health Organisation (WHO) estimates that nearly a quarter of the world's population or 1.5 billion people across the world suffer from intestinal parasitic infections [1]. These are distributed widely across different regions but are mostly in sub-Saharan Africa, the Americas, China and East Asia [1]. While infections are usually more prevalent in low-income countries among the lower socio-economic strata with poor sanitation, increasing global trade in food and travel can cause an increase in the risk of acquiring certain parasitic infections anywhere in the world [2].

Importantly, women may be especially vulnerable to infections by food borne parasites, especially in developing countries, particularly because of their role in childcare, household work and food preparation [3]. Pregnancy has been shown to be an independent risk factor for helminthic intestinal infections [4]. Given that parasitic infections can have serious consequences in pregnancy such as anaemia, low weight gain, impaired fetal growth, preterm birth and maternal mortality [5]; it is important for clinicians to be aware of how they present, what is required to make a diagnosis and how to manage pregnant women with these infections.

The aim of this article was therefore, to present contemporary knowledge and evidence on the presentations and management of parasitic infections in pregnancy as well as the clinically relevant consequences of parasitic infections on pregnancy.

Methods

A literature search was carried out from 1st January 1990 to 1st February 2020, using the search terms intestinal parasite, helminths and pregnancy. The search was done on the following databases - Pubmed. Medline, Cochrane systematic reviews and Web of science. A total of 159 results were obtained. The abstracts were reviewed and full texts were accessed for 17 relevant studies. Only studies on pregnant populations were included. These relevant studies have been used to inform this review of literature.

Magnitude of the problem in the pregnant population

In areas of the world with high prevalence, 24 %–70 % of pregnant women have intestinal parasitic infections and, of these, a tenth have infections with more than one type of parasite [6,7]. The most common parasitic infections worldwide, by prevalence, have been reported to be amoebiasis, ascariasis, trichuriasis and

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PLOS ONE

RESEARCH ARTICLE

Corneal confocal microscopy demonstrates minimal evidence of distal neuropathy in children with celiac disease

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Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Abstract

Objectives

The aim of this study was to utilise corneal confocal microscopy to quantify corneal nerve morphology and establish the presence of sub-clinical small fibre damage and peripheral neuropathy in children with celiac disease.

Methods

This is a cross-sectional cohort study of twenty children with celiac disease and 20 healthy controls who underwent clinical and laboratory assessments and corneal confocal microscopy. Corneal nerve fiber density (no.mm^2), corneal nerve branch density (no.mm^2), corneal nerve fiber length (mm.mm^2), corneal nerve fiber tortuosity and inferior whorl length (mm.mm^2) were quantified manually.

Results

Corneal nerve fiber density (34.7±8.6 vs. 32.9±8.6; $P = 0.5$), corneal nerve branch density (47.2±24.5 vs. 47.3±20.0; $P = 0.1$) and corneal nerve fiber length (20.0±5.1 vs. 19.5±4.5; $P = 0.8$) did not differ between children with celiac disease and healthy controls. Corneal nerve fiber tortuosity (11.4±1.9 vs 13.5±3.0; $P = 0.01$) was significantly lower and inferior whorl length (20.0±5.5 vs 23.0±3.8; $P = 0.06$) showed a non-significant reduction in children with celiac disease compared to healthy controls. Inferior whorl length correlated significantly with corneal nerve fiber density (P = 0.005), corneal nerve branch density (P = 0.04), and corneal nerve fiber length (P = 0.002).

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ORIGINAL ARTICLE

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Further delineation of HIDEA syndrome

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Abstract

Recently, the genetic cause of HIDEA syndrome (hypotonia, hypoventilation, intellectual disability, dysautonomia, epilepsy, and eye abnormalities) was identified as biallelic pathogenic variants in *P4HTM*, which encodes an atypical member of the prolyl 4-hydroxylases (P4Hs) family of enzymes. We report seven patients from four new families in whom HIDEA was only diagnosed after whole-exome sequencing (WES) revealed novel disease-causing variants in *P4HTM*. We note the variable phenotypic expressivity of the syndrome except for cognitive impairment/developmental delay, and hypotonia, which seem to be consistent findings. One patient only presented with hypotonia, developmental delay, and abnormal eye movements, which highlights the challenge in diagnosing milder cases with this new syndrome. Other notable features include mild facial dysmorphism, obesity, and brain dysmyelination and atrophy. We conclude that HIDEA is a highly variable syndrome and suspect that a large fraction of patients will be diagnosed via reverse phenotyping after recessive *P4HTM* variants are identified by agnostic genomic sequencing assays.

KEYWORDS

developmental delay, HIDEA syndrome, hypoventilation, intellectual disability, P4HTM, reverse phenotyping

1 | INTRODUCTION

Prolyl 4-hydroxylases (P4Hs) catalyze the hydroxylation of prolines to 4-hydroxyproline in a reaction that requires Fe^{2+}, 2-oxoglutarate and molecular oxygen as cofactors (Kivirikko, Myllylä, & Pihlajaniemi, 1989). The substrate selectivity defines two types of P4Hs, ones that act on X-Pro-Gly sequences in pro-collagen chains and localize to the endoplasmic reticulum (ER), and others that act on the alpha subunits of hypoxia-inducible factor (HIF) and localize to the nucleus and cytosol. Whereas 4-hydroxylproline endows collagen with added stability, these modified proline residues mark HIFα for degradation as part of the hypoxia sensing regulatory process (Myllyharju, 2008). P4HTM is an unusual P4H in that despite its localization to the ER (ER membrane specifically with the catalytic domain protruding in the lumen), HIFα appears to be its primary substrate rather than collagen (Koivunen et al., 2007). HIF-mediated erythropoietin production was the first suggested physiological function of P4HTM, followed by the demonstration of an important role in the retina and the basement membrane of the kidneys based on zebrafish and mouse models (Hyvärinen et al., 2010; Laitala et al., 2012; Leinonen et al., 2016).

The first link between *P4HTM* and a human phenotype was in 2014 when an extended Finnish family with multiple members

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The impact of the COVID-19 pandemic on the perinatal mental health of women

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Abstract

Objectives: The physical health impact of the coronavirus disease infection (COVID-19) has received attention worldwide; however, data around the psychological impact of the pandemic is still emerging and little has been reported on psychological effects among vulnerable groups. This study was undertaken with the aim of studying the impact of the COVID-19 pandemic and related restrictions on perinatal mental health among women in Qatar.

Methods: A cross- sectional survey of women accessing maternity services in Qatar was carried out during the months of June and July 2020 at the local peak of the pandemic. Background data including relevant demographic details, pregnancy and mental health history, concerns, as well as helpful stress-reducing factors reported by women was collected. Depression and anxiety symptomatology was studied using the Patient Health Questionnaire Anxiety-Depression Scale (PHQ-ADS).

Results: The survey results revealed a high prevalence of anxiety and Depressive symptomatology (34.4 and 39.2% respectively), based on PHQ-ADS scoring. These rates appeared much higher than the reported pre-pandemic prevalence and were not affected by occupation, previous mental health problems or pregnancy complications. Women's most commonly reported concerns as well as coping factors are discussed.

Conclusions: Results indicate a marked increase in anxiety and depressive symptoms during the COVID-19 pandemic, among pregnant and puerperal individuals, who constitute a vulnerable group with respect to mental health morbidity. These findings can be used to inform public health interventions, among which, consideration should be given to routine mental health screening of vulnerable groups during major health crises.

Keywords: anxiety; COVID-19; depression; mental health; pandemic; perinatal; pregnancy; stress.

Introduction

From its start as an outbreak of pneumonia in China in December, 2019 [1], the spread of Coronavirus-2 infection has evolved dramatically into a major worldwide health crisis. The World Health Organization declared Coronavirus disease (COVID-19) a pandemic on March 11, 2020 [2].

As the pandemic unfolded, public concern about the risks to life and health, inadequate healthcare services and economic consequences grew. As part of infection-containment strategies, governments around the world imposed unprecedented restrictions, and these resulted in the compromise of personal and social liberty. Within a month of the declaration of the pandemic, 90% of the world's population was subject to some restriction of movement to limit infection spread [3]. The impact of the ensuing social isolation and loneliness along with the worries about risks of the infection and its economic fallout would appear likely to have an effect on mental health of the population. Indeed, increased mental health morbidity including anxiety and depression, in a similar context, has been reported previously with fears arising from the SARS outbreak [4]. Epidemiological data on the adverse impact of COVID-19 on mental health is emerging [5, 6]. The preliminary data has also shown that women have demonstrated a more significant psychological impact from the pandemic [6].

Tom Farrell and Shuja Reagu are first co-authors of the work.

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Original contribution

Comparative dose-response study of hyperbaric ropivacaine for spinal anesthesia for cesarean delivery in singleton versus twin pregnancies

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ABSTRACT

Study objective: It is controversial whether local anesthetic dose requirement for spinal anesthesia for cesarean delivery differs between patients with singleton and patients with multiple gestation pregnancies. The aim of this study was to determine and compare the ED_{50} and ED_{90} for hyperbaric ropivacaine used for spinal anesthesia for cesarean delivery in patients with singleton pregnancies versus patients with twin pregnancies.

Design: Prospective, randomized, comparative dose-finding study.

Setting: Operating room, Women's Hospital, Zhejiang University School of Medicine.

Patients: 100 patients with singleton pregnancies (Group S) and 100 patients with twin pregnancies (Group T) presenting for scheduled cesarean delivery under combined spinal-epidural anesthesia were enrolled in the study.

Interventions: Patients in Group S or Group T were randomly allocated to receive 9.5, 11, 12.5, 14 or 15.5 mg of hyperbaric ropivacaine intrathecally. A dose was considered effective when it achieved a bilateral sensory block level at the T6 dermatome or above within 10 min after intrathecal injection, there was no numerical rating scale (NRS) pain score ≥ 3 intraoperatively, and there was no requirement for epidural supplementation at any time during anesthesia and operation. Values for ED_{50} and ED_{90} for ropivacaine were determined using probit regression. The difference in ropivacaine dose requirement between patients with singleton pregnancies and patients with twin pregnancies was assessed by calculating relative median potency.

Measurements: Success rates for different intrathecal doses of ropivacaine, side effects and neonatal outcomes were recorded.

Main results: The estimated (95% confidence interval) values for ED_{50} and ED_{90} of intrathecal ropivacaine in patients with singleton pregnancies were 11.2 (10.2 to 12.0) mg and 15.7 (14.4 to 18.3) mg, respectively. The values for ED_{50} and ED_{90} in patients with twin pregnancies were 10.5 (9.5 to 11.3) mg and 14.8 mg (13.6 to 17.0) mg, respectively. The estimate of relative median potency for ropivacaine between patients with singleton and twin pregnancies was 0.94 (95% confidence interval 0.83 to 1.04).

Conclusion: Patients with singleton and twin pregnancies have similar dose requirement for hyperbaric ropivacaine used for spinal anesthesia for cesarean delivery in the setting of combined spinal-epidural (CSE) anesthesia, no opioids, low weight cohort, insertion with the patients in the right lateral position, and norepinephrine boluses.

Abbreviations: ED_{50}, the dose effective in 50% of patients; ED_{90}, the dose effective in 90% of patients; ASA, American Society of Anesthesiologists; SPF, the distance between the symphysis pubis and the fundus; CSE, combined spinal-epidural anesthesia; NRS, numerical rating scale; CIs, confidence intervals; SD, standard deviation; CONSORT, Consolidated Standards of Reporting Trials; CSF, cerebrospinal fluid

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ORIGINAL ARTICLE

Anxiety, Depression and Behavioural Changes in Junior Doctors and Medical Students Associated with the Coronavirus Pandemic: A Cross-Sectional Survey

Uma Pandey[1] · Gillian Corbett[2] · Suruchi Mohan[3] · Shuja Reagu[4] · Shubham Kumar[1] · Thomas Farrell[4] · Stephen Lindow[2]

Received: 11 May 2020 / Accepted: 28 July 2020

Abstract

Introduction Medical students are known to have high levels of depression, anxiety and stress from the high-pressure environments that they study and train in. The coronavirus pandemic presents source of stress and anxiety to large populations in general, and to healthcare professionals in particular. This study was undertaken to assess the psychological effects of this pandemic on the mental health of medical students and trainees.

Materials and Methods An online questionnaire was designed to capture information on the participant's anxieties related to the pandemic and included a validated tool for the assessment of anxiety and depression symptoms (GAD-7 and PHQ-9, respectively). The questionnaire was prepared on Google Forms, and the link to the questionnaire was disseminated to 113 medical students and junior doctors on 19 April 2020, and the survey closed on 22 April 2020 midnight.

Results The survey was sent to 113 students, and 83 students participated. Of the participants, 47 (56.6%) were female and 36 (43.4%) were male, and 80 (96.4%) were aged less than 30 years old. Formal anxiety and depression scores using the GAD-7 and PHQ-9 tools indicated 15/82 (18.3%) had anxiety scores of 0 (lowest possible) and 21/82 (25.6%) had the lowest possible depression score of 0. However, 6/82 (7.3%) had scores that were classified as severe depression. Females had significantly higher median anxiety (5 v 2, $p < 0.002$) and depression scores (5 v 3, $p = 0.025$) than male participants. Direct patient care and care of patients with Covid-19 did not result in significant deterioration in anxiety and depression.

Conclusion Female students/junior doctors showed higher anxiety and depression scores than males. Direct patient care and care of patients with Covid-19 did not result in a measurable deterioration in anxiety and depression in this study. In this stressful pandemic situation, it is imperative to look after the mental health of healthcare workers as well as patients.

Keywords Covid-19 · Anxiety · Depression · Medical students · Self-isolation

Introduction

Pandemic infections do not just affect physical health, but the mass spread of infection can impact the mental health of affected populations from anxieties and fear related to the infection as well as restrictions to social interactions [1]. Healthcare workers are at increased risk of exposure, and therefore, the mental health impacts on these individuals may be greater [2]. The pandemic caused by the novel coronavirus detected in December 2019 in Wuhan, China, is now affecting more than 210 countries and territories, raising concerns of widespread panic and increasing anxiety in individuals subjected to the threat of the virus.

In the past, there have been global infections, e.g. Spanish flu, MERS, SARS-1, H1N1, but with the Covid-19 infection

Gillian Corbett, Registrar in Obs and Gynae; Suruchi Mohan, Consultant in Obs & Gynae; Shuja Reagu, Consultant in Psychiatry; Shubham Kumar, Final Year Medical Student; Thomas Farrell, Consultant in Obs & Gynae; Stephen Lindow, Director of Masters Projects.

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Digital pattern recognition for the identification and classification of hypospadias using artificial intelligence vs. experienced pediatric urologist.

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Key words: hypospadias; machine learning; classification system; prognosis; penile curvature; artificial intelligence.

Abstract:

Objective: To improve hypospadias classification system, we hereby, show the use of machine learning/image recognition to increase objectivity of hypospadias recognition and classification. Hypospadias anatomical variables such as meatal location, quality of urethral plate, glans size and ventral curvature have been identified as predictors for post-operative outcomes but there is still significant subjectivity between evaluators.

Materials and Methods: A hypospadias image database with 1169 anonymized images (837 distal and 332 proximal) was used. Images were standardized (ventral aspect of the penis including the glans, shaft and scrotum) and classified into distal or proximal and uploaded for training with TensorFlow®. Data from the training was outputted to TensorBoard, to assess for the loss function.
The model was then run on a set of 29 "Test" images randomly selected. Same set of images were distributed amongst expert clinicians in pediatric urology. Inter and intrarater analysis were performed using Fleiss Kappa statistical analysis using the same 29 images shown to the algorithm.

Results After training with 627 images, detection accuracy was 60%. With1169 images, accuracy increased to 90%. Inter-rater analysis amongst expert pediatric urologists was k= 0.86 and intra-rater 0.74. Image recognition model emulates the almost perfect inter-rater agreement between experts.

Conclusion: Our model emulates expert human classification of patients with distal/proximal hypospadias. Future applicability will be on standardizing the use of these technologies and their clinical applicability. The ability of using variables different than only anatomical will feed deep learning algorithms and possibly better assessments and predictions for surgical outcomes.

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Readiness assessment for implementation of a large scale child maltreatment prevention program in Qatar

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Preparedness
Prevention
Qatar

ABSTRACT

Background and objectives: Child maltreatment is a worldwide problem, with lifelong consequences for the survivors. The focus is shifting from Child Maltreatment Protection to Child Maltreatment Prevention. The objective of this descriptive study was to assess readiness for child maltreatment among stakeholders before implementation of large-scale prevention programs in Qatar.

Methods: The study involved structured interviews with 45 representatives of various stakeholders in sectors of national and local entities of Qatar. A survey was conducted among these stakeholders, to explore their perception and level of awareness of child maltreatment in Qatar. All of them responded, with a response rate of 100%. A multidimensional tool, developed by WHO and collaborators from several middle and low-income countries, was used to assess ten dimensions of readiness.

Results: Child maltreatment prevention readiness in Qatar is low with a total score of 37.8 on a scale of 0–100. The respondents scored high ($\geq$ 5) in knowledge of child maltreatment (5.3), legislation, mandates and policies (6.8) and informal social resources (non-institutional) (5.6). Participants, however, scored low ($\leq$ 5) in their knowledge about current program implementation and evaluation (1.1), human and technical resources (1.7), institutional resources and links (2.3), material resources (2.8), scientific data on child maltreatment prevention (3.1), attitude towards child maltreatment prevention (4.3) and will to address the problem (4.8).

Conclusion: Child maltreatment prevention readiness in Qatar is low and requires improvement in some of the areas. It highlighted the need for capacity building among organizations across Qatar for a large scale CMP program to be successfully implemented.

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Perinatal perfusion editorial

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ORIGINAL RESEARCH
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Successful Establishment of the First Neonatal Respiratory Extracorporeal Membrane Oxygenation (ECMO) Program in the Middle East, in Collaboration With Pediatric Services

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Background: Extracorporeal membrane oxygenation (ECMO) is a complex life-saving support for acute cardio-respiratory failure, unresponsive to medical treatment. Starting a new ECMO program requires synergizing different aspects of organizational infrastructures and appropriate extensive training of core team members to deliver the care successfully and safely.

Objectives: To describe the process of establishing a new neonatal ECMO program and to evaluate the program by benchmarking the ECMO respiratory outcomes and mechanical complications to the well-established Extracorporeal Life Support Organization (ELSO) registry data.

Materials and Methods: We reviewed the processes and steps involved in planning and setting up the new ECMO program. To assess the success of the ECMO implementation program, we retrospectively reviewed data of clinical outcomes and technical complications for the first 11 patients who have received ECMO therapy for respiratory indications since program activation (July 2018–May 2020). We analyzed mechanical complications as a tool to measure infrastructures and our effective training for the core team of ECMO specialists. We also looked at all clinical complications and benchmarked these numbers with the last 10 years of ELSO registry data (2009–2019) in the corresponding categories for comparison. Chi-square test was used to compare, and outcomes are presented in percentage; a p-value of <0.05 is considered significant.

Results: A total of 27 patients underwent ECMO in the hospital, out of which 11 (six neonatal and five pediatric) patients had acute respiratory failure treated with venovenous (VV) ECMO or veno-arterial (VA) ECMO over a 22-month period. We had a total of 3,360 h of ECMO run with a range from 1 day to 7 weeks on ECMO. Clinical outcomes and mechanical complications are comparable to ELSO registry data (no significant difference); there were no pump failure, oxygenator failure, or pump clots.

Pediatric Health, Medicine and Therapeutics

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ORIGINAL RESEARCH

Parental Perception of a Dental Home for Children with Special Needs

This article was published in the following Dove Press journal:
Pediatric Health, Medicine and Therapeutics

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Background and Objectives: There is a major gap in the literature that addresses parental perception of acquiring a dental home for children with special healthcare needs (CSHCN). The objectives of this study are to assess parental perceptions and challenges in acquiring a dental home for their CSHCN.

Methods: Cross-sectional prospective study using a questionnaire.

Results: A total of 302 questionnaires were completed by caregivers. More than 70% of children had developmental delay, 20% had musculoskeletal disabilities, and the rest had respiratory compromise on non-invasive ventilation, learning disability, and visual and hearing disabilities; 75% of the caregivers do not believe pediatricians are qualified to contribute in oral hygiene. Moreover, 70% of children had not had a routine dentist visit in the 12 months preceding the interview. The reasons given for the lack of such visits included the long time of appointments (25%), difficulty in child's mobility (17%), the perception that dental care is expensive (9%), and a lack of dentist experience in dealing with children with special needs (5%). When asked what factors would encourage caregivers to choose a dental home for their children, 63% mentioned quick appointments, followed by dentists specialized in children with special needs (51%), child friendly atmosphere (21%), low cost (26.6%), close to home (20%), and others (6%). Interestingly, the majority of parents (75%) believed that the primary pediatrician of the child should initiate the dental home process.

Conclusion: Despite proper resources, children with special healthcare needs lack proper oral healthcare. This could be attributed to the lack of a dental home. A pediatrician's role is crucial in initiating the process of acquiring a dental home for this special population.

Keywords: dental home, children, special needs, pediatric

Introduction

The Maternal and Child Health Bureau has defined children with special healthcare needs (CSHCN) as those who "have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health and related services of a type or amount beyond that required by children generally."[1]

Oral health issues in patients with special needs are often linked to mental and physical abilities,[2] and put them at high risk for poor dental health. The causes could be attributed to frequent oral infections and periodontal disease, craniofacial birth defects, and enamel abnormalities.[3,4] Certain medications, special diets, and hardship in sustaining daily hygiene further disturb dental health and increase the risk of dental caries in CSHCN.[5,6] The American Academy of Pediatric Dentistry (AAPD) emphasizes that a dental home should provide comprehensive, easily

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Original Article

Parental perceptions of child's healthy diet: Evidence from a rapidly developing country

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Abstract

Background: There are no studies in Qatar or in the Middle East to investigate parental perception of healthy diet in childhood. **Purpose:** To investigate parental perception of childhood healthy diet in the State of Qatar. **Methods:** Cross-sectional prospective study at Hamad Medical Corporation, State of Qatar. Parents of children <14 years old were invited to complete a questionnaire. **Results:** A total of 398 parents agreed to participate, while 22 parents refused (response rate 94%). About 80% of parents were between 20 and 39 years of age, and 77% were females. Around 230 (58%) parents had ≥1 housemaid to help with housework, including food preparation. Whilst 151 children (37%) fell into the overweight and obese category, only 68 parents (17%) perceived that their child was in this category. Less than half the participants (n = 179, 45%) stated that childhood weight should be monitored prior to 5 years of age, while around 35% stated the same, but for children ages 5–14 years. Most participants (n = 324, 81%) agreed that parental eating habits could influence childhood weight. In terms of food preparation at home, mothers cooked almost 50% of the times, housemaids 30%, followed by grandmothers (16.6%), and fathers (3.4%). When asked about the frequency of school meals being prepared at home, 237 parents (60%) prepared their children's lunch box only 1-2 times per week. Moreover, 63% of parents chose the quality of food based on nutritional values, while 44% and 35% chose it based on safety and taste, respectively. When queried about whether the child's pediatrician or the primary care physician counsel families regarding childhood healthy diet, 187 families (47%) had not received counseling by their children's health care providers. Most families agreed that healthy diets lead to better school performance (n = 372, 94%) and better physical activity quality (n = 379, 96%). Compared to families living in the rural areas, parents living in the capital Doha had better insights that healthy diets result in better in school performance (p = 0.032). **Conclusion:** Parental perception is an important target for public health interventions. Within the current sample, families were aware of the positive impact of healthy diet on overall wellbeing. Qatar is a well-resourced country and it would be cost effective to train and professionally develop pediatricians and primary care physicians to be more proactive in tackling childhood obesity.

Keywords: Children, healthy diet, parental perception, Qatar

Introduction

The childhood obesity epidemic has significant public health concern as obesity is linked to many chronic and life-threatening physical and psychological health conditions.[1,2] Obesity is defined as weight to height of >3 standard deviations above the

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Case Report

A Novel Mutation of *VPS33B* Gene Associated with Incomplete Arthrogryposis-Renal Dysfunction-Cholestasis Phenotype

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Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome is an autosomal recessive disorder caused by mutations of the *VPS33B* encoding the vacuolar protein sorting 33B (VPS33B), which is involved in the intracellular protein sorting and vesicular trafficking. We report a rare case of ARC syndrome without arthrogryposis caused by a novel mutation of *VPS33B*. A female patient of Greek origin presented on the 14th day of life with renal tubular acidosis, Fanconi syndrome, nephrogenic diabetes insipidus, and cholestasis with normal gamma-glutamyl transpeptidase, without arthrogryposis and dysmorphic features. She was born to apparently healthy, nonconsanguineous parents. Additional features included dry and scaling skin, generalized hypotonia, hypoplastic corpus callosum, neurodevelopmental delay, failure to thrive, short stature, recurrent febrile episodes with and without infections, and gastrointestinal bleeding. DNA testing revealed that the patient was homozygous for the novel c.1098_1099delTG (p.Glu367Alafs ∗ 17) mutation of exon 14 of *VPS33B* gene (NM_018668) on chromosome 15q26.1, leading to a nonsense frameshift variant of VPS33B with premature termination of translation. Her parents were heterozygous for the same *VPS33B* mutation. The prognosis was predictably poor in the context of the intractable polyuria necessitating long-term parenteral fluid administration via indwelling central catheter leading to catheter-related sepsis, to which she eventually succumbed at the age of 7 months. This is the first published *VPS33B* mutation in an ARC patient of Greek origin. The current case adds to the spectrum of ARC-associated *VPS33B* mutations and provides evidence supporting the existence of incomplete ARC phenotype. Increased awareness and early genetic testing for ARC are suggested in cases with isolated cholestasis and/or renal tubular dysfunction, even in the absence of arthrogryposis.

1. Introduction

Arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome (OMIM #208085 and #613404) is an autosomal recessive disorder caused by mutations of the *VPS33B* and *VIPER* genes. The *VPS33B* encodes the vacuolar protein sorting 33B (VPS33B) that is involved in intracellular protein sorting and vesicular trafficking [1–4]. VPS33B is ubiquitously expressed in human tissues including both liver and kidneys. Consequently, dysfunction of VPS33B may lead to disruption of cell polarization in many organs, thereby resulting in a multisystem disorder with Fanconi syndrome (FS), myoskeletal anomalies, and cholestasis with normal gamma-glutamyl transpeptidase (GGT) being the core manifestations [5, 6]. Additional features of ARC include nephrogenic diabetes insipidus (NDI), failure to thrive, anomalies of the corpus callosum with neurodevelopmental delay, ichthyosis, platelet dysfunction, recurrent infections, dysmorphic features, congenital heart disease, hypothyroidism, and keratitis. The disease is more

RESEARCH ARTICLE

Improving Youth Suicide Risk Screening and Assessment in a Pediatric Hospital Setting by Using The Joint Commission Guidelines

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ABSTRACT

OBJECTIVES: Hospitals accredited by The Joint Commission (TJC) are now required to use a validated screening tool and a standardized method for assessment of suicide risk in all behavioral health patients. Our aims for this study were (1) to implement a TJC-compliant process of suicide risk screening and assessment in the pediatric emergency department (ED) and outpatient behavioral health clinic in a large tertiary care children's hospital, (2) to describe characteristics of this population related to suicide risk, and (3) to report the impact of this new process on ED length of stay (LOS).

METHODS: A workflow using the Columbia Suicide Severity Rating Scale was developed and implemented. Monthly reviews of compliance with screening and assessment were conducted. Descriptive statistics were used to define the study population, and multivariable regression was used to model factors associated with high suicide risk and discharge from the ED. ED LOS of behavioral health patients was compared before and after implementation.

RESULTS: Average compliance rates for screening was 83% in the ED and 65% in the outpatient clinics. Compliance with standardized assessments in the ED went from 0% before implementation to 88% after implementation. The analysis revealed that 72% of behavioral health patients in the ED and 18% of patients in behavioral health outpatient clinics had a positive suicide risk. ED LOS did not increase. The majority of patients screening at risk was discharged from the hospital after assessment.

CONCLUSIONS: A TJC-compliant process for suicide risk screening and assessment was implemented in the ED and outpatient behavioral health clinic for behavioral health patients without increasing ED LOS.

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Deidentified individual participant data will not be made available.

Ms Chan-Salcedo, Ms Badolato, and Dr McKinley completed initial data collection and analyses; Ms Newton designed and wrote the environmental safety checklist; Dr Robb critically reviewed the manuscript; Dr Latif drafted the initial manuscript; and all authors were involved in conceptualizing and designing the project and study, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Africa, Britain, and beyond: diversity and equality in the British Paediatric Neurology Association

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This commentary is on the invited editorial by Smith on page 5 of this issue.

Martin Smith's editorial about diversity within the British Paediatric Neurology Association (BPNA) is very timely.[1] I was the first African member of the BPNA council, and over two decades the association has become my second family. More recently, many colleagues from Sudan and Africa in general have joined the association. A particular highlight occurred in 2015 when we hosted the first BPNA-sponsored pediatric epilepsy training course in Khartoum, Sudan.

In 1993 I was the recipient of the Lord Kitchener Medal for the best medical graduate from the University of Khartoum. The faculty was founded in 1924 as the Kitchener School of Medicine, named after Lord Kitchener (1850–1916), the notorious British Army officer and colonial administrator. I was the last recipient of this prize; the authorities then decided to rename the medal to honour Albaghdadi, a generous donor to the college. A decade later, I was chairing the Scientific Committee at the Annual Meeting of the BPNA in Liverpool, a few yards from the docks that were a hub for the slave trade of many centuries gone.

In my view, Africa is emerging tall and proud from the shadows of slavery, perhaps even from the bitter legacy of the colonial era. Many African countries are struggling to regenerate both politically and economically, but overall we are leaving the past behind and moving towards a future of democracy, peace, and prosperity.

Today, the descendants of Africans and Afro-Caribbeans and more recent first-generation immigrants live and work in the UK by choice. My children pride themselves as being both British and African. It strikes me how well this generation understands diversity, at a level that my own generation could not quite master when we first encountered life in the west.

Black lives matter. I was moved watching individuals from all around the world and from all ethnic backgrounds coming together to continue the fight for racial justice and honour those who had been unjustly sacrificed. This is a genuine call for togetherness, not division or discrimination; for being equal and also being equally diverse. The current COVID-19 pandemic shows us how vulnerable we all are, but also how diverse in terms of immunity, response, and willingness to share and help.[2,3]

This brings me back to our own extended community, the BPNA. As with any other large organization, more can be done to tackle inequalities and encourage diversity, and better understand the differences and grievances that exist within our own ranks. I have been very proud to be part of this wonderful association.

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SAGE

Autoimmune thyroid diseases, autoimmune hepatitis, celiac disease and type 1 diabetes mellitus in pediatric systemic lupus erythematosus: Results from the CARRA Legacy Registry

Ohoud AlAhmed[1], Vidya Sivaraman[1], Melissa Moore-Clingenpeel[2], Stacy P Ardoin[1,3] and Sharon Bout-Tabaku[4,5]; for the CARRA registry investigators

Abstract

Objective: Polyautoimmunity (PA) with systemic lupus erythematosus (SLE) is reported as a poor prognostic factor, but little is known about its effect in childhood-onset SLE (cSLE). We describe PA in cSLE within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Legacy Registry and evaluate its association to lupus disease outcomes.
Methods: CARRA Legacy Registry is the largest pediatric rheumatology registry that collected data at enrollment and every 6 months thereafter. We describe the co-occurrence of selected autoimmune disorders (autoimmune thyroid diseases, autoimmune hepatitis, celiac disease and type 1 diabetes mellitus) in cSLE. To assess outcomes, we studied measures of lupus disease activity, complications, and patient's quality of life (QoL). Comparisons by PA status were made using chi-square, Fisher's exact test, two-sample t-tests, Wilcoxon rank sum tests, and mixed effects models as appropriate.
Results: 1285 patients met the American College of Rheumatology criteria for SLE. Of those, 388 (30%) had data on comorbidity. The prevalence of PA was 8.8%. Patients with PA reported more hospitalizations and aggressive immunotherapy use. SLEDAI and PGA scores improved over time, but did not differ by PA status. No significant differences were found in QoL measures or their trajectory over time by PA status.
Conclusion: In cSLE, PA is associated with more hospitalizations and aggressive immunotherapy use. Although lupus disease activity improved over time, patients' QoL neither improved over time nor differed by having other autoimmune disease. Prospective, case-control, long-term follow-up studies on cSLE are needed to validate our results.
MeSH Key Indexing Terms: Pediatric systemic lupus erythematosus; Autoimmune diseases; Outcome assessment

Keywords
Systemic lupus erythematosus, renal lupus, thrombosis

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Introduction

Systemic lupus erythematosus (SLE, lupus) is an autoimmune disorder that can affect multiple organ systems with variable severity. Moreover, childhood-onset SLE (cSLE) is known to result in more aggressive disease and worse outcomes.[1] Of the known prognostic factors, the impact of other autoimmune disorders on lupus disease outcomes is reported to be poor.[2,3]

Polyautoimmunity (PA), which is the presence of more than one autoimmune disease in a single patient,

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Physiological weight loss in term newborn infants

SCENARIO

A 3-day-old full-term girl born by elective caesarean section (CS) and exclusively breast fed is noted to have lost 10% of her birth weight (BW). She is clinically well on examination and the midwife reports that the infant is breast feeding frequently with a good latch and suck. You wonder if this is an acceptable weight loss and what intervention, if any, is needed?

STRUCTURED CLINICAL QUESTION

What is an acceptable physiological weight loss in healthy full-term newborn infants in the immediate postnatal period?

SEARCH

A literature search was performed in Medline and EMBASE using key words 'weight loss' OR 'weight change' OR 'weight reduction' AND 'newborn' OR 'neonates' OR 'infants' between the years 2000 and 2020. Inclusion criteria used are term and 'near-term' infants (≥36 weeks, BW ≥2500 g), not needing admission to neonatal unit (healthy) in either hospital or community setting. Studies that included infants born at <36 weeks or with a medical condition or needing admission to a neonatal unit were excluded.

OUTPUT

A total of 517 studies were initially identified in the literature search. These were independently screened by both the authors and based on the title and abstract 10 articles were identified for full review. Five most relevant studies meeting the criteria described above were selected to be included in the review (table 1). These were all large cohort studies (two each from the UK and the USA; one study from India) of healthy term infants in the immediate postnatal period.

SUMMARY

Commentary

All newborn infants experience weight loss postnatally mainly due to extracellular water loss; with the nadir occurring around days 3–4 of life.[1 2] The American Academy of Paediatrics[1] recommends that weight loss for healthy term newborn infants should not exceed 7% of their BW. In the UK, the National Institute for Health and Care Excellence guidelines[3] recommend 10% as the maximum acceptable weight loss in healthy term infants. This review of literature shows that large cohort studies have demonstrated that term newborn infants frequently lose >10% of their BW in the absence of organic disease and the incidence of complications such as hypernatraemic dehydration is very rare.

Flaherman *et al*[4] reported data from all newborn infants born at ≥36 weeks gestation in the Northern California Kaiser Permanente hospitals between 2009 and 2013. In their large cohort of 108 907 infants (who were discharged home healthy) 30% of infants had lost >10% of their BW by 72 hours. This was predominantly in infants delivered by CS as compared with vaginally delivered babies (25% vs 5%). The authors were able to produce weight loss nomograms which can be used to predict and track physiological weight loss in term infants based on mode of delivery and mode of feeding (available at http://www.newbornweight.org).

Macdonald *et al*[5] provided data from 971 consecutive term newborn infants with BW ≥2.5 kg in a single maternity service in Glasgow, UK. In their cohort of healthy infants the 95th centile for weight loss was 11.8%, 11.5% and 8.4% for infants receiving exclusive breast feeding, mixed feeding and exclusive formula feeding, respectively. The 97.5th centile for weight loss was 12.8% and 9.5% in exclusively breastfed and exclusively formula-fed infants. All infants who lost >10% of their BW underwent a medical assessment including serum electrolyte measurement. Hypernatraemia (>145 mmol/L) occurred in 73% of breastfed infants who lost >11.2% of BW and in 100% of infants who lost >12.1% of BW. Significant hypernatremia (>150 mmol/L) only occurred when infants lost >12.1% of BW.

Similarly Wright *et al*[6] also showed in their cohort of 961 full-term infants that 3% lost >10% of their BW and had no evidence of either organic disease or complications related to weight loss. In a single-centre cohort study from India[7] 13% of full-term newborn infants lost >10% of their BW and infants born to primiparous mothers were at increased risk of losing more weight. In the study by DiTomasso *et al*[8] infants born

Table 1 Summary of evidence

Citation	Study group	Study type	Outcome	Key results	Comments
Flaherman *et al*[4]	108 907 healthy exclusively breastfed infants, ≥36 weeks gestation, born in Northern California Kaiser Permanente hospitals in 2009–2013	Retrospective cohort study	Weight loss at 48 hours (vaginal birth) Weight loss at 72 hours (CS) compared with birth weight	5% of vaginally delivered infants lost >10% 25% of infants born by CS lost >10%	Weight loss nomograms were produced from this cohort (available at http://www.newbornweight.org). All infants remained well on exclusive breast feeding.
Macdonald *et al*[5]	937 healthy newborns, ≥37 weeks with BW ≥2500 g in Glasgow, UK. 45% breast feeding, 13% mixed feeding and 42% formula feeding	Prospective cohort study		97.5th centile for maximal weight loss: breast fed 12.8%, formula fed 9.5%	Hypernatraemia (>150 mmol/L) in 80% of infants who lost >97.5th percentile. 97.5th percentile for regaining BW: breast fed: 21 days, formula fed: 16.7 days.
Wright *et al*[6]	961 healthy term infants in Gateshead, UK. 51% breast feeding (remaining—not specified)	Prospective cohort study		3% of infants lost >10% of BW at 5 days of age. Only weighed on day 5 of life.	BW positively correlated with % of weight loss; lower the BW smaller the weight loss.
Joshi *et al*[7]	250 healthy exclusively breastfed term infants Hospital in South India from December 2013 to March 2015	Prospective cohort study		8% infants lost <5% of BW; 79% lost 5%–10%; 13% lost >10%	Infants born to primipara and with *inadequate* breast feeding at more risk of losing >10% of BW.
DiTomasso *et al*[8]	151 healthy, exclusively breastfed, term infants from a community hospital in the USA	Prospective, cohort study		Some infants lost >11% of BW (mean (SD) weight loss 9.2%(1.9%)) by day 4 and took up to 17 days of life to regain BW	7% weight loss appeared to be the driving force behind formula use with 13% of infants receiving mixed feeding by 14 days of life

BW, birth weight; CS, caesarean section.

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ORIGINAL ARTICLE

Paediatric and Perinatal Epidemiology WILEY

Emotional responses of parents participating for the first time in caregiving for their baby in a neonatal unit

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Abstract

Background: Parents of term and preterm infants hospitalised at birth experience a stressful situation. They are considered as primary caregivers in neonatal units and are encouraged to participate in their child's care.

Objectives: The aim of our study was to analyse the feelings of parents participating for the first time in caregiving for their baby admitted at birth in a neonatal unit in France and to compare the feelings reported by parents of term and preterm infants.

Methods: An online survey was created in 2014 for parents who had a baby hospitalised at birth. We analysed parents' responses to this open-ended question: "How did you feel when you participated in caregiving for your baby for the first time?" using a qualitative discourse analysis by two analysts. Themes were identified and coded.

Results: Between February 2014 and March 2018, 1603 parents of preterm infants and 239 parents of term infants responded to this open-ended question. Twenty-five per cent of parents expressed positive feelings exclusively (confidence, ease, joy, pride, feeling supported by healthcare professionals, by their family and feeling of being a parent), 41% expressed negative feelings exclusively (stress, fear, feeling of being judged, frustration, anger, uselessness and clumsiness) and 34% expressed mixed feelings (both positive and negative). Parents of term infants expressed less frequent feelings of stress and fear than parents of preterm infants: with a relative risk (RR) of 0.69, 95% confidence interval (CI) 0.56, 0.87. Parents of term babies more frequently expressed feelings of frustration: RR 2.40 (95% CI 1.33, 4.32).

Conclusions: Infant- and Family-Centred Developmental Care supportive programmes are recommended within neonatal units in order to improve the experience of parents participating in caregiving for their baby hospitalised at birth.

KEYWORDS

emotions, hospitalisation, newborn, parents, patient-centred care, quality of health care

Laurence Caeymaex and Charlotte Tscherning share last authorship.

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ORIGINAL ARTICLE

One-year experience of hybrid closed-loop system in children and adolescents with type 1 diabetes previously treated with multiple daily injections: drivers to successful outcomes

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Abstract

Objective To evaluate the effect of a 1-year hybrid closed-loop (HCL) system on glycemic control in children and adolescents with type 1 diabetes (T1D) previously treated with multiple daily injections (MDI).

Methods This was a 1-year observational study, as a continuation of the previous 3 months prospective study of pediatric patients with T1D conducted at Sidra Medicine in Qatar. The study enrolled individuals aged 7–18 years with T1D > 1 year, on MDI with self-monitoring of blood glucose or continuous glucose monitoring, with no prior pump experience, and with an HbA1c level < 12.5% (< 113 mmol/mol). After the first 3 months of HCL use, patients were followed at 6, 9 and 12 months, where HbA1c was obtained and pump data were collected.

Results All 30 participants (age 10.24 ± 2.6 years) who initiated HCL completed 12 months of HCL system use in Auto Mode. The participants used the sensor 88.4 ± 6.5% of the time with Auto Mode usage 85.6 ± 7.4% during 12 months of HCL system use. HbA1c decreased from 8.2 ± 1.4% (66 ± 15.3 mmol/mol) at baseline, to 6.7 ± 0.5% (50 ± 5.5 mmol/mol) at 3 months ($p = 0.02$) and remained stable to 7.1 ± 0.6 (54 ± 6.6 mmol/mol) at 12 months ($p = 0.02$). TIR (70–180 mg/dL) increased from 46.9% at baseline to 71.9% at 1 month and remained above 70% during the 12 months of HCL use.

Conclusion HCL system (MiniMed 670G) in children and adolescents previously treated with MDI significantly improves glycemic outcomes (HbA1c and Time in Ranges) immediately during the first month. This improved glycemic control was maintained over the 1 year following Auto Mode initiation.

Keywords Type 1 diabetes · Continuous subcutaneous insulin infusion · Continuous glucose monitoring · Diabetes education · Closed-loop systems

Introduction

The use of diabetes technology is a promising treatment strategy to improve diabetes outcomes. The use of Continious Subcutaneous Insulin Infusion (CSII) and Continious Glucose Monitoring (CGM) is associated with a reduction in HbA1c, both when used separately and together [1]. Recent technological advances have integrated CSII with CGM, where insulin delivery can be automated by sensor glucose (SG) driven algorithms. Insulin delivery suspension when reaching a low glucose level [2, 3] or in the prediction of a low glucose level [4, 5] has demonstrated a significant reduction in hypoglycemia exposure. Closed-loop systems are designed to maintain glucose levels at a predetermined target by linking CGM information with an insulin dosing algorithm for automated subcutaneous insulin delivery by a pump [6].

The MiniMed 670G [7] is the first hybrid closed-loop (HCL) insulin delivery system for use in diabetes care since 2017 and uses an algorithm to adjust basal insulin delivery automatically every 5 min based on SG values [8]. Several short-term studies on the HLC system have shown improved HbA1c, time in target range, and

Managed by Massimo Porta.

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Performance evaluation of five ELISA kits for detecting anti-SARS-COV-2 IgG antibodies

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Abstract

Objectives: To evaluate and compare the performances of five commercial ELISA assays (EDI, AnshLabs, Dia.Pro, NovaTec, and Lionex) for detecting anti-SARS-CoV-2 IgG. **Methods**: 70 negative control samples (collected before the COVID-19 pandemic) and samples from 101 RT-PCR-confirmed SARS-CoV-2 patients (collected at different time points from symptoms onset: ≤7, 8-14, and >14 days) were used to compare the sensitivity, specificity, agreement, positive and negative predictive values of each assay with RT-PCR. A concordance assessment between the five assays was also conducted. Cross-reactivity with other HCoV, non-HCoV respiratory viruses, non-respiratory viruses, and nuclear antigens was investigated. **Results:** Lionex showed the highest specificity (98.6%, 95%CI: 92.3-99.8), followed by EDI and Dia.Pro (97.1%, 95%CI: 90.2-99.2), NovaTec (85.7%, 95%CI: 75.7-92.1), then AnshLabs (75.7%, 95%CI: 64.5-84.2). All ELISA kits cross-reacted with one anti-MERS IgG positive sample except Lionex. The sensitivity was low during the early stages of the disease but improved over time. After 14 days from symptoms onset, Lionex and NovaTec showed the highest sensitivity at 87.9% (95%CI: 72.7-95.2) and 86.4% (95%CI: 78.5-91.7), respectively. The agreement with RT-PCR results based on Cohen's kappa was as follows: Lionex (0.89)> NovaTec (0.70)> Dia.Pro (0.69)> AnshLabs (0.63)> EDI (0.55). **Conclusion:** The Lionex ELISA, which measures antibodies solely to the S1 protein, demonstrated the best performance.

Key Words: COVID-19; SARS-CoV-2; serology; IgG; ELISA; sensitivity; specificity

1. Introduction

Since the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in December 2019 in Wuhan, China, the virus has rapidly spread and become a major

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Full length article

Post-exposure prophylaxis for Blood-Borne Viral (BBV) Infections

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ABSTRACT

Viral infections, such as human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV), are transmitted either sexually or through blood-borne contamination. The later causes enormous concern within health establishments and health care-workers.

Post-exposure management of HIV rests on the use of triple Anti-Retroviral Therapy (ART), but special care must be taken to choose the right combination for particular circumstances, especially when the subject is pregnant or likely to get pregnant from the event.

New-borns of mothers living with HIV require special attention, as maternal viral load plays a central role in their management. When viral load is not detectable, there is a good argument to avoid ART in these infants. Continued maternal ART is encouraged more so in women who intend to breastfeed.

The management of exposure to Hepatitis B requires a detailed risk assessment of the source. In high-risk cases, Hep B immunoglobulin will be necessary otherwise passive immunisation with HBV vaccine will suffice.

The use of anti-viral treatment for exposure to Hepatitis C remains controversial. New and potent drugs have been introduced but are quite expensive, and the cost-effectiveness of post-exposure therapy should be considered. Curative treatment now exists for HCV, and an option might be to follow exposed subjects up and give them definitive treatment if seroconversion occurs.

This review discusses in details the practical steps in the management of sexual and occupational exposure to HIV and other blood-borne viruses with emphasis on preventing infections. Healthcare facilities should have tightly managed protocols for the management of exposure and the ability to start medication as early as possible when indicated.

1 Introduction

Viral infections, such as human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV), are transmitted either sexually or through blood-borne contamination. Exposure to these viruses does not necessarily imply subsequent infection. However, for the small numbers that develop the disease, the consequences can be severe. It is for this reason that post-exposure prophylaxis (PEP) aiming to minimise the risk of the person exposed to any of these viruses developing the infection is considered an essential constituent of prevention. Those at risk include sexual partners of those living with the viruses, sharing contaminated needles, health-care professionals and new-borns (exposed to the virus at the time of birth or during breast-feeding).

Health care professionals (HCPs) are at risk of acquiring blood-borne viruses (BBV) following exposure to blood and other bodily fluids in health-care settings. The Centre for Disease Control (CDC) estimates that over 380,000 percutaneous-related injuries occur annually in the United States among hospital employees and approximately half of such exposures go unreported [1]. The most notable of these blood-borne viruses (BBVs) are hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) [1]. If not managed appropriately, the consequences to health-care practitioners (HCP) can be significant, leading to chronic infection, loss of person-hours at work and psychological sequelae[2,3]. Post-exposure prophylaxis has been shown to reduce the risk of transmission of some of these BBVs [3].

The risk of transmission can be minimised with preventive measures such as safer sharps disposal management, devices with safety features, personnel protection and educational training [4]. Furthermore, occupational health programs within health-care institutions and the promotion of hepatitis B vaccination are fundamental in minimising risks to HCPs [4].

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Levetiracetam for convulsive status epilepticus in childhood: systematic review and meta-analysis

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ABSTRACT

Importance Prolonged seizures are life-threatening emergencies associated with significant morbidity.

Objective To determine the efficacy and safety of levetiracetam in treating convulsive status epilepticus (CSE) in childhood.

Data sources and study selections PubMed, Embase, the Cochrane Central Register of Controlled Trials and Cumulative Index to Nursing and Allied Health Literature were searched from inception up to April 2020. Only randomised controlled trials (RCTs) that included children aged 1 month–18 years were assessed. Two reviewers performed data assessment and extraction.

Data extraction and synthesis Ten studies out of the 20 637 citations identified were included.

Main outcomes Cessation of seizure activities, time to cessation of seizure activities, need for rapid sequence intubation (RSI), intensive care unit (ICU) admission, recurrence of seizures at 24 hours, adverse events and all-cause mortality.

Results We included 10 RCTs (n=1907). There was no significant difference in cessation of seizure activities when levetiracetam was compared with phenytoin (risk ratio (RR)=1.03, 95% CI 0.98 to 1.09), levetiracetam to fosphenytoin (RR=1.16, 95% CI 1.00 to 1.35) or levetiracetam to valproate (RR=1.10, 95% CI 0.94 to 1.27). No differences were found in relation to the timing of cessation of seizures for levetiracetam versus phenytoin (mean difference (MD)=−0.45, 95% CI −1.83 to 0.93), or levetiracetam versus fosphenytoin (MD=−0.70, 95% CI −4.26 to 2.86). There were no significant differences with regard to ICU admissions, adverse events, recurrence of seizure at 24 hours, RSI and all-cause mortality.

Conclusion Levetiracetam is comparable to phenytoin, fosphenytoin and valproate as a second line treatment of paediatric CSE.

What is already known on this topic?

- There is no clear consensus as to which second-line therapeutic agent should be used if benzodiazepines fail to terminate the convulsive episode.
- Levetiracetam might be useful for benzodiazepine-resistant seizures because it appears to be well tolerated and to have a good safety profile.

What this study adds?

- Evidence from this systematic review and meta-analysis shows levetiracetam is comparable to phenytoin, fosphenytoin and valproate for the treatment of paediatric convulsive status epilepticus.
- No serious adverse events were associated with levetiracetam use in these children.
- The overall quality of the evidence is limited due to heterogeneity, inconsistency and small sample size in some of the primary studies.

INTRODUCTION

Convulsive status epilepticus (CSE) is a common paediatric neurological emergency associated with significant morbidity and mortality.[1 2] The International League against Epilepsy defines status convulsive epilepticus at two time points: the first point at 5 min, when the episode is regarded as a continuous seizure activity; and the second time point at 30 min, when the convulsive episode is associated with long-term sequelae such as hippocampal volume loss, reinforces the need for timely intervention.[2 3] Benzodiazepines are effective first-line treatment in CSE.[4 5] There is no clear consensus as to which second-line therapeutic agent should be used if benzodiazepines fail to terminate the episode.[6] Phenytoin is frequently chosen as a second-line agent, although the evidence base for its use is minimal.[7 8] Levetiracetam is proving useful for benzodiazepine-resistant seizures because it appears to be well tolerated and to have a good safety profile.[9] The aim of this systematic review was to examine the evidence for efficacy and safety of levetiracetam in the treatment of CSE.

MATERIALS AND METHODS

Study selection and search strategy

We searched the following databases: MEDLINE (1946–April 2020), Embase (1974–April 2020), CINAHL (1982–April 2020) and the Cochrane Central Register of Controlled Trials (CENTRAL, issue 4, 2020). Reference lists from included studies were inspected for additional citations. We also searched specific websites (www.clinicaltrials.gov and www.controlled-trials.com) for ongoing unpublished clinical trials. Search terms used can be found in the online supplemental file, appendix B: search strategy. PROSPERO registration number CRD 420201155606

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From COVID-19 to clot: the involvement of the complement system

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ABSTRACT

In December 2019, the world observed an unexpected outbreak of an emerging disease named coronavirus (COVID-19) that was first reported in Wuhan city of Hubei province of China. Recent literature has shown the association between COVID-19 infection and derangement in the coagulation profile. In this paper, we are discussing thrombo-genesis, especially the role of the complement system in the immune response against COVID-19 and the pathogenesis associated with tissue inflammation and thrombosis. This role can stipulate a groundwork for further investigation of the pathophysiologic importance of complement in COVID-19, and could propose targets for specific intervention. In addition, we delineated current treatments for thrombosis and the potential therapies by using agents to block the terminal complement pathway. Low molecular weight heparin for all (unless contraindicated) hospitalized COVID-19 patients can be lifesaving. Agents that inhibit the terminal events of the complement cascade might be crucial for ensuring an efficient treatment, decrease clots and permit early discharge in relation to COVID-19.

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COVID-19; clot; treatment; pathophysiology

1. Introduction

In December 2019, the world observed an unexpected outbreak of an emerging disease named coronavirus (COVID-19) that was first reported in Wuhan city of Hubei province of China (Pant et al., 2020).

Three months later, the World Health Organization (WHO) announced that the COVID-19 outbreak has progressed into a global pandemic (Wu et al., 2020). Recent literature has shown the association between COVID-19 infection and derangement in the coagulation profile (Wu et al., 2020), that can lead to disseminated intravascular coagulation (DIC) in up to 70% of non-surviving COVID-19 patients (Tang et al., 2020). Within this framework, the association between coagulation disorder and the clinical progression to acute respiratory distress syndrome has been a substantial complication with poor outcomes (Wu et al., 2020), including organ dysfunction (Tang et al., 2020; Zhu et al., 2020).

Main targets of COVID-19 can comprise the vascular endothelial cell, lung epithelial cell, and lymphocytes that can eventually present with severe presentation such as shock, acute respiratory distress syndrome (ARDS) and coagulopathy (Guan et al., 2020; Wang, Hu, et al., 2020). The pathological observations of bacterial sepsis-associated ARDS are outlined as austere interstitial and alveolar edema with significant neutrophil infiltration, vascular permeability, stenosis of the vascular lumen, vasculature including wall thickening, and micro-thrombus formation (Luo et al., 2020).

Despite the overwhelming data portraying the effect of COVID-19 on respiratory failure in up to 20% of symptomatic patients (Marini & Gattinoni, 2020), minute attention has been given to endothelial dysfunction and clotting outcomes in severe infection (Hendaus & Jomha, 2020; Roumenina et al., 2016). Patients with severe COVID-19 can develop extensive microvascular thrombosis and the utilization of coagulation factors. This is revealed by the elevation of D-dimer, thrombocytopenia, decreased fibrinogen levels and prolongation of the prothrombin time (Tang et al., 2020). In addition, microangiopathy with schistocytes has been detected on the peripheral smear in COVID-19 patients (Lee et al., 2020).

In this paper, we are discussing thrombo-genesis, especially the role of the complement system in the immune response against COVID-19 and the pathogenesis associated tissue inflammation and thrombosis. This role can stipulate a groundwork for further investigation of the pathophysiologic importance of complement in COVID-19, and could propose targets for specific intervention.

In addition, we delineated current treatments for thrombosis and the potential therapies by using agents to block the terminal complement pathway.

2. Clinical studies

Thus far, there have been several studies reporting coagulation activation, particularly in critically ill patients with COVID-19 infection. In three studies, the clinical characteristics of novel coronavirus pneumonia (NCP) patients have been explored, and mortalities ranged from 4.3% to 14.6%,

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ORIGINAL ARTICLE

Does Trimethoprim-Sulfamethoxazole prophylaxis induce myelosuppression in primary immune deficiency disease patients; A retrospective, 3 groups comparative study

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Abstract

Background: The possible myelosuppression side effect of Trimethoprim-Sulfamethoxazole (TMP-SMX) on primary immune deficiency (PID) patients has not been established yet.

Objective: Identify if the PID patients are at higher risk of developing myelosuppression secondary to the use of TMP-SMX.

Method: Retrospective, three groups study, of PID patients (on and off TMP-SMX prophylaxis) and urinary tract infection (UTI) patients received prophylaxis TMP-SMX. Data about CBC results (WBC, ANC, Lymphocytes, RBC, Hemoglobin, and Platelet counts) at baseline, first, and maximum myelosuppression observed during the period of TMP-SMX administration were collected.

Results: A total of 122 patients were included in this study (41 PID patients on TMP-SMX prophylaxis, 45 PID patients not on TMP-SMX prophylaxis, and 36 UTI patients on prophylaxis TMP-SMX). There are significant differences noticed in the percentage of patients who developed clinical myelosuppression (i.e. less than normal value for age) in ANC (39.0% vs. 8.9% vs. 16.7%, p = 0.002), RBC (36.6% vs. 13.3% vs. 13.9%, p = 0.014), WBC (41.5% vs. 13.3% vs. 13.9%, p = 0.003), and platelet (24.4% vs. 15.6% vs. 2.8%, p = 0.028) in group 1, 2, and 3, respectively. Significant difference in myelosuppression between the groups was most likely due to the combination of TMP-SMX effect on PID patients rather than the disease or the drug itself.

Conclusion: Primary immune deficiency (PID) patients are at higher risk of developing myelosuppression secondary to TMP-SMX prophylaxis (especially ANC) comparing to immune-competent patients or other PID patients who did not receive prophylactic TMP-SMX. Future larger prospective study is required to confirm this association.

Key words: TMP-SMX; myelosuppression; primary immune deficiency; prophylaxis, Neutropenia

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Introduction

Trimethoprim-sulfamethoxazole (TMP-SMX), also known as co-trimoxazole, is a combination of two antimicrobial agents that act synergistically to treat a variety of bacterial infections.[1,2] It is considered the drug of choice for the treatment and prevention of Pneumocystis jiroveci (carinii) pneumonia (PCP).[3-6] TMP-SMX is a well-tolerated drug where adverse drug reactions occur in only 6-8% of patients.[7] One of the serious TMP-SMX side effect is myelosuppression, which is believed to be due to its anti-folate DNA suppression mechanism.[8-10]

Few studies highlighted and reported the myelosuppression or hematologic abnormalities associated with TMP-SMX use. One study showed that neutropenia occurred in 34% and thrombocytopenia in 12% of children who received oral TMP-SMX.[11] Another study evaluated 120 children found that neutropenia appeared only in those who were treated with

Antenatal corticosteroids and short-term neonatal outcomes in term and near-term infants of diabetic mothers. Analysis of the Qatar PEARL-peristat registry.

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Abstract

Objectives

A recent discussion surrounding the extension of antenatal corticosteroid (ACS) use beyond 34 weeks of gestation did not include the subgroup of infants of diabetic mothers (IDM). We aimed to examine the association between ACS exposure and outcomes in neonates born at term and at near-term gestation in a large cohort of IDMs.

Methods

We selected 13976 eligible near-term and term infants who were included in the PEARL-Peristat Perinatal Registry Study (PPS). We assessed the association of ACS exposure with neonatal outcomes in a multivariate regression model that controlled for diabetes mellitus (DM) and other perinatal variables.

Results

The incidence of DM was 28% (3,895 of 13,976) in the cohort. Caesarean section was performed in one-third of the study population. The incidence of ACS exposure was low (1.8%) and typically occurred>2 weeks before delivery. The incidence rates of respiratory distress syndrome (RDS)/ transient tachypnoea of newborns (TTN), all-cause neonatal intensive care unit (NICU) admissions, NICU admissions for hypoglycaemia, and low 5-min Apgar scores were 3.5, 8.8, 1.3, and 0.1%, respectively. In a multivariate regression model, ACS was associated with a slight increase in NICU admissions (OR: 1.44; 95% CI: 1.04-2.03; p=0.028), but not with RDS/TTN.

Conclusions

Although the low exposure rate was a limitation, ACS administration did not reduce respiratory morbidity in near-term or term IDMs. It was independently associated with an increase in NICU admissions. Randomized controlled trials are required to assess the efficacy and safety of ACS administration in diabetic mothers at late gestation.

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Review Article

Sample-size estimation is not reported in 24% of randomised controlled trials of inflammatory bowel disease: A systematic review

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Zipporah Iheozor-Ejiofor[1], Svetlana Lakunina[2], Morris Gordon[2], Daniel Akintelure[2], Vasiliki Sinopoulou[2] and Anthony Akobeng[3]

Abstract

Background: Sample-size estimation is an important factor in designing a clinical trial. A recent study found that 65% of Cochrane systematic reviews had imprecise results.

Objective: This study set out to review the whole body of inflammatory bowel disease (IBD) randomised controlled trials systematically in order to identify the reporting of sample-size estimation.

Methods: We conducted a comprehensive hand search of the Cochrane Library and Cochrane IBD Specialized Trials Register. We extracted information on relevant features and the results of the included studies. We produced descriptive statistics for our results.

Results: A total of 242 randomised controlled trials were included from 44 Cochrane systematic reviews. About 25% of the studies failed to report on sample-size estimation. Of those that did report on sample-size estimation, 33% failed to recruit their target sample size.

Conclusions: Around half of the randomised controlled trials in IBD either do not report sample-size estimation or reach their recruitment target with the level of detail in reporting being limited.

Keywords

Gastroenterology, IBD, inflammatory bowel disease, Crohn's disease, ulcerative colitis

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Introduction

The number of study participants, or sample size, is an important factor to consider when designing a clinical trial. The larger the sample size, the more precise the results are and the higher the likelihood of detecting statistically significant results.[1] Studies with very small sample sizes may not be sufficiently powered to detect an important difference.[2] On the other hand, sample sizes that are too large can detect statistically significant differences even when they might not be clinically important.[3] This could result in the recommendation of treatments that are not effective. It is therefore important to carry out a sample-size calculation.

Typically, a sample-size estimation (SSE) would require the following components: the probability of a type I error (concluding that there is an effect when in reality there is not), the probability of a type II error (concluding that there is no effect when in reality there

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REVIEW ARTICLE

Estimating insertion length of umbilical arterial and venous catheters in newborn infants: time for change

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ABSTRACT

Background: Umbilical catheters are inserted through the umbilical artery or vein at birth and are crucial in neonatal care. There are several different methods of estimating adequate insertion length of umbilical catheters based on one of two hypotheses; that the insertion length of the UC is correlated to either the infant's birth weight or an external length measurement.

Aim: To review the published literature on methods of estimating insertion lengths of umbilical arterial catheters (UACs) and umbilical venous catheters (UVCs) in newborn infants.

Methods: Systematic search on Medline was undertaken using keywords for relevant papers up to March 2019. Papers were selected by manual search of titles and abstracts.

Results: Formulae for predicting umbilical catheter insertion length are unreliable, particularly for UVCs. There is also conflicting evidence around whether birth weight-based formulae are more reliable than external length-based formulae. Studies comparing various methods to determine their efficacy to show that current formulae have a low accuracy for determining both UVC and UAC positioning.

Conclusions: Current formulae for estimating insertion length of umbilical catheters are not fit for purpose. We propose a new observational study which uses a new external length measurement, the sternal notch to umbilicus length, to develop a more reliable formula for the insertion of UVC and UAC to an adequate length.

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Neonates; umbilical catheter; critical care; formula; regression

Introduction

Umbilical arterial and venous catheters (UAC and UVC) are an integral part of care for critically ill neonates for vascular access and monitoring. These catheters are positioned after using a variety of methods to estimate a safe initial length of insertion [1]. Considering risk *versus* benefit, correct positioning of the catheter tip on the first attempt is important to minimize additional handling for catheter re-manipulation, further radiological exposure and other complications including dislodgement [2]. Malposition has been identified as one of the most common complications, which can lead to perforation of surrounding structures, false aneurysms, hematomas, pericardial effusion, hepatic necrosis, cardiac arrhythmias and sciatic nerve palsy [3–6].

The British Association of Perinatal Medicine (BAPM) published guidelines in 2015 [1] suggesting that the ideal placement of a UVC should be at the thoracic 8–9 (T8–9) vertebral level on an anterio-posterior radiograph and outside of the cardiac silhouette, with a higher risk of serious complications for lower placement [7]. The UAC should lie in a high position above the level of the diaphragm in the descending aorta and below the subclavian artery [3,8,9]. This correlates to being positioned between the upper border of T6 and the lower border of T10. The ideal position for a UAC is at T8 which is associated with fewer vascular complications [1,3]. The catheter position is confirmed using radiological imaging in the form of anteroposterior chest and abdominal radiographs.

Prior to umbilical catheter insertion, it is routine practice to calculate the estimated length required for

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Cooling methods for paediatric heat-induced illnesses

CLINICAL SCENARIO

A 5-year-old male presented to the Paediatric Emergency Department (PED) after being accidentally left in a locked car for 3 hours, where the external temperature was 49 °C. His mother realised that the child was missing; she went to the car where she found him unresponsive. The ambulance services were called. The child was noted to be unresponsive with Glasgow Coma Scale score of 3 with a core rectal temperature of 40.6 °C. The patient's airway was secured with a Guedel support during the transfer then he was intubated and ventilated in PED. His circulation was managed appropriately with a bolus of 20 mL/kg of normal saline and maintenance fluids initiated. Passive cooling was started during the transfer using direct fanning and removal of clothing. How should the child's temperature be managed?

CLINICAL QUESTION

In [children presenting with heat-induced illnesses] is [cold/ice water immersion more effective than evaporation technique/passive cooling] at [reducing body temperature]?

SEARCH CRITERIA

PubMed, Embase and Cochrane Central Register of controlled trials were searched from inception to May 2020 and reference lists searched using ((heat stroke) AND (cooling methods)). A total of 112 unique records were identified, and 8 were included.[1–8]

Three reviews were considered relevant and are presented in table 1.[1 2 7]

SUMMARY

Heat-related illnesses carry significant concerns for emergency physicians. First, there is little knowledge about the management of these cases in paediatrics compared with the adult world, and second, because of the potential severity of the complications that sequel the presentation. There are two types of heat-related illnesses: classic and exertional.[9] A population at extreme age are more prone to the classic presentation, whereas exertional heatstroke tends to occur in young fit athletes or military personnel. The paediatric population are characterised by a greater surface area to body mass, production of more heat per kilogram due to higher metabolic rate and a slower rate of sweating all compared with adults.[9] As the skin temperature soars above 35–40°C, thermoregulation fails to maintain the balance. Oxidative phosphorylation becomes uncoupled, and varieties of enzymes stop functioning, which leads to end-organ failure.[9] As a result of that, patients can develop acute hepatic failure, pulmonary oedema, encephalopathy, seizures, disseminated intravascular coagulation and haemorrhagic shock.[9 10] These changes depend on the duration of hyperthermia rather than the temperature reached[1]; therefore, rapid cooling reverses the thermoregulatory failure. The effectiveness of cooling modalities is based on the cooling rate: ideal cooling modalities provide a cooling rate equal to or higher than 0.2°C/min.[7] Best prognosis and outcome are directly related to the initiation of rapid cooling during the first hour after collapse; thus, the term 'Golden hour' that applies to sepsis and trauma is also applied to the management of heat-related illnesses.[11] It is thus important to early recognise and prompt manage heat-related illness.[1 9–13]

This paper will focus on two cooling methods that are widely used for the management of heat-related illness: cold/ice water immersion and evaporation technique/passive cooling.[2] These two methods have been proven to be effective in heat dissipation by increasing the temperature gradient between the skin and the environment without compromising the blood flow to the skin.[14]

Most of the studies have examined adults, and there are limited data on paediatrics.[15] In cases of children affected by heat-related illnesses, the same adult cooling techniques were used.[12] Several non-invasive cooling methods have been discussed in the studies; each has a specific cooling rate. In our review, we focused on the two more commonly used methods, ice water immersion (IWI) at 2°C and cold water immersion (CWI) at various degrees (2°C to 20°C), and evaporative techniques. Other methods (body

Clinical bottom line

- Initiate rapid cooling techniques (aiming for a rate of 0.2°C/min) within the first hour to minimise complications in exercise-induced heat-related illness (grade A).
- Ice water and cold water immersion cools twice as fast as passive recovery (grade B); however, ice water immersion in a ventilated monitored patient remains technically challenging to perform.
- There is insufficient evidence to support the use of one different cooling method over another in the paediatric population (grade D).

Table 1 Summary of main studies

Citation, date	Study group	Study type	Intervention	Key results and outcome	Study weakness/comments
Bouchama *et al* 2007[2]	19 studies 556 adults Exertional heatstroke and classic heatstroke	Systematic review	*CWI to conductive cooling and evaporative techniques*	IWI was superior to other methods in cooling rate but with higher mortality and morbidity	Systematic review taking evidence from case series No specific comment about bias and grade of evidence but comments of lack of reliability, small study numbers, heterogeneity
Demartini *et al* 2015[1]	274 adults, age 34±3 years	Case reviews	CWI (10°C) within 30 min of the diagnosis 'Golden half hour'	Cooling rate: 0.22°C/min±0.11°C/min Survival rate 100%	Case reviews only Low-grade evidence
Zhang *et al* 2015[7]	19 studies 233 adults Healthy exertional heat stroke	Meta-analysis	CWI compared with passive recovery	CWI twice as fast as passive cooling Mean difference 0.03°C/min (95% CI 0.03 to 0.04)	Variable immersion levels: hands only to total body Risk of bias assessed by PEDRo score (0–10) all papers 7–8 except one of high risk of bias score 4 Heterogeneity 94.5%

PEDro: Physiotherapy Evidence Database scale.[8]
CWI, cold water immersion, usually 10°C (1°C–15°C); IWI, ice water immersion.

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PERSPECTIVES

The Clinical Approach on Receipt of an Unexpected Laboratory Test Result

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International Journal of General Medicine

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Abstract: Approximately 70% of all healthcare decisions affecting diagnosis and treatment involve the use of tests performed within pathology laboratories. The utilisation of diagnostic laboratory services continues to increase, with growth both in volume of tests requested, as well as in the breadth of test repertoire. Every year in the United Kingdom, approximately 1 billion tests are run in hospital laboratories, equivalent to 14 tests per person. Fifty million tests are requested in primary care. Accordingly, there is an inevitable increase in the number of unexpected laboratory results which clinicians review. This is an important, and potentially time-consuming, issue, which we considered to merit a more detailed discussion. Unexpected laboratory results may be critical or non-critical in nature. They may be absolutely genuine, reflecting a clinical change in the patient's condition, a differential diagnosis not previously considered, or an additional test specifically added by the laboratory. However, such results may also occur due to a variety of different circumstances, including much more rarely laboratory error. As there is little published evidence or guidance available, herein we discuss aspects of the clinical approach for physicians after receiving an unexpected laboratory test result.

Keywords: pathology, critical, non-critical, error, communication, diagnosis, assay

Introduction

It has been reported that approximately 70% of all healthcare decisions affecting diagnosis and treatment involve the use of tests performed within Pathology laboratories, though the exact figure is difficult to determine.[1,2] The utilisation of diagnostic laboratory services continues to increase, with growth both in volume of tests requested, as well as in the breadth of test repertoire. Every year in the United Kingdom, approximately 1 billion tests are run in hospital laboratories within the National Health Service, equivalent to 14 tests per person. Fifty million reports are sent from laboratories to general practitioners.[3] Accordingly, there is an inevitable increase in the number of unexpected laboratory results which physicians will receive, and need to act upon. This is an important, and potentially time-consuming, issue, which we considered to merit more detailed discussion as there is little published guidance available.[4,5] In this article, we discuss aspects of the clinical approach after physicians receive an unexpected laboratory test result.

Causes of Unexpected Laboratory Results

Unexpected laboratory results can be either "critical", ie test results that are significantly outside the normal (reference) range and which indicate an immediate

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Full length article

Implications of non-invasive prenatal testing for identifying and managing high-risk pregnancies

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ABSTRACT

Non-invasive prenatal testing is regularly used to screen for aneuploidies and Rhesus status of a fetus. Since 1997 when free fetal DNA (ffDNA) in the maternal circulation was first identified, it has been hypothesized that it may be possible to use non-invasive prenatal testing (NIPT) to identify high-risk pregnancies including pre-eclampsia, growth restriction and preterm birth. Since then there has been much interest in this area as a way to identify and understand disease processes. This review presents the current evidence for this approach. For pre-eclampsia the hypothesis is that ffDNA would increase but the evidence for this is heterogenous across studies and trimesters. There is however increasing agreement between studies that by the third trimester ffDNA is more likely to be raised in pre-eclamptic patients than controls. For preterm birth, again, the main hypothesis is that ffDNA should increase. The results are also heterogenous, with some studies finding increased ffDNA prior to preterm birth, and others finding no change. For fetal growth restriction, there are competing theories for reduced and increased ffDNA and some studies suggest that levels are raised and some reduced. There are complexities in interpreting all of this evidence as the studies' designs, patient populations, and especially in the context of growth restriction, the definitions are not clear. Furthermore, authors use different biochemical tests and different units to describe their results, making meta-analysis difficult. All of these issues and conflicting findings lead us to the conclusion that currently there is yet no definitive place in clinical practice for NIPT to support the diagnosis and management of high-risk pregnancies. However, it is vital that this research continues as it could open the door to better understanding of the disease process and novel approaches to management.

Non-invasive prenatal testing (NIPT) became a possibility when fetal DNA in maternal blood was identified by Lo et al in 1997.[1] This breakthrough led to the development and establishment of NIPT to screen for aneuploidies and define the fetal Rhesus status.[2,3]

Cell-free fetal DNA (ffDNA) is likely to come from the placenta as it is detectable from the 5th week of pregnancy and is also detectable in anembryonic pregnancies.[4] Its levels increase with advancing pregnancy,[5] but it is then rapidly cleared following delivery.[6]

These findings led to the theory that ffDNA could be used to identify high-risk pregnancies based on the hypotheses that poor clearance of the ffDNA in pregnancies with abnormal placentation [7], leads to ffDNA rises immediately prior to onset of preterm labour [8], and that a lower ffDNA fraction could be due to a smaller placental mass of a dysfunctional placenta.[9]

Why is there such interest in NIPT for high-risk pregnancies?

NIPT could enable early diagnosis of a condition (e.g. pre-eclampsia) and indicate impending disease.[7] It may also aid difficult diagnoses, for example invasive placenta.[10] Along with the relative ease of the simple blood test, is the benefit of predicting such conditions from the first or early second trimester. A pregnancy specific risk is provided due to the speed of clearance of ffDNA. It may be particularly useful in an unselected population

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Original research

Phosphatidylinositol 4-kinase β mutations cause nonsyndromic sensorineural deafness and inner ear malformation

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ABSTRACT

Congenital hearing loss is a common disorder worldwide. Heterogeneous gene variation accounts for approximately 20–25% of such patients. We investigated a five-generation Chinese family with autosomal-dominant nonsyndromic sensorineural hearing loss (SNHL). No wave was detected in the pure-tone audiometry, and the auditory brainstem response was absent in all patients. Computed tomography of the patients, as well as of two sporadic SNHL cases, showed bilateral inner ear anomaly, cochlear maldevelopment, absence of the osseous spiral lamina, and an enlarged vestibular aqueduct. Such findings were absent in nonaffected persons. We used linkage analysis and exome sequencing and uncovered a heterozygous missense mutation in the *PI4KB* gene (p.Gln121Arg) encoding phosphatidylinositol 4-kinase β (PI4KB) from the patients in this family. In addition, 3 missense *PI4KB* (p.Val434Gly, p.Glu667Lys, and p.Met739Arg) mutations were identified in five patients with nonsyndromic SNHL from 57 sporadic cases. No such mutations were present within 600 Chinese controls, the 1000 genome project, gnomAD, or similar databases. Depleting *pi4kb* mRNA expression in zebrafish caused inner ear abnormalities and audiosensory impairment, mimicking the patient phenotypes. Moreover, overexpression of 4 human missense *PI4KB* mutant mRNAs in zebrafish embryos resulted in impaired hearing function, suggesting dominant-negative effects. Taken together, our results reveal that *PI4KB* mutations can cause SNHL and inner ear malformation. *PI4KB* should be included in neonatal deafness screening.

1. Introduction

Congenital deafness adversely affects childhood growth and development. In China, there exist 800,000 deaf-mute children aged < 7 years. The deafness rate is increasing by approximately

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Using Artificial Intelligence to Measure Facial Expression following Facial Reanimation Surgery

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Summary: Social interactions are largely dependent on the interpretation of information conveyed through facial expressions. Although facial reanimation seeks restoration of the facial expression of emotion, outcome measures have not addressed this directly. This study evaluates the use of a machine learning technology to directly measure facial expression before and after facial reanimation surgery. Fifteen study subjects with facial palsy were evaluated both before and after undergoing cross-facial nerve grafting and free gracilis muscle transfer. Eight healthy volunteers were assessed for control comparison. Video footage of subjects with their face in repose and with a posed, closed-lip smile was obtained. The video data were then analyzed using the Noldus FaceReader software application to measure the relative proportions of seven cardinal facial expressions detected within each clip. The facial expression recognition application detected a far greater happy signal in postoperative (42 percent) versus preoperative (13 percent) smile videos ($p < 0.0001$), compared to 53 percent in videos of control faces smiling. This increase in postoperative happy signal was achieved in exchange for a reduction in the sad signal (15 percent to 9 percent; $p = 0.092$) and the neutral signal (57 percent to 37 percent; $p = 0.0012$). For video clips of patients in repose, no significant difference in happy emotion was detected between preoperative (3.1 percent) and postoperative (1.4 percent) states ($p = 0.5$). This study provides the first proof of concept for the use of a machine learning software application to objectively quantify facial expression before and after surgical reanimation. (*Plast. Reconstr. Surg.* 146: 1147, 2020.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Diagnostic, IV.

Social interactions are largely dependent on the interpretation of information conveyed through facial expressions.[1] Humans have a uniquely broad and complex array of facial mimetic movements that allow for the delivery of nonverbal cues ranging from dramatic to nuanced. Seven cardinal facial movement patterns have been detected universally, corresponding to the emotions of happiness, sadness, anger, surprise, fear, disgust, and neutral.[2] Any impairment in the ability to legibly and appropriately express these emotions represents a significant social disability.[3–5] The attenuated or incongruous facial expressions that are associated with facial palsy[4,6] can lead to stress, social misinterpretation, embarrassment, and the ultimate avoidance of social engagement.[3–5,7,8] The evaluation of facial palsy and surgical reanimation, therefore, must not only consider static and dynamic measures of movement, vector, and power, but also be able to quantify emotional expression.[9,10]

We tested a commercially available artificial intelligence system trained and validated using the Amsterdam Dynamic Facial Expression Set,[11] a highly standardized set of images containing the different emotional expressions. This machine learning application is able to analyze video data and provide an objective measure of facial expression, generating a relative breakdown of each of

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ORIGINAL ARTICLE

Diagnosing type 2 diabetes using Hemoglobin A1c: a systematic review and meta-analysis of the diagnostic cutpoint based on microvascular complications

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Abstract

Aims Diabetic microvascular complications of retinopathy, nephropathy and neuropathy may occur at hemoglobin A1c levels (HbA1c) below the 6.5% (48 mmol/mol) diagnostic threshold. Our objective was to assess the validity of the HbA1c diagnostic cutpoint of 6.5% based upon published evidence of the prevalence of retinopathy, nephropathy and neuropathy as markers of diabetes.

Methods *Data Sources* PubMed, Embase, Cochrane, Scopus and CINAHL from 1990-March 2019, grey literature sources. *Study Selection* All studies reported after 1990 (to ensure standardized HbA1c values) where HbA1c levels were presented in relation to prevalence of retinopathy, nephropathy or neuropathy in subjects not known to have diabetes. *Data Extraction* Studies were screened independently, data abstracted, and risk of bias appraised. *Data Synthesis* Data were synthesized using HbA1c categories of < 6.0% (< 42 mmol/mol), 6.0–6.4% (42–47 mmol/mol) and ≥ 6.5% (≥ 48 mmol/mol). Random-effects meta-analyses were conducted for retinopathy, nephropathy and neuropathy prevalence stratified by HbA1c categories. Random-effects multivariable meta-regression was conducted to identify predictors of retinopathy prevalence and sources of between-study heterogeneity.

Results Pooled mean prevalence was: 4.0%(95% CI: 3.2–5.0%) for retinopathy, 10.5% (95% CI: 4.0–19.5%) for nephropathy, 2.5% (95% CI: 1.1–4.3%) for neuropathy. Mean prevalence when stratified for HbA1c < 6.0%, 6.0–6.4% and ≥ 6.5% was: retinopathy: 3.4% (95% CI: 1.8–5.4%), 2.3% (95% CI: 1.6–3.2%) and 7.8%(95% CI: 5.7–10.3%); nephropathy: 7.1% (95% CI: 1.7–15.9%), 9.6% (95% CI: 0.8–26.4%) and 17.1% (95% CI: 1.0–46.9%); neuropathy: 2.1% (95% CI: 0.0–6.8%), 3.4% (95% CI: 0.0–11.6%) and 2.8% (95% CI: 0.0–12.8%). Multivariable meta-regression showed HbA1c ≥ 6.5% (OR: 4.05; 95% CI: 1.92–8.57%), age > 55 (OR: 3.23; 95% CI 1.81–5.77), and African-American race (OR: 10.73; 95% CI: 4.34–26.55), to be associated with higher retinopathy prevalence. Marked heterogeneity in prevalence estimates was found across all meta-analyses (Cochran's Q-statistic $p < 0.0001$).

Conclusions The prevalence of nephropathy and moderate retinopathy was increased in subjects with HbA1c values ≥ 6.5% confirming the high specificity of this value for diagnosing T2DM; however, at HbA1c < 6.5% retinopathy increased at age > 55 years and, most strikingly, in African-Americans, suggesting there may be excess microvascular complication prevalence (particularly nephropathy) in individuals below the diabetes diagnostic threshold.

Keywords HbA1c · Type 2 diabetes · Microvascular complications

Introduction

The prevalence of diabetes has reached epidemic proportions globally, with 424.9 million affected adults (20–79 y), representing 8.8% of the global adult population. Current projections indicate that this figure will rise to 628.6 million by the year 2045, affecting almost 10% of the worldwide adult population [1]. Type 2 diabetes (T2DM) accounts for

Managed by Antonio Secchi.

Stephen L Atkin and W. Garry John are Joint senior authors.

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Extended author information available on the last page of the article

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Original Article

Clinical Characteristics and Outcomes of Children With WAGR Syndrome and Wilms Tumor and/or Nephroblastomatosis: The 30-Year SIOP-RTSG Experience

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BACKGROUND: WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and range of developmental delays) is a rare contiguous gene deletion syndrome with a 45% to 60% risk of developing Wilms tumor (WT). Currently, surveillance and treatment recommendations are based on limited evidence. **METHODS:** Clinical characteristics, treatments, and outcomes were analyzed for patients with WAGR and WT/nephroblastomatosis who were identified through International Society of Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) registries and the SIOP-RTSG network (1989-2019). Events were defined as relapse, metachronous tumors, or death. **RESULTS:** Forty-three patients were identified. The median age at WT/nephroblastomatosis diagnosis was 22 months (range, 6-44 months). The overall stage was available for 40 patients, including 15 (37.5%) with bilateral disease and none with metastatic disease. Histology was available for 42 patients; 6 nephroblastomatosis without further WT and 36 WT, including 19 stromal WT (52.8%), 12 mixed WT (33.3%), 1 regressive WT (2.8%) and 2 other/indeterminable WT (5.6%). Blastemal type WT occurred in 2 patients (5.6%) after prolonged treatment for nephroblastomatosis; anaplasia was not reported. Nephrogenic rests were present in 78.9%. Among patients with WT, the 5-year event-free survival rate was 84.3% (95% confidence interval, 72.4%-98.1%), and the overall survival rate was 91.2% (95% confidence interval, 82.1%-100%). Events (n = 6) did not include relapse, but contralateral tumor development (n = 3) occurred up to 7 years after the initial diagnosis, and 3 deaths were related to hepatotoxicity (n = 2) and obstructive ileus (n = 1). **CONCLUSIONS:** Patients with WAGR have a high rate of bilateral disease and no metastatic or anaplastic tumors. Although they can be treated according to existing WT protocols, intensive monitoring of toxicity and surveillance of the remaining kidney(s) are advised. ***Cancer* 2020;0:1-11**. © 2020 The Authors. Cancer published by Wiley Periodicals LLC on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

LAY SUMMARY:

- WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and range of developmental delays) is a rare genetic condition with an increased risk of developing Wilms tumor.
- In this study, 43 patients with WAGR and Wilms tumor (or Wilms tumor precursor lesions/nephroblastomatosis) were identified through the international registry of the International Society of Pediatric Oncology Renal Tumor Study Group (SIOP-RTSG) and the SIOP-RTSG network. In many patients (37.5%), both kidneys were affected. Disease spread to other organs (metastases) did not occur.
- Overall, this study demonstrates that patients with WAGR syndrome and Wilms tumor can be treated according to existing protocols. However, intensive monitoring of treatment complications and surveillance of the remaining kidney(s) are advised.

KEYWORDS: aniridia, pediatric, predisposition, surveillance, treatment, WAGR syndrome (Wilms tumor, aniridia, genitourinary anomalies, and range of developmental delays), Wilms tumor.

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Telehealth: improving maternity services by modern technology

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ABSTRACT

Hypertension is considered one of the most common medical disorders causing complexities in pregnancy. It could be a newly developed pregnancy-induced hypertension (PIH) or a pre-existing hypertension developing into superimposed pre-eclamptic toxaemia. PIH affects approximately 10% of pregnancies and can have a serious impact on both maternal and fetal well-being; hence requires frequent monitoring and timely intervention. National Institute for Health and Care Excellence (NICE) guidelines recommends once or twice weekly monitoring of blood pressure for such patients. The required frequent monitoring comes with certain implications for patients and healthcare services. An average patient with PIH would need to see her healthcare provider once or twice a week until delivery and 6 weeks thereafter. This certainly increases pressure on limited National Health Service (NHS) resources. Home-based monitoring using Telehealth technology can represent a potential solution for achieving good-quality care for the patient without increasing the workload for healthcare providers. We used 'Florence', a text-based technology platform to support home monitoring. We tested its acceptability, feasibility and safety to replace face-to-face appointments for blood pressure monitoring in selected patients with PIH. We implemented our project in three progressive phases using a plan, do, study, act methodology. Florence, telehealth technology was used for blood pressure monitoring instead of face-to-face appointments, and the effect of this innovative technology on the services and the patient experience was studied and necessary modifications were made before progression into the next phase. We recruited 75 patients over 12 months through the progressive phases and replaced around 800 face-to-face appointments by remotely supervised monitoring sessions with Florence successfully, with improved care and patient satisfaction. We also achieved better compliance with the NICE guidelines for blood pressure monitoring in PIH. Our project concluded that Telehealth can be a potential solution for improving care in maternity services, with lesser burden on NHS resources.

INTRODUCTION

Pregnancy-induced hypertension (PIH) complicates 6%–10% of pregnancies.[1] PIH is defined as new-onset hypertension with or without proteinuria after 20 weeks of gestation. It can lead to serious maternal and fetal consequences like pre-eclampsia, placental abruption, cerebrovascular haemorrhage, liver and renal failure. It can also lead to prematurity, intrauterine growth restriction and fetal death.[2]

The National Institute for Health and Care Excellence (NICE) guideline recommends once weekly monitoring for patients with mild hypertension (those with blood pressure (BP) equal or more than 140/90) and twice weekly for patients with moderate hypertension (those with BP equal or more than 150/100).[3] This can lead to an excess burden on National Health Service (NHS) resources.[4]

We assessed ourselves against these standards of vigilant monitoring in a busy district hospital with 4800 deliveries per year. Having more the ten thousand attendances to the maternity day assessment unit (DAU), we estimated that 22% of these were purely for BP monitoring. These were in addition to what would have been done in the community by midwives and general practitioners and yet, we could not fully comply with the NICE recommendations. It was estimated that the number of visits to the maternity DAU would have increased by more than 50% to achieve compliance with NICE guidelines recommendations which would cause a further burden on NHS maternity services.

From a patients' perspective, this frequent hospital-based monitoring would not be feasible either. Coming to the DAU for BP measurement requires taking time off work, arranging for childcare, paying for parking and waiting in antenatal clinic reception until a bed is free. It was estimated that the average time spent at the hospital was up to 2 hours (excluding journey time).

We established a case for change to find an innovative way of monitoring BP in selective patients to reduce the workload on maternity services and improve the patient experience without compromising safety and incurring additional cost for the NHS.

People have been trying to find smarter ways of monitoring chronic conditions at home to reduce frequent visits to healthcare facilities.[5] Telehealth is one of these tools used for managing chronic hypertension remotely. It is thought to be associated with a

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ORIGINAL RESEARCH

Association of asthma severity and educational attainment at age 6–7 years in a birth cohort: population-based record-linkage study

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ABSTRACT

Background There is conflicting research about the association between asthma and poor educational attainment that may be due to asthma definitions. Our study creates seven categories of current chronic and acute asthma to investigate if there is an association for poorer educational attainment at age 6–7 years, and the role of respiratory infections and school absence.

Methods This study used a population-based electronic cross-sectional birth cohort 1998–2005, in Wales, UK, using health and education administrative datasets. Current asthma or wheeze categories were developed using clinical management guidelines in general practice (GP) data, acute asthma was inpatient hospital admissions and respiratory infections were the count of GP visits, from birth to age 6–7 years. We used multilevel logistic regression grouped by schools to ascertain if asthma or wheeze was associated with not attaining the expected level in teacher assessment at Key Stage 1 (KS1) adjusting for sociodemographics, perinatal, other respiratory illness and school characteristics. We tested if absence from school was a mediator in this relationship using the difference method.

Results There were 85 906 children in this population representative cohort with 7-year follow-up. In adjusted multilevel logistic regression, only asthma inpatient hospital admission was associated with increased risk for not attaining the expected level at KS1 (adjusted OR 1.14 95% CI (1.02 to 1.27)). Lower respiratory tract infection (LRTI) GP contacts remained an independent predictor for not attaining the expected level of education. Absence from school was a potential mediator of the association between hospital admission and educational attainment.

Conclusions Clinicians and educators need to be aware that children who have inpatient hospital admissions for asthma or wheeze, or repeated LRTI, may require additional educational support for their educational outcomes.

Key messages

What is the key question?

► Is asthma or wheeze severity during the first six years of life associated with educational attainment at age 6–7 years, should we consider the influence of respiratory infections and does school absence explain the relationship?

What is the bottom line?

► After multivariable adjustment, asthma severity has no association with education outcomes at age 6–7 years, but inpatient hospital admissions for acute asthma or wheeze were associated with increased risk for not attaining the expected level of education for children. Lower respiratory tract infections were also an independent predictor for not attaining the expected level in education. School absence was found to potentially explain the association between acute asthma and lower educational attainment.

Why read on?

► This is the first study to consider interactions between asthma and respiratory infections coded in general practice consultations and hospital admissions on educational attainment. The cohort contained 85 000 children and rich covariate information, allowing us to adjust for numerous factors including sociodemographics, birth and school characteristics in modelling the association between asthma and education outcome.

INTRODUCTION

Asthma is a common childhood condition, with prevalence of current asthma (symptoms within the last year) at age 7 years estimated to be 12% in the UK,[1] similar to Australia[2] and the USA.[3] Cumulative prevalence of wheeze was found to be between 15% and 26% during the first 7 years of childhood in the UK,[4] with current wheeze at age 6–7 years from 7% in the Indian subcontinent to 21% in English language centres (UK, Australia, Canada, New Zealand) and Oceania (22%).[5] Healthcare and societal burden of asthma in the UK was thought to be in excess of £1.1 billion in 2011–2012.[6]

Clinicians mostly follow asthma management guidelines[7 8] that advise step changes in medication or a hospital admittance by age of the child. Decisions to step up or step down in the management plan are based on assessment usually after any hospital admission for acute exacerbation and include consideration of previous hospital admission, Paediatric Intensive Care Unit (PICU) admission, recent steroids, psychological and

ARTICLE | Genetics inMedicine

Biallelic variants in *HPDL*, encoding 4-hydroxyphenylpyruvate dioxygenase-like protein, lead to an infantile neurodegenerative condition

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Purpose: Dioxygenases are oxidoreductase enzymes with roles in metabolic pathways necessary for aerobic life. 4-hydroxyphenylpyruvate dioxygenase-like protein (HPDL), encoded by *HPDL*, is an orphan paralogue of 4-hydroxyphenylpyruvate dioxygenase (HPD), an iron-dependent dioxygenase involved in tyrosine catabolism. The function and association of HPDL with human diseases remain unknown.

Methods: We applied exome sequencing in a cohort of over 10,000 individuals with neurodevelopmental diseases. Effects of HPDL loss were investigated in vitro and in vivo, and through mass spectrometry analysis. Evolutionary analysis was performed to investigate the potential functional separation of HPDL from HPD.

Results: We identified biallelic variants in *HPDL* in eight families displaying recessive inheritance. Knockout mice closely phenocopied humans and showed evidence of apoptosis in multiple cellular lineages within the cerebral cortex. *HPDL* is a single-exonic gene that likely arose from a retrotransposition event at the base of the tetrapod lineage, and unlike HPD, HPDL is mitochondria-localized. Metabolic profiling of *HPDL* mutant cells and mice showed no evidence of altered tyrosine metabolites, but rather notable accumulations in other metabolic pathways.

Conclusion: The mitochondrial localization, along with its disrupted metabolic profile, suggests *HPDL* loss in humans links to a unique neurometabolic mitochondrial infantile neurodegenerative condition.

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Keywords: HPDL; HPD; 4-hydroxyphenylpyruvate dioxygenase-like protein; oxidoreductase; neurodegenerative disease

INTRODUCTION

Disorders involving neurometabolism can lead to both structural and functional disturbances of the nervous system through multiple mechanisms that include abnormal accumulation of toxic substrates, depletion of key energy or metabolic intermediates, or cell death.[1] Although pediatric-onset brain diseases are often associated with genetic abnormalities, the link between metabolic impairments and

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Cardiology in the Young

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Aortic atresia with interrupted aortic arch and bilateral arterial ductus: a successful initial palliation

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Brief Report

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Keywords:
Aortic atresia; interrupted aortic arch; bilateral arterial ductus; stent

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Abstract

A combination of aortic valve atresia and an interrupted aortic arch is a unique disease in which perfusion to the brain and myocardium depends on coexisting lesions or type of interruption. We report a case of aortic valve atresia with type B interrupted arch, bilateral arterial ductus in a neonate who was successfully palliated using a hybrid approach by placing stents in both arterial ductus and banding of branch pulmonary arteries.

A combination of aortic valve atresia and an interrupted aortic arch is a rare form of congenital heart disease that is incompatible with life unless blood supply to the myocardium and brain is provided through one of the different mechanisms. Prompt identification of this entity is important because these patients may need interventions in order to maintain a reliable source of brain and myocardial perfusion.

Case report

A term female newborn baby was admitted at 2 hours of life to the neonatal intensive care unit with low saturation. Echocardiogram showed double inlet left ventricle, non-restrictive ventricular septal defect, hypoplastic sub-aortic right ventricle, type B interrupted aortic arch (arch interrupted between the left common carotid and the left subclavian artery), large non-restrictive patent ductus arteriosus continue as descending aorta, and normal origin of the right subclavian artery. The aortic valve was atretic with a small (3 mm) ascending aorta and right-sided arterial ductus arising from the right pulmonary artery was supplying the brachiocephalic artery which in turn retrogradely perfusing the coronary arteries (Fig 1a). The baby was started on prostaglandin in order to maintain the ductal patency. Computed tomography (CT) angiogram showed aortic atresia, type B interrupted aortic arch and large arterial ductus from the left pulmonary artery continues as descending aorta, right-sided arterial ductus from the right pulmonary artery supplying the head and neck vessels, ascending aorta, and coronaries (Fig 1b). Management options we had for the baby were either do a Damus–Kaye–Stensel operation with an aortic arch repair or a hybrid procedure which include placing stents in both the ducti and bilateral pulmonary artery banding. Considering the high-risk status with primary surgical repair, it was decided to proceed with the later.

Cardiac catheterisation showed no forward flow the ventricle to the aorta. Blood supply to the ascending aorta and coronary arteries were provided by a right arterial duct which took origin from the right pulmonary artery. There was type B interrupted aortic arch. The descending aorta was perfused by a left arterial duct and the right subclavian was arising normally from the brachiocephalic artery. A 4-mm stent was deployed in the right arterial ductus and an 8-mm stent in the left arterial ductus (Fig 1c and d). The baby tolerated the procedure well; prostaglandin was discontinued, and bilateral pulmonary artery banding was done on the same day. The baby had an uneventful post-operative course, extubated on 2nd post-operative day, and discharged home after 10 days in stable clinical condition with a plan to proceed with single-ventricle palliation by doing a comprehensive stage 2 (Norwood operation and Glenn shunt) in the future.

Discussion

Aortic valve atresia and an interrupted aortic arch is a rare congenital heart disease in which the survival of the patient depends on the blood supply to the ascending aorta and myocardium. Most of the time associated lesions provide an alternate source of blood supply to the brain and heart. Different reported sources of blood supply to the blind ascending aortic segment are (1) aorto-pulmonary (AP) window, (2) double aortic arch, (3) bilateral arterial ductus, and (4) aberrant right subclavian artery.[1–3] When there are no above-mentioned sources of

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ESPR

Practical approach to imaging diagnosis of biliary atresia, Part 1: prenatal ultrasound and magnetic resonance imaging, and postnatal ultrasound

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Abstract
We present a practical approach to imaging in suspected biliary atresia, an inflammatory cholangiopathy of infancy resulting in progressive fibrosis and obliteration of extrahepatic and intrahepatic bile ducts. Left untreated or with failure of the Kasai procedure, biliary atresia progresses towards biliary cirrhosis, end-stage liver failure and death by age 3. Differentiation of biliary atresia from other nonsurgical causes of neonatal cholestasis is challenging because there is no single method for diagnosing biliary atresia, and clinical, laboratory and imaging features of this disease overlap with those of other causes of neonatal cholestasis. Concerning imaging, our systematic literature review shows that ultrasonography is the main tool for pre- and neonatal diagnosis. Key prenatal features, when present, are non-visualisation of the gallbladder, cyst in the liver hilum, heterotaxy syndrome and irregular gallbladder walls. Postnatal imaging features have a very high specificity when present, but a variable sensitivity. Triangular cord sign and abnormal gallbladder have the highest sensitivity and specificity. The presence of macro- or microcyst or polysplenia syndrome is highly specific but less sensitive. The diameter of the hepatic artery and hepatic subcapsular flow are less reliable. When present in the context of acholic stools, dilated intrahepatic bile ducts rule out biliary atresia. Importantly, a normal US exam does not rule out biliary atresia. Signs of chronic hepatopathy and portal hypertension (portosystemic derivations such as patent ductus venosus, recanalised umbilical vein, splenomegaly and ascites) should be actively identified for — but are not specific for — biliary atresia.

Keywords Biliary atresia · Imaging · Infant · Magnetic resonance imaging · Recommendations · Review · Ultrasound

Introduction

Biliary atresia is an important cause of obstructive jaundice in infants, causing progressive fibrosis and obliteration of extrahepatic and intrahepatic bile ducts, resulting in biliary cirrhosis in the absence of early surgery. Jaundice with pale stools and dark urine are present within the first days or weeks after birth. The prevalence of biliary atresia ranges from 1 in 5,000 to 1 in 20,000 depending on the geographic area, with the highest prevalence reported in Taiwan [1–3]. Biliary atresia aetiology is unknown and different causes were proposed including viral infections, genetic factors or toxins [4]. There are two forms of biliary atresia: the non-syndromic form, accounting for about 80% of cases; and the syndromic form, also called biliary atresia splenic malformation syndrome, accounting for about 20% of cases. The syndromic form is associated with polysplenia, intestinal malrotation, preduodenal portal vein, absent inferior vena cava, aberrant hepatic artery and abdominal heterotaxia [5]. Whatever the form, there are different subtypes of biliary atresia according to the extent of fibrosis on extrahepatic bile ducts and the presence of a cyst of the extrahepatic bile duct. In all cases intrahepatic bile ducts are fibrotic, explaining the absence of bile duct dilatation despite complete obstruction [6] (Fig. 1). The histology is characterised by bile duct proliferation, bile plugs, portal or

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Review Article

PROSPECT guideline for tonsillectomy: systematic review and procedure-specific postoperative pain management recommendations

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Summary

Tonsillectomy is one of the most frequently performed surgical procedures; however, pain management remains challenging. Procedure-specific efficacy as well as specific risks of treatment options should guide selection of pain management protocols based on evidence and should optimise analgesia without harm. The aims of this systematic review were to evaluate the available literature and develop recommendations for optimal pain management after tonsillectomy. A systematic review utilising preferred reporting items for systematic reviews and meta-analysis guidelines with procedure-specific postoperative pain management (PROSPECT) methodology was undertaken. Randomised controlled trials published in the English language up to November 2019 assessing postoperative pain using analgesic, anaesthetic or surgical interventions were identified. Out of the 719 potentially eligible studies identified, 226 randomised controlled trials met the inclusion criteria, excluding the studies examining surgical techniques. Pre-operative and intra-operative interventions that improved postoperative pain were paracetamol; non-steroidal anti-inflammatory drugs; intravenous dexamethasone; ketamine (only assessed in children); gabapentinoids; dexmedetomidine; honey; and acupuncture. Inconsistent evidence was found for local anaesthetic infiltration; antibiotics; and magnesium sulphate. Limited evidence was found for clonidine. The analgesic regimen for tonsillectomy should include paracetamol; non-steroidal anti-inflammatory drugs; and intravenous dexamethasone, with opioids as rescue analgesics. Analgesic adjuncts such as intra-operative and postoperative acupuncture as well as postoperative honey are also recommended. Ketamine (only for children); dexmedetomidine; or gabapentinoids may be considered when some of the first-line analgesics are contra-indicated. Further randomised controlled trials are required to define risk and combination of drugs most effective for postoperative pain relief after tonsillectomy.

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ESPR

Non-radiologist-performed point-of-care ultrasonography in paediatrics — European Society of Paediatric Radiology position paper

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Abstract
Non-radiologist point-of-care ultrasonography (US) is increasingly implemented in paediatric care because it is believed to facilitate a timely diagnosis, such as in ascites or dilated renal pelvicalyceal systems, and can be used to guide interventional procedures. To date, all policy statements have been published by non-radiologic societies. The European Society of Paediatric Radiology hereby issues a position statement on paediatric non-radiologist point-of-care US from the point of view of those leading on children's imaging, i.e. paediatric radiologists. In this position statement, we will address the boundaries, education, credentialing, quality control, reporting and storage of images in paediatric practice.

Keywords Bedside · Children · Non-radiologist · Nonspecialist · Position statement · Ultrasound

Introduction

Historically, ultrasonography (US) has been part of an integrated imaging strategy as performed by radiologists, but the method has also been used by gynaecologists, cardiologists and ophthalmologists, amongst others, as part of their clinical care. However, with the advent of smaller, cheaper, portable systems, other specialties have taken an interest in the use of US. This development was foreseen by the European Society of Radiology (ESR) in its 2009 position paper on US, stating: "Turf battles about the use of US continue to grow as more and more specialists are claiming US as part of their everyday's work, and the position of radiologists is progressively further undermined" [1]. In the past years, all major medical imaging companies have added handheld devices to their spectrum of imaging modalities [2]. The use of US by non-radiologists has become known as point-of-care ultrasonography (POCUS). As discussed previously in this journal, point-of-care US actually is a misnomer as radiologists also provide point-of-care US services [3]. We will therefore use the terminology non-radiologist point-of-care US throughout this position statement. The last decade has seen a significant uptake of non-radiologist point-of-care US, although to date mostly in adult and emergency medicine. As early as 1990, the American College of Emergency Physicians issued a statement on non-radiologist point-of-care US in emergency medicine [4]. Although it can be argued that it is a relatively new development, it already has been suggested that non-radiologist point-of-care US should be seen as the fifth pillar next to the four historical pillars of inspection, palpation, percussion and auscultation [5].

It goes without saying that there are several potential advantages to non-radiologist point-of-care US. First of all, it brings imaging to the bedside, directly at the patient-

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Research Article | Teaching Case Studies

^{18}F-FDG PET Imaging Predicts the Epileptogenic Zone Prospectively in Recurrent Cryptogenic Meningoencephalitis with Subsequent Simple Partial Visual Seizures

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Abstract

^{18}F-FDG PET scans have proven to be useful in the diagnosis and management of encephalitis patients. ^{18}F-FDG PET scans are also the standard of care in the evaluation of epilepsy patients before surgery. Encephalitis patients who later develop epilepsy may have useful imaging findings at the time of diagnosis. We present a case of ^{18}F-FDG PET imaging in a patient with recurrent cryptogenic meningoencephalitis. ^{18}F-FDG PET imaging after resolution of the encephalitis revealed hypometabolism in previously hypermetabolic areas. Hence, the initial ^{18}F-FDG PET scan prospectively predicted the epileptogenic zone and seizure-onset zone.

meningoencephalitis FDG PET epileptogenic zone seizures epilepsy

HIV in Pregnancy – an update

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Abstract:

Human immunodeficiency virus (HIV) is an infection with a global prevalence and currently no cure or vaccine. Women living with HIV who become pregnant or who acquire the virus during pregnancy are at risk of both maternal and perinatal morbidity and mortality mainly if the virus is poorly controlled. Furthermore, there is a risk of vertical transmission to the fetus during pregnancy labour and postpartum through breastfeeding.

Appropriate management must be instituted to reduce the consequences of HIV in pregnancy, ideally starting with preconception counselling and planning pregnancies when the viral load is minimum. During pregnancy, an appropriate combined anti-retroviral (cART) medication is mandatory with very close monitoring of the viral load, cluster of differentiation 4 (CD4) cell counts, blood counts, liver and kidney function tests.

Planning delivery should not be different in women on cART and suppressed viral loads. However, special care must be taken to limit vertical transmission in those who present late and in whom viral load is unknown or not controlled at the time of delivery.

Breastfeeding remains a potential source of infection for the baby and is being discouraged in high-income countries for women living with HIV; however, in low-income countries, the recommendation is exclusive breastfeeding. If breastfeeding must happen, it is best when viral load is suppressed, and cART continued until weaning.

Serodiscordant couples present unique problems, and their management should begin with the planning of pregnancy. Emphasis should be on taking steps to prevent HIV transmission to the negative partner and vertical transmission to the new-born.

First, we found that the incidence of atypical femur fracture was unrelated to BMD and only weakly related to age. Second, when we performed a subgroup analysis in the Kaiser Permanente cohort that was limited to women who were older than 65 years of age and who had a BMD T-score of less than –2.5, we found an incidence of atypical femur fracture similar to the incidence in the overall cohort (unpublished data). The correspondents question whether we overestimated the fracture benefit of 5 to 10 years of alendronate, since the FLEX trial[1] and observational data[2] showed no increase in the risk of clinical fracture after alendronate was discontinued after 5 years. However, studies involving patients with 5 years of previous treatment are not relevant, since our estimate of the fractures that were prevented with alendronate was based on a comparison of women who were never treated with those who were continuously treated. We agree that our findings that show large decreases in the risk of atypical femur fracture after the discontinuation of alendronate provide support for a drug holiday after 5 years, particularly for women at lower risk.

Garton questions whether an underestimation of the incidence of atypical femur fracture biases the ratio of such fractures to fragility fractures. However, we think that our adjudication, starting with all femoral-shaft or subtrochanteric fractures, identified virtually all complete unilateral and bilateral atypical femur fractures. However, incomplete fractures would not have been included unless they had been prophylactically repaired. We agree that accumulating microdamage is part of the pathophysiology of atypical femur fracture, but its effect on only a small minority of patients remains unexplained.[3] Regarding the consequences of atypical femur fracture as compared with hip fracture, several studies have suggested similar mortality[4] after either type of fracture, although surgical repair of atypical femur fractures can be more challenging.[3]

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JAK Inhibition in the Aicardi–Goutières Syndrome

TO THE EDITOR: Some reports,[1-3] including that of Vanderver et al. (Sept. 3 issue),[4] have indicated the potential of Janus kinase 1 (JAK1) blockade in the treatment of type I interferonopathies. We describe here the onset of the Aicardi–Goutières syndrome, despite the use of ruxolitinib for 10 months, in a patient who had been presymptomatic.

A 4-month-old male infant with biallelic *RNASEH2B* mutations was identified after an older sibling received a diagnosis of the Aicardi–Goutières syndrome. The infant's development had been normal until that time, but he had markers that were suggestive of interferon-signaling activation (Fig. S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Therefore, when he was 5 months of age, we initiated therapy with ruxolitinib at a

dose of 5 mg twice daily. When he was 11 months of age, the dose was increased to 7.5 mg twice daily (1 mg per kilogram of body weight per day).

At 12 months of age, the patient's neurologic status remained normal. At 13 months of age, he had weekly fevers. Ruxolitinib was discontinued twice, for 3 days on each occasion, in the 14th month of life. His immunization history included the administration of hepatitis A vaccine at 13 months of age (see the Supplementary Appendix). At 15 months of age, up to which time his neurologic status was normal, he had an abrupt onset of irritability and neurologic deterioration. At 17 months of age, he had spastic–dystonic tetraparesis and was no longer able to speak.

We observed that the concentration of ruxolitinib in the patient's cerebrospinal fluid (CSF) was approximately 10% of that in the plasma; a similar finding was observed in three other patients with the Aicardi–Goutières syndrome (Table S1). Better penetration into the central nervous system or combination therapy[5] might have prevented disease manifestation.

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Figure 1 (next page). Interferon-Signaling Gene (ISG) Expression Scores in the Context of Infection and Vaccination and Aicardi–Goutières Syndrome Scores in Patients Treated with Baricitinib.

In our study, one patient with homozygous *RNASEH2B* mutations had elevated ISG scores after influenza vaccination, which had been administered hours before the sample was obtained, and during a viral illness with fever (Panel A, left graph). Control values (from patients without interferonopathy) are shown in the right graph. In a different cohort,[1] a patient who had the Aicardi–Goutières syndrome with homozygous *SAMHD1* deletions had a decrease in ISG scores and improved clinical findings during baricitinib therapy (Panel B, left graph). During the study, the patient had three infections (a proteus urinary tract infection [UTI], sinusitis, and strep throat), which were treated with antibiotic agents and were associated with elevated ISG scores. Control values (from patients without interferonopathy or with CANDLE [chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperatures] or SAVI [stimulator of interferon genes–associated vasculopathy with onset in infancy]) are shown in the right graph. The specific methods for assessing the ISG scores shown in Panels A and B varied between the two study cohorts[1,2]; in both cases, higher scores indicate greater interferon signaling. In an additional patient, baricitinib therapy was interrupted owing to concerns with infection (Panel C). Subsequently, neurologic skills, as measured by the Aicardi–Goutières syndrome scale (on which scores range from 0 to 11, with increased scores indicating discrete milestones gained),[3] were lost. Evaluation of developmental milestones, assessed according to the Aicardi–Goutières syndrome scale, is shown for two sibling pairs in our study (Panel D); shown are scores from before treatment, the baseline visit at the initiation of baricitinib treatment, and the last available scores. The older siblings (red) met developmental milestones while they were receiving baricitinib, and the younger siblings (blue) met age-appropriate development milestones as of the last evaluation. Asterisks indicate the initiation of baricitinib therapy.

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Full length article

Viral Hepatitis in pregnancy

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ABSTRACT

The global prevalence of viral hepatitis is very high and seems to be rising over the years. The infection can profoundly affect pregnant women causing significant maternal and perinatal morbidity and mortality with some strains much worse than others.

Hepatitis A (HAV) and E (HEV) which are transmitted mainly through the faecal-oral route present as acute hepatitis during pregnancy and are responsible for most local epidemic outbreaks. HAV infection remains self-limiting during pregnancy, while HEV has a higher prevalence and causes significant morbidity. It is also associated with a very high maternal mortality rate (20 %) and requires special attention in endemic areas. HEV vaccines do exist, but the WHO has yet to approve them for general use. Hepatitis B is the most prevalent form and is part of the ante-natal screening program. The presence of HBeAg is associated with high viral loads and infectivity. Antiviral therapy, preferably tenofovir (TDF), is recommended for mothers with viral load $\geq$ 200,000 IU/mL$_2$), with the neonates receiving both active and passive immunisations. Hepatitis C and D are usually found as chronic infections in the pregnant and non-pregnant populations. Screening for hepatitis C during pregnancy and its subsequent management is still unsettled, but the introduction of direct-acting antiviral (DAA) drugs will change the picture if their safety is established in pregnancy. HDV is an incomplete virus linked to HBV and cannot establish an infection on its own. Controlling HBV is paramount to controlling HDV. HEV is quite prevalent and looked upon as hepatotropic. It seems to be quite prevalent in some blood donor populations and has a high co-infection rate with HCV. It has a high Mother-to-Child-Transmission (MTCT) but causes little or no illness in infected infants, and antenatal screening is not justified.

This review summarises the prevalence, clinical picture, maternal, perinatal effects, and the management and prevention of hepatitis A, B, C, D, E and G viral infections during pregnancy.

Introduction

Viral hepatitis is a widespread infection affecting both the pregnant and the non-pregnant population. In 2015 alone, there were more than 10 million new infections and 1.34 million deaths due to viral hepatitis [1]. This represents an increase of 22 % in the number of deaths from 2000 [1] and may be associated with rising cases of Hepatitis C in young intravenous drug users [2], but more so from poor detection of disease and treatment [1].

The global prevalence of Hepatitis C Virus (HCV) in 2015 was 71 million, and that of Hepatitis B Virus (HBV) in 2016 was 257 million [1] when compared with a prevalence of about 38 million living with HIV [3]. Hepatitis B and C are responsible for 96 % of all deaths from hepatitis [1].

Viral hepatitis is caused by a diverse collection of viruses with differing structural biology, transmission, endemic patterns, and chronicity that share a common propensity to infect and replicate in human hepatocytes. These are referred to as hepatotropic viruses, and cause most hepatitis in the pregnant and non-pregnant populations. Viruses included in this group are Hepatitis viruses A, B, C, and E (HAV, HBV, HCV, and HEV) [4,5]. Others include Hepatitis D (HDV) and Hepatitis G (HGV), which also pose risks of perinatal infections and transmission.

Hepatitis in much rarer conditions can also be caused by other non-hepatotropic viruses such as cytomegalovirus, herpesvirus, Epstein-Barr virus, and influenza virus. These viruses do not target the liver but affect it as part of a widespread acute viral illness [6,7] (Table 1).

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Molecular Characterization of Extended-Spectrum β-Lactamase–Producing *Escherichia coli* and *Klebsiella pneumoniae* Among the Pediatric Population in Qatar

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Introduction: Although extended-spectrum β-lactamase (ESBL)–producing Enterobacterales are a public health problem in the Arabian Peninsula, data on the molecular characteristic of their antimicrobial resistance determinants in children is limited.

Aim: To determine the molecular characteristics of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* in the pediatric population of Qatar.

Methods: Whole-genome sequencing was performed on ESBL-producing *E. coli* and *K. pneumoniae* isolates recovered from screening and clinical specimens from pediatric patients at Sidra Medicine in Doha from January to December 2018.

Results: A total of 327 ESBL producers were sequenced: 254 *E. coli* and 73 *K. pneumoniae*. Non-susceptibility rates to non-β-lactam antibiotics for both species were 18.1 and 30.1% for gentamicin, 0.8 and 4.1% for amikacin, 41.3 and 41.1% for ciprofloxacin, and 65.8 and 76.1% for cotrimoxazole. The most common sequence types (STs) were ST131 (16.9%), ST38 and ST10 (8.2% each) in *E. coli* and ST307 (9.7%), and ST45 and ST268 (6.9% each) in *K. pneumoniae*. CTX-M type ESBLs were found in all but one isolate, with CTX-M-15 accounting for 87.8%. Among other β-lactamases, TEM-1B and OXA-1 were coproduced in 41 and 19.6% of isolates. The most common plasmid-mediated quinolone resistance genes cocarried were *qnr A/B/E/S* (45.3%). Ninety percent of gentamicin non-susceptible isolates harbored genes encoding AAC(3) enzymes, mainly *aac(3)-IIa*. Only two of 57 isolates harboring *aac(6′)-Ib-cr* were non-susceptible to amikacin. Chromosomal mutations in genes encoding DNA gyrase and topoisomerase IV enzymes were detected in 96.2%

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A Neutrophil-Driven Inflammatory Signature Characterizes the Blood Transcriptome Fingerprint of Psoriasis

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Transcriptome profiling approaches have been widely used to investigate the mechanisms underlying psoriasis pathogenesis. Most researchers have measured changes in transcript abundance in skin biopsies; relatively few have examined transcriptome changes in the blood. Although less relevant to the study of psoriasis pathogenesis, blood transcriptome profiles can be readily compared across various diseases. Here, we used a pre-established set of 382 transcriptional modules as a common framework to compare changes in blood transcript abundance in two independent public psoriasis datasets. We then compared the resulting "transcriptional fingerprints" to those obtained for a reference set of 16 pathological or physiological states. The perturbations in blood transcript abundance in psoriasis were relatively subtle compared to the changes we observed in other autoimmune and auto-inflammatory diseases. However, we did observe a consistent pattern of changes for a set of modules associated with neutrophil activation and inflammation; interestingly, this pattern resembled that observed in patients with Kawasaki disease. This similarity between the blood-transcriptome signatures in psoriasis and Kawasaki disease suggests that the immune mechanisms driving their pathogenesis might be partially shared.

Keywords: psoriasis, transcriptomics, blood, Kawasaki disease, systems biology

INTRODUCTION

Inflammation has an important role to play as part of the host defense against infection. However, prolonged or excessive inflammation can cause notable pathology (1–3). One example of such a pathology is psoriasis, which affects ~100 million individuals worldwide (4). This common, immune-mediated disease results in a unique skin barrier abnormality caused by excessive epidermal proliferation and inflammation (5, 6). Psoriasis pathogenesis is likely driven by many factors, including environmental triggers, genetic susceptibility, and even microbiome composition

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OPEN

Personalized quantification of facial normality: a machine learning approach

Osman Boyaci[1], Erchin Serpedin[1] & Mitchell A. Stotland[2,3]✉

What is a *normal* face? A fundamental task for the facial reconstructive surgeon is to answer that question as it pertains to any given individual. Accordingly, it would be important to be able to place the facial appearance of a patient with congenital or acquired deformity numerically along their *own* continuum of normality, and to measure any surgical changes against such a personalized benchmark. This has not previously been possible. We have solved this problem by designing a computerized model that produces realistic, normalized versions of any given facial image, and objectively measures the perceptual distance between the raw and normalized facial image pair. The model is able to faithfully predict human scoring of facial normality. We believe this work represents a paradigm shift in the assessment of the human face, holding great promise for development as an objective tool for surgical planning, patient education, and as a means for clinical outcome measurement.

The human face is an indispensable, dynamic organ of social communication. Even excluding the rich signaling information provided by animative expression, a cursory glance at a face instantaneously prompts an array of subconscious interpretation within an observer. Consequently, the social implications of congenital and acquired forms of facial disfigurement on affected individuals are significant, and are underscored by the widespread desire of patients to seek normalizing interventions. For the facial reconstructive surgeon, the primary task during clinical assessment and planning is to determine what *normal* actually means as it pertains to any given individual face. Previous related research, though wide-ranging, has bypassed the issue of objectively customizing facial analysis, while considering matters such as the global determinants of beauty (e.g., proportion, symmetry, averageness)[1–5], communication and perception of emotion[6,7], personality inference[8,9], morphing techniques[10], regions of attraction[11–14], machine recognition[15], and computation of anthropometric and digital population norms[16]. Various methods of facial assessment introduced over the past decades, including expert ratings[17,18], anthropometric landmark measurements[19], stereophotogrammetry studies[20], crowdsourced surveys[21], patient-reported outcomes[22,23], and eye-tracking analyses[14,24], are not benchmarked against a given patient's own theoretical facial norm (nor do they lend themselves easily to application in the clinical setting). Further, despite the fact that population means for facial appearance can be determined using large database averaging techniques, it is important that reconstructive interventions be carried out within the context of a patient's own unique, anatomic features. This is because the distinctive facial features of any given patient—influenced by gender, age, race, etc.—are not likely to be reflected accurately by a calculated norm derived from the broader population. Attempting to address this issue by finely segmenting massive databases into increasingly narrow demographic classifications would be confounded by the historical admixture of human populations and a globalized world with increasingly mixed lineage. That is, building a library of facial norms to provide a credible reference source that faithfully matches the multidimensional singularity of any given patient seems unrealistic.

Beyond the importance of being able to define patient-specific normality, two particular measures currently unavailable would be beneficial assets for a treating clinician: (1) a means of placing an individual's facial appearance numerically along their *own* hypothetical continuum of normality, and (2) an objective, reproducible method to quantify the change effected by any reconstructive intervention. We have designed a novel solution to address these gaps by constructing the first computerized model capable of automatically producing realistic, normalized versions of any given face. Our approach melds raw (i.e., real) images of individuals, with images created by an open-source generative adversarial network (the "Style GAN")[25]. This GAN was designed using a 70,000-image database that is broadly distributed across gender, age, and ethnicity. Our model also employs

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REVIEW ARTICLE

Neurodevelopmental outcomes following bevacizumab treatment for retinopathy of prematurity: a systematic review and meta-analysis

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Abstract

Objective To systematically review the studies exploring the association between bevacizumab and neurodevelopmental outcomes.

Methods Embase, Medline, CINAHL, and Cochrane Library databases were searched for studies examining neurodevelopmental outcomes of preterm infants treated with bevacizumab compared to laser ablation or cryotherapy for severe retinopathy of prematurity (ROP).

Results Thirteen studies (clinical trial = 1; cohort studies = 12) were included. Random-effects model meta-analysis showed significant increased odds of cognitive impairment associated with bevacizumab treatment on both unadjusted (unadjusted odds ratio (OR) 1.61; 95% confidence interval (CI) 1.12, 2.30) and adjusted analyses (adjusted OR 1.90; 95% CI 1.22, 2.97). Infants treated with bevacizumab for severe ROP had significantly lower Bayley-III cognitive (mean difference (MD) −1.66; 95% CI −3.21, −0.12), and language composite scores (MD −5.50; 95% CI −8.24, −2.76) compared to infants treated with laser ablation or cryotherapy.

Conclusion Bevacizumab treatment for severe ROP is associated with increased risk of cognitive impairment and lower cognitive and language scores in preterm infants.

Introduction

Retinopathy of prematurity (ROP) is an important complication of prematurity that can lead to poor visual acuity and blindness in children [1]. ROP is classified from stage 1–V, and severe ROP (stage III or above) appears to be a marker for neurocognitive impairment among preterm infants [2]. Even without unfavorable ocular outcomes, the relationship between severe ROP and nonvisual disabilities persists [3]. Infants with severe ROP have higher rates of developmental delay, and the same process that leads to severe ROP may simultaneously injure the developing brain [4, 5]. ROP treatment is reserved for stage III or above or any stage with plus disease in zone I and stage III with plus disease in zone II. Although laser treatment is well-established for severe ROP, retreatment is needed in 11–20% of cases [6–9]. Besides, it is associated with ocular side effects and incurs risks of anesthesia [6–9]. Since the early 2000s, anti-vascular endothelial growth factor (VEGF) monoclonal antibodies like bevacizumab have appeared as an effective treatment for ROP and have been advocated as first-line therapy by many ophthalmologists [7, 10–16].

Possible benefits of bevacizumab over laser treatment include relatively simple procedure, bedside administration under local anesthesia, the additive response from direct VEGF inactivation, and administration in infants where

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Identifying Clinical Clues in Children With Global Developmental Delay / Intellectual Disability With Abnormal Brain Magnetic Resonance Imaging (MRI)

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Abstract

Global developmental delay / intellectual disability are common pediatric conditions. Brain magnetic resonance imaging (MRI), although an important diagnostic tool in the evaluation of these patients, often requires general anesthesia. Recent literature suggests that unnecessary general anesthesia exposure should be avoided in early years because of possible long-term negative neurodevelopmental sequelae. This study sought to identify clinical clues associated with brain MRI abnormalities in children with global developmental delay / intellectual disability in an attempt to provide guidance to physicians on selecting patients who would benefit from an MRI. Retrospective chart review analysis was conducted for patients presenting to a pediatric neurology tertiary care center between 2014 and 2017 for a first clinic evaluation for global developmental delay / intellectual disability. Detailed clinical history and physical examination findings were analyzed and correlated with brain MRI findings. The majority (218/327, 67%) of children referred for evaluation of global developmental delay / intellectual disability underwent complete clinical and radiologic evaluations. Mean age was 37.9 months ($\pm$32.5 standard deviation) and 116 were males (53%). Motor deficits were predominant in most subjects (122/218, 56%). Abnormal MRI findings were observed in 153 children (70%), with the most prevalent abnormalities noted within the white matter (104/153, 68%), corpus callosum (77/153, 50%), and the hippocampus (50/153, 33%). Abnormal MRI findings were prevalent in children with predominant motor delay (84, 69%) and cognitive disability (3, 100%) as well as those with visual and hearing impairment ($P < .05$). The presence of facial dysmorphisms (57/71, $P = .02$); cranial nerve abnormalities (79/100; $P = .007$) and abnormal reflexes (16, $P = .01$) on examination also correlated significantly with increased MRI abnormalities.

Keywords

developmental delay, brain magnetic resonance imaging (MRI), neuroimaging, intellectual disability

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Global developmental delay is defined as a significant delay in 2 or more developmental domains, including gross or fine motor, speech/language, cognitive, social/personal, and activities of daily living and is thought to predict a future diagnosis of intellectual disability.[1] According to the American Association on Intellectual and Developmental Disability (AAIDD), intellectual disability is defined as "a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills.[2]

The prevalence of global developmental delay/intellectual disability is estimated to be between 1% and 3%,[3] with a wide range of etiologies including genetic/metabolic, in utero exposure to toxins or infections, perinatal asphyxia, prematurity,

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Variant of Bladder Exstrophy With an Intact Penis: Surgical Options and Approach

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Variants of bladder exstrophy are a rare but diverse spectrum of bladder exstrophy-epispadias complex. This case series describes a group of 4 unique exstrophy variant cases who had an intact phallus, but a completely open bladder plate. These patients underwent exstrophy repair and concomitant umbilicoplasty at the Civil Hospital, Ahmedabad as part of the US-India Multi-institutional Bladder Exstrophy Collaboration and were followed at the same institution. We believe that a detailed assessment of bladder neck prior to reconstructive repair and bladder closure would be beneficial in these cases as the extent of bladder neck involvement would affect reconstructive approach. UROLOGY 149: e15–e17, 2021. © 2020 Elsevier Inc.

Bladder exstrophy-epispadias complex (BEEC) compromises a spectrum of complex urogenital malformations ranging from glanular epispadias to cloacal exstrophy with midline defects affecting the genitourinary system, pelvis, abdominal wall and sometimes the spine and anus. Bladder exstrophy is the most common entity of BEEC, occurring in 1:30,000. Variants of bladder exstrophy are less common, representing approximately 8% of total cases.[1]

Variants can be classified into 4 major types: skin-covered bladder exstrophy, duplicate bladder exstrophy, superior vesical fissure, and pseudoexstrophy.[2] Studies regarding variants of bladder exstrophy are sparse and largely limited to case reports because of the rarity of these conditions.

Here, we present a group of 4 unique exstrophy variant cases with an intact phallus, but completely open bladder plate. Presentation, surgical management, and patients' short- and long-term surgical outcomes, including dehiscence, fistula formation and urinary continence status, are described and compared to previously published case studies.

CASE PRESENTATIONS

All 4 of the patients are male patients of Indian origin with an exstrophic bladder and an intact phallus (Fig. 1), who were managed at the Civil Hospital, Ahmedabad as part of the US-India Multi-institutional Bladder Exstrophy Collaboration from January 2010 to January 2020.[3] Three patients underwent individualized repair of the bladder exstrophy spectrum defect, and 1 patient who had history of failed repair due to dehiscence underwent a redo repair. All patients who underwent exstrophy repair had normal renal function prior to surgery. Umbilicoplasty with rhomboid flap was performed for all patients simultaneous with bladder closure. The individual patients' presentations and outcomes are further discussed below.

The first patient was an 8-year-old male who presented with an exposed, easily depressible exstrophic bladder plate, with considerable squamous change and no umbilicus. He had no history of prior repair. On physical examination, his phallus was normal in size and appearance with an orthotopic meatus. A small protuberance of tissue was seen at the penopubic junction that was suspicious for a second, dorsal urethra that contained no lumen. He had continuous incontinence from his exstrophic bladder and normal, straight erections. During surgery, the lumen of his dorsal urethra could not be cannulated but it appeared to connect with the anterior wall of the bladder between the proximal corporal bodies with a separate trajectory from the more normally located ventral urethra that was associated with a competent bladder neck. The dorsal accessory urethra was excised and the bladder was closed. A perineal urethrostomy was created with the assistance of a transverse preputial island tube to bridge the distance between the blind ending ventral membranous urethra to the perineal skin just posterior to the scrotum (Fig. 2). On

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Declarations of Interest: *None.*

This work was approved by the B.J. Medical College and Civil Hospital Ethics Committee # 195/2018 and the CHOP IRB 19-017026.

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Case report

Lethal severe congenital tracheal stenosis with tracheal ring complicating respiratory distress syndrome in an extremely premature infant: first reported case in Qatar with a literature review

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Abstract

In the context of prematurity, lethal congenital airways malforamtion can be masked by the symptoms of respiratory distress syndrome. A high index of suspicion is required. We present the case of a 28-week preterm infant, with atypical protracted respiratory insufficiency despite the escalation of mechanical ventilation. The possibility of airway obstruction was considered in view of severe chest retraction while on the mechanical ventilator. It was also difficult to pass suction catheters beyond a certain depth in the trachea; however, intubation of the upper trachea was accomplished twice without difficulty. Flexible bronchoscopy revealed complete tracheal ring with severe tracheal stenosis; there was no evidence of tracheo-oesophageal fistula. Due to advanced multi-organ dysfunction at diagnosis, a decision was made with the family to re-orientate from intensive care to compassionate care. Ethical considerations in similar cases should incorporate the improved outcomes of prematurity and recent advances in tracheal reconstruction.

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Mini Review

"Current concepts in assisted mechanical ventilation in the neonate" - Part 2: Understanding various modes of mechanical ventilation and recommendations for individualized disease-based approach in neonates

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ABSTRACT

Mechanical ventilation is a lifesaving intervention in critically ill preterm and term neonates. However, it has the potential to cause significant damage to the lungs resulting in long-term complications. Understanding the pathophysiological process and having a good grasp of the basic concepts of conventional and high-frequency ventilation is essential for any medical or allied healthcare practitioner involved in the neonates' respiratory management. This review aims to describe the various types and modes of ventilation usually available in neonatal units. It also describes recommendations of an individualized disease-based approach to mechanical ventilation strategies implemented in the authors' institutions.

1. Introduction

Mechanical ventilation aims to achieve adequate gas exchange. There is a growing body of evidence to avoid invasive mechanical ventilation via the endotracheal tube whenever feasible. The indications for intubation and invasive mechanical ventilation are severe respiratory failure, as evidenced by severely impaired oxygenation and alveolar ventilation, reduced respiratory effort, and circulatory failure in certain instances [1]. Once the decision for invasive mechanical ventilation is taken, steps to minimize ventilation-induced lung injury (VILI) should be considered by choosing the appropriate mode and modality of ventilation and appropriate settings. The choice of conventional versus high-frequency ventilation is guided by the pathophysiology of the underlying disease and institutional practice. Depending on the neonatal respiratory disease static and dynamic compliance of the lungs, airway resistance, alveolar surface tension, work of breathing, and time constant may be very different [2]. This review article is focused on discussing the different modes and modalities of ventilation commonly used in neonatology. It provides (patho) physiology-based guidance for selecting appropriate invasive ventilatory supports in some common neonatal respiratory pathologies. For the purpose of this review a breath/inflation is defined as the inspiratory part of the respiratory cycle where a breath is a spontaneous breath and an inflation is defined as a ventilator-generated breath.

2. Conventional ventilation

The modalities of conventional ventilation are pressure targeted, volume targeted, and hybrid ventilation. In pressure-

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Somatostatin analogues for the treatment of hyperinsulinaemic hypoglycaemia

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***Abstract*:** Hyperinsulinaemic hypoglycaemia (HH) is a biochemical finding of low blood glucose levels due to the dysregulation of insulin secretion from pancreatic β-cells. Under normal physiological conditions, glucose metabolism is coupled to β-cell insulin secretion so that blood glucose levels are maintained within the physiological range of 3.5–5.5 mmol/L. However, in HH this coupling of glucose metabolism to insulin secretion is perturbed so that insulin secretion becomes unregulated. HH typically occurs in the neonatal, infancy and childhood periods and can be due to many different causes. Adults can also present with HH but the causes in adults tend to be different. Somatostatin (SST) is a peptide hormone that is released by the delta cells (δ-cells) in the pancreas. It binds to G protein-coupled SST receptors to regulate a variety of location-specific and selective functions such as hormone inhibition, neurotransmission and cell proliferation. SST plays a potent role in the regulation of both insulin and glucagon secretion in response to changes in glucose levels by negative feedback mechanism. The half-life of SST is only 1–3 min due to quick degradation by peptidases in plasma and tissues. Thus, a direct continuous intravenous or subcutaneous infusion is required to achieve the therapeutic effect. These limitations prompted the discovery of SST analogues such as octreotide and lanreotide, which have longer half-lives and therefore can be administered as injections. SST analogues are used to treat different forms of HH in children and adults and therapeutic effect is achieved by suppressing insulin secretion from pancreatic β-cells by complex mechanisms. These treatments are associated with several side effects, especially in the newborn period, with necrotizing enterocolitis being the most serious side effect and hence SS analogues should be used with extreme caution in this age group.

Keywords: hyperinsulinaemic hypoglycaemia, insulinoma, lanreotide, octreotide, somatostatin

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Introduction

Hypoglycaemia is a common biochemical finding in the newborn, infancy, childhood and adulthood periods. In children hypoglycaemia may be due to many different causes.[1] Adults can also present with hypoglycaemia but the underlying causes tend to be different. The most severe form of hypoglycaemia, in children and adults, is hyperinsulinaemic hypoglycaemia (HH). In HH the secretion of insulin from the pancreatic β-cell becomes unregulated and uncoupled from glucose metabolism, so that insulin secretion becomes inappropriate for the blood glucose level, leading to persistent and recurrent hypoglycaemia. In children the congenital forms of HH are more common than in adults and the clinical presentation in newborns and infants is typically with severe and persistent hypoglycaemia.[2] The medical management of newborns and infants with severe forms of HH is complex and some patients are treated with somatostatin analogues, both short and long acting (such as octreotide and lanreotide respectively) to suppress insulin secretion, so that blood glucose levels can be maintained within the normal range.[3] Somatostatin (SST) is a peptide hormone that is released by the delta cells (δ-cells) of the pancreas and has powerful effects on insulin and glucagon secretion from the pancreatic β-cell and α-cell respectively. Although SST analogues are widely used in the treatment of

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Full length article

Ebola infection in pregnancy, an ongoing challenge for both the global health expert and the pregnant woman—A review

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ABSTRACT

A new Ebola outbreak is currently ongoing in the Democratic Republic of Congo, after the most severe outbreak in West Africa in 2014–2016 was controlled. Ebola outbreaks are usually a significant cause of death among pregnant women. The clinical presentation of Ebola Virus infection in pregnancy often mimics common pregnancy related bleeding complications or febrile conditions common in pregnancy. The large amount of body fluids discharged during the management of these conditions make pregnancy a highly risky intervention for nosocomial infection transmission, especially to health workers.

In this review, we discuss the Ebola virus, its pathogenesis, clinical features, diagnosis and the current supportive intensive medical and obstetric- specific practices to ensure safe management of Ebola positive pregnant women. We present how Ebola may be managed in highly resourced settings where experience is limited in the management of pregnancy complicated by Ebola infection and how wherever these patients are managed, postpartum contraceptive support is necessary because of lingering concerns about sexual transmission. Wider issues highlighted by the Ebola outbreaks included the demonstration of how weak health systems from prolonged lack of investment, in the face of highly infectious diseases like Ebola Virus infection, can pose a risk to the global community, bringing sharply into focus the need for essential collaboration between national health departments and international health organizations such as the World Health Organization.

Introduction

Ebola virus has been causing local outbreaks of Ebola virus disease (EVD) in rural Africa for over 40yrs. The most severe outbreak which occurred from 2014 to 2016 affected mainly three West Africa states, resulting in more than 28,000 infected individuals and over 11,000 deaths. It spread globally to 7 countries including the UK and the United States of America causing significant morbidity and mortality and demonstrating how easily transmissible the virus is [1,2].

The case fatality rate (CFR) from Ebola virus disease in pregnancy was 90 % as reported from the 1976 outbreak [3]. A more recent systematic review of data from the 2014–2016 outbreak, however, estimated the CFR for pregnant women to be 64 % (106/165) – a rate indeed closer to 63 %, the overall CFR in the general population from that outbreak. The estimated overall mortality among pregnant women from 1976 to 2019 is about 72 % (179/274) in West Africa and 18 % in the western world. Mortality seems to have improved steadily, driven by advancements in supportive care [4,2].

The Ebola outbreak in West Africa also worsened the healthcare capacity of affected countries, having caused the death of about 500 healthcare workers and negatively affecting improvements in health service that had been previously made. The proportion of healthcare workers among confirmed Ebola Virus cases during the outbreak in the three West African countries was 3.9 % (815/20955) [5,6]. The risk of infection was 21–32 times higher in health workers compared with non-health workers who were ≥ 15 years of age [5]. There is also evidence that some healthcare professionals who either refused to report to work for fear of being infected or abandoned the profession altogether, during the outbreak. It will be many years before some of these West Africa countries can regain their previous levels of health service delivery beside the significant socio- economic ramifications. The World Bank estimates that, on average, the economy of some of these countries such as Sierra Leone, could shrink by 23 % and that the cost of recovery will completely outstrip the international support given them [6].

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ORIGINAL RESEARCH

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Phylogeny and biogeography of the Japanese rhinoceros beetle, *Trypoxylus dichotomus* (Coleoptera: Scarabaeidae) based on SNP markers

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Abstract

The Japanese rhinoceros beetle *Trypoxylus dichotomus* is one of the largest beetle species in the world and is commonly used in traditional Chinese medicine. Ten subspecies of *T. dichotomus* and a related *Trypoxylus* species (*T. kanamorii*) have been described throughout Asia, but their taxonomic delimitations remain problematic. To clarify issues such as taxonomy, and the degree of genetic differentiation of *Trypoxylus* populations, we investigated the genetic structure, genetic variability, and phylogeography of 53 specimens of *Trypoxylus* species from 44 locations in five Asian countries (China, Japan, Korea, Thailand, and Myanmar). Using specific-locus amplified fragment sequencing (SLAF-seq) techniques, we developed 330,799 SLAFs over 114.16M reads, in turn yielding 46,939 high-resolution single nucleotide polymorphisms (SNPs) for genotyping. Phylogenetic analysis of SNPs indicated the presence of three distinct genetic groups, suggesting that the various subspecies could be treated as three groups of populations. PCA and ADMIXTURE analysis also identified three genetic clusters (North, South, West), which corresponded to their locations, suggesting that geographic factors were important in maintaining within population homogeneity and between population divergence. Analyses of SNP data confirmed the monophyly of certain subspecies on islands, while other subspecies (e.g., *T. d. septentrionalis*) were found to be polyphyletic and nested in more than one lineage. AMOVA demonstrated high level of differentiation among populations/groups. Also, pairwise F_{ST} values revealed high differentiation, particularly between South and West, as well as between North and South. Despite the differentiation, measurable gene flow was inferred between genetic clusters but at varying rates and directions. Our study demonstrated that SLAF-seq derived markers outperformed 16S and COII sequences and provided improved resolution of the genetic differentiation of rhinoceros beetle populations from a large part of the species' range.

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Critically Ill Pediatric Oncology Patients: What the Intensivist Needs to Know? Pediatric Critical Care Medicine

Indian Journal Of Critical Care Medicine : Peer-Reviewed, Official Publication Of Indian Society Of Critical Care Medicine

Amin Al Haj Moussa, Ata Ur Rehman Maaz, Nesreen Faqih, Manu Sundaram

Abstract

Cancer is an evolving cause of morbidity and mortality in children worldwide. In recent decades, there has been a significant increase in the survival of children with cancer, after applying new methods and treatment protocols in practice. However, the complexity of the disease itself, as well as the intensity and toxicity of treatment is such that many children require admission to the pediatric intensive care unit (PICU) which should be well equipped and led by personnel who have adequate training and expertise to provide optimum care to these complex patients. Most oncology patients who require PICU admission categorized into oncological emergencies, and/or decompensation from treatment and its side effects. In this study, we provide a summary of the essential and most recent evidence-based recommendations from published reviews and articles to aid PICU physicians and to ensure the best treatment and outcome possible for the children with such disease. How to cite this article: Al Haj Moussa A, Maaz AUR, Faqih N, Sundaram M. Critically Ill Pediatric Oncology Patients: What the Intensivist Needs to Know? Pediatric Critical Care Medicine. Indian J Crit Care Med 2020;24(12):1256-1263.

Original Article

Comparison of the skin-to-epidural space distance at the thoracic and lumbar levels in children using magnetic resonance imaging

ABSTRACT

Background: Several studies have attempted to estimate the approximate distance from the skin-to-epidural space using different imaging modalities (computed tomography [CT], ultrasound, and magnetic resonance imaging [MRI]) and direct needle measurements. The objective of our study was to compare the distance from the skin to the epidural space (SED) at multiple levels, focusing on T_{6-7}, T_{9-10}, and L_{2-3} using MRI.

Methods: After institutional review board (IRB) approval, sagittal T2-weighted MRI images of the spine of 108 children in the age group ranging from 3 months to 8 years undergoing radiological evaluation in the supine position at our institution were analyzed. The SED at T_{6-7} and T_{9-10} levels (straight and inclined) and SED at L_{2-3} (straight) were determined and compared using repeated-measures ANOVA and paired *t*-tests with a Bonferroni correction for 10 pairwise comparisons ($P < 0.005$ was considered statistically significant).

Results: The average SED (measured straight and inclined) was 18.2 mm and 21.6 mm at T_{6-7}; 18.3 mm and 20.5 mm at T_{9-10}; and 21.8 mm (straight) at L_{2-3}. The repeated-measures ANOVA F-test indicated significant variability in SED ($P < 0.001$) among the 5 measurements obtained. At the $P < 0.005$ significance level, corrected for multiple comparisons, the SED (straight) at T_{9-10} straight was shorter than the other measured distances.

Conclusion: The distance from the skin to the epidural space is not constant at various vertebral levels. At the levels measured, it was greatest at the lumbar level and at least at the thoracic level of T_{9-10}. A single predictive formula was not applicable for calculating the approximate SED at all vertebral levels.

Key words: Epidural anesthesia; lumbar epidural; thoracic epidural

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Review

Photobiomodulation: A review of the molecular evidence for low level light therapy

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Summary Light energy is harnessed for therapeutic use in a number of ways, most recently by way of photobiomodulation (PBM). This phenomenon is a cascade of physiological events induced by the nonthermal exposure of tissue to light at the near infrared end of the visible spectrum. Therapeutic PBM has become a highly commercialized interest, marketed for everything from facial rejuvenation to fat loss, and diode-based devices are popular in both the clinic setting and for use at home. The lack of regulatory standards makes it difficult to draw clear conclusions about efficacy and safety but it is crucial that we understand the theoretical basis for PBM, so that we can engage in an honest dialogue with our patients and design better clinical studies to put claims of efficacy to the test. This article presents a summary of the science of PBM and examines the differences between laser light, on which much of the preclinical evidence is based and light from diodes, which are typically used in a clinical setting.

Contents

This work has not been presented at any meeting, wholly or in part.

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Review Article

TRPV2: A Cancer Biomarker and Potential Therapeutic Target

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The Transient Receptor Potential Vanilloid type-2 (TRPV2) channel exhibits oncogenicity in different types of cancers. TRPV2 is implicated in signaling pathways that mediate cell survival, proliferation, and metastasis. In leukemia and bladder cancer, the oncogenic activity of TRPV2 was linked to alteration of its expression profile. In multiple myeloma patients, TRPV2 overexpression correlated with bone tissue damage and poor prognosis. In prostate cancer, TRPV2 overexpression was associated with the castration-resistant phenotype and metastasis. Loss or inactivation of TRPV2 promoted glioblastoma cell proliferation and increased resistance to CD95-induced apoptotic cell death. TRPV2 overexpression was associated with high relapse-free survival in triple-negative breast cancer, whereas the opposite was found in patients with esophageal squamous cell carcinoma or gastric cancer. Another link was found between TRPV2 expression and either drug-induced cytotoxicity or stemness of liver cancer. Overall, these findings validate TRPV2 as a prime candidate for cancer biomarker and future therapeutic target.

1. Introduction

Cancer patients could get a significant clinical benefit from the identification of molecular targets that play a polar role in tumor cell growth and survival, amenable to an approach with preciseness in patient medication. Nowadays, the discovery of new cancer therapies or improvement of current ones requires an understanding of the mechanism(s) of cancer progression and identification of biomarkers that are causally connected to instead of merely related to the disease process. The concept of precision medicine, which consists of identifying the molecular signature of individual tumors that can be selected for the most appropriate therapeutic approach, has become the pivot of contemporary oncology. On this basis, for biomarkers to assume their rightful role, they need to be befittingly altered by effective therapeutic interventions and modify the definition of the populations of patients who presumably will benefit from precision medicine.

The TRPV2 channel has attracted the attention in many deadly cancers as one of several candidate channels that are involved in the proliferation and resistance of tumor cells to apoptotic cell death. Depending on the type of cancer, different alterations in the TRPV2 gene (i.e., loss, gain, and splicing) were found to exhibit oncogenic capacity linked to a tumor's growth and metastasis. This review focuses on the pathophysiological significance of the TRPV2 channel in many kinds of cancers, and we hope to offer the reader a flavor of how the measurable molecular changes in TRPV2 could validate its quality as a cancer biomarker and potential therapeutic target.