As an academic medical center, Sidra’s mission extends beyond provisioning world class clinical care to being an internationally recognized beacon for medical education and clinical research. Specifically, in alignment with Qatar’s National Research Strategy and Qatar’s National Vision 2030, Sidra’s mandate includes making discoveries that can benefit patients, society and public health in Qatar and beyond. Sidra thus aims to transform biomedical research by focusing first on improving our understanding of epidemiology and mechanisms of diseases affecting our population, and then developing better preventative and therapeutic tools to improve health outcomes of women and children in Qatar.

Achieving academic success requires alignment and momentum on a large scale, and for this we are grateful for the support the biomedical sciences continue to receive on a national level and for Qatar Foundation’s leadership and vision for transforming Qatar into a knowledge-based economy guides the development of our state-of-the-art laboratories and our exciting clinical-research programs. In addition, our positioning as the region’s largest genome sequencing facility has enabled us to become internationally competitive and support large-scale programs with global ambitions, both locally (eg. Qatar Genome Programme (QGP)), and internationally, as our scientists collaborate with >25 world-class institutions from around the world. These collaborations not only improve Sidra’s visibility and reputation, but also lead to high impact discoveries, as well as successful grant applications and publications every year.

In this volume, we are celebrating our academic output by compiling Sidra publications over the period of 2018-2019. During these two years, Sidra had a total of 429 publications. Among these, 72% of Research department publications were in journals with an impact factor above 3.2—representing the top 15% of all journals around the world—with an average impact factor of 6.6 for the Research Branch, and 3.5 for the Clinical Branch over the two years.

Since we moved to the Outpatient Clinic in 2016, Sidra’s publication record reflects more patient-derived discoveries over the years, emphasizing the importance of collaborations between hospital and research. In the coming years Sidra will continue its mission as an academic medical center, and prioritize investigations on biomedical problems that are of national relevance and also have a global impact.

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INTRODUCTION

The declining cost and increasing availability of next-generation DNA sequencing technologies has enabled the discovery of the genetic defects underlying many new Mendelian disorders, especially monogenic immune disorders. Although autoimmune diseases are generally considered polygenic, there have been a growing number of rare, monogenic autoimmune disorders in which the causative genetic defects have been identified.1-7 The study of these disorders facilitated a deeper understanding of the mechanisms involved in immune regulation and tolerance, especially in the role and function of regulatory T cells (Treg). Defects in various genes have been found to lead to Treg impairment, resulting in overlapping clinical disease features, one of the most prominent being inflammatory bowel-like (IBD-like) disease (Figure 1).

LESSONS FROM THE TREG DISORDERS

Inflammatory bowel disease (IBD), which includes Crohn’s disease and ulcerative colitis, is considered the result of a dysregulated immune response to the gut microbiota, causing chronic mucosal inflammation and ultimately resulting in mucosal tissue damage.8,9 IBD is generally a complex, polygenic disorder. However, monogenic diseases with Treg loss or impairment result in IBD-like disease, indicating the importance of Tregs in maintaining homeostasis at the mucosal interface between the host and microbiome.

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare autoimmune disorder10 caused by mutations in the gene FOXP3.11,12 IPEX is the epitome of Treg deficiency disorders as FOXP3 is the master transcription factor for CD4+ Tregs and is crucial for the development and maintenance of Tregs.13,14 IPEX results from the lack of Treg cells and is characterized by multisystem autoimmunity.15 Interestingly, one of the earliest and most prominent signs of IPEX is severe intractable diarrhea due to the development of IBD-like disease during infancy. Surprisingly, the lack of Foxp3 in scurfy mice results in multiorgan inflammatory conditions, but not colitis.16-18 This lack of colitis development may be due to the premature death of the mice at approximately 3 weeks of age. Sharma et al19,20 found that the transfer of scurfy lymphocytes into adult Rag1−/− mice causes colitis while transfer into Rag1−/− neonates only causes colitis after weaning. Changes in the microbiome likely contribute to this development of colitis as studies have demonstrated rapid changes in commensal community of the gut postweaning.21,22 Additionally, maternal milk may provide some protection as it contains immunoglobulin A and other protective and anti-inflammatory agents.23,24

Summary

Recently, several studies have investigated a number of rare monogenic autoimmune disorders, in which the causative genetic defects were identified and found to affect the development or function of regulatory T cells (Tregs). The studies of these disorders have facilitated a deeper understanding of the mechanisms involved in immune regulation and tolerance. Furthermore, these studies have highlighted the importance of Tregs in maintaining homeostasis at the mucosal interface between the host and microbiome. Here, we offer our perspective on these monogenic autoimmune disorders, highlighting their overlapping clinical features with inflammatory bowel disease.

KEYWORDS

CHAI, IBD, IL-10, IPEX, LATAIE, Treg
Original article

A curated collection of transcriptome datasets to investigate the molecular mechanisms of immunoglobulin E-mediated atopic diseases

Susie S.Y. Huang, Fatima Al Ali, Sabri Boughorbel, Mohammed Toufiq, Damien Chaussabel and Mathieu Garand*

Sidra Medicine, Al Gharrafa Street Ar-Rayyan, Doha, Qatar, PO. 26999

*Corresponding author: Tel.: +974-40037008; Email: mathieu.garand@gmail.com


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Abstract

Prevalence of allergies has reached ~20% of population in developed countries and sensitization rate to one or more allergens among school age children are approaching 50%. However, the combination of the complexity of atopic allergy susceptibility/development and environmental factors has made identification of gene biomarkers challenging. The amount of publicly accessible transcriptomic data presents an unprecedented opportunity for mechanistic discoveries and validation of complex disease signatures across studies. However, this necessitates structured methodologies and visual tools for the interpretation of results. Here, we present a curated collection of transcriptomic datasets relevant to immunoglobulin E-mediated atopic diseases (ranging from allergies to primary immunodeficiencies). Thirty-three datasets from the Gene Expression Omnibus, encompassing 1860 transcriptome profiles, were made available on the Gene Expression Browser (GXB), an online and open-source web application that allows for the query, visualization and annotation of metadata. The thematic compositions, disease categories, sample number and platforms of the collection are described. Ranked gene lists and sample grouping are used to facilitate data visualization/interpretation and are available online via GXB (http://ige.gxbsidra.org/dm3/geneBrowser/list). Dataset validation using associated publications showed good concordance in GXB gene expression trend and fold-change.

Database URL: http://ige.gxbsidra.org/dm3/geneBrowser/list
Biocompatibility and toxicity of novel iron chelator Starch-Deferoxamine (S-DFO) compared to zinc oxide nanoparticles to zebrafish embryo: An oxidative stress based apoptosis, physicochemical and neurological study profile

Gheyath K. Nasrallah a,b,1, Rola Salem b,1, Sahar Da’as c,d, Ola Loay Ahmad Al-Jamal b, Mark Scott e, Ibrahim Mustafa a,⁎

a Department of Biomedical Science, College of Health Sciences, Qatar University, Doha, Qatar
b Biomedical Research Centre, Qatar University, Doha, Qatar
c Sidra Medical and Research Centre, Doha, Qatar
d Hamad bin Khalifa University, Doha, Qatar
e Centre for Blood Research, University of British Columbia, Vancouver, Canada

ARTICLE INFO

Keywords: S-DFO Iron chelation Zebrafish Toxicity ZnO

ABSTRACT

Objectives: Clinically approved iron chelators are effective in decreasing significant transfusional iron accumulation. Starch-Deferoxamine (S-DFO), a novel high molecular weight iron chelator, was produced to increase binding capacity to iron and reduce toxicity. Although its efficacy was established in one small cohort clinical trial, its potential adverse effect was not adequately addressed.

Methods: We utilized zebrafish model to assess S-DFO toxicity using following assays: mortality, teratogenicity, hatching rate, tail flicking, Acridine Orange staining for apoptosis detection, o-dianisidine staining for hemoglobin synthesis, and the level of Hsp70 as a general stress indicator. Embryos were exposed to different concentrations of S-DFO, Zinc Oxide nanoparticle (ZnO) (positive control), along with untreated control (UC).

Results: S-DFO showed no significant mortality nor deformities at all tested concentrations (0.0–1000 μM). Thus, the LC50 is expected to > 1000 μM. 100 μM S-DFO treatment did not affect embryo development (as judged by hatching rate); neuromuscular activity (as judged by tail flicking); and hemoglobin synthesis. Neither apoptosis, nor increase in Hsp70 level was noticed upon S-DFO treatment.

Conclusion: Our assays demonstrate that S-DFO does not induce cellular or biochemical stress and has no adverse effect on organ development of zebrafish embryos, suggesting its safe use as an iron chelator.

1. Introduction

Blood transfusion is considered a life-saving therapy in many acute and chronic diseases associated with blood loss or ineffective erythropoiesis like thalassemia major, sickle cell anemia, prematurity, and malignant disorders. Although, chronic blood transfusion therapy effectively increases survival rate and improves quality of patient’s life, it is associated with many complications, especially transfusional iron overload. Excess iron in human body can accelerate the production of highly reactive oxygen species (ROS), thus increasing susceptibility of organs to be oxidatively injured (Ozment and Turi, 2009). ROS destroys cellular elements like proteins, and nucleic acids, and also induces peroxidation of lipids and de-polymerization of polysaccharides. Further, because iron is a vital element for almost all living organisms, excess iron also triggers growth of pathogenic organisms leading to increase vulnerability of transfusion-dependent patients to a broad range of infections (Flora, 2013). To decrease morbidity rate associated with significant iron accumulation, patients, who receive blood chronically, are given iron chelators (Ozment and Turi, 2009). Although clinically approved iron chelators are effective, one of the major
Diabetes Mellitus in a Patient With Lafora Disease: Possible Links With Pancreatic β-Cell Dysfunction and Insulin Resistance

Ramona C. Nicolescu 1∗†, Sara Al-Khawaga 2†, Berge A. Minassian 3 and Khalid Hussain 2

1 Division of Endocrinology and Diabetes, Department of Pediatrics, University of Liège, Centre Hospitalier Régional de la Citadelle, Liège, Belgium, 2 Division of Endocrinology, Department of Pediatrics, Sidra Medicine Outpatient Clinic, Doha, Qatar, 3 Division of Neurology, Department of Pediatrics, University of Texas Southwestern, Dallas, TX, United States

Lafora disease (LD) is a rare autosomal recessive disorder characterized by progressive myoclonic epilepsy followed by continuous neurological decline, culminating in death within 10 years. LD leads to accumulation of insoluble, abnormal, glycogen–like structures called Lafora bodies (LBs). It is caused by mutations in the gene encoding glycogen phosphatase (EPM2A) or the E3 ubiquitin ligase malin (EPM2B/NHLRC1). These two proteins are involved in an intricate, however, incompletely elucidated pathway governing glycogen metabolism. The formation of EPM2A and malin signaling complex promotes the ubiquitination of proteins participating in glycogen metabolism, where dysfunctional mutations lead to the formation of LBs. Herein, we describe a 13-years-old child with LD due to a NHLRC1 (c.386C > A, p.Pro129His) mutation, who has developed diabetes mellitus and was treated with metformin. We discuss how basic mechanisms of LD could be linked to β-cell dysfunction and insulin resistance.

Keywords: Lafora disease, EPM2A, EPM2B/NHLRC1, insulin resistance, diabetes, glycogen metabolism

BACKGROUND

Lafora disease (LD; OMIM 254780) is a fatal autosomal recessive inherited disease characterized by progressive myoclonic epilepsy followed by continued neurological decline due to polyglucosan inclusion bodies (insoluble glucans) accumulation in brain and other peripheral tissues culminating in death within 10 years (1). LD is particularly frequent in countries with high rates of consanguinity such as Mediterranean, Southern India, and the Middle East. The disease is extremely rare with an estimated overall frequency of ∼4 cases per million individuals globally (2, 3). LD is caused by mutation of two genes, EPM2A encoding the glucan phosphatase laforin (a dual specificity phosphatase), and EPM2B/NHLRC1 encoding E3 ubiquitin ligase malin (2). PRDM8 mutation has also been reported in a single family as an additional gene involved in LD associated with an earlier onset disease (4).

Laforin-malin complex regulates diverse cellular pathways, including ubiquitin-proteasome system and glycogen metabolism, where their defects in these processes lead to LD. The clinical symptoms of EPM2A and NHLRC1 gene mutation are similar; however, NHLRC1 mutation patients tend to live longer than the EPM2A gene mutation (5, 6). Protein targeting to glycogen (PTG), one of the regulatory subunits of protein phosphatase 1 targeting glycogen, modulates the protein phosphatase 1 (PP1) affinity to its substrates such as the glycogen synthase (GS)
DS86760016, a leucyl-tRNA synthetase inhibitor, with activity against *Pseudomonas aeruginosa*

Manoj Kumar,a,c,* Madhvi Rao,a Kedar P Purnapatre,a Tarani Kanta Barman,a Vattan Joshi,a
Amuliya Kashyap,a Tridib Chaira,b Ramesh B. Bambal,b Manisha Pandya,a Souhaila Al Khodor,c
Dilip J. Upadhyay,a,d Nobuhisa Masuda a

1Department of Microbiology, and 2Department of Pharmacokinetics and Metabolism, Daiichi Sankyo India Pharma Private Limited, Gurgaon, Haryana, India, 3Department of Immunology, Inflammation and Metabolism, Division of Translational Medicine, SIDRA Medicine, Doha, Qatar, 4Amity Institute of Virology and Immunology, Amity University, Noida, India.

Address correspondence to Manoj Kumar, mkumar@sidra.org

*Present address: Manoj Kumar, Immunology, Inflammation and Metabolism, Division of Translational Medicine, SIDRA Medicine, Doha, Qatar.

Running title: Activity of DS86760016 against *Pseudomonas aeruginosa*

M.K., M.R., and K.P.P. contributed equally to this work.

Keywords. Gram-negative bacteria, *Pseudomonas aeruginosa*, multidrug resistance, aminoacyl-tRNA synthesis, urinary tract infection.
Abstract

DS86760016 is a new leucyl-tRNA-synthetase inhibitor in the preclinical development stage. DS86760016 showed potent activity against extended spectrum multidrug-resistant *Pseudomonas aeruginosa* isolated from clinical samples and *in-vitro* biofilms. In a murine catheter associated urinary tract infection model, DS86760016 treatment resulted in significant eradication of *P. aeruginosa* counts from kidney, bladder and catheter without developing drug-resistance. Our data suggest that DS86760016 has the potential to act as a new drug for the treatment of *Pseudomonas* infections.
RESEARCH ARTICLE

Molecular characterization of low grade and high grade bladder cancer

Alessandro Apollo1*, Valerio Ortenzi2*, Cristian Scatena3, Katia Zavaglia3, Paolo Aretini4, Francesca Lessi3, Sara Franceschi3, Sara Tomei3, Carlo Alberto Sepich5, Paolo Viacava6, Chiara Maria Mazzanti3‡, Antonio Giuseppe Naccarato2‡

1 Genetic Unit of Biology Department, University of Pisa, Pisa, Italy, 2 Department of Pathology, University Hospital of Pisa, Pisa, Italy, 3 Section of Cancer Genomics, Fondazione Pisana per la Scienza, Pisa, Italy, 4 Omics Core and Biorepository, Sidra Medicine, Doha, Qatar, 5 Division of Urology, Versilia Hospital, Lido di Camaiore, Italy, 6 Division of Pathology, Hospital of Livorno, Livorno, Italy

☯ These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* alessandro.apollo@hotmail.com

Abstract

Background
Bladder cancer (BC) is the 9th most common cancer diagnosis worldwide. Low grade (LG) represents 70% of all BCs, characterized by recurrence and rare ability (10–15%) to progress to high grade (HG) and invade. The remaining 30% is high grade (HG), fast invasive BC, which is resistant to therapy. Identifying biomarkers for predicting those tumors able to progress is a key goal for patient outcome improvement. This study focuses on the most promising prognostic markers.

Materials and methods
TP53 and FGFR3 mutational status, Survivin, CK19, CK20, E-cadherin and CD44 gene expression analysis were performed on 66 BCs.

Results
Survivin was found associated to tumor grade (p<0.05). Moreover, Survivin correlated with CD44 in TP53 wild type (p = 0.0242) and FGFR3 wild type (p = 0.0036) tumors. In particular the Survivin-CD44 correlation was associated to HG FGFR3 wild type BCs (p = 0.0045).

Unsupervised hierarchical clustering based on gene expression data identified four distinct molecular groups reflecting the patient histology (p = 0.038).

Conclusion
We suggest Survivin, both as a biomarker associated to G3 BCs but negatively related to TP53 mutational status, and as a potential novel therapeutic target.
Tight Junction Proteins and Signaling Pathways in Cancer and Inflammation: A Functional Crosstalk

Ajaz A. Bhat, Srijayaprakash Uppada, Iman W. Achkar, Sheema Hashem, Santosh K. Yadav, Muralitharan Shanmugakonar, Hamda A. Al-Naemi, Mohammad Haris, and Shahab Uddin

The ability of epithelial cells to organize through cell-cell adhesion into a functioning epithelium serves the purpose of a tight epithelial protective barrier. Contacts between adjacent cells are made up of tight junctions (TJ), adherens junctions (AJ), and desmosomes with unique cellular functions and a complex molecular composition. These proteins mediate firm mechanical stability, serves as a gatekeeper for the paracellular pathway, and helps in preserving tissue homeostasis. TJ proteins are involved in maintaining cell polarity, in establishing organ-specific apical domains and also in recruiting signaling proteins involved in the regulation of various important cellular functions including proliferation, differentiation, and migration. As a vital component of the epithelial barrier, TJs are under a constant threat from proinflammatory mediators, pathogenic viruses and bacteria, aiding inflammation and the development of disease. Inflammatory bowel disease (IBD) patients reveal loss of TJ barrier function, increased levels of proinflammatory cytokines, and immune dysregulation; yet, the relationship between these events is partly understood. Although TJ barrier defects are inadequate to cause experimental IBD, mucosal immune activation is changed in response to augmented epithelial permeability. Thus, the current studies suggest that altered barrier function may predispose or increase disease progression and therapies targeted to specifically restore the barrier function may provide a substitute or supplement to immunologic-based therapies. This review provides a brief introduction about the TJs, AJs, structure and function of TJ proteins. The link between TJ proteins and key signaling pathways in cell proliferation, transformation, and metastasis is discussed thoroughly. We also discuss the compromised intestinal TJ integrity under inflammatory conditions, and the signaling mechanisms involved that bridge inflammation and cancer.

Keywords: tight junction, claudin, signaling molecules, tumor, metastasis

INTRODUCTION

Epithelial and endothelial cells serve as sentries in most of the living systems by providing protective barriers to the various organs from their surroundings and help maintaining homeostasis (Gibson and Perrimon, 2003; Marchiando et al., 2010a; Cheng and Mruk, 2012). These protective barriers are categorized as tight junctions (TJs), adherens junctions (AJs), and desmosomes. Proteins in...
A prospective cohort for the investigation of alteration in temporal transcriptional and microbiome trajectories preceding preterm birth: a study protocol


ABSTRACT

Introduction
Preterm birth (PTB) results from heterogeneous influences and is a major contributor to neonatal mortality and morbidity that continues to have adverse effects on infants beyond the neonatal period. This protocol describes the procedures to determine molecular signatures predictive of PTB through high-frequency sampling during pregnancy, at delivery and the postpartum period.

Methods and analysis
Four hundred first trimester pregnant women from either Myanmar or Thailand of either Karen or Burman ethnicity, with a viable, singleton pregnancy will be enrolled in this non-interventional, prospective pregnancy birth cohort study and will be followed through to the postpartum period. Fortnightly finger prick capillary blood sampling will allow the monitoring of genome-wide transcript abundance in whole blood. Collection of stool samples and vaginal swabs each trimester, at delivery and postpartum will allow monitoring of intestinal and vaginal microbial composition. In a nested case–control analysis, perturbations of transcript abundance in capillary blood as well as longitudinal changes of the gut, vaginal and oral microbiome will be compared between mothers giving birth to preterm and matched cases giving birth to term neonates. Placenta tissue of preterm and term neonates will be used to determine bacterial colonisation as well as for the establishment of coding and non-coding RNA profiles. In addition, RNA profiles of circulating, non-coding RNA in cord blood serum will be compared with those of maternal peripheral blood serum at time of delivery.

Ethics and dissemination
This research protocol aims to detect perturbations in molecular trajectories preceding adverse pregnancy outcomes was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University in Bangkok, Thailand (Ethics Reference: TMEC 15–062), the Oxford Tropical Research Ethics Committee (Ethics Reference: OxTREC 33–15) and the local Tak Province Community Ethics Advisory Board. The results of this cooperative project will be disseminated in multiple publications staggered over time in international peer-reviewed scientific journals.

Trial registration number
NCT02797327; Pre-results.
Spectrum of clinical heterogeneity of β-tubulin TUBB5 gene mutations

I. Madrigal⁎,1, R. Rabionet1, M.I. Alvarez-Mora, A. Sanchez, L. Rodríguez-Revenga, X. Estivill, M. Mila

A. Centre for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Barcelona, Spain
B. Centre for Genomic Regulation (CRG), Barcelona, Spain
C. Institute of Research Sant Joan de Dú, University of Barcelona, Spain
D. Institute of Biomedicine of the Universitat de Barcelona (IBUB), University of Barcelona, Spain
E. Dept. Genetica, Microbiologia & Estadística, Faculty of Biology, University of Barcelona, Spain
F. Sidra Medicine Research Center, Sidra Medicine, Doha, Qatar

ABSTRACT

Microcephaly is a rare condition in which the occipitofrontal circumference in a child is more than two standard deviations below the mean of children of the same age and gender. It is mainly caused by genetic abnormalities that interfere with the growth of the cerebral cortex during early months of fetal development. We present a case of a 12-year-old patient with microcephaly. To identify a possible genetic origin of the phenotype, we performed array CGH and exome sequencing in the patient. Exome sequencing revealed the presence of a de novo missense mutation in the TUBB5 gene (E401K). Mutations in the TUBB5 are mainly responsible for microcephaly but the clinical spectrum is wide, from patients with severe developmental delay, and the presence of different brain malformations, to patients with only slightly cognitive impairment and normal motor development. Our patient shows a milder phenotype than other patients carrying the same mutation. These differences in the clinical features suggest that other factors, presumably genetic or epigenetic, could be modulating clinical expressivity of TUBB5. It is therefore evident that more functional studies are needed to understand the pathology that underlies the clinical spectrum of tubulin associated disease states.

1. Introduction

The development of the cerebral cortex involves a complex series of highly regulated steps to generate the laminated structure of the adult neocortex. Newborn neurons migrate, differentiate, form their dendrites and axons, and establish neuronal connections at the correct time and place in the central nervous system during embryogenesis (Kriegstein and Noctor, 2004). Perturbation of these processes may lead to malformation of cerebellar cortex and malfunction. Microcephaly is a rare condition in which the occipitofrontal circumference (OFC) in a child is > 2 SD below the mean in children of the same age and gender (World Health Organization, n.d.). Many children born with microcephaly go on to develop epilepsy, cerebral palsy, learning disabilities, hearing loss and vision problems, but in some cases, children may present with microcephaly as an isolated feature (Heney et al., 1992; Woods et al., 2005; Chacon-Camacho et al., 2015). Microcephaly may be caused by genetic abnormalities, certain viruses, exposure to drugs, alcohol or certain toxic chemicals during pregnancy and postnatal damaging to the developing brain tissue. According to an evidence-based review on evaluation of children with microcephaly, hundreds of different syndromes include microcephaly among their characteristics. Genetic causes of microcephaly involve either chromosomal abnormalities or specific gene defects (Von der Hagen et al., 2014). Romero and collaborators have recently reviewed the genetics mechanisms leading to human cortical malformations (Romero et al., 2018). Among all described genes, > 20 are responsible for cortical...
Whole-methylome analysis of circulating monocytes in acute diabetic Charcot foot reveals differentially methylated genes involved in the formation of osteoclasts

Jennifer Pasquier1,2,3, Mark Spurgeon1,2,3, Martina Bradic2, Binitha Thomas1, Amal Robay1,3, Omar Chidiac2, Marie-Joe Dib1, Rebal Turjoman1, Alexandra Liberska3, Michelle Staadt1, Khalid A Fakhro1,4, Robert Menzies1, Amin Jayyousi8, Mahmoud Zirie8, Jassim Al Suwaidi6, Rayaz A Malik10, Talal Talal7, Arash Rafii2,3, Jason Mezey3,4, Juan Rodriguez-Flores3,4, Ronald G Crystal3 & Charbel Abi Khalil*1,3,9,10

1Epigenetics Cardiovascular Laboratory, Department of Genetic Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar
2Stem Cell and Microenvironment Laboratory, Department of Genetic Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar
3Department of Genetic Medicine, Weill Cornell Medicine, NY, NY-10021, USA
4Department of Biological Statistics and Computational Biology, Cornell University, Ithica, NY, NY-14850, USA
5Flow Cytometry Facility, Microscopy Core, Weill Cornell Medicine-Qatar, Doha, Qatar
6Department of Human Genetics, Sidra Medical and Research Center, Doha, Qatar
7Department of Podiatry, Hamad Medical Corporation, Doha, Qatar
8Department of Diabetes and Endocrinology, Hamad Medical Corporation, Doha, Qatar
9Heart Hospital, Hamad Medical Corporation, Doha, Qatar
10Joan and Sanford I. Weill Department of Medicine, Weill Cornell Medicine, NY, NY-10021, USA

Aim: To assess whether DNA methylation of monocytes play a role in the development of acute diabetic Charcot foot (CF).

Patients & methods: We studied the whole methylome (WM) of circulating monocytes in 18 patients with Type 2 diabetes (T2D) and acute CF, 18 T2D patients with equivalent neuropathy and 18 T2D patients without neuropathy, using the enhanced reduced representation bisulfite sequencing technique. Results & conclusion: WM analysis demonstrated that CF monocytes are differentially methylated compared with non-CF monocytes, in both CpG-site and gene-mapped analysis approaches. Among the methylated genes, several are involved in the migration process during monocyte differentiation into osteoclasts or are indirectly involved through the regulation of inflammatory pathways. Finally, we demonstrated an association between methylation and gene expression in cis- and trans-association.

First draft submitted: 5 September 2018; Accepted for publication: 16 October 2018; Published online: 1 November 2018

Keywords: Charcot foot • diabetes • DNA methylation • epigenetics • epigenomics • gene expression • genetics

Charcot foot (CF) disease is a devastating complication of diabetes, associated with an increased risk of soft tissue infections, foot ulcers and amputations [1]. It is characterized by an exaggerated bone resorption [2], believed to be induced by an increased numbers of osteoclasts and their activity [3,4]. Osteoclasts are derived from monocytes, mostly from CD14+ that have the highest potential to differentiate, following a differentiation pathway that results in mature functional osteoclasts whose role is to activate bone resorption [5].

Epigenetics modulates the differentiation of many adult cell types from the progenitor or primary cells with whom they share the same DNA sequence, and plays an important role in gene transcription through three major components: DNA methylation, noncoding RNAs and post-translational changes of histone proteins [6]. Methylome, which is the set of nuclear acid methylation modifications in an organism's genome or in a particular cell [7], also participate in the pathophysiology of several diseases by controlling cellular differentiation processes and transcriptional activities of genes [8]. Therefore, we hypothesized that the methylome of circulating monocytes in patients with acute diabetic CF could be involved in the pathogenesis of the disease.
Systemic translocation of *Staphylococcus* drives autoantibody production in HIV disease

Zhenwu Luo1, Min Li1, Yongxia Wu1, Zhefeng Meng2, Lisa Martin3, Lumin Zhang4, Elizabeth Ogunrinde1, Zejun Zhou1, Shenghui Qin1, Zhuang Wan1, Maria Anna Julia Westerink1, Stephanie Warth1, Hui Liu2, Ping Jin5, David Stroncek2, Quan-Zhen Li6, Ena Wang7, Xueling Wu8, Sonya L. Heath9, Zihai Li1, Alexander V. Alekseyenko10 and Wei Jiang1,9,9

Abstract

**Background:** Increased autoreactive antibodies have been reported in HIV disease; however, the mechanism accounting for autoantibody induction in HIV remains unknown.

**Results:** Herein, we show that seasonal influenza vaccination induces autoantibody production (e.g., IgG antinuclear antibody (ANA) and anti-double-stranded DNA antibody (anti-dsDNA)) in some viral-suppressed antiretroviral therapy (ART)-treated HIV+ subjects, but not in healthy controls. These autoantibodies were not derived from antigen-specific B cells but from activated “bystander” B cells analyzed by single-cell assay and by study of purified polyclonal ANAs from plasma. To explore the mechanism of autoantibody generation in HIV+ subjects, plasma level of microbial products, gene expression profile of B cells, and B cell receptor (BCR) repertoires were analyzed. We found that autoantibody production was associated with increased plasma level of microbial translocation; the patients with high autoantibodies had skewed B cell repertoires and upregulation of genes related to innate immune activation in response to microbial translocation. By analyzing circulating microbial 16S rDNA in plasma, the relative abundance of *Staphylococcus* was found to be associated with autoantibody production in HIV+ subjects. Finally, we found that injection of heat-killed *Staphylococcus aureus* promoted germinal center B cell responses and autoantibody production in mice, consistent with the notion that autoantibody production in HIV+ patients is triggered by microbial products.

**Conclusions:** Our results showed that translocation of *Staphylococcus* can promote B cell activation through enhancing germinal center response and induces autoantibody production. It uncovers a potential mechanism linking microbial translocation and autoimmunity in HIV+ disease and provides a strong rationale for targeting *Staphylococcus* to prevent autoantibody production.

**Keywords:** Autoantibodies, *Staphylococcus*, Plasma microbial 16S rDNA
The Genetic and Molecular Mechanisms of Congenital Hyperinsulinism

Sonya Galcheva 1, Hüseyin Demirbilek 2, Sara Al-Khawaga 3 and Khalid Hussain 3*

1 Department of Paediatrics, University Hospital St. Marina, Varna Medical University, Varna, Bulgaria, 2 Department of Paediatric Endocrinology, Hacettepe University Faculty of Medicine, Ankara, Turkey, 3 Division of Endocrinology, Department of Paediatric Medicine, Sidra Medicine, Doha, Qatar

Congenital hyperinsulinism (CHI) is a heterogenous and complex disorder in which the unregulated insulin secretion from pancreatic beta-cells leads to hyperinsulinaemic hypoglycaemia. The severity of hypoglycaemia varies depending on the underlying molecular mechanism and genetic defects. The genetic and molecular causes of CHI include defects in pivotal pathways regulating the secretion of insulin from the beta-cell. Broadly these genetic defects leading to unregulated insulin secretion can be grouped into four main categories. The first group consists of defects in the pancreatic KATP channel genes (ABCC8 and KCNJ11). The second and third categories of conditions are enzymatic defects (such as GDH, GCK, HADH) and defects in transcription factors (for example HNF1α, HNF4α) leading to changes in nutrient flux into metabolic pathways which converge on insulin secretion. Lastly, a large number of genetic syndromes are now linked to hyperinsulinaemic hypoglycaemia. As the molecular and genetic basis of CHI has expanded over the last few years, this review aims to provide an up-to-date knowledge on the genetic causes of CHI.

Keywords: hyperinsulinism, hypoglycaemia, molecular mechanisms, genetics, mutation

INTRODUCTION

Congenital hyperinsulinism (CHI) is a heterogeneous and complex biochemical disorder which is characterized by the dysregulated release of insulin from pancreatic β-cell (1). In normal physiological state, the secretion of insulin is tightly coupled to glucose metabolism within the β-cell so that the insulin release is regulated to keep the plasma glucose concentration around 3.5–5.5 mmol/L. However, in CHI the secretion of insulin becomes unrelated to glucose metabolism, so that there is inappropriate insulin release for the plasma glucose level (2).

The genetic and molecular cause of CHI includes defects in key genes regulating insulin secretion from the pancreatic β-cell. Molecular defects in previously described genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A, HNF1A, HK1, PGM1, and PMM2) have been reported (3). However, recent studies have linked the role of other genes (CACNA1D, FOXA2) to hyperinsulinaemic hypoglycaemia (HH) but in some of these cases the underlying molecular mechanisms are still not fully elucidated (Table 1). Understanding the molecular mechanisms of CHI due to these genetic abnormalities has provided unique insight into the normal physiological mechanisms which regulate the insulin release.
Next Generation Sequencing and Animal Models Reveal SLC9A3R1 as a New Gene Involved in Human Age-Related Hearing Loss

Giorgia Girotto1,2*, Anna Morgan1,2, Navaneethakrishnan Krishnamoorthy3,4, Massimiliano Cocca2, Marco Brumat1,2, Sissy Bassani1,2, Martina La Bianca2, Mariateresa Di Stazio1,2 and Paolo Gasparini1,2

1 Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy, 2 Institute for Maternal and Child Health – IRCCS “Burlo Garofolo”, Trieste, Italy, 3 Sidra Medical and Research Center, Doha, Qatar, 4 Heart Science Centre, National Heart and Lung Institute, Imperial College London, London, United Kingdom

Age-related hearing loss (ARHL) is the most common sensory impairment in the elderly affecting millions of people worldwide. To shed light on the genetics of ARHL, a large cohort of 464 Italian patients has been deeply characterized at clinical and molecular level. In particular, 46 candidate genes, selected on the basis of genome-wide association studies (GWAS), animal models and literature updates, were analyzed by targeted re-sequencing. After filtering and prioritization steps, SLC9A3R1 has been identified as a strong candidate and then validated by “in vitro” and “in vivo” studies. Briefly, a rare (MAF: 2.886e-5) missense variant c.539G>A, p.(R180Q) was detected in two unrelated male patients affected by ARHL characterized by a severe to profound high-frequency hearing loss. The variant, predicted as damaging, was not present in healthy matched controls. Protein modeling confirmed the pathogenic effect of p.(R180Q) variant on protein’s structure leading to a change in the total number of hydrogen bonds. In situ hybridization showed slc9a3r1 expression in zebrafish inner ear. A zebrafish knock-in model, generated by CRISPR-Cas9 technology, revealed a reduced auditory response at all frequencies in slc9a3r1R180Q/R180Q mutants compared to slc9a3r1+/+ and slc9a3r1+/R180Q animals. Moreover, a significant reduction (5.8%) in the total volume of the saccular otolith (which is responsible for sound detection) was observed in slc9a3r1R180Q/R180Q compared to slc9a3r1+/+ (P = 0.0014), while the utricular otolith, necessary for balance, was not affected in agreement with the human phenotype. Overall, these data strongly support the role of SLC9A3R1 gene in the pathogenesis of ARHL opening new perspectives in terms of diagnosis, prevention and treatment.

Keywords: hearing loss, new gene discovery, zebrafish model, CRISPR-Cas9, next-generation sequencing
Biallelic loss-of-function LACC1/FAMIN Mutations Presenting as Rheumatoid Factor-Negative Polyarticular Juvenile Idiopathic Arthritis

Raquel Rabionet1,4, Agustín Remesal1, Anna Mensa-Vilaró2, Sara Murias3, Rosa Alcobendas5, Eva González-Roca3, Estibaliz Ruíz-Ortiz1,6, Jordi Antó3,7, Estibaliz Iglesias3, Consuelo Modesto5, David Comas5, Anna Puig3, Oliver Drechsler8, Stephan Ossowski9, Jordi Yagüe4, Rosa Merino4, Xavier Estivill1,9 & Juan I. Aroestegui5

Juvenile idiopathic arthritis (JIA) is a complex rheumatic disease with both autoimmune and autoinflammatory components. Recently, familial cases of systemic-onset JIA have been attributed to mutations in LACC1/FAMIN. We describe three affected siblings from a Moroccan consanguineous family with an early-onset chronic, symmetric and erosive arthritis previously diagnosed as rheumatoid factor (RF)-negative polyarticular JIA. Autozygosity mapping identified four homozygous regions shared by all patients, located in chromosomes 3, 6 (n:2) and 13, containing over 330 genes. Subsequent whole exome sequencing identified two potential candidate variants within these regions (in FARS2 and LACC1/FAMIN). Genotyping of a cohort of healthy Moroccan individuals (n: 352) and bioinformatics analyses finally supported the frameshift c.128-129delGT mutation in the LACC1/FAMIN gene, leading to a truncated protein (p.Cys43Tryfs*6), as the most probable causative gene defect. Additional targeted sequencing studies performed in patients with systemic-onset JIA (n:23) and RF-negative polyarticular JIA (n: 44) revealed no pathogenic LACC1/FAMIN mutations. Our findings support the homozygous genotype in the LACC1/FAMIN gene as the defect underlying the family here described with a recessively inherited severe inflammatory joint disease. Our evidence provides further support to the involvement of LACC1/FAMIN deficiency in different types of JIA in addition to the initially described systemic-onset JIA.

Juvenile idiopathic arthritis (JIA) refers to an arthritis of unknown origin, starting before the 16th birthday and lasting for at least 6 weeks. It represents the most common pediatric rheumatic condition. Its diagnosis relies on the criteria of the International League of Associations of Rheumatology, defining seven different subtypes: Systemic onset JIA (Still's disease), oligoarticular, rheumatoid factor (RF)-positive polyarticular, RF-negative polyarticular, enthesitis-related, psoriatic and undifferentiated arthritis. All JIA subtypes are genetically complex disorders...
Clinical exome sequencing in 509 Middle Eastern families with suspected Mendelian diseases: The Qatari experience

Nader Al-Dewik1,2 | Howaida Mohd1 | Mariam Al-Mureikhi1 | Rehab Ali1 | Fatma Al-Mesaifri1 | Laila Mahmoud1 | Noora Shahbeck1 | Karen El-Akouri1 | Mariam Almulla1 | Reem Al Sulaiman1 | Sara Musa1 | Ajayeb Al-Nabet Al-Marri3 | Gabriele Richard4 | Jane Juusola4 | Benjamin D. Solomon4 | Fowzan S. Alkuraya5,6 | Tawfeg Ben-Omran1,7,8

1Clinical and Metabolic Genetics, Department of Pediatrics, Hamad Medical Corporation, Doha, Qatar
2College of Health and Life Sciences, Hamad Bin Khalifa University (HBKU), Doha, Qatar
3Laboratory Medicine and Pathology, Hamad Medical Corporation, Qatar
4Clinical Genomics Program, GeneDx, Inc., Gaithersburg, Maryland, USA
5Department of Genetics, Research Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
6Department of Anatomy and Cell Biology, College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
7Department of pediatric, Weill Cornell Medical College, Doha, Qatar
8Division of Genetic & Genomics Medicine, Sidra Medicine, Doha, Qatar

Background: Clinical exome sequencing (CES) is rapidly becoming the diagnostic test of choice in patients with suspected Mendelian diseases especially those that are heterogeneous in etiology and clinical presentation. Reporting large CES series can inform guidelines on best practices for test utilization, and improves accuracy of variant interpretation through clinically-oriented data sharing.

Methods: This is a retrospective series of 509 probands from Qatar who underwent singleton or trio CES either as a reflex or naïve (first-tier) test from April 2014 to December 2016 for various clinical indications.

Results: The CES diagnostic yield for the overall cohort was 48.3% (n = 246). Dual molecular diagnoses were observed in 2.1% of cases; nearly all of whom (91%) were consanguineous. We report compelling variants in 11 genes with no established Mendelian phenotypes. Unlike reflex-WES, naïve WES was associated with a significantly shorter diagnostic time (3 months vs. 18 months, p < 0.0001).

Conclusion: Middle Eastern patients tend to have a higher yield from CES than outbred populations, which has important implications in test choice especially early in the diagnostic process. The relatively high diagnostic rate is likely related to the predominance of recessive diagnoses (60%) since consanguinity and positive family history were strong predictors of a positive CES.

KEYWORDS
Arab, clinical exome sequencing, consanguinity, Mendelian diseases, Middle East, Qatar
Extracellular vesicles-mediated intercellular communication: roles in the tumor microenvironment and anti-cancer drug resistance

Selma Maacha1, Ajaz A. Bhat1, Lizandra Jimenez2, Afsheen Raza3, Mohammad Haris3,4, Shahab Uddin5 and Jean-Charles Grivel1*

Abstract
The tumor microenvironment represents a complex network, in which tumor cells not only communicate with each other but also with stromal and immune cells. Current research has demonstrated the vital role of the tumor microenvironment in supporting tumor phenotype via a sophisticated system of intercellular communication through direct cell-to-cell contact or by classical paracrine signaling loops of cytokines or growth factors. Recently, extracellular vesicles have emerged as an important mechanism of cellular interchange of bioactive molecules. Extracellular vesicles isolated from tumor and stromal cells have been implicated in various steps of tumor progression, such as proliferation, angiogenesis, metastasis, and drug resistance. Inhibition of extracellular vesicles secretion, and thus of the transfer of oncogenic molecules, holds promise for preventing tumor growth and drug resistance. This review focuses on the role of extracellular vesicles in modulating the tumor microenvironment by addressing different aspects of the bidirectional interactions among tumor and tumor-associated cells. The contribution of extracellular vesicles to drug resistance will also be discussed as well as therapeutic strategies targeting extracellular vesicles production for the treatment of cancer.

Keywords: Tumor microenvironment, Stroma, Metastasis, Extracellular vesicles, Drug resistance

Background
The last decades have revealed that the malignant properties and progression of tumors are not controlled by cancer cells exclusively [1]. The area surrounding the tumor contains various non-malignant cell types, including fibroblasts, lymphocytes, inflammatory cells, endothelial cells, adipose tissue, and mesenchymal stem cells [1]. In the early stages of tumorigenesis, the microenvironment displays anti-tumor immunity and controls tumor growth [2]. As the tumor continues to develop, the role of the microenvironment shifts over to be tumor promotive [2]. Cells found in the tumor microenvironment (TME) have been recognized as key regulators of tumor promotion by providing mitogenic growth factors, growth inhibitory signals or trophic factors [2].

*Correspondence: jsjima@sidra.org
1Division of Translational Medicine, Sidra Medicine, PO BOX 36999, Doha, Qatar
Full list of author information is available at the end of the article.

The complex heterotypic interactions between tumor cells and non-cancerous cells within the TME occur through direct contact between cells or paracrine signal exchange of cytokines and growth factors [2]. The most well-recognized cell-to-cell interaction within the TME is between tumor cells and macrophages or fibroblasts [2]. Macrophages play an integral role in host innate immune response against infections [3]. Tumor cells release factors, such as vascular endothelial growth factor (VEGF), colony stimulating factor 1 (CSF1), and platelet-derived growth factor (PDGF), that aid in the recruitment of macrophages to tumors [3]. Once the macrophages are recruited to the tumor, they can promote tumor progression by enhancing tumor cell proliferation, as well as by remodeling the tumor stroma to facilitate invasion and angiogenesis [3]. Fibroblasts are responsible for the production of extracellular matrix (ECM), such as collagen and fibronectin, and facilitate remodeling in wound healing [4]. Cancer-associated fibroblasts (CAFs)

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DATA NOTE
A curated transcriptome dataset collection to investigate the blood transcriptional response to viral respiratory tract infection and vaccination. [version 1; peer review: 2 approved]

Salim Bougarn, Sabri Boughorbel, Damien Chaussabel, Nico Marr
Systems Biology and Immunology Department, Sidra Medicine, Doha, Qatar

Abstract
The human immune defense mechanisms and factors associated with good versus poor health outcomes following viral respiratory tract infections (VRTI), as well as correlates of protection following vaccination against respiratory viruses, remain incompletely understood. To shed further light into these mechanisms, a number of systems-scale studies have been conducted to measure transcriptional changes in blood leukocytes of either naturally or experimentally infected individuals, or in individual’s post-vaccination. Here we are making available a public repository, for research investigators for interpretation, a collection of transcriptome datasets obtained from human whole blood and peripheral blood mononuclear cells (PBMC) to investigate the transcriptional responses following viral respiratory tract infection or vaccination against respiratory viruses. In total, Thirty one datasets, associated to viral respiratory tract infections and their related vaccination studies, were identified and retrieved from the NCBI Gene Expression Omnibus (GEO) and loaded in a custom web application designed for interactive query and visualization of integrated large-scale data. Quality control checks, using relevant biological markers, were performed. Multiple sample groupings and rank lists were created to facilitate dataset query and interpretation. Via this interface, users can generate web links to customized graphical views, which may be subsequently inserted into manuscripts to report novel findings. The GXB tool enables browsing of a single gene across projects, providing new perspectives on the role of a given molecule across biological systems in the diagnostic and prognostic following VRTI but also in identifying new correlates of protection. This dataset collection is available at: http://vri1.gxbsidra.org/dm3/geneBrowser/list.

Keywords
Transcriptomics, Bioinformatics, Software, Viral respiratory infection, Influenza viruses, Respiratory syncytial viruses (RSV), Rhinoviruses, Whole Blood, PBMC.

This article is included in the Sidra Medicine gateway.
Intramuscular injection of collagenase clostridium histolyticum may decrease spastic muscle contracture for children with cerebral palsy

Jason J. Howard MD*, James S. Huntley MBBS*, H. Kerr Graham MBBS**, Walter L. Herzog PhD***

*Division of Orthopedic Surgery Weill Cornell Medicine, Sidra Medicine, Doha, Qatar
**Department of Orthopedics, Royal Children’s Hospital, Melbourne, Australia
***Faculty of Kinesiology, University of Calgary, Calgary, Alberta, Canada

Corresponding Author:
Jason J. Howard
Division of Orthopedic Surgery
Department of Surgery
Weill Cornell Medicine
Sidra Medicine
Doha, Qatar
Email: jason.howard@me.com
Mobile: +974-7049-1687
Abstract

In cerebral palsy (CP), the spastic motor type is most common, associated with a velocity-dependent increase in muscle stiffness that precedes the development of fixed muscle contracture – a permanent shortening of the muscle tendon unit even when relaxed. Intra-muscular injections of botulinum toxin type A (BTX-A) have become popular for the treatment of spastic muscle contractures but unfortunately its use has not resulted in long-term functional benefits and, paradoxically, has been associated with a persistent loss of contractile material. Recent biomechanical work has shown that the stiffness of the CP muscle increases in proportion to total collagen content within the perimysial extra-cellular matrix. Thus, rather than the use of tone-reducing agents, we hypothesize that the focal use of a selective collagenase, injected into spastic muscle at an appropriate dilution and concentration, may serve to reduce the extent of muscle contracture, improving clinical range of motion and perhaps sarcomere length.
INTRODUCTION

The declining cost and increasing availability of next-generation DNA sequencing technologies has enabled the discovery of the genetic defects underlying many new Mendelian disorders, especially monogenic immune disorders. Although autoimmune diseases are generally considered polygenic, there have been a growing number of rare, monogenic autoimmune disorders in which the causative genetic defects have been identified. The study of these disorders has facilitated a deeper understanding of the mechanisms involved in immune regulation and tolerance, especially in the role and function of regulatory T cells (Tregs). Defects in various genes have been found to lead to Treg impairment, resulting in overlapping clinical disease features, one of the most prominent being inflammatory bowel-like (IBD-like) disease (Figure 1).

LESSONS FROM THE TREG DISORDERS

Inflammatory bowel disease (IBD), which includes Crohn’s disease and ulcerative colitis, is considered the result of a dysregulated immune response to the gut microbiota, causing chronic mucosal inflammation and ultimately resulting in mucosal tissue damage. IBD is generally a complex, polygenic disorder. However, monogenic diseases with Treg loss or impairment result in IBD-like disease, indicating the importance of Tregs in maintaining homeostasis at the mucosal interface between the host and microbiome. Here, we offer our perspective on these monogenic autoimmune disorders, highlighting their overlapping clinical features with inflammatory bowel disease.

Summary

Recently, several studies have investigated a number of rare monogenic autoimmune disorders, in which the causative genetic defects were identified and found to affect the development or function of regulatory T cells (Tregs). The studies of these disorders have facilitated a deeper understanding of the mechanisms involved in immune regulation and tolerance. Furthermore, these studies have highlighted the importance of Tregs in maintaining homeostasis at the mucosal interface between the host and microbiome.

KEYWORDS

CHAI, IBD, IL-10, IPEX, LATAIE, Treg

This article is part of a series of reviews covering Lessons primary immunodeficiencies teach about the healthy and diseased immune system appearing in Volume 287 of Immunological Reviews.
Whole genome sequencing for improved understanding of Mycobacterium tuberculosis transmission in a remote circumpolar region


1School of Population and Public Health, University of British Columbia, Vancouver, Canada; 2Yukon Communicable Disease Control, Health and Social Services, Government of Yukon, Whitehorse, Canada; 3British Columbia Centre for Disease Control, Vancouver, Canada; 4British Columbia Centre for Disease Control, Public Health Laboratory, Vancouver, Canada; 5Department of Pathology, Sidra Medical and Research Center, Doha, Qatar; 6Department of Health and Social Services, Government of Yukon, Whitehorse, Canada and 7Department of Medicine, University of British Columbia, Vancouver, Canada

Abstract
Few studies have used genomic epidemiology to understand tuberculosis (TB) transmission in rural and remote settings – regions often unique in history, geography and demographics. To improve our understanding of TB transmission dynamics in Yukon Territory (YT), a circumpolar Canadian territory, we conducted a retrospective analysis in which we combined epidemiological data collected through routine contact investigations with clinical and laboratory results. Mycobacterium tuberculosis isolates from all culture-confirmed TB cases in YT (2005–2014) were genotyped using 24-locus Mycobacterial Interspersed Repetitive Units-Variable Number of Tandem Repeats (MIRU-VNTR) and compared to each other and to those from the neighbouring province of British Columbia (BC). Whole genome sequencing (WGS) of genotypically clustered isolates revealed three sustained transmission networks within YT, two of which also involved BC isolates. While each network had distinct characteristics, all had at least one individual acting as the probable source of three or more culture-positive cases. Overall, WGS revealed that TB transmission dynamics in YT are distinct from patterns of spread in other, more remote Northern Canadian regions, and that the combination of WGS and epidemiological data can provide actionable information to local public health teams.

Introduction
Canada’s tuberculosis (TB) rate has been decreasing overall, yet rates remain elevated in particular populations and regions. Recent outbreaks in two areas of Canada’s North – Nunavik and Nunavut – resulted in annual incidence rates higher than many low-income countries [1, 2]. However, this is not the case in all circumpolar settings, where public health efforts have contributed to declining TB rates. From 2006 through 2012, Yukon Territory (YT) reported a rate of 12.1 cases per 100 000 population. While this is over twice the national average of 4.8 cases/100 000, it is the lowest rate amongst Canada’s Northern territories (25.4/100 000 in the Northwest Territories, immediately east of YT, and 194.3/100 000 in Nunavut) [2, 3]. Alaska, located west of YT, has seen a sharp decrease in cases over the last few decades, reporting an average incidence of 8.1/100 000 (2006–2012), with most cases concentrated in rural communities – many inaccessible by road [2, 4]. Thus, while northern remote settings are often viewed similarly by population and public health programmes, it is clear that with respect to TB, there are significant differences across these regions, likely explained by a combination of the robustness of regional public health, access to appropriate housing, geography, intra-community movement and the populations themselves [5]. Understanding the unique epidemiology of TB in each region is therefore vital to delivering tailored interventions to drive rates in circumpolar settings closer to the World Health Organization’s elimination goals.

Genotyping programmes have provided significant insights into the molecular epidemiology of TB in many low-incidence countries, helping to detect outbreaks [6, 7], and more recently, genome sequencing has dramatically improved our understanding of both clustering and TB transmission in communities worldwide [6–11]. However, only two studies to date have used this genomic epidemiology approach to examine transmission in remote Northern locations: one in Nunavik, Quebec [12] – an Arctic region of Canada’s North, and a second in Greenland, which used genomics to detect ‘hotspot cases’ responsible for chains of transmission [13]. To better understand the patterns of TB transmission in YT,
Successful treatment of a metastatic hepatocellular malignant neoplasm, not otherwise specified with chemotherapy and liver transplantation

Michaela S. Seng1,2 | Bligh Berry3 | Jonathan Karpelowsky4,5 | Gordon Thomas4,5 | Catherine Mews6 | Michael Stormon5,7 | Albert Shun4,5 | Catherine Cole8

1Department of Haematology and Oncology, Perth Children’s Hospital, Nedlands, Western Australia, Australia
2Department of Haematology and Oncology, KK Women’s and Children’s Hospital, Singapore, Singapore
3Department of Anatomical Pathology, Perth Children’s Hospital, Nedlands, Western Australia, Australia
4Department of Paediatric Surgery, Children’s Hospital at Westmead, Westmead, Australia
5Division of Child and Adolescent Health, University of Sydney, Sydney, Australia
6Department of Gastroenterology, Perth Children’s Hospital, Nedlands, Western Australia, Australia
7Department of Gastroenterology, Children’s Hospital at Westmead, Westmead, Australia
8Paediatric Haematology and Oncology, Sidra Medicine, Doha, Qatar

Correspondence
Catherine Cole, Chief of Paediatric Haematology and Oncology, Sidra Medicine, Doha, Qatar. Email: ccole@sidra.org
Albert Shun and Catherine Cole share senior authorship of this article.

Abstract
Hepatocellular malignant neoplasm, not otherwise specified (HCN-NOS) is a provisional entity describing a subset of rare malignant pediatric liver tumors with overlapping features of hepatoblastoma and hepatocellular carcinoma. We present a case illustration of metastatic HCN-NOS successfully treated with a backbone of hepatoblastoma chemotherapy, pulmonary metastasectomy, and liver transplantation, along with a literature review of the clinical outcomes of HCN.

KEYWORDS
hepatoblastoma with hepatocellular carcinoma features, hepatocellular malignant neoplasm, liver transplantation, NOS, transitional liver cell tumor, tumors

1 | INTRODUCTION

Hepatocellular malignant neoplasm, not otherwise specified (abbreviated herein HCN-NOS) is a rare subgroup of liver tumors with overlapping features of hepatoblastoma (HBL) and hepatocellular carcinoma (HCC), variably referred to as hepatocellular neoplasm, NOS; transitional liver cell tumor; HBL with HCC features; and hepatic embryonal malignancy, NOS. The outcomes of this rare subgroup of malignant liver tumors are now beginning to be understood through collaborative reporting.

We report a metastatic, unresectable case of HCN-NOS in good remission three years after HBL chemotherapy and liver transplantation, and conducted a literature review of clinical outcomes.

2 | CASE REPORT

An eight-year-old male, born prematurely at 27 weeks, presented with a one-month history of abdominal distension. Physical examination revealed an enlarged abdomen and a firm epigastric mass. CT abdomen revealed diffuse hepatomegaly $176 \times 197 \times 144$ mm with innumerable lesions involving all but one segment. Vascular invasion was indeterminate. His presenting alpha-fetoprotein (AFP) was 550,000 kIU/L. 18FDG-PET scan showed a low-grade FDG-avid liver tumor. CT chest revealed multiple pulmonary metastases, not discernible on 18FDG-PET (Supporting Information Figures S1A and S1B).

Prechemotherapy percutaneous liver biopsy proved complex with histological features of an HCC and a macrotrabecular variant of HBL.
Application of MALDI Biotyper System for Rapid Identification of Bacteria Isolated from a Fresh Produce Market

Israa Mohamad El-Nemr¹ · Mohanad Musthahia¹ · Sathyavathi Sundararaju² · Charmaine Fontejon² · Mohammed Suleiman² · Patrick Tang²,3 · Ipek Goktepe¹ · Mohammad Rubayet Hasan²,3

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Abstract
MALDI-TOF MS has revolutionized the identification of microorganisms and has become an indispensable part of routine diagnostics in the clinical microbiological laboratory. However, application of this technique in microbial surveillance outside of clinical settings is limited. In this study, we have evaluated the performance of a Bruker MALDI Biotyper System for the identification of bacteria isolated from the hand palms of fresh produce handlers and their surrounding environments in a wholesale fresh produce market in Doha, Qatar. The accuracy was verified against the results obtained by bacterial 16S rRNA gene sequencing. A total of 105 isolates were tested, of which 67 (64%) isolates were identified by MALDI-TOF MS and 101 isolates (96%) were identified by 16S rRNA gene sequencing, either at the genus level or species level. However, MALDI-TOF MS identified more isolates (41%) at the species level than 16S rRNA gene sequencing (28%). MALDI-TOF MS was particularly useful in the species level identification of Enterobacteriaceae. MALDI-TOF MS successfully identified most known human pathogens in a rapid and cost-effective manner but failed to identify a significant number of isolates that were of environmental origin, suggesting room for further expansion of the reference database.

Introduction

Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) is a matrix-assisted, soft-ionization principle-based mass spectrometry technique that keeps biomolecules intact after irradiation by laser pulses. The bioanaytes are then accelerated through an electrostatic field and allowed to travel, under vacuum, through a metal flight tube to reach a detector. The bioanaytes are separated by their time of flight and generate unique spectra or molecular fingerprints based on their mass to charge ratio. Although MALDI-TOF MS has been in use in chemistry for many decades, application of this technique in microbiology has recently revolutionized the way by which microorganisms are identified in clinical microbiology laboratories [1, 2]. Microbial identification is achieved by matching the mass spectra generated by peptides and proteins extracted from a specific microbial species with the reference spectra present in a database using a biostatistical scoring algorithm [3].

MALDI-TOF MS has now replaced the complex and lengthy biochemical identification processes in many clinical microbiology laboratories. It provides an easy, rapid, and low-cost means for identification of isolated bacteria and fungi from clinical samples [1, 4]. The clinical benefit of employing MALDI-TOF MS for bacterial identification is enormous, in particular, because of its ability to change the turn-around time from days to minutes, enabling early initiation of appropriate antimicrobial therapy and infection control measures. As a result, MALDI-TOF MS has come into widespread use in diagnostic microbiology over the past decade [5, 6]. The Bruker MALDI Biotyper is one of the most widely used MALDI-TOF MS systems in the market and has been extensively validated for identification of clinically important microorganisms [7–9]. However, the benefit and convenience of utilizing MALDI-TOF MS for rapid identification of microorganisms should not be limited to clinical...
Diabetes Mellitus in a Patient With Lafora Disease: Possible Links With Pancreatic β-Cell Dysfunction and Insulin Resistance

Ramona C. Nicolescu 1*, Sara Al-Khawaga 2†, Berge A. Minassian 3 and Khalid Hussain 2

1 Division of Endocrinology and Diabetes, Department of Pediatrics, University of Liège, Centre Hospitalier Régional de la Citadelle, Liège, Belgium, 2 Division of Endocrinology, Department of Pediatrics, Sidra Medicine Outpatient Clinic, Doha, Qatar, 3 Division of Neurology, Department of Pediatrics, University of Texas Southwestern, Dallas, TX, United States

Lafora disease (LD) is a rare autosomal recessive disorder characterized by progressive myoclonic epilepsy followed by continuous neurological decline, culminating in death within 10 years. LD leads to accumulation of insoluble, abnormal, glycogen–like structures called Lafora bodies (LBs). It is caused by mutations in the gene encoding glycogen phosphatase (EPM2A) or the E3 ubiquitin ligase malin (EPM2B/NHLRC1). These two proteins are involved in an intricate, however, incompletely elucidated pathway governing glycogen metabolism. The formation of EPM2A and malin signaling complex promotes the ubiquitination of proteins participating in glycogen metabolism, where dysfunctional mutations lead to the formation of LBs. Herein, we describe a 13-years-old child with LD due to a NHLRC1 (c.386C>A, p.Pro129His) mutation, who has developed diabetes mellitus and was treated with metformin. We discuss how basic mechanisms of LD could be linked to β-cell dysfunction and insulin resistance.

Keywords: Lafora disease, EPM2A, EPM2B/NHLRC1, insulin resistance, diabetes, glycogen metabolism

BACKGROUND

Lafora disease (LD; OMIM 254780) is a fatal autosomal recessive inherited disease characterized by progressive myoclonic epilepsy followed by continued neurological decline due to polyglucosan inclusion bodies (insoluble glucans) accumulation in brain and other peripheral tissues culminating in death within 10 years (1). LD is particularly frequent in countries with high rates of consanguinity such as Mediterranean, Southern India, and the Middle East. The disease is extremely rare with an estimated overall frequency of ∼4 cases per million individuals globally (2, 3). LD is caused by mutation of two genes, EPM2A encoding the glucan phosphatase laforin (a dual specificity phosphatase), and EPM2B/NHLRC1 encoding E3 ubiquitin ligase malin (2). PRDM8 mutation has also been reported in a single family as an additional gene involved in LD associated with an earlier onset disease (4).

Laforin-malin complex regulates diverse cellular pathways, including ubiquitin-proteasome system and glycogen metabolism, where their defects in these processes lead to LD. The clinical symptoms of EPM2A and NHLRC1 gene mutation are similar; however, NHLRC1 mutation patients tend to live longer than the EPM2A gene mutation (5, 6). Protein targeting to glycogen (PTG), one of the regulatory subunits of protein phosphatase 1 targeting glycogen, modulates the protein phosphatase 1 (PP1) affinity to its substrates such as the glycogen synthase (GS)
Oliguria and Acute Kidney Injury in Critically Ill Children: Implications for Diagnosis and Outcomes*

Ahmad Kaddourah, MD, MS1,2; Rajit K. Basu, MD2,3; Stuart L. Goldstein, MD2; Scott M. Sutherland, MD4; on behalf of the Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology (AWARE) Investigators

Objectives: Consensus definitions for acute kidney injury are based on changes in serum creatinine and urine output. Although the creatinine criteria have been widely applied, the contribution of the urine output criteria remains poorly understood. We evaluated these criteria individually and collectively to determine their impact on the diagnosis and outcome of severe acute kidney injury.


Patients: Critically ill children enrolled in Assessment of Worldwide Acute Kidney Injury, Renal Angina, and Epidemiology database.

Measurement: To assess the differential impact of creatinine and urine output criteria on severe acute kidney injury (Kidney Disease: Improving Global Outcomes stage ≥ 2). Patients were divided into four cohorts: no severe acute kidney injury, severe acute kidney injury by creatinine criteria only, severe acute kidney injury by urine output criteria only, and severe acute kidney injury by both creatinine and urine output criteria.

Results: Severe acute kidney injury occurred in 496 of 3,318 children (14.9%); 343 (69.2%) were creatinine criteria only, 90 (18.1%) were urine output criteria only, and 63 (12.7%) were both creatinine and urine output criteria. Twenty-eight-day mortality for children with severe acute kidney injury by urine output criteria only, to 165.7 (95% CI, 86.3–318.2) in both creatinine and urine output criteria. Twenty-eight-day mortality for children with severe acute kidney injury by urine output criteria only, to 165.7 (95% CI, 86.3–318.2) in both creatinine and urine output criteria. Twenty-eight-day mortality for children with severe acute kidney injury by urine output criteria only, to 165.7 (95% CI, 86.3–318.2) in both creatinine and urine output criteria. Twenty-eight-day mortality for children with severe acute kidney injury by urine output criteria only, to 165.7 (95% CI, 86.3–318.2) in both creatinine and urine output criteria. Twenty-eight-day mortality for children with severe acute kidney injury by urine output criteria only, to 165.7 (95% CI, 86.3–318.2) in both creatinine and urine output criteria. Twenty-eight-day mortality for children with severe acute kidney injury by urine output criteria only, to 165.7 (95% CI, 86.3–318.2) in both creatinine and urine output criteria.

Conclusions: Nearly one in five critically ill children with acute kidney injury do not experience increase in serum creatinine. These acute kidney injury events, which are only identified by urine output criteria, are associated with comparably poor outcomes as those diagnosed by changes in creatinine. Children meeting both criteria had worse outcomes than those meeting only one. We suggest oliguria represents a risk factor for poorer outcomes among children who develop acute kidney injury. Application of...
A survey of clinical laboratory instrument verification in the UK and New Zealand

Matthew Hand¹, Andrea Crampton², Annette Thomas³ and Eric S. Kilpatrick¹,⁴ and on behalf of the ACB National Audit Group

¹ Sidra Medicine, Doha, Qatar
² Charles Sturt University, Wagga Wagga, NSW, Australia
³ Weqas, Cardiff and Vale University Health Board, Cardiff, Wales
⁴ Weill Cornell Medicine, Doha, Qatar

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Correspondence to:
Eric S. Kilpatrick MD FRCPath FRCP Ed
Professor of Pathology and Laboratory Medicine
Weill Cornell Medicine
Division Chief, Clinical Biochemistry
Department of Pathology
Sidra Medicine
Doha, Qatar
Email ekilpatrick@sidra.org

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Ethical approval

The survey was approved by the Faculty of Science Human Low Risk Ethics Committee at Charles Sturt University, Bathurst, NSW, Australia (Reference # 400/2017/1).

Guarantor

Matthew Hand

Contributorship

MH, ESK and AC conceived the study and its design. AT facilitated the circulation of the questionnaire. MH performed the data analysis and wrote the paper with amendments from all other authors.

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Abstract

Background: Clinical laboratory instrument verification testing is often an accreditation requirement. However, it is not known what verification procedures are in routine use or how often the process identifies problems which need addressing prior to testing clinical samples.

Objective: To investigate which standards are currently being used for laboratory verification in UK and New Zealand (NZ) clinical laboratories, and to help establish if the activity justifies the effort required.

Methods: A survey of verification of clinical laboratory instrumentation was distributed to members of the Association for Clinical Biochemistry and Laboratory Medicine and New Zealand Institute of Medical Laboratory Scientists. The survey consisted of questions on the verification elements used and whether acceptance criteria were met.

Results: 19/72 (26%) of responders only used organisation developed protocols for verification, 20/72 (28%) solely used national/international guidelines, while 16/72 (22%) used a combination. Manufacturers’ claims were partly or entirely used as acceptance criteria for imprecision (89%), accuracy (64%) and analytical measuring range (AMR) (94%), with these being met on 61%, 67%, and 93% of occasions respectively. For patient comparison and linearity, acceptance criteria were met by 71% and 91%. Only 27-36% undertook any troubleshooting before accepting a failed component of verification.

Conclusions: Laboratories in the UK and NZ are currently using a variety of verification standards and acceptance criteria for instrument verification. It is common for instruments to fail, especially following the assessment of imprecision and accuracy. While this suggests the process is warranted, only a minority address failed elements before accepting verification.

Keywords:

Instrument; verification; standards; UK; New Zealand
The Possible Role of Placental Morphometry in the Detection of Fetal Growth Restriction

Nastaran Salavati1, Maddy Smies2, Wessel Ganzevoort2, Adrian K. Charles3, Jan Jaap Erwich1, Torsten Plösch1 and Sanne J. Gordijn1

1 Department of Obstetrics and Gynecology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands, 2 Department of Obstetrics and Gynecology, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands, 3 Department of Anatomical Pathology, Sidra Medicine, Doha, Qatar

Fetal growth restriction (FGR) is often the result of placental insufficiency and is characterized by insufficient transplacental transport of nutrients and oxygen. The main underlying entities of placental insufficiency, the pathophysiologic mechanism, can broadly be divided into impairments in blood flow and exchange capacity over the syncytiotrophoblastic membranes of the fetal placenta villi. Fetal growth restriction is not synonymous with small for gestational age and techniques to distinguish between both are needed. Placental insufficiency has significant associations with adverse pregnancy outcomes (perinatal mortality and morbidity). Even in apparently healthy survivors, altered fetal programming may lead to long-term neurodevelopmental and metabolic effects.

Although the concept of fetal growth restriction is well appreciated in contemporary obstetrics, the appropriate detection of FGR remains an issue in clinical practice. Several approaches have aimed to improve detection, e.g., uniform definition of FGR, use of Doppler ultrasound profiles and use of growth trajectories by ultrasound fetal biometry. However, the role of placental morphometry (placental dimensions/shape and weight) deserves further exploration. This review article covers the clinical relevance of placental morphometry during pregnancy and at birth to help recognize fetuses who are growth restricted. The assessment has wide intra- and interindividual variability with various consequences. Previous studies have shown that a small placental surface area and low placental weight are associated with a slower growth of the fetus. Parameters such as placental surface area, placental volume and placental weight in relation to birth weight can help to identify FGR. In the future, a model including sophisticated antenatal placental morphometry may prove to be a clinically useful method for screening or diagnosing growth restricted fetuses, in order to provide optimal monitoring.

Keywords: FGR, IUGR, SGA, fetal growth restriction, intra uterine growth restriction, small for gestational age, placenta morphometry, birth weight

BACKGROUND

The diagnosis of fetal growth restriction (FGR) has for long mainly be based on birth weight below a reference cut-off, most commonly the 10th percentile (p10) (Beune et al., 2018). Birth weight (BW) or estimated fetal weight (EFW) below p10 indicates that the BW or EFW is within the lowest 10% of BW compared to the reference population. This is in essence not FGR but small
Obstetric violence: Clinical staff perceptions from a video of simulated practice

Thomas Gray\textsuperscript{a,}\textasteriskcentered, Suruchi Mohan\textsuperscript{b}, Stephen Lindow\textsuperscript{b}, Tom Farrell\textsuperscript{b}

\textsuperscript{a}Sheffield Teaching Hospitals NHS Foundation Trust, Jessop Wing, Tree Root Walk, Sheffield, S10 2SF, UK
\textsuperscript{b}Sidra Medicine, Sidra Outpatient Building, Al Luqta Street, Education City North Campus, Qatar Foundation, PO BOX 26999, Doha, Qatar

\textbf{Objective(s):} Obstetric Violence refers to professional deficiencies in maternity care. Examples include non-dignified care, discrimination and abandonment of care. Obstetric violence has been described in both low and high resource settings. The objective of this study was to assess knowledge and attitudes towards obstetric violence in a cohort of multinational obstetric nursing/midwifery staff and obstetricians at a private maternity hospital in Qatar.

\textbf{Study design:} An online survey for anonymous completion was sent to the hospital email accounts of obstetric nursing/midwifery staff and obstetricians at Sidra Medicine (n = 640). The survey incorporated a video showing a dramatized scenario of obstetric violence. The survey assessed the participant's demographics and knowledge of the term obstetric violence. The participants scored their perceptions on the behaviors in the video using a visual analogue scale. The participants were then asked to reflect on their own practice. Comparisons of the survey responses were made between both doctors and nursing/midwifery staff members using student's t-test.

\textbf{Results:} 50 obstetricians and 167 obstetric nursing/midwifery staff fully completed the survey. Fifty two percent had previously heard of the term obstetric violence, and 48\% could define it correctly. 136 (63\%) had witnessed obstetric violence at some point in their career. Significant differences were seen when each professional group was asked to report on the behavior of the opposite professional team as depicted in the video (p = 0.01 and p < 0.001). Doctors completing the survey were also more critical of the doctors-in-training than were the midwifery/nursing staff (p = 0.06). Obstetricians and nursing/midwifery responders identified patient dignity, privacy and patient-centred care as the leading professional deficiencies seen in the video. Obstetricians were significantly less likely to change their perceptions of how a care team should interact with a patient compared to the obstetric nursing/midwifery group (p < 0.001).

\textbf{Conclusions:} This questionnaire study demonstrates that the majority of staff in this cohort were aware of obstetric violence and able to identify negative behaviours in the video and then reflect on how this impacts care they provide. Further studies are needed to identify ways in which obstetric violence can be prevented in both low resource and high resource settings.

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\textbf{Introduction} \\
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Respectful and dignified healthcare provision is a fundamental right for every pregnant woman, leading to a positive birth experience delivered by compassionate, skilled providers. The care provided to women in childbirth varies across the globe and in many settings there are examples of non-dignified and sometimes even abusive patterns of care being provided to pregnant women. The term ‘Obstetric Violence’ was coined to reflect the ‘professional’ deficiencies in healthcare provision to pregnant women. Obstetric Violence is defined as ‘the appropriation of the
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2580-1613/© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Pediatric oncology and stem cell transplant patients with healthcare-associated *Clostridium difficile* infection were already colonized on admission

Ghada N. Al-Rawahi | Abeer Al-Najjar | Rachel McDonald | Rebecca J. Deyell | George R. Golding | Rollin Brant | Peter Tilley | Eva Thomas | Shahrad R. Rassekh | Aisling O’Gorman | Peggy Wong | Lucy Turnham | Simon Dobson

1Department of Pathology and Laboratory Medicine, University of British Columbia, British Columbia Children’s Hospital, Vancouver, British Columbia, Canada
2Pediatric Infectious Diseases, Faculty of Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia
3Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada
4Division of Pediatric Hematology/Oncology/BMT, University of British Columbia, British Columbia Children’s Hospital, Vancouver, British Columbia, Canada
5National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, Manitoba, Canada
6Department of Statistics, University of British Columbia, British Columbia Children’s Hospital Research Institute, Vancouver, British Columbia, Canada
7Department of Pathology, Sidra Medicine and Weill Cornell Medical College in Qatar, Doha, Qatar

**Correspondence**
Ghada N. Al-Rawahi, Department of Pathology and Laboratory Medicine, University of British Columbia, Children’s and Women’s Health Centre of British Columbia, Room 2G27-4500 Oak Street, Vancouver, British Columbia V6H 3N1, Canada. Email: galrawahi@cw.bc.ca

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**Abstract**

*Clostridium difficile* is the leading cause of healthcare-associated infections worldwide. The diagnosis of *C. difficile* infection (CDI) in pediatric oncology patients is complex as diarrhea is common, and there is a high rate of colonization in infants and young children. This study was conducted to assess the accuracy of the surveillance definitions of healthcare-associated CDI (HA-CDI) and to determine the prevalence of toxigenic *C. difficile* colonization among pediatric oncology and stem cell transplant patients.

**Methods:** A prospective cohort study was conducted over a three-year period in an inpatient pediatric oncology and stem cell transplant setting. Baseline stool samples were collected within three days of admission and were genotypically compared with clinically indicated samples submitted after three days of admission.

**Results:** A total of 175 patients were recruited with a total of 536 admissions. The adjusted prevalence of baseline toxigenic *C. difficile* colonization among admissions was 32.8%. Seventy-eight percent of positive admissions did not have history of CDI. Colonization with a toxigenic strain on admission was predictive of CDI ($OR = 28.6$; 95% CI, 6.58–124.39; $P < 0.001$). Nearly all clinical isolates (8/9) shared identical pulsed-field gel electrophoresis patterns with baseline isolates or were closely related (1/9). Only one of the 11 cases that were considered HA-CDI was potentially nosocomially acquired.

**Conclusion:** The prevalence of colonization with toxigenic *C. difficile* in our cohort is high. Unfortunately, the current CDI surveillance definitions overestimate the incidence of HA-CDI in pediatric oncology and stem cell transplantation settings.

**KEYWORDS**

*Clostridium difficile*, colonization, healthcare-associated, pediatric oncology, transplant

**1 | INTRODUCTION**

*Clostridium difficile* is the leading cause of healthcare-associated infections worldwide. The scope of the problem has gained further recognition since the emergence and global spread of the North American pulsed-field gel electrophoresis (PFGE) type 1/ribotype 027 (NAP1/RT027) strain.$^{1,2}$
Article

A Randomized, Controlled Trial of Vitamin D Supplementation on Cardiovascular Risk Factors, Hormones, and Liver Markers in Women with Polycystic Ovary Syndrome

Zeeshan Javed 1, Maria Papageorgiou 1,2, Harshal Deshmukh 1, Eric S. Kilpatrick 3, Vincent Mann 4, Lynsey Corless 4, George Abouda 4, Alan S. Rigby 5, Stephen L. Atkin 6 and Thozhukat Sathyapalan 1,*

1 Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull HU3 2JZ, UK; Zeeshan.Javed@pkli.org.pk (Z.J.); m.papageorgiou@hull.ac.uk (M.P.); harshaldeshmukh@nhs.net (H.D.)
2 Department of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology, and Immunology, Medical University of Vienna, Vienna 1090, Austria
3 Department of Pathology, Sidra Medical and Research Centre, Doha PO Box 26999, Qatar; ekilpatrick@sidra.org
4 Gastroenterology Research Department, Hull Royal Infirmary, Hull HU3 2JZ, UK; Vincent.mann@hey.nhs.uk (V.M.); l.corless@hull.ac.uk (L.C.); George.Abouda@hey.nhs.uk (G.A.)
5 Hull York Medical School, University of Hull, Hull HU3 2JZ, UK; A.rigby@hull.ac.uk
6 Weill Cornell Medical College Qatar, Education City, Doha PO Box 24144, Qatar; sla2002@qatar-med.cornell.edu

* Correspondence: Thozhukat.Sathyapalan@hyms.ac.uk; Tel.: +44-148-267-5312

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Abstract: Polycystic ovary syndrome (PCOS) increases the risk of metabolic syndrome and non-alcoholic-fatty-liver disease (NAFLD). Vitamin D supplementation may exert positive effects on liver biochemistry in patients with NAFLD; however, its effects on PCOS are unknown. This randomized, double-blind, placebo-controlled study explored the effect of vitamin D supplementation on cardiovascular risk factors (high-sensitivity C-reactive protein (hs-CRP), weight, body mass index (BMI), lipid profile, glucose levels, insulin levels, the homeostatic model assessment-insulin resistance (HOMA-IR), hormones (free androgen index (FAI), testosterone, sex hormone binding globulin (SHBG), and liver markers (alanine aminotransferase (ALT), hyaluronic acid (HA), N-terminal pro-peptide of type III procollagen (PIIINP), tissue inhibitor of metallo-proteinases-1 (TIMP-1), and the enhanced liver fibrosis (ELF) score). Forty women with PCOS were recruited and randomized to vitamin D (3200 IU) or placebo daily for 3 months. All outcomes were measured at baseline and 3 months follow-up (FU). Greater increases in vitamin D levels were shown in the supplementation group (vitamin D, baseline: 25.6 ± 11.4 nmol/L, FU: 90.4 ± 19.5 nmol/L vs. placebo, baseline: 30.9 ± 11.1 nmol/L, FU: 47.6 ± 20.5 nmol/L, p < 0.001). Between groups comparisons (% baseline change) revealed significant differences in ALT (p = 0.042) and a weak effect indicating a greater reduction in the HOMA-IR in the vitamin D group (p = 0.051). No further between group differences were seen in other cardiovascular risk factor, liver markers, or hormones. This study supports beneficial effects of vitamin D supplementation on liver markers and modest improvements in insulin sensitivity in vitamin D deficient women with PCOS.

Keywords: polycystic ovary syndrome; vitamin D; liver markers; cardiovascular risk factors; hormones
ASSOCIATION OF VITAMIN D METABOLITES WITH EMBRYO DEVELOPMENT AND FERTILIZATION IN WOMEN WITH AND WITHOUT PCOS UNDERGOING SUBFERTILITY TREATMENT

Thomas Keith Cunningham 1,2 , Victoria Allgar 3, Soha R. Dargham 4, Eric Kilpatrick 5, Thozhukat Sathyapalan 2, Stephen Maguiness 1, Haira R. Mokhtar Rudin 6, Nour M. Abdul Ghani 6, Aishah Latiff 6 and Stephen L. Atkin 4

1 Hull IVF Unit, Women and Children's Hospital, Hull Royal Infirmary, Hull, United Kingdom, 2 Centre for Diabetes and Metabolic Research, Hull York Medical School, University of Hull, Hull, United Kingdom, 3 Department of Statistics, Hull York Medical School, University of Hull, Hull, United Kingdom, 4 Weill Cornell Medicine Qatar, Doha, Qatar, 5 Sidra Medical and Research Centre, Doha, Qatar, 6 Antidoping Laboratory Qatar, Doha, Qatar

Objective: The relationship between fertilization rates and 1,25-dihydroxyvitamin D (1,25(OH)2D3), 25-hydroxyvitamin D2 (25(OH)D2), 25-hydroxyvitamin D3 (25(OH)D3), 24,25-dihydroxyvitamin D (24,25(OH)2D3), and 25-hydroxy-3epi-Vitamin D3 (3epi25(OH)D3) concentrations in age and weight matched women with and without PCOS was studied.

Methods: Fifty nine non-obese women, 29 with PCOS, and 30 non-PCOS undergoing IVF, matched for age and weight were included. Serum vitamin D metabolites were taken the menstrual cycle prior to commencing controlled ovarian hyperstimulation.

Results: Vitamin D metabolites did not differ between PCOS and controls; however, 25(OH)D3 correlated with embryo fertilization rates in PCOS patients alone (p = 0.03). For all subjects, 3epi25(OH)D3 correlated with fertilization rate (p < 0.04) and negatively with HOMA-IR (p < 0.02); 25(OH)D2 correlated with cleavage rate, G3D3 and blastocyst (p < 0.05; p < 0.009; p < 0.002, respectively). 24,25(OH)2D3 correlated with AMH, antral follicle count, eggs retrieved and top quality embryos (G3D3) (p < 0.03; p < 0.003; p < 0.009; p < 0.002, respectively), and negatively with HOMA-IR (p < 0.01). 1,25(OH)2D3 did not correlate with any of the metabolic or embryo parameters. In slim PCOS, 25(OH)D3 correlated with increased fertilization rates in PCOS, but other vitamin D parameters did not differ to matched controls.

Conclusion: 3epi25(OH)D3, 25(OH)D2, and 24,25(OH)2D3, but not 1,25(OH)2D3, were associated with embryo parameters suggesting that vitamin D metabolites other than 1,25(OH)2D3 are important in fertility.

Keywords: vitamin D, vitamin D epimers, vitamin D metabolites, fertilization rates, PCOS
Evaluation of VITEK MS, Clin-ToF-II MS, Autof MS 1000 and VITEK 2 ANC card for identification of Bacteroides fragilis group isolates and antimicrobial susceptibilities of these isolates in a Chinese university hospital

Yao Wang a,b,c, Xin-Fei Chen a,b,c, Xiu-Li Xie a,b, Meng Xiao a,b, Yang Yang a,b, Ge Zhang a,b, Jing-jia Zhang a,b, Si-meng Duan a,b, Qian Zhang d, Peng Zhang e, Clement Tsui f,g, Ying-chun Xu a,b,*

a Department of Clinical Laboratory, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China
b Beijing Key Laboratory for Mechanisms Research and Precision Diagnosis of Invasive Fungal Diseases, Beijing, China
c Graduate School, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China
d Department of Clinical Laboratory, Qinghai Provincial People’s Hospital, Xining, China
e Department of Clinical Laboratory, Dalian Third People’s Hospital, Dalian, China
f Department of Pathology, Sidra Medicine, Doha, Qatar
g Department of Pathology and Laboratory Medicine, Weill Cornell Medicine-Qatar, Doha, Qatar

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KEYWORDS
MALDI-TOF MS; VITEK 2 ANC card; Bacteroides fragilis group; Identification; Antimicrobial susceptibility

Abstract
Background and purpose: Bacteroides fragilis group isolates are most frequently isolated anaerobic pathogens. This study aimed to evaluate the accuracy of VITEK MS, Clin-ToF-II MS, Autof MS 1000 and VITEK 2 ANC card on the identification of clinical B. fragilis group isolates, as well as to determine their antimicrobial susceptibilities.

Methods: A total of 138 isolates of B. fragilis group isolates were identified with the three MALDI-TOF MS systems and VITEK 2 ANC cards. 16S rRNA gene sequencing was used as the reference identification method for comparison. Antimicrobial susceptibilities were determined by agar dilution method to 19 antimicrobial agents recommended by Clinical and Laboratory Standards Institute (CLSI).

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1684-1182/© 2019, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Evaluation of VITEK MS, Clin-ToF-II MS, Autof MS 1000 and VITEK 2 ANC card

Introduction

Bacteroides fragilis group isolates are most frequently associated with intra-abdominal, pelvic, complicated skin and soft tissue and blood stream infections.

The two main commercial MALDI-TOF MS systems available for routine use are VITEK MS (bioMérieux, Marcy l’Etoile, France) and MALDI Biotyper systems (Bruker Daltonics, Bremen, Germany) have been evaluated and validated for the identification of anaerobes previously. Recently, two additional MALDI-TOF MS based systems Clin-ToF-II MS (Bioryg Technologies, Beijing, China) and Autof MS 1000 (Autobio Diagnostics, Zhengzhou, China), manufactured by Chinese technological companies, which have been employed mainly on the identification of aerobic bacteria and yeasts in many laboratories in China. However, their performance and application on the identification of anaerobes have not been fully evaluated. In addition, limited data is available on the antimicrobial susceptibilities of these anaerobes in China.

The purpose of this study was to evaluate the accuracy of VITEK MS, Clin-ToF-II MS, Autof MS 1000 and VITEK 2 ANC card (bioMérieux, Marcy l’Etoile, France) on the identification of B. fragilis group isolates using 16S rRNA gene sequencing as reference method, and to identify the antimicrobial susceptibilities of these anaerobic isolates in a Chinese university hospital.

Methods

Bacterial isolates

The study was conducted at the department of clinical laboratory, Peking union medical college hospital in Beijing, China. A total of one hundred and thirty-eight strains of non-duplicated B. fragilis group isolates were collected from August 2010 to September 2017. All the isolates were stored at −80 °C. Before identification, frozen isolates were subcultured twice on Brucella blood agar (BBL™, Sparks, MD, USA) supplemented with hemin and vitamin K, in an anaerobic atmosphere produced by GENbags (bioMérieux, Marcy l’Etoile, France) at 35 °C for 48 h.

16S rRNA gene sequencing

All the isolates were identified by 16S rRNA gene sequencing. DNA was extracted by dissolving the isolates in 250 μL of sterile water and heating for 10 min at 100 °C, followed by 1 min of centrifugation at 13,000 rpm. The sample DNA was stored at 4 °C. The primers used for amplification were F27 (5'-AGAGTTTGATCCTGGCTCAG-3') and R1522 (5'-AAGGAGGTGATCCAGCCGCA-3'). PCR mixtures were amplified by initial holding at 94 °C for 10 min, and then 30 cycles of denaturing at 94 °C for 45 s, annealing at 55 °C for 45 s, and extension at 72 °C for 90 s. The reaction ended with a final extension at 72 °C for 10 min and a hold at 4 °C. The PCR products were purified and sequenced by the same primers above. The sequences were compared to the GenBank database by nucleotide BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi). The criteria for genus- and species-level identifications were assigned as previously described: Identification at the species level (≥99% sequence identity with a reference entry), identification at the genus level (95.0–98.9% of sequence identify) and cannot be identified definitively (<95% identity to any reference sequence).

Identification by MALDI-TOF MS

All the isolates were identified by VITEK MS, Clin-ToF-II MS and Autof MS 1000 following the manufacturers’ instructions. For all the three MALDI-TOF MS systems, bacterial samples were prepared by direct deposit method. Briefly, a single colony was spotted onto target slide to form a homogenous smear, and then treated by the ready-to-use matrix solution of each brand, with α-cyano-4-

Results: Hundred thirty three isolates of Bacteroides spp. and 5 isolates of Parabacteroides spp. were identified by 16S rRNA sequencing. The rates of accurate identification at species level of VITEK MS, Clin-ToF-II MS, Autof MS 1000 and VITEK 2 ANC card were 94.2%, 94.2%, 98.6% and 94.9%, respectively, while that at genus level were 99.3%, 100%, 100% and 97.8%, respectively. Metronidazole and chloramphenicol were the most susceptible agents (99.3% and 92.8%, respectively), followed by meropenem, ertapenem, imipenem and piperacillin/tazobactam to which the susceptible rates ranged from 76.8% to 79.0%. The susceptible rates to carbapenems decreased 12.4–15.3% from 2010–2013 to 2014–2017.

Conclusion: All the four systems provided high accurate rate on the identification of B. fragilis group isolates. Metronidazole showed highest activity against these isolates. Attention should be paid to the higher resistant rates to carbapenems, clindamycin, moxifloxacin and tigecycline than the other countries.
A prospective cohort for the investigation of alteration in temporal transcriptional and microbiome trajectories preceding preterm birth: a study protocol

Tobias Brummaier,1,2,3 Basirudeen Syed Ahamed Kabeer,4 Justin C Konje,4 Sasithon Pukrittayaamee,5 Juerg Utzinger,2,3 Mohammed Toufio,4 Antonios Antoniou,4 Alexandra K Marr,5 Sangrawee Suriyakan,1 Tomoshige Kino,4 Souhaila Al Khodor,4 Annalisa Terranegra,1 François Nosten,1,6 Daniel H Paris,2,3 Rose McGready,1,6 Damien Chausserab4


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ABSTRACT

Introduction Preterm birth (PTB) results from heterogeneous influences and is a major contributor to neonatal mortality and morbidity that continues to have adverse effects on infants beyond the neonatal period. This protocol describes the procedures to determine molecular signatures predictive of PTB through high-frequency sampling during pregnancy, at delivery and the postpartum period.

Methods and analysis Four hundred first trimester pregnant women from either Myanmar or Thailand of either Karen or Burman ethnicity, with a viable, singleton pregnancy will be enrolled in this non-interventional, prospective pregnancy birth cohort study and will be followed through to the postpartum period. Fortnightly finger prick capillary blood sampling will allow the monitoring of genome-wide transcript abundance in whole blood. Collection of stool samples and vaginal swabs each trimester, at delivery and postpartum will allow monitoring of intestinal and vaginal microbial composition. In a nested case–control analysis, perturbations of transcript abundance in capillary blood as well as longitudinal changes of the gut, vaginal and oral microbiome will be compared between mothers giving birth to preterm and matched cases giving birth to term neonates. Placenta tissue of preterm and term neonates will be used to determine bacterial colonisation as well as for the establishment of coding and non-coding RNA profiles. In addition, RNA profiles of circulating, non-coding RNA in cord blood serum will be compared with those of maternal peripheral blood serum at time of delivery.

Ethics and dissemination This research protocol that aims to detect perturbations in molecular trajectories preceding adverse pregnancy outcomes was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University in Bangkok, Thailand (Ethics Reference: TMEC 15–062), the Oxford Tropical Research Ethics Committee (Ethics Reference: OxTREC: 33–15) and the local Tak Province Community Ethics Advisory Board. The results of this cooperative project will be disseminated in multiple publications staggered over time in international peer-reviewed scientific journals.

Trial registration number NCT02797327; Pre-results.
ORIGINAL STUDIES

A randomized, controlled, multi-center trial of the efficacy and safety of the Occlutech Figulla Flex-II Occluder compared to the Amplatzer Septal Occluder for transcatheter closure of secundum atrial septal defects

Damien Kenny MD1 | Andreas Eicken MD, PhD2 | Ingo Dähnert MD, PhD3 | Younes Boudjemline MD, PhD4 | Horst Sievert MD, PhD5 | Martin BE Schneider MD6 | Tommaso Gori MD, PhD7 | Ziyad M. Hijazi MD, MSc8 | for the Investigators

1Department of Cardiology, Our Lady's Children's Hospital, Dublin, Ireland
2German Heart Center, Munich, Germany
3Department of Pediatric Cardiology Heart Centre, University of Leipzig, Leipzig, Germany
4Department of Pediatric Cardiology, Centre de reference des Malformations Cardiaques Congénitales Complexes, Necker Hospital, Paris, France
5CardioVascular Center Frankfurt, Frankfurt, Germany & Anglia Ruskin University, Chelmsford, United Kingdom
6Department of Pediatric Cardiology, Charité Medical Center, Humboldt University, Berlin, Germany
7Zentrum für Kardiologie, Kardiologie I, University Medical Center, and DZHK Standort Rhein-Main, Mainz, Germany
8Sidra Cardiovascular Center of Excellence, Weil Cornell Medical College, Doha, Qatar

Correspondence
Damien Kenny, Our Lady's Children's Hospital, Crumlin, Dublin 12, Ireland.
Email: damien_kenny@icloud.com

Abstract

Aims: The aim of this study was to compare the efficacy and safety of the Occlutech Figulla Flex II Occluder (OFFII) with the Amplatzer Septal Occluder (ASO) in patients > 8kg undergoing transcatheter ASD closure.

Methods and results: Randomized, controlled, multi-center prospective clinical trial with randomization 2:1 in favor of the OFFII. Primary efficacy endpoint was the rate of successful device placement and defect closure without major complications at hospital discharge. All data were assessed through a core laboratory. Interim analysis was performed when 70% of the patients were treated to evaluate for noninferiority.

From a total of 176 randomized subjects, interim analysis was performed on the first 158 patients (65.2% female) (107 OFFII/51 ASO) undergoing device closure at a median weight of 42 kg (range 13-125 kg). Seventy-six percent (120 patients) completed 6-month follow-up. Successful device placement (first attempt) was achieved in 99.1% of the OFF group vs 90.2% of the ASO group (P < 0.05). Early efficacy success was achieved in 94.4% of the OFFII group vs 90.2% of the ASO group (P < 0.001). The incidence of major complications was 5.6% for the OFFII group compared to 9.8% for the ASO.

Conclusions: The OFFII device was not inferior to the ASO with less complications and greater efficacy than the ASO.

KEYWORDS
atrial septal defect, device, closure, transcatheter

1 INTRODUCTION

Although there have been a number of historical transcatheter atrial septal defect (ASD) occluders, the Amplatzer Septal Occluder (St Jude Medical, St Paul, MN, USA) evolved into the dominant closure device following the initial clinical report in 1997. Since this time, there have been multiple reports confirming efficacy in a variety of age groups, and a multicenter nonrandomized trial confirming significantly lower morbidity and length of hospital stay when compared to surgical ASD closure. However, concerns have been raised over the rare occurrence of cardiac erosions, with a reported incidence of 0.1-0.3%. Minimal device modification has occurred to address these concerns. Furthermore, attempts to provide a less rigid delivery system, facilitating tension-free alignment of the deployed device along the plane of the atrial septum have not proved successful. The first generation Occlutech ASD occluder (Occlutech International AB, Helsingborg, Sweden) achieved CE marking in 2007 with promising early clinical results. Two further generations have followed with design modifications leading to lack of a left sided-hub leading to a softer left-sided disc, and greater flexibility of the device following
Lung Ultrasound: The Emerging Role of Respiratory Therapists

Manjush Karthika, Duane Wong, Suresh G Nair, Lalitha V Pillai, and Chris Sara Mathew

Introduction

Lung ultrasound is a point-of-care imaging tool that is routinely used in acute care medicine. Traditionally, radiology physicians were the primary practitioners of diagnostic ultrasound, but with the recognition of its importance in intensive care medicine, critical care physicians have also adopted this practice. Within the intensive care unit inter-professional team is the respiratory therapist, who participates actively in the care of ventilated patients. Their scope of responsibility is expanding with newer technologies being brought into clinical use on a regular basis. This review focuses on the scope and benefits of ultrasound training within respiratory care-related areas. Key words: lung ultrasound; respiratory therapists; intensive care units.

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Introduction

The portable chest radiograph is a routine diagnostic tool used in the ICU setting to assess patient lung function.

The routine use of bedside chest radiography is supported by longstanding data, but there are studies that question its diagnostic impact and clinical efficacy. Portable chest radiography has gradually appeared to be less useful, as noted in a large meta-analysis of randomized, controlled trials and observational studies.

Computed tomography remains the accepted standard for all diagnostic and therapeutic procedures that require evaluation of lung function, whether for diagnostic purposes in pneumothorax, pneumonia, or pleural effusion, or for therapeutic purposes such as drainage of loculated or large effusions and for insertion of intercostal or pig-tail catheters. However, transporting a critically ill ICU patient with all of the accompanying monitoring equipment and emergency preparedness may not always be a practical option.

The advancement of lung ultrasound (LUS) in recent years with better quality and spatial resolution has resulted in greater diagnostic accuracy. Some of the advantages of
Original Article

Outcomes of type 1 diabetes mellitus in pregnancy: effect of excessive gestational weight gain and hyperglycaemia on fetal growth

Mohammed Bashir a, b, Emad Naem a, Faten Taha c, Justin C. Konje c, Abdul-Badie Abou-Samra a

a Qatar Metabolic Institute, Hamad Medical Corporation, Doha, Qatar
b Department of Obstetrics and Gynaecology, Women’s Wellness and Research Centre, Hamad Medical Corporation, Doha, Qatar
c Women’s Clinical Services Management Group (WCMG), Sidra Medicine, Doha, Qatar

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A B S T R A C T

Aims: To study pregnancy outcomes in patients with type 1 diabetes mellitus (T1DM) and the factors associated with poor outcomes.

Methods: A retrospective study of 110 patients with T2DM who attended our diabetes in pregnancy clinic at the Women’s Wellness and Research centre, Doha, between March 2015 and December 2016 and 1419 normoglycaemic controls.

Results: There was no difference in age, weight, and BMI between the two groups. The incidence of macrosomia, shoulder dystocia and stillbirth were similar in the two groups while that of pre-term labour, pre-eclampsia, Caesarean section (CS), large for gestational age (LGA), neonatal ICU (NICU) admission and neonatal hypoglycaemia were significantly higher in the T1DM than in the control group.

From a multivariate regression analysis, excessive gestational weight gain was associated with increased risk of LGA (OR 4.53; 95% CI [1.42–14.25]). Last trimester HBA1c was associated with increased risk for macrosomia [OR 2.46, 95% CI [1.03–5.86]]; LGA [ OR 3.25, 95% CI [1.65–6.40]]; increased risk for C-section [OR 1.96, 95% CI [1.12–3.45]], and increased risk of NICU admission (OR 2.46, 95% CI [1.04–5.86]).

The changes in HBA1C between the first and last trimester HBA1c was associated with a reduction in the risk of LGA [OR 0.46, 95% CI [(0.28–0.75)]

Conclusion: T1DM in pregnancy is associated with adverse pregnancy outcomes compared to the general population. Reducing gestational weight gain and improving glycaemic control might improve pregnancy outcomes.

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1. Introduction

Type 1 diabetes mellitus (T1DM) is associated with an undisputed increased risk of maternal and fetal morbidity and mortality [1]. One of the five years targets of the St. Vincent’s declaration was to “achieve pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman” [2]. It has been 29 years since this declaration was signed and this target has not been achieved by many countries [3]. Achieving normal or near normal glucose levels in patients with type 1 diabetes is challenging. The continuous change in food intake and insulin sensitivity during pregnancy result in unpredictable fluctuation in glucose levels needing frequent adjustment of insulin doses. As a result the risk of moderate and severe hypoglycaemia is increased substantially in patients with T1DM [4]. Most of the guidelines recommend to adjust the glucose targets during pregnancy in patients with T1DM to avoid undue hypoglycaemia [5,6]. In addition to poor glycaemic control, pre-pregnancy BMI, excessive gestational weight gain and smoking are recognised risk factors for poor pregnancy outcomes in patients with T1DM [7].

There is evidence that pregnancy outcomes in T1DM have improved over time in some countries [8]. There are not too many studies that have reported on pregnancy outcomes in T1DM patients from the Middle-East and North Africa (MENA) region. This study aims to describe the outcomes of pregnancies complicated with T1DM and to examine the effects of maternal weight and glycaemic control on pregnancy outcomes.
Evaluation of cationic channel TRPV2 as a novel biomarker and therapeutic target in Leukemia: Implications concerning the resolution of pulmonary inflammation

Kodappully S. Siveen1, Kirti S. Prabhu2, Aejaz S. Parray3, Maysalon Merhi7, Abdellah Arrodouani6, Mohamed Chikri4, Shahab Uddin5, Said Dermime4, Ramzi M. Mohammad6, Martin Steinhoff7, Ibrahim A. Janahi5 & Fouad Azzizi1

Patients treated during leukemia face the risk of complications including pulmonary dysfunction that may result from infiltration of leukemic blast cells (LBCs) into lung parenchyma and interstitium. In LBCs, we demonstrated that transient receptor potential vanilloid type 2 channel (TRPV2), reputed for its role in inflammatory processes, exhibited oncogenic activity associated with alteration of its molecular expression profile. TRPV2 was overexpressed in LBCs compared to normal human peripheral blood mononuclear cells (PBMCs). Additionally, functional full length isoform and nonfunctional short form pore-less variant of TRPV2 protein were up-regulated and down-regulated respectively in LBCs. However, the opposite was found in PBMCs. TRPV2 silencing or pharmacological targeting by Tranilast (TL) or SKF96365 (SKF) triggered caspace-mediated apoptosis and cell cycle arrest. TL and SKF inhibited chemotactic peptide FMLP-induced response linked to TRPV2 Ca2+ activity, and down-regulated expression of surface marker CD38 involved in leukemia and lung airway inflammation. Challenging lung airway epithelial cells (AECs) with LBCs decreased (by more than 50%) transepithelial resistance (TER) denoting barrier function alteration. Importantly, TL prevented such loss in TER. Therefore, TRPV2 merits further exploration as a pharmacodynamic biomarker for leukemia patients (with pulmonary inflammation) who might be suitable for a novel [adjvant] therapeutic strategy based on TL.

Leukemia covers a broad spectrum of hematological neoplasms characterized by profound genetic alterations of the bone marrow hematopoietic precursors which transform into different types of abnormal immature blasts cells exhibiting differentiation arrest, defective apoptosis, and increased proliferative potential. Ultimately, the bone marrow microenvironment is hijacked by LBCs through different not well understood molecular signaling pathways to promote cancer cells survival and spill out into the bloodstream:1

Accumulation of a large number of immature myeloid cells in [uncontrolled] leukemia can cause defects in both humoral and cellular immunity, thereby leading to impairment of the defense mechanisms of the host and contributing to the incidence of infection which is a major obstacle in the treatment of leukemia leading to life threatening situations or death. Particularly, respiratory complications due to infections are considered the major cause of morbidity and mortality in the immunocompromised leukemia patients.1

1Translational Research Institute, Academic Health System, Hamad Medical Corporation, Doha, Qatar. 2National Center for Cancer Care and Research-Hamad Medical Corporation, Doha, Qatar. 3Qatar Biomedical Research Institute, Qatar Foundation, Doha, Qatar. 4Department of Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, Michigan, USA. 5Division of Pediatric Pulmonology Sidra Medicine, Doha, Qatar. 6Kodappully S Siveen, Kirti S. Prabhu and Aejaz S. Parray contributed equally. Correspondence and requests for materials should be addressed to F.A. (email: fazizi@hamad.qa)
ERF-related craniosynostosis: The phenotypic and developmental profile of a new craniosynostosis syndrome

Graeme E. Glass1,2 | Justine O’Hara3 | Natalie Canham4 | Deirdre Cilliers5 |
David Dunaway3 | Aimee L. Fenwick6 | Noor-Owase Jeelani1,3 | David Johnson7 |
Tracy Lester8 | Helen Lord8 | Jenny E. V. Morton9,10 | Hiroshi Nishikawa11 |
Peter Noons9,10 | Kemmy Schwiebert12 | Caroleen Shipster3 | Alison Taylor-Beadling13 |
Stephen R. F. Twigg6 | Pradeep Vasudevan14 | Steven A. Wall7 |
Andrew O. M. Wilkie5,6,7 | Louise C. Wilson15

1Department of Surgery, Sidra Medicine, Doha, Qatar
2Division of Clinical Surgery, Weill Cornell Medical College, Doha, Qatar
3Department of Craniofacial Surgery, Great Ormond Street Hospital, London, United Kingdom
4North West Thames Regional Genetics Service, Kennedy Galton Centre, Northwick Park and St. Mark’s Hospitals, Harrow, United Kingdom
5Clinical Genetics Service, Oxford Centre for Genomic Medicine, Oxford University Hospitals NHS Foundation Trust, Nuffield Orthopaedic Centre, Oxford, United Kingdom
6Clinical Genetics Group, MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, United Kingdom
7Craniofacial Unit, Department of Plastic and Reconstructive Surgery, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, United Kingdom
8Oxford Genetics Laboratories, Oxford University Hospitals NHS Foundation Trust, The Churchill Hospital, Oxford, United Kingdom
9Department of Clinical Genetics, West Midlands Regional Clinical Genetics Service and Birmingham Health Partners, Birmingham, United Kingdom
10Department of Clinical Genetics, Birmingham Women’s and Children’s Hospitals, NHS Foundation Trust, Birmingham, United Kingdom
11Department of Craniofacial Surgery, Birmingham Children’s Hospital, Birmingham, United Kingdom
12Department of Clinical & Academic Ophthalmology, Great Ormond Street Hospital, London, United Kingdom
13Molecular Genetics Laboratory, North East Thames Regional Genetics Service, Great Ormond Street Hospital, London, United Kingdom
14Department of Clinical Genetics, University Hospitals of Leicester, Glenfield Hospital, Leicester, United Kingdom
15Clinical Genetics Service, Great Ormond Street Hospital, London, United Kingdom

Correspondence
Graeme E. Glass, Room C1-120, 1st Floor, Sidra Medicine OPC, Al Luqta St., Education City North Campus, PO Box 26999, Doha, Qatar.
Emails: gglass@sidra.org; drgraemeglass@gmail.com

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Mutations in the ERF gene, coding for ETS2 repressor factor, a member of the ETS family of transcription factors cause a recently recognized syndromic form of craniosynostosis (CRS4) with facial dysmorphism, Chiari-1 malformation, speech and language delay, and learning difficulties and/or behavioral problems. The overall prevalence of ERF mutations in patients with syndromic craniosynostosis is around 2%, and 0.7% in clinically nonsyndromic craniosynostosis. Here, we present findings from 16 unrelated probands with ERF-related craniosynostosis, with additional data from 20 family members sharing the mutations. Most of the probands exhibited multisutural (including pan-) synostosis but a pattern involving the sagittal and lambdoid sutures (Mercedes-Benz pattern) predominated. Importantly the craniosynostosis was often postnatal in onset, insidious and progressive with subtle effects on head morphology resulting in a median age at presentation of 42 months among the probands and, in some instances, permanent visual impairment due to unsuspected raised intracranial pressure (ICP). Facial dysmorphism (exhibited by all of the probands and many of the affected relatives) took the form of orbital hypertelorism,
mild exorbitism and malar hypoplasia resembling Crouzon syndrome but, importantly, a Class I occlusal relationship. Speech delay, poor gross and/or fine motor control, hyperactivity and poor concentration were common. Cranial vault surgery for raised ICP and/or Chiari-1 malformation was expected when multisutural synostosis was observed. Variable expressivity and nonpenetration among genetically affected relatives was encountered. These observations form the most complete phenotypic and developmental profile of this recently identified craniosynostosis syndrome yet described and have important implications for surgical intervention and follow-up.

**KEYWORDS**
Chiari-1 malformation, craniosynostosis, ERF, facial dysmorphism, intracranial pressure, phenotype

1 INTRODUCTION

Prevalence estimates for craniosynostosis, defined as the premature fusion of one or more of the cranial vault sutures, have ranged from 3.1 to 6.4 per 10,000 livebirths (Cornelissen et al., 2016). Around 30% of patients with craniosynostosis are identified as syndromic, with associated phenotypic and neurodevelopmental anomalies or malformations, or a positive family history (Wilkie et al., 2010; Wilkie, Johnson, & Wall, 2017). Among those for which the molecular basis has been identified (Twigg & Wilkie, 2015), the commonest include Muenke, Crouzon, Pfeiffer, Apert, Saethre-Chotzen and craniofrontonasal syndromes (Ko, 2016) and more recently TCF12-related craniosynostosis (Goos et al., 2016; Sharma et al., 2013), but there are many other rarer monogenic and chromosomal causes (Lattanzi, Barba, Di Pietro, & Boyadjiev, 2017).

ERF-related craniosynostosis was first described in 2013 in 12 unrelated families accounting for 7.1% of a cohort of 127 patients with undiagnosed clinical syndromic craniosynostosis, and 2.9% of a total cohort of 412 undiagnosed patients with syndromic or nonsyndromic craniosynostosis (Twigg et al., 2013). More recently, the overall prevalence in all syndromic craniosynostosis has been estimated at 2% and in clinically nonsyndromic craniosynostosis at 0.7% (Wilkie et al., 2017). It appeared to be associated particularly with sagittal and lambdoid synostosis, but also multisutural craniosynostosis and papyrinosynostosis. Chiari-1 malformations appeared to be more common, and there was a relatively high risk of pathologically raised intracranial pressure (ICP), behavioral problems, and speech and language delay. A presumptive diagnosis of Crouzon syndrome had been made for many of these patients. Examples of variable expression and nonpenetration were also reported (Twigg et al., 2013).

Since the initial report, two patients with ERF mutations have been described in a cohort of 40 patients with sagittal or multisutural synostosis (Chaudhry et al., 2015) and three patients with ERF mutations have been described in a cohort of 309 individuals with craniosynostosis who did not have a prior molecular diagnosis (Lee et al., 2018). A recent exome sequencing study of 291 parent-offspring trios with nonsyndromic midline craniosynostosis reported a novel frameshift ERF mutation in a father and his two offspring each of whom had nonsyndromic metopic synostosis (Timberlake et al., 2017). Elsewhere, a specific heterozygous ERF missense p.(Y89C) substitution has been found to cause Chitayat syndrome in four unrelated probands and one parent with hyperphalangism, characteristic facies, hallux valgus, and bronchomalacia (Balasubramanian et al., 2017). None was noted to have craniosynostosis although only one had been assessed by cranial computed tomography (CT), at 5.5 years of age.

Here, we report our experience of 16 unrelated probands and 20 additional family members with heterozygous ERF mutations confirming that they contribute significantly to the craniosynostosis case-load, and highlight particular issues of importance in the clinical management of patients and their wider families.

2 PATIENTS AND METHODS

2.1 Editorial policies and ethical considerations

Patients known to the U.K. supra-regional craniofacial units at Great Ormond Street Hospital (London), the John Radcliffe Hospital (Oxford), and Birmingham Children’s Hospital and who had been diagnosed since the initial description of ERF-related craniosynostosis (Twigg et al., 2013) were included for analysis. Most results have been generated as part of our routine clinical assessment and diagnostic service. Additional patients were ascertained through the Genetics of Craniofacial Malformations study (approved by London Riverside Research Ethics Committee [REC], reference 09/H0706/20) and the Deciphering Developmental Disorders study (approved by Cambridge South REC, reference 10/H0305/83). All subjects consented to the acquisition of this dataset. None of the patients have been reported previously and none have been ascertained through family follow-up of the initial cohort (Twigg et al., 2013).

Common to all three services, genetic investigation for patients with multisuture or suspected syndromic craniosynostosis and without a known familial etiology includes screening for mutations in FGFR1 (Exon 7), FGFR2 (Exons 8 and 10), FGFR3 (Exons 7 and 10) and TCF12 (Exon 1) sequencing and multiplex ligation-dependent probe amplification as a minimum. Those with normal results have further testing of FGFR2 (Exons 3, 5, 11, 14–17), EFNB1, ERF, TCF12, IL11RA...
The diagnostic accuracy and clinical utility of pediatric renal tumor biopsy: Report of the UK experience in the SIOP UK WT 2001 trial

Thomas J. Jackson1 | Richard D. Williams1 | Jesper Brok1,2 | Tanzina Chowdhury1,3 | Milind Ronghe4 | Mark Powis5 | Kathy Pritchard-Jones1 | Gordan M. Vujanić6,7 on behalf of the Children’s Cancer and Leukaemia Group (CCLG) Renal Tumours Group

1University College London Great Ormond Street Institute of Child Health, London, UK
2Department of Paediatric Oncology and Haematology, Rigshospitalet, Copenhagen, Denmark
3Department of Oncology, Great Ormond Street Hospital NHS Foundation Trust, London, UK
4Department of Paediatric Oncology, Royal Hospital for Children, Glasgow, UK
5Department of Paediatric Surgery, Leeds Teaching Hospital NHS Trust, Leeds, UK
6Department of Cellular Pathology, University Hospital of Wales, Cardiff, UK
7Department of Pathology, Sidra Medicine, Doha, Qatar

Correspondence
Thomas J. Jackson, University College London Great Ormond Street Institute of Child Health, London, UK.
Email: thomas.jackson4@nhs.net
Gordan M. Vujanić, Department of Pathology, Sidra Medicine, Doha, Qatar.
Email: gvujanic@sidra.org

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Abstract
Introduction: The International Society of Paediatric Oncology (SIOP) protocols recommend preoperative chemotherapy appropriate for Wilms tumors (WTs) in children with renal tumors aged ≥6 months, reserving biopsy for “atypical” cases. The Children’s Cancer and Leukaemia Group (CCLG) joined the SIOP-WT-2001 study but continued the national practice of biopsy at presentation.

Method: Retrospective study of concordance between locally reported renal tumor biopsies and central pathology review nephrectomy diagnoses of children enrolled by CCLG centers in the SIOP-WT-2001 study.

Results: Biopsy reports were available for 552/787 children with unilateral tumors. 36 of 552 (6.5%) were nondiagnostic: 2 normal tissue, 12 necrotic, 9 insufficient sample, and 13 indeterminate results (disproportionately non-WTs). The sensitivity and specificity of biopsy to identify tumors that did not require SIOP empirical preoperative chemotherapy were 86.0% and 99.6%, respectively. 13 of 548 (2.4%) biopsy results were discordant with nephrectomy; non-WTs other than renal cell carcinoma and clear cell sarcoma of the kidney (CCSK) were poorly recognized. In children aged 6-119 months, 480 of 518 (91.6%) had WT or nephroblastomatosis. 5 of 518 (1%) had benign tumors, and only one diagnosed on biopsy. Biopsy results correctly changed management in 25 of 518 (4.8%), including identifying 19 of 20 CCSKs, but would have led to overtreatment in 5 of 518 (1%) or undertreatment in 4 of 518 (0.8%). In children aged ≥10 years, biopsy correctly changed management in 5 of 19 (26%) cases with no discordance.

Conclusion: Biopsy is less effective at identifying non-WTs than WTs and rarely changes management in younger children. Biopsy should be reserved in SIOP protocols for children ≥10 years and in younger children with clinical or radiological features inconsistent with WT.

KEYWORDS diagnostic accuracy, pediatric, renal biopsy, sensitivity and specificity

1 INTRODUCTION

Renal tumors represent 7% of pediatric cancers, with Wilms tumor (WT) the most common, accounting for about 90% of renal cancers in European Cancer registries.1,2 WT has a median age of diagnosis of 3 years and generally has a good prognosis with 5-year overall survival 93% and 2-year event-free survival 87%.3 Non-WTs are rare in children and predominantly include mesoblastic nephroma (MN), clear cell sarcoma of the kidney (CCSK), rhabdoid tumor of the kidney (RTK), and renal cell carcinoma (RCC). MN is a tumor of low malignant potential usually requiring no further treatment than nephrectomy. It is the most common renal tumor among neonates but after 3 months of...
Pregnancy outcomes of early detected gestational diabetes: a retrospective comparison cohort study, Qatar

Mohammed Bashir,1 Khaled Baagar,1 Emad Naem,1 Fadi Elkhatib,2 Noor Alshaybani,3 Justin C Konje,3 Abdul-Badi Abou-Samra1

ABSTRACT

Objective To compare pregnancy outcomes in patients with early versus usual gestational diabetes mellitus (GDM). Design A retrospective cohort study. Settings The Women’s Hospital, Hamad Medical Corporation, Qatar. Participants GDM women who attended and delivered in the Women’s Hospital, between January and December 2016. GDM was diagnosed based on the 2013-WHO criteria. The study included 801 patients; of which, 273 E-GDM and 528 U-GDM. Early GDM (E-GDM) and usual GDM (U-GDM) were defined as GDM detected before and after 24 weeks’ gestation, respectively. Outcomes Maternal and neonatal outcomes and the impact of timing of GDM-diagnosis on pregnancy outcomes. Results At conception, E-GDM women were older (mean age 33.5±5.4 vs 32.0±5.4 years, p<0.001) and had higher body mass index (33.0±6.3 vs 31.7±6.1 kg/m², p=0.0059) compared with U-GDM. The mean fasting, and 1-hour blood glucose levels were significantly higher in E-GDM vs U-GDM, respectively (5.3±0.7 vs 4.0±0.7 mmol/L, p<0.001 and 10.6±1.7 vs 10.3±1.6 mmol/L, p<0.001). More patients in the E-GDM were managed on diet alone compared with E-GDM (53.6% vs 27.5%, p<0.001). E-GDM subjects gained less weight per week compared with U-GDM (0.02±0.03 vs 0.12±0.03 kg/week, p<0.0274). Maternal outcomes were similar between the two groups apart from a higher incidence of preterm labour (25.5% vs 14.4%, p<0.001) and caesarean section (52.4% vs 42.8%, p=0.01) in E-GDM vs U-GDM, respectively. After correction for covariates; gestational age at which GDM was diagnosed was associated with increased risk of macrosomia (OR 1.06, 95% CI 1.00 to 1.11; p<0.05) and neonatal hypoglycaemia (OR 1.05, 95% CI 1.00 to 1.11; p<0.05).

Conclusion Our data support the concept of early screening and treatment of GDM in high-risk patients. More data are needed to examine the optimal time for screening.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as hyperglycaemia first detected during pregnancy that is clearly not type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). There are not too many areas of diabetes that have generated as much debate, controversy and lack of consensus as GDM. The debates cover the diagnostic criteria, classification, timing of screening and method of screening (universal vs selective screening). The major strength is the large number of the study population and the low level of missing data. It is a single-centre study, all patients were treated with the same medical team using standardised protocols.

Strength and limitations of this study

- The main limitation of our study is the retrospective design.
- The duration between diagnosis and intervention was not available.
- The rate of gestational weight gain in each trimester was not available.
- The major strength is the large number of the study population and the low level of missing data.
- The rate of gestational weight gain in each trimester was not available.
Publish and Perish: The Dangers of Being Young and in a Hurry

James S. Huntley

1. Surgery, Sidra Medicine, Ar-Rayyan, QAT

Corresponding author: James S. Huntley, huntleyjs@gmail.com

Disclosures can be found in Additional Information at the end of the article

Abstract

Publications in peer-reviewed journals are a key and official requirement for progression to a consultant surgeon post. Paradoxically, a stipulation that should enhance the importance of surgical research may, in fact, contribute to a pressure that is one of the causes of research misconduct. Consultant trainers can go some way to mitigating against this danger with appropriate teaching and an emphasis on the core values surrounding research ethics.

Editorial

The experience of “research” is thought of as an important focus across training in most medical specialties. There is an intense pressure to publish, which runs counter to good science and may encourage bad practice. This pressure exists even within my own - the most practical specialty: orthopedics.

To qualify as an orthopedic consultant in the UK, a trainee must achieve a Certificate of Completion of Training, a goal demanding certain personalities be negotiated (trainers), hoops jumped (competencies attained), and barriers scaled (representative case numbers and the Fellowship exam). The stipulations from the Joint Committee on Surgical Training (JCST) [1] also include:

"Trainees must also complete two of the following: (1) Higher degree completed at any time (MSc, MPhil, MD, PhD). (2) Authorship in any position (including corporate or collaborative) of two PubMed-cited papers relevant to the specialty, not including case reports. (3) A minimum of two presentations at national or international meetings. (4) Evidence of recruiting ≥5 patients into a research ethics committee approved study or ≥10 patients into a multi-centre observational study."

It is not hard to make a case for the two publications because, despite some protests to the contrary, some aspects of surgery are scientific. Trainees should have the innate drive to engage with, question, and advance some aspect of technique or practice. Also, writing a paper and getting it published is itself an indicator of volition and tenacity. Candidates for consultant posts are likely to have similar credentials, and publications can be a critical discriminator. So, two publications are necessary and more/better publications are “highly desirable.”

I contend that across the broad scope of surgery, research and surgical science are not well
The Canadian pediatric surgery workforce: A 5-year prospective study☆

Sherif Emil a,b, Jacob C. Langer b, Geoffrey Blair c, Grant Miller d, Ann Aspirot e, Guy Brisseau f, B.J. Hancock g

a Department of Pediatric Surgery, McGill University Faculty of Medicine &The Montreal Children’s Hospital, McGill University Health Centre, Montreal, Quebec, Canada
b Division of Pediatric General and Thoracic Surgery, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada
c Division of Pediatric Surgery, BC Children’s Hospital, University of British Columbia, Vancouver, British Columbia, Canada
d Division of Pediatric Surgery, Royal University Hospital, University of Saskatchewan, Saskatoon, Saskatchewan, Canada
e Division of Pediatric Surgery, CHU Sainte-Justine, Université de Montréal, Montreal, Quebec, Canada
f Division of Pediatric Surgery, Sidra Medicine, Doha, Qatar
g Division of Pediatric Surgery, Children’s Hospital of Winnipeg, University of Manitoba, Winnipeg, Manitoba, Canada

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A B S T R A C T

Background: In 2014, a survey study of the Canadian pediatric surgery workforce predicted a need for 2 new pediatric surgeons/yr. in Canada. We sought to assess these predictions and evaluate the status of the workforce.

Methods: With IRB approval, a web-based survey was sent to pediatric surgery division chiefs in Canada each year (2013–2017). The survey data included: number of practicing pediatric surgeons, full time equivalent (FTE) positions, and fellowship graduates.

Results: There was a 100% response rate (18 divisions). From 2013 to 2017, the number of practicing pediatric surgeons and FTE positions increased (73 to 78, and 64.6 to 67.5, respectively). Eleven positions were vacated (4 retirement, 7 new practice), and 18 were filled. Eight were filled by new Canadian graduates, 7 by Canadians previously working in Canada or abroad, and 3 by European surgeons. Thirty-eight fellows completed training in Canada, including 24 non-Canadians who all left Canada. Nine Canadians who started practicing immediately after fellowship took positions in Canada (5) and the US (4).

Conclusions: Predictions made in 2014 were largely accurate. There has been modest growth in the Canadian pediatric surgery workforce over the last 5 years. A significant mismatch continues to exist between Canadian pediatric surgery graduates and attending staff positions.

Type of study: Survey.
Level of evidence: V

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Over the last two decades, there has been significant concern regarding the North American pediatric surgical workforce [1–13]. This concern has transcended the number of practicing pediatric surgeons to include issues of training, competence, quality of practice, subspecialization and academic output [1–14]. As we previously pointed out, American and Canadian pediatric surgical practice, although quite different in nature, is still closely interconnected [7]. The American–Canadian partnership, in a single North American pediatric surgical match, has existed for decades. This leads to significant cross-border exchange between Canada and the United States with respect to both training and practice of pediatric surgery [4,7]. A Canadian, the late Dr. Harvey Beardmore, is largely credited with establishing certification for pediatric surgeons in North America. This strong partnership, which has existed from the inception of our specialty, has arguably strengthened pediatric surgery through sharing of legacies, knowledge, research, and practice experiences.

Much has been written about pediatric surgery workforce issues in the United States [1–6,8–14]. In contrast, there has been very little literature on the same subject in Canada [7,15]. For example, the Medical Workforce Knowledgebase of the Royal College of Physicians and Surgeons of Canada shows a growth in the number of licensed general surgeons coupled with a steady decline in general surgery residency positions and graduates over the past 5 years, but does not provide any similar data for pediatric surgery [16]. In 2014, we published the first comprehensive study on the Canadian pediatric surgical workforce [7]. A major finding of that survey-based study was the near saturation of the Canadian pediatric surgical workforce, with a projected need of two new pediatric surgeons annually over a 10-year period [7]. Immediately following our publication, we embarked on a 10-year prospective study to accurately analyze changes in workforce and test our predictions. This paper reports our findings over the first five years of the study, 2013–2017.
Early phase I study of a $^{99m}$Tc labeled anti-PD-L1 single domain antibody in SPECT/CT assessment of programmed death ligand-1 expression in non-small cell lung cancer

Yan Xing§1, Gitasha Chand§1,2, Changchun Liu¹, Gary J. R. Cook³, Jim O’Doherty⁴,⁵ Lingzhou Zhao¹, Nicholas C. L. Wong², Levente K. Meszaros², Hong Hoi Ting²* and Jinhua Zhao¹*

¹ Department of Nuclear Medicine, Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, People’s Republic of China
² Nanomab Technology Limited, Shanghai, People’s Republic of China
³ Department of Cancer Imaging, School of Biomedical Engineering and Imaging Sciences, King’s College London, London, United Kingdom
⁴ Department of Molecular Imaging, Sidra Medicine, Doha, Qatar
⁵ Weill Cornell Medical College, Education City, Doha, Qatar

* Corresponding authors: hhting@nano-mab.com (H. Ting) and zhaojinhua1963@126.com (J. Zhao)

§ These authors equally contributed to this work.

First Authors: Gitasha Chand, 100 Haining Road, Shanghai. Phone: 86-13524200084, Email: gitashachand@nano-mab.com (not in training); Yan Xing, 100 Haining Road, Shanghai. Phone: 86-21-36126496, Email: xy.1@163.com (not in training).
ABSTRACT

Purpose: Immunotherapy with checkpoint inhibitor programmed cell death 1 (PD-1)/programmed death ligand (PD-L1) antibodies demonstrates improvements in treatment of advanced non-small cell lung cancer (NSCLC). Treatment stratification depends on immunohistochemical PD-L1 measurement of biopsy material, an invasive method that does not account for spatiotemporal heterogeneity. Using a single domain antibody (sdAb), NM-01, against PD-L1, radiolabeled site-specifically with technetium-99m (99mTc) for single photon emission computed tomography (SPECT) imaging, we aimed to assess the safety, radiation dosimetry and imaging characteristics of this radiopharmaceutical and correlate tumor uptake with PD-L1 immunohistochemistry results. Methods: Sixteen patients (mean age 61.7 years, 11 male) with NSCLC were recruited. Primary tumor PD-L1 expression was measured by immunohistochemistry. NM-01 was radiolabeled with $[^{99mTc}({\text{OH}}_2)_3({\text{CO}})_3]^+$ complex binding to its C-terminal hexahistidine tag. Administered activity was 3.8-10.4 MBq/kg, corresponding to 100 µg or 400 µg of NM-01. Whole body planar and thoracic SPECT/CT scans were performed at 1 and 2h post-injection in all patients and 5 patients had additional imaging at 10mins, 3 and 24h for radiation dosimetry calculations. All patients were monitored for adverse events. Results: No drug-related adverse events occurred in this study. The mean effective dose was $8.84 \times 10^{-3} \pm 9.33 \times 10^{-4}$ mSv/MBq (3.59 ± 0.74 mSv per patient). Tracer uptake was observed in the kidneys, spleen, liver and bone marrow.
SPECT primary tumor-blood pool ratios (T:BP) varied from 1.24 to 2.3 (mean=1.79) at 1h and 1.24 to 3.53 (mean=2.22) at 2h (p=0.005). 2h primary T:BP ratios correlated with PD-L1 immunohistochemistry results (r=0.68, p=0.014). 2h T:BP was lower in tumors with ≤1% PD-L1 expression (1.89 vs 2.49, p=0.048). Nodal and bone metastases showed tracer uptake. Heterogeneity (>20%) between primary tumor and nodal T:BP was present in 4 of 12 patients. Conclusion: This first in human study demonstrates that $^{99m}$Tc-labeled anti-PD-L1-sdAb SPECT/CT imaging is safe and associated with acceptable dosimetry. Tumor uptake is readily visible against background tissues, particularly at 2h when the T:BP ratio correlates with PD-L1 immunohistochemistry results.

Key Words: PD-L1; non-small cell lung cancer; SPECT/CT; Early Phase I; Single domain antibody (sdAb)
A novel 3’ untranslated region mutation in the SLC29A3 gene associated with pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus syndrome

Melissa Riachi1 | Firdevs Bas2 | Feyza Darendeliler2 | Khalid Hussain1,3

1Genetics and Genomic Medicine, UCL GOS Institute of Child Health, London, UK
2Department of Pediatrics, Pediatric Endocrinology Unit, Istanbul University, Istanbul, Turkey
3Department of Pediatrics, Division of Endocrinology, Sidra Medicine, Doha, Qatar

Correspondence
Prof. Khalid Hussain, MBChB, MD, MRCP, MRCPCH, MSc, Sidra Medicine, OIC, C6-340 PO Box 26999, Al Luqta Street, Education City North Campus, Doha, Qatar.
Email: khussain@sidra.org

Background: Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (PHID) is one of the rare H syndrome diseases mainly characterized by hyperpigmentation, hypertrichosis, sensorineural hearing loss, cardiac complications, developmental delay, and diabetes mellitus (DM). Mutations in the coding regions of the SLC29A3 gene that encodes for an equilibrative nucleoside transporter (ENT3) have been reported to cause the phenotypic spectrum of the H syndrome. Disease-causing mutations in the untranslated regions (UTRs) of the SLC29A3 gene have not been previously described in the literature. The aim of the study is to describe and assess the pathogenicity of a novel 3’UTR mutation in the SLC29A3 gene associated with the PHID phenotype in two Turkish patients.

Methods: The mutation was identified by a targeted gene approach. To understand the pathogenicity of this 3’UTR mutation, RNA and protein expression studies were performed by using the quantitative real-time polymerase chain reaction method and western blotting, respectively, using fibroblasts cultured from the patients’ skin biopsies.

Results: SLC29A3 and ENT3 expression levels were both decreased in the patients compared to controls matched for passage numbers, RNA, and protein extraction methods.

Conclusions: A novel 3’UTR mutation in the SLC29A3 gene is associated with the PHID syndrome, highlighting a potentially new pathological mechanism for this disease. The involvement of the 3’UTR has not been previously established in any of the H syndrome disease cluster or in any complex syndrome of DM.

Keywords
3’ untranslated region (3’UTR), diabetes mellitus (DM), hyperpigmentation, messenger RNA (mRNA), PHID syndrome

1 INTRODUCTION

Pigmentary hypertrichosis and non-autoimmune insulin-dependent diabetes mellitus (DM) syndrome, often referred to as PHID, is a rare autosomal recessive syndrome of severe multisystemic inflammation that has only been described using the PHID terminology only a handful of times in the literature.1,2 The PHID syndrome is an allelic variant of the H syndrome which is a cluster of disorders characterized by cutaneous hyperpigmentation, hearing impairment, heart abnormalities, hypertrichosis, hepatomegaly, hypogonadism, and histiocytosis.2,4 Additional features of the H syndrome can include short stature, hallux valgus, fixed flexion contractions of the proximal interphalangeal, and toe joints in addition to lymphadenopathy.1,4 The characteristic phenotype of this disease cluster is the cutaneous hyperpigmented,
Dose–Response Study of 4 Weight-Based Phenylephrine Infusion Regimens for Preventing Hypotension During Cesarean Delivery Under Combined Spinal–Epidural Anesthesia

Fei Xiao, MD,*† Bei Shen, MD,† Wen-ping Xu, MD,† Ying Feng, MD,* Warwick D. Ngan Kee, MD, FANZCA, FHKCA,‡ and Xin-zhong Chen, MD*

BACKGROUND: Prophylactic IV infusion of phenylephrine has been recommended to prevent hypotension during spinal anesthesia for cesarean delivery. However, the optimal infusion dose is unknown. This study aimed to determine the infusion dose of phenylephrine that would be effective in preventing hypotension in 50% (ED50) and 90% (ED90) of patients when administered as a prophylactic infusion at a fixed rate based on the individual body weight.

METHODS: Eighty parturients scheduled for elective cesarean delivery were randomly allocated to receive IV infusion of prophylactic phenylephrine at 0.25, 0.375, 0.5, or 0.625 µg/kg/min (n = 20 per group) starting immediately after intrathecal injection of 10 mg hyperbaric bupivacaine and 5 µg sufentanil using a combined spinal–epidural technique. An effective dose was defined by the occurrence of no hypotension (defined as a decrease in systolic blood pressure by ≥20% below baseline and to <90 mm Hg) during the interval from the initiation of spinal anesthesia to delivery of the infant. Values for ED50 and ED90 of prophylactic phenylephrine were calculated using probit analysis.

RESULTS: Hypotension occurred in 13/20, 8/20, 2/20, and 1/20 patients in the groups that received phenylephrine infusion at 0.25, 0.375, 0.5, or 0.625 µg/kg/min, respectively. The calculated values for ED50 and ED90 were 0.31 (95% CI, 0.24–0.36) and 0.54 (95% CI, 0.46–0.76) µg/kg/min, respectively. No difference was found in the incidence of adverse effects and neonatal outcomes among groups.

CONCLUSIONS: Under the conditions of this study, when phenylephrine was given as a fixed-rate prophylactic infusion during spinal anesthesia for cesarean delivery to prevent hypotension, the values for ED50 and ED90 were 0.31 (95% CI, 0.24–0.36) and 0.54 (95% CI, 0.46–0.76) µg/kg/min, respectively. (Anesth Analg 2020;130:187–93)

KEY POINTS

- Question: What is the dose–response relationship for phenylephrine given as a prophylactic continuous infusion at a fixed rate based on patient weight for preventing hypotension during combined spinal–epidural anesthesia for cesarean delivery?
- Findings: The ED50 and ED90 for phenylephrine were 0.31 (95% CI, 0.24–0.36) and 0.54 (95% CI, 0.46–0.76) µg/kg/min, respectively.
- Meaning: The dose–response relationship for weight-based fixed-rate phenylephrine infusions was determined.

Spinal anesthesia and combined spinal–epidural anesthesia are the most commonly used methods of anesthesia for cesarean delivery. However, their use is associated with a high incidence of hypotension.1,2 Phenylephrine is well accepted as a first-line vasopressor for preventing hypotension in this context.3,4 In particular, the use of phenylephrine by prophylactic infusion is increasingly considered a key preventive strategy.4,7–13 Previous studies have suggested that phenylephrine administered by prophylactic continuous infusion is superior to intermittent bolus administration in preventing hypotension and associated nausea and vomiting.5,11,14 However, limited data are available about optimal doses for prophylactic phenylephrine infusions. Moreover, most previous studies have utilized infusion rates not adjusted for patient body weight.6,10,13 Given that the weight of pregnant women varies considerably both within and among different populations, and because obesity is increasingly being recognized as a clinical challenge in obstetric anesthesia,15,16 investigation of
The Genetic and Molecular Mechanisms of Congenital Hyperinsulinism

Sonya Galcheva 1, Hüseyin Demirbilek 2, Sara Al-Khawaga 3 and Khalid Hussain 3*

1 Department of Pediatrics, University Hospital St. Marina, Varna Medical University, Varna, Bulgaria, 2 Department of Paediatric Endocrinology, Hacettepe University Faculty of Medicine, Ankara, Turkey, 3 Division of Endocrinology, Department of Paediatric Medicine, Sidra Medicine, Doha, Qatar

Congenital hyperinsulinism (CHI) is a heterogenous and complex disorder in which the unregulated insulin secretion from pancreatic beta-cells leads to hyperinsulinaemic hypoglycaemia. The severity of hypoglycaemia varies depending on the underlying molecular mechanism and genetic defects. The genetic and molecular causes of CHI include defects in pivotal pathways regulating the secretion of insulin from the beta-cell. Broadly these genetic defects leading to unregulated insulin secretion can be grouped into four main categories. The first group consists of defects in the pancreatic $K_{ATP}$ channel genes ($ABCC8$ and $KCNJ11$). The second and third categories of conditions are enzymatic defects (such as GDH, GCK, HADH) and defects in transcription factors (for example HNF1α, HNF4α) leading to changes in nutrient flux into metabolic pathways which converge on insulin secretion. Lastly, a large number of genetic syndromes are now linked to hyperinsulinaemic hypoglycaemia. As the molecular and genetic basis of CHI has expanded over the last few years, this review aims to provide an up-to-date knowledge on the genetic causes of CHI.

Keywords: hyperinsulinism, hypoglycaemia, molecular mechanisms, genetics, mutation

INTRODUCTION

Congenital hyperinsulinism (CHI) is a heterogeneous and complex biochemical disorder which is characterized by the dysregulated release of insulin from pancreatic β-cell (1). In normal physiological state, the secretion of insulin is tightly coupled to glucose metabolism within the β-cell so that the insulin release is regulated to keep the plasma glucose concentration around 3.5–5.5 mmol/L. However, in CHI the secretion of insulin becomes unrelated to glucose metabolism, so that there is inappropriate insulin release for the plasma glucose level (2).

The genetic and molecular cause of CHI includes defects in key genes regulating insulin secretion from the pancreatic β-cell. Molecular defects in previously described genes ($ABCC8$, $KCNJ11$, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A, HNF1A, HK1, PGM1, and PMM2) have been reported (3). However, recent studies have linked the role of other genes ($CACNA1D$, $FOX4A2$) to hyperinsulinaemic hypoglycaemia (HH) but in some of these cases the underlying molecular mechanisms are still not fully elucidated (Table 1). Understanding the molecular mechanisms of CHI due to these genetic abnormalities has provided unique insight into the normal physiological mechanisms which regulate the insulin release.
Stiffness of hip adductor myofibrils is decreased in children with spastic cerebral palsy

Timothy R. Leonard a, Jason J. Howard b, Kelly Larkin-Kaiser a, Venus Joumaa a, Karl Logan c, Benjamin Orlik c, Ron El-Hawary c, Luke Gauthier c, Walter Herzog a,*

⇑
a Faculty of Kinesiology, University of Calgary, Calgary, AB, Canada
b Weill Cornell Medicine, Sidra Medicine, Doha, Qatar
c IWK Health Centre, Halifax, NS, Canada

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Abstract
Cerebral palsy (CP) is the result of a static brain lesion which causes spasticity and muscle contracture. The source of the increased passive stiffness in patients is not understood and while whole muscle down to single muscle fibres have been investigated, the smallest functional unit of muscle (the sarcomere) has not been. Muscle biopsies (adductor longus and gracilis) from pediatric patients were obtained (CP n = 9 and control n = 2) and analyzed for mechanical stiffness, in-vivo sarcomere length and titin isoforms. Adductor longus muscle was the focus of this study and the results for sarcomere length showed a significant increase in length for CP (3.6 mm) compared to controls (2.6 mm). Passive stress at the same sarcomere length for CP compared to control was significantly lower in CP and the elastic modulus for the physiological range of muscle was lower in CP compared to control (98.2 kPa and 166.1 kPa, respectively). Our results show that CP muscle at its most reduced level (the myofibril) is more compliant compared to normal, which is completely opposite to what is observed at higher structural levels (single fibres, muscle fibre bundles and whole muscle). It is noteworthy that at the in vivo sarcomere length in CP, the passive forces are greater than normal, purely as a functional of these more compliant sarcomeres operating at long lengths. Titin isoforms were not different between CP and non-CP adductor longus but titin:nebulin was reduced in CP muscle, which may be due to titin loss or an over-expression of nebulin in CP muscles.

1. Introduction

Cerebral palsy (CP) is the most common cause of physical disability in children (Oskoui et al., 2013). The clinical manifestations are progressive with growth (Graham and Selber, 2003) and the spastic motor type is most commonly found in children with CP (Howard et al., 2005), first manifesting with a velocity-dependent increase in muscle stiffness, and progressing to a fixed increase in muscle stiffness over time. It is generally accepted that spastic CP muscle is stiffer than normal muscle, but there is little agreement on the mechanisms behind this observation. Previous research has shown that the sarcomere, the basic contractile unit of skeletal muscle, is overstretched in spastic muscle tissue compared to normal, and operates at long sarcomere lengths (Lieber and Fridén, 2002; Mathewson et al., 2015; Mathewson and Lieber, 2015; Smith et al., 2011). At these increased lengths, the overstretched sarcomeres would have low active force-generating capacity (Gordon et al., 1966) and high passive forces, which agrees with the clinical situation whereby muscles are not only tight but also weak. Despite the increased sarcomere length, the muscle portion of the muscle-tendon unit has been found to be shorter in CP muscle as compared to normal (Matthiasdottir et al., 2014; Wren et al., 2010), and has been associated with the development of static contracture.

The primary aim of these experiments was to compare passive stress generation under stretch (i.e. stiffness) between myofibril samples acquired from the adductor longus of children with CP and those from typically developing children. Given that the isolated myofibril is devoid of passive structural elements outside of the sarcomere, such as the extracellular matrix, this analysis provides crucial insight into the mechanics of sarcomeres and titin in CP. Our hypothesis was that the stresses generated by CP myofibrils under stretch are higher than for typically developing children, in accordance with results reported for single muscle fibre and fibre bundle preparations (Fridén and Lieber, 2003;...
Monoclonal Antibody Treatment of RSV Bronchiolitis in Young Infants: A Randomized Trial

Khalid Alansari, MD, FRCPC, FAAP (PEM), Fatih Hassan Toaimah, MD, Daher Helmi Almatar, MD, Lamiaa Awny El Tatawy, MD, CABP, Bruce L. Davidson, MD, MPH, Mohammad Ibrahim Mohammad Qusad, MD

BACKGROUND: Monoclonal antibody to respiratory syncytial virus (RSV; palivizumab) is recommend for prophylaxis of high-risk infants during bronchiolitis seasons but not for RSV bronchiolitis treatment. Our aim was to determine if palivizumab would be helpful in young infants with acute RSV bronchiolitis.

METHODS: Eligible infants ≤3 months old presenting to the pediatric emergency service with RSV-positive bronchiolitis requiring inpatient admission underwent double-blind random assignment to single-dose intravenous palivizumab (15 mg/kg) or placebo. The primary efficacy outcome was the need for inpatient readmission in the 3 weeks after discharge. Secondary outcomes were time to readiness for hospital discharge, need for PICU on the initial admission, and need for revisit not requiring readmission for the same illness during 3-week follow-up.

RESULTS: A total of 420 infants (median age 49 days) diagnosed with RSV bronchiolitis were randomly assigned; 417 received treatment, and 413 completed follow-up. Readmission during follow-up was needed for 23 (11%) patients on palivizumab and 19 (9.3%) patients in the placebo group (difference 1.8%; 95% confidence interval 2.4% to 7.7%; P = .51). Geometric mean time to readiness for discharge was 29.5 hours for the palivizumab group and 30.2 hours for the placebo group (ratio 0.98; 95% confidence interval 0.81 to 1.20). No safety issues were reported.

CONCLUSIONS: Intravenous palivizumab did not appear to help or harm young infants with acute RSV-positive bronchiolitis.

WHAT’S KNOWN ON THIS SUBJECT: Monoclonal antibody to respiratory syncytial virus (RSV; palivizumab) neutralizes RSV, suppresses replication, and is recommended for prophylaxis of high-risk infants during bronchiolitis seasons but not for RSV bronchiolitis treatment.

WHAT THIS STUDY ADDS: In this first blinded randomized trial of 420 young infants, palivizumab treatment did not prevent repeat readmissions after discharge nor shorten time to discharge or need for ICU during the index hospitalization.
ARTICLE

Bi-allelic Variants in TONSL Cause SPONASTRIME Dysplasia and a Spectrum of Skeletal Dysplasia Phenotypes

Lindsay C. Burrage,1,2,39 John J. Reynolds,3,39 Nissan Vida Baratang,4 Jennifer B. Phillips,5 Jeremy Wegner,5 Ashley McFarquhar,4 Martin R. Higgs,3 Audrey E. Christiansen,6 Denise G. Lanza,1 John R. Seavit,1 Mahim Jain,7 Xiaohui Li,1 David A. Parry,8 Vandana Raman,9 David Chitayat,10,11 Ivan K. Chinn,12,13 Alison A. Bertuch,1 Lefkothea Karavit,14 Alan E. Schlesinger,15,16 Dawn Earl,17 Michael Bamshad,17,18 Ravi Savarirayan,19 Harsha Doddapaneni,20 Donna Muzny,20 Shalini N. Jhangiani,20 Christine M. Eng,1,21 Richard A. Gibbs,1,20 Weimín Bi,1,21 Lisa Emrick,1,21,22 Jill A. Rosenfeld,1 John Postlethwait,5 Monte Westerfield,5 Mary E. Dickinson,1,6 Arthur L. Beaudet,1 Emmanuelue Ranza,23 Celine Huber,24 Valérie Cormier-Daire,24 Wei Shen,25,26 Rong Mao,25,26 Jason D. Heaney,1 Jordan S. Orange,13,27 University of Washington Center for Mendelian Genomics, Undiagnosed Diseases Network, Débora Bertola,28,29 Guillerme L. Yamamoto,28,29

SPONASTRIME dysplasia is an autosomal-recessive spondyloepimetaphyseal dysplasia characterized by spine (spondylar) abnormalities, midface hypoplasia with a depressed nasal bridge, metaphyseal striations, and disproportionate short stature. Scoliosis, coxa vara, childhood cataracts, short dental roots, and hypogammaglobulinemia have also been reported in this disorder. Although an autosomal-recessive inheritance pattern has been hypothesized, pathogenic variants in a specific gene have not been discovered in individuals with SPONASTRIME dysplasia. Here, we identified bi-allelic variants in TONSL, which encodes the Tonsoku-like DNA repair protein, in nine subjects (from eight families) with SPONASTRIME dysplasia, and four subjects (from three families) with short stature of varied severity and spondyloepimetaphyseal dysplasia with or without immunologic and hematologic abnormalities, but no definitive metaphyseal striations at diagnosis. The finding of early embryonic lethality in a Tonsél−/− murine model and the discovery of reduced length, spinal abnormalities, reduced numbers of neutrophils, and early lethality in a tontsl−/− zebrafish model both support the hypomorphic nature of the identified TONSL variants. Moreover, functional studies revealed increased amounts of spontaneous replication fork stalling and chromosomal aberrations, as well as fewer camptothecin (CPT)-induced RAD51 foci in subject-derived cell lines. Importantly, these cellular defects were rescued upon re-expression of wild-type (WT) TONSL; this rescue is consistent with the hypothesis that hypomorphic TONSL variants are pathogenic. Overall, our studies in humans, mice, zebrafish, and subject-derived cell lines confirm that pathogenic variants in TONSL impair DNA replication and homologous recombination-dependent repair processes, and they lead to a spectrum of skeletal dysplasia phenotypes with numerous extra-skeletal manifestations.

Introduction

SPONASTRIME dysplasia (MIM: 271510) is an autosomal-recessive spondyloepimetaphyseal dysplasia named for characteristic clinical and radiographic findings, including spine (spondylar) abnormalities, midface hypoplasia with a depressed nasal bridge, and striation of the metaphysis.1 Additional features include disproportionate short stature with exaggerated lumbar lordosis, scoliosis, coxa vara, limited elbow extension, childhood cataracts, short...
Fluid Overload in Children With Bronchiolitis*

Ricardo Garcia Branco, MD, PhD
Paediatric Intensive Care Unit
Department of Pediatrics
Sidra Medicine
Doha, Qatar

Fluid overload is common among critically ill children. Over the last decades, pediatric intensivists learned to administer fluids generously. Early and “aggressive” fluid administration became the treatment cornerstone for children with hemodynamic instability (1). This was reinforced by a number of studies showing resuscitation strategies that involved large amounts of IV fluid (e.g., Pediatric Advanced Life Support guidelines, goal-directed therapy) being effective in reducing morbidity and mortality in hemodynamically unstable children (2). A clear physiologic basis existed—that is, to restore circulating volume and improve cardiovascular status—so pediatric intensivist learned to accept IV fluids as a safe and effective therapy in emergency and PICUs. Fluid resuscitation was—and continues to be—a great success story. However, as intensive care science moves forward, we ask ourselves how much fluid is too much? There is now growing evidence that fluid accumulation is also linked to worsened clinical outcomes (3, 4). This does not undermine the importance of adequate fluid resuscitation but highlights the importance of continuously assessing fluid status. Studies are now showing that a more restrictive approach to fluid management can improve clinical outcomes of populations that often require large amounts of fluid resuscitation such as sepsis and acute respiratory distress syndrome (5), but restricting fluid in other populations such as patients undergoing major abdominal surgery may be harmful (6).

In this issue of Pediatric Critical Care Medicine, Flores-González et al (7) report their findings of a prospective multicenter study looking at the effect of fluid overload in children with severe acute bronchiolitis. This population is interesting because it comprises one of the largest groups of children requiring intensive care, carrying a significant volume burden to PICUs despite having a very low mortality rate. This population is also interesting because it has a pathology with primary pulmonary involvement and little hemodynamic effect. The high capillary density of the lungs and the propensity for lung capillary leak in response to inflammation potentiates the possible impact of fluid accumulation on clinical outcomes. Furthermore, the low hemodynamic impact of this illness naturally limits the confounding effect of fluid resuscitation for shock. In their analysis, the authors found that a positive fluid balance 24 hours after PICU admission was associated with longer duration of mechanical ventilation, as well as longer PICU and hospital stay. Some of these effects were also observed at 48 and 72 hours. These findings are in keeping with fluid management studies in other pediatric populations (8, 9). Although these results only show an association and do not imply causation, it is hard to ignore the vast amount of literature that is currently emerging point in the same direction: we need to improve our patient’s fluid management! We already recognize fluid overload as deleterious to our patients (10, 11), maybe it is time to recognize that our patient’s fluid “maintenance” requirements may be lower than our usual estimate for healthy children. We should also consider that critically ill children often have a hormonal response that will retain fluid, so diuresis may need to be stimulated when it is safe to do so. Perhaps we should look at fluid balances with as much attention as we look at vasoactive drug infusions or blood pressure targets and act on fluid overload with the same emphasis that we learned to treat hemodynamic instability.

An interesting aspect of the population studied was that even on the first day of admission most patients were receiving enteral feeding. It would be acceptable to think that as clinical status improve, patients may tolerate larger amounts of enteral feeding and a positive balance in this setting could be not so clinically relevant. However, the authors found that the effect of fluid overload in clinical outcome seems to be independent of route of fluid administration. This again emphasizes the importance of constant patient fluid assessment and that provision of adequate caloric intake should not be an excuse to tolerate a patient positive fluid balance.

Besides the fluid management data, the current study by Flores-González et al (7) also exposes other features of the real-life management of severe bronchiolitis in children. Despite extensive research, treatment of severe bronchiolitis remains mainly supportive, and this can be frustrating for both parents and attending physicians (12, 13). Parents often see their child deteriorating and “no one doing anything about it.” Physicians, especially intensivist, may feel powerless and struggle with the lack of treatment options. This often leads to attempts to use therapies that have been shown not to be effective in this population. Salbutamol, nebulized adrenaline, nebulized hypertonic saline, corticosteroids were very frequently used (either alone or in combination) in this population (7). It is clear that physicians wanted to do something and sometimes may have done too much. Used too many unproven therapies and too much fluid. Flores-González et al (7) from the BRUCIP study showed us that moderation is very much needed in the management of children with severe bronchiolitis.

REFERENCES


*See also p. e130.

Key Words: bronchiolitis; fluid balance; fluid overload; pediatric intensive care

Dr. Branco has disclosed that he does not have any potential conflicts of interest.

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What Is in a Word?? Defining Bleeding as the First Step…*

Heidi J. Dalton, MD, MCCM, FELSO
Adult and Pediatric ECLS
Pediatrics and INOVA Heart and Vascular Institute
Inova Fairfax Medical Center
Falls Church, VA; and
George Washington University
Washington, DC

Research is one of the most valuable ways medicine advances. Without it, new ways of managing patients, identifying “best practice”, challenging old dogmas and developing insights into where we need to go next would never occur. It is however, hard to do good research which is timely, accurate, meets the “scientifically valid” test and has enough patient volume to answer a specific study question.

In this issue of Pediatric Critical Care Medicine, Karam et al (1) provide an excellent example of one of the major limitations in clinical research—that of having definitions of a specific topic (bleeding, in this case) that are universally understood and agreed upon. The word definition is defined as “making something distinct, clear, giving meaning to a word or word group” (2). One might think that bleeding is an easily defined subject, but this survey shows us how variable the interpretation of this topic is. Bleeding in critically ill children is frequent, associated with morbidity and mortality and is a frequent underlying reason for transfusion (3, 4). As the authors establish, however, there is little agreement as to what actually constitutes bleeding within the pediatric critical care world (5). Establishing specific definitions for bleeding is required to perform accurate research on the role this plays in patient care. Although some aspects of bleeding can be fairly easily quantified, such as the milliliters coming from chest tube drains, other sources are more difficult. Weighing blood-soaked dressings, estimating loss on bed-sheets and from streaks in endotracheal or nasogastric tubes are often considered, but there is little exact science related to these procedures. Determining how much blood is contained within intracerebral lesions, which are often the most devastating, is also difficult. Although the study by Karam et al (1), based on a survey of international practitioners, does not answer what should be considered clinically relevant bleeding, it does add some granularity to how this should be defined. Once definitions are established, they will also need to be validated to insure that clinician researchers are truly all on the same page. Although such efforts exist in the adult world, there are no validated measures for “scoring” bleeding events in children. Karam et al (1) mention that a decline in hemoglobin and a change in vital signs are often the indicators used in adults of bleeding, but this fails to account for hemodilution, physiologic differences in kids, has not been validated as a scoring system in children, and thus provides little help in the pediatric realm (6). The issue of separating bleeding from transfusion is also important. Many articles have outlined the adverse effects of blood transfusions, although the specific reasons for transfusion are often not delineated (7–9). This is another important aspect of research planning—careful definitions for both bleeding and responses taken (transfusion or other) will also help us in future study planning and implementation.

*See also p. e137.

Key Words: bleeding; children; definitions; research; transfusion

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New Insights of Uterine Leiomyoma Pathogenesis: Endocannabinoid System

Thangesweran Ayakannu
Anthony H. Taylor
Timothy H. Marczyno
Justin C. Konje

Background: The aim of this study was to determine if components of the endocannabinoid system are modulated in uterine leiomyomas (fibroids). Components studied included cannabinoid receptors 1 (CB1) and 2 (CB2); the G protein-coupled receptor GPR55; transient potential vanilloid receptor 1 (TRPV1) and the endocannabinoid modulating enzymes N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and fatty acid amide hydrolase (FAAH), and their N-acyl ethanolamide (NAE) ligands: N-arachidonylethanolamine (AEA), N-oleoyl ethanolamine (OEA), and N-palmityl ethanolamine (PEA).

Material/Methods: Transcript levels of CB1, CB2, TRPV1, GPR55, NAPE-PLD, and FAAH were measured using RT-PCR and correlated with the tissue levels of the 3 NAEs in myometrial tissues. The tissues studied were: 1) fibroids, 2) myometrium adjacent/juxtaposed to the fibroid lesions, and 3) normal myometrium. Thirty-seven samples were processed for NAE measurements and 28 samples were used for RT-PCR analyses.

Results: FAAH expression was significantly lower in fibroids, resulting in a NAPE-PLD: FAAH ratio that favors higher AEA levels in pre-menopausal tissues, whilst PEA levels were significantly lower, particularly in post-menopausal women, suggesting PEA protects against fibroid pathogenesis. The CB1: CB2 ratio was lower in fibroids, suggesting that loss of CB1 expression affects the fibroid cell phenotype. Significant correlations between reduced FAAH, CB1, and GPR55 expression and PEA in fibroids indicate that the loss of these endocannabinoid system components are biomarkers of leiomyomata.

Conclusions: Loss of expression of CB1, FAAH, GPR55, and PEA production are linked to the pathogenesis of uterine fibroids and further understanding of this might eventually lead to better disease indicators or the development of therapeutic potentials that might eventually be used in the management of uterine fibroids.

MeSH Keywords: Biological Markers • Endocannabinoids • Leiomyoma • Therapeutics • Uterus

Full-text PDF: https://www.basic.medscimonit.com/abstract/index/idArt/914019

Corresponding Author: Thangesweran Ayakannu, e-mail: t.ayakannu@nhs.net
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Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children

Courtney E. French, Isabelle Delon, Helen Dolling, Alba Sanchis-Juan, Olga Shamardina, Karyn Mégy, Stephen Abbs, Topun Austin, Sarah Bowdin, Ricardo G. Branco, Helen Firth, NIHR BioResource—Rare Disease, Next Generation Children Project, David H. Rowitch and F. Lucy Raymond

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Abstract

Purpose: With growing evidence that rare single gene disorders present in the neonatal period, there is a need for rapid, systematic, and comprehensive genomic diagnoses in ICUs to assist acute and long-term clinical decisions. This study aimed to identify genetic conditions in neonatal (NICU) and paediatric (PICU) intensive care populations.

Methods: We performed trio whole genome sequence (WGS) analysis on a prospective cohort of families recruited in NICU and PICU at a single site in the UK. We developed a research pipeline in collaboration with the National Health Service to deliver validated pertinent pathogenic findings within 2–3 weeks of recruitment.

Results: A total of 195 families had whole genome analysis performed (567 samples) and 21% received a molecular diagnosis for the underlying genetic condition in the child. The phenotypic description of the child was a poor predictor of the gene identified in 90% of cases, arguing for gene agnostic testing in NICU/PICU. The diagnosis affected clinical management in more than 65% of cases (83% in neonates) including modification of treatments and care pathways and/or informing palliative care decisions. A 2–3 week turnaround was sufficient to impact most clinical decision-making.

Conclusions: The use of WGS in intensively ill children is acceptable and trio analysis facilitates diagnoses. A gene agnostic approach was effective in identifying an underlying genetic condition, with phenotypes and symptomatology being primarily used for data interpretation rather than gene selection. WGS analysis has the potential to be a first-line diagnostic tool for a subset of intensively ill children.

Keywords: Whole genome sequencing, Genetics, Genomics, Critically ill children, NICU, PICU
A 74-year-old female with recurrent infections receiving methotrexate for rheumatoid arthritis

Rheumatology key message
- Consider specific antibody deficiency in autoimmune patients with recurrent infection despite normal immunoglobulin levels.

Sn, We report a 74-year-old female with seropositive RA, who presented to Immunology clinic describing two episodes of bronchitis each winter for numerous years. Throughout childhood, she recalled an increased number of infections compared with her peers.

She had a history of asthma, RA for 25 years, hyperthyroidism, hypercholesterolaemia, hypertension, atrial fibrillation and type 2 diabetes. Her immunosuppressive medications were MTX 25 mg weekly and HCQ 200 mg daily. She had not received any previous RA treatments. She was a non-smoker with a family history of asthma and bronchitis.

Immunology investigations showed normal serum immunoglobulins but low serotype-specific pneumococcal antibodies despite previous pneumococcal polysaccharide vaccine (PPV). Her CT thorax showed mild bronchiectasis, and sputum culture isolated upper respiratory tract commensals.

A diagnosis of specific antibody deficiency (SPAD) was made, on the basis of inadequate response to PPV. Treatment options included a trial of antibiotic prophylaxis or monitoring her symptoms with as-required antibiotic courses. The pneumococcal conjugate vaccine (PCV), Prevenar 13, was advised.

The serotype-specific pneumococcal IgG antibody results are summarized in Table 1, indicating a lack of response to both PPV and PCV, with the response remaining protective to only 3/13 serotypes. There is debate about the minimum protective antibody level (≥0.35 μg/ml UK, >1.3 μg/ml USA); a minimum of 70% of serotypes tested should be protective, with at least a 2- or 4-fold increase when tested 4 weeks post-vaccination.

After 6 months, she had required three antibiotic courses for respiratory tract infections. Antibiotic prophylaxis was commenced with azithromycin three times weekly. A course of co-amoxiclav was advised for breakthrough infections. Antibiotic prophylaxis required. The ensuing 6 months required three antibiotic courses for breakthrough infections. Throughout this time, her RA symptoms have been stable on continued MTX.

Infections cause significant morbidity and mortality in RA patients [1]. This case highlights the importance of further investigation, despite normal immunoglobulin levels in immunosuppressed patients with RA with recurrent infections. It is important not to assume infections are always secondary or related to use of MTX or other immunosuppressive agents, including CSs. Asthma and diabetess would contribute to her infection risk; however, the poor pneumococcal antibody response was evident.

SPAD is a primary immunodeficiency disorder of the B cell compartment [2]. It is defined as the failure of response to polysaccharide antigens, in the context of recurrent infections with normal immunoglobulin isotypes and normal serologic responses to protein antigens in patients of ≥2 years of age [2]. In this case it is difficult to ascertain if the patient has a primary immunodeficiency or a secondary immunodeficiency as she is receiving MTX. In view of her history of recurrent childhood infections, it appears possible that she has a primary immunodeficiency disorder, but that MTX has exacerbated the immunodeficiency. We cannot be certain on a retrospective basis, as there is currently no genetic diagnosis available for SPAD [3]. Al Hamzi et al. [4] reported SPAD predating the diagnosis of SLE and introduction of immunosuppression.

Clinical manifestations of SPAD include recurrent sino-pulmonary infections, which can be severe and prolonged [2]. Chronic and recurrent otitis media is common [2]. A partial or temporary improvement with antibiotic therapy is often noted, followed by rapid return of infection after antibiotic discontinuation [5]. Patients are susceptible to encapsulated bacterial pathogens, commonly Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis [2].

RA patients should ideally be vaccinated prior to starting MTX, because the antibody response following PPV may be impaired compared with RA treated without MTX, or healthy controls [1, 6]. However, MTX use should not obviate vaccination, because a large proportion of patients already receiving MTX will still mount a response [6]. Measurement of pneumococcal antibodies a minimum of 4 weeks after vaccination is important to undertake routinely post-vaccination to ensure adequate response in this group. If the patient has not responded to PPV, then PCV should be administered, though a gap is recommended to reduce the risk of vaccine hyporesponsiveness (currently 1 year in The Advisory
Committee on Immunization Practices guidelines) [7]. As a protein-conjugated vaccine, PCV is a more potent immunogen, inducing a T cell-dependent antibody response. In contrast, PPV is a pure polysaccharide vaccine, a weaker immunogen inducing only a T cell-independent antibody response. One advantage of PPV over PCV is the breadth of response, because it includes 23 serotypes, whereas PCV has 13 serotypes.

Consideration of SPAD in patients with recurrent infection despite normal immunoglobulins is important. Early investigation and referral to Immunology is vital and recommended in patients with recurrent infection.

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Disclosure statement: The authors have declared no conflicts of interest.

TABLE 1 Serotype-specific pneumococcal IgG antibody levels

<table>
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<tbody>
<tr>
<td>1</td>
<td>0.23</td>
<td>0.61</td>
<td>0.44</td>
<td>0.24</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
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<td>0.02</td>
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</tr>
<tr>
<td>5</td>
<td>4.5</td>
<td>0.03</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>6B</td>
<td>0.03</td>
<td>0.04</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>15B</td>
<td>0.2</td>
<td>0.2</td>
<td>0.16</td>
<td>0.43</td>
</tr>
<tr>
<td>9V</td>
<td>0.16</td>
<td>0.15</td>
<td>0.08</td>
<td>0.04</td>
</tr>
<tr>
<td>8</td>
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<td>1.18</td>
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<td>1.78</td>
</tr>
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<td>14</td>
<td>0.01</td>
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<td>0.1</td>
</tr>
<tr>
<td>18C</td>
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<td>0.08</td>
<td>0.06</td>
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</tr>
<tr>
<td>19A</td>
<td>0.58</td>
<td>1.25</td>
<td>0.78</td>
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</tr>
<tr>
<td>12F</td>
<td>0.01</td>
<td>0.05</td>
<td>0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>23F</td>
<td>0.14</td>
<td>0.17</td>
<td>0.15</td>
<td>0.09</td>
</tr>
<tr>
<td>Low antibodies</td>
<td>10/13</td>
<td>10/13</td>
<td>10/13</td>
<td>10/13</td>
</tr>
</tbody>
</table>

Values in μg/ml. Protective level considered to be >0.35 μg/ml, in keeping with UK data. PPV: pneumococcal polysaccharide vaccine; PCV: pneumococcal conjugate vaccine; IGRT: immunoglobulin replacement therapy.

Committee on Immunization Practices guidelines) [7]. As a protein-conjugated vaccine, PCV is a more potent immunogen, inducing a T cell-dependent antibody response. In contrast, PPV is a pure polysaccharide vaccine, a weaker immunogen inducing only a T cell-independent antibody response. One advantage of PPV over PCV is the breadth of response, because it includes 23 serotypes, whereas PCV has 13 serotypes.

Consideration of SPAD in patients with recurrent infection despite normal immunoglobulins is important. Early investigation and referral to Immunology is vital and recommended in patients with recurrent infection.

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Outcomes and Treatment Strategies for Autoimmunity and Hyperinflammation in Patients with RAG Deficiency

Jocelyn R. Farmer, MD, PhD*a,†, Zsofia Foldvari, MD*b,†, Boglarka Ujhazi, MS†, Suk See De Ravin, MD, PhDd, Karin Chen, MD*e, Jack J.H. Bleesing, MD, PhD*, Catharina Schuetz, MDf, Wareed Al-Herz, MDg, Roshini S. Abraham, PhD*, Avni Y. Joshi, MD, Beatriz T. Costa-Carvalho, MDh, David Buchbinder, MDi, Claire Booth, MD, PhDj, Andreas Reiff, MDk, Polly J. Ferguson, MDl, Mohammed Al-Mahdi, MDm, Jack J.H. Bleesing, MD, PhDn, Catharina Schuetz, MD, Phdo, Andreas Reiff, MD, Phdp, Polly J. Ferguson, MD, Phdq, Asghar Aghamohammadi, MD, PhDq, Hassam Al-Ahmad, MD, PhD, Jennifer M. Puck, MD, Mehdii Adeli, MD, Caterina Cancrini, MD, PhDv, Paolo Palma, MD, PhDw, Alice Bertain, MD, PhDx, Franco Locatelli, MD, PhDy, Vincenzo Di Matteo, BS, PhDz, Ralf S. Geha, MDa, Maria G. Kanariou, MD, Phdb, Musa Karakoc-Aydiner, MD, PhDc, John W. Sleasman, MD, MMSO, Suhas Parikh, MD, CCE, Gloria Pinerro, CCRC, Bernard M. Fischer, DVM, PhD, Ghassan Dbaibo, MD, FAAP, Ekrem Unal, MD, Turkan Patiroglu, MD, Masa Karakucu, MD, Kholood Khalfia Al-Saad, MD, Meredith A. Dilley, MD, MPH, Sung-Yun Pai, MD, CCE, Cullen M. Dutmer, MD, Erwin W. Gelfand, MD, Christoph B. Geier, BSC, Martha M. Eibl, MD, Hermann M. Wolf, MD, Lauren A. Henderson, MD, MMSO, Melisa M. Hazen, MD, Carmem Bonfim, MD, PhD, Beata Wolska-Kusniercz, MD, PhD, Manish J. Butte, MD, PhD, Joseph D. Hernandez, MD, PhD, Sarah K. Nicholas, MD, Polina Stepensky, MD, Shambunanathan Chandramohan, MD, Maurizio Miano, MD, Emma Westermann-Clark, MD, Vera Goda, MD, Gergely Kriván, MD, PhDb, Steven M. Holland, MD, Olaumesofadu, MD, Sarah E. Henrikson, MD, PhDe, Ahmet Ozen, MD, Elif Karakoc-Aydiner, MD, Safa Baris, MD, Ayca Kiyik, MD, Robbert Bredius, MD, PhD, Birgit Hoeger, PhD, Kaan Boztug, MD, Olga Pashchenko, MD, PhD, Benedicte Neven, MD, PhD, Despina Moshous, MD, PhD, Jean-Pierre de Villaray, PhD, Ahmed Aziz Bousfiha, MD, Harry R. Hill, MD, Luigi D. Notarangelo, MD, and Jolan E. Walter, MD, PhD.

Boston, Mass; Radiumhospitalet, Norway; Saint Petersburg and Tampa, Fla; Bethesda, Md; Salt Lake City, Utah; Cincinnati and Columbus, Ohio; Ulm, Germany; Kuwait City, Kuwait; Rochester, Minn; Sao Paulo, Brazil; Irvine, Los Angeles, San Francisco, and Stanford, Calif; London, United Kingdom; Iowa City, Iowa; Tehran, Iran; Doha, Qatar; Rome, Italy; Athens, Greece; Durham, NC; Beirut, Lebanon; Kayseri, Turkey; Kingdom of Bahrain; Aurora and Denver, Colo; Vienna, Austria; Curitiba, Brazil; Warsaw, Poland; Houston, Texas; Jerusalem, Israel; Atlanta, Ga; Genova, Italy; Budapest, Hungary; Philadelphia, Pa; Istanbul, Turkey; Leiden, the Netherlands; Moscow, Russia; Paris, France; and Casablanca, Morocco

What is already known about this topic? Knowledge of autoimmunity in recombination activating gene (RAG) deficiency has been limited to small case series; herein, we introduce the largest international database of RAG-deficient cases with prominent autoimmune and hyperinflammatory disease, facilitating detailed outcomes and treatment analysis.

What does this article add to our knowledge? RAG diagnosis is delayed in the setting of autoimmunity or hyperinflammation (median, 5 years); autoimmune cytopenias are prevalent (84.1%), have early onset (median, 1.9-2.6 years), and lack of first-line treatment response correlates strongly with multilineage disease.

How does this study impact current management guidelines? RAG deficiency can present with autoimmunity/hyperinflammation; low naive (CD45RA+) T-cell counts are a useful diagnostic tool; and multilineage cytopenias are refractory to immunosuppressive treatment in most cases and should prompt expedited hematopoietic cell transplantation evaluation.
Effects of empagliflozin on metabolic parameters in polycystic ovary syndrome: A randomized controlled study

Zeeshan Javed1,2 | Maria Papageorgiou1,3 | Harshal Deshmukh1 | Alan S. Rigby4 |
Unaiza Qamar5 | Jehangir Abbas2 | Amer Y. Khan6 | Eric S. Kilpatrick7 |
Stephen L. Atkin8 | Thozhukat Sathyapalan1

1Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull, UK
2Department of Endocrinology and Diabetes, Pakistan Kidney & Liver Institute and Research Centre, Lahore, Pakistan
3Department of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology, and Immunology, Medical University of Vienna, Vienna, Austria
4Hull York Medical School, University of Hull, Hull, UK
5Department of Pathology, Pakistan Kidney & Liver Institute and Research Centre, Lahore, Pakistan
6Department of Medicine, Pakistan Kidney & Liver Institute and Research Centre, Lahore, Pakistan
7Department of Pathology, Sidra Medical and Research Center, Doha, Qatar
8Weill Cornell Medical College Qatar, Doha, Qatar

Correspondence
Thozhukat Sathyapalan, Department of Academic Diabetes, Endocrinology and Metabolism, Hull York Medical School, University of Hull, Hull, UK.
Email: Thozhukat.Sathyapalan@hyms.ac.uk

Funding information
University of Hull

Summary

Background: Empagliflozin is a sodium-glucose-cotransporter-2 inhibitor that improves cardiovascular risk and promotes weight loss in patients with type-2 diabetes. Polycystic ovary syndrome (PCOS) is associated with obesity and increased cardiovascular risk; therefore, empagliflozin may be of benefit for these women. The aim of this study was to compare the effects of empagliflozin vs metformin on anthropometric and body composition, hormonal and metabolic parameters in women with PCOS.

Materials and methods: A randomized open-label study was conducted in women with PCOS who were randomized to either empagliflozin 25 mg (n = 19) or metformin 1500 mg (n = 20) daily for 12 weeks. The main outcomes assessed were changes in anthropometric and body composition, hormonal and metabolic parameters.

Results: Univariate analysis showed significant differences in weight (empagliflozin: −1.4 ± 3.2% vs metformin: 1.2 ± 2.3%; P = 0.006), body mass index (empagliflozin: −1.4 ± 3.2% vs metformin: 1.1 ± 2.2%; P = 0.006), waist circumference (empagliflozin: −1.6 ± 2.8% vs metformin: 0.2 ± 2.1%; P = 0.029) and hip circumference (empagliflozin: −2.0 ± 3.0% vs metformin: 1.1 ± 1.9%; P = 0.001), basal metabolic rate (empagliflozin: −1.8 ± 2.9% vs metformin: 0.1 ± 1.9%; P = 0.024) and fat mass (empagliflozin: −0.7 ± 4.9% vs metformin, 3.2 ± 5.0%; P = 0.023) between the empagliflozin and the metformin groups. These differences were confirmed in linear regression analysis after adjustment for relevant covariates. There were no significant changes in hormonal or metabolic parameters between both groups.

Conclusion: There was a significant improvement in anthropometric parameters and body composition, in overweight and obese women with PCOS after 12 weeks of treatment with empagliflozin compared to metformin, although no changes were seen in hormonal or metabolic parameters.

Keywords
body composition, empagliflozin, hormones, metabolic parameters, polycystic ovary syndrome, SGLT2 inhibitors
The pediatric airway: Historical concepts, new findings, and what matters

Tariq M. Wani, Bruno Bissonnette, Thomas Engelhardt, Basharat Buchh, Hassan Arnous, Faris AlGhamdi, Joseph D. Tobias

1. Introduction

The funnel or conical shaped of the pediatric airway has been challenged by recent studies using various imaging modalities that provide three-dimensional evaluations of the airway. The following narrative reviews the historical evolution of pediatric airway studies, summarizes important scientific observations from recent investigations relevant to our clinical understanding of pediatric airway anatomy, and discusses the importance of these findings for pediatric airway management. An improved understanding of the dimensions and shape of the pediatric airway may impact the development of the airway devices including endotracheal tubes as well as the clinical practice of pediatric anesthesiology.

2. Pre-clinical investigations of the pediatric airway

The first well-detailed description of the pediatric airway with anatomical measurements of the glottic and subglottic areas dates back to 1897 when Bayeux studied 28 cadaveric larynxes from children ranging in age from 4 months to 14 years. He used lost wax castings and plaster bath techniques to study the shape of the airway while the airway size and dimensions were evaluated using calibration rods of increasing diameters with measurements taken at the cricoid ring, the glottis, and the trachea. He reported that the airway was different when viewed in anteroposterior and transverse sections. In the anteroposterior sections, the cricoid ring was the narrowest part of the larynx whereas in the transverse sections, these relations were inversed with the larynx being narrowest at the glottis (Fig. 1). This latter observation, that larynx is narrowest at the glottis in transverse sections, was not emphasized in the later literature, which often quoted and referred to his work.

Bayeux preferred using bougies rather than injecting the airway with solidifiable material. He justified using calibrated cylinders by comparing them to the technique utilized at that time to determine the extent of urethral stenosis. He emphasized the significant variability of dimensions when measurements were obtained using castings and opined that calibrated cylinders gave more precise measurements. In his study, he noted that the calibrated bougies abruptly stopped at the cricoid ring, but they would easily pass if the cricoid was incised. The gap needed to allow passage of the bougie was measured using calipers and the difference in bougie sizes between the cricoid ring, the trachea, and the glottis was noted. On the basis of these observations, Bayeux

New observations from novel imaging techniques regarding the anatomy, dimensions, and shape of the pediatric airway have emerged and provide insight for potential changes in the clinical management of the airway in infants and children. These new findings are challenging the historical concepts of a funnel-shaped upper airway with the cricoid ring as the narrowest dimension. Although these tenets have been accepted and used to guide clinical practice in airway management, there are limited clinical investigations in children to support the validity of these concepts. Imaging modalities such as magnetic resonance imaging, computed tomography (CT) scanning, multi-detector CT imaging, and videobronchoscopy suggest the need to revisit the historical view of the pediatric airway. This manuscript reviews the historical evolution of pediatric airway studies, summarizes important scientific observations from recent investigations relevant to our clinical understanding of pediatric airway anatomy, and discusses the importance of these findings for pediatric airway management.
SCAI expert consensus statement on operator and institutional requirements for PFO closure for secondary prevention of paradoxical embolic stroke

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Eric Horlick MD, FSCAI (Chair)\(^1\) | Clifford J. Kavinsky MD, PhD, MSCAI (Co-Chair)\(^2\) | Zahid Amin MD, MScAI\(^3\) | Konstantinos Dean Boudoulas MD, FSCAI\(^4\) | John D. Carroll MD, MScAI\(^5\) | Ziyad M. Hijazi MD, MScAI\(^6,7\) | Dana Leifer MD, FAAN\(^8\) | Helmi L. Lutsep MD, FAAN\(^9\) | John F. Rhodes MD, FSCAI\(^10\) | Jonathan M. Tobis MD, MScAI\(^11\)

\(^1\)Institute of Medical Science, University Health Network, Toronto, Ontario
\(^2\)Section of Structural and Interventional Cardiology, Rush University Medical Center, Chicago, Illinois
\(^3\)Division of Pediatric Cardiology, Augusta University, Augusta, Georgia
\(^4\)Division of Cardiovascular Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio
\(^5\)Department of Medicine-Cardiology, University of Colorado, Denver, Colorado
\(^6\)Department of Pediatrics, Sidra Medicine, Doha, Qatar
\(^7\)Department of Pediatrics, Weill Cornell Medicine, New York, New York
\(^8\)Department of Neurology, Weill Cornell Medicine, New York, New York
\(^9\)Department of Neurology, Oregon Health and Science University, Portland, Oregon
\(^10\)Congenital Heart Center, Medical University of South Carolina, Charleston, South Carolina
\(^11\)Department of Medicine, University of California, Los Angeles, California

Correspondence
Eric Horlick, University Health Network, 1 King's College Circle Toronto, ON M5S 1A8.
Email: eric.horlick@uhn.ca

Abstract

Until recently, evidence to support Patent Foramen Ovale (PFO) closure for secondary prevention of recurrent stroke has been controversial. Publication of high-quality evidence from randomized clinical trials and the subsequent FDA approval of two devices for percutaneous PFO closure is expected to increase the volume of PFO closure procedures not only in the United States but worldwide. As this technology is disseminated broadly to the public, ensuring the safe and efficacious performance of PFO closure is essential to mitigate risk and avoid unnecessary procedures. This document, prepared by a multi-disciplinary writing group convened by the Society for Cardiovascular Angiography and Interventions and including representatives from the American Academy of Neurology, makes recommendations for institutional infrastructure and individual skills necessary to initiate and maintain an active PFO/stroke program, with emphasis on shared decision making and patient-centered care.

KEYWORDS

ASD/PDA/PFO, comparative effectiveness/patient centered outcomes research, closure, evidence-based medicine, structural heart disease intervention

1 | PREAMBLE

Cryptogenic stroke in young to middle-aged individuals represents a significant problem in terms of disability and societal costs. The FDA approval of the Amplatzer Patent Foramen Ovale (PFO) Occluder in October 2016, and the Gore Cardioform device in March 2018, represents an important nonpharmacologic treatment to reduce the risk of recurrent stroke. These approvals cap an almost two-decade journey in
Whole blood human transcriptome and virome analysis of ME/CFS patients experiencing post-exertional malaise following cardiopulmonary exercise testing

Jerome Bouquet, Tony Li, Jennifer L. Gardy, Xiaoying Kang, Staci Stevens, Jared Stevens, Mark Van Ness, Christopher Snell, James Potts, Ruth R. Miller, Muhammad Morshed, Mark McCabe, Shoshana Parker, Miguel Uyaguari, Patrick Tang, Theodore Steiner, Wee-Shian Chan, Astrid-Marie De Souza, Andre Mattman, David M. Patrick, Charles Y. Chiu

1 Department of Laboratory Medicine, University of California San Francisco, San Francisco, California, United States of America. 2 Communicable Disease Prevention and Control Services, Vancouver, Canada. 3 School of Population and Public Health, University of British Columbia, Vancouver, Canada. 4 Workwell Foundation, Ripon, California, United States of America. 5 Department of Pediatrics, Division of Cardiology, University of British Columbia, Vancouver, Canada. 6 British Columbia Centre for Disease Control Public Health Laboratory, Vancouver, Canada. 7 Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada. 8 Centre for Health Evaluation Outcome Sciences, Vancouver, Canada. 9 Department of Pathology, Sidra Medical and Research Center, Doha, Qatar. 10 Department of Medicine, Division of Infectious Diseases, University of British Columbia, Vancouver, Canada. 11 Division of Cardiology, British Columbia’s Children’s Hospital, Vancouver, Canada. 12 Adult Metabolic Disease Clinic, Vancouver General Hospital, Vancouver, Canada. 13 Department of Medicine, Division of Infectious Diseases, University of California San Francisco, San Francisco, California, United States of America.

Abstract

Myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) is a syndrome of unknown etiology characterized by profound fatigue exacerbated by physical activity, also known as post-exertional malaise (PEM). Previously, we did not detect evidence of immune dysregulation or virus reactivation outside of PEM periods. Here we sought to determine whether cardiopulmonary exercise stress testing of ME/CFS patients could trigger such changes. ME/CFS patients (n=14) and matched sedentary controls (n=11) were subjected to cardiopulmonary exercise on 2 consecutive days and followed up to 7 days post-exercise, and longitudinal whole blood samples analyzed by RNA-seq. Although ME/CFS patients showed significant worsening of symptoms following exercise versus controls, with 8 of 14 ME/CFS patients showing reduced oxygen consumption (VO₂) on day 2, transcriptome analysis yielded only 6 differentially expressed gene (DEG) candidates when comparing ME/CFS patients to controls across all time points. None of the DEGs were related to immune signaling, and no DEGs were found in ME/CFS patients before and after exercise. Virome composition (P = 0.746 by chi-square test) and number of viral reads (P = 0.098 by paired t-test) were not significantly associated with PEM. These observations do not support transcriptionally-mediated immune cell dysregulation or viral reactivation in ME/CFS patients during symptomatic PEM episodes.
Effect of Sustained Inflations vs Intermittent Positive Pressure Ventilation on Bronchopulmonary Dysplasia or Death Among Extremely Preterm Infants
The SAIL Randomized Clinical Trial

Haresh Kirpalani, BM, MSc; Sarah J. Ratcliffe, PhD; Martin Keszler, MD; Peter G. Davis, MD, FRACP; Elizabeth E. Foglia, MD, MSCE; Arjan te Pas, MD, PhD; Melissa Fernando, MPH; Aasma Chaudhary, BS, RRT; Russell Localio, PhD; Anton H. van Kaam, MD, PhD; Wes Orlund, MD, PhD; Louise S. Owen, MD, FRACP; Daniel Klotz, MD; Burkhard Simma, MD; Vinay Nadkarni, MD, PhD; Anup Katheria, MD; Helmut Hummler, MD, MBA; Gianluca Lista, MD, PhD; Soraya Abbasi, MD; Daniel Klitz, MD; Russell Localio, PhD; Steven M. Donn, MD; Aasma Chaudhary, BS, RRT; Sara D. Weiss, MD, FRACP; Andrew O. Hooper, MD; Masanori Tamura, MD, PhD; on behalf of the SAIL Site Investigators

IMPORTANCE Preterm infants must establish regular respirations at delivery. Sustained inflations may establish lung volume faster than short inflations.

OBJECTIVE To determine whether a ventilation strategy including sustained inflations, compared with standard intermittent positive pressure ventilation, reduces bronchopulmonary dysplasia (BPD) or death at 36 weeks postmenstrual age without harm in extremely preterm infants.

DESIGN, SETTING, AND PARTICIPANTS Unmasked, randomized clinical trial (August 2014 to September 2017, with follow-up to February 15, 2018) conducted in 18 neonatal intensive care units in 9 countries. Preterm infants 23 to 26 weeks’ gestational age requiring resuscitation with inadequate respiratory effort or bradycardia were enrolled. Planned enrollment was 600 infants. The trial was stopped after enrolling 426 infants, following a prespecified review of adverse outcomes.

INTERVENTIONS The experimental intervention was up to 2 sustained inflations at maximal peak pressure of 25 cm H2O for 15 seconds using a T-piece and mask (n = 215); standard resuscitation was intermittent positive pressure ventilation (n = 211).

MAIN OUTCOME AND MEASURES The primary outcome was the rate of BPD or death at 36 weeks’ postmenstrual age. There were 27 prespecified secondary efficacy outcomes and 7 safety outcomes, including death at less than 48 hours.

RESULTS Among 460 infants randomized (mean [SD] gestational age, 25.3[0.97] weeks; 50.2% female), 426 infants (92.6%) completed the trial. In the sustained inflation group, 137 infants (63.7%) died or survived with BPD vs 125 infants (59.2%) in the standard resuscitation group (adjusted risk difference [aRD], 4.7% [95% CI, −3.8% to 13.1%]; P = .29). Death at less than 48 hours of age occurred in 16 infants (7.4%) in the sustained inflation group vs 3 infants (1.4%) in the standard resuscitation group (aRD, 5.6% [95% CI, 2.1% to 9.1%]; P = .002). Blinded adjudication detected an imbalance of rates of early death possibly attributable to resuscitation (sustained inflation: 11/16; standard resuscitation: 1/3). Of 27 secondary efficacy outcomes assessed by 36 weeks’ postmenstrual age, 26 showed no significant difference between groups.

CONCLUSIONS AND RELEVANCE Among extremely preterm infants requiring resuscitation at birth, a ventilation strategy involving 2 sustained inflations, compared with standard intermittent positive pressure ventilation, did not reduce the risk of BPD or death at 36 weeks’ postmenstrual age. These findings do not support the use of ventilation with sustained inflations among extremely preterm infants, although early termination of the trial limits definitive conclusions.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT02139800


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European Society of Paediatric Radiology abdominal imaging task force: statement on imaging in very early onset inflammatory bowel disease

Tom A. Watson1,2, Philippe Petit2, Thomas A. Augdal3, E. Fred Avni4, Costanza Bruno5, M. Beatrice Damasio6, Kassa Darge7, Damjana Kucevsek8, Stéphanie Franchi-Abella9, Donald Ibe10, Annemieke Littooy11, Luisa Lobo12, Hans J. Mentrze13, Marcello Napolitano14, Alkaterini Ntoula15, Michael Riccabona16, Samuel Stafrace17, Magdalena Wozniak18, Lil-Sofie Ording Müller19

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Abstract

Very early onset inflammatory bowel disease (VEO-IBD) is defined as disease presenting before the age of 6. These children require a tailored imaging approach because conventional imaging studies can be difficult to perform at such a young age. Unlike inflammatory bowel disease in older children and adults, colonic disease predominates in VEO-IBD, and small-bowel disease is rare. Distinguishing Crohn disease from ulcerative colitis is challenging both clinically and on histology. Radiology offers the greatest utility for detecting small-bowel disease because it helps to distinguish the two main disease entities and guide clinical management. Small-bowel ultrasound is recommended as the first-line investigation because it requires relatively little preparation, is readily available and is generally well tolerated in young children. We present these recommendations, based on the

1 Department of Radiology, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH, UK
2 Service d’Imagerie Pédiatrique et Préanale, Hôpital Timone Enfants, Marseille, France
3 Department of Radiology, University Hospital of North Norway, Tromsø, Norway
4 Department of Pediatric Radiology, CHRU de Lille, Lille, France
5 Department of Radiology, Radiology Institute, Verona, Italy
6 Department of Radiology, G. Gaslini Institute, Genoa, Italy
7 Department of Radiology, The Children’s Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA
8 Department of Diagnostic Imaging, University Children’s Hospital, Ljubljana, Slovenia
9 Department of Paediatric Radiology, Hôpital Bicêtre - Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Orsay, France
10 Department of Radiology, Ahmadu Bello University Teaching Hospital Shika, Zaria, Kaduna, Nigeria
11 Princess Maxima Center for Pediatric Oncology, Wilhelmina Children’s Hospital Utrecht/UMCU, Utrecht, the Netherlands
12 Department of Radiology, Hospital de Santa Maria-CHLN, University Hospital, Lisbon, Portugal
13 Section of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, University Hospital Jena, Jena, Germany
14 Department of Paediatric Radiology and Neuroradiology, Y. Zuzi Children’s Hospital, Milan, Italy
15 Department of Radiology, Poole Hospital NHS Foundation Trust, Poole, UK
16 Department of Radiology, Division of Pediatric Radiology, University Hospital Graz, Graz, Austria
17 Sidra Medicine, Doha, Qatar
18 Department of Pediatric Radiology, Medical University of Lublin, Lublin, Poland
19 Department of Radiology and Nuclear Medicine, Unit for Paediatric Radiology, Oslo University Hospital, Oslo, Norway

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current evidence for radiologic management in this group, and propose an imaging algorithm for investigating VEO-IBD.

**Keywords** Children · Computed tomography · Infant · Inflammatory bowel disease · Magnetic resonance imaging · Ultrasound

**Introduction**

The main objective of the European Society of Paediatric Radiology (ESPR) abdominal imaging task force is to develop proposals and protocols with the intention of optimising the radiologic management of conditions and pathology pertaining to the gastrointestinal and genitourinary tracts in children. To this end, a range of proposals was sent to the task force committee prior to the ESPR annual meeting in June 2018 in Berlin.

One of this year’s topics was “how to image children presenting with very early onset inflammatory bowel disease (VEO-IBD).” This condition is defined as disease presenting before the age of 6 years [1]. This group of patients can have different clinical presentations and disease courses from those seen in older children, and standard paediatric inflammatory bowel disease imaging protocols [2] are challenging to apply. Evidence-based imaging recommendations are scarce. It is proposed that these children need a different imaging strategy, and the task force addressed this particular problem. Our aim was to suggest a radiologic approach and to discuss the value of each imaging modality in these children. The task force performed a literature search and conducted discussions via email and in person at task force meetings. The resulting proposals were presented, discussed and approved at the public task force session at the ESPR 2018 annual meeting.

**Early onset inflammatory bowel disease**

25% of inflammatory bowel disease cases are diagnosed before the age of 20. Early onset inflammatory bowel disease is defined as a diagnosis before 10 years of age. There are subgroups defined as VEO-IBD (<6 years), infantile inflammatory bowel disease (<2 years) and neonatal inflammatory bowel disease. Fewer than 15% of children with inflammatory bowel disease are diagnosed before the age of 6 years.

Children with VEO-IBD might have a different phenotype and genotype compared to those of older children, adolescents and adults with inflammatory bowel disease. Of the known genetic mutations, those involving pathways encoding IL-10, XIAP and IPLEX have the largest evidence base [1, 3].

Colonic disease is common in VEO-IBD. Ileal disease is relatively rare in young children [4]. Very young children with certain genetic mutations can present with fulminant perianal disease requiring surgical input (Fig. 1) [5].

Differentiating Crohn disease from ulcerative colitis in this young age group can be very challenging clinically and histopathologically. One might also expect considerable overlap on imaging. Pancolitis is a frequent presentation in VEO-IBD, and backwash ileitis is associated with it. In cases where isolated terminal ileal disease is seen at imaging, the radiologist should be cautious to interpret this as Crohn disease, especially if there is history of significant proximal colitis. Contiguous colonic disease is not always seen in early onset ulcerative colitis, and cases with rectal sparing should be treated with similar caution. In light of these challenges, many children are labelled as inflammatory bowel disease-unclassified (IBD-U). The definitive treatment for ulcerative colitis is a panproctocolectomy and ileo-anal pouch. Premature diagnosis of ulcerative colitis can result in surgery being performed in a child who is subsequently diagnosed with Crohn disease [6].

Differential diagnoses include the following:

- Cow’s milk protein allergy, which is sometimes a precursor of paediatric inflammatory bowel disease [7]. This results in a severe colitis that resembles ulcerative colitis. It is often diagnosed after improvement on an exclusion diet. Children might demonstrate high serum-immunoglobulin E levels.
- Infection (bacterial, e.g., Yersinia spp., Campylobacter spp., Salmonella spp., Shigella spp., tuberculous; parasitic, e.g., Giardia spp.; and viral, e.g., cytomegalovirus, human immunodeficiency virus [HIV]).
- Coeliac disease.
- Inflammation (e.g., vasculitis with gastrointestinal involvement).

Where possible, the radiologist should assess for positive indicators of these differentials as part of the initial workup. In children without a prior histological diagnosis, the radiologist should be cautious to assert a specific diagnosis to the radiologic findings because there can be considerable overlap between inflammatory bowel disease and these conditions.

**Imaging**

There are limited data on the optimum imaging strategy in these young children. The standard imaging approach used in older children, adolescents and adults might not be appropriate [7]. Magnetic resonance imaging (MR) enterography/enteroclysis is difficult because these children often need a general anaesthetic that precludes conventional luminal
Congenital Mid Ureteric Valve Stenosis Revisited: Case Report and Review of the Literature

Mohammed Elifranji1*, Abderrahman Elkadahi1, Adrian Charles2 and Tariq O. Abbas1,3,4

1 Department of Pediatric Surgery, Hamad General Hospital, Doha, Qatar, 2 Pathology Department, Sidra Medicine, Doha, Qatar, 3 College of Medicine, Qatar University, Doha, Qatar, 4 Surgery Department, Weil Cornell Medicine-Qatar, Doha, Qatar

Congenital mid ureteric valve (MUV) stenosis is a very rare entity. Definitive preoperative diagnosis is clinically challenging, and most patients are misdiagnosed preoperatively. Intraoperative identification is therefore very important. Curative treatment consists of excision of the involved ureteric segment and anastomosis. This report describes the clinical findings in a patient with congenital mid ureteric valve stenosis, including radiological and histological workup and operative management. Routine intraoperative retrograde pyelography is important in the diagnosis of such rare pathologies.

Keywords: congenital, PUJ obstruction, valve, hydronephrosis, ureter, retrograde pyelography

INTRODUCTION

Congenital mid ureteric valve (MUV) stenosis is a very rare cause of ureteric obstruction and hydronephrosis (HN) in children. Since initially described in 1877, only about 65 patients have been diagnosed with congenital MUV stenosis (1). Most children who present with this condition are initially diagnosed with more common conditions, including pelviureteric junction (PUJ) obstruction and megaureter (MU) (2). Therefore, a high level of suspicion is required. This report describes the clinical findings in a patient with congenital MUV stenosis, including radiological and histological workup, and operative management.

CASE REPORT

The patient was a 4-month-old boy born at gestational age of 36 weeks by elective cesarean section because of placenta previa. During the third trimester, he was found to have right hydronephrosis, with an anteroposterior diameter (APD) of 27 mm and SFU 4. His left kidney and urinary bladder were normal, as were his initial physical examination and laboratory workup at birth. A voiding cystourethrogram at 1 day of age showed a normal bladder and urethra and no evidence of vesicoureteric reflux. Ultrasound examination showed right hydronephrosis with an APD of 26 mm (Figure 1). Diuretic renal scintigraphy with Tc 99m DTPA showed right renal pelvic dilatation with an obstructive pattern of radiotracer washout and a differential renal function of 40% (Figure 2). Follow-up renal ultrasound at 2 months of age showed the persistence of high grade right hydronephrosis with mild thinning of the renal cortex.

Based on a preoperative working diagnosis of right pelviureteric junction obstruction, the patient was scheduled for right pyeloplasty. Routine intraoperative cystoscopy and right retrograde pyelography prior to pyeloplasty showed that the contrast was unable to pass beyond a proximal ureteric narrowing, with subsequent application of higher pressure resulting in reflux toward the urinary bladder (Figure 3).
Impact of Glabellar Paralysis on Facial Expression of Emotion

Mitchell L. Wyffels, MD; Belinda B. Ray, MA; Jason T. Laurita, MD; Natalia Zbib, BA; Kinan Bachour, BS; Graeme E. Glass, PhD, FRCS (Plast); and Mitchell A. Stotland, MD, MS, FRCSC (Plast)

Dr Wyffels is an Attending Surgeon, Orthopedic Surgery and Sports Medicine of Sanford Health, Bemidji, MN. Ms Ray is a Health Coach, Center for Shared Decision Making, Dartmouth Hitchcock Medical Center, Lebanon, NH. Dr Laurita is a Resident, Department of Orthopedic Surgery, Oregon Health and Sciences University, Portland, OR. Ms Zbib and Mr Bachour are Medical Students, Geisel School of Medicine at Dartmouth, Hanover, NH. Dr Glass is an Associate Professor of Clinical Surgery and Dr Stotland is an Associate Professor of Clinical Surgery and Chief, Division of Plastic and Craniofacial Surgery, Sidra Medicine, Weill Cornell Medical College, Doha, Qatar.

Corresponding Author: Dr Mitchell A. Stotland, Room C1-121, Sidra Medical and Research Center, Weill Cornell Medical College-Qatar, Qatar Foundation, PO Box 26999, Doha, Qatar
E-mail: mstotland@sidra.org; Twitter: @mitch_stotland

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Level of Evidence: 4 (Therapeutic)


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Abstract

**Background:** Many prospective patients remain wary of the effects that glabellar muscle paralysis may have on their ability to normally communicate emotion with their face.

**Objective:** We undertook a direct empirical test of the effects of glabellar onabotulinum toxin type A injections on the ability to convey six universally recognized facial expressions of emotion.

**Methods:** Fifty-two female subjects ("expressors") were recorded on hidden camera while viewing video clips using a mood induction procedure that stimulates the six cardinal emotions (amusement, anger, disgust, fear, sadness, surprise). The subjects were then injected with 25 units of onabotulinum toxin A in the glabellar region. The subjects returned one month later and were again recorded while being spontaneously induced to express emotion. All video clips from both time periods from the 10 maximal expressors were extracted and shown to a group of 31 "perceivers" who rated the facial expressions for intensity (Likert 1-7) and identity of emotion (% correct emotion identified).

**Results:** Glabellar paralysis significantly diminished mean perceived intensity of anger (50.4% relative reduction, p<0.001) and surprise (20.6% relative reduction, p<0.001). The mean intensity of disgust increased (39.0%, p<0.001). Importantly, however, glabellar paralysis did not result in a significant change in observers' ability to discern provoked cardinal emotions.

**Conclusions:** We believe these findings provide a measure of reassurance to patients and their providers that the use of onabotulinum toxin A to paralyze the glabellar musculature for aesthetic purposes may not pose a meaningful risk to the overall ability to express emotion during social interaction.
Editorial

Rebound stridor in children with croup after nebulised adrenaline: does it really exist?

Laryngotracheobronchitis is a common childhood illness affecting 3% of children. Most of the affected children are aged between 6 months and 3 years, with a peak incidence of 60 per 1000 child-years in those children aged between 1 and 2 years [1]. Epidemiological studies suggest that 1–5% of children with croup are admitted to hospital and 2–3% of those admitted children, require intubation [2]. Death is extremely rare and has been estimated to occur in no more than 1 in 30000 cases [2]. Parainfluenza (types 1 and 3), and influenza A and B are the most common viral agents causing croup. Respiratory syncytial virus (RSV), rhinovirus, coronavirus, metapneumovirus and adenovirus are also responsible for this illness. There is seasonality to the prevalence with more presentations in the autumn. There is an annual pattern influenced by the variability of the viruses in the community for that year [2].

Croup is characterised by a “barking” cough, hoarse voice, stridor and respiratory distress caused by generalised airway inflammation and oedema of the upper airway mucosa. Most children have mild illness which resolves spontaneously without any specific treatment. However, some children have severe illness with stridor, respiratory distress and hypoxaemia requiring intubation. Current evidence strongly supports the use of glucocorticoids for the management of croup [3]. Previously it was felt that steroids took up to 6 h to have an effect on the airway [4], but a recent Cochrane review concluded that glucocorticoids improve croup symptoms at 2 h with the effect lasting at least 24 h [3]. Glucocorticoids also reduce rates of return visits, admissions and readmissions. When treated with placebo, 204 out of every 1000 children will return for medical care. When treated with glucocorticoids, 74–153 out of every 1000 children will return for medical care [3]. Glucocorticoids reduce the length of stay by 15 h (range 6–24 h), but make no difference to the need for additional treatments. Dexamethasone 0.15 mg·kg⁻¹ or prednisolone 1 mg·kg⁻¹ would be the recommended treatment dosing [2], although other guidelines suggest doses up to 0.6 mg·kg⁻¹ of dexamethasone [3].

Nebulised adrenaline/epinephrine is recommended for use in severe and life-threatening croup [5], although some guidelines use it for those children with moderate symptoms [6]. Nebulised adrenaline has been associated with a clinically and statistically significant transient reduction in croup symptoms 30 min post-treatment [5] and can “buy time” for steroids to act. Children with croup develop swelling of inner mucosal layers of the larynx and trachea. Nebulised adrenaline is thought to act by stimulating α-adrenergic receptors in subglottic mucous membranes, producing vasoconstriction and decreased mucosal oedema. The clinical effect is sustained for at least 1 h, but disappears after 2 h. Studies of nebulised adrenaline treatment of croup have used both racemic and L-adrenaline. One small trial found that L-adrenaline (5.0 mL, 0.1% (1:1000)) was as effective and safe as racemic adrenaline (0.5 mL, 2.25%) [7]. When racemic and L-adrenaline are compared, there is no difference in croup score at 30 min (standardised mean difference 0.33, 95% CI −0.42–1.08), but at 2 h L-adrenaline shows a small reduction in croup score compared to racemic adrenaline.
Monoallelic expression in melanoma

Lee Silcock1, Hakeem Almabrazy1, Younes Mokrab1, Puthen Jithesh1, Muna Al-Hashmi1, Nicola James1, Rebecca Mathew1, Valentina Mattei1, Davide Bedognetti1, Francesca Lessi2, Ramzi Temanni3, Barbara Seliger3, Rashid Al-Ali3, Francesco M. Marincola4, Ena Wang1 and Sara Torelli1,5

Abstract

Background: Monoallelic expression (MAE) is a frequent genomic phenomenon in normal tissues, however its role in cancer is yet to be fully understood. MAE is defined as the expression of a gene that is restricted to one allele in the presence of a diploid heterozygous genome. Constitutive MAE occurs for imprinted genes, odorant receptors and random X inactivation. Several studies in normal tissues have showed MAE in approximately 5–20% of the cases. However, little information exists on the MAE rate in cancer. In this study we assessed the presence and rate of MAE in melanoma. The genetic basis of melanoma has been studied in depth over the past decades, leading to the identification of mutations/ genetic alterations responsible for melanoma development.

Methods: To examine the role of MAE in melanoma we used 15 melanoma cell lines and compared their RNA-seq data with genotyping data obtained by the parental TIL (tumor infiltrating lymphocytes). Genotyping was performed using the Illumina HumanOmni1 beadchip. The RNA-seq library preparation and sequencing was performed using the Illumina TruSeq Stranded Total RNA Human Kit and subsequently sequenced using a HiSeq 2500 according to manufacturer’s guidelines. By comparing genotyping data with RNA-seq data, we identified SNPs in which DNA genotypes were heterozygous and corresponding RNA genotypes were homozygous. All homozygous DNA genotypes were removed prior to the analysis. To confirm the validity to detect MAE, we examined heterozygous DNA genotypes from X chromosome of female samples as well as for imprinted and olfactory receptor genes and confirmed MAE.

Results: MAE was detected in all 15 cell lines although to a different rate. When looking at the B allele frequencies we found a preferential pattern of complete monoallelic expression rather than differential monoallelic expression across the 15 melanoma cell lines. As some samples showed high differences in the homoygous and heterozygous call rate, we looked at the single chromosomes and showed that MAE may be explained by underlying large copy number imbalances in some instances. Interestingly these regions included genes known to play a role in melanoma initiation and progression. Nevertheless, some chromosome regions showed MAE without CN imbalances suggesting that additional mechanisms (including epigenetic silencing) may explain MAE in melanoma.

Conclusion: The biological implications of MAE are yet to be realized. Nevertheless, our findings suggest that MAE is a common phenomenon in melanoma cell lines. Further analyses are currently being undertaken to evaluate whether MAE is gene/pathway specific and to understand whether MAE can be employed by cancers to achieve a more aggressive phenotype.

Keywords: Monoallelic expression, Melanoma, RNA-seq
Arrhythmogenic calmodulin E105A mutation alters cardiac RyR2 regulation leading to cardiac dysfunction in zebrafish

Sahar I. Da’as,1,2 Angelos Thanassoulas,3 Brian L. Calver,4 Konrad Beck,4 Rola Salem,5 Alaaeldin Saleh,5 Iris Kontogianni,3 Ali Al-Maraghi,5 Gheyath K. Nasrallah,6,7 Bared Safieh-Garabedian,5 Egon Toft,5 George Nounesis,3 F. Anthony Lai,4,5,6 and Michail Nomikos5

1Translational Medicine, Sidra Medicine, Doha, Qatar. 2College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar. 3National Center for Scientific Research “Demokritos,” Agia Paraskevi, Greece. 4College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK. 5College of Medicine, Member of QU Health, Qatar University, Doha, Qatar. 6Biomedical Research Center, Qatar University, Doha, Qatar. 7Department of Biomedical Sciences, College of Health Science, Qatar University, Doha, Qatar

Address for correspondence: Michail Nomikos, College of Medicine, Member of QU Health, Qatar University, Doha, P.O. Box: 2713, Qatar. mixosn@yahoo.com

Calmodulin (CaM) is a universal calcium (Ca2+)–binding messenger that regulates many vital cellular events. In cardiac muscle, CaM associates with ryanodine receptor 2 (RyR2) and regulates excitation–contraction coupling. Mutations in human genes CALM1, CALM2, and CALM3 have been associated with life-threatening heart disorders, such as long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia. A novel de novo LQTS-associated missense CaM mutation (E105A) was recently identified in a 6-year-old boy, who experienced an aborted first episode of cardiac arrest. Herein, we report the first molecular characterization of the CaM E105A mutation. Expression of the CaM E105A mutant in zebrafish embryos resulted in cardiac arrhythmia and increased heart rate, suggestive of ventricular tachycardia. In vitro biophysical and biochemical analysis revealed that E105A confers a deleterious effect on protein stability and a reduced Ca2+–binding affinity due to loss of cooperativity. Finally, the CaM E105A mutation resulted in reduced CaM–RyR2 interaction and defective modulation of ryanodine binding. Our findings suggest that the CaM E105A mutation dysregulates normal cardiac function by a complex mechanism involving alterations in both CaM–Ca2+ and CaM–RyR2 interactions.

Keywords: calmodulin; calcium; ryanodine receptor 2; arrhythmia; long QT syndrome; zebrafish


Introduction

Calmodulin (CaM) is a ubiquitous, highly conserved calcium (Ca2+)–binding protein that binds and regulates a number of different protein targets, thereby affecting a wide range of vital cellular processes.1 CaM acts as an intracellular Ca2+ sensor, decoding downstream Ca2+ signals and by undergoing conformational changes, binds specifically to its multiple protein partners in a Ca2+-dependent manner.2 CaM is a relatively small protein composed of 148 amino acids with a very basic domain architecture. Based on its crystal structure, it
Original Article

Clinical, Immunologic, and Molecular Spectrum of Patients with LPS-Responsive Beige-Like Anchor Protein Deficiency: A Systematic Review

Sima Habibi, MSca, Majid Zaki-Dizaji, PhDb, Hosein Rafiemanesh, PhDb, Bernice Lo, PhDc, Mahnaz Jamee, MDe, Laura Gámez-Diaz, PhDf, Fereshte Salami, MScg, Ali N. Kamali, PhDh, Hamed Mohammadi, Phdi, Hassan Abolhassani, MD, PhDi, Reza Yazdani, PhDj, Asghar Aghamohammadi, MD, PhDj, Juan-Manuel Anaya, MD, PhDi, and Gholamreza Azizi, PhDk

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Corresponding author: Gholamreza Azizi, PhD, Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran. E-mail: azizi@abzums.ac.ir.

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What is already known about this topic? LPS-responsive and beige-like anchor protein (LRBA) deficiency leads to a broad spectrum of clinical phenotypes including autoimmunity, chronic diarrhea, hypogammaglobulinemia, and recurrent infections.

What does this article add to our knowledge? LRBA deficiency is an immune dysregulation syndrome without any genotype-phenotype correlation. Autoimmune disorders are the main clinical manifestations in LRBA deficiency.

How does this study impact current management guidelines? LRBA deficiency should be included in the list of monogenic autoimmune diseases and should be routinely screened for in patients with immune dysregulation. Hematopoietic stem cell transplantation is a promising treatment for LRBA-deficient patients with severe and complicated clinical manifestations.

BACKGROUND: LPS-responsive beige-like anchor protein (LRBA) deficiency is a primary immunodeficiency and immune dysregulation syndrome caused by biallelic mutations in the LRBA gene. These mutations usually abrogate the protein expression of LRBA, leading to a broad spectrum of clinical phenotypes including autoimmunity, chronic diarrhea, hypogammaglobulinemia, and recurrent infections.

OBJECTIVE: Our aim was to systematically collect all studies reporting on the clinical manifestations, molecular and laboratory findings, and management of patients with LRBA deficiency.

METHODS: We searched in PubMed, Web of Science, and Scopus without any restrictions on study design and publication time. A total of 109 LRBA-deficient cases were identified from 45 eligible articles. For all patients, demographic information, clinical records, and immunologic and molecular data were collected.

RESULTS: Of the patients with LRBA deficiency, 93 had homozygous and 16 had compound heterozygous mutations in LRBA. The most common clinical manifestations were autoimmunity (82%), enteropathy (63%), splenomegaly (57%), and pneumonia (49%). Reduction in numbers of CD4+ T cells and regulatory T cells as well as IgG levels was recorded for 21.6%, 65.6%, and 54.2% of evaluated patients, respectively. B-cell subpopulation analysis revealed low numbers of switched-memory and increased numbers of CD21low B cells in 73.5% and 77.8% of patients, respectively. Eighteen (16%) patients underwent hematopoietic stem cell transplantation due to the severity of complications and the outcomes improved in 13 of them.

CONCLUSIONS: Autoimmune disorders are the main clinical manifestations of LRBA deficiency. Therefore, LRBA deficiency should be included in the list of monogenic autoimmune diseases, and screening for LRBA mutations should be routinely
L amino acid transporter structure and molecular bases for the asymmetry of substrate interaction

Ekaitz Errasti-Murugarren, Joana Fort, Paola Bartocci, Lucía Díaz, Els Pardon, Xavier Carpena,Meritxell Espino-Guarch, Antonio Zorzano, Christine Ziegler, Jan Steyaert, Juan Fernández-Recio, Ignacio Fita & Manuel Palacín

L-aminoc acid transporters (LATs) play key roles in human physiology and are implicated in several human pathologies. LATs are asymmetric amino acid exchangers where the low apparent affinity cytoplasmic side controls the exchange of substrates with high apparent affinity on the extracellular side. Here, we report the crystal structures of an LAT, the bacterial alanine-serine-cysteine exchanger (BasC), in a non-occluded inward-facing conformation in both apo and substrate-bound states. We crystallized BasC in complex with a nanobody, which blocks the transporter from the intracellular side, thus unveiling the sidedness of the substrate interaction of BasC. Two conserved residues in human LATs, Tyr 236 and Lys 154, are located in equivalent positions to the Na1 and Na2 sites of sodium-dependent APC superfamily transporters. Functional studies and molecular dynamics (MD) calculations reveal that these residues are key for the asymmetric substrate interaction of BasC and in the homologous human transporter Asc-1.
The Complex Etiology of Childhood Obesity in Arabs Is Highlighted by a Combination of Biological and Socio-Economic Factors

Naser Elkum1,2*, Monira Alarouj2, Abdullah Bennakhi2 and Azza Shaltout2

1 Research Department, Sidra Medicine, Doha, Qatar; 2Department of Clinical Services, Dasman Diabetes Institute, Kuwait City, Kuwait

Objectives: To identify predictors of childhood and adolescent obesity in Kuwaitis with Arab ethnicity.

Methods: A cross-sectional sample of 6–18 year-old schoolchildren was randomly selected from 244 public schools across all six governorates in the State of Kuwait. Anthropometric data were measured from 6,574 Arab Kuwaiti schoolchildren, and a structured questionnaire was used to collect information on possible risk factors associated with obesity. Overweight and obesity were defined in accordance with the Center for Disease Control and Prevention criteria.

Results: The prevalence of overweight and obesity in children (aged 6–18 years) were 17.7% and 33.7%, respectively. The likelihood of childhood obesity increased with birth weights >4.0 Kg [odds ratio (OR) = 2.3; p < 0.0001], maternal employment (OR = 1.26, p = 0.0006), maternal age at pregnancy >30 years (OR = 1.24; p = 0.0016) and family size of <6 members (OR = 1.16, p = 0.0106).

Conclusions: Public health professionals should be aware that advanced maternal age, maternal employment, smaller family size, and high birthweight may predict the risk of obesity in Kuwaiti Arab children and adolescents.

Keywords: obesity, children, Arabs, prevalence, risk factors

INTRODUCTION

Childhood obesity is one of the most serious public health challenges worldwide. It has been shown that progression of obesity from childhood to adulthood is associated with the development of type 2 diabetes (T2D) (1, 2) and cardiovascular diseases (CVDs) (3). Our previous report (4) has demonstrated a markedly high prevalence of childhood obesity in Kuwait that exceeded those reported in neighboring countries and North America. This public health crisis requires a serious investigation to identify the key factors contributing to the high prevalence of childhood obesity in Kuwait.

A number of childhood obesity-related etiological factors have been identified, such as genetic, environmental and socio-economic risk factors (5–7). In addition, it is becoming increasingly evident that birthweight, short sleep duration, physical inactivity, parental obesity, and parental income are important predictive factors of childhood overweight and obesity in various countries. However, the majority of these factors were identified and their effects were studied only in Western
eDiVA—Classification and prioritization of pathogenic variants for clinical diagnostics

Mattia Bosio1,2,3 | Oliver Drechsel4 | Rubayte Rahman5 | Francesc Muyas1,2 | Raquel Rabionet1,2,6 | Daniela Bezdan1,2 | Laura Domenech Salgado1,2 | Hyun Hor7 | Jean-Jacques Schott8,9 | Francina Munell10 | Roger Colobran10 | Alfons Macaya10 | Xavier Estivill11,12 | Stephan Ossowski1,2,13

1Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Barcelona, Spain
2Universitat Pompeu Fabra (UPF), Barcelona, Spain
3Barcelona Supercomputing Center (BSC), Barcelona, Spain
4Bioinformatics Unit (MF1), Department for Methods Development and Research Infrastructure, Robert Koch Institute, Berlin, Germany
5NKI Netherlands Cancer Institute, The Netherlands
6Institut de Recerca Sant Joan de Déu, University of Barcelona, Barcelona, Spain
7Department of Neurology, University Hospital Zurich, Zurich, Switzerland
8L’Institut du Thorax, INSERM, CNRS, Univ Nantes, Nantes, France
9Service de Cardiologie, L’institut du thorax, CHU Nantes, Nantes, France
10Vall d’Hebron Institut de Recerca (VHIR), Barcelona, Spain
11Sidra Medicine, Doha, Qatar
12Women’s Health Dexeus, Barcelona, Spain
13Institute of Medical Genetics and Applied Genomics, University of Tübingen, Tübingen, Germany

Correspondence
Stephan Ossowski, Institute of Medical Genetics and Applied Genomics, University of Tübingen, Calwerstr. 7, 72076 Tübingen, Germany.
Email: Stephan.Ossowski@med.uni-tuebingen.de

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Abstract
Mendelian diseases have shown to be an and efficient model for connecting genotypes to phenotypes and for elucidating the function of genes. Whole-exome sequencing (WES) accelerated the study of rare Mendelian diseases in families, allowing for directly pinpointing rare causal mutations in genic regions without the need for linkage analysis. However, the low diagnostic rates of 20–30% reported for multiple WES disease studies point to the need for improved variant pathogenicity classification and causal variant prioritization methods. Here, we present the exome Disease Variant Analysis (eDiVA; http://ediva.crg.eu), an automated computational framework for identification of causal genetic variants (coding/splicing single-nucleotide variants and small insertions and deletions) for rare diseases using WES of families or parent-child trios. eDiVA combines next-generation sequencing data analysis, comprehensive functional annotation, and causal variant prioritization optimized for familial genetic disease studies. eDiVA features a machine learning-based variant pathogenicity predictor combining...
Chapter 20

Combined Genome and Transcriptome (G&T) Sequencing of Single Cells

Iraad F. Bronner and Stephan Lorenz

Abstract

The simultaneous examination of a single cell’s genome and transcriptome presents scientists with a powerful tool to study genetic variability and its effect on gene expression. In this chapter, we describe the library generation method for combined genome and transcriptome sequencing (G&T-seq) originally described by Macaulay et al. (Nat Protoc 11(11):2081–2103, 2016; Nat Methods 12(6):519–522, 2015). This includes some alterations we made to improve robustness of this process for both the novice user and laboratories that want to deploy this method at scale. Using this method, genomic DNA and full-length mRNA from single cells are separated, amplified, and converted into Illumina sequencer-compatible sequencing libraries.

Key words Single cell, Transcriptome, Genome, MDA, WGA, SNV detection, Copy number variation, Gene expression, NGS

1 Introduction

Recently, a sequencing library-generation method for combined genome and transcriptome sequencing (G&T-seq) on single cells was described by Macaulay et al. [1, 2]. Until then, single-cell sequencing methods had only allowed to either determine individual cellular expression profiles or to examine genomic variation (i.e., copy-number variations or single nucleotide variants). By combining transcriptome and genome amplification methods in one protocol, a tool was created that could correlate genetic variability and its effect on gene expression [1]. We have seen a great need for the implementation of the G&T-seq protocol as part of our automated high-throughput single-cell pipeline at the Wellcome Sanger Institute. The original Nature Protocol written by Macaulay et al. [1] gives a very accurate description of the process and can be implemented by skilled scientists. However, it is a very complex protocol that is hard to scale to high sample numbers and is also sensitive to experimental errors. During the implementation
Human macular Müller cells rely more on serine biosynthesis to combat oxidative stress than those from the periphery

Ting Zhang1†, Ling Zhu1*, Michele C Madigan1,2, Wei Liu3, Weiyong Shen1, Svetlana Cherepanoff4, Fanfan Zhou5, Shaoxue Zeng1, Jianhai Du6,7, Mark C Gillies1

1 Save Sight Institute, Sydney Medical School, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia; 2 School of Optometry and Vision Sciences, University of New South Wales, Sydney, Australia; 3 Clinical Genomics Laboratory, Sidra Medicine, Doha, Qatar; 4 Department of Anatomical Pathology, St Vincent’s Hospital, Darlinghurst, Australia; 5 Faculty of Pharmacy, The University of Sydney, Sydney, Australia; 6 Department of Ophthalmology, West Virginia University, Morgantown, United States; 7 Department of Biochemistry, West Virginia University, Morgantown, United States

Abstract The human macula is more susceptible than the peripheral retina to developing blinding conditions such as age-related macular degeneration, diabetic retinopathy. A key difference between them may be the nature of their Müller cells. We found primary cultured Müller cells from macula and peripheral retina display significant morphological and transcriptomic differences. Macular Müller cells expressed more phosphoglycerate dehydrogenase (PHGDH, a rate-limiting enzyme in serine synthesis) than peripheral Müller cells. The serine synthesis, glycolytic and mitochondrial function were more activated in macular than peripheral Müller cells. Serine biosynthesis is critical in defending against oxidative stress. Intracellular reactive oxygen species and glutathione levels were increased in primary cultured macular Müller cells which were more susceptible to oxidative stress after inhibition of PHGDH. Our findings indicate serine biosynthesis is a critical part of the macular defence against oxidative stress and suggest dysregulation of this pathway as a potential cause of macular pathology.

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Introduction

The macula, a specialized region located at the posterior pole of the primate retina, has the greatest density of cone photoreceptors for the highest visual acuity (Sharon et al., 2002). The impact of common pathologies such as age-related macular degeneration (AMD), diabetic retinopathy (DR) and macular telangiectasia type 2 (MacTel) are most devastating at the macula, leading to vision loss and blindness. Understanding the unique biochemical and anatomic specializations of the macula may provide new ways to prevent and treat these diseases.

A major difference between the macula and peripheral retina is the density of the retinal neurons. Although the macula occupies less than 1.4% of the retina area, it contains ~8.4% of cones, ~3.4% of rods and ~60% of the ganglion cells (Curcio and Allen, 1990). The ratio of cones to rods is much higher in the macula (1:8) than that in the peripheral retina (1:20) (Curcio et al., 1990). The high density of neurons in the macula is associated with a high metabolic rate and increased levels of oxidative stress (Handa, 2012).
Privacy-Preserving Analysis of Distributed Biomedical Data: Designing Efficient and Secure Multiparty Computations Using Distributed Statistical Learning Theory

Fida K Dankar¹, PhD; Nisha Madathil¹, MS; Samar K Dankar², PhD; Sabri Boughorbel³, PhD

¹United Arab Emirates University, Abu Dhabi, United Arab Emirates
²Independent Scientist, Ottawa, ON, Canada
³Sidra Medicine, Doha, Qatar

Corresponding Author:
Fida K Dankar, PhD
United Arab Emirates University
College of IT, Al Ain
Abu Dhabi, 15551
United Arab Emirates
Phone: 971 37673333 ext 5569
Email: fida.dankar@uaeu.ac.ae

Abstract

Background: Biomedical research often requires large cohorts and necessitates the sharing of biomedical data with researchers around the world, which raises many privacy, ethical, and legal concerns. In the face of these concerns, privacy experts are trying to explore approaches to analyzing the distributed data while protecting its privacy. Many of these approaches are based on secure multiparty computations (SMCs). SMC is an attractive approach allowing multiple parties to collectively carry out calculations on their datasets without having to reveal their own raw data; however, it incurs heavy computation time and requires extensive communication between the involved parties.

Objective: This study aimed to develop usable and efficient SMC applications that meet the needs of the potential end-users and to raise general awareness about SMC as a tool that supports data sharing.

Methods: We have introduced distributed statistical computing (DSC) into the design of secure multiparty protocols, which allows us to conduct computations on each of the parties’ sites independently and then combine these computations to form a single estimator for the collective dataset, thus limiting communication to the final step and reducing complexity. The effectiveness of our privacy-preserving model is demonstrated through a linear regression application.

Results: Our secure linear regression algorithm was tested for accuracy and performance using real and synthetic datasets. The results showed no loss of accuracy (over nonsecure regression) and very good performance (20 min for 100 million records).

Conclusions: We used DSC to securely calculate a linear regression model over multiple datasets. Our experiments showed very good performance (in terms of the number of records it can handle). We plan to extend our method to other estimators such as logistic regression.

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KEYWORDS
data analytics; data aggregation; personal genetic information; patient data privacy

Introduction

Background and Significance

Human genome research promises to transform health care through personalized medicine. It enables the determination of an individual’s unique molecular characteristics, which can be used to diagnose diseases, select individualized treatments (with a higher success rate), and reduce possible adverse reactions [1]. However, before this becomes a reality, more research is needed to understand the complex relationship between genome and health. Such research often requires large cohorts and necessitates the sharing of biomedical data with researchers around the world, which raises many privacy, ethical, and legal concerns.
Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors

Birth weight variation is influenced by fetal and maternal genetic and non-genetic factors, and has been reproducibly associated with future cardio-metabolic health outcomes. In expanded genome-wide association analyses of own birth weight (n = 321,223) and offspring birth weight (n = 230,069 mothers), we identified 190 independent association signals (129 of which are novel). We used structural equation modeling to decompose the contributions of direct fetal and indirect maternal genetic effects, then applied Mendelian randomization to illuminate causal pathways. For example, both indirect maternal and direct fetal genetic effects drive the observational relationship between lower birth weight and higher later blood pressure: maternal blood pressure-raising alleles reduce offspring birth weight, but only direct fetal effects of these alleles, once inherited, increase later offspring blood pressure. Using maternal birth weight-lowering genotypes to proxy for an adverse intrauterine environment provided no evidence that it causally raises offspring blood pressure, indicating that the inverse birth weight-blood pressure association is attributable to genetic effects, and not to intrauterine programming.

To date, 65 genetic loci have been associated with birth weight in genome-wide association studies (GWASs), implicating biological pathways that may underlie observational associations with adult disease. However, most of these studies did not distinguish between maternal and fetal genetic influences. Evidence from monogenic human models and variance component analyses demonstrates that birth weight is influenced by genotypes inherited from the fetus and by maternal genotypes that influence the intrauterine environment. To date, GWASs of own birth weight and maternal GWASs of offspring birth weight have produced overlapping signals due to the correlation between maternal and fetal genotypes. Identified birth weight variants might have (1) a direct fetal effect only; (2) an indirect maternal effect only; or (3) some combination of the two. Performing separate GWAS analyses of own or offspring birth weight precludes full resolution of the origin of the identified genetic effects.

To address these issues, we performed greatly expanded GWASs of own (n = 321,223) and offspring birth weight (n = 230,069 mothers) using data from the Early Growth Genetics (EGG) Consortium and the UK Biobank (2017 release). We applied a structural equation model that we recently developed to partition genetic effects on birth weight into maternal and fetal components at genome-wide-significant loci. We then extended the method to estimate maternal- and fetal-specific genetic effects across the genome in a computationally efficient manner, and used the results for downstream analyses. Our ability to resolve maternal and fetal genetic contributions provides substantial insights into the underlying biological regulation of birth weight, as well as the origins of observational relationships with T2D and blood pressure.

Results

Meta-analyses of fetal and maternal GWASs. We conducted GWAS meta-analyses of own (fetal) genetic variants on own birth weight (Supplementary Fig. 1 and Supplementary Tables 1 and 2) and maternal genetic variants on offspring birth weight (Supplementary Fig. 2 and Supplementary Tables 3 and 4) in individuals of European ancestry. We then performed approximate conditional and joint multiple single-nucleotide polymorphism (SNP) analyses (COJO) and a trans-ethnic meta-analysis to identify further independent SNPs (Methods). The GWAS meta-analysis of own birth weight (n = 321,223) identified 146 independent SNPs at genome-wide significance (P < 6.6 × 10^{-8}, Supplementary Figs. 3, 4 and 5a, Supplementary Table 5a and Methods). The GWAS meta-analysis of offspring birth weight (n = 230,069 mothers) identified 72 independent SNPs (P < 6.6 × 10^{-8}, Supplementary Figs. 3, 4 and 5b, Supplementary Table 5b and Methods). Applying the more lenient significance threshold used previously (P < 5 × 10^{-8}), 211 and 105 SNPs reached significance for own and offspring birth weight, respectively (Supplementary Table 5b). SNPs at 30 genome-wide-significant loci (within 500 kilobases (kb) and linkage disequilibrium (LD) r² ≥ 0.1) were identified in the GWASs of both own and offspring birth weight. Of these, 9 loci had

A full list of authors and affiliations appears at the end of the paper.
Soluble TNF-R1, VEGF and other cytokines as markers of disease activity in systemic lupus erythematosus and lupus nephritis

Z Adhya 1,2, M El Anbari 3, S Anwar 2, A Mortimer 5, N Marr 3,6 and MY Karim 2,7,8

1 Immunology, King’s College Hospital, London, UK; 2 Immunology, Guy’s & St Thomas’ Hospitals, London, UK; 3 Research Branch, Sidra Medicine, Doha, Qatar; 4 Section of Nephrology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; 5 Pathway Diagnostics Ltd, Dorking, UK; 6 College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar; 7 Lupus Unit, Guy’s & St Thomas’ Hospitals, London, UK; and 8 Pathology, Sidra Medicine, Doha, Qatar

Background: Current non-invasive methods of assessing disease activity in systemic lupus erythematosus (SLE) are of limited sensitivity and specificity. Testing includes acute phase markers, autoantibodies and complement levels. Although measurements of dsDNA antibodies and complement C3/C4 levels are routine, they remain of limited value. Improved blood and urine markers may help in early detection of flare, distinction between flare and chronic damage, and monitoring response to therapy. Methods: A total of 87 patients with SLE were tested for the following cytokines in serum and urine: monocyte chemoattractant protein 1 (MCP-1), regulated upon activation, normal T cell expressed and secreted (RANTES), soluble tumour necrosis factor receptor 1 (sTNF-R1), interferon-inducible protein 10 (IP-10), monocyte inhibitory protein 1α (MIP-1α) and vascular endothelial growth factor (VEGF). Patients attending the Lupus Unit at St Thomas’ Hospital, London, UK were divided into active lupus nephritis (LN), inactive LN and non-renal SLE groups based on their renal pathology and SLE disease activity index (SLEDAI). Cytokine testing was performed using the FIDIS multiplex bead assay. Results: The mean level of serum sTNF-R1 was higher in the active LN group compared with both inactive LN and non-renal SLE groups (p < 0.001). For urine measurements there were significant differences between active LN and non-renal SLE for VEGF (p = 0.016), after statistical correction for multiple testing. Both urinary and serum sTNF-R1 and IP-10 levels correlated with SLEDAI scores (p < 0.001), while serum VEGF correlated weakly with SLEDAI (p = 0.025). The optimum combination for differentiating active from inactive LN patients was serum VEGF, sTNF-R1, MCP-1 and glomerular filtration rate plus urinary sTNF-R1 and protein-creatinine ratio. Conclusion: These results indicate that for active LN, sTNF-R1 could be a useful serum cytokine marker, with potential for VEGF in the urine. This study has confirmed the ability of the multiplex bead technique to detect cytokines in a good analytical range, including very low and high levels, in both serum and urine. Combining serum and urine markers provided additional sensitivity in distinguishing active from inactive LN. Lupus (2019) 28, 713–721.

Key words: Lupus; nephritis; renal; Luminex; FIDIS; biomarkers; cytokines; tumour necrosis factor

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterized by intermittent flares of disease activity, which often arise unpredictably. Renal involvement occurs in 30–50% of adult SLE,1 and requires long-term monitoring as recurrent flares as well as progressive deterioration of function can lead to end-stage renal disease. Current laboratory methods of assessing SLE activity include testing acute phase markers, autoantibodies and complement levels. Renal involvement and monitoring is assessed by urinalysis, serum biochemistry and urine protein excretion. However, these routine laboratory tests are of limited sensitivity and specificity and they cannot always distinguish between active inflammation and chronic damage. For example, although a relationship between dsDNA antibodies and disease activity exists, meta-analysis has indicated low overall predictive value.2 Likewise measurement of complement C3
Ion Transporters, Channelopathies, and Glucose Disorders

Huseyin Demirbilek 1, Sonya Galcheva 2, Dogus Vuralli 1©, Sara Al-Khawaga 3,4 and Khalid Hussain 3,*

1 Department of Paediatric Endocrinology, Hacettepe University Faculty of Medicine, 06230 Ankara, Turkey; dr_huseyin@hotmail.com (H.D.); dvuralli@hotmail.com (D.V.)
2 Department of Paediatrics, Varna Medical University/University Hospital “St. Marina”, Varna 9002, Bulgaria; sonya_galcheva@abv.bg
3 Department of Paediatric Medicine, Division of Endocrinology, Sidra Medicine, Doha, Qatar; SarAlKhawaga@hbku.edu.qa
4 College of Health & Life Sciences, Hamad Bin Khalifa University, Qatar Foundation, Education City, Doha, Qatar

* Correspondence: khussain@sidra.org; Tel.: +974-4003-7608

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Abstract: Ion channels and transporters play essential roles in excitable cells including cardiac, skeletal and smooth muscle cells, neurons, and endocrine cells. In pancreatic beta-cells, for example, potassium K ATP channels link the metabolic signals generated inside the cell to changes in the beta-cell membrane potential, and ultimately regulate insulin secretion. Mutations in the genes encoding some ion transporter and channel proteins lead to disorders of glucose homeostasis (hyperinsulinaemic hypoglycaemia and different forms of diabetes mellitus). Pancreatic K ATP, Non-K ATP, and some calcium channelopathies and MCT1 transporter defects can lead to various forms of hyperinsulinaemic hypoglycaemia (HH). Mutations in the genes encoding the pancreatic K ATP channels can also lead to different types of diabetes (including neonatal diabetes mellitus (NDM) and Maturity Onset Diabetes of the Young, MODY), and defects in the solute carrier family 2 member 2 (SLC2A2) leads to diabetes mellitus as part of the Fanconi–Bickel syndrome. Variants or polymorphisms in some ion channel genes and transporters have been reported in association with type 2 diabetes mellitus.

Keywords: beta cell; K ATP channel; voltage-gated calcium channels; membrane transporters; neonatal diabetes; hyperinsulinaemic hypoglycaemia

1. Introduction

Ion channels and transporters are membrane-embedded proteins which play a key role in transporting ions and biomolecules across cell membranes. Although both ion channels and transporters are membrane-bound proteins, they have some differences. Ion channels are typically formed by the assembly of several different proteins and they function to allow the movement of specific ions (selectivity). The flow of ions across the channel (transmembrane flux) creates an electrical signal or action potential which is essential for the function of the particular channel [1]. Another property of ion channels is gating, which allows the channels to open and close in response to certain specific stimuli. An example of an ion channel is the adenosine triphosphate (ATP)-dependent potassium channel (K ATP) that allows the rapid and selective flow of K+ ions across the cell membrane, and thus generates electrical signals in cells. Distinct from ion channels, some ion transporters may function as ion pumps, thereby moving ions across the plasma membrane against the electrochemical gradient.

Ion channels and transporters play essential roles in excitable cells including cardiac, skeletal and smooth muscle cells, neurons, and endocrine cells. In pancreatic beta-cells, K ATP channels link...
Vitamin D Deficiency in the Gulf Cooperation Council: Exploring the Triad of Genetic Predisposition, the Gut Microbiome and the Immune System

Parul Singh, Manoj Kumar and Souhaila Al Khodor*

Research Department, Sidra Medicine, Doha, Qatar

Vitamin D is a fat soluble secosteroid that is primarily synthesized in the skin upon exposure to Ultraviolet B (UVB) sun rays. Vitamin D is essential for the growth and development of bones and helps in reducing inflammation by strengthening muscles and the immune system. Despite the endless supply of sunlight in the Gulf Cooperation Council (GCC) countries which includes United Arab Emirates, Qatar, Kuwait, Bahrain, Saudi Arabia, and Oman, Vitamin D deficiency in the (GCC) general population at various age groups remains alarmingly high. In parallel runs the increasing prevalence of acute and chronic illnesses including, autoimmune diseases, cancer, type 1 diabetes mellitus, cardiovascular disease and Inflammatory bowel disease in the adult as well as the pediatric population of these countries. The exact association between Vitamin D deficiency and chronic disease conditions remains unclear; however, studies have focused on the mechanism of Vitamin D regulation by assessing the role of the Vitamin D associated genes/proteins such as VDR (Vitamin D receptor), VDBP (Vitamin D Binding protein), CYP27B1 as these are integral parts of the Vitamin D signaling pathway. VDR is known to regulate the expression of more than 200 genes across a wide array of tissues in the human body and may play a role in controlling the Vitamin D levels. Moreover, reduced Vitamin D level and downregulation of VDR have been linked to gut dysbiosis, highlighting an intriguing role for the gut microbiome in the Vitamin D metabolism. However, this role is not fully described yet. In this review, we aim to expand our understanding of the causes of Vitamin D deficiency in the GCC countries and explore the potential relationship between the genetic predisposition, Vitamin D levels, immune system and the gut microbiome composition. Trying to unravel this complex interaction may aid in understanding the mechanism by which Vitamin D contributes to various disease conditions and will pave the way toward new therapeutics treatments for Vitamin D deficiency and its associated outcomes.

Keywords: hypovitaminosis D, microbial dysbiosis, VDR, VDBP, CYP27B1, GCC
Evaluation of Methods for the Extraction of Microbial DNA From Vaginal Swabs Used for Microbiome Studies

Valentina Mattei†, Selvasankar Murugesan†, Muna Al Hashmi, Rebecca Mathew, Nicola James, Parul Singh, Manoj Kumar, Arun Prasath Lakshmanan, Annalisa Terranegra, Souhaila Al Khodor*† and Sara Tomei*†

Research Branch, Sidra Medicine, Doha, Qatar

Background: The composition of the microbiome in human body sites plays an important role in health. The vaginal environment is colonized by several species of bacteria that have a major influence on reproductive health. The advancement of sequencing technologies has made the assessment of the composition of the microbiota possible through microbial DNA extraction and sequencing. Therefore, it is of paramount importance to select a sensitive and reproducible DNA extraction method, that facilitates isolation of microbial DNA with a sufficient quantity and purity, from microbial species living in the vaginal environment. Here, we have evaluated four different DNA extraction protocols from self-collected vaginal swabs.

Methods: Five healthy female volunteers were enrolled in the study. Each donor was asked to self-collect 4 samples using Copan ESwab. DNA was extracted using Qiagen DNeasy kit and three modified protocols of the MoBio PowerSoil kit (“DNeasy PowerSoil” after acquisition from Qiagen). DNA quantity and integrity was checked through Nanodrop and LabChip GX. DNA was further tested through quantitative real-time PCR (qPCR) and 16S sequencing. Vaginal microbiota diversities were determined using MiSeq-Illumina high-throughput sequencing of bacterial 16S rDNA V1–V3 fingerprint. Sequencing data were analyzed using QIIME pipeline.

Results: Qiagen DNeasy protocol resulted in the highest DNA yield as compared to the modified protocols of MoBio Powersoil kit. The size of the DNA extracted using each protocol was ~40kb. Qiagen DNeasy protocol gave the highest Genomic Quality Score (average ± standard deviation: 4.24 ± 0.36), followed by the different MoBio Powersoil protocols. A substantial variability in microbial DNA abundance was found across the protocols. The vaginal microbiota of the healthy volunteers was dominated by Lactobacillus species. MoBio Powersoil kit provided a significantly higher alpha diversity as compared to the Qiagen DNeasy kit, while beta diversity measures did not reveal any significant cluster changes, except when the Bray-Curtis method was applied.
Schlafen-11 expression is associated with immune signatures and basal-like phenotype in breast cancer

Edoardo Isnaldi1 · Domenico Ferraioli1,2 · Lorenzo Ferrando1 · Sylvain Brohée3 · Fabio Ferrando1,4 · Piero Fregatti1,4 · Davide Bedognetti5 · Alberto Ballestro1,4 · Gabriele Zoppoli1,4,6

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Abstract
Purpose Breast cancer (BC) is a heterogeneous disorder, with variable response to systemic chemotherapy. Likewise, BC shows highly complex immune activation patterns, only in part reflecting classical histopathological subtyping. Schlafen-11 (SLFN11) is a nuclear protein we independently described as causal factor of sensitivity to DNA damaging agents (DDA) in cancer cell line models. SLFN11 has been reported as a predictive biomarker for DDA and PARP inhibitors in human neoplasms. SLFN11 has been implicated in several immune processes such as thymocyte maturation and antiviral response through the activation of interferon signaling pathway, suggesting its potential relevance as a link between immunity and cancer. In the present work, we investigated the transcriptional landscape of SLFN11, its potential prognostic value, and the clinicopathological associations with its variability in BC.
Methods We assessed SLFN11 determinants in a gene expression meta-set of 5061 breast cancer patients annotated with clinical data and multigene signatures.
Results We found that 537 transcripts are highly correlated with SLFN11, identifying “immune response”, “lymphocyte activation”, and “T cell activation” as top Gene Ontology processes. We established a strong association of SLFN11 with stromal signatures of basal-like phenotype and response to chemotherapy in estrogen receptor negative (ER-) BC. We identified a distinct subgroup of patients, characterized by high SLFN11 levels, ER- status, basal-like phenotype, immune activation, and younger age. Finally, we observed an independent positive predictive role for SLFN11 in BC.
Conclusions Our findings are suggestive of a relevant role for SLFN11 in BC and its immune and molecular variability.

Keywords Schlafen-11 · Immune signatures · Basal-like phenotype · Breast cancer · Biomarker

Abbreviations
BC · Breast cancer
DDA · DNA damaging agents
DFS · Disease-free survival
ER · Estrogen receptor
HT · Hormone treatment
ICR · Immunological constant of rejection
MCA · Multiple correspondence analysis
SLFN11 · Schlafen-11
TNBC · Triple-negative breast cancer

Introduction
Breast cancer (BC) is the second most common cancer in the world and, by far, the most frequent neoplasm among women [1].
Abatacept as a Long-Term Targeted Therapy for LRBA Deficiency

Ayca Kiykim, MD; Ismail Ogulur, PhD; Esra Dursun, MD; Louis Marie Charbonnier, PhD; Ercan Nain, MD; Sukru Cekic, MD; Dilek Dogruel, MD; Nesilhan Edeer Karaca, MD; Mujda Tuba Cogru, MD; Ozlem Arman Bilir, MD; Murat Cansever, MD; Hasan Kapakli, MD; Dilek Baser, MSc; Nurhan Kasap, MD; Seyhan Kutlug, MD; Derya Ufuk Altintas, MD; Ahmad Al-Shaibi, MSc; Nourhen Agerbi, PhD; Manolya Kara, MD; Ayda Guven, MD; Ayber Somer, MD; Cigdem Aydogmus, MD; Nurya Aktay Ayaz, MD; Ayse Metin, MD; Metin Aydogan, MD; Ayse Uncuoglu, MD; Turkan Patiroglu, MD; Alisan Yildiran, MD; Sukru Nail Guner, MD; Sevgi Keles, MD; Ismail Reisli, MD; Guzide Aksu, MD; Necil Kutukculer, MD; Sara S. Kilic, MSc; Mustafa Yilmaz, MD; Sukru Cekic, MD; Dilek Dogruel, MD; Nesilhan Edeer Karaca, MD; Mujde Tuba Cogru, MD; Mustafa Yilmaz, MD; Ismail Reisli, MD; Guzide Aksu, MD; Necil Kutukculer, MD; Sara S. Kilic, MSc; Mustafa Yilmaz, MD; Istanbul, Bursa, Adana, Izmir, Kocaeli, Ankara, Kayseri, Konya, and Samsun, Turkey; Boston, Mass; and Doha, Qatar

What is already known about this topic? LPS-responsive beige-like anchor deficiency presents with susceptibility to infections, autoimmunity, and lymphoproliferation. Abatacept treatment can control immune dysregulatory disease manifestations.

What does this article add to our knowledge? Long-term treatment with abatacept is effective in controlling disease activity. Superior clinical responses are achieved with a weekly or biweekly drug-dosing regimen. Lymphoproliferation and chronic diarrhea demonstrated the best responses to abatacept therapy, followed by other immune dysregulatory manifestations. The circulating T follicular helper cells are a reliable biomarker for monitoring disease activity.

How does this study impact current management guidelines? The results of this study may be helpful in the management, follow-up, and prediction of the response rate to abatacept as a tailored therapy for LPS-responsive beige-like anchor deficiency.

BACKGROUND: LPS-responsive beige-like anchor deficiency presents with susceptibility to infections, autoimmunity, and lymphoproliferation. The long-term efficacy of abatacept as targeted therapy for its immune dysregulatory features remains to be established.

REFERENCES:

1. Division of Pediatric Allergy and Immunology, Marmara University School of Medicine, Istanbul, Turkey
2. Division of Immunology, Boston Children’s Hospital and Department of Pediatrics, Harvard Medical School, Boston, Mass
3. Division of Pediatric Allergy and Immunology, Faculty of Medicine, Uludag University, Bursa, Turkey
4. Division of Pediatric Allergy-Immunology, Faculty of Medicine, Gazi University, Adana, Turkey
5. Division of Pediatric Allergy and Immunology, Faculty of Medicine, Ege University, Izmir, Turkey
6. Division of Pediatric Allergy and Immunology, Faculty of Medicine, Kocaeli University, Kocaeli, Turkey
7. Division of Pediatric Hematology, Ankara Children’s Hematology Oncology Training and Research Hospital, Ankara, Turkey
8. Division of Pediatric Immunology and Rheumatology, Faculty of Medicine, Erciyes University, Kayseri, Turkey
9. Division of Pediatric Allergy and Immunology, Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey
10. Division of Pediatric Allergy and Immunology, Faculty of Medicine, Ondokuz Mayis University, Samsun, Turkey
11. Division of Translational Medicine, Research Branch, Sidra Medicine, Doha, Qatar
12. Division of Pediatric Infectious Diseases, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey
13. Division of Pediatric Endocrinology Clinic, Medical Faculty, Zeynep Kamil Women and Children Hospital, Saglik Bilimleri University, Istanbul, Turkey

cyclosporine T-lymphocyte-associated antigen 4-immunoglobulin (abatacept) as targeted therapy for its immune dysregulatory features remains to be established.

14. Division of Pediatric Allergy and Immunology, Kocaeli University, Kocaeli, Turkey
15. Division of Pediatric Immunology and Rheumatology, Faculty of Medicine, Uludag University, Bursa, Turkey
16. Istanbul Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Istanbul, Turkey
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Cytotoxic T-lymphocyte protein-4 is a key immune checkpoint protein that is constitutively expressed on forkhead box T follicular helper cells and function have been demonstrated in LRBA-deficient patients. Consequent upon this, LRBA deficiency may manifest as an immune dysregulation, polyendocrinopathy, enteropathy, and X-linked—like disease with early onset autoimmunity. LRBA was originally described as a common variable immunodeficiency—like disease with autoimmunity. Two longitudinal cohorts were subsequently published that dwelt on the clinical and immunologic features of LRBA deficiency. To date, different agents have been applied in the treatment of LRBA deficiency, including corticosteroids, intravenous immunoglobulin therapy, sirolimus, infiximab, rituximab, and azathioprine. Some patients also benefit from hematopoietic stem cell transplantation (HSCT), which can be curative. More recently, studies have suggested the effectiveness of abatacept, a CTLA4-immunoglobulin fusion protein, in controlling disease-related immune dysregulatory phenotypes. In addition, some biomarkers such as soluble CD25 and circulating T follicular helper (cTfh) cells were described as useful to monitor patients’ disease activity. Nevertheless, the long-term effectiveness of abatacept is not well documented. Also, there is no established consensus as to the dose and frequency of abatacept therapy for the treatment of LRBA deficiency and which biomarker is most reliable for follow-up of patients. The spectrum of the clinical responses of LRBA-deficient patients to abatacept treatment is also obscure.

In this report, we present the findings on a well-defined LRBA-deficient cohort, in which we prospectively evaluated the clinical and immunologic responses to abatacept therapy. Our studies establish the efficacy of long-term abatacept therapy in curbing the immune dysregulatory features of this disease in most cases and also highlight the limitations of this therapy in occasional patients with severe disease phenotype.

### METHODS

#### Patient and inclusion criteria

The study included 22 patients with proven LRBA mutation. The patients were recruited from 12 different pediatric immunology centers in Turkey. They were enrolled into the study at different time points starting from November 2016 and followed up prospectively until December 2018. The study protocol was approved by the local ethics committee of Marmara University (institutional review board no. IRB00009067), and a written informed consent was obtained from all parents. Because of the young age of our patients, a simple oral description of the study was presented to participating children in the presence of their parent(s) and a verbal assent was requested.

#### Study design

The LRBA-deficient patients were enrolled to the study prospectively from related centers. During the study, baseline demographic, clinical, and immunologic data were collected. Blood samples from all the participating patients from the respective medical centers were sent to the Marmara University Pediatric Allergy and Immunology laboratory for immunologic assessment, including extensive lymphocyte subset analysis, cTfh cell enumeration, and intracellular LRBA and CTLA4 staining. The changes in lymphocyte subsets and cTfh cells were evaluated at sixth month and compared with baseline values. The detailed methods used for
Transcriptomic profiles conducive to immune-mediated tumor rejection in human breast cancer skin metastases treated with Imiquimod

Mariya Rozenbliut, Wouter Hendrickx, Adriana Heguy, Luis Chiriboga, Cynthia Loomis, Karina Ray, Farbod Darvishian, Mikala Egeblad, Sandra Demaria, Francesco M. Marincola, Davide Bedognetti & Sylvia Adams

Imiquimod is a topical toll-like-receptor-7 agonist currently used for treating basal cell carcinoma. Recently, imiquimod has demonstrated tumor regression in melanoma and breast cancer skin metastases. However, the molecular perturbations induced by imiquimod in breast cancer metastases have not been previously characterized. Here, we describe transcriptomic profiles associated with responsiveness to imiquimod in breast cancer skin metastases. Baseline and post-treatment tumor samples from patients treated with imiquimod in a clinical trial were profiled using Nanostring technology. Through an integrative analytic pipeline, we showed that tumors from patients who achieved a durable clinical response displayed a permissive microenvironment, substantiated by the upregulation of transcripts encoding for molecules involved in leukocyte adhesion and migration, cytotoxic functions, and antigen presentation. In responding patients, imiquimod triggered a strong T-helper-1 (Th-1) cytokine response, characterized by the coordinated upregulation of Th-1 chemokines, migration of Th-1 and cytotoxic T cells into the tumor, and activation of immune-effector functions, ultimately mediating tumor destruction. In conclusion, we have shown that topical imiquimod can induce a robust immune response in breast cancer metastases, and this response is more likely to occur in tumors with a pre-activated microenvironment. In this setting, imiquimod could be utilized in combination with other targeted immunotherapies to increase therapeutic efficacy.

Breast cancer is the second cause of death in women and the second most common cancer to metastasize to the skin after melanoma. Treatment of breast cancer skin metastases remains a challenge. Initial management usually consists of resection and radiotherapy but skin metastases often recur and can lead to chest wall ulceration, bleeding, and pain.

Imiquimod is a Toll-like Receptor (TLR)-7 agonist that can activate the innate immune system and shape the ensuing adaptive immune response. Imiquimod induces the production of several pro-inflammatory cytokines such as IFN-α, TNF-α, IL-1, IL-6, and IL-8 and leads to the recruitment and activation of dendritic cells. In basal and squamous cell carcinoma, imiquimod induces infiltration of the tumor with effector T cells, increases

1Department of Hematology Oncology, Yale University School of Medicine, New Haven, Connecticut, USA. 2Tumor Biology, Immunology, and Therapy Section, Immunology, Inflammation, and Metabolism Department, Division of Translational Medicine, Sidra Medicine, Doha, Qatar. 3Department of Pathology, New York University School of Medicine, New York, New York, USA. 4Genome Technology Center, Division of Advanced Research Technologies, University of New York School of Medicine, New York, New York, USA. 5Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, New York, USA. 6Department of Radiation Oncology Well Cornell Medical College, New York, New York, USA. 7Refuge Biotechnologies Inc, Menlo Park, CA, USA. 8Laura & Isaac Perlmutter Cancer Center, New York University School of Medicine, New York, New York, USA. Davide Bedognetti and Sylvia Adams contributed equally. Correspondence and requests for materials should be addressed to D.B. (email: dbbedognetti@sidra.org) or S.A. (email: Sylvia.Adams@nyumc.org)
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.

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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].

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 isothiocynate, 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
ARTICLE

Transcriptional profiling unveils type I and II interferon networks in blood and tissues across diseases

Akul Singhania & et al.

Understanding how immune challenges elicit different responses is critical for diagnosing and deciphering immune regulation. Using a modular strategy to interpret the complex transcriptional host response in mouse models of infection and inflammation, we show a breadth of immune responses in the lung. Lung immune signatures are dominated by either IFN-γ and IFN-inducible, IL-17-induced neutrophil- or allergy-associated gene expression. Type I IFN and IFN-γ-inducible, but not IL-17- or allergy-associated signatures, are preserved in the blood. While IL-17-associated genes identified in lung are detected in blood, the allergy signature is only detectable in blood CD4+ effector cells. Type I IFN-inducible genes are abrogated in the absence of IFN-γ signaling and decrease in the absence of IFNAR signaling, both independently contributing to the regulation of granulocyte responses and pathology during Toxoplasma gondii infection. Our framework provides an ideal tool for comparative analyses of transcriptional signatures contributing to protection or pathogenesis in disease.
Management of Coarctation of The Aorta in Adult Patients: State of The Art

Wail Alkashkari, MD1,2,3, Saad Albugami, MD1,2,3, and Ziyad M. Hijazi, MD4,5

1King Saud Bin Abdulaziz University for Health Science, Jeddah, Saudi Arabia
2Department of Cardiology, King Faisal Cardiac Center, Ministry of national Guard Health Affairs, Jeddah, Saudi Arabia
3King Abdullah international medical research center Jeddah, Saudi Arabia
4Department of Pediatrics, Sidra Heart Center, Sidra Medicine, Doha, Qatar
5Weill Cornell Medicine, New York, NY, USA

ABSTRACT

Coarctation of the aorta (CoA) is a common form of congenital heart disease. Adult patients with CoA may be asymptomatic or may present with hypertension. Over the last few years, endovascular management of adult patients with CoA emerged as the preferred strategy. Stent implantation, though technically challenging, offers the best and most lasting therapy. In this paper, we will review technical considerations and outcome of patients undergoing stent implantation for CoA.

Keywords: Stents; Aortic Coarctation; Balloon angioplasty; Cardiac Catheterization

INTRODUCTION

Coarctation of the aorta (CoA) is the sixth most common congenital heart disease (CHD) accounting for 4–8% of all CHD and occurs in 4 out of 1,000 live births with a male predominance. CoA can occur as an isolated lesion, but is often associated with other cardiovascular lesions, such as bicuspid aortic valve (BAV) in 50–75% of the cases, aortic arch hypoplasia, subaortic stenosis, mitral valve abnormalities, ventricular and atrial septal defects and patent ductus arteriosus (PDA). The most important non-cardiac associated lesion is cerebral aneurysm present in up to 10% of patients, which is approximately 5 times higher than that in the general population.

CoA is defined as a localised narrowing of the aortic lumen by a ridge, composed of medial wall thickening and infolding of aortic wall tissue. The narrowing is commonly located opposite to the insertion of the PDA (juxtaductal); however, it may also be located proximal (preductal) or distal (postductal) to the PDA. Infrequently, it can also exist in the transverse aortic arch and abdominal aorta, or be a part of a long segment arch hypoplasia.

PATHOGENESIS

The underlying pathogenesis of CoA is not fully understood. However, there are three theories that may shed some light on this:
Research Paper

Assessment of Food Safety Knowledge, Self-Reported Practices, and Microbiological Hand Hygiene Levels of Produce Handlers in Qatar

ISRAA EL-NEMR,1 MOHANAD MUSHTAHA,1 PATRICK IRUNGU,2 HAMMAD ASIM,1 PATRICK TANG,3,4 MOHAMMAD HASAN,3,4 AND IPEK GOKTEPE1,*

1Department of Biological and Environmental Sciences, College of Arts & Sciences, and 2College of Business & Economics, Qatar University, P.O. Box 2713, Doha, Qatar (ORCID: http://orcid.org/0000-0002-1419-143X[J.G.]); 3Department of Pathology, Sidra Medicine, P.O. Box 26999, Doha, Qatar; and 4Well Cornell Medical College in Qatar, P.O. Box 24144, Doha, Qatar

ABSTRACT

Food handling across the custody chain from production to consumption is one of the most important stages in which microbes can enter food from infected food handlers or due to cross-contamination. The wholesale produce market (WSPM), located in Doha, Qatar, is a good example of a custody chain in which a large amount of produce from different origins are purchased daily by restaurants, retailers, and individuals. However, no information is available on the food handling practices applied at the WSPM. Hence, this study was conducted to assess the self-reported hygiene practices and food safety knowledge of produce handlers at the WSPM as a baseline for food safety outreach. One hundred twenty produce handlers participated in this study to complete a structured questionnaire assessing food safety knowledge and hygiene practices. In addition, survey respondents’ hands were swabbed to determine microbiological hand hygiene levels. Survey results revealed that none of the produce handlers had food safety knowledge or received training on safe produce handling practices. The median age group was 31 to 40 years, and over 57% had less than high school education. The level of self-reported knowledge on “food safety practices” displayed by produce handlers was not influenced by demographically based differences (e.g., age and years of experience), except education level. Note that 77% of produce handlers claimed to wash their hands four times per day; however, this good self-reported practice was not reflected in the microbial assessment of produce handlers’ hands that had total aerobic and coliform counts ≥2 log CFU/cm². Bacillus circulans (40%), Staphylococcus sciuri (25%), and Klebsiella pneumoniae (17%) were the most common bacteria isolated from produce handlers’ hands. These findings may help public health agencies in Qatar establish guidelines for compulsory on-site training for produce handlers to improve knowledge on safe produce handling.

HIGHLIGHTS

- Workers’ hygiene is one of the most important risk factors in transferring pathogens to foods.
- Produce handlers lacked basic knowledge on personal hygiene and food safety.
- Produce handlers’ hand hygiene levels were below set standards.
- This study is the first of its kind in the region; thus, it helps fill an existing knowledge gap.

Key words: Food safety knowledge; Good handling practices; Hand hygiene; Produce handlers; Wholesale produce market

Food handlers who are trained in good hygiene practices represent the first defense against contamination of food across the supply chain. According to the U.S. Food and Drug Administration (47), the spread of pathogenic microorganisms can be reduced by applying basic hygiene practices such as appropriate hand washing routines. The palms of the hands of the food handlers can carry several types of microorganisms, such as Escherichia coli O157:H7, Shigella spp., Salmonella Typhi, nontyphoidal Salmonella, norovirus, and hepatitis A virus, all of which come from human fecal residue and the environment. In addition, touching raw food materials can lead to the colonization of hands with bacteria, such as Salmonella spp. and E. coli O157:H7 (47). These pathogens can be easily transferred from food handlers’ palms to food products during handling or preparation.

The problem of food safety and outbreaks of foodborne diseases in the last decade has shifted from the traditional food culprits, meat, poultry, and eggs, to fresh produce (13), as the demand for fresh produce has increased worldwide in the last 10 years. Fresh produce is considered a major
**ORIGINAL ARTICLE**

**HDAC4 mutations cause diabetes and induce β-cell FoxO1 nuclear exclusion**

Maolian Gong1,2* | Yong Yu3* | Lei Liang1,4 | Dogus Vuralli5 | Sebastian Froehler3 | Peter Kuehnen6 | Philipp Du Bois1 | Jingjing Zhang7 | Aidi Cao1 | Yuantao Liu2 | Khalid Hussain8 | Jens Fielitz1,9 | Shiqi Jia3,10 | Wei Chen11 | Klemens Raile1,12

1Experimental and Clinical Research Center (ECRC), a joint cooperation between the Charité Medical Faculty, Max-Delbrueck-Center for Molecular Medicine (MDC), Berlin, Germany
2Qingdao Municipal Hospital, Qingdao, China
3Max-Delbrück Center for Molecular Medicine, Berlin, Germany
4Department of Pediatrics, Anhui Provincial Children’s Hospital, Hefei, China
5Division of Paediatric Endocrinology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey
6Institute for Experimental Pediatric Endocrinology, Berlin, Germany
7Affiliated Hospital of Guangdong Medical University, Zhanjiang, China
8Division of Endocrinology, Department of Paediatric Medicine, Sidra Medical & Research Center, Doha, Qatar
9German Center for Cardiovascular Research (DZHK), partner site Greifswald & Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany
10The First Affiliated Hospital of Jinan University, Guangzhou, China
11Department of Biology, Southern University of Science and Technology, Shenzhen, China
12Department of Pediatric Endocrinology and Diabetology, Charité, Berlin, Germany

**Correspondence**

Maolian Gong, Experimental and Clinical Research Center (ECRC), a joint cooperation between the Charité Medical Faculty and the Max-Delbrueck-Center for Molecular Medicine (MDC), Berlin, Germany.

Email: Maolian@mdc-berlin.de

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**Abstract**

**Background:** Studying patients with rare Mendelian diabetes has uncovered molecular mechanisms regulating β-cell pathophysiology. Previous studies have shown that Class IIA histone deacetylases (HDAC4, 5, 7, and 9) modulate mammalian pancreatic endocrine cell function and glucose homeostasis.

**Methods:** We performed exome sequencing in one adolescent nonautoimmune diabetic patient and detected one de novo predicted disease-causing **HDAC4** variant (p.His227Arg). We screened our pediatric diabetes cohort with unknown etiology using Sanger sequencing. In mouse pancreatic β-cell lines (Min6 and SJ cells), we performed insulin secretion assay and quantitative RT-PCR to measure the β-cell function transfected with the detected **HDAC4** variants and wild type. We carried out immunostaining and Western blot to investigate if the detected **HDAC4** variants affect the cellular translocation and acetylation status of Forkhead box protein O1 (FoxO1) in the pancreatic β-cells.

*These authors contributed equally to this study

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Results: We discovered three HDAC4 mutations (p.His227Arg, p.Asp234Asn, and p.Glu374Lys) in unrelated individuals who had nonautoimmune diabetes with various degrees of β-cell loss. In mouse pancreatic β-cell lines, we found that these three HDAC4 mutations decrease insulin secretion, down-regulate β-cell-specific transcriptional factors, and cause nuclear exclusion of acetylated FoxO1.

Conclusion: Mutations in HDAC4 disrupt the deacetylation of FoxO1, subsequently decrease the β-cell function including insulin secretion, resulting in diabetes.

KEYWORDS
diabetes, FoxO1, HDAC4 mutations, pancreatic β-cells

1 | INTRODUCTION

About 3% of diabetic patients involve single-gene mutations (Mendelian) that may also cause type 2 diabetes (Yang & Chan, 2016). More than twenty genes highly expressed in pancreatic β-cells have been identified within these mono- genic subtypes (Alkorta-Aranburu et al., 2014). Recently, two national surveys revealed that most patients with monogenic diabetes are likely to be unrecognized and misdiagnosed as type 1 or type 2 diabetes (Delvecchio et al., 2017; Johansson et al., 2017). Genetic diagnosis leads to improved treatment, better prediction of disease prognosis and progression, genetic counseling, and possibly prevention. The benefit of a molecular genetic diagnosis has been shown in the patients with monogenic diabetes caused by a mutation in the ABCC8, KCNJ11, HNF1A, or HNF4A; all these patients were sensitive to sulfonylureas, which greatly improved glycemic control and quality of life (Hattersley & Patel, 2017). However, patients with a mutation in GCK typically do not require pharmacological intervention (Ajjan & Owen, 2014). Therefore, identification of novel disease-related loci may provide further opportunities to derive new drug targets.

Histone deacetylases (HDACs) have a broad impact on the development of human disease by regulating histone modification and gene transcription (Mathias, Guise, & Cristea, 2015; Mielcarek, Zielonka, Carnemolla, Marcinkowski, & Guidez, 2015). Class II HDAC4, 5, 7, and 9 modulate endocrine cell function and glucose homeostasis in skeletal muscles, adipose tissue, and liver (Daneshpajooh et al., 2017; Lenoir et al., 2011; Mathias et al., 2015; Mihaylova et al., 2011). In addition, HDAC4 was also found to be a key regulator controlling the pancreatic β6 lineage during embryogenesis (Lenoir et al., 2011). Makinistoglu et al. found that in osteoblast-specific Hdac4 gene-deleted (−/−) mice, HDAC4 regulates not only the spatial learning and memory, male fertility, and appetite, but also glucose metabolism through its expression in osteoblasts. They observed that the insulin content and β-cell area in the pancreas, as well as insulin levels and insulin secretion in the circulation blood, were significantly decreased in Hdac4−/− compared with the control littermates (Makinistoglu & Karsenty, 2015), indicating that HDAC4 regulates insulin content, secretion, and sensitivity through direct or indirect pathways. In humans, HDAC4 was found to be expressed in the pancreas as well, and associated with type 2 diabetes (Rani et al., 2017).

We report three pediatric hyperglycemic patients harboring individual HDAC4 (OMIM: 605314) mutations. These HDAC4 variants decreased the insulin secretion and down-regulated the key β-cells transcriptional factors of pancreatic β-cells. Furthermore, deacetylation of FoxO1 was inhibited by these HDAC4 mutations resulting in FoxO1 acetylation and nuclear exporting, therefore decreasing β-cell functions.

2 | PATIENTS AND METHODS

2.1 | Ethical compliance

The Charité committee on human subjects’ research approved the study (EA-No EA2/054/11) and written informed consent was obtained.

2.2 | Patients

All individuals with hyperglycemia tested negative for β-cell autoantibodies and developed diabetes before the age of 18 years. They were recruited from Charité and international diabetes centers. We excluded mutations in known genes causing monogenic diabetes (GCK, HNF4A, HNF1A, HNF1B, ABCC8, KCNJ11, and INS) by Sanger sequencing.

2.3 | Variants discovery with exome sequencing and Sanger sequencing

We conducted exome sequencing in one patient and his healthy parents and analyzed the sequencing results with our reported pipeline (Kuhnen et al., 2014) for rare de novo
The Effect of Exenatide on Cardiovascular Risk Markers in Women With Polycystic Ovary Syndrome

Alison J. Dawson 1, Thozhukat Sathyapalan 2, Rebecca Vince 3, Anne-Marie Coady 4, Ramzi A. Ajjan 5, Eric S. Kilpatrick 6 and Stephen L. Atkin 7,8*

1 Department of Diabetes and Endocrinology, University of Hull, Hull, United Kingdom, 2 Department of Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, Heslington, United Kingdom, 3 Department of Sports Science, University of Hull, Hull, United Kingdom, 4 Department of Ultrasound, Hull and East Yorkshire Women’s and Children’s Hospital, Hull, United Kingdom, 5 Division of Cardiovascular and Diabetes Research, Leeds Institute for Genetics, Health and Therapeutics, University of Leeds, Leeds, United Kingdom, 6 Sidra Medical Research Centre, Doha, Qatar, 7 Royal College of Surgeons in Ireland (Bahrain), Al Muharraq, Bahrain

Background: Polycystic ovary syndrome (PCOS) is associated with an adverse cardiovascular risk profile including a prothrombotic state. Exenatide has been shown to be effective at improving insulin sensitivity and weight loss in PCOS; therefore this study was undertaken to assess its effects on weight, endothelial function, inflammatory markers, and fibrin structure/function in overweight/obese women with PCOS.

Methods: Thirty overweight/obese anovulatory women with all 3 Rotterdam criteria received exenatide 5 mcg bd for 4 weeks then 10 mcg bd for 12 weeks. The primary outcome was change in weight; secondary outcomes were changes in endothelial function [Reactive Hyperemia-Peripheral Arterial Tonometry (RH-PAT)], serum endothelial markers (ICAM-1, VCAM-1, E-selectin, and P-selectin), change in inflammation (hsCRP), and alteration in clot structure and function [maximum absorbance (MA), and time from full clot formation to 50% lysis (LT)].

Results: Twenty patients completed the study. Exenatide reduced weight 111.8 ± 4.8 to 108.6 ± 4.6 kg (p = 0.003). Serum endothelial markers changed with a reduction in ICAM-1 (247.2 ± 12.9 to 231.3 ± 11.5 ng/ml) (p = 0.02), p-selectin (101.1 ± 8.2 to 87.4 ± 6.6 ng/ml) (p = 0.01), and e-selectin (38.5 ± 3.3 to 33.6 ± 2.6 ng/ml) (p = 0.03), without an overt change in endothelial function. Inflammation improved (CRP; 8.5 ± 1.4 to 5.6 ± 0.8 mmol/L) (p = 0.001), there was a reduction in clot function (LT; 2.987 ± 494 to 1.926 ± 321 s) (p = 0.02) but not clot structure.

Conclusion: Exenatide caused a 3% reduction in weight, improved serum markers of endothelial function, inflammation, and clot function reflecting an improvement in cardiovascular risk indices in these women with PCOS. This suggests exenatide could be an effective treatment for obese women with PCOS.

Clinical Trial Registration: ISRCTN81902209.

Keywords: polycystic ovary syndrome, exenatide, cardiovascular risk, endothelial function, inflammation, blood clot function, GLP-1 receptor agonists
Stillbirth: Perceptions among hospital staff in the Middle East and the UK

Suruchi Mohan a,*, Thomas Gray b, Weiguang Li c, Mohamed Alloub d, Andrew Farkas a, Stephen Lindow a, Tom Farrell b

a Sidra Medicine, Sidra Outpatient Building, Al Luqa Street, Education City North Campus, Qatar Foundation, PO BOX 26999, Doha, Qatar
b Sheffield Teaching Hospitals NHS Foundation Trust, Jessop Wing, Tree Root Walk, Sheffield, S10 2SF, UK
c York Teaching Hospital NHS Foundation Trust, Wigan Hospital Road, York, Y031 4RY, UK
d Al Walra Hospital, Hamad Medical Corporation, Qatar

A R T I C L E   I N F O

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A B S T R A C T

Objectives Stillbirth is an important and yet relatively unacknowledged public health concern in many parts of the world. Public awareness of stillbirth and its potentially modifiable risk factors is a prerequisite to planning prevention measures. Cultural and regional differences may play an important role in awareness and attitudes to stillbirth prevention. The objective of this study was to evaluate and compare the awareness of stillbirth among hospital staff in Qatar and the UK, representing two culturally different regions.

Study design An online population survey for anonymous completion was sent to the hospital email accounts of all grades of staff (clinical and non-clinical) at two hospitals in Qatar and one tertiary hospital Trust in the UK. The survey was used to gather information on the participants’ demographic background, the experience of stillbirth, knowledge of stillbirth, awareness of information and support sources, as well as attitude towards investigation and litigation. Data were analysed using descriptive and comparative statistics (Chi-Square test and Fisher’s exact test).

Results 1002 respondents completed the survey, including 349 in the Qatar group and 653 in the UK group. There were significant differences in group demographics in terms of language, religion, gender, nationality and experience of stillbirth. The groups also differed significantly in the knowledge of stillbirth, its incidence and risk factors. The two groups took different views on apportioning blame on healthcare services in cases of stillbirth. The Qatar group showed significantly less awareness of available support organisations and relied significantly more on online sources of information for stillbirths (p < 0.001).

Conclusions This comparative study demonstrated significant differences between the two culturally distinct regions in the awareness, knowledge and attitudes towards stillbirths. The complex cultural and other factors that may be contributory should be further studied. The results highlight the need for increasing public awareness around stillbirth as part of effective prevention strategies.

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Introduction

Stillbirth, defined as a baby delivered with no signs of life known to have died after 24 completed weeks of pregnancy, remains a taboo subject despite an estimated 2.6 million occurring annually worldwide [1]. Despite the profound emotional, social and economic impact a stillbirth can have on individuals and families; initiatives to reduce stillbirth have until recently largely been ignored [2]. The incidence of stillbirth is often considered as a surrogate measure of the performance of a country’s public health system [2–4]. In high-income settings, stillbirth rates have stabilised over recent years but have risen in lower income parts of the world [5]. Therefore, there is a need for acknowledgment and discussion of stillbirth on a wider scale than is currently the case, so that healthcare and health-education resources can be appropriately targeted to reduce stillbirth rates.

An awareness of the risk factors of stillbirth is an essential prerequisite to inform healthcare planning. There is evidence associating stillbirth with maternal obesity, smoking, gestational diabetes and fetal growth restriction [6]. However, there is also

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Australian Aboriginal children have higher hospitalization rates for otitis media but lower surgical procedures than non-Aboriginal children: A record linkage population-based cohort study

Darren W. Westphal 1,2*, Deborah Lehmann 1, Stephanie A. Williams 2, Peter C. Richmond 1,3, Francis J. Lannigan 4,5, Parveen Fathima 1, Christopher C. Blyth 1,3,6,7, Hannah C. Moore 1

1 Wesfarmers Centre for Vaccines and Infectious Diseases, Telethon Kids Institute, The University of Western Australia, Perth, Western Australia, Australia, 2 National Centre for Epidemiology & Population Health, Australian National University, Canberra, Australian Capital Territory, Australia, 3 Division of Paediatrics, School of Medicine, The University of Western Australia, Perth, Western Australia, Australia, 4 Division of Surgery, Paediatrics and Child Health, The University of Western Australia, Perth, Western Australia, Australia, 5 Sidra Medicine, Doha, Qatar, 6 Department of Infectious Diseases, Perth Children’s Hospital, Perth, Western Australia, Australia, 7 Department of Microbiology, PathWest Laboratory Medicine, QEII Medical Centre, Perth, Western Australia, Australia

* Current address: Western Australia Department of Health, East Perth, Western Australia, Australia

**Darren.westphal@health.wa.gov.au

Abstract

Introduction

Otitis media (OM) is one of the most common infectious diseases affecting children globally and the most common reason for antibiotic prescription and paediatric surgery. Australian Aboriginal children have higher rates of OM than non-Aboriginal children; however, there are no data comparing OM hospitalization rates between them at the population level. We report temporal trends for OM hospitalizations and in-hospital tympanostomy tube insertion (TTI) in a cohort of 469,589 Western Australian children born between 1996 and 2012.

Materials and methods

We used the International Classification of Diseases codes version 10 to identify hospitalizations for OM or TTI recorded as a surgical procedure. Using age-specific population denominators, we calculated hospitalization rates per 1,000 child-years by age, year and level of socio-economic deprivation.

Results

There were 534,674 hospitalizations among 221,588 children hospitalized at least once before age 15 years. Aboriginal children had higher hospitalization rates for OM than non-Aboriginal children (23.3/1,000 [95% Confidence Interval (CI) 22.8,24.0] vs 2.4/1,000 [95%
Involving parents in road safety decision making: Keeping our children safe

Mohamed A. Hendaus,1,2,3 Reem Wassaf,4 Manwa Salat,4 Tasneem Riyad Abdal-karim,4 and Ahmed H. Alhannadi1,2,3

1Department of Pediatrics, Section of Academic General Pediatrics, Sidra Medicine, Doha, Qatar
2Department of Pediatrics, Hamad General Corporation, Doha, Qatar
3Department of Clinical Pediatrics, Weill-Cornell Medicine, Doha, Qatar
4Pediatric Residency Program, Hamad General Corporation, Doha, Qatar

Address for correspondence: Dr. Mohamed A. Hendaus, Department of Pediatrics, Sidra Medicine, Doha - 26999, Qatar. E-mail: mhendaus@yahoo.com

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Abstract

Purpose:

The purpose of the study was to delineate parental concept of road safety in the state of Qatar, integrate parental thoughts and ideas into public safety, and share our data with authorities to assist in implementing campaigns against speeding in a country with a high rate of motor vehicle accidents.

Methods:

A cross-sectional prospective study was conducted at Hamad Medical Corporation (HMC), the only tertiary care and academic hospital in the state of Qatar. Parents of children younger than 18 years of age and residents of the State of Qatar were offered an interview survey.

Results:

A total of 200 questionnaires were completed (response rate = 98%). Approximately 80% of parents were in between 20 and 40 years of age, and 61% of them were females. Almost 40% of participating families reside outside of the city of Doha. Interestingly, only 1 in 2 parents thought their children were safe while riding with them in the car. Moreover, only 47% of parents always used car seats, seatbelts, and proper restraints. This is inspite that nearly 82% of parents felt that these restraints protect children in case of an accident. Parents were also asked of the best place to receive information regarding road safety. Almost 50% preferred to receive the information through social media, whereas 44.3% opted for local television. Role modeling was also assessed and it showed that 85% of parents believed that the most effective way in teaching children and young people to use roads in a safe way is to always provide a positive role model when using the roads.

Conclusion:
Parental perception of fluoridated tap water

Mohamed A. Hendaus, Khaled Siddiq, Mohanad AlQadi, Faisal Siddiqui, Shafeeqe Kunhiabdullah, Ahmed H. Alharmadi

1Department of Pediatrics, Section of Academic General Pediatrics, Hamad General Corporation, 2Department of Pediatrics, Section of Academic General Pediatrics, Sidra Medical and Research Center, 3Department of Clinical Medicine, Well-Cornell Medicine, 4Department of Pediatrics, Academic General Pediatrics Fellowship Program, Hamad General Corporation, 5Department of Pediatrics, Pediatric Residency Program, Hamad General Corporation, Doha, Qatar

ABSTRACT

Purpose: The purpose of this study was to investigate parental knowledge and preference of tap water in a country where faucet water is fluoridated according to international standards and where the average percentage of dental caries in young children reaches up to approximately 73%. Materials and Methods: A cross-sectional perspective study was conducted at Hamad Medical Corporation, the only tertiary care and academic hospital in the state of Qatar. Parents of children older than 1 year of age were offered an interview survey. Results: A total of 200 questionnaires were completed (response rate = 100%). The mean age of participant children was 6 ± 4 years. One of the main findings in our study was that primary care physicians never discussed the topic of the best water choice for children in our community, as expressed by more than 86% of parents. More than two-third of parents used bottled water. The main concerns of why parents did not allow their children to drink tap water were taste (8.94%), smell (9.73%), concerns of toxins content (32.52%), and concerns that tap water might cause unspecified sickness (52.03%). Amid revealing participants that our tap water is safe and that fluorine can prevent dental caries, 33% of parents would use tap water due to its fluoride content. The study also showed that 65% of parents would allow their children to drink tap water if it is free from any toxic ingredients. Conclusion: Actions to augment fluoridated water acceptability in the developing world, such as focusing on safety and benefits, could be important in the dissemination of implementation of the use of faucet water. Ultimately, a slump in the prevalence of dental caries among children will depend on the ability of pediatricians and dental professionals to institute evidence-based and preventive approach that can benefit oral health in childhood. These data will also allow us to propose the use of tap water safely in young children in the state of Qatar while simultaneously advocating awareness of oral health.

Keywords: Fluoride, oral health, pediatrics, tap water

Introduction

Dental caries is a major health issue in most developing and developed countries and is regarded as the most widespread chronic disease in childhood. More than 50% of elementary school children have at least one cavity or filling. Besides, children of low-income families have higher risk of having dental caries compared with their peers of higher economic status. The prevalence of dental caries in Qatar is 73%, compared with 28% in the United States and 60% in Brazil. Dental treatment is pricey and can inundate the healthcare budget in some developing countries. Meanwhile, dental caries prevention actions in a primary healthcare framework can distinctly reduce healthcare costs. Fluoride in water supplies, toothpastes, and professionally applied are illustrous ways of preventing dental caries. Since its commencement in 1945, supplementing public water supplies with fluoride has resulted in decrease in dental decay, with some communities reporting 50%-60% fewer decays.

Address for correspondence: Dr. Mohamed A. Hendaus,
Department of Pediatrics, Hamad Medical Corporation.
Doha, Qatar 3050.
E-mail: mohendaus@yahoo.com

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MR Imaging Evaluation of Pediatric Genital Disorders:
MR Technologic Overview and Interpretation

Jennifer K. Son, MDa, Sumera Ali, MD, Noor Al Khori, MD, Edward Y. Lee, MD, MPHd, *

KEYWORDS
- Pediatric
- Müllerian duct anomalies (MDA)
- Disorders of sex development (DSD)
- Magnetic resonance imaging (MRI)
- Genital neoplasm
- Vaginal and ovarian cysts

KEY POINTS
- Pediatric genital disorders encompass a variety of conditions, which may be congenital or acquired.
- Congenital conditions include disorders of sex development and Müllerian duct anomalies and some acquired conditions in the pediatric population include cysts and malignancy.
- MR imaging is considered the standard modality in the evaluation of Müllerian duct anomalies.
- MR imaging provides superior soft tissue contrast, multiplanar capabilities, and is not limited by patient attributes such as body habitus or bowel gas and stool.
- MR imaging is often performed to obtain additional information in the evaluation of genital tumors such as extent of disease and tissue characteristics.

INTRODUCTION
The ability to image genital disorders in children has undergone significant advancement over the years. Although ultrasound remains the favored modality for the initial evaluation of pediatric patients with a suspected genital abnormality, ultrasound imaging is limited to the transabdominal and/or transperineal approach for most pediatric patients.1 Ultrasound examination may also be limited by bowel gas and stool, as well as the body habitus of the patient. Fluoroscopy (genitography) is useful in assessing perineal orifices including the presence or absence of the vagina and its relationship with the urethra. However, this technique is invasive and requires ionizing radiation. Computed tomography scanning is little used in the evaluation of pediatric genital disorders owing to the ionizing radiation and inferior soft tissue contrast.2

MR imaging has become an invaluable tool for the further assessment of the uterus and genitalia and is useful in the evaluation of associated intraabdominal abnormalities.1, 3–5 MR imaging allows for multiplanar imaging with excellent soft tissue resolution. Significant progress has

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* Corresponding author.
E-mail address: Edward.Lee@childrens.harvard.edu

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Soluble TNF-R1, VEGF and other cytokines as markers of disease activity in systemic lupus erythematosus and lupus nephritis

Z Adhya 1,2, M El Anbari 3, S Anwar 3, A Mortimer 5, N Marr 3,6 and MY Karim2,7,8

1Immunology, King’s College Hospital, London, UK; 2Immunology, Guy’s & St Thomas’ Hospitals, London, UK; 3Research Branch, Sidra Medicine, Doha, Qatar; 4Section of Nephrology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; 5Pathway Diagnostics Ltd, Dorking, UK; 6College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar; 7Lupus Unit, Guy’s & St Thomas’ Hospitals, London, UK; and 8Pathology, Sidra Medicine, Doha, Qatar

Background: Current non-invasive methods of assessing disease activity in systemic lupus erythematosus (SLE) are of limited sensitivity and specificity. Testing includes acute phase markers, autoantibodies and complement levels. Although measurements of dsDNA antibodies and complement C3/C4 levels are routine, they remain of limited value. Improved blood and urine markers may help in early detection of flare, distinction between flare and chronic damage, and monitoring response to therapy. Methods: A total of 87 patients with SLE were tested for the following cytokines in serum and urine: monocyte chemoattractant protein 1 (MCP-1), regulated upon activation, normal T cell expressed and secreted (RANTES), soluble tumour necrosis factor receptor 1 (sTNF-R1), interferon-inducible protein 10 (IP-10), monocyte inhibitory protein 1α (MIP-1α) and vascular endothelial growth factor (VEGF). Patients attending the Lupus Unit at St Thomas’ Hospital, London, UK were divided into active lupus nephritis (LN), inactive LN and non-renal SLE groups based on their renal pathology and SLE disease activity index (SLEDAI). Cytokine testing was performed using the FIDIS multiplex bead assay. Results: The mean level of serum sTNF-R1 was higher in the active LN group compared with both inactive LN and non-renal SLE groups (p < 0.001). For urine measurements there were significant differences between active LN and non-renal SLE for VEGF (p = 0.016), after statistical correction for multiple testing. Both urinary and serum sTNF-R1 and IP-10 levels correlated with SLEDAI scores (p < 0.001), while serum VEGF correlated weakly with SLEDAI (p = 0.025). The optimum combination for differentiating active from inactive LN patients was serum VEGF, sTNF-R1, MCP-1 and glomerular filtration rate plus urinary sTNF-R1 and protein-creatinine ratio. Conclusion: These results indicate that for active LN, sTNF-R1 could be a useful serum cytokine marker, with potential for VEGF in the urine. This study has confirmed the ability of the multiplex bead technique to detect cytokines in a good analytical range, including very low and high levels, in both serum and urine. Combining serum and urine markers provided additional sensitivity in distinguishing active from inactive LN.

Key words: Lupus; nephritis; renal; Luminex; FIDIS; biomarkers; cytokines; tumour necrosis factor

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterized by intermittent flares of disease activity, which often arise unpredictably. Renal involvement occurs in 30–50% of adult SLE,1 and requires long-term monitoring as recurrent flares as well as progressive deterioration of function can lead to end-stage renal disease. Current laboratory methods of assessing SLE activity include testing acute phase markers, autoantibodies and complement levels. Renal involvement and monitoring is assessed by urinalysis, serum biochemistry and urine protein excretion. However, these routine laboratory tests are of limited sensitivity and specificity and they cannot always distinguish between active inflammation and chronic damage. For example, although a relationship between dsDNA antibodies and disease activity exists, meta-analysis has indicated low overall predictive value.2 Likewise measurement of complement C3
Commentary on: Fibroblasts Derived From Human Adipose Stem Cells Produce More Effective Extracellular Matrix and Migrate Faster Compared to Primary Dermal Fibroblasts

Graeme Ewan Glass, BSc, MB, PhD, FRCS (Plast)

Residing within adipose tissue is a small population of mesenchymal stem cells that are genetically stable, resistant to senescence in culture, and capable of trilineage differentiation. This population is attractive for tissue engineering because these cells are technically straightforward to acquire, the cell yield is favorable compared with other methods of stem cell acquisition, and the harvest of tissue from which they are derived is surgically convenient, aesthetically desirable, and functionally tolerable.\(^1\) The use of stem cells as a source of fibroblasts in regenerative medicine and in a wide range of wound-healing applications is currently the source of intense interest and it is curious that there are not more reports comparing differentiated fibroblasts from primary dermal fibroblasts. This paper aims to address this deficiency by comparing ex vivo–engineered fibroblasts differentiated from adipose stem cells with primary dermal fibroblasts harvested from the same donor.\(^2\) To do this the authors have compared the expression profiles of extracellular matrix proteins and have also compared migration using scratch test assays. They found that, compared with primary dermal fibroblasts, engineered fibroblasts exhibited enhanced expression of elastin, fibronectin, and collagen-1, and diminished expression of α-smooth muscle actin and matrix metalloproteinase-1 (MMP-1). The MMP-1 to metalloproteinase inhibitor 1 (TIMP-1) ratio, an important determinant of the matrix remodeling environment, was much higher at day 90 for primary dermal fibroblasts, suggesting delayed matrix remodeling relative to engineered fibroblasts. Expression of collagen-3 was enhanced early (day 1) and late (day 90) in engineered fibroblasts relative to primary dermal fibroblasts. Engineered fibroblasts were also shown to exhibit the enhanced capacity for cell migration.

What these results really demonstrate is that, although the population of fibroblastically differentiated cells engineered from adipose-derived stem cells (ADSCs) share morphologic and phenotypic similarities with mature dermal fibroblasts, they nevertheless demonstrate substantial expressive and behavioral differences, the nature of which might be exploited to enhance wound healing. In one sense this argument might be distilled down to a semantic discussion of what makes a stem cell a stem cell and what makes a fibroblast a fibroblast, but I will stay clear of this argument because, clinically, it is largely irrelevant. What matters in tissue engineering is understanding the properties and potential of the cell populations we have at our disposal. The convincing conclusion that may be drawn...
from this study is that adipose tissue is an attractive source of cells with fibroblastic potential and an appealing proteomic profile.

Although this study focuses on a simple, central concept of establishing the major differences between engineered and primary dermal fibroblasts in terms of basic proteomic and transcriptomic profiles of relevance to wound healing, a complete understanding of the differences requires a thorough genomic, transcriptomic, proteomic, and metabolomic approach, and there are, perhaps, many more interesting features of these cells that have yet to be investigated. Although the study reported enhanced migration by engineered fibroblasts, therapeutic exploitation of this finding requires identification of the chemokines (and associated receptors) involved. Additionally, differences in the expression of α-smooth muscle actin and collagen-3 suggests different predispositions towards myofibroblast differentiation. Moreover, age- and gender-dependent differences have yet to be studied here.

In order to confirm differentiation of ADSCs to fibroblasts, the authors observed increased expression of the fibroblast marker EPHB3 and reduced expression of CD34 and CD105. It should be acknowledged that, according to the position statement produced by the International Society for Cellular Therapy (ISCT), the markers for mesenchymal stem cells include CD73, CD90, and CD105, but explicitly not CD34, which is a marker for primitive hemopoetic and endothelial progenitors. The presence of CD34 probably reflects early passage number, population heterogeneity and cell isolation, and culture protocols. The controversy of phenotypic markers aside, the authors have designed the study with insight. Using cells prior to passage 8 circumvents the variable and donor-specific phenomenon of cellular senescence in culture, whereas the use of only abdominal fat acknowledges observations of region-specific variability in gene expression profiles and differentiation potential even though including both pre- and sub-Scarpa’s fat risks complicating the analyses.

In a landscape where commercial exploitation has long exceeded evidence-backed, hypothesis-driven paradigms, the scientific foundations on which this exciting field will eventually come to rest will be built on high-quality studies, and mechanistic evidence as presented in this paper forms an important part of this. The authors are to be commended on this work.

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REFERENCES
The Effects of Soy Protein and Cocoa With or Without Isoflavones on Glycemic Control in Type 2 Diabetes. A Double-Blind, Randomized, Placebo-Controlled Study

Judit Konya1, Thozhukat Sathyapalan1, Eric S. Kilpatrick2 and Stephen L. Atkin3*

1 Diabetes Research Centre, University of Hull, Kingston upon Hull, United Kingdom, 2 Sidra Research Centre, Doha, Qatar, 3 Weill Cornell Medicine, Doha, Qatar

Objective: Soy and cocoa have been suggested to be beneficial for diabetes. The aim of this study was to identify the effects of soy protein, isoflavones, and cocoa on glycemic control parameters.

Research design and methods: The study was a parallel, double-blind, placebo-controlled study where patients with diet or metformin controlled type 2 diabetes were randomized to, casein soy protein with or without isoflavones (SPI, SP), and with or without cocoa (SPIC, SPC) arms for an 8 week period. Glycemic control and cardiovascular risk factors were assessed prior to and after the completion of the dietary intervention. Sixty participants completed the study.

Results: Soy protein improved HbA1c compared to casein (p < 0.05). The addition of isoflavones improved indices of insulin resistance and LDL [delta QUICKIE (SPI: −0.12 ± 0.04 vs. SP: 0.03 ± 0.06, p = 0.03); delta LDL (−0.27 ± 0.41 vs. 0.22 ± 0.43, p = 0.02); percentage change in HOMA (31.02 ± 54.75 vs. −14.42 ± 27.07, p = 0.02); percentage change in QUICKIE (−3.89 ± 7.07 vs. 6.11 ± 10.54, p = 0.01)]. However, the addition of cocoa provided no benefit with or without isoflavones.

Summary: Soy protein had intrinsic activity on glycemic control compared to casein. Isoflavones improved both insulin resistance and LDL, but cocoa did not have added benefit on these indices.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT01754662.

Keywords: type 2 diabetes, soy, cocoa, glycemia control, isoflavones

INTRODUCTION

The number of patients with diabetes is projected to rise to 592 million in the next 25 years (1). The prevalence of cardiovascular disease is three times higher in patients with type 2 diabetes (2) with a four-to six-fold higher mortality (3).

Lifestyle and diet modification remains the first step in improving glycemic control and soy has been shown to improve insulin resistance in both primate studies and post-menopausal women
Ion Transporters, Channelopathies, and Glucose Disorders

Huseyin Demirbilek 1, Sonya Galcheva 2, Dogus Vuralli 1, Sara Al-Khawaga 3,4 and Khalid Hussain 3,*

1 Department of Paediatric Endocrinology, Hacettepe University Faculty of Medicine, 06230 Ankara, Turkey; dr_huseyin@hotmail.com (H.D.); dvuralli@hotmail.com (D.V.)
2 Department of Paediatrics, Varna Medical University/University Hospital “St. Marina”, Varna 9002, Bulgaria; sonya_galcheva@abv.bg
3 Department of Paediatric Medicine, Division of Endocrinology, Sidra Medicine, Doha, Qatar;
SarAlKhawaga@hbku.edu.qa
4 College of Health & Life Sciences, Hamad Bin Khalifa University, Qatar Foundation, Education City, Doha, Qatar
* Correspondence: khussain@sidra.org; Tel.: +974-4003-7608

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Abstract: Ion channels and transporters play essential roles in excitable cells including cardiac, skeletal and smooth muscle cells, neurons, and endocrine cells. In pancreatic beta-cells, for example, potassium K ATP channels link the metabolic signals generated inside the cell to changes in the beta-cell membrane potential, and ultimately regulate insulin secretion. Mutations in the genes encoding some ion transporter and channel proteins lead to disorders of glucose homeostasis (hyperinsulinaemic hypoglycaemia and different forms of diabetes mellitus). Pancreatic K ATP, Non-K ATP, and some calcium channelopathies and MCT1 transporter defects can lead to various forms of hyperinsulinaemic hypoglycaemia (HH). Mutations in the genes encoding the pancreatic K ATP channels can also lead to different types of diabetes (including neonatal diabetes mellitus (NDM) and Maturity Onset Diabetes of the Young, MODY), and defects in the solute carrier family 2 member 2 (SLC2A2) leads to diabetes mellitus as part of the Fanconi–Bickel syndrome. Variants or polymorphisms in some ion channel genes and transporters have been reported in association with type 2 diabetes mellitus.

Keywords: beta cell; K ATP channel; voltage-gated calcium channels; membrane transporters; neonatal diabetes; hyperinsulinaemic hypoglycaemia

1. Introduction

Ion channels and transporters are membrane-embedded proteins which play a key role in transporting ions and biomolecules across cell membranes. Although both ion channels and transporters are membrane-bound proteins, they have some differences. Ion channels are typically formed by the assembly of several different proteins and they function to allow the movement of specific ions (selectivity). The flow of ions across the channel (transmembrane flux) creates an electrical signal or action potential which is essential for the function of the particular channel [1]. Another property of ion channels is gating, which allows the channels to open and close in response to certain specific stimuli. An example of an ion channel is the adenosine triphosphate (ATP)-dependent potassium channel (K ATP) that allows the rapid and selective flow of K* ions across the cell membrane, and thus generates electrical signals in cells. Distinct from ion channels, some ion transporters may function as ion pumps, thereby moving ions across the plasma membrane against the electrochemical gradient.

Ion channels and transporters play essential roles in excitable cells including cardiac, skeletal and smooth muscle cells, neurons, and endocrine cells. In pancreatic beta-cells, K ATP channels link...
Infants with congenital heart disease have a higher incidence of low birth weight. Advances in perinatal medicine have led to dramatic improvements in survival among low-birth-weight infants. This has resulted in increasing numbers of low-birth-weight infants with congenital heart defects requiring therapy. However, mortality among premature and low-birth-weight infants undergoing surgery for congenital heart defects remains high. Therefore, catheter-based interventions as a palliative and therapeutic option have been increasingly used to improve the mortality of high-risk low-birth-weight infants. Few large studies reporting their catheterisation experience have shown increased risk of mortality and complications in low-birth-weight infants. Nevertheless, technical feasibility, outcome, and complications of cardiac catheterisation in this specific population need clarifications. That is why this procedure for low-birth-weight infants is still very debated by neonatologists and paediatricians. Patent ductus arteriosus is very frequent in the population of premature babies. Its transcatheter closure has been reported and is expanding. In this context and before expansion, we think that morbidity and mortality of cardiac catheterisation, in general, in this peculiar population of low-birth-weight infants should be provided. The objective of our study was to share our experience with low-birth-weight infants describing the results of cardiac catheterisation in small infants weighing <2500 g.

Methods

The population

We performed a retrospective review of patients weighing <2500 g who underwent cardiac catheterisation in our centre from January 2000 to July 2016. Informed consent was obtained from parents. The study was performed with approval from our institutional review board.

Data collection

Demographic data were recorded, including gender, gestational age, birth weight, comorbidity, and type of ventilation used, if any. All procedures were divided according to their interventional or diagnostic nature. To better categorise the risk of procedures, procedures were classified
Child and adolescent psychiatry training and services in the Middle East region: a current status assessment

Carolyn E. Clausen1, Khalid Bazaid2, Muhammad Waqar Azeem3, Fathelalim Abdelrahim4, Ahmed A. Abd Elgawad5, Bibi Alamiri6, Ahmed Malalla AlAnsari7, Ali Alhamzawi8, Ahmad Mohammed Al Mai9, Aisha Motwakil Bakhtiet10, Mahmoud Bashtawi11, Füsun Çuhadaroğlu12, Mazen Hedari13, Mohammad Holdar14, Samah Jabri15, Ather Sajjad Jafri16, Amjad Jumaian17, Suad Moussa18, Abdelgadir Hussein Osman4, Katayoon Razjouyan19, Eyad Yanes19, Anthony Guerrero20, Norbert Skokauskas1 on behalf of Consortium on Academic Child, Adolescent Psychiatry in the Middle East (CACAP ME)

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Abstract
Mental health is a key component of health, yet appropriate care is limited. Evidence concerning child and adolescent mental health has predominantly come from western countries, while the Middle East region, with a large youth population, has reported very little on it. This original, cross-sectional study of child and adolescent psychiatry in the Middle East provides an assessment of current postgraduate programs, services and what is needed to build workforce capacity. Academic psychiatrists from 16 Middle East countries were invited to form a Consortium to map current postgraduate training as one of the determinants of available child and adolescent psychiatry services, identify gaps in the distribution of child and adolescent psychiatrists, and propose potential steps to improve access to child and adolescent mental health care. The study collected data from 15 of the 16 countries invited (no data provided from Yemen). The study revealed underdeveloped child and adolescent psychiatry academic systems throughout the region. Despite recognition of the specialty in a majority of the countries (11/15), only six countries had established a designated child and adolescent psychiatry training program. The overall shortage of child and adolescent mental health specialists varied, yet all Consortium members reported a need for additional child and adolescent psychiatry specialists and allied professionals. Lack of child and adolescent psychiatry specialized programs in place throughout the region has evidently contributed to the shortage of qualified child and adolescent mental health workforce in the Middle East.

Keywords Child and adolescent psychiatry (CAP) · Postgraduate training · Middle East (ME) · Child and adolescent mental health

Introduction
Mental health has been acknowledged as a vital aspect of health and key to a stable life, yet the global burden associated with mental illness has persisted, with the prevalence of mental health disorders remaining high and the available workforce of qualified mental health professionals unable to meet the demand for care [1].

To improve access to mental health services, the United Nations’ Sustainable Development Goals (SDGs) have emphasized the need to address capacity building of care services from a sustainable approach [2, 3]. As part of this sustainable approach, the third SDG specifically calls for every country to “promote the well-being and capabilities of all of their citizens,” with “special attention given to early childhood and youth” [2].

Youth comprise approximately 40% of the global population, with children under the age of 20 accounting for one-third of the population and those younger than 15 years of age accounting for nearly 25% [3-6]. Not only do children
The levonorgestrel-releasing intrauterine device induces endometrial decidualisation in women on tamoxifen

Sarah Philip, Anthony H. Taylor, Justin C. Konje and Marwan Habib

Introduction

Tamoxifen is a selective oestrogen receptor modulator that acts as a competitive oestrogen receptor antagonist and significantly improves overall survival in women with oestrogen receptor positive breast cancer (Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), 2005). It exerts a proliferative, oestrogen-like effect on the endometrium thus increasing the risk of endometrial polyps, hyperplasia and cancer. A recent Cochrane review concluded that the insertion of the levonorgestrel-releasing intra-uterine system (LNG-IUS) Mirena® in tamoxifen users led to a significant reduction in the incidence of endometrial polyps over 12 months (OR 0.22, 95% CI 0.08–0.64) and 24–60 months (OR 0.22, 95% CI 0.13–0.39). In addition, the LNG-IUS reduced the incidence of endometrial hyperplasia over long-term follow-up (OR 0.13, 95% CI 0.03–0.6), possibly through decidualisation (Dominick et al. 2015).

Levonorgestrel is a synthetic 19-nortestosterone progestin derivative that is widely used in contraception and postmenopausal hormone therapy. The LNG-IUS releases 20 µg of levonorgestrel per 24 h into the uterine cavity. The local effect predominates but maximum serum levonorgestrel...
Obstetric and neonatal outcomes of clozapine exposure in pregnancy: a consecutive case series

Thinh Nguyen1,2 · Jasmine Mordecai3 · Felice Watt4 · Jacqueline Frayne1,5

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Abstract
Clozapine is an effective antipsychotic that can lead to symptom resolution and functional recovery in patients with schizophrenia. Its available pregnancy safety data remain limited, which presents a challenge for clinicians managing women of reproductive age on clozapine. We retrospectively studied a consecutive case series of nine pregnancies where there was clozapine exposure. Our case series demonstrates that pregnant women on clozapine treatment can remain stable psychiatrically, but are vulnerable obstetrically, with high rates of obesity and gestational diabetes. Their babies also have poor neonatal adjustment, often requiring neonatal resuscitation. Furthermore, we report on clozapine-related side effects, changes in clozapine levels during pregnancy as well as variation in foetal wellbeing monitoring. These findings have implications for pregnancy care for women taking clozapine and require further exploration.

Keywords Clozapine · Pregnancy · Obstetric complication · Neonatal complication

Introduction
Schizophrenia is a devastating psychotic disorder that affects women in their reproductive prime. The availability and effectiveness of the second generation antipsychotics (SGA) and recovery-based treatment approaches have resulted in many women with schizophrenia becoming parents. Recovery can potentially come at a cost to physical ill health, and this is particularly relevant to treatment with clozapine. Clozapine appears to be the most effective antipsychotic medication for treatment-resistant schizophrenia (Kane et al. 2001) and its benefits can be considerable, sometimes leading to functional recovery. It is, however, associated with a multitude of adverse effects including agranulocytosis, myocarditis and metabolic syndrome, as well as gastrointestinal problems like constipation and ileus (Young et al. 1998). As a second generation antipsychotic, it does not tend to increase prolactin, and therefore may be fertility sparing in women (Volavka et al. 2004).

Clinicians managing women of reproductive age on clozapine can be faced with the challenge of planned and unplanned pregnancies in their patients, given that associated pregnancy data are limited and there is a lack of suitable alternative psychotropics. While concerns from clinicians largely revolve around teratogenicity, a recent review showed that although congenital malformations do occur in women taking clozapine during pregnancy, the risk does not appear to be greater than the general population (Mehta and Van Lieshout 2017). A necessary caveat is that the studies reviewed are not of large numbers with variable methodology and therefore an individualised risk benefit analysis and close monitoring is still required in all cases. Notwithstanding this area of anxiety for women and their clinicians, studies of pregnancy exposure

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Thinh Nguyen
Thinh.Nguyen@uwa.edu.au

Jasmine Mordecai
Jasmine.Mordecai@health.wa.gov.au

Felice Watt
f.watt@sidra.org

Jacqueline Frayne
Jacqueline.Frayne@uwa.edu.au

1 School of Medicine, The University of Western Australia, 35 Stirling Highway, Crawley, WA 6009, Australia
2 Peel and Rockingham Kwinana Mental Health Service, Rockingham, WA 6168, Australia
3 Department of Health, Perth, Western Australia, Australia
4 Sidra Medicine, Al Gharrafa Street, Ar-Rayyan, Doha, Qatar
5 Women and Newborn Health Service, Subiaco, Western Australia, Australia
Traditional cauterisation in an infant

A 5-month-old infant presented to a clinic to monitor growth following premature birth as one of twins at 24 weeks gestation. The mother reported the child to have a cough, abdominal distension and decreased feeding over the last week. The child was well, with a normal examination but multiple scab marks were noted to her trunk and extremities (figures 1 and 2). There were no other concerns reported since hospital discharge. The mother, who was a Bedouin-Arab, confirmed having cauterisation performed in the family home with subsequent improvement in feeding and sleeping.

The traditional Arab practice of cauterisation, also known as Kaiy, Sabra or Wasm, involves application of a heated metal instrument to the skin for treatment of various illnesses and disorders. The location of cauterised skin points and number, ranging from one to seven points, depend on the specific ailment being treated. Cauterisation is often used to treat jaundice, diarrhoea, colic, cough, vomiting, abdominal distension and excessive crying. The practice is painful and can lead to scarring, infection, inflammation, septic shock, tetanus and even death. Untreated pain in the infant may also produce a relatively permanent shift in basal autonomic arousal which may have long-term sequelae. Healthcare providers should be aware of this traditional practice and educate patients who subscribe to this treatment belief about the potential complications and harmful effects associated with cauterisation.

Tawny Lowe, Nadeem Jilani, Khalid Al Ansari, Colin Powell
1Emergency Medicine, Sidra Medical and Research Center, Doha, Qatar
2Division of Population Medicine, Cardiff University, Cardiff, UK
Correspondence to Professor Colin Powell, Emergency Medicine, Sidra Medical and Research Center, Doha, Qatar, PowellC7@cardiff.ac.uk; cpowell@sidra.org
Contributors TL was involved with the patient management, collected consent from the family and wrote the initial manuscript and put together the images. KAA and NJ are part of the Sidra Safeguarding and Child protection team and contributed the writing of the article. CP contributed to the writing and editing of the text and submission of the manuscript.

Competing interests None declared.
Patient consent for publication Parental/guardian consent obtained.
Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCE
Identification of Novel Predictive Biomarkers for Endometrial Malignancies: N-Acylethanololamines

Thangesweran Ayakannu, Anthony H. Taylor, Timothy H. Marczylo, Mauro Maccarrone, and Justin C. Konje

Objective: To identify new biochemical markers for endometrial cancer (EC). Recent evidence suggests that members of the endocannabinoid system (N-acylethanolamines) that bind to and activate receptors that are dysregulated in EC are involved in this tumour's biology. These observations suggest increased N-acylethanolamine levels in the tissue that might appear in plasma and could be used as disease biomarkers.

Methods: N-arachidonylethanolamine (anandamide, AEA) and the N-acylethanolamine substances, N-oleoylethanolamine (OEA), and N-palmitoylethanolamine (PEA) were quantified in plasma and endometrial tissue collected from 31 EC and seven atrophic controls using UHPLC-MS/MS. Receiver-operating characteristics (ROC) and logistic regression were used to determine diagnostic accuracy. Cannabinoid receptor 1 (CB1) and 2 (CB2) protein levels were determined by specific immunohistochemistry and histomorphometric analyses. Correlations between plasma and tissue levels of the three N-acylethanolamines and tissue levels of the three N-acylethanolamines and CB1 and CB2 receptor expression levels were determined using correlation analysis.

Results: Plasma and tissue AEA and PEA levels were significantly (p < 0.05) higher in EC than controls whilst OEA levels were significantly elevated in type 1 EC tissues but not in plasma. There were significant positive correlations between plasma and tissue levels of AEA (R² = 0.302, p = 0.008) and PEA (R² = 0.182, p = 0.047), but not for OEA (R² = 0.022, p = 0.506). The diagnostic accuracies for EC were: sensitivity of 53.3%, specificity of 100% for plasma AEA (>1.36 nM); sensitivity of 73.3%, specificity of 100% for plasma PEA (>27.5 nM); and sensitivity of 93.3%, specificity of 28.6% for plasma OEA (>4.97 nM). Logistic regression increased the area under the ROC curve (AUC) from 0.781 for AEA, 0.857 for PEA, and 0.543 for OEA to a combined AUC of 0.933 for EC diagnosis. Significant inverse correlations between tissue AEA (R² = 0.343, p = 0.003) and PEA (R² = 0.384, p < 0.0001) levels and CB1 expression were observed.
Does Simian Virus 40 (SV40) Have a Role in UK Malignant Pleural Mesothelioma? No Role is Identified in a Sensitive RNA In Situ Hybridization Study on Potentially Affected Birth Cohorts

Fouad S. Alchami, MD, FRCpath,* † Richard L. Attanoos, MD, FRCpath,* ‡ Allen Gibbs, MD,* Fiona Morgan, BSc,* and Bharat Jasani, PhD, MBChB, FRCPath* †

Background: Simian virus 40 (SV40)-contaminated polio vaccine was accidentally administered to about one-third of the UK population receiving polio vaccines between 1956 and 1962. SV40 was subsequently demonstrated to be a carcinogenic virus in experimental and animal models. Since then, the SV40 oncogenic protein large T antigen (SV40 Tag) has been shown to cause malignant transformation of asbestos-treated human pleural mesothelial cells and malignant pleural mesotheliomas in asbestos-exposed SV40 Tag transgenic mice. The present study was designed to investigate the possible association of SV40 Tag with human malignant pleural mesothelioma samples from birth cohorts of the UK population exposed to combined peak levels of asbestos and SV40-contaminated polio vaccines.

Materials and Methods: Tumor and background lung tissue microarrays were prepared from archival surgical specimens of 139 pleural mesothelioma cases, collected over a period of 8 years (1998 to 2005), were analyzed. These represented birth cohorts overlapping with the period 1950 to 1960, exposed to a high level of asbestos and SV40-contaminated live polio vaccines. SV40 Tag mRNA expression was investigated using a highly sensitive and specific SV40 Tag RNA in situ hybridization detection method on the basis of the novel RNAscope technology.

Results: SV40 Tag RNA was not detected in any of the 127 evaluable tumor cases, despite appropriate results obtained for the external positive and negative controls.

Conclusion: The complete absence of SV40 Tag mRNA expression in this large series of cases contradicts experimental evidence suggestive of SV40 link with asbestos-exposed malignant pleural mesotheliomas in the UK population. Alternative explanations of the negative findings are discussed to exclude possible confounding factors.

Key Words: human malignant pleural mesothelioma, simian virus 40, SV40 large T antigen, SV40 Tag, polio vaccines, immunohistochemistry, RNA in situ hybridization, RNAscope

Simian virus 40 (SV40) is a double-stranded DNA polyomavirus which is known to occur naturally in Asian macaques. Its intrinsic oncogenic capacity was initially identified in animals.1,2 This prompted investigations into a variety of tumors in humans following the realization that “live” SV40 had accidentally contaminated mainly poliovirus vaccine preparations.3,4 The contaminated vaccines were distributed mainly in the period 1956 to 1962, with some oral vaccines containing the virus after this initial period.5,6

The health risk from exposure to SV40 is considered to vary according to the geographical areas where the contaminated vaccine was used and the type of vaccine used.7 Human infections by SV40 were found to be associated with the use of SV40-contaminated oral polio vaccines associated with high titers of “live” SV40 compared with the chemically killed vaccine. Also, the route of vaccine exposure was more natural with the orally applied live vaccine compared with the intramuscularly administered Salk vaccine.8 Nevertheless, there was a concern as any amount of “live” SV40 was considered to carry a potential carcinogenic risk.

SV40 was first recognized to be associated with human tumors including choroid plexus papilloma, ependymoma, and osteosarcoma through the detection of large T-antigen (Tag) DNA or protein presence detected using the polymerase chain reaction (PCR) and immunohistochemistry.9,12 In the 1990s, a large number of studies investigating the link between SV40 and malignant mesothelioma raised considerable interest in SV40 as a cause or co-carcinogen for malignant mesothelioma in human.13,14 However, there was considerable controversy regarding the validity of the detection of the SV40 presence by immunohistochemistry and DNA
Genotype and phenotype analysis of a cohort of patients with congenital hyperinsulinism based on DOPA-PET CT scanning

Jinwen Ni 1 · Jingjie Ge 2 · Miaoying Zhang 1 · Khalid Hussain 3 · Yihui Guan 2 · Ruqian Cheng 1 · Li Xi 1 · Zhangqian Zheng 1 · Shuhua Ren 2 · Feihong Luo 1

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Abstract
Congenital hyperinsulinism (CHI) is a clinically, genetically, and morphologically heterogeneous disorder. 18F DOPA-PET CT scanning greatly improves its clinical outcome. Here, we presented the first Chinese 18F DOPA-PET CT scanning–based CHI cohort highlighting the variable ethnic clinical phenotypes and genotypes. Fifty CHI patients were recruited. Median age at presentation was 2 days. Median fasting time was 2 h. Mean insulin level was 25.6 μIU/ml. Fifty-two percent of patients were diazoxide-unresponsive with significantly shorter fasting tolerance time and higher serum insulin level compared with the responsive patients. Seventy-four percent of patients experienced at least one adverse drug reaction. Tremendously increased focal lesions (32%) were detected and 75% of them were cured through surgery. Thirty-one nucleotide sequence changes were identified in 48% patients. Four novel variants (Q608X, Q1347X, Q289X, F1489S) in ABC8 gene and 2 novel variants (G132A, V138E) in KCNJ11 gene were detected. Of the variants, 87.1% harbored in ABC8 and KCNJ11 genes. T1042Qs→T5 in ABC8 gene was the most common mutation.

Conclusion: Highly increased portion of focal lesion was presented in Chinese CHI patients compared with that of the previous reports. Intolerance to diazoxide was much more evident in Chinese or East Asian than other populations. Certain hotspot mutations harbored in Chinese CHI patients.

What is Known: • 18F DOPA-PET CT scanning can provide informative guidance for surgical procedure when medical therapy is not well responded in CHI patients.
What is New: • Intolerance to diazoxide is much more evident in Chinese and East Asian CHI patients compared with the other ethnic populations.
• Novel mutations were detected in ABC8 and KCNJ11 gene. Hotspot mutations such as T1042Qs→T5, I1531K, E501K, G111R in ABC8 gene, and R34H in KCNJ11 gene are predominantly responsible for Chinese CHI patients.

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1 Feihong Luo
luofhf@fudan.edu.cn
Jinwen Ni
16111240022@fudan.edu.cn
Jingjie Ge
lovejingjie@126.com
Miaoying Zhang
miaoyingzh@126.com
Khalid Hussain
khusan@sidra.orgt
Yihui Guan
yuanyihua@hotmail.com
Ruqian Cheng
chengr78@163.com
Li Xi
dnlx1@163.com
Zhangqian Zheng
dr_zhengzhangqian@126.com
Shuhua Ren
karen96_ren@126.com
1 Department of Endocrinology and Inborn Metabolic Diabases, Children’s Hospital of Fudan University, 399 Wanyuan Road, Shanghai 201102, China
2 PET CT Center, Division of Nuclear Medicine, Huaishan Hospital, Fudan University, 518 East Wuzhong Road, Shanghai 200835, China
3 Department of Pediatrics, Division of Endocrinology, Sidra Medicine OPC, C6-340 PO Box 26999, Al Luqta Street Education City North Campus, Doha, Qatar
Draft Genome Sequences of Two *Streptococcus pneumoniae* Strains Causing Invasive Infections in Children in Qatar

Clement K. M. Tsui, a,b Sathyavathi Sundararaju, a Hassan Al Mana, a Eva Thomas, a,b Patrick Tang, a,b Mohammad Rubayet Hasan, a,b Andres Perez-Lopez a,b

a Department of Pathology, Sidra Medicine, Doha, Qatar
b Department of Pathology and Laboratory Medicine, Weill Cornell Medicine—Qatar, Doha, Qatar

**ABSTRACT**  Invasive pneumococcal infections are a major cause of morbidity and mortality in the pediatric population. We report the draft genomes of two clinical *Streptococcus pneumoniae* isolates associated with severe infections in children in Qatar. The genome statistics are described, along with the strain types and serotypes predicted from the assembled genomes.

*Streptococcus pneumoniae* is the leading cause of invasive bacterial infections in the pediatric population worldwide, with a wide spectrum of clinical syndromes ranging from occult bacteremia to meningitis (1, 2). The increase in antimicrobial resistance in invasive pneumococcal disease (IPD), particularly to β-lactam antibiotics and macrolides, has become a major public health concern (3). The advent of the 7-valent and 13-valent pneumococcal conjugate vaccines (PCV-7 and PCV-13, respectively) has led to a dramatic decrease in the incidence of IPD caused by serotypes included in vaccine formulations in children (1). However, an increase in the incidence of severe forms of IPD caused by nonvaccine serotypes has been reported (4). On the other hand, it has also been speculated that the rise of IPD caused by certain nonvaccine serotypes may have been driven by capsular switching and serotype replacement among some pneumococcal genotypes (5, 6). For example, the increased proportion of IPD caused by serotype 19A after the introduction of PCV-7 could be attributed to capsular switching in sequence types (STs) which were previously associated with vaccine serotype 4 (7). PCV-7 was introduced in the routine immunization program in children in Qatar in 2005, followed by PCV-13 in 2010 (8–10), which is why the local study of serotype and genotype distribution of IPD is important.

Herein, we report the genome sequences of two *S. pneumoniae* strains (BC18042556 and BC19010893) isolated from the bloodstream from a 22-month-old boy with meningitis and a 3-month-old girl with septic arthritis of the shoulder. Microorganisms were identified on sheep blood agar by optochin susceptibility and bile solubility testing. The MICs were determined by a Vitek 2 automated system (bioMérieux, Marcy-l’Étoile, France) and the Etest method and interpreted according to the Clinical and Laboratory Standards Institute guidelines. Genomic DNA was extracted using the automated platform NucliSENS easyMag (bioMérieux) and quantified by Qubit (Thermo Fisher, Waltham, MA). The paired-end DNA libraries were constructed with a Nextera XT kit (Illumina, San Diego, CA) according to the manufacturer’s instructions and sequenced on an Illumina MiSeq machine with 2 × 300-bp cycles.

The sequence data were evaluated using FastQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) and trimmed with Trim Galore (http://www.bioinformatics.babraham.ac.uk/projects/trim_galore/) using the following conditions: length, 60; quality, 20; retain_unpaired -r1 69 -r2 69; phred33). The trimmed sequence data were assembled using SPAdes v.3.9.0 (11) and assessed using QUAST v.2.3 (12). Smaller
Core temperature after birth in babies with neonatal encephalopathy in a sub-Saharan African hospital setting

Christabel Enweronu-Laryea, Kathryn A Martinello, Maggie Rose, Sally Manu, Cally Tann, Judith Meek, Kojo Ahor-Essel, Geraldine B Boylan, and Nicola J Robertson

1Department of Child Health, University of Ghana School of Medicine and Dentistry, Accra, Ghana
2Neonatal Intensive Care Unit, Korle Bu Teaching Hospital, Accra, Ghana
3Institute for Women’s Health, University College London, London, UK
4Robinson Research Institute, University of Adelaide, Adelaide, Australia
5Neonatology, University College London Hospital NHS Foundation Trust, London, UK
6Maternal, Adolescent, Reproductive and Child Health Centre, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK
7INFANT Research Centre, University College Cork, Cork, Ireland
8Department of Paediatrics & Child Health, University College Cork, Cork, Ireland,
9Division of Neonatology, Sidra Medicine, Doha, Qatar

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Key points

- Therapeutic hypothermia (HT) to 33.0–34.0°C for 72 h provides optimal therapy for infants with neonatal encephalopathy (NE) in high-resource settings. HT is not universally implemented in low- and middle-income countries as a result of both limited resources and evidence.
- Facilitated passive cooling, comprising infants being allowed to passively lower their body temperature in the days after birth, is an emerging practice in some West African neonatal units.
- In this observational study, we demonstrate that infants undergoing facilitated passive cooling in a neonatal unit in Accra, Ghana, achieve temperatures within the HT target range ~20% of the 72 h. Depth of HT fluctuates and can be excessive, as well as not maintained, especially after 24 h.
- Sustained and deeper passive cooling was evident for severe NE and for those that died.
- It is important to prevent excessive cooling, to understand that severe NE babies cool more and to be aware of facilitated passive cooling with respect to the design of clinical trials in low- and mid-resource settings.

Christabel Enweronu-Laryea is an Associate Professor of Paediatrics and Child Health, University of Ghana, and a Consultant Paediatrician at Korle Bu Teaching Hospital in Accra, Ghana. Her observations of the evolution of perinatal asphyxia in low-resource tropical settings led to present study being conducted. Perinatal asphyxia is a major cause of preventable death and long-term impairment in sub-Saharan Africa. Accordingly, her research aspirations include finding cost-effective interventions that improve the health outcomes of affected infants. Kathryn Martinello is a consultant neonatologist at Great Ormond Street Hospital, London, UK, and an honorary research associate with the Institute for Women’s Health, University College London. She is a PhD candidate at the Robinson Research Institute, University of Adelaide, Australia, supervised by Assistant Professor Michael Stark and Professor Nicola Robertson (UCL). Her research, both clinical and preclinical, is centred on improving neurodevelopmental outcome and protecting the newborn brain following perinatal asphyxia across all settings.

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**Abstract** Neonatal encephalopathy (NE) is a significant worldwide problem with the greatest burden in sub-Saharan Africa. Therapeutic hypothermia (HT), comprising the standard of care for infants with moderate-to-severe NE in settings with sophisticated intensive care, is not available to infants in many sub-Saharan African countries, including Ghana. We prospectively assessed the temperature response in relation to outcome in the 80 h after birth in a cohort of babies with NE undergoing 'facilitated passive cooling' at Korle Bu Teaching Hospital, Accra, Ghana. We hypothesized that NE infants demonstrate passive cooling. Thirteen infants (69% male) ≥36 weeks with moderate-to-severe NE were enrolled. Ambient mean ± SD temperature was 28.3 ± 0.7°C. Infant core temperature was 34.2 ± 1.2°C over the first 24 h and 35.0 ± 1.0°C over 80 h. Nadir mean temperature occurred at 15 h. Temperatures were within target range for HT with respect to 18 ± 14% of measurements within the first 72 h. Axillary temperature was 0.5 ± 0.2°C below core. Three infants died before discharge. Core temperature over 80 h for surviving infants was 35.3 ± 0.9°C and 33.96 ± 0.7°C for those that died (P = 0.043). Temperature profile negatively correlated with Thompson NE score on day 4 (r² = 0.66): infants with a Thompson score of 0–6 had higher temperatures than those with a score of 7–15 (P = 0.021) and a score of 16+/deceased (P = 0.007). More severe NE was associated with lower core temperatures. Passive cooling is a physiological response after hypoxia–ischaemia; however, the potential neuroprotective effect of facilitated passive cooling is unknown. An awareness of facilitated passive cooling in babies with NE is important for the design of clinical trials of neuroprotection in low and mid resource settings.

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**Corresponding author** N. Robertson: Institute for Women’s Health, University College London, 74 Huntley Street, London WC1E 6HX, UK. E-mail: n.robertson@ucl.ac.uk

Introduction

Intrapartum-related hypoxic events are a major cause of neonatal mortality and morbidity in low- and mid-income countries (LMIC). Neonatal encephalopathy (NE) secondary to intrapartum events is estimated to affect 1.16 million babies per year, with the highest rates occurring in sub-Saharan Africa (Lee et al. 2013). NE manifests with neurological dysfunction in the first days of life, including difficulty initiating and sustaining respiration, abnormal level of consciousness, depression of tone and reflexes, and, in many cases, seizures (Nelson & Leviton, 1991). Globally each year, NE is estimated to cause 287,000 deaths and over 50 million disability adjusted life years (Lee et al. 2013). NE is the second most common cause of avoidable childhood neurodevelopmental disability worldwide (Lawn et al. 2014). Reducing preventable neonatal death is a global Sustainable Development Goal (United Nations, 2015).

Ghana is a middle-income country with ≈800,000 births per year. Intrapartum-related hypoxic events account for around one-third of all newborn deaths and are among the top 10 causes of all deaths in the country (WHO, 2016). NE is a major cause of disability in Ghanaian children (Adei-Atiemo et al. 2015). During a 6 month period in 2015, birth asphyxia accounted for 30% of the 966 neonatal unit admissions at Korle Bu Teaching Hospital (KBTH) in Accra, Ghana (Samba, 2017). Twenty-two percent of cases referred to KBTH with perinatal asphyxia died. Four out of five normal birth weight term deaths at KBTH neonatal unit were associated with intrapartum-related hypoxic events.

Therapeutic hypothermia (HT) is standard clinical care for infants with moderate-to-severe NE in high-income countries (National Institute for Health and Care Excellence, 2010). Cooling to 33.5°C for 72 h within 6 h of birth improves outcomes of death and neurodisability in the short (Edwards et al. 2010; Jacobs et al. 2013) and longer term (Guillet et al. 2012; Shankaran et al. 2012). In high income settings, the implementation of HT over the past decade has benefited patients, society and the economy (Azzopardi et al. 2012).

Despite the high burden of NE in Ghana and other LMIC, there is no readily available and affordable evidence-based therapy for NE beyond supportive care. Modern technologies for providing HT and comprehensive monitoring of affected babies remain beyond the reach of many hospitals. A systematic review combining studies from LMIC settings suggested that HT was not associated with a reduction in neonatal mortality, although the confidence intervals were wide (Pauliah et al. 2013). Indeed, it is possible that HT may not be beneficial in low resource settings without sophisticated neonatal intensive care unit (NICU) care: a pilot study in a sub-Saharan African hospital showed that cooling for 72h with water bottles was feasible but was associated with increased mortality, although the study was not powered for outcome measures (Robertson et al. 2008).
Evaluation of needle biopsy as a potential risk factor for local recurrence of Wilms tumour in the SIOP WT 2001 trial

Sabine Irtan a,b,*, Harm Van Tinteren c, Norbert Graf d, Marry M. van den Heuvel-Eibrink c,e, Hugo Heij c,e, Christophe Bergeron f, Beatriz de Camargo g, Tomas Acha h, Filippo Spreafico i, Gordan Vujanic j, Mark Powis k, Bruce Okoye l, Jim Wilde m, Jan Godzinski n, Kathy Pritchard-Jones a

a Cancer Section, Developmental Biology & Cancer Programme, UCL Great Ormond Street Institute of Child Health, University College London, London, UK
b Paediatric Surgery Department, Trousseau Hospital – Assistance Publique des Hôpitaux de Paris, Paris, France
c Biostatistics Department, Netherlands Cancer Institute – Antonie van Leeuwenhoekhuis Plesmanlaan, Amsterdam, Netherlands
d Saarland University, Department of Pediatric Oncology & Hematology, Homburg, Germany
e Princess Maxima Center for Pediatric Oncology, Utrecht, the Netherlands
f Pediatric Oncology Unit, Centre Léon Bérard, Lyon, France
g Pediatric Hematology and Oncology Program, Research Center, Instituto Nacional de Cáncer, Rio de Janeiro, Brazil
h Department of Pediatric Oncology, Hospital Materno-Infantil, Malaga, Spain
i Department of Clinical Oncology and Hematology, Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy
j Department of Pathology, Sidra Medicine, Doha, Qatar
k Department of Paediatric Surgery, Leeds Teaching Hospitals NHS Trust, Leeds, UK
l St. Georges Healthcare NHS Trust, Tooting, London, UK
m Division of Pediatric Surgery, Geneva University Hospitals, University Center of Pediatric Surgery of Western Switzerland, Geneva, Switzerland
n Department of Paediatric Surgery, Marciniak Hospital, and Dept. of Paediatric Traumatology and Emergency Medicine, Medical University, Wroclaw, Poland

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* Corresponding author: Service de Chirurgie Pédiatrique Viscérale et Néonatale, Hôpital Trousseau - APHP, 26 Avenue du Dr Arnold Netter, 75012 Paris France. Fax: +33 1 44 73 69 79.
E-mail addresses: Sabine.irtan@gmail.com (S. Irtan), h.v.tinteren@nki.nl (H. Van Tinteren), Norbert.Graf@uniklinikum-saarland.de (N. Graf), m.m.vandenheuvel-eibrink@prinssesmaxacentrum.nl (M.M. van den Heuvel-Eibrink), hugo.heij@icloud.com (H. Heij), christophe.bergeron@ihoppe.fr (C. Bergeron), bdccamar@terra.com.br (B. de Camargo), tachavalls@gmail.com (T. Acha), filippo.spreafico@istitutotomouri.mi.it (F. Spreafico), gvujanic@sidra.org (G. Vujanic), Mark.Powis@nhs.uk (M. Powis), bruce.okoye@nhs.net (B. Okoye), jim.wilde@hcuge.ch (J. Wilde), igodzinski@wp.pl (J. Godzinski), k.pritchard-jones@ucl.ac.uk (K. Pritchard-Jones).

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0959-8049/© 2019 Elsevier Ltd. All rights reserved.
Abstract | Rationale: The impact of biopsying Wilms tumour (WT) at diagnosis on assigning the tumour stage and recommended treatment remains controversial. To address this important question, we analysed the potential association of all types of biopsy with local recurrence in patients treated in the SIOP WT 2001 trial, where needle biopsy was permitted without ‘upstaging’ the tumour to stage III. Only open biopsy required treatment as stage III. Methods: Among 2971 patients with unilateral WT (stages I-IV), 420 relapsed (139 local). Risk factors for recurrence were analysed by Cox proportional hazard methods. Results: Biopsy was performed in 969 of 2971 (33%) patients (64% cutting needle, 30% fine needle aspiration [FNA] and 6% open biopsy). Biopsied patients were older, with larger tumours and a greater proportion with high-risk histology. In multivariate analysis that included all factors associated with local recurrence in univariate analysis, only high-risk histology (hazard ratio [HR] = 2.32; 95% confidence interval [CI]: 1.58–3.42, p < 0.0001), age ≥2 years (HR = 2.24; 95% CI: 1.22–4.09, p = 0.01) and preoperative tumour volume (HR = 1.07 per 100 ml; 95% CI: 1.02–1.12, p = 0.01) were significant. The HR for the association of local recurrence and event-free and overall survival with biopsy was not significant (HR = 1.4; 95% CI: 0.9–2.17, p = 0.13; HR = 1.1; 95% CI: 0.85–1.42, p = 0.46 and HR = 1.13; 95% CI: 0.79–1.62, p = 0.51, respectively). These results were not materially different whether FNA or open biopsy were included in the biopsy group or not. Conclusions: This post hoc analysis provides some reassurance that needle biopsy is not an independent adverse factor for either local recurrence or survival after adjustment for all relevant risk factors. Needle biopsy should not be an automatic criterion to ‘upstage’ WT.

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1. Introduction

The clinical impact of biopsy on Wilms tumour (WT) staging is controversial because of debated results on the possible relationship between biopsy and the risk of local recurrence. Based on the results of the National Wilms Tumour Study (NWTS) 3–4 trials, showing that patients with stage II disease and local spillage had worse outcome than those with no spillage, the Children’s Oncology Group (COG) AREN0532 protocol now considers any patient with local spillage to have a stage III tumour [1,2]. Any biopsy, regardless of the type—fine needle aspiration (FNA), percutaneous cutting needle biopsy (PCNB or ‘Trucut’) or open surgery—is considered as tumour spillage [2]. By contrast, the most recent trial of the International Society of Paediatric Oncology Renal Tumour Study Group (SIOP–RTSG, trial protocol SIOP WT 2001) permitted tumour biopsy by FNA or PCNB without affecting tumour stage assignment, with the latter determined by the pathological stage of the nephrectomy specimen [3].

In the UKW3 randomised trial, that compared immediate nephrectomy with a preoperative chemotherapy approach, UK clinicians had routinely biopsied patients assigned to delayed nephrectomy using PCNB without affecting tumour staging [4]. Therefore, when the UK joined the SIOP WT 2001 trial, this national group had continued their national practice of biopsying patients before starting chemotherapy [4,5]. However, concerns about a higher rate of local relapse in the UKW3 trial led to a post hoc analysis that showed equivocal results with an association between biopsy and local relapse on univariate analysis (UVA) that lost statistical significance on multivariable analyses after adjustment for other known risk factors for recurrence [6]. Interpretation was made more difficult by the small number of events and the fact that the biopsy group contained an excess of larger and more advanced stage tumours in older patients [6].

The SIOP WT 2001 trial data set provides a unique opportunity to analyse the potential association of biopsy as a risk factor for local recurrence or adverse survival outcome in a cohort of patients treated uniformly with a preoperative chemotherapy approach, taking into account multivariable analysis (MVA) of the confounding factors that influence prognosis. We, therefore, conducted a retrospective post hoc analysis of the SIOP WT 2001 trial database, using the same patient inclusion/exclusion criteria that had been applied to the UKW3 trial data set, to test the hypothesis that biopsy may be an independent risk factor for local recurrence.

2. Methods

2.1. Eligible patients

Between 2001 and 2011, 3313 patients were registered in the SIOP WT 2001 trial with localised or metastatic unilateral WT (Supplemental Fig. 1). Thirty patients were excluded because of missing information on whether and how biopsy was performed. As the main
Bringing Pediatric Rehabilitation to the Intensive Care*

Kirsty Foster, BSc (Hons)
Ricardo Garcia Branco, MD, PhD
Pediatric Intensive Care Unit
Sidra Medical and Research Center
Doha, Qatar

The evolution of pediatric critical care knowledge and technologies has led to substantial reduction in mortality of critically ill children. However, a number of children who now survive critical illness have significant deterioration in their quality of life (1). Although some of this deterioration can be accounted for by the primary insult, intensive care factors (such as sedation and reduced mobility) also contribute for this deterioration. Among adults and elderly populations, reduced mobility alone can lead to deconditioning, a complex process of physiologic changes that result in functional losses in such areas as mental status, degree of continence, and ability to accomplish activities of daily living (2). These losses can be minimized and/or reversed with the implementation of early rehabilitation strategies. During critical illness, the deconditioning process can be significantly potentiated, and the term postintensive care syndrome (PICS) has been used to describe the disability that remains in the critical illness survivor, comprising of impairment in cognition, psychologic health, and physical function. This has been well characterized in adults and more recently in children (3–5).

The use of early rehabilitation to prevent/treat PICS has been widely studied in adults, with a rapidly growing body of evidence supporting early rehabilitation as a safe and feasible intervention in critically ill patients (6, 7). In children, however, evidence to support early rehabilitation is scarce, and particularities of the pediatric population have limited implementation of early rehabilitation practices in PICUs.

In this issue of Pediatric Critical Care Medicine, Treble-Barna et al (8) report the result of an international survey looking at physician’s opinions and practices regarding use of rehabilitation therapies for critically ill children. The authors emailed invitations to participate in the survey to members of some of the larger PICU research network groups, as well as made it available for visitors of the World Federation of Pediatric Intensive and Critical Care Societies website. The survey showed that only a small number of institutions from participants had guidelines for rehabilitation therapies in critically ill children, despite great interest from the responders on the development of these guidelines. When guidelines were available, there was significant variation in the recommendations provided. Physicians also felt that human resource limitations, lack of prioritization, and patient severity of illness were the most important barriers for implementation of rehabilitation therapies. Interestingly, physicians also reported the lack of guidelines as a significant institutional limitation to implement rehabilitation in PICUs. This is similar to the result of a previous survey of early mobilization (EM) in PICU (9).

On this EM survey, physiotherapist reported that the absence of guidelines was less important, but the need for a physician order was a significant barrier to implement EM. The survey also revealed that in response to practice scenarios, physicians tended to involve multiple rehabilitation services when treating critically ill children, and most of these consultations were timely initiated within 48–72 hours of admission to PICU. This is also in line with previous surveys findings suggesting that physicians believe that early rehabilitation is important and can improve outcome of critically ill children (9, 10). However, physicians have also stated that there is “little” or “moderate” evidence only to support the development of PICU based rehabilitation guidelines. Although there is growing evidence that rehabilitation can be performed safely on PICUs (11–14), most of the evidence showing clinical benefits of early rehabilitation in critical illness comes from adult studies.

Despite the strong physicians claim for the development of guidelines for rehabilitation in PICUs in this survey, it is unlikely that international evidence-based guidelines could provide strong recommendations for the implementation of rehabilitation in pediatric critical care. We need more good quality research in this field to be able to define crucial aspect of early rehabilitation such as timing and duration of therapies, identification of children at risk of complications, and tailored therapy options for population subgroups.

It is important to highlight that the development of rehabilitation services need to be truly multidisciplinary. Lack of prioritization by physicians and need for physician consultation orders are barriers highlighted in this and in previous surveys (8, 9) that could be easily minimized by a true multidisciplinary approach. Empowering the multidisciplinary team to initiate consultations and implementation of routine multidisciplinary rounds would spread the burden from physicians and provide a more dynamic environment for early initiation of rehabilitation therapies.

The study by Treble-Barna et al (8) also has a number of limitations. It is somewhat disappointing to realize that despite the author’s great efforts to in creating this important

*See also p. e274.

Key Words: mobilization; pediatric intensive care; physiotherapy; post-intensive care syndrome; rehabilitation

The authors have disclosed that they do not have any potential conflicts of interest.

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Virtual Reality: Can It Improve the PICU Experience?

Melinda F. Hamilton, MD, MS
Department of Critical Care Medicine
UPMC Children’s Hospital of Pittsburgh
Pediatric Programs
Peter M. Winter Institute for Simulation, Education, and Research (WISER)
Pittsburgh, PA

Virtual reality (VR) is the interaction between an individual and a computer-generated environment. VR can stimulate many of the senses, including visual, auditory, and haptics (1). VR in healthcare began in the early 2000s, and much of the early work focused on VR as an educational tool for endoscopic or laparoscopic surgery. VR has been shown to decrease the operating time and improve operative performance of surgical trainees in terms of laparoscopy (2). As a teaching tool in endoscopy training, such as colonoscopy or flexible sigmoidoscopy, VR training resulted in greater unassisted insertion depth, higher completion rates, and higher technical accuracy, among other findings (3). In both studies, VR was found to be an acceptable form of technical skills’ training, especially in novice learners (2, 3). In terms of non-technical skills’ training, VR simulation has been shown to be a successful educational modality among nurses, physicians, and residents or postgraduate trainees. In a systematic review by Braq et al (4), it was noted that the use of VR in healthcare

REFERENCES
Gastro-oesophageal reflux is not a major cause of brief resolved unexplained events in infants

Introduction

The clinical scenario of an infant presenting to the emergency department with the parents reporting a history of the child stopping breathing, choking or "turning blue" at home is a well-recognised event and accounts for between 2.5 and 4.1 hospital admissions per 1000 live births [1, 2]. The infant is often back to their normal self with a normal clinical examination. This event used to be called an apparent life-threatening event (ALTE) [1] and recently it has been suggested that it should now be called a brief resolved unexplained event (BRUE) [2]. Gastro-oesophageal reflux (GOR) has long been considered to be a common reason for an ALTE and some studies have listed it as an underlying cause in up to 54% of patients [3–6]. Does the evidence support this belief?

ALTEs and BRUEs

The term ALTE was proposed in 1986 [1] and, prior to this, such events were classified as “near-miss sudden infant death syndrome (SIDS)” [6]. It became clear that babies with near-miss events were not at increased risk of SIDS, and this terminology was replaced with the term ALTE [1, 6]. It was considered that this new term was both vague and subjective. Symptoms appearing frightening to caregivers, such as periodic breathing, could be manifestations of normal neonatal physiology [7]. In 2016, the American Academy of Pediatrics (AAP) released a clinical guideline for practitioners recommending that the term ALTE be replaced by BRUE [2]. The aim was to allay the anxiety to the caregivers brought about by the use of the term ALTE, as well as to give practitioners clear management guidance by stratifying such infants into high- and low-risk groups.

It should be clear that a BRUE is diagnosed only when there is no other explanation for a qualifying event, following an appropriate history and thorough physical examination. The AAP guidelines give clear guidance for the management of low-risk infants and these infants can be managed safely at home. A recent meta-analysis of the risk of death in infants who have experienced a BRUE supports the return-home management approach. The risk of death is about the same as the baseline risk of death during the first year of life. For patients evaluated in an emergency department and deemed as low risk, there is no need for them to be investigated and admitted to hospital [8]. The AAP guideline does not provide recommendations for investigation of those that are stratified in the high-risk group.

GOR and gastro-oesophageal reflux disease

National Institute for Health and Care Excellence (NICE) guidelines published in 2015 are very clear about the definitions of GOR and gastro-oesophageal reflux disease (GORD). GOR is “The passage of gastric contents into the oesophagus.” It is a common condition that affects many infants and causes discomfort and distress. GORD is a more severe condition that can lead to complications such as scarring of the oesophagus and difficulty swallowing.

Although it is often stated that gastro-oesophageal reflux is the most common cause of a brief resolved unexplained event or apparent life-threatening event, there are very few data to support the hypothesis of cause and effect. There is no evidence to support the claim that GOR or GORD causes brief resolved unexplained events. The evidence is not strong enough to support the claim that GOR or GORD is a major cause of brief resolved unexplained events in infants.
Molding the shape of congenial and structural interventional cardiology: interviews with directors of major congresses

Sebastian Goreczny1,2, Ziyad M. Hijazi3, Shakeel A. Qureshi4, Mario Carminati5, Damien Kenny6 and Gareth J. Morgan1,7

1Department of Cardiology, Colorado Children’s Hospital, University of Colorado Hospital, Aurora, CO, USA; 2Department of Cardiology, Polish Mother’s Memorial Hospital, University of Colorado Hospital, Aurora, CO, USA; 3Department of Cardiology, Polish Mother’s Memorial Hospital, Research Institute, Lodz, Poland; 4Department of Pediatrics, Weill Cornell Medicine & Sidra Heart Center, Doha, Qatar; 5Department of Pediatric and Adult Congenital Heart Disease, Evelina London Children’s Hospital, Guy’s and St Thomas’ NHS Foundation Trust, London, UK; 6Department of Pediatric Cardiology and Adult with Congenital Heart Disease, IRCCS San Donato Hospital, Milan, Italy; 7Department Cardiology, Our Ladies Children’s Hospital & The Mater Misericordiae University Hospital, Dublin, Ireland and 8Department of Adult Congenital Cardiology, University of Colorado Hospital, Aurora, CO, USA

Abstract

The range and number of educational and networking events that are available for fellows, trainees, and junior faculty to attend grows every year. Each meeting useful in its own way; each adding value to the development and the growth of an interventionist. Within paediatric, congenital, and structural heart disease, three of the standout meetings are: Pediatric and Interventional Cardiac Symposium (PICS-AICS), Congenital and Structural Interventions (CSI), and International Workshop on Interventional Pediatric and Adult Congenital Cardiology (IPC). All of these were started by leaders in our field; people known to be passionate educators and innovators. International congresses focusing more broadly on congenital cardiac disease in children and adults are rare. These forums allow more interdisciplinary discussions between the interventionist, surgeon, and non-invasive specialists. Purely interventional meetings are essential to allow colleagues to debate and explore the nuances and intricacies of technique and approach, developing concepts to be challenged in wider forums. During the recent 21st PICS-AICS meeting Prof. Ziyad M. Hijazi, Shakeel A. Qureshi, Mario Carminati, and Dr Damien Kenny shared their time to engage in frank, recorded conversations which provide a unique insight in to the process and concepts behind three of our most important educational congresses.

Conferences, courses, global summits, hands on courses, implanters meetings, fellows training programs, etc. The range and number of events that are available for fellows, trainees, and junior faculty to attend grows every year. Each meeting useful in its own way; each adding value to the development and the growth of an interventionist. Within the milieus of paediatric, congenital, and structural heart disease, three of the standout meetings are Pediatric and Interventional Cardiac Symposium (PICS-AICS), Congenital and Structural Interventions (CSI), and International Workshop on Interventional Pediatric and Adult Congenital Cardiology (IPC). All of these were started by leaders in our field; people known to be passionate educators and innovators. In the challenging funding environment created by the Sunshine act in the USA and Eucomed in Europe, the existence and development of these meetings is under pressure. International congresses focusing more broadly on congenital cardiac disease in children and adults are rare. Therefore, to complement our intervention meetings, we must continue to recognise the benefit of conferences such as the World Congress of Paediatric Cardiology and Cardiac Surgery.

Under the leadership of Prof. Ziyad M. Hijazi, the PICS-AICS directed the track for interventional cardiology at the 2017 World Congress of Pediatric Cardiology and Cardiac Surgery in Barcelona, Spain, and will direct the track for interventional cardiology at the 2021 World Congress of Pediatric Cardiology and Cardiac Surgery in Washington DC, United States. These forums allow more interdisciplinary discussions between the interventionist, surgeon, and non-invasive specialists. Our purely interventional meetings are essential to allow colleagues to debate and explore the nuances and intricacies of technique and approach, developing concepts to be challenged in wider forums such as the World Congress of Paediatric Cardiology and Cardiac Surgery.

Dr Sebastian Goreczny, currently spending a Senior Fulbright Scholarship year with our team at the Heart Institute, Children’s Hospital of Colorado, and usually based in Polish Mother’s Memorial Hospital, Research Institute, Lodz, Poland, sat down with some giants of
CORRECTION

Correction to: Plea for a standardized imaging approach to disorders of sex development in neonates: Consensus proposal from European Society of Paediatric Radiology task force

Fred E. Avni 1 · Heloise Lerisson 1 · Maria-Luisa Lobo 2 · Maryse Cartigny 3 · Marcello Napolitano 4 · Hans-J. Mentzel 5 · Michael Riccabona 6 · Magdalena Wozniak 7 · Damjana Kljucevsek 8 · Thomas A. Augdal 9 · Bruno Constanza 10 · Donald Ibe 11 · Kassa Darge 12 · Samuel Stafrace 13 · Philippe Petit 14 · Lil-Sofie Ording Müller 15

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Correction to: Pediatric Radiology 2019

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The above article was published online with an incorrect author name. The correct spelling is Hans-J. Mentzel, presented in the author list above, instead of Hans-J Menzel.

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Fred E. Avni
Freddy.Avni@chru-lille.fr

1 Department of Pediatric Imaging Jeanne de Flandre Hospital, Lille University Hospitals, 2 Avenue Eugène Aminée, 59037 Lille-Cedex, France
2 Department of Radiology, Hospital de Santa Maria-CHULN, Lisbon, Portugal
3 Department of Pediatric Endocrinology Jeanne de Flandre Hospital, Lille University Hospitals, Lille, France
4 Department of Pediatric and Neuro-radiology, V. Buzzi Children’s Hospital, Milan, Italy
5 Department of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, University Hospital Jena, Jena, Germany
6 Department of Radiology, Division of Pediatric Radiology, University Hospital LKH Graz, Graz, Austria
7 Department of Pediatric Radiology, Medical University of Lublin, Lublin, Poland
8 Department of Radiology, University Children’s Hospital Ljubljana, Ljubljana, Slovenia
9 Department of Radiology, University Hospital of Northern Norway, Tromso, Norway
10 Department of Radiology AOU, Verona, Italy
11 Department of Radiology, Ahmadu Bello University Teaching Hospital, Zaria, Kaduna State, Nigeria
12 Department of Radiology, the Children’s Hospital of Philadelphia, Philadelphia, PA, USA
13 Department of Medical Imaging, Sidra Medicine, Doha, Qatar
14 Department of Prenatal and Pediatric Imaging, Timone Children’s Hospital, Marseille, France
15 Division of Radiology and Nuclear Medicine, Department of Pediatric Radiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway

Springer
RESEARCH ARTICLE

Relationship of muscle morphology to hip displacement in cerebral palsy: a pilot study investigating changes intrinsic to the sarcomere

Kelly A. Larkin-Kaiser1, Jason J. Howard2, Timothy Leonard1, Venus Jourma1, Luke Gauthier2, Karl Logan2, Benjamin Otting2, Ron El-Hawary2 and Walter Herzog1

Abstract

Background: Cerebral palsy (CP) is the most common cause of childhood disability, typified by a static encephalopathy with peripheral muscular skeletal manifestations—most commonly related to spasticity—that are progressive with age. Hip displacement is one of the most common manifestations, observed to lead to painful degenerative arthritis over time. Despite the key role that spasticity-related adductor muscle contractures are thought to play in the development of hip displacement in CP, basic science research in this area to date has been limited. This study was initiated to correlate hip adductor muscle changes intrinsic to the sarcomere—specifically, titin isoforms and sarcomere length—to the severity of hip displacement in children with spastic cerebral palsy.

Methods: Single gracilis muscle biopsy specimens were obtained from children with CP (Gross Motor Function Classification System (GMFCS) II-V, n = 10) who underwent adductor muscle release surgery for the treatment of hip displacement. Gel electrophoresis was used to estimate titin molecular weight. Sarcomere lengths were measured from muscle fascicles using laser diffraction. The severity of hip displacement was determined by measuring by Reimers migration percentage (MP) from anteroposterior pelvic x-rays. Correlation analyses between titin, sarcomere lengths, and MP were performed.

Results: The mean molecular weight of titin was 3588 kDa. The mean sarcomere length was 3.51 μm. Increased MP was found to be associated with heavier isoforms of titin ($R^2 = 0.65, p < 0.05$) and with increased sarcomere lengths ($R^2 = 0.65, p < 0.05$). Heavier isoforms of titin were also associated with increased sarcomere lengths ($R^2 = 0.80, p < 0.05$).

Conclusions: Our results suggest that both larger titin isoforms and sarcomere lengths are positively correlated with increased severity of hip displacement and may represent adaptations in response to concomitant increases in spasticity and muscle shortening.

Trial registration: As this study does not report the results of a health care intervention on human participants, it has not been registered.

Keywords: Hip displacement, Cerebral palsy, Sarcomere, Titin, Adductor muscles

* Correspondence: jason.howard@line.com
1 Weill Cornell Medicine, Sidra Medicine, Al Dhafras St, Al Rayyan, P.O. Box 26099, Doha, Qatar
Full list of author information is available at the end of the article

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Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines

Vaccination against measles, mumps, and rubella (MMR) and yellow fever (YF) with live attenuated viruses can rarely cause life-threatening disease. Severe illness by MMR vaccines can be caused by inborn errors of type I and/or III interferon (IFN) immunity (mutations in IFNAR2, STAT1, or STAT2). Adverse reactions to the YF vaccine have remained unexplained. We report two otherwise healthy patients, a 9-year-old boy in Iran with severe measles vaccine disease at 1 yr and a 14-year-old girl in Brazil with viscerotropic disease caused by the YF vaccine at 12 yr. The Iranian patient is homozygous and the Brazilian patient compound heterozygous for loss-of-function mutations in IFNAR1. Compound heterozygous IFNAR1 deficiency can result in life-threatening complications of vaccination with live attenuated measles and YF vaccines in previously healthy individuals.
Blockade of TGF-β signaling to enhance the antitumor response is accompanied by dysregulation of the functional activity of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> and CD4<sup>+</sup>CD25<sup>-</sup>Foxp3<sup>+</sup> T cells

Magdalena J. Polanczyk<sup>1</sup>, Edwin Walker<sup>1,2</sup>, Daniel Haley<sup>1</sup>, Bella S. Guerrouahen<sup>3</sup> and Emmanuel T. Akporiaye<sup>1,2</sup>

Abstract

Background: The pleiotropic cytokine, transforming growth factor (TGF)-β, and CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells (Tregs) play a critical role in actively suppressing antitumor immune responses. Evidence shows that TGF-β produced by tumor cells promotes tolerance via expansion of Tregs. Our group previously demonstrated that blockade of TGF-β signaling with a small molecule TGF-β receptor I antagonist (SM16) inhibited primary and metastatic tumor growth in a T cell dependent fashion. In the current study, we evaluated the effect of SM16 on Treg generation and function.

Methods: Using BALB/c, Foxp3eGFP and Rag<sup>-/-</sup> mice, we performed FACS analysis to determine if SM16 blocked de novo TGF-β-induced Treg generation in vitro and in vivo. CD4<sup>+</sup> T cells from lymph node and spleen were isolated from control mice or mice maintained on SM16 diet, and flow cytometry analysis was used to detect the frequency of CD4<sup>+</sup>CD25<sup>-</sup>Foxp3<sup>+</sup> and CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T cells. In vitro suppression assays were used to determine the ability to suppress naive T cell proliferation in vitro of both CD4<sup>+</sup>CD25<sup>-</sup>Foxp3<sup>+</sup> and CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> T cell sub-populations. We then examined whether SM16 diet exerted an inhibitory effect on primary tumor growth and correlated with changes in Foxp3<sup>+</sup>expression. ELISA analysis was used to measure IFN-γ levels after 72 h co-culture of CD4<sup>+</sup>CD25<sup>+</sup> T cells from tumor-bearing mice on control or SM16 diet with CD4<sup>+</sup>CD25<sup>-</sup> T cells from naive donors.

Results: SM16 abrogates TGF-β-induced Treg generation in vitro but does not prevent global homeostatic expansion of CD4<sup>+</sup> T cell sub-populations in vivo. Instead, SM16 treatment causes expansion of a population of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg-like cells without significantly altering the overall frequency of Treg in lymphoproliferative naive and tumor-bearing mice. Importantly, both the CD4<sup>+</sup>CD25<sup>-</sup>Foxp3<sup>+</sup> T cells and the CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Tregs in mice receiving SM16 diet exhibited diminished ability to suppress naive T cell proliferation in vitro compared to Treg from mice on control diet.

Conclusions: These findings suggest that blockade of TGF-β signaling is a potentially useful strategy for blunting Treg function to enhance the anti-tumor response. Our data further suggest that the overall dampening of Treg function may involve the expansion of a quiescent Treg precursor population, which is CD4<sup>+</sup>CD25<sup>-</sup>Foxp3<sup>+</sup>.

Keywords: TGF-β, SM16, Mice, Treg subsets, Anti-tumor response
Activation of STAT3 signaling is mediated by TFF1 silencing in gastric neoplasia

Mohammed Soutto1,2, Zheng Chen1,2, Ajaz A. Bhat2,3, Lihong Wang4, Shoumin Zhu5, Ahmed Gomaa6, Andrea Bates4, Nadeem S. Bhat2, Dunfa Peng6, Abbes Belkhir4, M. Blanca Piazuelo5, M. Kay Washington6, Xi Chen Steven7, Richard Peek Jr.5 & Wael El-Rifai1,2,8

TFF1, a secreted protein, plays an essential role in keeping the integrity of gastric mucosa and its barrier function. Loss of TFF1 expression in the TFF1-knockout (KO) mouse leads to a pro-inflammatory phenotype with a cascade of gastric lesions that include low-grade dysplasia, high-grade dysplasia, and adenocarcinomas. In this study, we demonstrate nuclear localization of p-STAT3Y705, with significant overexpression of several STAT3 target genes in gastric glands from the TFF1-KO mice. We also show frequent loss of TFF1 with nuclear localization of STAT3 in human gastric cancers. The reconstitution of TFF1 protein in human gastric cancer cells and 3D gastric glands organoids from TFF1-KO mice abrogates IL6-induced nuclear p-STAT3Y705 expression. Reconstitution of TFF1 inhibits IL6-induced STAT3 transcription activity, suppressing expression of its target genes. TFF1 blocks IL6Rx-GP130 complex formation through interfering with binding of IL6 to its receptor IL6Rx. These findings demonstrate a functional role of TFF1 in suppressing gastric tumorigenesis by impeding the IL6-STAT3 pro-inflammatory signaling axis.
Correction to: Schlafen-11 expression is associated with immune signatures and basal-like phenotype in breast cancer

Edoardo Isnaldi1 · Domenico Ferraioli1,2 · Lorenzo Ferrando1 · Sylvain Brohéé3 · Fabio Ferrando1,4 · Piero Fregatti1,4 · Davide Bedognetti5 · Alberto Ballestrero1,4 · Gabriele Zoppoli1,4

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Correction to: Breast Cancer Research and Treatment
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In the original publication of the article, the funding information was incorrectly published. The corrected funding statement is given in this correction article.

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Gabriele Zoppoli
 gabriele.zoppoli@unige.it

1 Department of Internal Medicine (DiMI), University of Genoa and Ospedale Policlinico San Martino, Viale Benedetto XV, 6, 16132 Genoa, Italy
2 Comprehensive Cancer Center Leon Berard, Lyon, France
3 Institut de Pathologie Et de Génétique a.s.b.l, Charleroi, Belgium
4 Ospedale Policlinico San Martino IRCCS per l’Oncologia, Genoa, Italy
5 Sidra Medical Center, Doha, Qatar

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APE1 upregulates MMP-14 via redox-sensitive ARF6-mediated recycling to promote cell invasion of esophageal adenocarcinoma

Heng Lu¹, Ajaz A. Bhat², Dunfa Peng¹, Zheng Chen¹,³, Shoumin Zhu¹, Jun Hong⁴, Selma Maacha², Jin Yan⁵, David J. Robbins⁴, M. Kay Washington⁶, Abbes Belkhiri⁴, Wael El-Rifai¹,³,⁷

¹Department of Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA
²Division of Translational Medicine, Research Branch, Sidra Medicine, Doha, Qatar
³Department of Veterans Affairs, Miami Healthcare System, Miami, Florida, USA
⁴Department of Surgery, Vanderbilt University Medical Center, Nashville, TN, USA
⁵The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
⁶Department of Pathology, Vanderbilt University Medical Center, Nashville, TN, USA
⁷Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, Florida, USA

*Corresponding author
Wael El-Rifai, M.D., Ph.D.
Rosenstiel Med Science Bldg.
1600 NW 10th Ave, Room 4007
Miami, FL 33136-1015
Phone: +1 (305) 243 9648
E-mail: welrifai@med.miami.edu

Running Title: APE1 promotes cell invasion via activation of ARF6-MMP14

Disclosure of Potential Conflicts of Interest: No potential conflicts of interest were disclosed.

Keywords: APE-1/Ref-1, Barrett’s, esophageal adenocarcinoma, ARF6, MMP-14,
Abstract

Esophageal adenocarcinoma (EAC) is an aggressive malignancy with poor clinical outcome. The incidence of EAC has been rising rapidly in the past three decades. Here, we showed that apurinic/apyrimidinic endonuclease (APE1) is overexpressed in EAC cell lines, and patients' samples of dysplasia and EAC. Downregulation of APE1 or inhibition of its redox function significantly repressed invasion. Overexpression of a redox-defective mutant, C65A, abrogated the pro-invasive phenotype of APE1. APE1 regulated invasion via upregulation of matrix metalloproteinase MMP-14 which subsequently activated MMP-2 leading to degradation of the extracellular matrix (ECM) in a redox-dependent manner. Downregulation of APE1 or inhibition of its redox function decreased the rate of endocytosis and recycling of MMP-14 protein. APE1 interacted with ARF6, a key regulator of MMP-14 recycling, which maintained ARF6 activity in an APE1-redox-dependent manner, promoting its ability to regulate MMP-14 recycling to the cell surface. In summary, these findings identify a novel redox-sensitive APE1-ARF6-MMP-14 signaling axis that mediates cellular invasion in esophageal carcinogenesis.

Significance: This study demonstrates the association between oxidative stress and the development and metastatic behavior of esophageal adenocarcinoma.
The Effect of High-Dose Postpartum Maternal Vitamin D Supplementation Alone Compared with Maternal Plus Infant Vitamin D Supplementation in Breastfeeding Infants in a High-Risk Population. A Randomized Controlled Trial

Adekunle Dawodu 1,*, Khalil M. Salameh 2, Najah S. Al-Janahi 3, Abdulbari Bener 4 and Naser Elkum 5

1 Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, OH 45267, USA
2 Division of Pediatrics, Al-Wakra Hospital, Hamad Medical Corporation, Doha, Qatar
3 Department of Obstetrics and Gynecology, Women’s Hospital, Hamad Medical Corporation, Doha, Qatar
4 Department of Biostatistics and Medical Informatics, Cerrahpasa Faculty of Medicine, Istanbul University Cerrahpasa and Istanbul Medipol University, 34098 Cerrahpasa-Istanbul, Turkey
5 Sidra Medicine, Doha, Qatar

* Correspondence: adekunle_dawodu@yahoo.com or dawodua@ucmail.uc.edu; Tel.: +15136971546

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Abstract: In view of continuing reports of high prevalence of severe vitamin D deficiency and low rate of infant vitamin D supplementation, an alternative strategy for prevention of vitamin D deficiency in infants warrants further study. The aim of this randomized controlled trial among 95 exclusively breastfeeding mother–infant pairs with high prevalence of vitamin D deficiency was to compare the effect of six-month post-partum vitamin D₃ maternal supplementation of 6000 IU/day alone with maternal supplementation of 600 IU/day plus infant supplementation of 400 IU/day on the vitamin D status of breastfeeding infants in Doha, Qatar. Serum calcium, parathyroid hormone, maternal urine calcium/creatinine ratio and breast milk vitamin D content were measured. At baseline, the mean serum 25-hydroxyvitamin D (25(OH)D) of mothers on 6000 IU and 600 IU (35.1 vs. 35.7 nmol/L) and in their infants (31.9 vs. 29.6) respectively were low but similar. At the end of the six month supplementation, mothers on 6000 IU achieved higher serum 25(OH)D mean ± SD of 98 ± 35 nmol/L than 52 ± 20 nmol/L in mothers on 600 IU (p < 0.0001). Of mothers on 6000 IU, 96% achieved adequate serum 25(OH)D (≥50 nmol/L) compared with 52% in mothers on 600 IU (p < 0.0001). Infants of mothers on 600 IU and also supplemented with 400 IU vitamin D₃ had slightly higher serum 25(OH)D than infants of mothers on 6000 IU alone (109 vs. 92 nmol/L, p = 0.03); however, similar percentage of infants in both groups achieved adequate serum 25(OH)D ≥50 nmol/L (91% vs. 89%, p = 0.75). Mothers on 6000 IU vitamin D₃/day also had higher human milk vitamin D content. Safety measurements, including serum calcium and urine calcium/creatinine ratios in the mother and serum calcium levels in the infants were similar in both groups. Maternal 6000 IU/day vitamin D₃ supplementation alone safely optimizes maternal vitamin D status, improves milk vitamin D to maintain adequate infant serum 25(OH)D. It thus provides an alternative option to prevent the burden of vitamin D deficiency in exclusively breastfeeding infants in high-risk populations and warrants further study of the effective dose.

Keywords: vitamin D deficiency; supplementation; breastfeeding; mothers; infants
Cell Type-Specific TGF-β Mediated EMT in 3D and 2D Models and Its Reversal by TGF-β Receptor Kinase Inhibitor in Ovarian Cancer Cell Lines

Wafa Al Ameri 1,2, Ikhlak Ahmed 1, Fatima M. Al-Dasim 1, Yasmin Ali Mohamoud 3, Iman K. Al-Azwani 2,3, Joel A. Malek 1,3 and Thasni Karedath 1,*

1 Department of Genetic Medicine, Weill Cornell Medicine-Qatar, Education City, Qatar Foundation, Doha P.O. Box No. 24144, Qatar
2 Sidra Medicine, Doha P.O. Box No. 26999, Qatar
3 Genomics Core, Weill Cornell Medicine-Qatar, Education City, Qatar Foundation, Doha, Qatar
* Correspondence: tka2001@qatar-med.cornell.edu; Tel.: +974-3338-4832

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Abstract: Transcriptome profiling of 3D models compared to 2D models in various cancer cell lines shows differential expression of TGF-β-mediated and cell adhesion pathways. Presence of TGF-β in these cell lines shows an increased invasion potential which is specific to cell type. In the present study, we identified exogenous addition of TGF-β can induce Epithelial to Mesenchymal Transition (EMT) in a few cancer cell lines. RNA sequencing and real-time PCR were carried out in different ovarian cancer cell lines to identify molecular profiling and metabolic profiling. Since EMT induction by TGF-β is cell-type specific, we decided to select two promising ovarian cancer cell lines as model systems to study EMT. TGF-β modulation in EMT and cancer invasion were successfully depicted in both 2D and 3D models of SKOV3 and CAOV3 cell lines. Functional evaluation in 3D and 2D models demonstrates that the addition of the exogenous TGF-β can induce EMT and invasion in cancer cells by turning them into aggressive phenotypes. TGF-β receptor kinase I inhibitor (LY364947) can revert the TGF-β effect in these cells. In a nutshell, TGF-β can induce EMT and migration, increase aggressiveness, increase cell survival, alter cell characteristics, remodel the Extracellular Matrix (ECM) and increase cell metabolism favorable for tumor invasion and metastasis. We concluded that transcriptomic and phenotypic effect of TGF-β and its inhibitor is cell-type specific and not cancer specific.

Keywords: TGF-β; ovarian cancer; EMT; SKOV3; 3D models

1. Introduction

Ovarian cancer is one of the most lethal gynecological malignancies, which accounts for 5% cancer deaths among women [1]. The overall survival of ovarian cancer patients is less than 30% as its diagnosis occurs after the metastatic spread with a very high rate of recurrence and chemoresistance [2,3]. The long-term cure for the later stage cancer is challenging as little is known about the underlying mechanisms promoting ovarian cancer progression [4]. Most of the cancer studies rely on in vitro tumor models, like established cell lines and mouse xenograft models. Most of the tumor models fail to explain the aggressive phenotype represented in the real situation. These models usually help to identify the tumorigenicity of cancer cells and the involvement of the surrounding microenvironment. However, these systems are usually not sufficient to explain the initial metastatic event cascades, like tumor invasion and EMT [5]. Studying these events is crucial as it may lead to a better understanding of key metastatic events occurring primarily. Also, it may help to identify important molecular targets involved in increasing metastatic potential of some tumor subtypes. Identification of a sensitive molecular target
A deep intronic splice mutation of STAT3 underlies hyper IgE syndrome by negative dominance

Joëlle Khouriieh,b, Geetha Rao5,1, Tanvir Habib4,1, Danielle T. Avery5,1, Alain Lefèvre-Utilia,b,1
Marié-Olivia Chandressa,b, Azziz Belkadi,a,b, Maya Chrabieha,b, Hanan Alwaseem,a, Virginie Grandina,b, François Sarrot-Reynauda,b, Agathe Sénéchalc, Olivier Lortholarya,b, Xiaofei Konga,b, Stéphanie Boisson-Dupuisa,b,1, Capucine Picarda,b,2, Anne Puel,b,2, Vivien Béziat,b,2, Qian Zhangb, Laurent A beb,2,1, Henrik Molina1, Nico Marrimb,2,3, and Bertrand Boissona,2,3

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Significance

Heterozygous in-frame mutations in human STAT3 underlie the only known autosomal dominant form of hyper IgE syndrome (AD HIES). About 5% of familial cases remain unexplained. The mutant proteins are loss-of-function and dominant-negative when tested following overproduction in recipient cells. However, the production of mutant proteins has not been detected and quantified in the cells of heterozygous patients. We report a deep intronic heterozygous STAT3 mutation, c.1282-89C>T, in 7 relatives with AD HIES. This mutation creates a new exon in the STAT3 complementary DNA, which, when overexpressed, generates a mutant STAT3 protein (D427ins17) that is loss-of-function and dominant-negative in terms of tyrosine phosphorylation, DNA binding, and transcriptional activity. In immortalized B cells from these patients, the D427ins17 protein was 2 kDa larger and 4-fold less abundant than wild-type STAT3, on phosphorylation, DNA binding, and transcriptional activity. In immortalized B cells from these patients, the D427ins17 protein was 2 kDa larger and 4-fold less abundant than wild-type STAT3, on mass spectrometry. The patients’ primary B and T lymphocytes responded poorly to STAT3-dependent cytokines. These findings are reminiscent of the impaired responses of leukocytes from other patients with AD HIES due to typical STAT3 coding mutations. STAT3 is further evidence of the mutational potential of the intronic exon. These findings highlight the importance of sequencing STAT3 introns in patients with HIES without candidate variants in coding regions and essential splice sites. They also show that AD HIES-causing STAT3 mutant alleles can be dominant-negative even if the encoded protein is produced in significantly smaller amounts than wild-type STAT3.

Hypervigil syndrome (HIES) is a primary immunodeficiency (Online Mendelian Inheritance in Man #147060), first described in 1966 by Wedgewood and coworkers as Job’s Syndrome (1–4). In 1972, Buckley and coworkers reported additional features of this condition, including high serum IgE levels (5). Further studies documented the autosomal dominant (AD) inheritance of this disorder and gradually delineated various clinical phenotypes (6). AD HIES confers chronic selective susceptibility to infection with certain bacteria, including various staphylococci infecting the skin and lungs, and certain fungi, causing chronic mucocutaneous candidiasis (CMC) in particular (7). One of the hallmarks of these infections is that the associated inflammation is mild or delayed, corresponding to the “cold abscesses” originally reported by Davis et al. (4). Patients also display cutaneous and systemic allergic manifestations and extrahematopoietic features, including facial dysmorphism, the retention of deciduous teeth, osteopenia, hyperextensibility, and vascular abnormalities (6, 8). Clinical outcome is very poor, due largely to the immunodeficiency and infectious diseases of these patients, and patient management is difficult. Hematopoietic stem cell transplantation (HSCT) has been reported for 5 patients, and was apparently successful in 3, with a normalization of STAT3 signaling in hematopoietic cells and a restoration of the corresponding immune responses (9, 10). The other 2 patients had poorer outcomes: One died from posttransplantation complications (11), whereas the other is still alive with severe infections (12).

Heterozygous in-frame mutations in human STAT3 coding regions underlie the only known autosomal dominant form of hyper IgE syndrome (AD HIES). About 5% of familial cases remain unexplained. We report a deep intronic heterozygous STAT3 mutation, c.1282-89C>T, in 7 relatives with AD HIES. This mutation creates a new exon, encoding a new mRNA (D427ins17) and a mutant loss-of-function, dominant-negative STAT3 protein. This mutant protein was not detected in heterozygous cells from the patient. We show that the D427ins17 mutant allele is dominant-negative despite the production of significantly smaller amounts of mutant than of wild-type protein in heterozygous cells. These findings highlight the importance of searching for deep intronic mutations in STAT3 before considering alternative genetic etiologies of HIES.


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Hypervigil syndrome (HIES) is a primary immunodeficiency (Online Mendelian Inheritance in Man #147060); first described in 1966 by Wedgewood and coworkers as Job’s Syndrome (1–4). In 1972, Buckley and coworkers reported additional features of this condition, including high serum IgE levels (5). Further studies documented the autosomal dominant (AD) inheritance of this disorder and gradually delineated various clinical phenotypes (6). AD HIES confers chronic selective susceptibility to infection with certain bacteria, including various staphylococci infecting the skin and lungs, and certain fungi, causing chronic mucocutaneous candidiasis (CMC) in particular (7). One of the hallmarks of these infections is that the associated inflammation is mild or delayed, corresponding to the “cold abscesses” originally reported by Davis et al. (4). Patients also display cutaneous and systemic allergic manifestations and extrahematopoietic features, including facial dysmorphism, the retention of deciduous teeth, osteopenia, hyperextensibility, and vascular abnormalities (6, 8). Clinical outcome is very poor, due largely to the immunodeficiency and infectious diseases of these patients, and patient management is difficult. Hematopoietic stem cell transplantation (HSCT) has been reported for 5 patients, and was apparently successful in 3, with a normalization of STAT3 signaling in hematopoietic cells and a restoration of the corresponding immune responses (9, 10). The other 2 patients had poorer outcomes: One died from posttransplantation complications (11), whereas the other is still alive with severe infections (12).
Sugar alcohol provides imaging contrast in cancer detection

Puneet Bagga, Neil Wilson, Laurie Rich, Francesco M. Marincola, Mitchell D. Schnall, Hari Harirhan, Mohammad Haris, & Ravinder Reddy

Clinical imaging is widely used to detect, characterize and stage cancers in addition to monitoring the therapeutic progress. Magnetic resonance imaging (MRI) aided by contrast agents utilizes the differential relaxivity property of water to distinguish between tumorous and normal tissue. Here, we describe an MRI contrast method for the detection of cancer using a sugar alcohol, malitol, a common low-caloric sugar substitute that explains the chemical exchange saturation transfer (CEST) property of the labile hydroxyl group protons on malitol (malCEST). In vitro studies pointed toward concentration and pH-dependent CEST effect peaking at 1 ppm downfield to the water resonance. Studies with control rats showed that intravenously injected malitol does not cross the intact blood-brain barrier (BBB). In glioma carrying rats, administration of malitol resulted in the elevation of CEST contrast in the tumor region only owing to permeable BBB. These preliminary results show that this method may lead to the development of malitol and other sugar alcohol derivatives as MRI contrast agents for a variety of preclinical imaging applications.

Medical imaging is widely used to monitor structural, functional, and molecular changes in cancer and the use of contrast agents has significantly improved the detection by providing enhanced contrast between normal and pathological tissues. Positron Emission Tomography using 18F-fluoro-2-deoxy-glucose (18F-FDG-PET) combined with either computed tomography (CT) or magnetic resonance imaging (MRI) has gained widespread application as a molecular and metabolic imaging modality of cancers based on the high glycolytic activity of tumors. However, owing to the high metabolic activity of surrounding neurons, 18F-FDG uptake in the normal brain tissue limits its use for the imaging of cerebral gliomas. In addition to conventional MRI, dynamic contrast enhanced (DCE) MRI utilizes the relaxivity perturbation potential of gadolinium-based contrast agents (GBCAs) to detect and characterize cancer. Although, recent studies have reported the deposition of GBCAs in the brain and bone matrix, further studies are required to evaluate the long-term effects of gadolinium (Gd) accumulation on normal tissue function.

The Chemical Exchange Saturation Transfer (CEST) MRI technique probes the exchange of labile protons of the solute with bulk water protons. By applying low-power frequency-selective radio-frequency (RF) pulses for a long time, magnetization of exchangeable protons on a metabolite can be saturated. The chemical exchange mediated accumulation of these saturated protons with water decreases the bulk water signal in a concentration and pH dependent manner. The difference in the water signal obtained with and without RF saturation can be measured as the CEST contrast. CEST MRI has been used to image different metabolites and macromolecules in vivo, with applications in several human disorders. Since the CEST method provides orders of magnitude higher sensitivity than traditional proton MR spectroscopy (1H MRS), it enables detection of subtle changes in the level of metabolite of interest. Various groups have reported the use of glucose and its analogues as CEST contrast agent to study cancer and neurodegeneration.

In this study, we introduce a new contrast agent, malitol, a sugar alcohol commonly used as a sweetener due to its less caloric value. We exploited the CEST behavior of labile hydroxyl (-OH) protons on malitol with those of the bulk water and termed this new method as malCEST. The concentration and pH dependence of malCEST contrast was measured in vitro in solution phantoms. The potential of malCEST as an MR imaging method to image cancer was assessed in a rat glioma model and compared with gadolinium-diethylenetriamine-pentaacetic-acid (Gd-DTPA) contrast enhanced MRI.

4 Center for Magnetic Resonance and Optical Imaging, Department of Radiology, University of Pennsylvania, Philadelphia, PA, USA. 5 Research Branch, Sidra Medical and Research Center, Doha, Qatar. Correspondence and requests for materials should be addressed to R.R. (email: krr@pennmedicine.upenn.edu)
A transcriptomic atlas of mammalian olfactory mucosae reveals an evolutionary influence on food odor detection in humans

Luis R. Saraiva1,2,3,4*, Fernando Riveros-McKay2, Massimo Mezzavilla5, Eman H. Abou-Moussa1, Charles J. Arayata4, Melanie Macklouf2, Casey Trimmer1, Xinmei Ibara-Soria2, Mona Khan1, Laura Van Gerven6, Mark Jorissen2, Matthew Gibbs3, Gian O’Flynn2, Scott McGrane2, Peter Mombaerts5, John C. Marioni2,3,8, Joel D. Mainland4,9, Darren W. Logan2,4,7*

The mammalian olfactory system displays species-specific adaptations to different ecological niches. To investigate the evolutionary dynamics of olfactory sensory neuron (OSN) subtypes across mammalian evolution, we applied RNA sequencing of whole olfactory mucosa samples from mouse, rat, dog, marmoset, macaque, and human. We find that OSN subtypes, representative of all known mouse chemosensory receptor gene families, are present in all analyzed species. Further, we show that OSN subtypes expressing canonical olfactory receptor receptors are distributed across a large dynamic range and that homologous subtypes can be either highly abundant across all species or species/order specific. Highly abundant mouse and human OSN subtypes detect odors with similar sensory profiles and sense ecologically relevant odorants, such as mouse semiochemicals or human key food odorants. Together, our results allow for a better understanding of the evolution of mammalian olfaction in mammals and provide insights into the possible functions of highly abundant OSN subtypes.

INTRODUCTION
Odor detection in mammals is initiated by the activation of olfactory receptors (ORs) expressed in olfactory sensory neurons (OSNs), which populate the whole olfactory mucosa (WOM) (1). Most mature OSNs (mOSNs) predominantly express one allele of a single OR gene (2, 3). Smaller subsets of mOSNs express other families of chemosensors, such as trace amine–associated receptors (TAARs), guanylate cyclases (GCs), or members of the membrane-spanning 4-pass A (MS4As) gene family (4). These receptors define the molecular identity and odorant response profile of OSNs, and OSNs apply a combinatorial strategy to discriminate a number of odorants vastly greater than the number of receptors present in the genome (2, 3). From a phylogenetic perspective, OR genes are divided in two classes: class I, which preferentially binds hydrophilic odorants, and class II, which tends to recognize hydrophobic odorants (6, 7). The complex evolutionary dynamics of OR genes have resulted in notably different species-specific repertoires, which are presumably shaped by the chemosensory information that is required for survival in each species’ niche (4, 8). While cataloging the presence of orthologous OR genes among species has provided some insight into the drivers of selection (8), knowing the relative abundance of each OSN subtype both within and among species may provide a better understanding of these evolutionary dynamics.

Using an RNA sequencing (RNA-seq)–based approach, we have previously profiled the complete mouse and zebrafish OSN repertoires and found that they are stratified into hundreds to thousands of functionally distinct subtypes, represented across a large dynamic range of abundance in both species (3, 9, 10). While this OSN distribution is stereotyped among genetically identical mice, it varies greatly among different strains (11). These distributions are largely genetically controlled and have thus likely diverged under evolutionary pressures (11). The abundance of OSNs expressing a given OR correlates with the total volume of corresponding glomeruli in the olfactory bulb (12). Increasing the number of OR-expressing OSNs in mouse lowers detection thresholds (13), raising the possibility that more abundant expression increases sensitivity to the receptor’s ligands, providing a mechanism for adaptation to enhance the detection of important ecological olfactory cues. Therefore, olfactory transcriptome analysis is a critical first step toward identifying the most functionally relevant among the hundreds of OSN subtypes without identified odorants. Here, we investigated the transcriptional dynamics and putative functions of the olfactory systems of six mammalian species, spanning ~95 million years of evolution.

RESULTS
We performed RNA-seq on the WOM of male dog (Canis familiaris), mouse (Mus musculus), rat (Rattus norvegicus), marmoset (Callithrix jacchus), macaque (Macaca mulatta), and human (Homo sapiens) (Fig. 1A). We processed three biological replicates for each species, except for macaque, where we profiled four (see data file S1 for quality metrics and all gene expression data). On average, 83.85 ± 1.66% of the total reads were mapped uniquely to each corresponding genome. The intraspecific variability level among WOM replicates is extremely low (Spearman’s rho, ρx = 0.95 to 0.98; P < 0.0001), consistent with previous studies in laboratory animals (9–11).

To investigate the broad gene expression dynamics of the WOM across mammalian evolution, we focused on the 9725 genes that (i) have 1:1 orthology across the six species, (ii) share ≥40% amino acid identity with the human ortholog, and (iii) are expressed in at least...
Review Article
Enhancing Mesenchymal Stromal Cell Immunomodulation for Treating Conditions Influenced by the Immune System

Bella S. Guerrouahen(✉), Heba Sidahmed(✉), Asma Al Sulaiti(✉), Moza Al Khulaifi(✉), and Chiara Cugno(✉)

Sidra Medicine, Member of Qatar Foundation, Doha, Qatar

Correspondence should be addressed to Bella S. Guerrouahen; bguerrouahen@sidra.org

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Mesenchymal stromal cells (MSCs), formerly known as mesenchymal stem cells, are nonhematopoietic multipotent cells and are emerging worldwide as the most clinically used and promising source for allogeneic cell therapy. MSCs, initially obtained from bone marrow, can be derived from several other tissues, such as adipose tissue, placenta, and umbilical cord. Diversity in tissue sourcing and manufacturing procedures has significant effects on MSC products. However, in 2006, the International Society for Cellular Therapy (ISCT) established the minimum criteria for designating MSCs derived from various origins: adherence to plastic in standard culture conditions; expression of nonspecific surface molecules such as CD105/endoglin, CD90/thy1, and CD73/5′-nucleotidase; lack of expression of CD34, CD45, CD14 or CD11b, CD79a or CD19, and HLA-DR (<2%); and trilineage differentiation potential due to the expression of several pluripotency genes. The weak expression of major histocompatibility complex (MHC) class I protects MSCs from natural killer (NK) cell-mediated killing; additionally, the lack of MHC class II expression confers to these cells the ability to evade immune recognition by CD4+ T cells. MSCs present minimal expression for HLA-DR (<2%) and do not express costimulatory proteins (CD80, CD86, and CD40), endothelial or hematopoietic surface molecule markers, such as the minimum criteria for designating MSCs derived from various origins: adherence to plastic in standard culture conditions; expression of different nonspecific surface molecules such as CD105/endoglin, CD90/thy1, and CD73/5′-nucleotidase; lack of expression of CD34, CD45, CD14 or CD11b, CD79a or CD19, and HLA-DR (<2%); and trilineage differentiation potential due to the expression of several pluripotency genes. The weak expression of major histocompatibility complex (MHC) class I protects MSCs from natural killer (NK) cell-mediated killing; additionally, the lack of MHC class II expression confers to these cells the ability to evade immune recognition by CD4+ T cells. MSCs present minimal expression for HLA-DR (<2%) and do not express costimulatory proteins (CD80, CD86, and CD40), endothelial or hematopoietic surface molecule markers, such as

1. Background

Mesenchymal stromal cells (MSCs) are nonhematopoietic cells which possess self-renewal, proliferative, and clonogenic potential and have the ability to commit to different cell types including adipocytes, chondrocytes, and osteocytes depending on the environmental conditions [1–3]. They can be easily isolated from human tissues and have exceptional biological properties for advanced therapies [4]. Traditionally derived from bone marrow (BM) [5], MSC populations may also be obtained from other various tissue sources, such as maternal decidua basalis of the placenta, adipose tissue (AT), foreskin, or neonatal birth-associated tissues (fetal part of the placenta and umbilical cord (UC)) [6, 7]. In 2006, the International Society for Cellular Therapy (ISCT) established
Research Article

Analysis of Bacterial and Fungal Infections after Cytoreduction Surgery and Hyperthermic Intraperitoneal Chemotherapy: An Observational Single-Centre Study

Talat A. M. Albukhari,1 Hanaa Nafady-Hego,1,2,3 Hamed Elgendy,4,5,6,7 Hanan M. Abd Elmoneim,8,9 Asmaa Nafady,10,11 and Abdulaziz M. Alzahrani12

1Hematology and Immunology Department, Faculty of Medicine, Umm Alqura University, Mecca, Saudi Arabia
2Microbiology and Immunology Department, Faculty of Medicine, Assiut University, Assiut, Egypt
3Division of Translational Medicine, Sidra Medical and Research Center, Doha, Qatar
4Anesthesiology Department, Faculty of Medicine, Assiut University, Assiut, Egypt
5Department of Anesthesiology, King Abdullah Medical City, Mecca, Saudi Arabia
6Department of Anesthesiology, Hamad Medical Corporation, Doha, Qatar
7Weill Cornell Medicine, Doha, Qatar
8Department of Pathology, Faculty of Medicine, Minia University, Minia, Egypt
9Department of Pathology, Faculty of Medicine, Umm Alqura University, Mecca, Saudi Arabia
10Department of Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt
11Department of Clinical and Chemical Pathology, Qena Faculty of Medicine, South Valley University, Qena, Egypt
12Department of Surgery, King Abdullah Medical City, Mecca, Saudi Arabia

Correspondence should be addressed to Hanaa Nafady-Hego; hanaal205@gmail.com

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Introduction. While hyperthermic intraperitoneal chemotherapy (HIPEC) after cytoreduction surgery (CRS) has been shown to improve patient survival and disease-free progression in peritoneal carcinoma (PC) patients, the procedure relates to a high postoperative infection rate. Hence, we report the bacterial and fungal infections after CRS and HIPEC from a single institution in Saudi Arabia. Patients and Methods. A prospective observational study was conducted on 38 patients with PC selected for CRS/ HIPEC procedure between 2012 and 2015 in our centre. Results. Postoperative bacterial and fungal infection within 100 days was 42.2%, bacterial infection was reported always, and fungal infection was reported in 5 (13.2%) cases. Infections from the surgical site were considered the most common infection site. Multidrug-resistant extended-spectrum beta-lactamase (ESBL) Escherichia coli was the most frequent isolate, followed by multidrug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa. Lower preoperative albumin and a prolonged preoperative activated partial thromboplastin time (APTT) are associated with postoperative infections, while a prolonged preoperative hospital stay (hazard ratio (HR) = 1.06; confidence interval (CI) = 1.002–1.112; P = 0.042) and more intraoperative blood loss (>10%) (HR = 3.919; 95% CI = 1.024–14.995; P = 0.046) were independent risk factors for postoperative infections. Three cases died during the follow-up period; all were due to infection. Discussion. The infection rate in our centre compared to previous studies of comparable patients was matching. Effective management of postoperative infections should be considered, and identified risk factors in this study can help to focus on effective prevention and treatment strategies.

1. Introduction

In the past, peritoneal carcinomas (PCs) were considered an untreatable situation, with poor prognosis and short life expectancy following diagnosis. Recently, cytoreduction surgery (CRS), with hyperthermic intraperitoneal chemotherapy (HIPEC) is being used more and more in selected PC patients and offers a promising
Transketolase and vitamin B1 influence on ROS-dependent neutrophil extracellular traps (NETs) formation

Donporn Riyapa1, Darawan Rinchai2,3, Veerachat Muangsombut4, Chayanin Wuttinontananchai1, Mohammed Toufiq2, Damien Chaussabel2, Manabu Ato5, Jenefer M. Blackwell6,7, Sunee Korbsrisate4*

1 Center for Research and Innovation, Faculty of Medical Technology, Mahidol University, Nakhon Pathom, Thailand, 2 Systems Biology and Immunology Department, Sidra Medicine, Doha, Qatar, 3 Immunology, Inflammation & Metabolism Department, Sidra Medicine, Doha, Qatar, 4 Department of Immunology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 5 Department of Immunology, National Institute of Infectious Diseases, Shinjuku, Tokyo, Japan, 6 Telethon Kids Institute, The University of Western Australia, Nedlands, Australia, 7 Department of Pathology, The University of Cambridge, Cambridge, United Kingdom

Abstract

Neutrophil extracellular traps (NETs) are a recently identified, web-like, extracellular structure composed of decondensed nuclear DNA and associated antimicrobial granules. NETs are extruded into the extracellular environment via the reactive oxygen species (ROS)-dependent cell death pathway participating in inflammation and autoimmune diseases. Transketolase (TKT) is a thiamine pyrophosphate (vitamin B1)-dependent enzyme that links the pentose phosphate pathway (PPP) to glycolytic intermediates [1, 2]. The PPP is required for ribonucleotide synthesis, and it also

Introduction

Transketolase (TKT) plays pivotal roles in connecting the pentose phosphate pathway (PPP) to glycolytic intermediates [1, 2]. The PPP is required for ribonucleotide synthesis, and it also
A Spectrum of Clinical Findings from ALPS to CVID: Several Novel LRBA Defects

Deniz Cagdas 1, Sevil Oskay Halaş 2, Çağman Tan 2, Bernice Lo 3, Pınar Gür Çetinkaya 1, Salih Hoca 1, Betül Karaatmaca 1, Helen Matthews 4, Burcu Balci-Hayta 5, Tuba Ankoğlu 6, Fatih Ezgü 7, Elifcan Aladağ 8, İnci N. Saltik-Temizel 9, Hulya Demir 10, Barış Kuşkonmaä 10, Visal Okur 10, Fatma Gümürük 10, Hakan Göker 8, Duygu Çetinkaya 10, Kaan Boztuğ 11, Michael Lenardo 10, Ozden Sanal 1, İlhan Tezcan 1

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Abstract
Introduction Autosomal recessively inherited lipopolysaccharide-responsive beige-like anchor (LRBA) protein deficiency was shown to be responsible for different types of inborn errors of immunity, such as common variable immunodeficiency (CVID) and autoimmune lymphoproliferative syndrome (ALPS). The aim of this study was to compare patients with LRBA-related ALPS and LRBA-related CVID, to describe their clinical and laboratory phenotypes, and to prepare an algorithm for their diagnosis and management.

Methods Fifteen LRBA-deficient patients were identified among 31 CVID and 14 possible ALPS patients with Western blotting (WB), primary immunodeficiency disease (PIDD) gene, next-generation panel screening (NGS), and whole exome sequencing (WES).

Results The median age on admission and age of diagnosis were 7 years (0.3–16.5) and 11 years (5–44), respectively. Splenomegaly was seen in 93.3% (14/15) of the patients on admission. Splenectomy was performed to 1/5. Recurrent upper respiratory tract infections (93.3% (14/15)), autoimmune cytopenia (80% (12/15)), chronic diarrhea (53.3% (8/15)), chronic diarrhea (53.3% (8/15)), lower respiratory tract infections (53.3% (8/15)), lymphoma (26.6% (4/15)), Evans syndrome (26.6% (4/15)), and autoimmune thyroiditis (20% (3/15)) were common clinical findings and diseases. Lymphopenia (5/15), intermittent neutropenia (4/15), eosinophilia (4/15), and progressive hypogammaglobulinemia are recorded in a given number of patients. Double negative T cells (TCRαβ⁺CD4⁻CD8⁻) were increased in 80% (8/10) of the patients. B cell percentage/numbers were low in 60% (9/15) of the patients on admission. Decreased switched memory B cells, decreased naive and recent thymic emigrant (RTE) Th helper (Th) cells, markedly increased effector memory/effector memory RA⁺ (TEMRA) Th were documented. Large PDI⁺ population, increased memory, and enlarged follicular helper T cell population in the CD4⁺ T cell compartment was seen in one of the

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1 Department of Pediatrics, Division of Pediatric Immunology, Hacettepe University Medical School, Ankara, Turkey
2 Institute of Child Health, Immunology, Hacettepe University, Ankara, Turkey
3 Sidra Medical and Research Center, Al Rayyan, Qatar
4 National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD, USA
5 Department of Medical Biology, Hacettepe University Medical School, Ankara, Turkey
6 Department of Pediatrics, Division of Allergy and Immunology, Mersin University Medical School, Mersin, Turkey
7 Department of Pediatrics, Division of Pediatric Inborn Metabolic Disorders, Metabolism and Genetics, Gazi University Medical School, Ankara, Turkey
8 Department of Internal Medicine, Division of Hematology, Hacettepe University Medical School, Ankara, Turkey
9 Department of Pediatrics, Division of Pediatric Gastroenterology, Hacettepe University Medical School, Ankara, Turkey
10 Department of Pediatrics, Division of Pediatric Hematology, Hacettepe University Medical School, Ankara, Turkey
11 CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria

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patients. Most of the deleterious missense mutations were located in the DUF1088 and BEACH domains. Interestingly, one of the two siblings with the same homozygous LRBA defect did not have any clinical symptom. Hematopoietic stem cell transplantation (HSCT) was performed to 7/15 (46.6%) of the patients. Transplanted patients are alive and well after a median of 2 years (1–3). In total, one patient died from sepsis during adulthood before HSCT.

**Conclusion** Patients with LRBA deficiency may initially be diagnosed as CVID or ALPS in the clinical practice. Progressive decrease in B cells as well as IgG in ALPS-like patients and addition of IBD symptoms in the follow-up should raise the suspicion for LRBA deficiency. Decreased switched memory B cells, decreased naive and recent thymic emigrant (RTE) Th cells, and markedly increased effector memory/effector memory RA⁺ Th cells (TEMRA Th) cells are important for the diagnosis of the patients in addition to clinical features. Analysis of protein by either WB or flow cytometry is required when the clinicians come across especially with missense LRBA variants of uncertain significance. High rate of malignancy shows the regulatory T cell’s important role of immune surveillance. HSCT is curative and successful in patients with HLA-matched family donor.

**Keywords** LRBA deficiency · LATAIE · Hsct · Malignancy

**Introduction**

Primary immunodeficiencies are an extremely heterogeneous group of disorders generally inherited by Mendelian pattern. Lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency was separately discovered by two different groups in 2012 [1, 2]. According to the recent reports, LRBA defects have been suggested to be one of the most common autosomal recessive defects causing common variable immunodeficiency (CVID) [3], and it is also shown to be responsible from autoimmune lymphoproliferative syndrome (ALPS)-like (ALPS-like) disease [4].

LRBA molecule has a role in regulating cell surface expression of CTLA-4 [5]. As CTLA-4 is a checkpoint inhibitor of T cell function, LRBA deficiency is associated especially with the loss of regulatory T cell (Treg) function. Autoimmune cytopenia and early-onset and persistent diarrhea are among the leading manifestations [1, 6, 7]. It causes a highly variable disease, “LRBA deficiency with autoantibodies, Treg defects, autoimmune infiltration, and enteropathy” (LATAIE) disease [5].

Immunologic abnormalities reported in LRBA-deficient patients have included deficient T cell activation/proliferation, increased circulating follicular helper T cells [8], defects in specific antibody response, decreased IgG antibody production, decreased autophagy, and increased apoptosis in B lymphocytes [2]. The majority of LRBA-deficient patients have low switched memory B cells and plasmablasts [2, 9].

As ALPS-like or CVID-like presentation is commonly seen in patients with LRBA deficiency, the aim was to evaluate and compare patients with LRBA-ALPS and LRBA-CVID and prepare an algorithm to ease the diagnosis and follow-up of the patients with LRBA. We performed LRBA gene sequencing and protein studies in the patients with “probable ALPS” and CVID.

**Patients and Methods**

**Patients**

Fifteen LRBA-deficient patients from 14 families diagnosed and followed up with the diagnosis of CVID and possible ALPS between years 2012 and 2019 in Hacettepe University Immunology unit were enrolled into the study. One homozygous LRBA defective 16-year-old female patient was excluded as LRBA and CTLA-4 expressions were found to be normal in FACS analysis.

The patients were defined in cohorts of CVID (Project number GO13/228 and GO15/370) and ALPS (probable ALPS) (Project number GO13/265 and GO11/19-23) patients.

The criteria of probable ALPS in the study of Oliviera et al. were fulfilled in for the patients with ALPS [10].

**Methods**

**Flow Cytometry**

**Lymphocytes** The analysis of peripheral blood lymphocyte populations was performed by 6-color flow cytometry (Attune Nxt, Thermo Fisher, USA), using 100 μl of whole blood stained with 20 μl of monoclonal antibodies with fluorescein isothiocyanate (FITC), phycoerythrin (PE), allophycocyanin (APC), or peridinin–chlorophyl–protein (PerCP) against T and B subset markers (obtained from eBioscience, Thermo Fisher, USA) and incubated in the dark for 15 min at room temperature. For lymphocyte analysis, CD3(FITC), CD4(FITC), CD8(PE), CD16/56(PE), and CD19(PE) were used and for T and B lymphocyte subgroup analysis, CD4(FITC), CCR7(PE), CD31(PE), CD45RA (APC), and CD8(PerCP) (Beckton Dickinson, BD, USA) were used.
The Immune Landscape of Cancer


The Cancer Genome Atlas Research Network, Alexander J. Lazar,21 Jonathan S. Serody,26 Elizabeth G. Demicco,33,36 Mary L. Disis,6,36 Benjamin G. Vincent,1,26 and Ilya Shmulevich1,12

1Institute for Systems Biology, 401 Terry Ave N, Seattle, WA 98109, USA
2Canada’s Michael Smith Genome Sciences Centre, BC Cancer Agency, Vancouver, BC V5S 4S6, Canada
3University of California, San Francisco, Box 0808, 2340 Sutter Street, S433, San Francisco, CA 94115, USA
4Lineberger Comprehensive Cancer Center, Curriculum in Bioinformatics and Computational Biology, University of North Carolina, 125 Mason Farm Road, Chapel Hill, NC 27599-7295, USA
5Department of Systems Biology and Department of Electrical Engineering, Columbia University, New York, NY 10027, USA
6Barcelona Supercomputing Institute, La Jolla, CA 92037, USA
7The Eli and Edythe L. Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, MA 02142, USA
8School of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ 85281, USA
9Sage Bionetworks, 2901 Third Ave, Suite 330, Seattle, WA 98121, USA
10Department of Medicine, Institute for Human Genetics, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, 1450 3rd St, San Francisco, CA 94143, USA
11Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
12Irving Cancer Research Center, Room 913,1130 St. Nicholas Avenue, New York, NY 10032, USA
13Department of Computer Science, Institute for Computational Medicine; Johns Hopkins University, Baltimore, MD 21218, USA
14Departments of Medicine and Biomedical Data Science, Stanford University, Stanford, CA 94305, USA
15Seven Bridges Genomics, Cambridge, MA 02142, USA
16Department of Oncology, University of Calgary, Calgary, AB T2N 4N1, Canada
17Université libre de Bruxelles (ULB), Computer Science Department, Faculty of Sciences, Boulevard du Triomphe - CP212, 1050 Bruxelles, Belgium
18Department of Bioinformatics and Computational Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
19Medical Scientist Training Program, University of Alabama at Birmingham, Birmingham, AL 35294, USA
20Center for Epigenetics, Van Andel Research Institute, Grand Rapids, MI 49503, USA
21Department of Biomedical Informatics, Stony Brook Medicine, 100 Nicolls Rd, Stony Brook, NY 11794, USA
22Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9659 Medical Center Dr., Bethesda, MD 20892, USA
23Department of Pathology, Genomics Medicine and Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd-Unit 85, Houston, TX 77030, USA
24Department of Medicine and Microbiology and Lineberger Comprehensive Cancer Center, 125 Mason Farm Road, Chapel Hill, NC 27599-7295, USA
25Mount Sinai Hospital, Department of Pathology and Laboratory Medicine, 600 University Ave., Toronto, ON M5G 1X5, Canada
26Department of Medical Oncology, 850 Republican Street, Brotman Building, 2nd Floor, Room 221, Box 358050, University of Washington, Seattle, WA 98109-4714, USA
27Institute for Stem Cell Biology and Regenerative Medicine and Department of Biomedical Data Science, Stanford University, Stanford, CA 94305, USA
28Department of Medicine, Institute for Human Genetics, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, 1450 3rd St, San Francisco, CA 94143, USA
29Department of Genetics, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil
30Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
31Departments of Pathology, Genomics Medicine and Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd-Unit 85, Houston, TX 77030, USA
32Department of Oncology, University of Calgary, Calgary, AB T2N 4N1, Canada
33Departments of Medicine and Biomedical Data Science, Stanford University, Stanford, CA 94305, USA
34Institute for Systems Biology, 401 Terry Ave N, Seattle, WA 98109, USA
35Department of Computer Science, Institute for Computational Medicine; Johns Hopkins University, Baltimore, MD 21218, USA
36Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
37Lead Author
*Correspondence: vesteinn.thorsson@systemsbiology.org (V.T.), benjamin.vincent@unchealth.unc.edu (B.G.V.), ilya.shmulevich@systemsbiology.org (I.S.)
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In the originally published version of this article, the authors neglected to include Younes Mokrab and Aaron M. Newman as co-authors and misspelled the names of authors Charles S. Rabkin and Ilya Shmulevich. The author names have been corrected here and online.

In addition, the concluding sentence of the subsection “Immune Signature Compilation” in the Method Details in the original published article was deemed unclear because it did not specify differences among the gene set scoring methods. The concluding sentences now reads “Gene sets from Bindea et al., Senbabaoglu et al., and the MSigDB C7 collection were scored using single-sample gene set enrichment (ssGSEA) analysis (Barbie et al., 2009), as implemented in the GSVA R package (Hänzelmann et al., 2013). All other signatures were scored using methods found in the associated citations.”
The clinical and genetic characteristics of permanent neonatal diabetes (PNDM) in the state of Qatar

Sara Al-Khawaga\textsuperscript{1,2,3} | Idris Mohammed\textsuperscript{1,2} | Saras Saraswathi\textsuperscript{2} | Basma Haris\textsuperscript{2} | Reem Hasnah\textsuperscript{2} | Amira Saeed\textsuperscript{2} | Hakeem Almabraz\textsuperscript{2} | Najeeb Syed\textsuperscript{4} | Puthen Jithesh\textsuperscript{4} | Ahmed El Awwa\textsuperscript{2,5} | Amal Khalifa\textsuperscript{2} | Fawziya AlKhalaf\textsuperscript{2} | Goran Petrovski\textsuperscript{2} | Essam M. Abdelalim\textsuperscript{1,3} | Khalid Hussain\textsuperscript{2}

\textsuperscript{1}College of Health \& Life Sciences, Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar
\textsuperscript{2}Division of Endocrinology, Department of Pediatric Medicine, Sidra Medicine, Doha, Qatar
\textsuperscript{3}Diabetes Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar
\textsuperscript{4}Biomedical Informatics Division, Sidra Medicine, Doha, Qatar
\textsuperscript{5}Faculty of medicine, Alexandria University, Alexandria, Egypt

Correspondence
Khalid Hussain, Division Chief-Endocrinology, Department of Pediatric Medicine, Sidra Medicine, Doha, Qatar.
Email: khussain@sidra.org

Abstract

\textbf{Background:} Neonatal diabetes mellitus (NDM) is a rare condition that occurs within the first six months of life. Permanent NDM (PNDM) is caused by mutations in specific genes that are known for their expression at early and/or late stages of pancreatic beta-cell development, and are either involved in beta-cell survival, insulin processing, regulation, and release. The native population in Qatar continues to practice consanguineous marriages that lead to a high level of homozygosity. To our knowledge, there is no previous report on the genomics of NDM among the Qatari population. The aims of the current study are to identify patients with NDM diagnosed between 2001 and 2016, and examine their clinical and genetic characteristics.

\textbf{Methods:} To calculate the incidence of PNDM, all patients with PNDM diagnosed between 2001 and 2016 were compared to the total number of live births over the 16-year-period. Whole Genome Sequencing (WGS) was used to investigate the genetic etiology in the PNDM cohort.

\textbf{Results:} PNDM was diagnosed in nine (\(n = 9\)) patients with an estimated incidence rate of 1:22,938 live births among the indigenous Qatari. Seven different mutations in six genes (\textit{PTF1A}, \textit{GCK}, \textit{SLC2A2}, \textit{EIF2AK3}, \textit{INS}, and \textit{HNF1B}) were identified. In the majority of cases, the genetic etiology was part of a previously identified autosomal recessive disorder. Two novel de novo mutations were identified in \textit{INS} and \textit{HNF1B}.

\textbf{Conclusion:} Qatar has the second highest reported incidence of PNDM worldwide. A majority of PNDM cases present as rare familial autosomal recessive disorders. Pancreas associated transcription factor 1a (\textit{PTF1A}) enhancer deletions are the most common cause of PNDM in Qatar, with only a few previous cases reported in the literature.

\textbf{KEYWORDS}
Fanconi–Bickel Syndrome (FBS), \textit{GCK}, \textit{HNF1B}, \textit{INS}, pancreatic agenesis, Permanent neonatal diabetes (PNDM), \textit{PTF1A}, Whole Genome Sequencing (WGS), Wolcott–Rallison Syndrome (WRS)
Single-Voxel $^1$H MR spectroscopy of cerebral nicotinamide adenine dinucleotide (NAD$^+$) in humans at 7T using a 32-channel volume coil

Puneet Bagga$^1$ | Hari Hariharan$^1$ | Neil E. Wilson$^1$ | Joanne C. Beer$^2$ | Russell T. Shinohara$^{2,3}$ | Mark A. Elliott$^1$ | Joseph A. Baur$^4$ | Francesco M. Marincola$^5$ | Walter R. Witschey$^1$ | Mohammad Harris$^{1,6,7}$ | John A. Detre$^8$ | Ravinder Reddy$^1$

$^1$Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania
$^2$Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania
$^3$Center for Biomedical Image Computing and Analytics, Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania
$^4$Department of Physiology and Institute of Diabetes, Obesity and Metabolism, University of Pennsylvania, Philadelphia, Pennsylvania
$^5$Refuge Biotechnologies Inc., Menlo Park, California
$^6$Research Branch, Sidra Medical and Research Center, Doha, Qatar
$^7$Laboratory Animal Research Center, Qatar University, Doha, Qatar
$^8$Department of Neurology, University of Pennsylvania, Philadelphia, Pennsylvania

**Correspondence**
Puneet Bagga, B1 Stellar-Chance Laboratories, Department of Radiology, University of Pennsylvania, 422 Curie Blvd, Philadelphia, PA.
Email: puneetb@upenn.edu

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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 $90^\circ$ pulse. PRESS localization was achieved using optimized Shinnar-Le Roux $180^\circ$ 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 ($\beta = -1.24 \mu$M/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...
miRNA-dependent regulation of STIM1 expression in breast cancer

Rashmi P. Kulkarni1,2,5, Asha Elnim2,3, Ethel Alcantara-Adap1,2, Satany Hubrack1,2,6, Nancy Nader1,2, Fang Yu1,2, Maya Dib1,2, Vimal Ramachandran1, Hani Najafi Shoushtari1,2 & Khaled Machaca1,2

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Store-operated Ca2+ entry (SOCE) has been shown to be important for breast cancer metastasis in xenograft mouse models. The ER Ca2+ sensor STIM1 and Orai plasma membrane Ca2+ channels molecularly mediate SOCE. Here we investigate the role of the microRNA machinery in regulating STIM1 expression. We show that STIM1 expression is regulated post-transcriptionally by the miRNA machinery and identify miR-223 and miR-150 as regulators of STIM1 expression in the luminal non-aggressive MCF7 breast cancer cell line. In contrast, STIM1 expression in the more aggressive basal triple-negative MDA-MB-231 cell line is not significantly modulated by a single miRNA species but is rather upregulated due to inhibition of the miRNA machinery through downregulation of Ago2. Consistently, overexpression of Ago2 results in decreased STIM1 protein levels in MDA-MB-231 cells. Clinically, STIM1 and Ago2 expression levels do not correlate with breast cancer progression, however in the basal subtype high STIM1 expression is associated with poorer survival. Our findings show that STIM1 expression is differentially regulated by the miRNA machinery in different cell types and argue for a role for this regulation in breast cancer.

Breast cancer is the most common cancer in women representing the leading cause of cancer deaths in this gender and accounts for ~25% of all cancer cases. Notwithstanding significant advances in breast cancer treatment ~30% of patients relapse resulting in a death toll of >450,000 annually. Over 90% of the mortality associated with breast cancer is due to metastatic disease and not the primary tumor. Metastasis in a multistep complex process that involves cells in the primary tumor losing their cell-cell contact with adjacent cells, migrating to the lymphatic or blood circulation, infiltrating the circulatory system, penetrating the target tissue through the capillary endothelium, and colonizing and surviving is the secondary site. Cell migration requires the formation of membrane protrusions at the front edge of the cell and detachment at the back end, both of which being Ca2+-dependent processes. Furthermore, store-operated Ca2+ entry (SOCE) has been implicated in modulating the actin cytoskeleton and cell mobility.

SOCE is mediated by the STIM and Orai family of proteins. STIM1 is a Ca2+ sensor that senses Ca2+ load in the ER and forms clusters in response to store depletion that localize to ER-plasma membrane (PM) junctions where they recruit and gate open the highly Ca2+ selective channel Orai1. The deregulation of SOCE has been associated with a variety of diseases, including breast cancer. STIM1 and Orai1 have been shown to be required for breast cancer metastasis in xenograft models. The role of SOCE has been further extended to migration and metastasis of other cancers, including cervical, melanoma, and colorectal cancer. Interestingly, STIM1 (GOK) was initially identified as a tumor-suppressor. These findings support a central role for SOCE in cancer metastasis.

MicroRNAs (miRNAs) are endogenous single-stranded RNAs (21–24 nucleotides) that function in post-transcriptional regulation of gene expression. miRNAs typically recognize target genes through their seed sequence (2–7 nt) binding at the 3' untranslated regions (3'UTR). This leads to target miRNA degradation and/or inhibition of translation. Any given 3'UTR may have multiple binding sites for many of different miRNAs. Conversely, any single miRNA can bind to 3'UTRs of several target genes. This mechanism allows precise regulation of genes by several miRNAs as well as co-regulation of genes by a single miRNA.

1Department of Physiology and Biophysics, Weill Cornell Medicine Qatar, Qatar Foundation, Doha, Qatar. 2Calcium Signaling Group, Weill Cornell Medicine Qatar, Doha, Qatar. 3College of Health and Life Sciences, Hamad bin Khalifa University, Qatar Foundation, Doha, Qatar. 4Department of Cell Biology, Weill Cornell Medicine Qatar, Doha, Qatar. 5Present address: Managing Partner, Integrated Group, P.O. Box 47039, Doha, Qatar. 6Present address: Sidra Medicine, Doha, Qatar. Rashmi P. Kulkarni and Asha Elnim contributed equally. Correspondence and requests for materials should be addressed to K.M. (email: kshm2002@qatar-med.cornell.edu)
Dose and time effects of solar simulated ultraviolet radiation on the in vivo human skin transcriptome

Running head: ultraviolet radiation and in vivo human skin transcriptome

M. Bustamante,1,2,3,4* C. Hernandez-Ferrer,1,3,4,5 A. Tewari,6 Y. Sarria,1,3,4 G.I. Harrison,6 E. Puigdecanet,7 L. Nonell,7 W. Kang,8 M.R. Friedländer,8 X. Estivill,2,3,4,9 J.R. González,1,3,4 M. Nieuwenhuijsen1,3,4 and A.R. Young6*

1ISGlobal, Barcelona Institute for Global Health, Barcelona, Spain
2Centre for Genomic Regulation (CRG), The Barcelona Institute of Science and Technology, Barcelona, Spain
3Universitat Pompeu Fabra (UPF), Barcelona, Spain
4CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
5Computational Health Informatics Program (CHIP), Boston Children’s Hospital, Boston, USA
6King’s College London (KCL), St John’s Institute of Dermatology, London, UK
7Servei d’Anàlisi de Microarrays, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
8Science for Life Laboratory, Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, Stockholm, Sweden
9Genetics Program, Sidra Medical Center, Al Rayyan Municipality, Qatar

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The authors wish it to be known that, in their opinion, the two first and last two authors should be regarded as joint First and joint Last Authors.

*Corresponding authors:
Mariona Bustamante, Av. Dr Aiguader 88, 08003, Barcelona, Spain, mariona.bustamante@isglobal.org
Antony Young, St John’s Institute of Dermatology, 9th Floor, Tower Wing, Guy’s Hospital, Great Maze Pond, SE1 9RT, London, UK, antony.young@kcl.ac.uk

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Competing financial interests
None of the participants has any conflict of interest.

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Bullet statements

What was known about the topic?

The skin’s transcriptional profile underpins its adverse (i.e. inflammation) and adaptive molecular, cellular and clinical responses (i.e. tanning, hyperkeratosis) to solar ultraviolet radiation (UVR). However, few studies have assessed miRNA and gene expression in vivo in humans, and there is a lack of information on dose, time, and waveband effects.

What does this study add?

Acute doses of fluorescent solar simulated radiation (FSSR), of similar magnitude to those received daily in holiday situations, markedly altered the skin’s transcriptional profiles. The number of differentially expressed genes was FSSR dose-dependent, reached a peak at 6h and returned to baseline at 24h. The initial transcriptional response involved apoptosis and keratinization, followed by inflammation and immune activation. In these conditions, miRNA expression was less affected than gene expression.
Summary

Background: Terrestrial ultraviolet radiation (UVR) causes erythema, oxidative stress, DNA mutations and skin cancer. Skin can adapt to these adverse effects by DNA repair, apoptosis, keratinization and tanning.

Objectives: To investigate the transcriptional response to fluorescent solar simulated radiation (FSSR) in sun-sensitive human skin in vivo.

Methods: Seven healthy male volunteers were exposed to 0, 3 and 6 standard erythemal doses (SED). Skin biopsies were taken at 6h and 24h post-exposure. Gene and miRNA expression were quantified with next generation sequencing. A set of candidate genes was validated by quantitative PCR (qPCR); and wavelength dependence was examined in other volunteers through microarrays.

Results: The number of differentially expressed genes increased with FSSR dose and decreased with time post-exposure. Six hours after 6 SED, 4071 genes were differentially expressed, but only 16 genes were affected at 24h after 3 SED. Genes for apoptosis and keratinization were prominent at 6h, while inflammation and immunoregulation genes were predominant at 24h. Validation by qPCR confirmed the altered expression of 9 genes detected under all conditions; genes related to DNA repair and apoptosis, immunity and inflammation, pigmentation and vitamin D synthesis. In general, candidate genes also responded to UVA1 and/or UVB, but with variations in wavelength dependence and peak expression time. Only four miRNAs were differentially expressed by FSSR.

Conclusions: The UVR doses of this acute study are readily achieved daily during sunny holidays, suggesting that skin transcriptional profile of “typical” holiday makers is markedly deregulated.

Abbreviations

UVR: ultraviolet radiation
UVA: ultraviolet radiation type A (315-400nm)
UVA1: ultraviolet radiation type A1 (340-400nm)
UVB: ultraviolet radiation type B (280-315nm)
FSSR: fluorescent solar simulated radiation

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Abstract

Objective

Asphyxia of newborns is a severe and frequent challenge of the peri- and postnatal period. The purpose of this study was to study early morphological, immunological and structural alterations in lung tissue after asphyxia and hemorrhage (AH).

Methods

44 neonatal piglets (age 32 hrs) underwent asphyxia and hemorrhage (AH) and were treated according to the international liaison committee of resuscitation (ILCOR) guidelines. For this study, 15 piglets (blood transfusion (RBC) n = 9; NaCl n = 6, mean age 31 hrs) were randomly picked. 4 hours after ROSC (return of spontaneous circulation), lung tissue and blood samples were collected.

Results

An elevation of myeloperoxidase (MPO) activity was observed 4 hrs after AH accompanied by an increase of surfactant D after RBC treatment. After AH tight junction proteins Claudin 18 and junctional adhesion molecule 1 (JAM1) were down-regulated, whereas Occludin was increased. Furthermore, after AH and RBC treatment dephosphorylated active form of Connexin 43 was increased.

Conclusions

AH in neonatal pigs is associated with early lung injury, inflammation and alterations of tight junctions (Claudin, Occludin, JAM-1) and gap junctions (Connexin 43) in lung tissue, which contributes to the development of lung edema and impaired function.
Eye tracking in cytotechnology education: “visualizing” students becoming experts

Maheswari Mukherjee, PhD, MSc, BPT, CT (ASCP)CMa,*, Amber Donnelly, PhD, MPH, SCT (ASCP)a, Blake Rose, CT (ASCP)b, David E. Warren, PhDc, Elizabeth Lyden, MSd, Nikolaos Chantziantoniou, BSc, ART(CSMLS), CFIACe, Brian Dimmitt, SCT (ASCP)CMf, Karyn Varley, MS, SCT(ASCP)CMg, Liron Pantanowitz, MDh

a Cytotechnology Education, College of Allied Health Professions, University of Nebraska Medical Center, Omaha, Nebraska
b Department of Pathology and Microbiology, Nebraska Medicine, Omaha, Nebraska
c Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, Nebraska
d Department of Biostatistics, College of Public Health, Omaha, Nebraska
e Department of Pathology, Sidra Medicine, Doha, State of Qatar
f Department of Anatomic Pathology, Carle Foundation Hospital, Urbana, Illinois
g Department of Pathology, University of Pittsburgh Medical Center Magee-Womens Hospital, Pittsburgh, Pennsylvania
h Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

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Introduction This study reports the potential of eye-tracking technology in determining screening skills of cytotechnology (CT) students while examining digital images (DI).

Materials and methods Twenty-five static DI of gynecologic cytology specimens were serially displayed on a computer monitor for evaluation by 16 CT students and 3 cytotechnologists at 3 locations. During evaluation, participant’s eye movements were monitored with a Mirametrix S2 eye tracker (iMotions, Boston, Massachusetts). Financial relationships or interest to disclose: Dr. Liron Pantanowitz is on the medical advisory board for Leica & Ibex, and a consultant for Hamamatou. All the other authors have no financial relationships or interest to disclose.

Key words Eye tracking; Digital images; Cytotechnology; Education

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MA) and EyeWorks software (Eyetracking, Solana Beach, CA). Students completed the protocol at: Period1 (P1)—4 months, Period2 (P2)—7 months, Period3 (P3)—11 months during their 1-year training; and the cytotechnologists only once. A general linear mixed model was used to analyze the results.

Results The proportion of agreement on interpretations for cytotechnologists, students during P1, and students during P3 were 0.83, 0.62, and 0.70 respectively. The mean task duration in seconds for cytotechnologists, students during P1, and students during P3 were 14.5, 52.2, and 35.3, respectively. The mean number of gaze observations of cytotechnologists, students during P1, and students during P3 on region of interest (ROI) 1 were 77.93, 181.12, and 123.83, respectively; and, ROI 2 were 38.90, 142.79, and 92.46, respectively.

Conclusions This study demonstrated that students had decreased time, number of fixation points, gaze observations on ROI, and increased agreement with the reference interpretations at the end of the training program, indicating that their screening skills were progressing towards the level of practicing cytotechnologists.

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Introduction

Whole slide imaging (WSI) or virtual microscopy (VM) involves scanning glass slides at high resolution to convert them into digital images (DI). These DI may be stored on a server and made remotely accessible online. With the help of image viewer software, these DI can be displayed and manipulated on a computer monitor. VM simulates the experience of examining a glass slide under the light microscope (LM) as the user can pan (navigate) (along x and y axes), zoom (at different magnifications) and sometimes focus (along the z axis) the DI. Investigation of the efficacy of VM in the University of Nebraska Medical Center (UNMC) cytotechnology (CT) program recognized that VM is a valuable teaching tool and demonstrated the application of learning cytology through VM to glass slide screening using LM. Therefore, VM has been incorporated into the UNMC CT program and extensive teaching modules, virtual scope sessions and training exercises have been developed using DI. Recent literature states that VM technology may not only replace the conventional way of viewing slides using LM but may also provide emerging insights into how the slides are examined when making a diagnosis by tracking end-user eye movements.

Eye movements represent one of the most frequent sensorimotor activities in humans, and recent advances in technology have allowed for the study of eye gaze or eye tracking during the acquisition of visual expertise. Eye tracking measures gaze behaviors during task execution, visualizing what areas on a screen are inspected—thus providing clues about information on the decision-making process. Eye tracking systems allow the visualization of a subject’s gaze and provide opportunities to create computerized graphic representations of eye-scanning patterns. Eye-movement tracking technology is an innovative and contemporary research topic that is being used in various medical domains including pathology, radiology, and intensive care. Eye-tracking systems that have been used so far included a screen-based method (also called remote or desktop), glasses (also called mobile), and a view path tracking method that has been integrated with the WSI software platform. Remote eye trackers are becoming increasingly popular because they are easy to set up and they enable measurement of where a person looks while allowing for free head movement. Several outcome measures have been analyzed using eye trackers, including fixation locations (what the eyes are looking at), saccade distance (distance between successive fixations), fixation durations, task durations (total length of a task), and fixations in regions of interest (the total number of fixations falling within the defined boundary of a region).

Although eye tracking technology has been found to be helpful in various medical domains, there still exists a knowledge gap regarding the potential of eye tracking technology in CT training and education. The CT programs involved in this study continuously investigates the best method of training to convert students into competent cytotechnologists upon graduation. Therefore, the programs intended to take advantage of its existing VM resources to evaluate the potential of eye-tracking technology in determining screening skills of CT students while examining DI. The primary aim of this study was to compare the eye movements of CT students at 3 different time periods (Period1 [P1]—4 months, Period2 [P2]—7 months, Period3 [P3]—11 months) of their 1-year training program in interpreting gynecologic cytology static DI with regard to: interpretations, task duration, number of fixation points, and gaze observations on the regions of interest (ROI). The secondary aim was to compare the eye movements of qualified cytotechnologists to CT students at 3 different time periods of the training program in interpreting static DI with regard to the same aforementioned parameters.

For the primary aim, we expected to see an increase in the agreement of interpretations of the DI to the reference interpretation, decrease in task duration, decrease in the number of fixation points, and decrease in gaze observations on ROI as
Pediatric Cervicofacial Actinomycosis: Lessons From a Craniofacial Unit

Graeme E. Glass, PhD, FRCS(Plast), Robert M.T. Staruch, MBBS, MRCS, Karen Bradshaw, MRCP, FRCR, Adrian K. Charles, FRCP, FRC(Path) and Mitchell A. Stotland, MD, FRCS

Abstract: Actinomycosis is a rare disease that remains difficult to diagnose and manage. Prompted by 2 recent cases the authors sought evidence-based conclusions about best practice. A systematic review was conducted using standard PRISMA methodology. The study was registered prospectively (PROSPERO: CRD42018115064). Thirty-three children from 23 series are described. The mean age was 8 years (range 3–17). Fifty-five percent were female. Twenty cases involved bone (usually mandible); 13 cases involved cervicofacial soft tissue. Poor dental hygiene and oral trauma were implicated. The median diagnostic delay was 12 weeks (range 1–156 weeks). The median duration of definitive antibiotic therapy was 17 weeks (range 1–130 weeks). Although diagnostic delay did not correlate with number of surgeries, bony involvement was associated with more procedures (P = 0.008, unpaired t test). All (6) cases with residual infection had bony involvement (P = 0.06, Fisher exact test). Neither diagnostic delay nor number of surgeries significantly influenced infection-free outcome which, instead, relies on aggressive surgical debridement and prolonged antibiotic therapy. Mandibular involvement exhibits a higher surgical burden and chronicity in around a third of cases. As dental caries are implicated in mandibular disease, preventative strategies must focus on improving pediatric oral hygiene.

Key Words: Actinomyces spp., actinomycosis, bacterial infection, cervicofacial actinomycosis, cervicofacial osteomyelitis, dental caries, tooth decay

From the Department of Surgery, Sidra Medicine, Doha, Qatar; Weill-Cornell Medical College, Az-Rayyan, Qatar; Pan Thames Plastic Surgery Residency, London, UK; Department of Radiology, Sidra Medicine, Doha, Qatar; and Department of Pathology, Sidra Medicine, Doha, Qatar.

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Address correspondence and reprint requests to Graeme E. Glass, PhD, FRCS(Plast), Room C1-120, 1st Floor OPC, Al Luqta Street, Education City North Campus, Qatar Foundation, PO BOX 26999, Doha, Qatar; E-mail: gglass@sidra.org.

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CLINICAL STUDY

Pediatric Actinomycosis is a rare disease. Although once common in both humans and livestock, it is seldom included in the differential diagnosis of craniomaxillofacial lesions in this age group. However, observational studies of alarming disparities in pediatric dental hygiene across ethnic and socioeconomic boundaries raise the prospect of the reemergence of this disease. As many of the clinical reports are historical, definitive contemporary management remains unclear with no consensus regarding the duration and mode of administration of antibiotic therapy. In addition, although the combined approach of prolonged antibiotic therapy and surgical debridement has been advocated since 1960, details of successful surgical interventions are sparse and not particularly instructive. Thus, when recently faced with such problems in our children’s hospital, we were poorly placed to recognize it and treat it effectively. Here, we present 2 recent cases together with a systematic review of the literature that highlight lessons learned and summarize the best evidence for managing these unusual cases. Special mention is made of ascertaining evidence for the influence of surgical debridement on infection-free recovery.

MATERIALS AND METHODS

Search
We searched PubMed, EMBASE (OvidSP), Medline (OvidSP), Google Scholar, and the Cochrane Database of Systematic Reviews.
Acute LPS sensitization and continuous infusion exacerbates hypoxic brain injury in a piglet model of neonatal encephalopathy

Kathryn A. Martinello1,2, Christopher Meehan1, Adnan Audic-Belltheau1, Ingrain Lingam1, Sara Ragab1, Mariya Hristova1, Callum J. Tann1,3, Donald Peebles1, Henri Hagberg5,6, Tim G. A. M. Wolfs7, Nigel Klein1, Ilias Tachtsidis8, Xavier Goly8, Boris W. Kramer9, Bobbi Fleiss5,10, Pierre Gressens5,10 & Nicola J. Robertson1,11

Co-existing infection/inflammation and birth asphyxia potentiates the risk of developing neonatal encephalopathy (NE) and adverse outcome. In a newborn piglet model we assessed the effect of E. coli lipopolysaccharide (LPS) infusion started 4 h prior to and continued for 48 h after hypoxia on brain cell death and systemic haematological changes compared to LPS and hypoxia alone. LPS sensitized hypoxia resulted in an increase in mortality and in brain cell death (TUNEL positive cells) throughout the whole brain, and in the internal capsule, periventricular white matter and sensorimotor cortex. LPS alone did not increase brain cell death at 48 h, despite evidence of neuroinflammation, including the greatest increases in microglial proliferation, reactive astrocytosis and cleavage of caspase-3. LPS exposure caused splenic hypoperty and platelet count suppression. The combination of LPS and hypoxia resulted in the highest and most sustained systemic white cell count increase. These findings highlight the significant contribution of acute inflammation sensitization prior to an asphyxial insult on NE illness severity.

Intrapartum-related neonatal encephalopathy (NE) is estimated to affect 1.16 million babies per year, causing 287,000 deaths and resulting in 50.2 million disability adjusted life years. NE is a clinical diagnosis encompassing a constellation of disorders neurological function in the newborn. Intrapartum-related NE refers to NE attributable to complications around the time of birth. The etiology of NE is multifactorial, as well as sentinel hypoxic-ischemic events, antenatal and placental pathology, genetic susceptibility and perinatal infection/inflammation contribute to brain injury and adverse outcomes.

Antenatal inflammation is an established independent risk factor for the development of life-long brain injury. Epidemiological and observational clinical studies have associated perinatal inflammation with NE incidence and outcome. Clinical factors linked with inflammation, including prolonged rupture of membranes and maternal fever, are associated with NE. Histological chorioamnionitis and funisitis are more commonly found in the placenta of term infants with NE compared with healthy term controls. Infection, inflammation, leading to raised pro-inflammatory cytokines at birth, is associated with higher risks of cerebral palsy (CP) and
Screening for Anaplastic Lymphoma Kinase (ALK) gene rearrangements in non-small cell lung cancer (NSCLC) in New Zealand

Author details

1) McKeage, Mark James
Professor, Co-Director and Medical Oncologist, m.mckeage@auckland.ac.nz, University of Auckland, Department of Pharmacology and Clinical Pharmacology and the Auckland Cancer Society Research Centre Auckland, NZ; Auckland City Hospital, Medical Oncology, Auckland, NZ.

2) Tin Tin, Sandar
Senior Research Fellow, stintin@auckland.ac.nz, University of Auckland, Section of Epidemiology and Biostatistics, Auckland, NZ

3) Khwaounjoo, Prashannata
Clinical Research Manager, p.khwaounjoo@auckland.ac.nz, University of Auckland, Department of Pharmacology and Clinical Pharmacology, Auckland, NZ

4) Sheath, Karen
Medical Laboratory Technologist, KSheath@adhb.govt.nz, Auckland City Hospital, LabPLUS, Auckland, NZ

5) Dixon-McIver, Amanda
Medical Laboratory Technologist, a.dixon-mciver@igenz.co.nz, IGENZ, Auckland, NZ

6) Ng, Daniel
Medical Laboratory Technologist, d.ng@igenz.co.nz, IGENZ, Auckland, NZ

7) Sullivan, Richard
Medical Oncologist and Deputy Chief Medical Officer, RSullivan@adhb.govt.nz, Auckland City Hospital, Medical Oncology, Auckland, NZ

8) Cameron, Laird
Medical Oncologist, LairdC@adhb.govt.nz, Auckland City Hospital, Medical Oncology, Auckland, NZ

9) Shepherd, Philip
Medical Laboratory Technologist, p.shepherd@auckland.ac.nz, University of Auckland, Auckland, NZ

10) Laking, George Robert

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Medical Oncologist, georgeL@adhb.govt.nz, Auckland City Hospital, Medical Oncology, Auckland, NZ

11) Kingston, Nicola
Anatomical Pathologist, NKingston@adhb.govt.nz, Auckland City Hospital, LabPLUS, Auckland, NZ

12) Strauss, Magreet
Anatomical Pathologist, MagreetS@adhb.govt.nz, Auckland City Hospital, LabPLUS, Auckland, NZ

13) Lewis, Christopher
Respiratory Physician, CLewis@adhb.govt.nz, Auckland City Hospital, Respiratory Services, Auckland, NZ

14) Elwood, Mark
Professor, mark.elwood@auckland.ac.nz, University of Auckland, Section of Epidemiology and Biostatistics, Auckland, NZ

15) Love, Donald R
Current position: Division Chief, dlove@sidra.org, Pathology Genetics, Sidra Medicine, Pathology Genetics, Doha, Qatar
Previous position: Director, DonaldL@adhb.govt.nz, Diagnostic Genetics, Auckland City Hospital, LabPLUS Auckland, NZ

Corresponding author

McKeage, Mark James
m.mckeage@auckland.ac.nz, Postal address Room 504-236A, Grafton Campus, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland NZ +6421859588

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Abstract
Background: Lung cancer is a major cause of death in New Zealand. In recent years, targeted therapies have improved outcomes.

Aim: To determine the uptake of ALK testing, and the prevalence, demographic profile and outcomes of ALK-positive NSCLC, in NZ, where no national ALK-testing guidelines or subsidized ALK tyrosine kinase inhibitor (TKI) therapies are available.

Methods: A population-based observational study reviewed databases to identify patients presenting with nonsquamous NSCLC over 6.5 years in northern NZ. We report the proportion tested for ALK gene rearrangements and the results. NSCLC samples tested by Fluorescence In Situ Hybridisation (FISH) were retested by Next Generation Sequencing (NGS) and ALK immunohistochemistry (IHC). A survival analysis compared ALK-positive patients treated or not treated with ALK TKI therapy.

Results: From a total of 3130 patients diagnosed with nonsquamous NSCLC, 407 (13%) were tested for ALK gene rearrangements, and patient selection was variable and inequitable. Among those tested, 34 (8.4%) had ALK-positive NSCLC. ALK-positive disease was more prevalent in younger versus older patients, nonsmokers versus smokers, and in Māori, Pacific or Asian ethnic groups than in NZ Europeans. FISH, IHC and NGS showed broad concordance for detecting ALK-positive disease under local testing conditions. Among patients with ALK-positive metastatic NSCLC, those treated with ALK TKIs survived markedly longer than those not treated with ALK TKIs (median overall survival 5.12 versus 0.55 years).

Conclusion: Lung cancer outcomes in NZ may be improved by providing national guidelines and funding policy for ALK testing and access to subsidized ALK TKI therapy.

Keywords: anaplastic lymphoma kinase, non-small cell lung cancer, ALK testing, tyrosine kinase inhibitor, overall survival
Vasopressin in the Amelioration of Social Functioning in Autism Spectrum Disorder

Mohamed A. Hendaus 1,2,3, *, Fatima A. Jomha 4 and Ahmed H. Alhammadi 1,2,3

1 Department of Pediatrics, Section of Academic General Pediatrics, Sidra Medicine, Doha 26999, Qatar
2 Department of Pediatrics, Section of Academic General Pediatrics, Hamad Medical Corporation, Doha 3050, Qatar
3 Department of Clinical Pediatrics, Weill-Cornell Medical College, Doha 26999, Qatar
4 School of Pharmacy, Lebanese International University, Khiara 146404, Lebanon

* Correspondence: Mhendaus@yahoo.com

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Abstract: Autism spectrum disorder (ASD) is a developmental disability described by diagnostic criteria that comprise deficits in social communication and the existence of repetitive, restricted patterns of behavior, interests, or activities that can last throughout life. Many preclinical studies show the importance of arginine vasopressin (AVP) physiology in social functioning in several mammalian species. Currently, there is a trend to investigate more specific pharmacological agents to improve social functioning in patients with ASD. Neurobiological systems that are crucial for social functioning are the most encouraging conceivable signaling pathways for ASD therapeutic discovery. The AVP signaling pathway is one of the most promising. The purpose of this commentary is to detail the evidence on the use of AVP as an agent that can improve social functioning. The pharmacologic aspects of the drug as well as its potential to ameliorate social functioning characteristics in human and animal studies are described in this manuscript. AVP, especially in its inhaled form, seems to be safe and beneficial in improving social functioning including in children with autism. Larger randomized studies are required to implement a long awaited safe and feasible treatment in people with a deficiency in social functioning.

Keywords: autism; functioning; social; vasopressin

1. Introduction

Autism spectrum disorder (ASD) is a developmental disability described by diagnostic criteria comprised of deficits in social communication and the existence of repetitive, restricted patterns of behavior, interests, or activities that can last throughout life [1]. According to the World Health Organization (WHO), the worldwide prevalence of ASD is 0.62% [2], but it is higher (1.68%) in some countries such as the United States [3]. ASD exists in all ethnic, racial, and socioeconomic groups, and it is four times more common among boys than girls [4]. Genetics might play a role in acquiring ASD. The literature indicates that the concurrence rate of ASD can range from 36 to 95% in identical twins and 0–31% in non-identical twins [5–8], and the recurrence rate can reach up to 10% [9,10]. The CDC (https://www.cdc.gov/ncbddd/autism/data.html#references) noted that if the child is born prematurely, with low birth weight, and those born to older parents are at a higher risk for having ASD [4].

ASD tends to occur more often in people who have certain developmental, psychiatric, neurologic, genetic, or chromosomal conditions [2]. Approximately 10% of children with autism also have tuberous sclerosis, Down syndrome (https://www.cdc.gov/ncbddd/birthdefects/downsyndrome.html), fragile X syndrome (https://www.cdc.gov/ncbddd/fxs/facts.html), or other genetic disorders [11–14].
Quality control failures exceeding the weekly limit (QC FEWL): a simple tool to improve assay error detection

Eric S. Kilpatrick MD, FRCPath, FRCP Edin

Division of Clinical Biochemistry, Sidra Medicine, Doha, Qatar
and Weill Cornell Medicine, Qatar

Running Title: QC FEWL to improve assay error detection

Correspondence to:
Professor Eric S. Kilpatrick
Division Chief, Clinical Biochemistry
Department of Pathology, 2nd Mezzanine Level
Sidra Medicine
PO BOX 26999 Doha, Qatar
t. +974-4003-3008
e-mail ekilpatrick@sidra.org

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Annals of Clinical Biochemistry
Abstract

Background
Even when a laboratory analyte testing process is in control, routine quality control (QC) testing will fail with a frequency that can be predicted by the number of QC levels used, the run frequency and the control rule employed. We explored whether simply counting the number of assay QC run failures during a running week, and then objectively determining if there was an excess, could complement daily QC processes in identifying an out-of-control assay.

Methods
Binomial statistics were used to determine the threshold number of QC run failures in any rolling week which would statistically exceed that expected for a particular test. Power function graphs were used to establish error detection (P_{ed}) and false rejection rates compared to popular control rules.

Results
Identifying QC failures exceeding the weekly limit (QC FEWL) is a more powerful means of detecting smaller systematic (bias) errors than traditional daily control rules (12s, 13s, or 1_{3s}/2_{2s}/R_{4s}) and markedly superior in detecting smaller random (imprecision) errors while maintaining false identification rates below 2%. Error detection rates also exceeded those using a within- and between-run Westgard multirule (1_{3s}/2_{2s}/4_{1s}/10_{6s}).

Conclusions
Daily review of tests shown to statistically exceed their rolling week limit of expected QC run failures is more powerful than traditional QC tools at identifying potential systematic and random test errors and so offers a supplement to daily QC practices that has no requirement for complex data extraction or manipulation.

Keywords:
Quality control; error detection; laboratory error, power function graph.
Asymptomatic Pharyngeal Carriage of *Kingella kingae* Among Young Children in Vancouver, British Columbia, Canada

Shazia Masud, MD, †Janet Greenman, MD, ‡§Kishore Mulpuri, MBBS, MHSc, ‧Mohammad R. Hasan, PhD, ††David M. Goldfarb, MD, ‡§Peter Tilley, MD, ‡§Vijay J. Gadkar, PhD, ‡§ and Ghada N. Al-Rawahi, MD ‡§

**Background:** *Kingella kingae* has emerged as a significant cause of osteoarticular infections in young children. Pharyngeal colonization is considered a prerequisite for invasive *K. kingae* infection. We conducted a prospective study to estimate the prevalence of pharyngeal carriage of *K. kingae* among healthy young children in Vancouver.

**Methods:** From March 2016 to May 2017, children between 6 and 48 months of age visiting British Columbia Children’s Hospital outpatient clinics for noninfectious causes were included in the study. Another set of participants was enrolled from a day-care center located at British Columbia Children’s Hospital. A single-throat swab was collected after obtaining consent from parent/guardian. The samples were stored at −70°C and tested using an in-house developed real-time polymerase chain reaction assay. Epidemiologic characteristics and risk factors for *K. kingae* colonization were collected via a study questionnaire.

**Results:** A total of 179 children were enrolled in the study, but only 174 samples were eligible for testing. Of the 174 samples, 5 had indeterminate results and the remaining 169 samples were negative by *K. kingae* polymerase chain reaction. The median age of participants was 23 months. About 36% of children were attending day care and had another sibling <5 years of age. Previous history of cold symptoms and antibiotic use was reported in 42% and 12%, respectively.

**Conclusions:** The results of our study showed no prevalence of asymptomatic pharyngeal carriage of *K. kingae* in young children in Vancouver. Additional multicenter studies may help to understand the differences in pharyngeal carriage rate among healthy children.

**Key Words:** pharyngeal carriage, *Kingella kingae*, osteoarticular infections

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**METHODS**

**Study Participants**

The study was conducted from March 2016 to May 2017. Children between 6 and 48 months of age, presenting at various outpatient clinics at BCCH with noninfection-related illness or “well child” visits, were enrolled in the study. Another set of participants (*n* = 23) was enrolled from a day-care center located at BCCH. Informed consent was obtained from parents/guardians following institutional research ethics approval.

**Data Collection**

A standardized study questionnaire was designed to obtain demographic information as well as information on exposure to risk factors associated with pharyngeal carriage of *K. kingae* such as antibiotic use, cold symptoms, number of people living in the same household and day-care attendance.

**Sample Collection**

Throat swabs were collected from the study participants using eNAT swabs (eNAT; specimen collection and preservation swab kit; COPAN Italia SpA, Brescia, Italy) and were stored at...
BASIC SCIENCE ARTICLE

Tissue damage in the heart after cardiac arrest induced by asphyxia and hemorrhage in newborn pigs

Birte Weber1, Marc Robin Mendler2, Ina Lackner1, Jochen Pressmar1, Melanie Haffner-Luntzer3, Severin Höfler1, Christian Karl Braun4, Helmut Hummler2,5, Stephan Schwarz5 and Miriam Kalbitz6

BACKGROUND: Asphyxia of newborns is a severe and frequent challenge of the peri- and postnatal period.

METHODS: Forty-four neonatal piglets underwent asphyxia and hemorrhage (AH), followed by resuscitation with blood or crystalloid transfusion. In this study, 15 piglets (blood n = 9, NaCl n = 6, mean age 31 h) were randomly chosen. Four hours after return of spontaneous circulation, heart tissue and blood were collected. Analyses of heart fatty acid binding protein (HABP), cardiac troponin I (TnI) levels, and activation of the complement system were performed. Histological staining for connexin 43 (Cx43) and complement C5a receptor 1 (C5aR1) was performed.

RESULTS: Following AH, systemic elevation of cardiac TnI and HABP revealed cardiac damage in both groups. Systemic activation of the complement system and the appearance of extracellular histones in plasma of the blood transfusion group were observed. The Cx43 was translocated from the intercalated discs to the cytosol after AH. Cardiac glycogen concentration was reduced in both groups. A significant reduction of C5aR1 in the left ventricle and a significant elevation of the heart injury score were investigated after blood transfusion.

CONCLUSION: AH leads to alteration of the heart, particularly in Cx43 and glycogen reserves, as well as local inflammation.

INTRODUCTION

Asphyxia is a severe challenge during the peri- and postnatal period, occurring in 2 of 1000 births.1 It is defined as a severe disturbance of the oxygen supply to the fetus1 with an intrapartum pH of <7.00 and a base deficit > -12 mmol/L.1 In particular, the cardiac consequences of asphyxia are crucial, because impairment of the heart is linked to prolonged organ hypoperfusion. Ventricular diastolic dysfunction was present in more than 50% of asphyxiated neonates.4 Furthermore, well-known cardiac consequences of asphyxia include tricuspid valve and mitral valve regurgitation, pulmonary hypertension, and transient myocardial ischemia.2 Human infants, who did not survive asphyxia, presented ventricular dilatation and hypertrophy, as well as papillary muscle necrosis.6

Systemic elevation of cardiac troponin (TnI) (>4.6 ng/mL) in newborns with perinatal asphyxia has been correlated with higher mortality.6 This is important because troponin is a classical marker of cardiomyocyte (CM) injury.7 Furthermore, preterm infants have a tenfold increase in baseline TnI levels compared to term newborns, which was associated with cardiac dysfunction in the preterm group.7 In neonatal respiratory distress syndrome and asphyxia, elevated troponin levels were correlated with myocardial dysfunction assessed by echocardiography.8 Experimentally, in newborn piglets after asphyxia, a reduction of cardiac myosin light chain 1 and an increase in nitrate levels in the heart has been described,9 which has been associated with cardiac dysfunction.10 Furthermore, alterations in the distribution and the amount of the gap junction protein connexin 43 (Cx43) and mitochondrial injury were observed after asphyxia in adult rats.11 Cx43 is the most important gap junction protein in the heart and is responsible for the electrical coupling. Cx43 is important for the myocytes to act as a functional syncytium and could be responsible for the development of arrhythmias.12 For this reason, alterations in the Cx43 might be of interest for cardiac function after asphyxia and hemorrhage (AH).

Furthermore, the complement system is well described as a mediator of CM dysfunction, particularly in the context of septic CMs, and should be considered in cardiac analysis after trauma, sepsis, and ischemic injury.11 14 The present study aims to clarify the role of systemic activation of the complement system based on complement hemolysis CH50 measurements and systemic C5a levels, and we further determined local complement-induced changes on the heart.

The present study aims to investigate the consequences of neonatal AH in newborn pigs on cardiac damage patterns and on local and systemic inflammation. In accordance with the international guidelines of the International Liaison Committee on Resuscitation (ILCOR), asphyxia in neonates was treated with ventilation, cardiopulmonary resuscitation (CPR), epinephrine, and either with red blood cell (RBC) transfusion or saline (NaCl). Successful resuscitation was achieved in all animals independent of group assignment and without differences in the time to return...
A process-environment model for mentoring undergraduate research students

Jason E. Hickeya,⁎, Mohamoud Adamb, Icra Elwadiab, Shaheen Nasserc, Anne E. Toppingd,e

a University of Calgary in Qatar, PO Box 23133, Doha, Qatar
b Sidra Medical and Research Center, PO Box 26699, Doha, Qatar
c Hamad General Hospital, PO Box 3050, Doha, Qatar
d University of Birmingham, Birmingham B15 2TT, UK
e University Hospitals Birmingham NHS Foundation Trust, Mindelsohn Way, Edgbaston, Birmingham B15 2TH, UK

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ABSTRACT

Undergraduate nursing student engagement in research remains much contested. The debate centers on whether undergraduate education is preparation for application of research findings to practice versus early exposure and engagement to discovery of new knowledge focused research as is done in graduate education. We take the position that involvement in research is beneficial but mentorship is required if the endeavor is to be meaningful. In the absence of a model to guide effective mentorship for undergraduate co-researchers we synthesized the available undergraduate mentorship literature and relevant pedagogy to develop a mentorship model for use by nurse educators who undertake research with nursing students. This was applied and refined through active engagement in, and reflection on, the execution of a research project exploring peoples’ experiences of mental illness. Synthesis of the evidence and reflections led to the development of a process-environment mentorship model. This model provides an evidence- and experientially-based framework for mentoring undergraduate student co-researchers.

Introduction

Nearly 20 years ago, the Boyer Commission on Educating Undergraduates in the Research University (1998) argued that undergraduate students were frequently isolated from the research activity that is highly valued by higher education institutions. The commission argued that research-intensive universities should “make the baccalaureate experience an inseparable part of the whole” (p.7). That position is somewhat in tension with the trend in healthcare professional undergraduate education, especially nursing, away from individual student engagement in empirical research. Increasingly, nursing students are encouraged to undertake secondary data analysis, or literature-based projects, as the basis for individual summative assessment. The reasons for this are many, but not least is the safety of participants in human subject research (Richman & Alexander, 2006) for what could be deemed futile research (Evans, 1997).

Nevertheless, the arguments predicated in the Boyer blueprint that students should expect, and have opportunities to work with, “talented senior researchers” (Boyer Commission on Educating Undergraduates in the Research University, 1998, p. 12) are powerful. The salience of research exposure has become embedded in many national policies that recognize the benefits of research capability and capacity building (see for example, National Institutes of Health, 2017). Likewise, the strategic visioning of many universities across the globe, particularly those that promote themselves as research focused, talk of the research-enriched student experience (Hordern, 2013). Although nursing research has matured and some higher education institutions are at the forefront of nursing scholarship, not all nursing students are similarly exposed.

In Qatar, where work for this project was undertaken, the Qatar National Research Fund has prioritized undergraduate exposure to research by creating a funding stream that requires the involvement of undergraduates as co-researchers. While preparing a funding application for this program on people’s experiences of mental illness in Qatar, we were unable to identify an adequate model to guide our own mentorship efforts. Thus, we undertook a concurrent project to develop a mentorship model that could enhance the research learning environment. This article reports the development of a process-environment mentorship model that resulted from our synthesis of the
BASIC SCIENCE ARTICLE

Short-term effects of early initiation of magnesium infusion combined with cooling after hypoxia–ischemia in term piglets

Ingran Lingam1, Chris Meehan1, Adnan Avdić-Beltheus1, Kathryn Martinello2, Mariya Hristova1, Pardis Kaynezhad2, Cornelius Bauer2, Illias Tachtsidis3, Xavier Golay4,5 and Nicola J. Robertson1,4

BACKGROUND: Neuroprotection from therapeutic hypothermia (HT) is incomplete, therefore additional strategies are necessary to improve long-term outcomes. We assessed the neuroprotective efficacy of magnesium sulfate (MgSO4) bolus and infusion over 48 h plus HT in a piglet model of term neonatal encephalopathy (NE).

METHODS: Fifteen newborn piglets were randomized following hypoxia–ischemia (HI) to: (i) MgSO4 180 mg/kg bolus and 8 mg/kg/h infusion with HT (Mg+HT) or (ii) HT and saline 0.5 ml/h (HT). Treatments were initiated 1 h post-HI HT administered for 12 h (33.5 °C). HI was performed by transient carotid occlusion and inhalation of 6% O2 for 20–25 min. Primary outcomes included aEEG, magnetic resonance spectroscopy (MRS) at 24, and 48 h, and immunohistochemistry.

RESULTS: MgSO4 bolus and infusion was well tolerated (no hypotension) and doubled serum magnesium (0.72 vs 1.52 mmol/L) with modest (16%) rise in CSF. In Mg+HT compared to HT, there was overall reduced cell death (p = 0.01) and increased oligodendrocytes (p = 0.002). No improvement was seen on aEEG recovery (p = 0.084) or MRS (LCO/NAA; PCr/PI; NTP/epc) (p > 0.05) at 48 h.

CONCLUSION:Doubling serum magnesium with HT was safe; however, the small incremental benefit of Mg+HT compared to HT is unlikely to translate into substantive long-term improvement. Such an incremental effect might justify further study of MgSO4 in combination with multiple therapies.

INTRODUCTION

Neonatal encephalopathy (NE) represents a significant global health burden and is the second leading cause of mortality in infants aged <28 days.1 Therapeutic hypothermia (HT) is currently the only routine neuroprotective strategy shown to be effective in intensive care settings; however, mortality and morbidity remain high at almost 50% despite treatment.2 Optimizing HT by cooling to lower temperatures (32–33 °C) and for longer duration (120 h) failed to improve neurological outcomes3 and attention is now directed toward adjunct pharmacological agents.

Magnesium sulfate (MgSO4) is a cheap and widely available drug with a well-documented side effect profile. It has recently been shown to reduce the incidence of cerebral palsy in preterm infants when administered antenatally;4 MgSO4 may have potential as an adjunct treatment with HT in term NE. Experimental data suggest increasing serum magnesium to twice baseline values is neuroprotective5; however, studies demonstrating efficacy have been confounded by co-existing accidental hypothermia6 and those controlling core body temperature failed to demonstrate benefit.7 Clinical studies of MgSO4 in term infants with NE mostly predate the implementation of hypothermia and were limited by small numbers, variable dosing regimens, and inconsistent outcome measures.8 These trials implemented a daily bolus regimen of MgSO4, resulting in significant peaks and troughs in serum magnesium, limiting exposure to supra-systemic magnesium concentrations. Such peaks and troughs in the serum magnesium have been associated with hypotension in a large animal model of NE.9

MgSO4 provides neuroprotection through the blockade of the glutamatergic N-methyl-D-aspartate (NMDA) receptors at postsynaptic neuronal membranes, preventing excessive calcium entry that would otherwise activate several injurious cellular pathways, including catabolic enzyme induction and increased production of reactive oxygen species. Experimental data suggest that MgSO4 may also be anti-inflammatory: MgSO4 modified the inflammatory cytokine response in pregnant rodents following exposure to a bacterial endotoxin, lipopolysaccharide (LPS).10 Both MgSO4 and HT are thought to reduce excitotoxicity and modulate inflammation,11 and therefore it is plausible that these therapies may work synergistically. Indeed, combining MgSO4 with HT in rodent models of NE has been shown to reduce infarct size compared to cooling alone.12

We aimed to assess the neuroprotective benefit of a MgSO4 bolus and constant infusion in combination with HT (Mg+HT) compared to hypothermia (HT) in a clinically translational piglet model of NE. Primary outcome measures included amplitude-integrated electroencephalogram (aEEG) recovery after

1Neonatology, Institute for Women’s Health, University College London, London, UK; 2Department of Medical Physics and Biomedical Engineering, University College London, London, UK; 3Institute of Neurology, University College London, London, UK and 4Neonatology, Sidra Medicine, Al Luqta Street, Education City, North Campus, Qatar FoundationPO Box 26999, Doha, Qatar
Correspondence: Ingran Lingam (ingranlingam@ucl.ac.uk)
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Assessment of knowledge about childhood autism spectrum disorder among healthcare workers in Makkah- Saudi Arabia

Aalia Akhtar Hayat1, Areej Habib Meny2, Nabila Salahuddin3, Faisal M. Alnemary4, Kumar Ricky Ahuja5, Muhammad Waqar Azeem6

ABSTRACT

Objective: To measure the knowledge of healthcare professionals about increasingly prevalent Autism Spectrum Disorder (ASD) along with perceptions around its management and prognosis and comparison across various specialties.

Methods: This Cross sectional survey based comparative analysis took place at Maternity and Children Hospital and King Faisal Hospital Makkah from December 2017 to May 2018. The validated self-administered “Knowledge about childhood autism among health workers” questionnaire was used along with additional questions regarding perceptions about ASD. The mean and mean percent scores were calculated. Chi squared test and ANOVA were applied to find the association between quantitative and qualitative variables respectively.

Results: Out of 162 participants, 153 returned the questionnaire and 147 were included in final analysis. Physicians constituted 81.6% (120) of participants. The mean score for participants was 9.80(±0.32) where non-physicians yielded higher mean score (11.2±4.41) as compared to physicians (9.6±3.28) (p=0.113). Psychiatrists had highest score of 16/19 while general physicians had lowest (6/19). Participants with more years of experience had higher mean scores (p-value = 0.01). About 72.10% (106) of participants opted for medication as a treatment option. Nearly 38.1% (56) of participants were skeptical about improvement of ASD with early interventions.

Conclusion: There is a lack of knowledge about ASD amongst healthcare professionals in Saudi Arabia. Experienced professionals working with ASD children can be utilized to deliver targeted trainings nationwide.

KEYWORDS: ASD, ASD symptoms, Autism, Autism spectrum disorder, Healthcare professionals, Knowledge about autism, Neurodevelopmental disorders.

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INTRODUCTION

One in every 68 children are estimated to have autism spectrum disorder (ASD), making it one of the most common neurodevelopmental disorders.1 ASD is marked by deficiencies in communication, behaviors and social interaction skills that may have negative impact on people with autism and their caregivers.2 In Arab Gulf countries, prevalence ranging between 1.4-29/10,000 has been reported.3
Hypertension in Childhood Nephrotic Syndrome

Ibrahim F. Shatat, Lauren J. Becton and Robert P. Woroniecki

Arterial hypertension (HTN) is commonly encountered by clinicians treating children with steroid sensitive (SSNS) and steroid resistant nephrotic syndrome (SRNS). Although the prevalence of HTN in SSNS is less documented than in SRNS, recent studies reported high prevalence in both. Studies have estimated the prevalence of HTN in different patient populations with NS to range from 8 to 59.1%. Ambulatory HTN, abnormalities in BP circadian rhythm, and measures of BP variability are prevalent in patients with NS. Multiple mechanisms and co-morbidities contribute to the pathophysiology of HTN in children with NS. Some contributing factors are known to cause acute and episodic elevations in blood pressure such as fluid shifts, sodium retention, and medication side effects (steroids, CNIs). Others are associated with chronic and more sustained HTN such as renal fibrosis, decreased GFR, and progression of chronic kidney disease. Children with NS are more likely to suffer from other cardiovascular disease risk factors, such as obesity, increased measures of arterial stiffness [increased carotid intima-media thickness (cIMT)], endothelial dysfunction, increased pulse wave velocity (PWV), impaired glucose metabolism, dyslipidemia, left ventricular hypertrophy (LVH), left ventricular dysfunction, and atherosclerosis. Those risk factors have been associated with premature death in adults. In this review on HTN in patients with NS, we will discuss the epidemiology and pathophysiology of hypertension in patients with NS, as well as management aspects of HTN in children with NS.

Keywords: nephrotic syndrome, hypertension, pediatric, ambulatory blood pressure, blood pressure variability

INTRODUCTION

Nephrotic syndrome (NS) is one of the most common childhood kidney diseases worldwide, with a reported incidence of 2–16.9/100,000 children (1, 2). NS encompasses several primary and secondary renal diseases that have common physical changes in glomerular filtration barrier, which result in a massive leak of serum proteins into the urine. The great majority of cases are steroid responsive, with only <20% of children with NS being steroid resistant (3). Minimal change disease (MCD) is the most common glomerular pathology. Although MCD carries an excellent prognosis with low risk of progression to ESRD, its relapsing nature necessitates that children receive frequent courses of steroid therapy and other steroid-sparing medications, many of which are known to affect blood pressure (BP). NS was once thought to be associated with normal or low blood pressure, as described by Volhard’s comment, “One of
A SLC16A1 Mutation in an Infant With Ketoacidosis and Neuroimaging Assessment: Expanding the Clinical Spectrum of MCT1 Deficiency

Sara Al-Khawaga 1,2,3, Jehan AlRayahi 1,4, Faiyaz Khan 1, Saras Saraswathi 2, Reem Hasnah 2, Basma Haris 2, Idris Mohammed 1,2, Essam M. Abdelalim 1,3 and Khalid Hussain 2*

1 College of Health and Life Sciences, Hamad Bin Khalifa University, Qatar Foundation, Education City, Doha, Qatar; 2 Division of Endocrinology, Department of Pediatric Medicine, Sidra Medicine, Doha, Qatar; 3 Diabetes Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar; 4 Division of Neuroradiology, Diagnostic Imaging, Sidra Medicine, Doha, Qatar

The solute carrier family 16 member 1 (SLC16A1) gene encodes for monocarboxylate transporter 1 (MCT1) that mediates the movement of monocarboxylates, such as lactate and pyruvate across cell membranes. Inactivating recessive homozygous or heterozygous mutations in the SLC16A1 gene were described in patients with recurrent ketoacidosis and hypoglycemia, a potentially lethal condition. In the brain where MCT1 is highly localized around axons and oligodendrocytes, glucose is the most crucial energy substrate while lactate is an alternative substrate. MCT1 mutation or reduced expression leads to neuronal loss due to axonal degeneration in an animal model. Herein, we describe a 28 months old female patient who presented with the first hypoglycemic attack associated with ketoacidosis starting at the age of 3 days old. Whole exome sequencing (WES) performed at 6 months of age revealed a c.218delG mutation in exon 3 in the SLC16A1 gene. The variant is expected to result in loss of normal MCT1 function. Our patient is amongst the youngest presenting with MCT1 deficiency. A detailed neuroimaging assessment performed at 18 months of age revealed a complex white and gray matter disease, with heterotopia. The threshold of blood glucose to circumvent neurological sequelae cannot be set because it is patient-specific, nevertheless, neurodevelopmental follow up is recommended in this patient. Further functional studies will be required to understand the role of the MCT1 in key tissues such as the central nervous system (CNS), liver, muscle and ketone body metabolism. Our case suggests possible neurological sequelae that could be associated with MCT1 deficiency, an observation that could facilitate the initiation of appropriate neurodevelopmental follow up in such patients.

Keywords: SLC16A1, MCT1, ketoacidosis, hypoglycemia, heterotopia, white matter disease, gray matter disease
Iatrogenic antibody deficiency from B-cell targeted therapies in autoimmune rheumatic diseases

Sonali Wijetilleka,1 David Jayne,2 Chetan Mukhtyar,3 Mohammed Yousuf Karim4

ABSTRACT

B-cell targeted therapies (BCTT) are now widely used in autoimmune rheumatic diseases, including SLE, antineutrophil cytoplasmic antibody-associated vasculitis and rheumatoid arthritis. Early studies suggested that rituximab did not influence serum immunoglobulins. However, subsequently, with increased patient numbers, longer follow-up duration and many patients having received multiple BCTT courses, multiple subsequent studies have identified hypogammaglobulinaemia as a potential side effect. Patients developing hypogammaglobulinaemia appear to fit into two principal categories: the majority who develop transient, often mild reduction in immunoglobulins without increased infection and a much smaller but clinically significant group with a more sustained antibody deficiency, who display increased risk of infection. Monitoring immunoglobulin levels represents an opportunity for the early detection of hypogammaglobulinaemia, and the prevention of avoidable morbidity. In the two major studies, approximately 4%–5% of BCTT-treated patients required immunoglobulin replacement due to recurrent infections in the context of hypogammaglobulinaemia. Despite this, monitoring of immunoglobulins is suboptimal, and there remains a lack of awareness of hypogammaglobulinaemia as an important side effect.

Over the last 15 years, B-cell targeted therapies (BCTT) have been widely used for treatment of autoimmune rheumatic diseases (AIRD), particularly in severe/resistant cases of SLE, and in antineutrophil cytoplasmic antibody-associated vasculitis (AAV). These medications are also employed in rheumatoid arthritis (RA) and multiple sclerosis.1

Initial studies suggested that rituximab, the earliest and still most widely reported BCTT, did not influence serum immunoglobulins. This was based on early studies of limited doses and duration, and the premise that plasma cells did not express surface CD20, the molecular target of rituximab. It was also proposed that protective antimicrobial antibodies were not significantly affected, in contrast to reduction in pathogenic autoantibodies; based on findings that B-cell clones producing antinucleosome and antidouble-stranded DNA antibodies, had a relatively rapid turnover compared with B-cell clones with other specificities.2

Over time, large numbers of patients have been treated, with longer follow-up duration, and many patients have received multiple BCTT courses. In this context, multiple subsequent studies have now identified hypogammaglobulinaemia as a potential side effect. The patients developing hypogammaglobulinaemia appear to fall into two main categories: the majority who develop transient, often mild reduction in immunoglobulins without increased infection and a much smaller but clinically significant group with a more sustained antibody deficiency, who display increased risk of infection.3 This may result from prolonged depletion of plasma cell precursors, with consequent effects on replenishment of mature plasma cells.

Monitoring immunoglobulin levels represents an opportunity for the early detection of hypogammaglobulinaemia, and can be performed using cheap, simple and widely available assays. The American Academy of Allergy, Asthma & Immunology, British Society for Rheumatology (BSR) and European League against Rheumatism (EULAR) advocate testing immunoglobulins at baseline, and BSR and EULAR at varying times after commencement of BCTT in AAV and RA. Although the 2018 BSR SLE guidelines advocate baseline and follow-up testing of immunoglobulins patients treated with rituximab (also with other drugs such as mycophenolate and cyclophosphamide), monitoring is not mentioned in the 2019 EULAR SLE recommendations.4

There still appears to be little awareness of this important side effect, with a lack of widespread adoption of immunoglobulin monitoring in patients treated with BCTT. This represents a lost opportunity in early prevention of avoidable morbidity. In a large Boston study, 3824/4479 (85%) of rituximab-treated
Transthoracic Echocardiography of the Neonatal Laboratory Piglet

Stephan Schwarz1†, Miriam Kalbitz2†, Helmut D. Hummler1,3 and Marc R. Mendler1*

1 Division of Neonatology and Pediatric Critical Care, Department of Pediatrics and Adolescent Medicine, Ulm University, Ulm, Germany, 2 Department of Traumatology, Hand-, Plastic-, and Reconstructive Surgery, Center of Surgery, Ulm University, Ulm, Germany, 3 Division of Neonatology, Department of Pediatrics, Sidra Medicine, Doha, Qatar

Background: Newborn piglets are commonly used in biomedical research. However, cardiovascular imaging of this species is quite challenging. For point of care diagnostics of heart function transthoracic echocardiography may be used, which appears to differ comparing newborn piglets with adult pigs. To date, there are few data or studies on the feasibility and quality of measurement of functional echocardiographic parameters in very small neonatal piglets.

Objectives: To study the feasibility of transthoracic echocardiography in very small newborn piglets in supine position.

Methods: In 44 anesthetized and intubated newborn piglets, positioned in supine position [age 32 h (12–44 h), weight 1,220 g (1,060–1,495 g), median (IQR)] transthoracic echocardiography was performed using a point of care ultrasound device (M-Turbo©, FujiFilm SonoSite BV, Amsterdam, Netherlands), and a standard ultrasound transducer.

Results: Using 2D- and M-mode-imaging left- and right-sided heart structures were accessible to transthoracic echocardiography in neonatal piglets. Diameters of the interventricular septum, the left ventricle, and the posterior wall were measured and ejection fraction and shortening fraction was calculated. Both left and right ventricular outflow tract could be imaged, and ventricular filling and systolic function could be evaluated. Furthermore, we were able to assess shunts of fetal circulation, such as patent ductus arteriosus, structure of the heart valves and congenital heart defects including ventricular septal defect.

Conclusions: In summary, transthoracic echocardiography is feasible for assessment of cardiovascular function even in very small newborn laboratory piglets in supine position.

Keywords: neonatal transthoracic echocardiography, piglets, hemodynamic monitoring, ventricular function, swine

INTRODUCTION

Swine is one of the larger animal species commonly used in biomedical research. Many of their anatomical and physiological features are comparable to humans (1). Therefore, assessment of cardiac function is useful for many research questions. Invasive continuous monitoring of pressures is commonly used. Catheters can easily insert through the femoral vessels to measure arterial blood pressure or central venous pressure (2). The so-called Millar catheter is available in different versions and is being used for different applications. For experimental research different sizes allow its use in various animal species, from mice (3) to larger animals (4). Various types support measurement of physiological pressures, such as airway or cardiovascular pressures, such as left
Sarcopenia, Cerebral Palsy, and Botulinum Toxin Type A

Iqbal Multani, HSc, MD
Jamil Manji, MSc, MD
Min Jia Tang, MBBS
Walter Herzog, PhD
Jason I. Howard, BEng, BMedSci, MD, FRCSC
H. Kerr Graham, MD, FRACS

Investigation performed at Royal Children’s Hospital, Parkville, Victoria, Australia

Abstract

» Sarcopenia is common in both the elderly and children with cerebral palsy.
» Children with cerebral palsy have muscles that are much smaller than muscles in typically developing peers.
» Injections of botulinum toxin type A (BoNT-A) result in acute muscle atrophy in animal models and in human subjects.
» It is not known when or if muscles recover fully after injection of BoNT-A.
» These findings have implications for management protocols.

In 2016, sarcopenia was recognized as a disease entity in the International Classification of Diseases, 10th Edition, Clinical Modification (ICD-10-CM)1. The European consensus on the definition of sarcopenia, published in 2010, describes sarcopenia as “a loss of function (either walking speed or grip strength) associated with a loss of muscle mass.”1-3 Deren et al. used computed tomography (CT) to measure the cross-sectional area of muscle in patients who were >60 years old who presented with a closed fracture of the acetabulum4. They found that sarcopenia was common in elderly patients and was associated with lower-energy fractures and a higher risk of 1-year mortality5. Sarcopenia also has been reported to contribute to the inability of older patients to maintain weight-bearing restrictions following a hip fracture6. Sarcopenia and osteoporosis may develop insidiously and simultaneously6. Some of the factors that predispose to sarcopenia in the elderly, including malnutrition and type-2 diabetes, are potentially modifiable6,7.

In children with cerebral palsy, muscle weakness is the predominant negative feature of upper motor neuron (UMN) syndrome and is a substantial determinant of gross motor function. It has been suggested that the negative features of UMN syndrome (weakness, loss of selective motor control, and impairments of balance and sensation) are stronger determinants of a child’s ambulatory potential than the more obvious positive features (spasticity, hypertonia, and cocontraction). The positive and negative features of UMN syndrome can all be considered pathologic and have been discussed in detail previously8. In an attempt to delay the need for surgery, intramuscular injections of botulinum toxin type A (BoNT-A) have become popular as a focal treatment for spasticity in children with cerebral palsy, with reportedly few side effects8. Recent animal studies have shown that the use of BoNT-A may...
Prognostic significance of age in 5631 patients with Wilms tumour prospectively registered in International Society of Paediatric Oncology (SIOP) 93-01 and 2001


1 Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands, 2 Department of Biometrics, Netherlands Cancer Institute, Amsterdam, The Netherlands, 3 Department of Paediatric Surgery, Marcinik Hospital, Wroclaw, Poland, 4 Department of Paediatric Traumatology and Emergency Medicine, Medical University, Wroclaw, Poland, 5 Department of Pathology, Sidra Medicine, Doha, Qatar, 6 Department of Radiotherapy, Academic Medical Center, Amsterdam, The Netherlands, 7 Paediatric Haematology-Oncology Program, Instituto Nacional de Cancer (INCA), Rio de Janeiro, Brazil, 8 Department of Paediatric Oncology, Hospital Universitario Virgen del Rocio, Seville, Spain, 9 Department of Paediatric Oncology, Institut d’Hematologie et d’Oncologie Pédiatrique, Centre Léon Bérard, Lyon, France, 10 UCL Great Ormond Street Institute of Child Health, University College London, London, United Kingdom, 11 Department of Paediatric Oncology & Haematology, Saarland University, Homburg, Germany

* j.hol@prinsesmaximacentrum.nl

Abstract

Background

To enhance risk stratification for Wilms tumour (WT) in a pre-operative chemotherapy setting, we explored the prognostic significance and optimal age cutoffs in patients treated according to International Society of Paediatric Oncology Renal Tumour Study Group (SIOP-RTSG) protocols.

Methods

Patients (6 months-18 years) with unilateral WT were selected from prospective SIOP 93–01 and 2001 studies (1993–2016). Martingale residual analysis was used to explore optimal age cutoffs. Outcome according to age was analyzed by uni- and multivariable analysis, adjusted for sex, biopsy(yes/no), stage, histology and tumour volume at surgery.

Results

5631 patients were included; median age was 3.4 years (IQR: 2–5.1). Estimated 5-year event-free survival (EFS) and overall survival (OS) were 85% (95% CI 83.5–85.5) and 93% (95% CI 92.0–93.4). Martingale residual plots detected no optimal age cutoffs. Multivariable analysis showed lower EFS with increasing age (linear trend P < 0.001). Using previously described age categories, EFS was lower for patients aged 2–4 (HR 1.34, P = 0.02), 4–18 (HR 1.83, P < 0.0001) and 10–18 years (HR 1.74, P = 0.01) as compared to patients aged 6
Radiologic Image-Guided Tube Stoma Insertion in Neonatal Short Bowel Syndrome: First Case Report in the Literature

Mohammed Elifranji, MD, FEBPS,1 Ashley Robinson, MB ChB, FRCPC,2 Saleem Mammo, MBBS, MCh,1 Abdalla Zarroug, MD, FACS,1 and Basem A. Khalil, FRCS, PhD1

Abstract

Background: The management of neonatal short bowel syndrome can be challenging, and it is critical that these babies are managed in a multidisciplinary team setting with specialists who are experienced in the complex management of these children. One of the surgical strategies, initially published by the Bianchi team in Manchester, UK, is controlled tissue expansion program (CTE) which is done via the insertion of catheters into the proximal and distal bowel in the form of tube stomas. The clamping of the proximal tube allows for an increase in length and circumferential diameter of the proximal bowel for a period of time, whilst the distal tube stoma allows for easy refeeding of proximal bowel contents into the distal bowel.

Method: CTE is associated with the risk of dislodgement and exposing patients to further surgical procedures with the risk of losing more bowel length. This article describes a new method in the management of such a complication through a less invasive approach of an image-guided procedure by interventional radiologists.

Conclusion: Radiologically guided tube stoma reinsertion in a child with ultrashort bowel syndrome is a promising technique and should be considered in a CTE program in the management of short bowel syndrome.

Keywords: short bowel, bowel expansion, tube stoma, minimal invasive

Introduction

Short bowel syndrome (SBS) can be defined as a multisystem disorder caused by malabsorption of nutrients due to inadequate bowel length. It is a common cause of intestinal failure especially in the neonatal period. The significant reduction in the functional gut mass below a critical threshold causes disturbances in growth, hydration, and/or electrolyte balance.1,3

It was recorded in 0.7% (89/12,316) of very low birth weight infants born during the period 2002–2005 at the National Institute of Child Health and Development (NICHD) neonatal research network centers. Its frequency increased in an inverse relationship with birth weight.3 Necrotizing enterocolitis is the most common cause of SBS in neonates followed by gastrochisis, intestinal atresia, and intestinal malrotation/volvulus.3

The management of SBS patients is complex and needs a multidisciplinary approach. Advances in medical management and liver salvageable parenteral nutrition (PN) have significantly improved the outcome of these patients.1 Surgical techniques, which include bowel expansion, different types of bowel lengthening, and restoration of bowel continuity, have been integrated in the medical management of these children. Such an integrated system of management has produced improved results in recent years in highly specialized and experienced centers.1,5

The controlled tissue expansion (CTE) program for children with severe SBS was initially described by Bianchi, and a series was reported by the Manchester team in the United Kingdom in 2011.5 The program aims to increase the length and circumferential diameter of the bowel for a period of time. This makes a new and greater surface area for absorption and more tissue for lengthening and tailoring.

Tube stomas are created surgically by inserting catheters into the proximal and distal bowel in a way similar to the standard surgical formation of gastrostomies. The catheters are brought out through the skin through separate stab incisions in the anterior abdominal wall. CTE is done through clamping the proximal tube stoma in a graded manner with

1Division of Paediatric and Thoracic Surgery, Sidra Medicine, Doha, Qatar.
2Division of Paediatric Interventional Radiology, Sidra Medicine, Doha, Qatar.
Hot topics in interventional cardiology: Proceedings from the Society for Cardiovascular Angiography and Interventions (SCAI) 2019 Think Tank

Srihari S. Naidu MD, FSCAI | Matthew J. Daniels MD | Sammy Elmirah MD, MPH, FSCAI | Santiago Garcia MD, FSCAI
Andrew J. Klein MD, FSCAI | Dmitriy N. Feldman MD, FSCAI | Frank F. Ing MD, FSCAI | Clifford J. Kavinsky MD, MScA
Chandan Devireddy MD, FSCAI | Ehtisham Mahmud MD, FSCAI | Cindy L. Grines MD, MScA | Timothy D. Henry MD, MScA
Peter L. Duffy MD, MMM, FSCAI | Zahid C. Amin MD, MScA | Herbert D. Aronow MD, FSCAI | Subhash Banerjee MD FSCAI
Emmanouil S. Brilakis MD, PhD, FSCAI | Howard C. Herrmann MD, MScA | Ziyad M. Hijazi MD, MScA | Farouc A. Jaffer MD, FSCAI
Faisal Latif MD, FSCAI | John C. Messenger MD, FSCAI | Sahil A. Parikh MD, FSCAI | Marie-France Poulin MD, FACC
John P. Reilly MD, FSCAI | Kenneth Rosenfield MD, MScA | Molly Szerlip MD, FSCAI | Robert N. Vincent MD, MScA
David A. Cox MD, MScA | And the members of the SCAI 2019 Think Tank Consortium: | David Baker | Narinder Bhalla MD, FSCAI | Rosanne Bowen
Callie Camp | Devi Govender MD | Kurt Haggstrom | Nick Hargus
Denise Hite | Joie Meikle | Beth Mylor | Valerie Pierce | Brett Prince
Jeff Roach | Jason Rudy | Belinda Schludi | Jason Struck | Andrew Tochterman
Mercy Tolve | David M. William | Susan Yowe

1Westchester Medical Center and New York Medical College, Valhalla, New York
2John Radcliffe University of Oxford Hospitals NHS Trust, Oxford, UK
3Massachusetts General Hospital, Boston, Massachusetts
4Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis, Minnesota
5Piedmont Heart Institute, Atlanta, Georgia
6New York Presbyterian Hospital/Cornell, New York, New York
7UC Davis Medical Center, Los Angeles, California
8Rush University Medical Center, Chicago, Illinois
9Emory University, Atlanta, Georgia
INTRODUCTION

The Society for Cardiovascular Angiography and Interventions (SCAI) Think Tank is a collaborative venture held annually, bringing together interventional cardiologists, administrative partners, and select members of the cardiovascular industry community. During the SCAI 2019 Scientific Sessions, relevant topics in interventional cardiology were identified with the goals of defining the state of the field, current challenges, and future directions. Topics were determined by nomination, and solidified through a voting process ultimately vetted by SCAI leadership and the industry relations committee. The 2019 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 (ELM) program. This document presents the proceedings to the wider cardiovascular community in order to enhance participation in this discussion, and create additional dialogue to aid SCAI in developing specific action items in the future.

CORONARY

How should maintenance of skill/competency programming for less frequently used, but critical technologies (atherectomy, mechanical support, PFO closure, etc.) be developed? Should SCAI play a larger role in developing standards and confirming these requirements within the community of providers and practice settings? What would be the ideal role for device manufacturers? Who are other potential stakeholders to consider?

The practice of interventional cardiology has been transformed in the last 20 years.1–5 Introduction and refinement of new procedural techniques and medical devices have resulted in significant reduction in morbidity and mortality for patients with cardiovascular disease.6 The complexity of procedures performed by interventional cardiologists in 2019 requires specific manual and cognitive skills as well as
familiarity with multiple devices. The group discussed how to balance access to these therapeutic devices while ensuring optimal patient care (i.e., rational dispersion of technology). The discussion centered around three less frequently used but essential novel technologies in the cardiac catheterization laboratory, which might serve as examples to be utilized more broadly. These included coronary atherectomy, mechanical circulatory support (MCS), and patent foramen ovale (PFO) closure. The committee also discussed how to ensure optimal training in complex percutaneous coronary interventions (PCI) procedures such as left main stenting, coronary bifurcations, intracoronary imaging with intravascular ultrasound (IVUS) and optical coherence tomography (OCT), and chronic total occlusions (CTOs).

The primary challenge when considering the optimal roll out of novel procedures and/or medical devices intended for niche applications, as opposed to high volume procedures, is that (a) there is a clinical need for widespread access to these technologies, yet (b) given their smaller total procedural volume, it is challenging to maintain a high level of operator competency and to measure uniform quality metrics.

Core competency training in procedures fundamental to the practice of interventional cardiology is required and determined by the Accreditation Council for Graduate Medical Education (ACGME). However, newer technologies and procedures are rapidly introduced in the field and often at a pace much faster than the evolution of the competency guidelines. This is especially applicable to the less frequently used technologies and procedures in the catheterization laboratory but nonetheless have a critical role such as the use of lesion modification tools, chronic total occlusion PCI, and large bore peripheral access, among others. Access to these procedures must be available to all patients within a certain geography, but perhaps concentrated in centers or individuals who have received adequate training and are able to maintain their expertise. The discussion also reviewed the benefits and hazards of designated centers of excellence, including potential misuse by hospitals to drive business. It was also acknowledged that existing training standards for these procedures and techniques are heterogeneous and incongruent (Table 1).

Consensus therefore emerged around several overriding themes relevant to the specific issues outlined above:

1. SCAI, as the professional organization for interventional cardiology, has the central role in developing standards for core competencies and the use of novel technology in partnership with other stakeholders.
2. The group recognized that pathways for achieving mastery of a particular device or procedure may be different for practicing interventional cardiologists relative to interventional cardiology fellows as techniques that may be transferable readily to an experienced interventional cardiologist might require a different level or extent of training during fellowship.
3. At the fellowship level, SCAI in partnership with the ACGME, should define and regularly update core competencies relevant to the contemporary practice of interventional cardiology, determining what constitutes a core technique or procedure versus an add-on or niche-based technique or procedure.
4. For practicing interventional cardiologists, the group agrees that access to educational activities and opportunities for training in both new core competencies and novel technology or procedures is required. The group also agrees that as standards are set for new competencies, SCAI’s role is to identify or aid in creating

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<tr>
<th>Device</th>
<th>Industry standard</th>
<th>SCAI position-novice operators</th>
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<tbody>
<tr>
<td>Amplatzer PFO occluder (Abbott)</td>
<td>(1) Didactic in-service training (2) Self-certification letter 25 cases as the primary implanter</td>
<td>(1) Peer-to-peer training (2) Ten cases during interventional fellowship plus proctor present for first 3–5 cases for each new device (3) Maintenance of certification: &gt;15 PFO procedures annually</td>
</tr>
<tr>
<td>Cardioform Septal occluder (Gore)</td>
<td>(1) Didactic training (2) One training case (PFO or ASD)</td>
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<tr>
<td>Impella (Abiomed)</td>
<td>Impella 2.5 or CP = 2 cases Impella 5.0 = 1 case Impella RP = 1 case Renewal of certification = 5 case per year or 10 every 2 years</td>
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<tr>
<td>Rotational atherectomy (BSCI)</td>
<td>(1) Online didactic training (2) Wet heart hands-on simulation (3) Complete three cases, one under the supervision of a physician proctor and two under the supervision of BSCI</td>
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<td>Orbital atherectomy (CSI)</td>
<td>Completion of an e-learning module and minimum of six proctored cases by a CSI representative prior to independent certification</td>
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<td>Intravascular ultrasound (IVUS) and optical coherence tomography (OCT)</td>
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ORIGINAL ARTICLE

The clinical and genetic characteristics of permanent neonatal diabetes (PNDM) in the state of Qatar

Sara Al-Khawaga1,2,3 | Idris Mohammed1,2 | Saras Saraswathi2 | Basma Haris2 | Reem Hasnah2 | Amira Saeed2 | Hakeem Almabraz4 | Najeeb Syed4 | Puthen Jithesh4 | Ahmed El Awwa2,5 | Amal Khalifa2 | Fawziya AlKhalaf2 | Goran Petrovski2 | Essam M. Abdelalim1,3 | Khalid Hussain2

1College of Health & Life Sciences, Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar
2Division of Endocrinology, Department of Pediatric Medicine, Sidra Medicine, Doha, Qatar
3Diabetes Research Center, Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Qatar Foundation, Doha, Qatar
4Biomedical Informatics Division, Sidra Medicine, Doha, Qatar
5Faculty of medicine, Alexandria University, Alexandria, Egypt

Correspondence
Khalid Hussain, Division Chief-Endocrinology, Department of Pediatric Medicine, Sidra Medicine, Doha, Qatar.
Email: khussain@sidra.org

Abstract

Background: Neonatal diabetes mellitus (NDM) is a rare condition that occurs within the first six months of life. Permanent NDM (PNDM) is caused by mutations in specific genes that are known for their expression at early and/or late stages of pancreatic beta-cell development, and are either involved in beta-cell survival, insulin processing, regulation, and release. The native population in Qatar continues to practice consanguineous marriages that lead to a high level of homozygosity. To our knowledge, there is no previous report on the genomics of NDM among the Qatari population. The aims of the current study are to identify patients with NDM diagnosed between 2001 and 2016, and examine their clinical and genetic characteristics.

Methods: To calculate the incidence of PNDM, all patients with PNDM diagnosed between 2001 and 2016 were compared to the total number of live births over the 16-year-period. Whole Genome Sequencing (WGS) was used to investigate the genetic etiology in the PNDM cohort.

Results: PNDM was diagnosed in nine (n = 9) patients with an estimated incidence rate of 1:22,938 live births among the indigenous Qatari. Seven different mutations in six genes (PTF1A, GCK, SLC2A2, EIF2AK3, INS, and HNF1B) were identified. In the majority of cases, the genetic etiology was part of a previously identified autosomal recessive disorder. Two novel de novo mutations were identified in INS and HNF1B.

Conclusion: Qatar has the second highest reported incidence of PNDM worldwide. A majority of PNDM cases present as rare familial autosomal recessive disorders. Pancreas associated transcription factor 1a (PTF1A) enhancer deletions are the most common cause of PNDM in Qatar, with only a few previous cases reported in the literature.

KEYWORDS
Fanconi–Bickel Syndrome (FBS), GCK, HNF1B, INS, pancreatic agenesis, Permanent neonatal diabetes (PNDM), PTF1A, Whole Genome Sequencing (WGS), Wolcott–Rallison Syndrome (WRS)
Immunoglobulin abnormalities are frequent in patients with lupus nephritis

M. J. Cuadrado, I. Calatayud, M. Urquizu-Padilla, S. Wijetilleka, S. Kiani-Alikhan and M. Y. Karim

Abstract

Background: Hypogammaglobulinemia is a complication of B-cell targeting therapies (BCTT), used in vasculitis, rheumatoid arthritis and systemic lupus erythematosus (SLE). Since autoimmune diseases are associated with underlying and induced immune abnormalities, several societies recommend assessing immune function before and during rituximab treatment. In SLE, polyclonal hypergammaglobulinemia is the typical alteration of gammaglobulins, though hypogammaglobulinemia has also been reported.

Methods: This is a cross-sectional study describing immunoglobulin levels measured as part of routine care in patients with lupus nephritis, a group with multiple factors contributing to immunoglobulin abnormalities, including immune dysregulation, immunosuppression and nephrotic syndrome.

Results: Polyclonal hypergammaglobulinemia occurred in 15/83 (18.1%) patients. In contrast, low levels of immunoglobulins were found as follows: selective IgA deficiency 2/83 (2.4%), reduced IgG levels 7/83 (8.4%), reduced IgM 14/83 (16.9%). Only 1 patient required immunoglobulin replacement.

Conclusions: Immunoglobulin abnormalities are frequently found in lupus nephritis, ranging from polyclonal hypergammaglobulinemia to hypogammaglobulinemia. Consequently, immunoglobulin levels should be assessed prior to commencing BCTT.

Keywords: Immunoglobulins, SLE, Lupus nephritis, Hypogammaglobulinemia, Rituximab, Autoimmune, B-cells

Background

With widespread use of B-cell targeting therapies (BCTT), hypogammaglobulinemia is gaining recognition as a potential complication [1, 2]. BCTT is used in a range of autoimmune rheumatic diseases (AIRD), including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The American Academy of Asthma, Allergy, and Immunology emphasized checking baseline immune function before rituximab treatment in autoimmune disease [3]. The European League against Rheumatism guidelines in AAV and RA recommend testing serum immunoglobulins before each rituximab course and in those developing recurrent infection [4, 5]. The British Society for Rheumatology guidelines for rituximab in RA recommend testing immunoglobulin levels before commencing treatment, 4–6 months after infusions and before re-treatment [6]. However, there is a lack of data regarding the nature of immunoglobulin abnormalities which might be found at baseline prior to starting BCTT.

Various immunoglobulin abnormalities are reported in SLE. Polyclonal hypergammaglobulinemia is well described. Hypogammaglobulinemia has been associated with SLE itself, with immunosuppression, and nephrotic syndrome [7]. Both IgA and IgM deficiencies have been reported in SLE [8]. Therefore, it is important when monitoring immunoglobulins as recommended above, to be aware of the likely baseline immunoglobulin results. In this report, we describe results of a cross-sectional study of immunoglobulin levels in lupus nephritis. This group is likely to have multiple factors contributing to immunoglobulin abnormalities (including corticosteroids, immunosuppressive agents, severe nephrotic syndrome, and associated immunodysregulatory disorders) [1, 7–9]. These patients will usually require immunosuppressive therapy, which may include BCTT. Here, in this concise communication, we report immunoglobulin...
Acute flaccid myelitis: early recognition is the key

Archivist was reminded of acute flaccid myelitis (AFM) when he was involved with a few cases following an enterovirus D68 mini outbreak a few years ago. It is a rare diagnosis in the UK. Part of the role of the general paediatrician is to be aware of these rarities and diagnose promptly. In a small case series, reported by Matesanz S et al. [1] J Pediatr 2019 Aug. pii: S0022-3476(19)30489-2. doi: 10.1016/j.jpeds.2019.07.015 the diagnostic features were highlighted. Acute flaccid myelitis (AFM) is defined as the acute onset of focal limb weakness with corresponding spinal cord grey matter-specific abnormalities spanning one or more spinal segments on MRI, sometimes with associated brainstem and posterior fossa abnormalities. Weakness typically begins in the setting of a recent or current respiratory and/or febrile illness and may be rapidly progressive. The diagnosis is often delayed and the evidence base for treatment is poor. This was a chart review of all children diagnosed with AFM at the Children’s Hospital of Philadelphia between September 2014 and October 2016. They recorded demographic, epidemiologic, clinical, treatment, and outcome data from medical records on all confirmed cases in a retrospective case series. All the children had weakness on presentation, which was more pronounced proximally. Five children had prominent single limb involvement (four upper extremity, 1 lower extremity), and nine had multiple limb involvement. Of the 13 children who had a lumbar puncture, they all had a lymphocytic predominant pleocytosis and variably elevated protein consistent with the diagnosis of AFM. Spinal MRI in all children demonstrated intraspinal grey matter T2 hyperintensities consistent with the case definition, most commonly in mid-cervical and lower thoracic regions. The paper discusses the few treatment options. Those patients with enterovirus D68 had the worst outcome.

Although the case series was retrospective and with small numbers, their important conclusion was that despite meeting the clinical criteria for AFM at presentation, 6 (43%) of the children had a delay in the initial diagnosis. The initial diagnoses were: a viral syndrome with neck pain (n=3), Guillain-Barre syndrome (n=1), viral syndrome with brachial nerve palsy (n=1), and toxic synovitis (n=1). Four of these children were initially discharged from an emergency room, and on re-presentation with worsening symptoms, 2 required emergent intubation and ultimately required tracheostomy.

The clinical features are well described in the paper. The pattern is of a rapidly progressive, asymmetric, proximal greater than distal weakness in the context of current or recent fever but the absence of sensory finding. Proximal weakness, can be easy to miss on a screening general medical examination where pain is present. Pain was part of the clinical presentation in most of these children, in this case series. The presence of a recent or current febrile illness with asymmetry in motor function, even if initially attributed to pain, should prompt a thorough neurologic examination and consideration of AFM.

Competing interests None

Patient consent for publication Not required.

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United Nations Convention on the Rights of the Child in acute paediatrics

The United Nations Convention on the Rights of the Child (CRC) was created in 1989 and has provided us a framework for the structure of a Children’s rights delivered clinical service, standards for clinical care and indeed undergraduate curriculum for medical students. It is worthwhile reminding yourself of some of the Articles. Article 17 states, ‘Children have the right to get information that is important to their health and well-being’ and Article 24 focuses on health and health services, stating, ‘Children have the right to good quality healthcare—the best healthcare possible—to safe drinking water, nutritious food, a clean and safe environment, and information to help them stay healthy.’ It is clear that some children are given inadequate support and information in some healthcare environments. Przybylska MA et al. [BMJ Paediatrics Open 2019;3: e000445; http://dx.doi.org/10.1136/bmjpo-2019-000445] identified this gap in information available for children and have highlighted this need in acute settings. They examined local resources provided to paediatric inpatients who had been admitted to the acute admissions unit and compared this information given to children with planned admissions via process observations in their quaternary Childrens Hospital. They also interviewed two play specialists, thirty families and nine children (aged 3–13 years) to collate a qualitative angle and finally they reviewed thirty six (UK, Australian and US) hospitals assessing child-specific information resources and systematically compared the information available on nine hospital websites. At the study site, no child-specific information resources were available for acute admissions, whereas planned admissions were offered significant information face-to-face with supplemental resources. Child, parent and play specialist interviews highlighted gaps in information provision regarding hospital practicalities and processes. Twelve external child-specific resources were identified, for 4–14 year olds, explaining key care information: medical procedures, equipment and staff. These resources could positively respond to the topics cited as lacking by the interviewed patients and families at the study site. International hospital websites provided more detailed information compared with UK hospitals. They concluded that the hospital experience of children can be improved by ensuring they are provided with adequate information relating to their hospital stay. It is essential that suitable high-quality resources are consistently available and that feedback from children informs the process of resource development. The UK government published a report in 2015 on the role of the CRC and how it should influence healthcare provision. In 2017, the Royal College of Paediatrics and Child Health (RCPCH) paper on the ‘State of Child Health’ outlined aspirations for child health from a care, workforce and service delivery perspective with subsequent publication of outcomes across the UK. This national focus on CRC in 2016 and the RCPCH recommendations focused this team from Edinburgh to ask what resources and support they were providing for acutely admitted medical paediatric patients. Review the provisions that you have in your hospital. Using the Articles in the UNCRC to review the clinical service you deliver for children, is a useful exercise. They should underpin what we do and how we do it.

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Adrenal disorders in pregnancy, labour and postpartum – an overview

Madhavi Manoharana, Prabha Sinhab and Shabnum Sibtain

Women's Clinical Management Group, Sidra Medicine, Doha, Qatar; Department of Obstetrics and Gynaecology, Oman Medical College, Muscat, Oman; Department of Obstetrics and Gynaecology, Azra Naheed Medical College, Lahore, Pakistan

ABSTRACT
Adrenal disorders may manifest during pregnancy for the first time, or present from before pregnancy as either undiagnosed or diagnosed and treated. They may present as hormonal hypofunction or hyperfunction, or with mass effects or other non-endocrine effects. Adrenal disorders such as Cushing's syndrome, Addison's disease, pheochromocytoma, primary hyper-aldosteronism and adreno-cortical carcinoma are rare in pregnancy. Pregnancy presents special problems in the evaluation of the hypothalamic–pituitary–adrenal and renin–angiotensin–aldosterone axis as these undergo major changes during pregnancy. Diagnosis is challenging as symptoms associated with pregnancy are also seen in adrenal diseases. A timely diagnosis and treatment is critical as these disorders can cause maternal and foetal morbidity and mortality. A high index of suspicion must be maintained as they can go unrecognised and untreated. An early diagnosis and treatment often improves outcomes. The aim of this article is to review the patho-physiology, clinical manifestation, diagnosis and management of various adrenal disorders during pregnancy.

INTRODUCTION
Disease of the adrenal gland is rare in pregnancy. It can manifest as over- or under activity of the cortex or medulla. Adrenal disease such as Cushing syndrome, Addison disease, pheochromocytoma and primary hyperaldosteronism is associated with impaired fertility. During pregnancy, they are associated with significant impact on maternal and foetal health. Given the rarity of these conditions in the general population, and therefore even lower prevalence in the pregnant population, limited and contradictory data exist on maternal and neonatal outcomes in pregnancies. Management is based on observational findings from case reports, and more recently several larger population-based studies. This review aims to describe the patho-physiology, clinical manifestation, with updates on diagnostic modalities and treatment options of common adrenal disorders in pregnancy.

MATERIALS AND METHODS
We searched the Medline, PubMed, Ovid and Cochrane Library using the following keywords: ‘Adrenal disorders in pregnancy’, ‘Cushing’s syndrome in pregnancy’, ‘Primary Hyperaldosteronism in pregnancy’, ‘Adrenal carcinoma in pregnancy’, ‘Addison’s disease in pregnancy’. All studies from January 1st 1990 till January 31st 2019, which described case reports, case series and review of literature were included. Only publications in English language were chosen. Articles were screened by titles and abstracts and then full text papers were obtained.

DISCUSSION
Pregnancy modifies the hypothalamic–pituitary–adrenal (HPA) axis with increase in placental corticotropin-releasing hormone (CRH), and adreno-corticotrophic hormone (ACTH) production. During the first trimester, a substantial increase in CRH and ACTH is observed. This is balanced by an increased production of CRH-binding protein in pregnancy. Maternal circadian rhythm of ACTH secretion is maintained thought out the pregnancy despite the increase in placental hormones (Nolten et al. 1980). There is a significant increase in levels of cortisol during the first trimester, and a two to threefold increase in cortisol levels during second and third trimester (Carr et al. 1981). Both ACTH and cortisol levels increase in labour and the diurnal variation of cortisol production is maintained during pregnancy.

HPA axis normalises in the postpartum period, CRH and ACTH levels decreases within 2 h of delivery and cortisol levels within 1 week of delivery (Okamoto et al. 1989). Corticosteroid-binding globulin (CBG) concentrations returns to normal levels in 3–6 weeks post-delivery and occasionally can take up to 3 months (Magiakou et al. 1996).

Many changes occur in renin–angiotensin–aldosterone system during pregnancy. Renin is produced by the ovaries, decidua and kidney stimulated by oestrogen. Plasma renin activity increases fourfold in early first two months of pregnancy.
Glucose control during Ramadan fasting in a teenager with type 1 diabetes on MiniMed 670G hybrid closed-loop system

Goran Petrovska1, Fawziya Al Khalaf2, Judith Campbell1, Khalid Hussain1, Hannah Fisher1, Fareeda Umer1

Introduction

Fasting during the month of Ramadan includes abstinence from drink and food from dawn till sunset and can be from several hours to more than 20 h per day. Prepubertal children and people with acute or chronic medical conditions are excused from fasting, which may aggravate their condition [1]. Children with type 1 diabetes (T1D) are considered a high-risk population, and it is recommended not to fast during Ramadan. However, a significant number of patients prefer to fast to respect their religion.

One of the treatment’s options for T1D is the MiniMed 670G hybrid closed-loop (HCL) system (Medtronic, USA), which uses an algorithm capable of automatically adjusting basal insulin delivery in response to glucose sensor readings transmitted to the insulin pump every 5 min.

We present the case with T1D where the glucose control was managed using the MiniMed 670G HCL system during the month of the Ramadan. To the best of our knowledge, this is the first patient to be reported on fasting during Ramadan and HCL system.

Case presentation

A 13-year-old male patient with a 4-year history of T1D using MiniMed 670G HCL system was fasting for the first time around 14 h per day for the month of Ramadan. Patient had HbA1c levels between 8.2 and 11.8% (66–105 mmol/mol) with previous treatment (multiple daily injections with self-monitoring of blood glucose). MiniMed 670G HCL system was initiated 5 months before the study, and HbA1c of 6.6% (49 mmol/mol) and time in range (70–180 mg/dl; 3.9–10.0 mmol/l) of 76% were achieved. The patient uploaded the HCL system on Carelink Personal Software on days 1, 14 and 30 during the Ramadan, and consultation was given by phone. Glucose and insulin metrics were analyzed 1 month before and during Ramadan period.

Patient broke the fast twice in the afternoon period during the first week of Ramadan due to a mild hypoglycemic event. We advised him to use temporary target for 2–4 h if glucose levels reached 80 mg/dl (4.4 mmol/l) to avoid further glucose decrease.

Despite correct carbohydrate counting, a slight increase in glucose values (18–00 h) was noted due to breaking the daily fast with eating at evening meal, iftar (as shown in Fig. 1). We recommended to increase the meal bolus by 10–20%, if the meal contained more than 100 g (e.g., to increase the bolus by 20% when 110 g of carbohydrates were eaten, 132 g of carbohydrates was entered into the bolus wizard calculator) and to split bolus insulin 40–50% before and 50–60% after the meal, as the “dual wave” and “square” boluses are disabled in MiniMed 670G HCL system.

Average auto-basal/basal insulin amount per day (as shown in Fig. 1) was significantly lower in the period 4 am–6 pm in fasting hours during Ramadan compared to the same period in the non-fasting hours before Ramadan (p < 0.05).

We did not find any significant differences in time spent in AM, AM exits, sensor wear and total daily insulin per day before and during Ramadan (as shown in Fig. 1). No diabetic ketoacidosis and severe hypoglycemia were detected during and before Ramadan.
Colposcopic and Histological Outcome of Atypical Squamous Cells of Undetermined Significance and Atypical Squamous Cell of Undetermined Significance Cannot Exclude High-Grade in Women Screened for Cervical Cancer

Osman Ortashi*, Dana Abdalla

Abstract

Objectives: The objectives of the study are to assess the prevalence of colposcopic and histological abnormalities in patients diagnosed with ASCUS and ASC-H and to compare the prevalence of CIN in each group. Methods: Population-based cross-sectional retrospective study was conducted in one of tertiary hospitals in UAE. All cervical smears reported as ASCUS or ASC-H in 2015 were included in this study. The local guideline in 2015 was to refer all cases of ASC for colposcopy assessment. Results: Overall, 7,418 cervical smears were processed at our laboratory service, 5.6% (n=413) were reported as ASC. 95% of them (n=394) were ASCUS and 5% (n=19) were ASC-H. The overall prevalence of high grade CIN in patients with ASC-H is 26% compared with 0.8% for patients with ASCUS regardless the age. The relative risk of patients with ASC-H is 8 folds higher than patients with ASCUS to have low grade CIN but 29 fold higher risk of having High grade CIN and the P value =0.001. Conclusion: ASC-H cytology confers a substantially higher risk for high grade CIN than ASCUS regardless of age. HPV test is an important triage test in patients with ASCUS to predict cellular changes and CIN.

Keywords: Cervical smear- Pap smear- ASCUS

Introduction

Organized cervical cancer screening has been proved to be one of the most successful cancer prevention strategies. Countries with established organized cervical cancer screening programs witnessed significant reduction in the incidence of cervical cancer of approximately 70%. (Luhn et al., 2007). Cervical smear or (Pap smear) smear is the standard screening test for cervical cancer and cervical dysplasia (Tambouret, 2013). The test was developed by Georgios Papanikolaou in 1941. The cervical smear test is based on collection of cells from the cervix and vagina and to detect cellular abnormalities that arise mainly from the transformation zone where almost all cervical dysplasia and cancers arise. The cervical smear which is screening test yields cytological result but not histological diagnosis. The Bethesda System for reporting cervical cytology was developed in 1988, and was widely embraced after it was adopted by the National Cancer Institute in the same year. The system was revised and updated in 1991 and 2001 to provide a uniform system of terminology that would promote clear management guidelines (Davey 2003; Solomon, 2002). ASC referred to atypical squamous cells and this category includes both ASC-US (Atypical squamous cells of undetermined significance) and ASC-H (Atypical squamous cells, cannot exclude high grade squamous intraepithelial lesion). ASC represents 3.6% of all cervical smears (Gupta et al., 2007), ASCUS account for 2.8% of all cervical smears worldwide (Solomon et al., 2002), while ASC-H represents only 0.2% of cytological abnormalities as reported by the College of American Pathologists in 2003-2003 (Sherman et al., 2007). ASC-H represents about 8.2% of all patients diagnosed with atypical squamous cells (ASC) which is approximately one in ten cervical cytological specimens that are interpreted as ASC (Srodon et al., 2006).

The objectives of the study are to assess the prevalence of colposcopic and histological abnormalities in patients diagnosed with ASCUS and ASC-H and to compare the prevalence of CIN in each group.

Materials and Methods

This is population-based cross-sectional retrospective study was from Jan 2014 to Dec 2014 to look at colposcopic and histological abnormalities in patients diagnosed with

1Sidra Medical and Research Center, Qatar, Specialist Physician, Womens Health Institute, Al Ain Hospital, United Arab Emirates. *For Correspondence: osmanortashi@hotmail.com
The current status of non-radiologist-performed abdominal ultrasonography in pediatrics – a scoping literature review protocol

Elsa A. van Wassenaer1 · Joost G. Daams2 · Marc A. Benninga1 · Karen Rosendahl3 · Bart G. P. Koot1 · Samuel Stafrace4 · Owen J. Arthurs5 · Rick R. van Rijn6

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Abstract
In recent years as a result of decreasing prices and the increasing availability of portable systems, ultrasonography (US), which historically has primarily been the domain of radiologists, has become more widely available to non-radiologists as well. This has increased the use of point-of-care paediatric US performed by non-radiologists. With this scoping review, focused on abdominal imaging, we aim to gain an overview of the current practices in the paediatric setting and to assess its impact in daily practice. We present the background and study design of a scoping review for non-radiologist-performed abdominal point-of-care paediatric US using a formal scoping framework. The information shall be derived from published studies. We will submit the review report to a peer-reviewed scientific journal and explore other scientific venues for presenting the work. Based on the completed review, the officers of the European Society of Paediatric Radiology will issue a position statement on non-radiologist-performed point-of-care paediatric US.

Keywords Adolescents · Children · Point-of-care ultrasound · Scoping review · Ultrasound

Introduction
One of the most widely used imaging techniques in paediatric radiology is ultrasonography (US). This is a fast, relatively cheap and radiation-free approach to cross-sectional imaging, making it very suitable for use in the vulnerable paediatric patient population. US can be performed under many circumstances ranging from the high-tech environment of a paediatric university hospital to a Third World outpatient clinic. In recent years a paradigm shift has occurred. US, which historically has primarily been the domain of radiologists, has become more widely available to non-radiologists as well. This is mainly due to the fact that US systems have become cheaper and even portable systems that can work on a smartphone have become available. This has resulted in a much wider use of US at the level of primary point-of-care providers and inclusion of US in medical training curricula [1, 2].

Use of US at this level is known as Point-of-Care US (POCUS). However, as pointed out in an editorial in Pediatric Radiology, this is a somewhat equivocal term as it only implies care being provided at the patient level [3]. It would be better to additionally specify who provides POCUS, i.e. a radiologist, a radiological technician or a non-radiologist. Therefore, we will use the term Non-Radiologist POCUS (NR-POCUS). There are several advantages to NR-POCUS: Physicians can gain more specific information in a
Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the Phase 2 NURTURE study


Departments of Neurology and Pediatrics, Columbia University Irving Medical Center, New York, NY, USA
Unit of Neuromuscular and Neurodegenerative Disorders, Post-Graduate Bambino Gesù Children’s Research Hospital, IRCCS, Rome, Italy
Department of Neurology, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA
Departments of Medical Genetics and Pediatrics, National Taiwan University Hospital, Taipei, Taiwan
Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
†Division of Neurology, Department of Pediatrics, Nemours Children’s Hospital, Orlando, FL, USA

§Department of Neuropediatrics and Muscle Disorders, Faculty of Medicine, University of Freiburg, Freiburg, Germany

¶Department of Neuropediatrics, University Medical Hospital, Bonn, Germany

#Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago, IL, USA

†Children’s Hospital of Colorado, University of Colorado School of Medicine, Aurora, CO, USA

‡Royal Children’s Hospital, University of Melbourne and Murdoch Children’s Research Institute, Melbourne, Australia

#University of Utah, Department of Pediatrics and Neurology, Salt Lake City, UT, USA

∗Department of Pediatric Neurology, Hacettepe University, Ankara, Turkey

+Sidra Medicine, Department of Pediatrics, Qatar Foundation, Doha, Qatar

©Division of Clinical and Metabolic Genetics, Department of Pediatrics, Hamad Medical Corporation, Doha, Qatar

†‡NEMO Clinical Center - NEuroMuscular Omniservice, Milan, Italy

†§Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy

†¶Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University; Departments of Pediatrics and Laboratory Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

†#Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA
Declaration of interest

D.C. De Vivo reports serving as an advisor/consultant for AveXis, Biogen, Cytokinetics, Ionis, Mallinckrodt, METAFOREA, PTC Therapeutics, Roche, Sanofi, Sarepta, Scholar Rock, the Spinal Muscular Atrophy Foundation, and Ultragenyx, with no financial interests in these companies; grants from the US Department of Defense, Glut 1 Deficiency Foundation, Hope for Children Research Foundation, the National Institutes of Health, and the Spinal Muscular Atrophy Foundation.

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**D. Kerr** reports being an employee, founder, and equity holder of Generation Bio.

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**K. Johnson** reports being an employee of and holding stock-stock options in Biogen.
R. Foster reports being an employee of and holding stock/stock options in Biogen.
S. Gheuens reports being an employee of and holding stock/stock options in Biogen.
I. Bhan reports being an employee of and holding stock/stock options in Biogen.
S.P. Reyna reports being an employee of and holding stock/stock options in Biogen.
S. Fradette reports being an employee of and holding stock/stock options in Biogen.
W. Farwell reports being an employee of and holding stock/stock options in Biogen.

*Corresponding author.

Darryl C. De Vivo, MD, Departments of Neurology and Pediatrics, Columbia University Irving Medical Center, New York, NY, 10032, USA; Tel: (212) 305-5244; Fax: (212) 305-7036; Email address: dcd1@cumc.columbia.edu.

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Spinal muscular atrophy (SMA) is a neurodegenerative disease associated with severe muscle atrophy and weakness in the limbs and trunk. We report interim efficacy and safety outcomes as of March 29, 2019 in 25 children with genetically diagnosed SMA who first received nusinersen in infancy while presymptomatic in the ongoing Phase 2, multisite, open-label, single-arm NURTURE trial. Fifteen children have two SMN2 copies and 10 have three SMN2 copies. At last visit, children were median (range) 34.8 [25.7–45.4] months of age and past the expected age of symptom onset for SMA Types I or II; all were alive and none required tracheostomy or permanent ventilation. Four (16%) participants with two SMN2 copies utilized respiratory support for ≥6 hours/day for ≥7 consecutive days that was initiated during acute, reversible illnesses. All 25 participants achieved the ability to sit without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) achieved walking independently.

Eight infants had adverse events considered possibly related to nusinersen by the study investigators. These results, representing a median 2.9 years of follow up, emphasize the importance of proactive treatment with nusinersen immediately after establishing the genetic diagnosis of SMA in presymptomatic infants and emerging newborn screening efforts.

Keywords (up to 6): Spinal muscular atrophy; Clinical trial; Neurofilament; Newborn screening; Nusinersen; Presymptomatic.
Identification of human genetic variants controlling circular RNA expression

Ikhlak Ahmed1,2, Thasni Karedath1 Fatima M. Al-Dasim1 Joel A. Malek1,3

1 Department of Genetic medicine Weill Cornell Medicine-Qatar
2 Biomedical Informatics Sidra Medicine Qatar
3 Genomics Core Weill Cornell Medicine-Qatar

Author Email Addresses:
Ikhlak Ahmed email: iahmed2@sidra.org
Thasni Karedath email: tka2001@qatar-med.cornell.edu
Fatima M. Al-Dasim email: fma2003@qatar-med.cornell.edu
Joel A. Malek email: jom2042@qatar-med.cornell.edu

Correspondence should be addressed to

Joel Malek
Director of the Genomics Core/ Assistant Professor of Genetic Medicine
Weill Cornell Medicine-Qatar (WCM-Q)
Education City P.O. Box 24144
Doha Qatar
Office +974 - 44928420
Email: jom2042@qatar-med.cornell.edu

Keywords: circular RNA eQTL circQTL 1000 genomes RNA-Seq
Abstract

Circular RNAs (circRNAs) are abundant in eukaryotic transcriptomes and have been linked to various human disorders. However, understanding genetic control of circular RNA expression is in early stages. Here we present the first integrated analysis of circRNAs and genome sequence variation from lymphoblastoid cell lines of the 1000 genomes project. We identified thousands of circRNAs in the RNA-seq data and show their association with local single nucleotide polymorphic sites referred to as circQTLs, which influence the circRNA transcript abundance. Strikingly, we found that circQTLs exist independently of eQTLs with most circQTLs having no effect on mRNA expression. Only a fraction of the polymorphic sites are shared and linked to both circRNA and mRNA expression with mostly similar effects on circular and linear RNA. A shared intronic QTL rs55928920 of HMSD gene drives the circular and linear expression in opposite directions, potentially modulating circRNA levels at the expense of mRNA. Finally, circQTLs and eQTLs are largely independent and exist in separate linkage disequilibrium (LD) blocks with circQTLs highly enriched for functional genomic elements and regulatory regions. This study reveals a previously uncharacterized role of DNA sequence variation in human circular RNA regulation.
Original Research

Factors Affecting Stabilization Times in Neonatal Transport

Muzafar Gani Abdul Wahab, MBBS, MD 1, Sumesh Thomas, MBBS, DCH, MRCPCH, FRCPCH 2, Prashanth Murthy, MBBS, MD, MRCPCH 2, Aravanan Anbu Chakkarapani, MBBS, MD, RCPS(C) affiliate 3,4,*

1 Neonatologist, Associate Professor, Division of Neonatology, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
2 Neonatologist, Clinical Associate Professor, Division of Neonatology, Department of Pediatrics, University of Calgary, Calgary, Canada
3 Neonatologist, Division of Neonatology, Department of Pediatrics, Sidra Medicine, Doha, Qatar
4 Assistant Professor of Clinical Pediatrics, Weill Cornell Medicine-Qatar

ABSTRACT

Objective: During transport, the time spent in stabilizing sick infants before repatriation is crucial in optimizing the outcome and effective use of resources. The study aim was to assess individual components of neonatal transport time to identify opportunities to minimize delay, optimize care, and improve the overall efficiency of transport.

Methods: A single-center prospective observational study conducted at McMaster Children’s Hospital, Hamilton, Ontario, Canada, with a dedicated transport team for over 12 months. The stabilization time was defined as the time interval between arrival and departure from the referring hospital.

Results: Of 223 neonatal transfers, 67 required no procedural or therapeutic intervention before mobilization to the receiving unit, with a mean stabilization time of 113 ± 52 minutes. In 156 transport events, 1 or more interventions were required, with a significantly higher mean stabilization time of 165 ± 89 minutes (P < .0001).

Conclusion: This study found that the local stabilization time was more than 1.5 times that of the comparable published data. The reasons identified for this delay were mostly because of waiting times for vehicle mobilization, waiting for blood and radiology results, and bed availability. Modifying these factors could save up to 28% of the stabilization time.

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In most countries with well-established neonatal services, regionalization of perinatal care via managed clinical networks maintains equity of access for neonates and high-risk pregnant mothers. Managed clinical networks also enable the use of established referral pathways and the shared use of evidence-based guidelines and policies. Central to this model is a reliable and effective neonatal transport service. Regional networks have invested in dedicated transport teams to transfer neonates requiring varying levels of care within the network. Although every effort is made to ensure the antenatal transfer of high-risk mothers to an appropriate perinatal facility, a proportion of neonates continue to be outborn, requiring postdelivery transfer to a level II or III neonatal intensive care unit (NICU) for ongoing care. The significant resources required for neonatal transport services justify the demand for high-quality and cost-effective service. There is little consensus on the parameters for evaluating the performance of transport services. Several indicators, including the time to retrieval, safety, and user satisfaction surveys, have been used. Looking at retrieval times in both neonatal and pediatric patients, Abdel-Latif and Berry concluded that establishing reference times could be a valuable quality assurance tool.

Stabilization periods in neonatal transports are dependent on several factors including illness severity, need for procedures, and availability of local resources as well as capacity in an appropriate care facility. Therefore, stabilization time, including waiting times at referral sites, can be quite variable. The present study was a single-center prospective observational study of factors affecting stabilization times in neonatal transport. The transport program considered the median time intervals for pretransport discussions, mobilization...
Pros, cons and future perspectives – three questions on three dimensional guidance for cardiac catheterization in congenital heart disease

Sebastian Góreczny1,2, Gregor Krings1, Ziyad M. Hijazi4, Thomas Fagan5, Darren Berman6, Damien Kenny7,8, Gareth J. Morgan2

1Department of Cardiology, Polish Mother’s Memorial Hospital, Research Institute, Lodz, Poland
2Department of Cardiology, Colorado Children’s Hospital, Aurora, Colorado, USA
3Pediatric Heart Center, Utrecht, Netherlands
4Department of Pediatrics, Weill Cornell Medicine and Sidra Heart Center, Doha, Qatar
5Cleveland Clinic Children’s Hospital, Lerner College of Medicine, Cleveland, USA
6The Heart Center, Nationwide Children’s Hospital, Columbus, Ohio, USA
7Our Ladies Children’s Hospital, Dublin, Ireland
8The Mater Misericordiae University Hospital, Dublin, Ireland

Abstract

Step changes in angiographic imaging are not commonplace. Since the move from analogue to digital and flat detector plates, two-dimensional imaging technology has certainly evolved but not jumped forward. Of all the routine imaging techniques used in cardiology, angiography has been the last modality to embrace the third dimension. Although the development of rotational angiography was initially for the benefit of neuroimaging and fusion of cross sectional datasets was aimed at the treatment of descending aortic pathology, interventional physicians in congenital and structural cardiology have immersed themselves in this technology over the last 10 years. Like many disruptive technologies, its introduction has divided opinion. We aimed to explore the mindset of those in the field of interventional cardiology who are driving imaging forward. These structured interviews recorded during the 21st Pediatric and Adult Interventional Cardiac Symposium illustrate the challenges and sticking points as well as giving an insight into the direction of travel for three-dimensional imaging and fusion techniques. Covering a wide range of career development, seniority and experience, the interviewees in this article are probably responsible for the majority of the published literature on invasive three-dimensional imaging in congenital heart disease.

Key words: cardiac imaging, fusion imaging, percutaneous treatment, congenital heart defects.

Introduction

Step changes in angiographic imaging are not commonplace. The last major advance was probably the move from analogue to digital and flat detector plates in the 1980s and early 90s [1, 2]. Since then, two-dimensional (2D) imaging technology has certainly evolved but not jumped forward. All the time we have been conscious of the need to minimize exposure to ionizing radiation and ionic contrast whilst improving the accuracy of our data and integrating it with modern cross-sectional techniques such as computed tomography (CT), magnetic resonance imaging (MRI) and three-dimensional (3D) echocardiography [3–8]. Of all the routine imaging techniques used in cardiology, angiography has been the last modality to embrace the third dimension [5]. Although the development of rotational angiography (Figure 1) was initially for the benefit of neuroimaging and fusion of cross sectional datasets (Figure 2) was aimed at the treatment of peripheral vascular pathology, interventional physicians in congenital cardiology have immersed themselves in this technology over the last 10 years [9–18]. Like many disruptive technologies, its introduction has divided opinion. Cost, benefit, radiation and contrast exposure have fed the natural resistance to change and
Commentary

Asthma exacerbation related to viral infections: An up to date summary

Mehdi Adeli¹,²,³, Tamara El-Shareif¹, Mohamed A. Hendaus¹,²,³

¹Department of Pediatrics, Section of Academic General Pediatrics, Sidra Medicine, ²Department of Pediatrics, Hamad General Corporation, ³Department of Clinical Pediatrics, Weill- Cornell Medicine, Doha, Qatar

Abstract

Asthma exacerbation can be a major life threatening event. Viruses have been pinned as the cause behind the vast majority of these exacerbations. The purpose of this short review is to explore the mechanisms behind these exacerbations, focusing mostly on viral infections as triggers. We will also be discussing the phenotypes prone to asthma exacerbation, the pathophysiology of viral induced asthma and ventilation patterns of asthmatic lungs. This manuscript will assist primary care physicians in delineating the proper pathophysiology of the disease as well as the management.

Keywords: Asthma, exacerbations, pulmonary function, virus-induced asthma

Introduction

Asthma is considered as one of the most common chronic diseases. Its global prevalence reaches up to 334 million people. Being a longstanding disease, it constitutes a high burden on patients' families, and health systems. In the United States alone, there are over 15 million annual clinic visits, and 2 million Emergency Room (ER) visits related to asthma. In addition to this, there are more than 500,000 yearly hospitalizations for severe asthma exacerbations.

Asthma exacerbation is defined as a respiratory attack that requires emergency treatment, hospitalization or treatment with systemic corticosteroids. Moreover, in terms of pulmonary function tests, an asthma exacerbation is defined as a reduction in forced expiratory volume (FEV1) of more than 20% from baseline, or a decrease in peak expiratory flow of >50% from baseline for 2 consecutive days at any time during the period of treatment. Exacerbations might lead to accelerated decline in pulmonary function.

On top of the financial burden, asthma exacerbations can lead to a reduction in the patient's work or school attendance, as well as an increase in mortality.

Asthma-related deaths may not seem as striking as other diseases and often do not make headlines. However, according to the World Health Organization (WHO) report on chronic illnesses, there are approximately 250,000 avoidable deaths related to asthma.

The most prominent trigger of asthma exacerbations is viral respiratory tract illness. This review will further discuss viral infection in relation to asthma, and how rhinovirus (RV) can be the most causative viral agent responsible for predisposing asthma exacerbations in children and adults.

Asthma exacerbations are preceded by about 7-10 days of airflow reduction and gradual increase in symptoms. This process continues till the symptoms become very notable, resulting in

Address for correspondence: Dr. Mehdi Adeli, Department of Pediatrics, Sidra Medicine, Doha - 25999, Qatar. E-mail: madeli@sidra.org

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Evaluating the feasibility of creatine-weighted CEST MRI in human brain at 7 T using a Z-spectral fitting approach

Anup Singh1,2 | Ayan Debnath1,3 | Kejia Cai4 | Puneet Bagga3 | Mohammad Haris3,5 | Hari Hariharan3 | Ravinder Reddy3

1 CBME, Indian Institute of Technology Delhi, New Delhi, India
2 Department of Biomedical Engineering, AIIMS, Delhi, India
3 CMROI, Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania
4 Radiology, University of Illinois at Chicago, Chicago, Illinois
5 Research Branch, Sidra Medical and Research Center, Doha, Qatar

Correspondence
Anup Singh, PhD, Block II, Room No. 299, Centre for Biomedical Engineering, Indian Institute of Technology (IIT) Delhi, Hauz Khas, New Delhi 110016, India. Email: anups.minhas@gmail.com; anupsm@iitd.ac.in

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The current study aims to evaluate the feasibility of creatine (Cr) chemical exchange saturation transfer (CEST)-weighted MRI at 7 T in the human brain by optimizing the saturation pulse parameters and computing contrast using a Z-spectral fitting approach. The Cr-weighted (Cr-w) CEST contrast was computed from phantoms data. Simulations were carried out to obtain the optimum saturation parameters for Cr-w CEST with lower contribution from other brain metabolites. CEST-w images were acquired from the brains of four human subjects at different saturation parameters. The Cr-w CEST contrast was computed using both asymmetry analysis and Z-spectral fitting approaches (models 1 and 2, respectively) based on Lorentzian functions. For broad magnetization transfer (MT) effect, Gaussian and Super-Lorentzian line shapes were also evaluated. In the phantom study, the Cr-w CEST contrast showed a linear dependence on concentration in physiological range and a nonlinear dependence on saturation parameters. The in vivo Cr-w CEST map generated using asymmetry analysis from the brain represents mixed contrast with contribution from other metabolites as well and relayed nuclear Overhauser effect (rNOE). Simulations provided an estimate for the optimum range of saturation parameters to be used for acquiring brain CEST data. The optimum saturation parameters for Cr-w CEST to be used for brain data were around B1 rms = 1.45 μT and duration = 2 seconds. The Z-spectral fitting approach enabled computation of individual components. This also resulted in mitigating the contribution from MT and rNOE to Cr-w CEST contrast, which is a major source of underestimation in asymmetry analysis. The proposed modified Z-spectra fitting approach (model 2) is more stable to noise compared with model 1. Cr-w CEST contrast obtained using fitting was 6.98 ± 0.31% in gray matter and 5.45 ± 0.16% in white matter. Optimal saturation parameters reduced the contribution from other CEST effects to Cr-w CEST contrast, and the proposed Z-spectral fitting approach enabled computation of individual components in Z-spectra of the brain. Therefore, it is feasible to compute Cr-w CEST contrast with a lower contribution from other CEST and rNOE.

Abbreviations used: ARPE, absolute relative percentage error; CEST, chemical exchange saturation transfer; CEST@1 ppm, CEST pool centered at 1 ppm; CEST@3.5 ppm, CEST pool centered at 3.5 ppm; Cr-w, creatine-weighted; GM, gray matter; RF, radio frequency; rNOE, relayed nuclear Overhauser effect; WM, white matter

Anup Singh and Ayan Debnath share equal first authorship.
Point of Care Exome Sequencing Reveals Allelic and Phenotypic Heterogeneity Underlying Mendelian disease in Qatar

Khalid A. Fakhro1,2, Amal Robay2, Juan L. Rodrigues-Flores3, Jason G. Mezey,3,4 Alya A. Al-Shakaki2, Omar Chidiac2, Dora Stadler2, Joel A. Malek2, Abu Bakr Imam6, Arwa Sheikh7, Asmaa Azzam6, Ibrahim Janahi6, Izzat Khanjar6, Kamal Osman6, Maen Abu Ziki8, Mohamed Adnan Mahmah6, Mohamed Selim6, Nuha Numeiri6, Rehab Ali6, Shenela Lakhani9, Fizza Butt10, Tawfeg Ben Omran6, and Ronald G. Crystal9

1Department of Human Genetics Sidra Medicine,
2Department of Genetic Medicine Weill Cornell Medical College – Qatar Doha, Qatar,
3Department of Genetic Medicine Weill Cornell Medical College New York, NY
4Department Biological Statistics and Computational Biology Cornell University Ithaca, NY
5Department of Medicine Weill Cornell Medical College in Qatar Doha, Qatar,
6Hamad Medical Corporation Doha, Qatar
7Rochester Regional Health, Unity Hospital Rochester, NY
8Yale New Haven Medical Center, Yale University, New Haven, CT
9Center for Neurogenetics, Weill Cornell Medicine New York, NY
10Al Shefa Polyclinic, Doha, Qatar

Running head: Qatari Mendelian Program

*Correspondence: Department of Genetic Medicine Weill Cornell Medical College 1300 York Avenue, Box 96 New York, New York 10065 Phone: (646) 962-4363 Fax: (646) 962-0220 E-mail: geneticmedicine@med.cornell.edu
Abstract

The effectiveness of next generation sequencing at solving genetic disease has motivated the rapid adoption of this technology into clinical practice around the world. In this study, we use whole exome sequencing (WES) to assess 48 patients with Mendelian disease from 30 serial families as part of the “Qatar Mendelian Disease pilot program” – a coordinated multi-center effort to build capacity and clinical expertise in genetic medicine in Qatar. By enrolling whole families (parents plus available siblings), we demonstrate significantly improved discriminatory power for candidate variant identification over trios for both de novo and recessive inheritance patterns. For the same index cases, we further demonstrate that even in the absence of families, variant prioritization is improved up to 8-fold when a modest set of population-matched controls is used vs large public databases, stressing the poor representation of Middle Eastern alleles in presently available databases. Our in-house pipeline identified candidate disease variants in 27 of 30 families (90%), 23 of which (85%) harbor novel pathogenic variants in known disease genes, pointing to significant allelic heterogeneity and founder mutations underlying Mendelian disease in the Middle East. For 6 of these families, the clinical presentation was only partially explained by the candidate gene, suggesting phenotypic expansion of known syndromes. Our pilot study demonstrates the utility of WES for Middle Eastern populations, the dramatic improvement in variant prioritization conferred by enrolling population-matched controls and/or enrolling additional unaffected siblings at the point-of-care, and 25 novel disease-causing alleles, relevant to newborn and premarital screening panels in regional populations.
Perioperative management and postoperative outcome of patients undergoing cytoreduction surgery with hyperthermic intraperitoneal chemotherapy

Hamed Elgendy1,2,3, Hanna Nafady-Hego4,8, Hanan M Abd Elmoniem4,7, Taiba Youssef5, Abdulaziz Alzahrani5

Departments of 1Anesthesia and 2Microbiology and Immunology, Faculty of Medicine, Assiut University, Assiut, Egypt, 3Department of Pathology, Faculty of Medicine, Minia University, Minia, Egypt, Departments of 4Anesthesia and 5Surgery, King Abdullah Medical City, Mecca, Saudi Arabia, 6Department of Pathology, Faculty of Medicine, Umm Alqura University, Mecca, Saudi Arabia, 7Department of Internal Medicine, Prince Mohammad Bin Abdul-Aziz Hospital, Ministry of National Guard, Al Madinah, Saudi Arabia, 8Department of Anesthesia, HAMAD Medical Corporation and Weill Cornell Medicine, Doha, Qatar, 9Division of Translational Medicine, Sidra Medical and Research Center, Doha, Qatar

ABSTRACT

Background and Aims: The existence of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) as a multidisciplinary approach for peritoneal cancer gains acceptance in many countries including Saudi Arabia. The aim of our study is to describe the perioperative management of patients who received CRS/HiPEC and to report their outcomes and complications at our tertiary centre. Methods: The preoperative characteristics, surgical variables, perioperative management, postoperative course and outcomes of 38 CRS/HiPEC patients were prospectively collected and analysed. Results: The mean age of our patients was 52 years, and 23 (60.5%) of them were females. The overall postoperative mortality was 42.1%. Univariate analyses of risk factors for deaths after HIPEC demonstrated that low preoperative (haemoglobin, potassium, calcium and albumin), high tumour marker (CA19.9), intraoperative transfusion of human plasma protein (HPP), colloids, postoperative activated partial thromboplastin time and bacterial infections were potential risk factors for patient’s mortality. Multivariate analysis of those variables demonstrated that low preoperative calcium [hazard ratio (HR) = 0.116, 95% confidence interval (CI) = 0.033–0.407; P = 0.001], high intraoperative HPP transfusion (HR = 1.004; 95% CI = 1.001–1.003; P = 0.012) and presence of postoperative bacterial infection (HR = 5.987; 95% CI = 1.009–35.54; P = 0.048) were independent predictors of patient’s death. Seventy morbidities happened after HIPEC; only bacterial infection independently predicted postoperative mortality. Conclusion: To improve postoperative outcome of CRS/HiPEC, optimisation of transfusion, temperature, electrolytes and using broader-spectrum prophylaxis to manage postoperative infections should be warranted.

Key words: Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, morbidity, mortality

INTRODUCTION

Previously, peritoneal carcinoma (PC) was considered a lethal disease with a poor prognosis and a high mortality rate. At the beginning, the procedure of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) was not popular because of its high cost[1] and high rates of associated potentially life-threatening complications.
Inducible Slc7a7 Knockout Mouse Model Recapitulates Lysinuric Protein Intolerance Disease

Susanna Bodoy 1,2,3,*, Fernando Sotillo 1,4, Meritxell Espino-Guarch 4, Maria Pia Sperandeo 5, Aida Ormazabal 3,6,7, Antonio Zorzano 1,8,9, Gianfranco Sebastio 5, Rafael Artuch 3,6,7 and Manuel Palacín 1,3,9,*

1 Institute for Research in Biomedicine (IRB Barcelona), the Barcelona Institute of Science and Technology (BIST), 08028 Barcelona, Spain
2 Department of Biosciences, University of Vic, 08500 Vic, Spain
3 Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), 08003 Barcelona, Spain
4 Sidra Medicine, Translational Medicine Department, Doha 26999, Qatar
5 Department of Translational Medicine, Section of Pediatrics, Federico II University of Naples, 80138 Naples, Italy
6 Department of Clinical Biochemistry, Hospital Sant Joan de Déu (HSJD), Esplugues del Llobregat, 08950 Barcelona, Spain
7 Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, 08950, Spain
8 Centro de Investigación Biomédica en Obesidad (CIBEROB), Madrid, 28029, Spain
9 Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona, 08028 Barcelona, Spain
* Correspondence: susanna.bodoy@irbbarcelona.com (S.B.); manuel.palacín@irbbarcelona.org (M.P.);
Tel.: +34-934034700 (S.B.)
† These authors contributed equally to this work.
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Abstract: Lysinuric protein intolerance (LPI) is a rare autosomal disease caused by defective cationic amino acid (CAA) transport due to mutations in SLC7A7, which encodes for the y+LAT1 transporter. LPI patients suffer from a wide variety of symptoms, which range from failure to thrive, hyperammonemia, and nephropathy to pulmonary alveolar proteinosis (PAP), a potentially life-threatening complication. Hyperammonemia is currently prevented by citrulline supplementation. However, the full impact of this treatment is not completely understood. In contrast, there is no defined therapy for the multiple reported complications of LPI, including PAP, for which bronchoalveolar lavages do not prevent progression of the disease. The lack of a viable LPI model prompted us to generate a tamoxifen-inducible Slc7a7 knockout mouse (Slc7a7−/−). The Slc7a7−/− model resembles the human LPI phenotype, including malabsorption and impaired reabsorption of CAA, hypoargininemia and hyperammonemia. Interestingly, the Slc7a7−/− mice also develops PAP and neurological impairment. We observed that citrulline treatment improves the metabolic derangement and survival. On the basis of our findings, the Slc7a7−/− model emerges as a promising tool to further study the complexity of LPI, including its immune-like complications, and to design evidence-based therapies to halt its progression.

Keywords: LPI; rare disease; amino acid transporter; y+LAT1; hypoargininemia; hyperammonemia; pulmonary alveolar proteinosis

1. Introduction

Lysinuric protein intolerance (LPI, MIM222700) is a rare autosomal recessive disorder caused by defective cationic amino acid (CAA) transport due to mutations in SLC7A7, which encodes for the...
Long-Chain Acyl-CoA Synthetase 1 Role in Sepsis and Immunity: Perspectives From a Parallel Review of Public Transcriptome Datasets and of the Literature

Jessica Roelands 1,2*, Mathieu Garand 1, Emily Hinchcliff 2, Ying Ma 4, Parin Shah 4, Mohammed Toufiq 1, Mohamed Alfaki 1, Wouter Hendrickx 1, Sabri Boughorbel 1, Darawan Rinchai 1, Amir Jazaeri 3, Davide Bedognetti 1 and Damien Chaussabel 1*

1 Sidra Medicine, Doha, Qatar, 2 Department of Surgery, Leiden University Medical Center, Leiden, Netherlands, 3 Department of Gynecologic Oncology and Reproductive Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, 4 Department of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

A potential role for the long-chain acyl-CoA synthetase family member 1 (ACSL1) in the immunobiology of sepsis was explored during a hands-on training workshop. Participants first assessed the robustness of the potential gap in biomedical knowledge identified via an initial screen of public transcriptome data and of the literature associated with ACSL1. Increase in ACSL1 transcript abundance during sepsis was confirmed in several independent datasets. Querying the ACSL1 literature also confirmed the absence of reports associating ACSL1 with sepsis. Inferences drawn from both the literature (via indirect associations) and public transcriptome data (via correlation) point to the likely participation of ACSL1 and ACSL4, another family member, in inflammasome activation in neutrophils during sepsis. Furthermore, available clinical data indicate that levels of ACSL1 and ACSL4 induction was significantly higher in fatal cases of sepsis. This denotes potential translational relevance and is consistent with involvement in pathways driving potentially deleterious systemic inflammation. Finally, while ACSL1 expression was induced in blood in vitro by a wide range of pathogen-derived factors as well as TNF, induction of ACSL4 appeared restricted to flagellated bacteria and pathogen-derived TLR5 agonists and IFNG. Taken together, this joint review of public literature and omics data records points to two members of the acyl-CoA synthetase family potentially playing a role in inflammasome activation in neutrophils. Translational relevance of these observations in the context of sepsis and other inflammatory conditions remain to be investigated.

Keywords: sepsis, neutrophils, OMICS data, long-chain acyl-CoA synthetase, lipid metabolism

INTRODUCTION

Long-chain acyl-CoA synthetases (ACSLs) are essential enzymes that activate fatty acids (FA) by converting them to FA acyl-CoA esters. This activation is required for both synthesis of cellular lipids, such as triacylglycerol (TAG), phospholipids, and cholesterol esters as part of anabolic lipid metabolism, as well as their degradation via β-oxidation as part of catabolic lipid
Photodynamic Therapy Based on Graphene and MXene in Cancer Theranostics

Arianna Gazzi1,2, Laura Fusco1,2,3, Anooshay Khan4, Davide Bedognetti3, Barbara Zavan5,6, Flavia Vitale7,8*, Acelya Yilmazer4,9* and Lucia Gemma Delogu2,10*

1 Department of Chemical and Pharmaceutical Sciences, University of Trieste, Trieste, Italy, 2 Fondazione Istituto di Ricerca Pediatrica Città della Speranza, Padua, Italy, 3 Sidra Medical and Research Center, Doha, Qatar, 4 Department of Biomedical Engineering, University of Ankara, Ankara, Turkey, 5 Department of Medical Sciences, University of Ferrara, Ferrara, Italy, 6 Maria Cecilia Hospital, GVM Care & Research, Ravenna, Italy, 7 Department of Neurology, Bioengineering, Physical Medicine & Rehabilitation, Center for Neuroengineering and Therapeutics, University of Pennsylvania, Philadelphia, PA, United States, 8 Center for Neurotrauma, Neurodegeneration, and Restoration, Corporal Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, United States, 9 Stem Cell Institute, University of Ankara, Ankara, Turkey, 10 Department of Biomedical Sciences, University of Padua, Padua, Italy

Cancer is one of the leading causes of death in the world. Therefore, the development of new advanced and targeted strategies in cancer research for early diagnosis and treatment has become essential to improve diagnosis outcomes and reduce therapy side effects. Graphene and more recently, MXene, are the main representatives of the family of two-dimensional (2D) materials and are widely studied as multimodal nanoplatforms for cancer diagnostics and treatment, in particular leveraging their potentialities as photodynamic therapeutic agents. Indeed, due to their irreplaceable physicochemical properties, they are virtuous allies for photodynamic therapy (PDT) in combination with imaging, photothermal therapy, as well as drug and gene delivery. In this review, the rapidly progressing literature related to the use of these promising 2D materials for cancer theranostics is described in detail, highlighting all their possible future advances in PDT.

Keywords: photodynamic therapy, theranostics, graphene, MXene, nanomedicine

INTRODUCTION

Photodynamic therapy (PDT) is a form of phototherapy aimed at achieving cell death via the generation of cytotoxic reactive oxygen species (ROS). Although PDT is still an emerging therapeutic modality, it has already been established as a clinically approved method for the treatment of various malignant diseases, including cancer (Agostinis et al., 2011).

Clinically, PDT is usually used in conjunction with other forms of treatments, such as surgery, radiotherapy (RT), and chemotherapy (CT). Due to its local activation and limited tissue penetration, PDT has relatively low invasiveness, and in many cases, good cosmetic results. Therefore, this therapy is particularly suitable for the treatment of exposed skin and sensitive areas, like the head and neck. Moreover, even though it may induce prolonged periods of skin photosensitivity, during which patients need to avoid light, it lacks the serious adverse events (AE) seen in RT and systemic CT. Surgery represents the first-choice treatment and, for the majority of tumor types, the only curative intervention for early diagnosed cancer. However, since most patients are usually diagnosed at late stages, treatments such CT and RT are then preferred. In case of inoperable disease and failure or refusal of other
Interpreting patient-specific risk prediction using contextual decomposition of BiLSTMs: application to children with asthma

Rawan AlSaad1, Qutaibah Malluh2, Ibrahim Janahi3 and Sabri Boughorbel1

Abstract

Background: Predictive modeling with longitudinal electronic health record (EHR) data offers great promise for accelerating personalized medicine and better informs clinical decision-making. Recently, deep learning models have achieved state-of-the-art performance for many healthcare prediction tasks. However, deep models lack interpretability, which is integral to successful decision-making and can lead to better patient care. In this paper, we build upon the contextual decomposition (CD) method, an algorithm for producing importance scores from long short-term memory networks (LSTMs). We extend the method to bidirectional LSTMs (BiLSTMs) and use it in the context of predicting future clinical outcomes using patients’ EHR historical visits.

Methods: We use a real EHR dataset comprising 11071 patients, to evaluate and compare CD interpretations from LSTM and BiLSTM models. First, we train LSTM and BiLSTM models for the task of predicting which pre-school children with respiratory system-related complications will have asthma at school-age. After that, we conduct quantitative and qualitative analysis to evaluate the CD interpretations produced by the contextual decomposition of the trained models. In addition, we develop an interactive visualization to demonstrate the utility of CD scores in explaining predicted outcomes.

Results: Our experimental evaluation demonstrates that whenever a clear visit-level pattern exists, the models learn that pattern and the contextual decomposition can appropriately attribute the prediction to the correct pattern. In addition, the results confirm that the CD scores agree to a large extent with the importance scores generated using logistic regression coefficients. Our main insight was that rather than interpreting the attribution of individual visits to the predicted outcome, we could instead attribute a model’s prediction to a group of visits.

Conclusion: We presented a quantitative and qualitative evidence that CD interpretations can explain patient-specific predictions using CD attributions of individual visits or a group of visits.

Keywords: Interpretability, Deep learning, Predictive models, Electronic health record

Background

The exponential surge in the amount of digital data captured in electronic health record (EHR) offers promising opportunities for predicting the risk of potential diseases and better informs decision-making. Recently, deep learning models have achieved impressive results, compared to traditional machine learning techniques, by effectively learning non-linear interactions between features for several clinical tasks [1–5]. Among a variety of deep learning methods, recurrent neural networks (RNNs) could incorporate the entire EHR to produce predictions for a wide range of clinical tasks [6–11]. Consequently, there is a growing realization that, in addition to predictions, deep learning models are capable of producing knowledge about domain relationships contained in data; often referred to as interpretations [12, 13].

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Association of genes with phenotype in autism spectrum disorder

Sabah Nisar1, Sheema Hashem1, Ajaz A. Bhat1, Najeeb Syed1, Santosh Yadav1, Muhammad Waqar Azeem2,3, Shahab Uddin4, Puneet Bagga5, Ravinder Reddy5, Mohammad Haris1,6

1Research Branch, Sidra Medicine, Doha, Qatar
2Department of Psychiatry, Sidra Medicine, Doha, Qatar
3Weill Cornell Medicine, Doha, Qatar
4Translational Research Institute, Hamad Medical Corporation, Doha, Qatar
5Center for Magnetic Resonance and Optical Imaging, Department of Radiology, Perelman School of Medicine at The University of Pennsylvania, Philadelphia, PA 19104, USA
6Laboratory Animal Research Center, Qatar University, Doha, Qatar

Correspondence to: Mohammad Haris; email: mharis@sidra.org, harissgpgi@gmail.com
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ABSTRACT

Autism spectrum disorder (ASD) is a genetic heterogeneous neurodevelopmental disorder that is characterized by impairments in social interaction and speech development and is accompanied by stereotypical behaviors such as body rocking, hand flapping, spinning objects, sniffing and restricted behaviors. The considerable significance of the genetics associated with autism has led to the identification of many risk genes for ASD used for the probing of ASD specificity and shared cognitive features over the past few decades. Identification of ASD risk genes helps to unravel various genetic variants and signaling pathways which are involved in ASD. This review highlights the role of ASD risk genes in gene transcription and translation regulation processes, as well as neuronal activity modulation, synaptic plasticity, disrupted key biological signaling pathways, and the novel candidate genes that play a significant role in the pathophysiology of ASD. The current emphasis on autism spectrum disorders has generated new opportunities in the field of neuroscience, and further advancements in the identification of different biomarkers, risk genes, and genetic pathways can help in the early diagnosis and development of new clinical and pharmacological treatments for ASD.

INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurological disorder that affects an individual’s development by impairing social interaction and communication and causes stereotypical behaviors that disrupt the anatomy and functional connectivity in the brain. Most common psychiatric comorbidities found to be associated with autism include anxiety and intellectual disability. Individuals with autism have impaired speech [1, 2] and tend to have limited social interaction mostly due to their own limitation of social skills and due to their failure to understand self-inner mental states [3]. The impairment of speech in affected individuals depends on the severity of the autism disorder as autistic individuals tend to repeat certain words or phrases they hear others say, their speech might sound more formal and they exhibit repetitive behaviors [4]. The prevalence of autism is on the rise and the global prevalence of ASD has been reported to be 1 in 160 persons, according to the World Health Organization (WHO) (2014). Based on a parent survey, the recent prevalence of ASD in the U.S. is reported to be 1 in 45 children [5]. A study conducted in 2006 in the United Kingdom reported an ASD prevalence of 38.9/10,000 in 9 to 10-year-olds [6], while another study conducted by the National Autistic Society (2014) reported that 1/100 children are affected with ASD. In Gulf Cooperation Council (GCC) countries, the
The Cross Talk between Cancer Stem Cells/Cancer Initiating Cells and Tumor Microenvironment: The Missing Piece of the Puzzle for the Efficient Targeting of these Cells with Immunotherapy

Shilpa Ravindran¹ · Saad Rasool¹ · Cristina Maccalli¹

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Abstract
Cancer Stem Cells/Cancer Initiating Cells (CSCs/CICs) is a rare sub-population within a tumor that is responsible for tumor formation, progression and resistance to therapies. The interaction between CSCs/CICs and tumor microenvironment (TME) can sustain “stemness” properties and promote their survival and plasticity. This cross-talk is also pivotal in regulating and modulating CSC/CIC properties. This review will provide an overview of the mechanisms underlying the mutual interaction between CSC/CICs and TME. Particular focus will be dedicated to the immunological profile of CSCs/CICs and its role in orchestrating cancer immunosurveillance. Moreover, the available immunotherapy strategies that can target CSCs/CICs and of their possible implementation will be discussed. Overall, the dissection of the mechanisms regulating the CSC/CIC-TME interaction is warranted to understand the plasticity and immunoregulatory properties of stem-like tumor cells and to achieve complete eradication of tumors through the optimization of immunotherapy.

Keywords Cancer stem cells/Cancer initiating cells · Immunosurveillance · Adaptive immune responses · Innate immune responses · Tumor microenvironment · Immunotherapy

Abbreviations
ALDH  Aldehyde dehydrogenase
APC  Antigen presenting cells
APM  Antigen processing machinery
CAR  Chimera antigen receptor
CIC  Cancer initiating cell
CRC  Colorectal cancer
CT  Cancer testis
CTLA-4  Cytotoxic lymphocyte antigen-4
CSPG4  Chondroitin sulphate proteoglycan 4
HLA  Human leukocyte antigen
IDO  Indoleamine 2,3-dioxygenase
GBM  Glioblastoma multiforme
GDF-15  Growth differentiation factor-15
IFN  Interferon
IL-4  Interleukin 4
IL-10  Interleukin 10
IL-13  Interleukin 13
IL-13α2  α2 chain of IL-13 receptor
mAb  Monoclonal antibody
MDSC  Myeloid derived suppressor cell
NSCLC  Non-small cell lung cancer
PD-1  Programmed death 1
PD-L1  Programmed death ligand 1
RCC  Renal cell carcinoma
STAT3  Signal transducer and activator of transcription 3
TGFβ  Transforming growth factor beta
TAA  Tumor associated antigen
Treg  T regulatory cell.

Introduction
Tumors are composed by heterogeneous cellular components including a rare subpopulation bearing “stemness properties” and being responsible of tumor initiation and progression. These cells have been denominated cancer stem cells (CSCs) or cancer initiating cells (CICs) [1–6]. CSCs/CICs
Paradoxical association between blood modular interferon signatures and quality of life in patients with systemic lupus erythematosus

Julie Seguier1, Elisabeth Jouve2, Mickaël Bobot3,4, Elisabeth Whalen5, Bertrand Dussol3,4, Stéphanie Gentile2, Stéphane Burtey3,4, Philippe Halfon6, Frédérique Retornaz6, Damien Chaussabel7, Laurent Chiche6 and Noémie Jourde-Chiche3,4

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 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

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,
IMMUNODEFICIENCIES

Chronic mucocutaneous candidiasis and connective tissue disorder in humans with impaired JNK1-dependent responses to IL-17A/F and TGF-β

Juan Li1, Marco Ritelli2, Cindy S. Ma3,4, Geetha Rao15, Tanwir Habib3,6, Emilie Corvilain1,7,8, Salim Bougarr9, Sophie Cypowyj1,10, Lucie Grodecka14, Romain Levy2,7, Vivien Béziat6,7, Lei Shang11, Kathryn Payne3, Danielle T. Avery3, Mélanie Migaud6,7, Vivien Béziat6,7, Nicoletta Zoppi2, Laurent Abel1,6,7‡, Tomáš Freiberger8,13‡, Harry C. Dietz14,15‡, Nico Marr5,16‡, Yuval Itan1,9,10, Bertrand Boisson1,6,7, Valérie Cormier-Daire7,11, Delfien Syx12, Fransiska Malfait12, Stuart G. Tangye3,4‡, Marina Colombi2‡, Jean-Laurent Casanova1,6,7,17,18§.

Genetic etiologies of chronic mucocutaneous candidiasis (CMC) disrupt human IL-17A/F–dependent immunity at mucosal surfaces, whereas those of connective tissue disorders (CTDs) often impair the TGF-β–dependent homeostasis of connective tissues. The signaling pathways involved are incompletely understood. We report a three-generation family with an autosomal dominant (AD) combination of CMC and a previously undescribed form of CTD that clinically overlaps with Ehlers-Danlos syndrome (EDS). The patients are heterozygous for a private splice-site variant of MAPK8, the gene encoding c-Jun N-terminal kinase 1 (JNK1), a component of the MAPK signaling pathway. This variant is loss-of-expression and loss-of-function in the patients’ fibroblasts, which display AD JNK1 deficiency by haploinsufficiency. These cells have impaired, but not abolished, responses to IL-17A and IL-17F. Moreover, the development of the patients’ T(+) cells was impaired ex vivo and in vitro, probably due to the involvement of JNK1 in the TGF-β–responsive pathway and further accounting for the patients’ CMC. Consistently, the patients’ fibroblasts displayed impaired JNK1- and c-Jun/ATF-2–dependent induction of key extracellular matrix (ECM) components and regulators, but not of EDS-causing gene products, in response to TGF-β. Furthermore, they displayed a transcriptional pattern in response to TGF-β different from that of fibroblasts from patients with Loey-Dietz syndrome caused by mutations of TGFBR2 or SMAD3, further accounting for the patients’ complex and unusual CTD phenotype. This experiment of nature indicates that the integrity of the human JNK1-dependent MAPK pathway is essential for IL-17A– and IL-17F–dependent mucocutaneous immunity to Candida and for the TGF-β–dependent homeostasis of connective tissues.

INTRODUCTION

Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent lesions of the skin, nails, oral, and genital mucosae caused by Candida albicans (1). Patients with profound and broad inherited T cell immunodeficiencies present with CMC as one of their many infections (2). Most patients heterozygous for dominant-negative STAT3 mutations (3) or gain-of-function STAT3 mutations (4), and most patients with autosomal recessive (AR) RORC (5) or ZNF341 deficiency (6, 7) have CMC among the infections suffered, the range of which is smaller than for patients with severe T cell deficiencies. Patients with these various forms of syndromic CMC (SCMC) share a paucity of circulating T helper 17 (T(+)17) cells (5–13). Patients with AR autoimmune regulator (AIRE) deficiency display not only autoimmunity but also CMC as their only infection due to the production of neutralizing autoantibodies against interleukin-17A (IL-17A) and/or IL-17F (14, 15). Last, isolated forms of CMC (ICMC), in which CMC is the predominant or only clinical manifestation in otherwise healthy individuals, can be due to autosomal dominant (AD) IL-17F deficiency, or inborn errors of the IL-17–responsive pathway, such as AR IL-17RA, IL-17RC, and ACT1 deficiencies (16–20).

1 St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY 10065, USA. 2 Division of Biology and Genetics, Department of Molecular and Translational Medicine, University of Brescia, 25123 Brescia, Italy. 3 Immunology Division, Garvan Institute of Medical Research, Darlinghurst, New South Wales 2010, Australia. 4 St. Vincent’s Clinical School, Faculty of Medicine, University of New South Wales, Sydney, New South Wales 2010, Australia. 5 Sirad Medicine, P.O. Box 26999, Doha, Qatar. 6 Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, 75015 Paris, France. 7 Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Bimo 65691, Czech Republic. 8 The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. 9 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA. 10 Department of Medical Genetics, INSEEM U1163, Necker Hospital for Sick Children, 75015 Paris, France. 11 Center for Medical Genetics, Ghent University Hospital, 9000 Ghent, Belgium. 12 Faculty of Medicine and Central European Institute of Technology, Masaryk University, Brno 62500, Czech Republic. 13 McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA. 14 Howard Hughes Medical Institute, Baltimore, MD 21205, USA. 15 College of Health and Life Sciences, Hamad Bin Khalifa University, P.O. Box 34110, Doha, Qatar. 16 Pediatric Hematology-Immunology Unit, Necker Hospital for Sick Children, 75015 Paris, France. 17 Howard Hughes Medical Institute, New York, NY 10065, USA.

These authors contributed equally to this work.

‡Present address: Pfizer Emerging Science and Innovation, Cambridge, MA 02139, USA.

§These authors contributed equally to this work.

*Corresponding author. Email: jean-laurent.casanova@rockefeller.edu (J.-L.C.); anne.puel@inserm.fr (A.P.).
A Teaching Intervention Increases the Performance of Handheld Ultrasound Devices for Assessment of Left Ventricular Ejection Fraction

Smita Anilkumar1, Sajad Adhiraja1, Bassam Albizrehi1, Rajvir Singh2, Naser Elkum3, Alessandro Salustri1

1Non-Invasive Cardiology, Department of Cardiology, Hamad Medical Corporation, 2Department of Biostatistics, Hamad Medical Corporation, 3Qatar Cardiovascular Research Center, Sidra Medical and Research Center, Doha, Qatar

ABSTRACT

Background: Few studies have demonstrated the utility of a teaching program for evaluation of left ventricular ejection fraction (LVEF) of echocardiographic images acquired with high-end machines. No study to date explored the value of similar programs when a handheld ultrasound device is used. The aim of this study was to determine whether a teaching intervention could improve the accuracy and the reliability of LVEF visual assessment of echocardiographic images acquired with HUD.

Materials and Methods: Twenty echocardiograms acquired with a hand-held ultrasound device with a spectrum of LVEF were presented to 26 participants with varying experience in echocardiography (range 2-12 years) for single-point LVEF visual estimates. After this baseline assessment, participants underwent three training sessions which included analysis of the individual baseline results and review and interpretation of additional 60 cases from the same platform. After 2 months, 20 new echocardiograms were presented to the same 26 participants for visual LVEF assessment. For each participant, the visual LVEF for each case was compared with the reference LVEF (quantitative measurements by experts), and a difference of ≥5% was considered a misclassification.

Results: The misclassification rate was 61% preintervention and decreased to 41% after intervention (P < 0.0001). The mean absolute differences in LVEF between visual estimates and reference before and after intervention for all readers were −7.9 ± 9.6 and −1.2 ± 7.8, respectively (P < 0.0001). Inter-rater repeatability analysis was performed using the intraclass correlation coefficient. The intraclass correlation coefficient for Inter-rater reliability was fair preintervention (0.65, 95% confidence interval [CI] 0.59-0.71) and good after intervention (0.80, 95% CI 0.73-0.87), and there were no differences when categorized according to the level of experience.

Conclusions: A teaching intervention can improve the accuracy and the reliability in the visual LVEF assessment of images acquired with handheld ultrasound device.

Key words: Handheld ultrasound devices, left ventricular ejection fraction, quality improvement

INTRODUCTION

Although not recommended by the American Society of Echocardiography/European Association of Cardiovascular Imaging (EACVI)...

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A Systematic Review of Childhood Diabetes Research in the Middle East Region

Saras Saraswathi1†, Sara Al-Khawaga1,2†, Naser Elkum3 and Khalid Hussain1*

1 Division of Endocrinology, Department of Pediatrics, Sidra Medicine, Doha, Qatar; 2 College of Health & Life Sciences, Hamad Bin Khalifa University, Qatar Foundation, Education City, Doha, Qatar; 3 Biostatistics Section, Clinical Research Center, Research Services, Sidra Medicine, Doha, Qatar

Background: Diabetes mellitus (DM) is a common chronic disorder in children and is caused by absolute or relative insulin deficiency, with or without insulin resistance. There are several different forms of childhood DM. Children can suffer from neonatal diabetes mellitus (NDM), type 1 diabetes (T1DM), type 2 diabetes (T2DM), Maturity Onset Diabetes of the Young (MODY), autoimmune monogenic, mitochondrial, syndromic and as yet unclassified forms of DM. The Middle East has one of the highest incidences of several types of DM in children; however, it is unclear whether pediatric diabetes is an active area of research in the Middle East and if ongoing, which research areas are of priority for DM in children.

Objectives: To review the literature on childhood DM related to research in the Middle East, summarize results, identify opportunities for research and make observations and recommendations for collaborative studies in pediatric DM.

Methods: We conducted a thorough and systematic literature review by adhering to a list recommended by PRISMA. We retrieved original papers written in English that focus on childhood DM research, using electronic bibliographic databases containing publications from the year 2000 until October 2018. For our final assessment, we retrieved 429 full-text articles and selected 95 articles, based on our inclusion and exclusion criteria.

Results: Our literature review suggests that childhood DM research undertaken in the Middle East has focused mainly on reporting retrospective review of case notes, a few prospective case studies, systemic reviews, questionnaire-based studies, and case reports. These reported studies have focused mostly on the incidence/prevalence of different types of DM in childhood. No studies report on the establishment of National Childhood Diabetes Registries. There is a lack of consolidated studies focusing on national epidemiology data of different types of childhood DM (such as NDM, T1DM, T2DM, MODY, and syndromic forms) and no studies reporting on clinical trials in children with DM.

Conclusions: Investing in and funding basic and translational childhood diabetes research and encouraging collaborative studies, will bring enormous benefits financially, economically, and socially for the whole of the Middle East region.

Keywords: T1DM, Middle-East, childhood, MODY, insulin-resistance, prevention, epidemiology, registry
Flow-Cytometry Platform for Intracellular Detection of FVIII in Blood Cells: A New Tool to Assess Gene Therapy Efficiency for Hemophilia A

Muhammad Elnaggar, Anjude Al-Mohannadi, Dhanya Kizhakayil, Christophe Michel Raynaud, Sharefa Al-Mannai, Giusy Gentilcore, Igor Pavlovski, Abbirami Sathapan, Nicholas Van Panhuys, Chiara Borsotti, Antonia Follenzi, Jean-Charles Grivel, and Sara Deola

Detection of factor VIII (FVIII) in cells by flow cytometry is controversial, and no monoclonal fluorescent antibody is commercially available. In this study, we optimized such an assay and successfully used it as a platform to study the functional properties of phosphoglycerate kinase (PGK)-FVIII lentiviral vector-transduced cells by directly visualizing FVIII in cells after different gene transfer conditions. We could measure cellular stress parameters after transduction by correlating gene expression and protein accumulation data. Flow cytometry performed on transduced cell lines showed that increasing MOI rates resulted in increased protein levels, plateauing after an MOI of 30. We speculated that, at higher MOI, FVIII production could be impaired by a limiting factor required for proper folding. To test this hypothesis, we interfered with the unfolded protein response by blocking proteasomal degradation and measured the accumulation of intracellular misfolded protein. Interestingly, at higher MOIs the cells displayed signs of toxicity with reactive oxygen species accumulation. This suggests the need for identifying a safe window of transduction dose to avoid consequent cell toxicity. Herein, we show that our flow cytometry platform for intracytoplasmic FVIII protein detection is a reliable method for optimizing gene therapy protocols in hemophilia A by shedding light on the functional status of cells after gene transfer.

INTRODUCTION

Hemophilia A (HA) is a monogenic bleeding disorder caused by defective or absent FVIII. The available current treatment is FVIII replacement therapy from either recombinant or plasma-derived sources. Roughly 30%–40% of the patients develop anti-FVIII alloantibodies that render the replacement therapy ineffective. Even achieving subphysiological FVIII levels can alleviate the hemophilic phenotype. This made gene therapy (GT) an attractive strategy to treat this disease; accordingly, several clinical trials are currently recruiting patients, and promising clinical results were shown after intravenous administration of AAV5-FVIII therapeutic viral vector.

Gene therapy strategies targeted on CD34+ hematopoietic stem cells (HSCs) have been proposed for clinical trials to develop corrected downstream lineages, including not only megakaryocytes, but also myeloid/monocytic cell lines, both proven to be a good source of FVIII. While FVIII is widely measured intracellularly with immuno-histochemistry staining methods, a reliable protocol for flow cytometry (FC) staining is still not available. Few publications are describing controversial results on FC detection of FVIII in blood cells, with the clearest results only shown in platelets, where membrane unspecific binding of antibodies (Abs) is not a relevant issue.

To facilitate the evaluation of FVIII gene modification protocols, we optimized a FC assay to measure and functionally test intracellular FVIII in human cell lines, CD34+ HSCs, and peripheral blood mononuclear cells (PBMCs).

Such an assay could also potentially be of use in the diagnosis of hemophilia cases, especially in clinical cases where a functional protein is present but not secreted, and in cases where an intracellular evaluation is needed.

RESULTS

Choice of Cell Lines

FVIII protein is naturally produced by endothelial cells, hepatocytes, and megakaryocytes. In addition, a wide number of cells contain FVIII mRNA, and might produce small amounts of protein, for biological reasons that remain undefined. To choose reliable FVIII-producing cell lines, we selected HECV endothelial cells, as “professional” FVIII producer cells, and the HeLa cancer cell line, as, being derived from cervical tissue, it expresses high levels of FVIII mRNA. We also included U937 cells, a pre-monsoicytic cell line, representative of myeloid blood cell capacity for FVIII assembly and production.
Melanoma: Prognostic Factors and Factors Predictive of Response to Therapy

Martina Strudel1,4, Lucia Festino1,4,*, Vito Vanella1, Massimiliano Beretta2, Francesco M. Marincola1 and Paolo A. Ascierto1

1Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Cancer Immunotherapy and Innovative Therapy Unit, Naples, Italy; 2Centro di Riferimento Oncologico, Department of Medical Oncology, Aviano (PN), Italy; 3Research Branch, Sidra Medical and Research Centre, Doha, Qatar

Abstract: Background: A better understanding of prognostic factors and biomarkers that predict response to treatment is required in order to further improve survival rates in patients with melanoma.

Prognostic Factors: The most important histopathological factors prognostic of worse outcomes in melanoma are sentinel lymph node involvement, increased tumor thickness, ulceration and higher mitotic rate. Poorer survival may also be related to several clinical factors, including male gender, older age, axial location of the melanoma, elevated serum levels of lactate dehydrogenase and S100B.

Predictive Biomarkers: Several biomarkers have been investigated as being predictive of response to melanoma therapies. For anti-Programmed Death-1(PD-1)/Programmed Death-Ligand 1 (PD-L1) checkpoint inhibitors, PD-L1 tumor expression was initially proposed to have a predictive role in response to anti-PD-1/PD-L1 treatment. However, patients without PD-L1 expression also have a survival benefit with anti-PD-1/PD-L1 therapy, meaning it cannot be used alone to select patients for treatment, in order to affirm that it could be considered a correlative, but not a predictive marker. A range of other factors have shown an association with treatment outcomes and offer potential as predictive biomarkers for immunotherapy, including immune infiltration, chemokine signatures, and tumor mutational load. However, none of these have been clinically validated as a factor for patient selection. For combined targeted therapy (BRAF and MEK inhibition), lactate dehydrogenase level and tumor burden seem to have a role in patient outcomes.

Conclusion: With increasing knowledge, the understanding of melanoma stage-specific prognostic features should further improve. Moreover, ongoing trials should provide increasing evidence on the best use of biomarkers to help select the most appropriate patients for tailored treatment with immunotherapies and targeted therapies.

Keywords: Biomarkers, BRAF inhibitors, immunotherapy, MEK inhibitors, melanoma, PD-1, PD-L1, prognostic factors.

1. INTRODUCTION

The incidence of cutaneous melanoma is rising in Caucasian populations [1], which may be, in part, attributable to behavioral and societal changes resulting in increased sun-exposure [2]. While cutaneous melanoma continues to be associated with high mortality, its increasing incidence has fortunately not been accompanied by an increase in mortality rate, probably due to earlier diagnosis as well as the increasing availability of more effective treatments for metastatic disease in recent years [3]. However, in order to further improve survival in melanoma, a better understanding of prognostic factors (i.e. measurable clinical or biologic characteristics that provide information on the likely outcome) is required. Similarly, increased knowledge of predictive factors (i.e. clinical or biologic characteristics that provide information on the likely benefit from treatment, either in terms of tumor shrinkage or sur-
Genetic Variation in CCL5 Signaling Genes and Triple Negative Breast Cancer: Susceptibility and Prognosis Implications

Jingxuan Shan 1,2,3, Aziz Chouchane 4, Younes Mokrab 5, Mohamad Saad 6, Salha Boujassoum 7, Rosalyn W. Sayaman 8,9,10, Elad Ziv 10,11, Noureddine Bouaouina 12,13, Yasmine Remadi 13, Sallouha Gabbouj 13, Jessica Roelands 14, Xiaojing Ma 2, Davide Bedognetti 14 and Lotfi Chouchane 1,2,3 *

1 Department of Genetic Medicine, Weill Cornell Medicine, New York, NY, United States, 2 Department of Microbiology and Immunology, Weill Cornell Medicine, New York, NY, United States, 3 Laboratory of Genetic Medicine and Immunology, Weill Cornell Medicine-Qatar, Doha, Qatar, 4 Facolta di Medicina e Chirurgia, Universita Cattolica del Sacro Cuero, Rome, Italy, 5 Translational Genetics and Bioinformatics Section, Research Division, Sidra Medicine, Doha, Qatar, 6 Qatar Computing Research Institute, Hamad Bin Khalifa University, Doha, Qatar, 7 Department of Medical Oncology, National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar, 8 Department of Population Sciences, City of Hope, Duarte, CA, United States, 9 Department of Laboratory Medicine at UCSF, San Francisco, CA, United States, 10 Helen Diller Family Comprehensive Cancer Center at UCSF, San Francisco, CA, United States, 11 Division of General Internal Medicine, Department of Medicine, Institute for Human Genetics at UCSF, San Francisco, CA, United States, 12 Service de Cancérologie Radiothérapie, CHU Farhat Hached, Sousse, Tunisia, 13 Laboratoire d’Immuno-Oncologie Moléculaire, Faculté de Médecine de Monastir, Université de Monastir, Monastir, Tunisia, 14 Tumor Biology Section, Research Division, Sidra Medicine, Doha, Qatar

Triple-negative breast cancer (TNBC) accounts for ~15–20% of breast cancer (BC) and has a higher rate of early relapse and mortality compared to other subtypes. The Chemokine (C-C motif) ligand 5 (CCL5) and its signaling pathway have been linked to TNBC. We aimed to investigate the susceptibility and prognostic implications of genetic variation in CCL5 signaling genes in TNBC in the present study. We characterized variants in CCL5 and that of six other CCL5 signaling genes (CCND1, ZMIZ1, CASP8, NOTCH2, MAP3K21, and HS6ST3) among 1,082 unrelated Tunisian subjects (544 BC patients, including 196 TNBC, and 538 healthy controls), assessed the association of the variants with BC-specific overall survival (OVS) and progression-free survival (PFS), and correlated CCL5 mRNA and serum levels with CCL5 genotypes. We found a highly significant association between the CCND1 rs614367-TT genotype (OR = 5.14; P = 0.004) and TNBC risk, and identified a significant association between the rs614367-T allele and decreased PFS in TNBC. A decreased risk of lymph node metastasis was associated with the MAP3K21 rs1294255-C allele, particularly in rs1294255-GC (OR = 0.47; P = 0.001). CCL5 variants (rs2107538 and rs2280789) were linked to CCL5 serum and mRNA levels. In the TCGA TNBC/Basal-like cohort the MAP3K21 rs1294255-G allele was associated with a decreased OVS. High expression of CCL5 in breast tumors was significantly associated with an increased OVS in all BC patients, but particularly in TNBC/Basal-like patients. In conclusion, genetic variation in CCL5 signaling genes may predict not only TNBC risk but also disease aggressiveness.

Keywords: CCL5, CCL5 signaling genes, triple negative breast cancer, prognosis, susceptibility
Integrating omics for a better understanding of Inflammatory Bowel Disease: a step towards personalized medicine

Manoj Kumar, Mathieu Garand and Souhaila Al Khodor

Abstract
Background: Inflammatory Bowel Disease (IBD) is a multifactorial chronic disease. Understanding only one aspect of IBD pathogenesis does not reflect the complex nature of IBD nor will it improve its clinical management. Therefore, it is vital to dissect the interactions between the different players in IBD pathogenesis in order to understand the biology of the disease and enhance its clinical outcomes.

Aims: To provide an overview of the available omics data used to assess the potential mechanisms through which various players are contributing to IBD pathogenesis and propose a precision medicine model to fill the current knowledge gap in IBD.

Results: Several studies have reported microbial dysbiosis, immune and metabolic dysregulation in IBD patients, however, this data is not sufficient to create signatures that can differentiate between the disease subtypes or between disease relapse and remission.

Conclusions: We summarized the current knowledge in the application of omics in IBD patients, and we showed that the current knowledge gap in IBD hinders the improvements of clinical decision for treatment as well as the prediction of disease relapse. We propose one way to fill this gap by implementing integrative analysis of various omics datasets generated from one patient at a single time point.

Keywords: Crohn’s disease, Ulcerative colitis, Multi-omics, Systems biology

Background
Inflammatory Bowel Disease (IBD) is an inflammatory disorder of the gastrointestinal (GI) tract, resulting from the complex interactions between genetic makeup, microbiome composition, environmental factors, and mucosal immune response [1]. IBD is characterized by the repeated alternating cycles of clinical relapse and remission [2] and in the absence of an adequate treatment, a chronic inflammation leading to irreversible intestinal damages [3]. Based on the disease manifestation, IBD is classified into three major subtypes [4]: Ulcerative Colitis (UC), which primarily affects the colon, Crohn’s disease (CD) which affects various GI sites [5], and a third subtype where histology assessments done on patients do not categorize to either UC or CD. This subtype is defined as “Inflammatory Bowel Disease, type unclassified” or “Undetermined” (IBD-U) [6, 7]. IBD is a lifelong disease that substantially reduces the quality of life for the patients and their families [8].

Although the first case of UC was reported in Europe in 1875 [9] and CD was first reported in USA in 1932 [10], IBD was still a rare disease until the second half of the 20th century. Post-World War II, a rapid increase in the incidence of UC and CD had been reported, with more than 5 million people affected worldwide [11–13]. This drastic increase in IBD patterns suggest that other factors aside from industrialization must be involved in driving
Research Article

RNA-seq Reveals Dysregulation of Novel Melanocyte Genes upon Oxidative Stress: Implications in Vitiligo Pathogenesis

Konduru Seetharama Sastry, Haroon Naeem, Younes Mokrab, and Aouatif Ismail Chouchane

1Dermatology Research Unit, Division of Translational Medicine, Research Department, OPC 5th Floor, Sidra Medicine, Doha, PO Box 26999, Qatar
2Human Genetics, Translational Medicine, OPC 5th Floor, Sidra Medicine, Doha, PO Box 26999, Qatar

Correspondence should be addressed to Konduru Seetharama Sastry; skonduru@sidra.org and Aouatif Ismail Chouchane; achouchane@sidra.org

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Oxidative stress is known to induce melanocyte death, but the underlying mechanisms are incompletely understood. To identify oxidative stress-induced global gene expression changes in melanocytes, we treated PIG1 melanocytes with \( \text{H}_2\text{O}_2 \) in a dose- and time-dependent manner and performed RNA-seq. This approach allowed us to capture the events occurring early as well as late phase after treatment with \( \text{H}_2\text{O}_2 \). Our bioinformatics analysis identified differentially expressed genes involved in various biological processes of melanocytes which are known to contribute to the vitiligo development, such as apoptosis, autophagy, cell cycle regulation, cell adhesion, immune and inflammatory responses, melanocyte pluripotency, and developmental signaling such as WNT and NOTCH pathways. We uncovered several novel genes that are not previously described to be involved in melanocytic response to stress nor in vitiligo pathogenesis. Quantitative PCR and western blot analysis of selected proteins, performed on PIG1 and primary human epidermal melanocytes, confirmed the RNA-seq data. Interestingly, we discovered an aberrant regulation of several transcription factors that are involved in diabetes, neurological, and psychiatric diseases, all of which are comorbid conditions in patients with vitiligo. Our results may lead to a better understanding of the molecular mechanisms underlying vitiligo pathogenesis and help developing new drug targets for effective treatment.

1. Introduction

Reactive oxygen species (ROS) such as hydrogen peroxide (\( \text{H}_2\text{O}_2 \)), superoxide anion radical, and hydroxyl radical are generated in the cells endogenously as well as through exposure to extrinsic factors. Under physiological conditions, cells can maintain the intracellular redox homeostasis by scavenging the ROS. However, excessive ROS production disrupts the redox homeostasis and damages the organelles and biomolecules, resulting in the manifestation of a variety of diseases including skin conditions. Thus, ROS can affect diverse biological processes through multiple mechanisms [1].

Skin interfaces with the environment and thus is a major source of ROS. Additionally, ROS are continuously generated during the melanogenesis process in epidermal melanocytes, and this excessive ROS can lead to melanocyte cell death, resulting in skin conditions such as vitiligo [2]. Vitiligo is a progressive skin condition in which functional melanocytes in the epidermis are stressed and selectively destroyed leading to the absence of melanin and a consequent skin depigmentation. Numerous hypotheses about the etiology of vitiligo have been proposed, but it remains unclear what causes damage or death of melanocytes.

There is a compelling evidence that increased production of ROS and their accumulation is one of the major reasons for the death of melanocytes in vitiligo [2]. Very high levels of \( \text{H}_2\text{O}_2 \) have been reported in the epidermis and serum of vitiligo patients [3, 4]. Compared to melanocytes from healthy individuals, those from vitiligo patients showed increased sensitivity and cell death to oxidative stress caused
Approaching two decades of cystic fibrosis research in Qatar: a historical perspective and future directions

Samer Hammoudah1, Wessam Gadelhak1, Atqah AbdulWahab2, Mona Al-Langawi3 and Ibrahim A. Janahi1*

* Correspondence: janahi@sidra.org
1Pediatric Pulmonology, Pediatric Medicine, Sidra Medicine, PO Box 26999, Doha, Qatar
2 Full list of author information is available at the end of the article

Abstract
Cystic fibrosis (CF) is a genetic disease caused by a defect of CF transmembrane conductance regulator (CFTR) gene. CF affects multiple systems, predominantly with respiratory involvement. In Qatar, researchers have been exploring various aspects of the disease for almost 20 years. PubMed and Google Scholar were reviewed for articles related to CF in Qatar. The first publication appeared in the year 2000. Since then, several studies have been conducted on CF patients in Qatar considering a variety of topics. The presence of the CFTR II.234 mutation in a certain Arab tribe stands out as a distinguishing characteristic of CF patients in Qatar when compared to the larger Arab region or even worldwide. We aim here to summarize the existing CF research conducted in Qatar over the years as well as to introduce topics for future research.

Keywords: Qatar, Cystic fibrosis, Cystic fibrosis transmembrane conductance regulator, CFTR II.234 mutation, Pancreatic sufficient

Background
Cystic fibrosis (CF) is a multisystem autosomal recessive disease caused by a mutation in the CF transmembrane conductance regulator (CFTR) gene [1]. Six classes of mutations currently exist, with the most common mutation being F508del, which is classified as a class II mutation [1]. Clinical manifestations include a range of symptoms involving the pulmonary, gastrointestinal, endocrine, and reproductive systems [2]. Morbidity and mortality related to CF are mainly due to respiratory disease [3] and gastrointestinal involvement [4].

CF has been diagnosed to date in a variety of ethnic and racial groups [5]; however, the global epidemiology of CF varies based on a number of factors involving health facilities, clinical awareness, registration systems, and research activities [6]. The prevalence of CF in Northern Europe is reported to be 1 in 2,500 to 3,000, with a carrier rate of 1 in 20 to 30 [5]. Separately, the prevalence of CF among non-Hispanic whites, Hispanics, African-Americans, and Asian-Americans is reported to be 1 in 3,200; 9,200, 15,000, and 31,000, respectively [5].

In Qatar, the total number of CF patients is 82, including 34 adults (18 males and 16 females) and 48 children (22 males and 26 females). In the pediatric population (n = 48), Qatars constitute 62.5% (n = 30) of cases, while non-Qatars constitute 37.5% (n = 18). The majority of these children 63% (n = 31) have the CFTR II.234 mutation, while 35% (n = 17) have other mutations [7]. Based on figures by the Planning and Statistics Authority in Qatar, the population of Qatar is 2,772,294 as of April 2019 [8]. The majority of the population is made of expatriates (88.4%), as Qataris represent the remaining 11.6% of the total population. The majority of the non-Qatari population comes from Asia: India 24%, Nepal 16%, Philippines 11%, Bangladesh 5%, and Sri Lanka 5%. The gender ration is highly skewed toward males (75%) which is due to a large influx of male laborers [9].

In the present study, PubMed and Google Scholar were reviewed for articles related to CF in Qatar, using the keywords "cystic fibrosis" AND "Qatar." The references of identified articles were also searched for any additional relevant articles. This paper aims to briefly review the known research related to CF conducted in Qatar and to
Growth of Clinically Important Gram-Negative Bacteria on MacConkey Agar under aerobic versus CO2-enriched environment

Mohammad Rubayet Hasan1,2*, Mohammed Suleiman1, Elizabeth Ilagan1, Nigel Crouch1, Andres Perez Lopez1,2, Eva Thomas1,2, Patrick Tang1,2

1Department of Pathology, Sidra Medicine; 2Weill Cornell Medical College in Qatar, Doha, Qatar

Corresponding author: Mohammad Rubayet Hasan, PhD, FCCM, D(ABMM)
Clinical Molecular Microbiologist, Department of Pathology
Assistant Professor of Clinical Pathology and Laboratory Medicine
Weill Cornell Medical College in Qatar (WCMC-Q)

Sidra Medicine
Office no: H2M-24093
PO Box 26999, Doha, Qatar
Direct: +974 4003 2996
Mobile: +974 3003 5501
mhasan@sidra.org / http://www.sidra.org/doctors/mohammad-rubayet-hasan/
Functional assessment of variants associated with Wolfram syndrome

Melissa Riachi¹, Sebahat Yilmaz⁵, Erdal Kurnaz⁵, Zehra Aycan⁵, Semra Çetinkaya⁵, Lisbeth Tranebjærg³,⁴, Nanna Dahl Rendtorff⁵, Maria Bitner-Glindzicz¹, Detlef Bockenhauer⁶,⁷ and Khalid Hussain¹,²,*

¹Genetics and Genomic Medicine, UCL GOS Institute of Child Health, London, UK ²Department of Pediatrics, Division of Endocrinology, Sidra Medicine, Doha, Qatar ³Department of Clinical Genetics, The Kennedy Center, University Hospital, Copenhagen, Denmark ⁴Institute of Clinical Medicine (IKM), The Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark ⁵Dr. Sami Ulus Obstetrics and Gynecology, Pediatric Health and Disease Training and Research Hospital, Pediatric Endocrinology Clinic, Ankara, Turkey ⁶Department of Renal Medicine, UCL, London, UK and ⁷Renal Unit, Great Ormond Street Hospital for Children, London, UK

*To whom correspondence should be addressed at: Sidra Medicine, OPC, CS-340/PO Box 26999, Al Luqta Street, Education City North Campus, Doha, Qatar
Tel: +974-4003-7608, +974-30322007; E-mail: khussain@sidra.org

Abstract

Wolfram syndrome (WS) is a heterogeneous multisystem neurodegenerative disorder with two allelic variations in addition to a separate subtype known as WS type 2. The wide phenotypic spectrum of WS includes diabetes mellitus and optic atrophy which is often accompanied by diabetes insipidus, deafness, urological and neurological complications in combination or in isolation. To date, the understanding of the genotype-phenotype relationship in this complex syndrome remains poorly understood. In this study, we identified and explored the functionality of rare and novel variants in the two causative WS genes WFS1 and CISD2 by assessing the effects of the mutations on the encoded proteins Wolframin and ERIS, in a cohort of 12 patients with autosomal recessive WS, dominant WS and WS type 2. The identified pathogenic variants included missense changes, frameshift deletions and insertions in WFS1 and an exonic deletion in CISD2 which all altered the respective encoded protein in a manner that did not correlate to the phenome previously described. These observations suggest the lack of genotype-phenotype correlation in this complex syndrome and the need to explore other molecular genetic mechanisms. Additionally, our findings highlight the importance of functionally assessing variants for their pathogenicity to tackle the problem of increasing variants of unknown significance in the public genetic databases.

Introduction

Wolfram syndrome 1 (WS) (OMIM 222300), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness), is a widely heterogeneous autosomal recessive multisystem neurodegenerative disorder that was first described by Wolfram and Wagener (1). The first and earliest diagnosing feature of WS is non-autoimmune and non–HLA-linked diabetes
Full length article

Prediction of preterm labour from a single blood test: The role of the endocannabinoid system in predicting preterm birth in high-risk women

P. Bachkangia, A.H. Taylorab, Monica Baric, Mauro Maccarrone, Justin C. Konjeacd,e,a

a Endocannabinoid Research Group, Reproductive Sciences Section, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, UK
b Department of Molecular and Cell Biology, University of Leicester, Leicester, Department of Medicine, UK
c Università di Roma Tor Vergata, Italy
d Università Campus Bio-Medico di Roma, Italy
e Department of Obstetrics and Gynaecology, Sidra Medicine, Doha and Wellness Women's Research Center, HMC, Doha, Qatar

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Oleylethanolamide
Palmitoylethanolamide
Preterm labour
Prediction

A B S T R A C T

Objective: To determine if plasma concentrations of the N-acyl ethanolamines (NAEs) N-arachidonyl-
lethanolamine (AEA), N-oleylethanolamide (OEA) and N-palmitoylethanolamide (PEA) increase in women at high risk for preterm birth (PTB) and whether these could be used to predict preterm delivery and so, how they compare with current methods.

Design: Prospective cohort study.

Setting: A large UK teaching hospital.

Population: 217 pregnant women were recruited between 24 and 34 gestational weeks at ‘high-risk’ for PTB, recruited from a premature prevention clinic or antenatal wards.

Methods: Plasma AEA, OEA, and PEA concentrations were measured using ultra-high performance liquid chromatography-tandem mass spectrometry whilst FAAH enzyme activity was measured by fluorometric radiometric assay and CL by ultrasound scan. The clinical usefulness of these measurements were determined by ROC and multivariate analyses.

Results: AEA and PEA concentrations were significantly higher in women who delivered prematurely. An AEA concentration >1.095 nM predicted PTB, the gestational age at delivery and the recruitment to delivery interval (RTDI). A PEA concentration >17.50 nM only predicted PTB; FAAH enzyme activity was not related to these changes. Multivariate analysis (all variables) generated an equation to accurately predict the RTDI.

Conclusions: A single plasma AEA or PEA measurement can predict PTB. A single AEA measurement predicts the gestational age of delivery and the remaining period of pregnancy with reasonable accuracy and better than existing conventional tests thus offering a better window for primary prevention of PTB.

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Introduction

Preterm birth (PTB), defined as delivery before 37 completed weeks of gestation [1], constitutes 9.6% of all births worldwide [1]. 7.3% in the UK [2], and is responsible for 75% of all perinatal mortalities and many long-term morbidities for the surviving infants [3]. Its aetiology is poorly defined but threatens preterm labour (PTL), which is multifactorial [4–8] results in preterm birth in a significant number of cases. Of the many factors that have been investigated as predictors of PTB, oeno-fetal fibroinect (ofFN), and insulin-like growth factor-binding protein-1 (IGFBP-1) in cervico-vaginal swabs are commonly used in clinical practice on symptomatic women, but shown only to identify those who are unlikely to go into PTL [9–15]. The best predictive test for PTB in high-risk women is, however, sonographic cervical length measurement (CL) [16–22], with a long cervix (> 30 mm) indicative of low risk, while a cervix of ≤15 mm indicative of high risk. The actual risk of PTB, however, is dependent on when the measurement is made and the skill of the sonographer making that measurement; e.g. for a length of ≤15 mm there is a 90% risk at ≤28 weeks of gestation and 50–60% at 28–32 weeks of gestation [16,17,21]. Furthermore, CL measurement is often used in
Is radiotherapy required in first-line treatment of stage I diffuse anaplastic Wilms tumor? A report of SIOP-RTSG, AIEOP, JWiTS, and UKCCSG

Raquel Dávila Fajardo1,2 | Marry M. van den Heuvel-Eibrink2 | Harm van Tinteren4 | Filippo Spreafico3 | Thomas Acha5 | Christophe Bergeron6 | Beatriz de Camargo7 | Foppe Oldenburger8 | Christian Rübe9 | Takaharu Oue10 | Christian Vokuhl-L’Hermine14 | Paola Collini15 | Lorenza Gandola16 | Kathy Pritchard-Jones17 | Norbert Graf18 | Geert O. Janssens1,2 | Martine van Grotel2

1Department of Radiation Oncology, University Medical Centre Utrecht, Utrecht, The Netherlands
2Department of Pediatric Oncology, Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands
3Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
4Department of Statistics, The Netherlands Cancer Institute, Amsterdam, The Netherlands
5Department of Pediatric Oncology, Hospital Materno-Infantil, Málaga, Spain
6Department of Pediatric Oncology, Centre Leon Berard, Lyon, France
7Department of Pediatric Hematology and Oncology, Instituto Nacional Do Cancer (INCA), Rio de Janeiro, Brazil
8Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands
9Department of Radio-Oncology, University Hospital of Saarland, Homburg, Germany
10Department of Pediatric Surgery, Hyogo College of Medicine, Nishinomiya City, Hyogo Prefecture, Osaka, Japan
11Institute of Pediatric Pathology, University of Kiel, Kiel, Germany
12Department of Pathology, Sidra Medicine, Doha, Qatar
13Department of Histopathology, Great Ormond Street Hospital, London, UK
14Department of Pathology, Hopitaux Universitaires Est Parisien, Paris, France
15Department of Pathology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
16Department of Radiation Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
17Institute of Child Health, University College London, London, UK
18Department of Pediatric Oncology, University Hospital of Saarland, Homburg, Germany

Correspondence
Martine van Grotel, Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, 3584 CS Utrecht, The Netherlands.
Email: m.vangrotel@prinsesmaximacentrum.nl

Abstract
Background: As a significant proportion of relapses occurred in the tumor bed or abdomen on patients with the fifth National Wilms Tumor Study stage I anaplastic Wilms tumor (WT), flank radiotherapy was added for stage I anaplastic WT in the subsequent study of the Children’s Oncology Group (AREN0321). Preliminary results revealed reduction of relapse rate and improved survival. In cases treated with preoperative chemotherapy, such as in International Society of...
Pediatric Oncology (SIOP), the value of radiotherapy has never been studied. The aim of this observational study is to describe the pattern of recurrence and survival of patients with stage I diffuse anaplastic WT (DAWT) after induction chemotherapy.

**Methods:** Retrospective data analysis of the pattern of relapse and survival of all patients with stage I DAWT were included in recent SIOP, L’Associazone Italiana Ematologica Oncologia Pediatrica (AIEOP), Japan Wilms Tumor Study Group (JWITS), United Kingdom Children’s Cancer Study Group (UKCCSG) renal tumor registries. Postoperative treatment consisted of actinomycin D, vincristine, and doxorubicin for 28 weeks without local irradiation.

**Results:** One hundred nine cases with stage I DAWT were identified, of which 95 cases received preoperative chemotherapy. Of these, seven patients underwent preoperative true-cut biopsy. Sixteen of the 95 patients relapsed (17%), six locally, four at distant site, and six combined, and all treated according to SIOP 2001 relapse protocol, which resulted in a 5-year overall survival of 93%.

**Conclusion:** Despite 13% locoregional relapse rate, an excellent rescue rate was achieved after salvage treatment, in patients with stage I DAWT whose first-line treatment comprised three-drug chemotherapy (including doxorubicin), without flank irradiation. Therefore, we continue not to advocate the use of radiotherapy in first-line treatment after preoperative chemotherapy in stage I DAWT in the next SIOP protocol.

**Keywords**
diffuse anaplasia, radiotherapy, stage I, Wilms tumor

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**1 | INTRODUCTION**

Outcome for children with Wilms tumor (WT) has significantly improved over the past decades, as illustrated by overall survival (OS) rates of approximately 90%.\(^1\)\(^-\)\(^4\) Recognized prognostic factors for survival include age, stage, gender, and histology.\(^2\)\(^-\)\(^5\)\(^-\)\(^10\) Among the high-risk cases that can be identified based on histology, there is a subgroup characterized by diffuse anaplasia (DA).\(^1\)\(^,\)\(^11\)\(^,\)\(^12\) Presence of anaplasia is observed in 5% to 10% of all WT and, especially DA, is associated with adverse outcome.\(^11\)\(^-\)\(^12\) In the fifth National Wilms Tumor Study (NWTS-5), 79% of all anaplastic tumors presented with DA, while 21% had focal anaplasia (FA).\(^11\) This is concordant with International Society of Pediatric Oncology (SIOP) data that showed 81% DA and 19% FA.\(^12\) Five-year OS for all stages of diffuse anaplastic WT (DAWT) does not exceed 60%, in contrast to the higher than 90% OS that is observed in nonanaplastic tumors.\(^14\)

In general, DAWT is usually treated with more intensive regimens in order to improve cure rates. Interestingly, the results of the NWTS-5 revealed a significantly lower 4-year event-free survival (EFS) and OS for stage I DAWT after initial nephrectomy (68% and 78%, respectively) compared to 92% and 98%, respectively, for stage I favorable histology patients.\(^11\) The relatively high proportion of local and combined relapses in stage I anaplastic WT observed in NWTS-5 advocates for the use of doxorubicin as well as adjuvant radiotherapy in this specific group of patients in the subsequent AREN0321 protocol. Preliminary data showed an improvement in EFS and OS in patients treated according to the more intensive study regimen including radiotherapy in stage I.\(^15\) Whether flank radiotherapy also benefits patients with stage I DAWT undergoing preoperative chemotherapy, such as in the SIOP setting, has never been evaluated.

To address this question, we invited all non-COG (Children’s Oncology Group) national and multinational renal tumor study groups to provide available information on patients with stage I DAWT who received preoperative chemotherapy and were registered in their recent studies in Europe and Japan (International Society of Pediatric Oncology-Renal Tumor Study Group [SIOP-RTSG; including Brazil], L’Associazone Italiana Ematologica Oncologia Pediatrica [AIEOP], United Kingdom Children’s Cancer Study Group [UKCCSG], and Japan Wilms Tumor Study group [JWITS]), in order to find evidence for the use of adjuvant radiotherapy in this rare subset of patients.

**2 | PATIENTS AND METHODS**

This observational study selected prospectively registered data of all patients with stage I DAWT included until 2015, in the most recent renal studies of the SIOP-RTSG 93-01/2001 studies, AIEOP TW-2003 study, JWITS-1 and 2 studies, and the UKCCSG (UKW3 trial).

DAWT was confirmed based on the international definitions.\(^12\)\(^,\)\(^16\) Briefly, DA was defined as (a) nonlocalized anaplasia and/or anaplasia beyond the original tumor capsule; (b) anaplastic cells present in intra- or extrarenal vessels, renal sinus, extracapsular invasive sites, or metastatic deposits; (c) the anaplasia is focal but nuclear atypia approaching the criteria for anaplasia (so-called unrest nuclear change) is present elsewhere in the tumor; (d) anaplasia that is not clearly demarcated from nonanaplastic tumor; and (e) anaplasia present in a
Optimized peripheral blood progenitor cell mobilization for autologous hematopoietic cell transplantation in children with high-risk and refractory malignancies

Eliska Furlong1 | Jesper Jensen2 | Mark Woodard3,4 | Katherine Griffiths3 | Geoff Knight3,5 | Marian Sturm6 | Fiona Kerr1 | Hazel Gough1 | Natasha Bear7 | Tina L. Carter1,2,5 | Catherine H. Cole5,8 | Rishi S. Kotecha1,5,9 | Shanti Ramachandran1,5

1Department of Paediatric and Adolescent Haematology, Oncology, Blood and Marrow Transplantation, Perth Children's Hospital, Perth, WA, Australia
2PathWest Laboratory Medicine WA, Perth, WA, Australia
3Paediatric Intensive Care Unit, Perth Children's Hospital, Perth, WA, Australia
4School of Nursing, Midwifery and Paramedicine, Curtin University, Perth, WA, Australia
5Division of Paediatrics, School of Medicine, University of Western Australia, Perth, WA, Australia
6Cell and Tissue Therapy, Royal Perth Hospital, Perth, WA, Australia
7Department of Clinical Research and Education, Perast Children's Hospital, Perth, WA, Australia
8Paediatric Haematology and Oncology, Sidra Medicine, Doha, Qatar
9Division of Children's Leukaemia and Cancer Research, Telethon Kids Cancer Centre, Telethon Kids Institute, Perth, WA, Australia

Correspondence
Eliska Furlong and Shanti Ramachandran, Department of Paediatric and Adolescent Haematology, Oncology, Blood and Marrow Transplantation, Perth Children's Hospital, 15 Hospital Avenue, Nedlands, WA 6009, Australia.
Emails: Eliska.Furlong@health.wa.gov.au (EF); Shanti.Ramachandran@health.wa.gov.au (SR)

Funding Information
Medical Research Council

Abstract

Background: Autologous hematopoietic stem cell transplantation (aHSCT) using hematopoietic progenitor cells (HPCs) has become an important therapeutic modality for patients with high-risk malignancies. Current literature on standardized method for HPC apheresis in children is sparse and failure rate reported as high as 30%.

Patients/Methods: A retrospective study of 125 pediatric patients with high-risk malignancies undergoing aHSCT in Western Australia between 1997 and 2016 was conducted.

Results: Mobilization was achieved by means of chemotherapy and granulocyte colony-stimulating factor (G-CSF). Patients underwent apheresis the day after CD34+ counts reached ≥20/µL and an additional dose of G-CSF. Peripheral arterial and intravenous lines were inserted in pediatric intensive care unit under local anesthetic and/or sedation, omitting the need for general anesthesia as well as facilitating an uninterrupted apheresis flow. Larger apheresis total blood volumes were processed in patients weighing ≤20 kg. The minimal dose of ≥2 × 10^6 CD34+ cells/kg was successfully collected in 98.4% of all patients. The optimal dose of 3-5 × 10^6 CD34+ cells/kg was collected in 96% of patients scheduled for a single aHSCT, 87.5% for tandem, and 100% for triple aHSCT. All HPC collections were completed in one apheresis session. Mobilization after ≤3 chemotherapy cycles and cycles including cyclophosphamide resulted in a significantly higher yield of CD34+ cells.

Conclusion: Our approach to HPC mobilization by means of chemotherapy and single myeloid growth factor combined with optimal collection timing facilitated by continuous apheresis flow resulted in highly effective HPC harvest in children and adolescents with high-risk cancers.

Keywords
granulocyte colony-stimulating factor, hematopoietic progenitor cell mobilization, peripheral blood progenitor cell apheresis

Abbreviations: aHSCT, autologous hematopoietic stem cell transplantation; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor; HPC-A, hematopoietic progenitor cells obtained by means of apheresis; HPCs, hematopoietic progenitor cells; HSCT, hematopoietic stem cell transplantation; PNET, primitive neuroectodermal tumor.
Skin trophicity improvement by mechanotherapy for lipofilling-based breast reconstruction postradiation therapy

Kais Razzouk MD | Philippe Humbert MD, PhD | Bruno Borens MD | Marie Gozzi | Noor Al Khori MD | Jennifer Pasquier PhD | Arash Rafii Tabrizi MD, PhD

1Nice Breast Institute, Nice Breast institute, Nice, France
2Centre d’Etudes et de Recherche sur le Tégument (CERT), INSERM UMR1098, SFR FED 4234 IBCT, University of Franche-Comté, Besançon, France
3Polyclinique Santa Maria, Nice, France
4Department of Diagnostic Imaging, Sidra Medicine, Doha, Qatar
5Weill Cornell Medicine in Qatar, Education City, Doha, Qatar

Correspondence
Kais Razzouk, Nice Breast Institute, 57 bld de la Californie, 06000 Nice, France.
Email: kais.razzouk@gmail.com

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Abstract
Background: Post-mastectomy irradiation severely impairs skin trophicity resulting in poor prosthetic implant outcome. Autologous fat grafting improves skin quality allowing minimally invasive approach with prosthetic reconstruction. Here, we report our pilot experience of preoperative mechanotherapy to optimize lipofilling and subsequent prosthetic reconstruction outcome.

Methods: We retrospectively included 65 women that had breast reconstruction using autologous fat grafting and implant placement from 2012 to 2018 benefiting or not from mechanotherapy before the reconstructive procedure. Demographic and surgical outcomes were recorded.

Results: The volume of fat injected was significantly superior in the mechanotherapy group compared with the controls for the first and second lipofilling (259.3 mL vs 150.6 mL and 251.8 mL vs 154 mL, respectively). Sixteen patients among controls required a pre-expansion prosthesis compared with none in the endermology group. The prosthesis volume was smaller in the endermology group. Six patients in the endermology group had a reconstruction without prosthesis. The aesthetic score evaluated by patients was 4.8 with no statistically significant difference between the two groups.

Conclusion: Preoperative skin mechanotherapy and postoperative skin mechanotherapy increase skin compliance. It is associated with a higher volume of fat injection and lower prosthesis volume. If confirmed in a prospective study, endermology could become a standard in patients’ preparation for lipofilling-based reconstruction.

KEYWORDS
breast reconstruction, irradiated skin, mecanisation, post-mastectomy

1 INTRODUCTION

Despite the increasing prevalence of lumpectomy for early detected tumors, mastectomy remains a commonly performed procedure.1,2 Women who undergo mastectomy may choose to have breast reconstruction either with a prosthetic implant, a flap, or a combination of both. Flap-based reconstruction is currently the standard when patients received radiation therapy. Prosthetic outcome in patients with mastectomy and radiation therapy is quite poor and associated with high morbidity rate. Indeed radiation therapy decreases epithelial tissue thickness, worsens blood circulation in dermal tissue, and inhibits regenerative ability of the skin.3,4 Autologous fat grafting (AFG) or lipofilling has been used for aesthetic and reconstructive indications.5-10 AFG is a minimally invasive procedure associated with low morbidity and can be used as an autologous filler but also to reverse fibrotic changes and rejuvenate irradiated skin.5 In order to improve lipofilling outcome, external expansion devices have been developed to prepare recipient site.11,12
Bacteriuria in pregnancy varies with the ambiance: a retrospective observational study at a tertiary hospital in Doha, Qatar

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Abstract

Objective: To explore the influence of ambient temperature and humidity on significant bacteriuria (SB) and urinary bacterial isolates in pregnant women.

Methods: A retrospective observational study was conducted in the sole tertiary-care hospital in Doha, Qatar. A sample of 1588 pregnant women delivering between June 2012 and March 2013 was randomly selected. Meteorological variables including ambient average daily temperature and humidity were sourced from online meteorological data, and patient information such as demographic data, urine culture results and bacterial isolates were collected from patient files. The receptor operative curve (ROC) analysis was used to determine the cutoff for temperature and humidity. Statistical analyses of associations between SB and bacterial isolates with respect to the ambient temperature and humidity were performed using Pearson’s correlation, the chi-square (χ²) test and the Kruskal-Wallis test.

Results: Of the 21.24% positive cultures, 11.25% had SB. SB showed a significant strong positive (r = +0.677, n = 17, P = 0.003) and moderate negative (r = −0.587, n = 17, P = 0.013) correlation with average monthly temperature and humidity, respectively, with doubling of rates noted with temperatures ≥35°C (11.3% vs. 3.6%; P < 0.0001) and humidity ≤50% (10.6% vs. 3.2%; P < 0.0001). Escherichia coli and Group B Streptococcus (GBS) were the most common isolates.

Conclusion: This is the first study in this region that demonstrates maternal risk with SB, with ambient temperatures of ≥35°C and humidity ≤50%. The effect of these variables on the growth of various urinary bacteria has also been shown.

Keywords: climatic variation in pregnancy; significant bacteriuria; urinary tract infection (UTI).

Introduction

Urinary tract infection (UTI) is the most common infection in young healthy pregnant women, and it is associated with significant maternal morbidity [1]. Approximately, a third of untreated bacteriuria can progress to pyelonephritis. This is promoted by immunosuppression, anatomical and physiological changes of pregnancy, and other factors such as maternal age, socioeconomic status, sexual activity, urinary tract anomalies and systemic disease [2].

The influence of environmental factors on human health is recognized as a significant contribution to a range of clinical morbidities. The incidence of infectious diseases is known to vary with the seasons, mainly due to changes in the virulence of organisms in relation to temperature and humidity, human behavior and physiology [3]. However, the impact of climatic patterns on UTI, specifically in pregnant women, has not been adequately studied. A retrospective analysis of 3221 house calls in Greece showed an increase due to urinary tract infective symptoms during higher temperatures and decreased humidity in men and women [4]. A longitudinal analysis conducted in the UK showed autumnal seasonality for UTI consultation in primary care demonstrated over 7 years [5]. However, a retrospective study done in 1132 pregnant women in Iran showed more than 50% of infections occurring in winter [6]. The inconsistencies reported are more likely due to methodological flaws.
Self-Stigmatization in children receiving mental health treatment in Lahore, Pakistan

Amna Khalil, Fazila Gondal, Nazish Imran, Muhammad Waqar Azeem

A Department of Child and Family Psychiatry, King Edward Medical University, Lahore, Pakistan
B Child & Family Psychiatry Department, King Edward Medical University/Mayo Hospital, Lahore, Pakistan
C Department of Psychiatry, Sidra Medicine, Professor of Psychiatry, Weill Cornell Medicine, Cornell University, Doha, Qatar

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ABSTRACT

Introduction: Self-stigma has a negative impact on the lives of children with mental health illnesses. It is a massive obstacle in the way of seeking professional help and poses a challenge to clinician’s efforts to timely intervene and provide treatment.

Aim: The aim of our study was to measure the stigma associated with mental illness in children with a variety of psychiatric diagnoses.

Methods: Following Institutional Review Board approval, an interviewer-based questionnaire was administered to children (aged 8–12 years), receiving treatment in Child Psychiatry Department at a tertiary care hospital in Lahore. The questionnaire comprised of Demographic Information Form and Paediatric Self-Stigmatization Scale (PaedS). In addition, parent / caregiver also completed a modified sub scale of the PaedS measuring the children’s rejection by others due to their mental health difficulties.

Results: 110 children with various psychiatric problems, were interviewed with a mean age of 10 years ± 1.7. Widespread presence of self-stigmatization was found in these children with particularly high scores for the scales of Societal Devaluation (2.6 ± 0.54), Secrecy (2.85 ± 0.59) and Self stigma (2.7 ± 0.70). Almost two third of parents also answered in affirmative to statements about their children rejection by others due to their mental health difficulties. Children with emotional/ behavioral difficulties had statistically significant scores on secrecy and personal rejection subscales (P value < .05).

Conclusions: Significant self-stigmatization amongst the children diagnosed with mental health illnesses in Lahore, Pakistan emphasize negative societal attitudes, which need to be addressed effectively in a timely manner.

1. Introduction

The word stigma has been defined by many and although it is not an alien terminology anymore, the experience of being subjected to stigma is distinctive for each person. Stigma has been described as a “deeply discrediting attribute”, which “reduces the bearer from a whole and usual person to a tainted, discounted one” (Goffman, 1963; Bruce, 2001). This results in prejudice and discrimination from others against the stigmatized individual, and at its worst leads to internalization of the negatively held beliefs by the recipient (Kaushik et al., 2017). This internalization is termed as self-stigma. Stigma manifests in many ways, is echoed through various mediums, presents itself in a multitude of arenas and the saddest part is that it is perpetuated at times unknowingly by many surrounding the individual. Across the past several decades, the range of literature on stigmatization of individuals with mental illness, has become large and multifaceted. Most studies, however are based on adults and are derived from Western countries. Given the discussion about the increasing prevalence of psychiatric disorders in children and use of psychiatric medication, there is a lack of empirical evidence about public perceptions of pediatric psychiatric disorders and the parents and children who experience them (Pescosolido et al., 2007; Pescosolido, 2007). Therefore, although often assumed to be a significant factor in child mental health services research, the role of stigma is under-conceptualized and under-researched in this domain (Heinger and Hinshaw, 2010) In developing countries that fall under the Asian belt, there is a higher prevalence of stigma

Abbreviations: PaedS, Paediatric Self-Stigmatization Scale; KEMU, King Edward Medical University; DIF, Demographic Information Form

* Corresponding author.

E-mail addresses: amnakhalil15@gmail.com (A. Khalil), fazilaijazgondal92@gmail.com (F. Gondal), nazishimrandr@gmail.com (N. Imran), mazeem@sidra.org (M.W. Azeem).

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Original Articles

“Teratoid” Wilms Tumor

The Extreme End of Heterologous Element Differentiation, Not a Separate Entity

D’Hooghe, Ellen MD*; Mifsud, William MD, PhD, FRCPath†; Vujanić, Gordan M. MD, PhD, FRCPath‡

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Abstract

Wilms tumor (WT) may show a diverse range of heterologous elements (HEs). Cases with predominant/prominent HEs have been reported as “teratoid” WT, albeit on the basis of poorly defined criteria. It has been suggested that “teratoid” WTs are rare, and associated with a poor response to chemotherapy, but a good outcome. However, these claims have not been tested previously in any large cohort of cases. Here, we performed a systematic study to determine the incidence, diversity, and clinicopathologic association of HEs in 691 WTs, all of which were treated according to the same protocol, which included preoperative chemotherapy, and all with central pathology review. We found that 4% (28/691) of WTs showed ≥3 HEs (“teratoid” WT in our study), which was comparable to the numbers of completely necrotic, epithelial, focal anaplastic, and blastemal WTs. “Teratoid” WTs were strongly associated with younger age at presentation (21 vs. 39 mo, \(P=0.0001\)), bilateral disease (28.6% vs. 7.2%, \(P=0.001\)), stromal-type WT (57.1% vs. 11.0%, \(P<0.00001\)), and intralobar nephrogenic rests (35.7% vs. 11.9%, \(P=0.0001\)), when compared with non-“teratoid” WT. We also found that stromal-type WT, regardless of HE differentiation, was itself associated with younger age, bilateral disease, and intralobar nephrogenic rest. Furthermore, >80% of cases with ≥3 HEs, and also of cases with 2 HEs and 1 HE, showed ≥50% stroma in their viable components. We conclude that a tendency toward stromal differentiation is a strong and unifying factor in HE formation. “Teratoid” WT represents the more extreme end of HE differentiation, rather than a separate entity, and therefore the term should not be used in the final diagnosis. The prognosis of WTs depends only on their overall histologic type and stage, and it is not additionally influenced by the presence of “teratoid” features.

The term “teratoid” Wilms tumor (tWT) was first used by Variend et al\(^1\) to describe a case of Wilms tumor (WT), in which a wide diversity of epithelial and mesenchymal differentiation was observed. In 1988, Fernandes et al\(^2\) reported 3 additional cases with similar features and suggested that these cases constituted a separate WT entity, in which there is a clear predominance of heterologous elements (HEs), comprising >50% of the tumor, and with a strong tendency to occur in patients with bilateral renal tumors. Since then, another 40 cases have been reported, including unilateral tumors, extrarenal tumors, and also tWT in adults.\(^3-34\) The term “teratoid” implies the
Recessive Mutations in AP1B1 Cause Ichthyosis, Deafness, and Photophobia

Lynn M. Boyden, Lihi Atzmony, Claire Hamilton, Jing Zhou, Young H. Lim, Ronghua Hu, John Pappas, Rachel Rabin, Joseph Ekstien, Yoel Hirsch, Julie Prendiville, Richard P. Lifton, Shawn Ferguson, and Keith A. Choate

We describe unrelated individuals with ichthyosis, failure to thrive, thrombocytopenia, photophobia, and progressive hearing loss. We find bi-allelic mutations in AP1B1, the gene encoding the β subunit of heterotetrameric adaptor protein 1 (AP-1) complexes, which mediate endosome polarization, sorting, and transport. In affected keratinocytes the AP-1 β subunit is lost, and the γ subunit is greatly reduced, demonstrating destabilization of the AP-1 complex. Affected cells and tissue contain an abundance of abnormal vesicles and show hyperproliferation, abnormal epidermal differentiation, and derangement of intercellular junction proteins. Transduction of affected cells with wild-type AP1B1 rescues the vesicular phenotype, conclusively establishing that loss of AP1B1 function causes this disorder.

Within eukaryotic cells, vesicular transport is the main mechanism for moving proteins between organelles. As components of the vesicle protein coats, adaptor protein (AP) complexes coordinate vesicle formation and cargo selection at multiple sites within the endosome system, which includes the trans-Golgi network (TGN), endosomes, lysosomes, and the plasma membrane. There are at least seven AP complexes in mammals (AP-1A, -1B, -2, -3A, -3B, -4, and -5), two of which are tissue-specific (AP-1B and -3B). Each of these are heterotetramers composed of two large subunits, a medium subunit, and a small subunit. The large subunits (α, γ, δ, or ε) mediate target membrane binding and coat recruitment. A medium subunit (μ) contributes to cargo sorting, and together with a small subunit (σ) stabilizes the complex.

Most epithelial cells contain two types of AP-1 complex, the ubiquitously expressed AP-1A and the epithelium-specific AP-1B. These complexes function in clathrin-coated vesicle budding within the TGN and endosomes, as well as in polarized transport of proteins to the basolateral membrane. Both AP-1 complexes are composed of β, γ, μ, and σ subunits and are distinguished from one another by the μ subunit (μLA in AP-1A and μLB in AP-1B). Both share a β subunit encoded by AP1B1 (MIM: 600157; GenBank: NM_001127.3).

The entire AP1B1 protein sequence is highly conserved; residue identity between the human sequence and that for dogs is >98%, for chickens >95%, and for cavefish >88%, and there is near-total orthologous conservation in the N-terminal two-thirds of the protein. There is >84% residue identity with the paralogous AP2B1, the β subunit in AP-2 complexes. The AP1B1 probability of loss intolerance, a constraint metric based on the difference between observed and expected numbers of loss-of-function mutations in the human gene, is 0.99 (extremely intolerant of loss-of-function mutations). Immunostaining reveals that AP1B1 is expressed throughout the epidermis (Figure S1).

The Yale Human Investigation Committee approved the study protocol, and participants provided verbal and written informed consent. Within a large cohort of individuals with keratinization disorders with and without associated syndromic features, exome sequencing revealed two individuals with recessive loss-of-function mutations in AP1B1. The mutations were confirmed by Sanger sequencing. Individual 424 is compound heterozygous for AP1B1 mutations c.430T>C; c.2335delC (p.Cys144Arg; p.Leu779Serfs*26), inherited from the affected individual’s mother and father, respectively (Figure 1A). Cysteine at position 144 is completely conserved in orthologs. Modeling of p.Cys144Arg within the AP-1 crystal structure demonstrates that, although the wild-type cysteine does not form any disulfide bonds, the substitution replaces a charged and hydrophilic residue with a charged and hydrophobic residue and breaks buried hydrogen bonds. Individual 1325 is homozygous for AP1B1 mutation c.2374G>T (p.Glu792*) with identity by descent; her parents are second cousins once removed (Figure 1B). The family is Ashkenazi Jewish. None of these mutations are found in databases of human genetic variation or in in-house unaffected controls. To establish the effect of AP1B1 mutations on the AP-1 complex, we examined the amounts of both AP1B1 and the γ AP-1 subunit AP1G1 by immunoblotting of lysates from keratinocytes.

1Department of Genetics, Yale University School of Medicine, New Haven, CT 06510, USA; 2Department of Dermatology, Yale University School of Medicine, New Haven, CT 06510, USA; 3Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 6997801, Israel; 4Department of Pediatrics, New York University School of Medicine, New York, NY 10016, USA; 5Dor Yeshorim, Committee for Prevention of Jewish Genetic Diseases, Brooklyn, NY 11211, USA; 6Department of Pediatrics, Sidra Medical and Research Center, Doha, Qatar; 7Department of Cell Biology, Yale University School of Medicine, New Haven, CT 06510, USA; 8Department of Pathology, Yale University School of Medicine, New Haven, CT 06510, USA

*Correspondence: keith.choate@yale.edu

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Anti hypertensive agents: a long way to safe drug prescribing in children

Nida Siddiqi1 • Ibrahim F. Shatat2,3,4 ©

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Abstract
Recently updated clinical guidelines have highlighted the gaps in our understanding and management of pediatric hypertension. With increased recognition and diagnosis of pediatric hypertension, the use of antihypertensive agents is also likely to increase. Drug selection to treat hypertension in the pediatric patient population remains challenging. This is primarily due to a lack of large, well-designed pediatric safety and efficacy trials, limited understanding of pharmacokinetics in children, and unknown risk of prolonged exposure to antihypertensive therapies. With newer legislation providing financial incentives for conducting clinical trials in children, along with publication of pediatric-focused guidelines, literature available for antihypertensive agents in pediatrics has increased over the last 20 years. The objective of this article is to review the literature for safety and efficacy of commonly prescribed antihypertensive agents in pediatrics. Thus far, the most data to support use in children was found for angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), and calcium channel blockers (CCB). Several gaps were noted in the literature, particularly for beta blockers, vasodilators, and the long-term safety profile of antihypertensive agents in children. Further clinical trials are needed to guide safe and effective prescribing in the pediatric population.

Keywords Anti hypertensive agents • Clinical trials • Drug therapy • Hypertension • Pediatric • Safety

Introduction
Hypertension (HTN) in children and adolescents is defined as an average clinic measured systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) > 95th percentile (on the basis of age, sex, and height percentiles) [1]. Historically, pediatric HTN was considered a secondary phenomenon until proven otherwise. However, recent evidence describes primary HTN as being more likely than secondary HTN among children referred to subspecialty care for evaluation of elevated blood pressure (BP). Furthermore, the prevalence of HTN in children has been rising alongside the prevalence of obesity and increased awareness and screening among pediatricians and general practitioners. It is estimated that 3.5% of children and adolescents suffer from HTN, with prevalence as high as 25% in obese and overweight adolescents [2, 3].

In children and adolescents diagnosed with HTN, the treatment goal with non-pharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to < 90th percentile or < 130/80 mm Hg, whichever is lower [1]. It is widely acceptable and recommended that lifestyle modifications should be the first-line management approach for HTN in children and adolescents. Antihypertensive medications are reserved for children with hypertensive urgencies and emergencies, evidence of target organ damage, co-existent comorbidities, and failed first-line management [1].

Clinical practice guidelines for screening and management of high BP in children and adolescents [1] recommend a stepwise therapeutic approach, starting with a single medication at the low end of the dosing range, and increasing every 2 to 4 weeks until BP is controlled (< 90th percentile), the maximal dose is reached, or adverse effects occur. If BP remains uncontrolled, a second agent can be added and dose can be titrated up as with the first agent. To balance the salt and water retention that occurs with many antihypertensive medications, a thiazide diuretic may be preferred as the second agent [1].

1 Department of Pharmacy, Sidra Medicine, Doha, Qatar
2 Pediatric Nephrology and Hypertension, Sidra Medicine, HB. 7A, 106A, PO Box 26999, Doha, Qatar
3 Weill Cornell College of Medicine-Qatar, Ar-Rayyan, Qatar
4 Medical University of South Carolina, Charleston, SC, USA

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Interpreting patient-specific risk prediction using contextual decomposition of BiLSTMs: application to children with asthma

Rawan AlSaad1,2*, Qutaibah Malluhi2, Ibrahim Janahi3 and Sabri Boughorbel1

Abstract

Background: Predictive modeling with longitudinal electronic health record (EHR) data offers great promise for accelerating personalized medicine and better informs clinical decision-making. Recently, deep learning models have achieved state-of-the-art performance for many healthcare prediction tasks. However, deep models lack interpretability, which is integral to successful decision-making and can lead to better patient care. In this paper, we build upon the contextual decomposition (CD) method, an algorithm for producing importance scores from long short-term memory networks (LSTMs). We extend the method to bidirectional LSTMs (BiLSTMs) and use it in the context of predicting future clinical outcomes using patients’ EHR historical visits.

Methods: We use a real EHR dataset comprising 11071 patients, to evaluate and compare CD interpretations from LSTM and BiLSTM models. First, we train LSTM and BiLSTM models for the task of predicting which pre-school children with respiratory system-related complications will have asthma at school-age. After that, we conduct quantitative and qualitative analysis to evaluate the CD interpretations produced by the contextual decomposition of the trained models. In addition, we develop an interactive visualization to demonstrate the utility of CD scores in explaining predicted outcomes.

Results: Our experimental evaluation demonstrate that whenever a clear visit-level pattern exists, the models learn that pattern and the contextual decomposition can appropriately attribute the prediction to the correct pattern. In addition, the results confirm that the CD scores agree to a large extent with the importance scores generated using logistic regression coefficients. Our main insight was that rather than interpreting the attribution of individual visits to the predicted outcome, we could instead attribute a model’s prediction to a group of visits.

Conclusion: We presented a quantitative and qualitative evidence that CD interpretations can explain patient-specific predictions using CD attributions of individual visits or a group of visits.

Keywords: Interpretability, Deep learning, Predictive models, Electronic health record

Background

The exponential surge in the amount of digital data captured in electronic health record (EHR) offers promising opportunities for predicting the risk of potential diseases and better informs decision-making. Recently, deep learning models have achieved impressive results, compared to traditional machine learning techniques, by effectively learning non-linear interactions between features for several clinical tasks [1–5]. Among a variety of deep learning methods, recurrent neural networks (RNNs) could incorporate the entire EHR to produce predictions for a wide range of clinical tasks [6–11]. Consequently, there is a growing realization that, in addition to predictions, deep learning models are capable of producing knowledge about domain relationships contained in data; often referred to as interpretations [12, 13].
A Prospective, Randomized, Double-Blinded Study of the Effect of Intravenous Ondansetron on the Effective Dose in 50% of Subjects of Prophylactic Phenylephrine Infusions for Preventing Spinal Anesthesia–Induced Hypotension During Cesarean Delivery

Fei Xiao, MD,* Changna Wei, MD,‡ Xiangyang Chang, MD,* Yinfa Zhang, MD,* Lili Xue, MD,‡ Huaxiang Shen, MD,‡ Warwick D. Ngan Kee, MD, FANZCA, FHKCA,* and Xinzhong Chen, MD†

BACKGROUND: Ondansetron has been shown to reduce the incidence of hypotension and vasopressor requirement during spinal anesthesia for obstetric and nonobstetric surgery. However, the magnitude of this effect has not been fully quantified. In this parallel-group, randomized, double-blinded study, we determined the effective dose in 50% of subjects (ED50) of a prophylactic phenylephrine infusion for preventing hypotension in patients who received a single dose of intravenous ondansetron 4 mg or saline control before combined spinal–epidural anesthesia for elective cesarean delivery. ED50 values obtained were compared to estimate the effect of ondansetron versus placebo on vasopressor requirement.

METHODS: Sixty parturients were randomly assigned to receive ondansetron (group O) or saline control (group C) 10 minutes before positioning for induction of spinal anesthesia. A prophylactic phenylephrine infusion was used to prevent hypotension. The first patient in each group received a phenylephrine infusion at the rate of 0.5 µg/kg/min. The infusion rate for each subsequent patient was varied with increments or decrements of 0.05 µg/kg/min based on the response of the previous patient, and the effective dose of the phenylephrine infusion for preventing hypotension in 50% of patients (ED50) was calculated for each group and compared using up-down sequential analysis. Probit regression was applied as a backup and sensitivity analysis was used to compare ED50 values for phenylephrine between groups by comparing calculated relative mean potency.

RESULTS: The ED50 (mean [95% confidence interval (CI)]) of the rate of phenylephrine infusion was lower in group O (0.24 µg/kg/min [0.10–0.38 µg/kg/min]) compared with group C (0.32 µg/kg/min [0.14–0.47 µg/kg/min]) (P < .001). The total consumption of phenylephrine (mean ± standard deviation [SD]) until delivery was lower in group O (316.5 ± 25.9 µg) than in group C (387.7 ± 14.7 µg, P = .02). The estimate of relative median potency for phenylephrine for group O versus group C was 0.74 (95% CI, 0.37–0.95).

CONCLUSIONS: Under the conditions of this study, intravenous ondansetron 4 mg reduced the ED50 of a prophylactic phenylephrine infusion by approximately 26% in patients undergoing cesarean delivery under combined spinal–epidural anesthesia. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

• Question: By how much does ondansetron reduce phenylephrine requirement during spinal anesthesia for cesarean delivery?
• Findings: Compared with a control group, intravenous ondansetron 4 mg decreased the effective dose in 50% of subjects (ED50) of the rate of intravenous phenylephrine infusion from 0.32 to 0.24 µg/kg/min.
• Meaning: A single dose of ondansetron significantly reduced phenylephrine requirement during spinal anesthesia for cesarean delivery.

GLOSSARY

5-HT3 = 5-hydroxytryptamine subtype 3; CI = confidence interval; CO = cardiac output; CONSORT = Consolidated Standards of Reporting Trials; ED50 = effective dose in 50% of subjects; HR = heart rate; IQR = interquartile range; IRB = institutional review board; SBP = systolic blood pressure; SD = standard deviation

From the *Department of Anesthesia, Jiaxing University Affiliated Women and Children Hospital, Jiaxing City, China; ‡Department of Anesthesia, Women’s Hospital, Zhejiang University School of Medicine, Hangzhou, China; ¶Department of Obstetrics, Jiaxing University Affiliated Women and Children Hospital, Jiaxing City, China, and §Department of Anesthesiology, Sidra Medicine, Doha, Qatar.

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Reprints will not be available from the authors.

Address correspondence to Xinzhong Chen, MD, Department of Anesthesia, Women’s Hospital, Zhejiang University School of Medicine, Xueshi Rd, 1#, Hangzhou, China 310006. Address e-mail to chenxinz@zju.edu.cn.
ABSTRACT

Objective To identify the core components of successful early warning systems for detecting and initiating action in response to clinical deterioration in paediatric inpatients.

Methods A hermeneutic systematic literature review informed by translational mobilisation theory and normalisation process theory was used to synthesise 82 studies of paediatric and adult early warning systems and interventions to support the detection of clinical deterioration and escalation of care. This method, which is designed to develop understanding, enabled the development of a propositional model of an optimal afferent component early warning system.

Results Detecting deterioration and initiating action in response to clinical deterioration in paediatric inpatients involves several challenges, and the potential failure points in early warning systems are well documented. Track and trigger tools (TTT) are commonly used and have value in supporting key mechanisms of action but depend on certain preconditions for successful implementation into practice. Several supplementary interventions have been proposed to improve the effectiveness of early warning systems but there is limited evidence to recommend their wider use, due to the weight and quality of the evidence; the extent to which systems are conditioned by the local clinical context; and the need to attend to system component relationships, which do not work in isolation. While it was not possible to make empirical recommendations for practice, the review methodology generated theoretical inferences about the core components of an optimal system for early warning systems. These are presented as a propositional model conceptualised as three subsystems: detection, planning and action.

Conclusions There is a growing consensus of the need to think beyond TTTs in improving action to detect and respond to clinical deterioration. Clinical teams wishing to improve early warning systems can use the model to consider systematically the constellation of factors necessary to support detection, planning and action and consider how these arrangements can be implemented in their local context.

PROSPERO registration number CRD42015015326.

INTRODUCTION

Failure to recognise and act on signs of clinical deterioration in the hospitalised child is an acknowledged safety concern.1 Track and trigger tools (TTT) are a common response to this problem. A TTT consists of sequential recording and monitoring of physiological, clinical and observational data. When a certain score or trigger is reached then a clinical action should occur including, but not limited to, altered frequency of observation, senior review or more appropriate treatment or management. Tools may be paper based or electronic and monitoring can be automated or undertaken manually by staff.

Despite the growing use of TTTs there is limited evidence of their effectiveness as a single intervention in reducing mortality or arrest rates in hospitalised children.2 3 Results from the largest international cluster randomised controlled trial of a TTT (the Bedside Paediatric Early Warning System...
Association of Umbilical Cord Milking vs Delayed Umbilical Cord Clamping With Death or Severe Intraventricular Hemorrhage Among Preterm Infants

Anup Katheria, MD; Frank Reister, MD; Ichen Essers, MD; Marc Mendler, MD; Helmut Hummler, MD; Akila Subramaniam, MD; Waldemar Carlo, MD; Alan Tita, MD; Giang Truong, MD; Shareece Davis-Nelson, MD; Georg Schmölzer, MD; Radha Chari, MD; Joseph Kaempf, MD; Mark Tomlinson, MD; Toby Yanowitz, MD; Stacy Beck, MD; Hyagriv Simhan, MD; Eugene Dempsey, MD; Keelin O’Donoghue, MD; Shazia Bhat, MD; Matthew Hoffman, MD; Arij Faksh, MD; Kathy Armell, RN; Wade Rich, RRT; Neil Finner, MD; Yvonne Vaucher, MD; MPH; Paritosh Khanna, MD; Mariana Meyers, MD; Michael Varner, MD; Phillip Allman, MS; Jeff Szychowski, PhD; Gary Cutter, PhD

IMPORTANCE Umbilical cord milking as an alternative to delayed umbilical cord clamping may provide equivalent benefits to preterm infants, but without delaying resuscitation.

OBJECTIVE To determine whether the rates of death or severe intraventricular hemorrhage differ among preterm infants receiving placental transfusion with umbilical cord milking vs delayed umbilical cord clamping.

DESIGN, SETTING, AND PARTICIPANTS Noninferiority randomized clinical trial of preterm infants (born at 23-31 weeks’ gestation) from 9 university and private medical centers in 4 countries were recruited and enrolled between June 2017 and September 2018. Planned enrollment was 750 per group. However, a safety signal comprising an imbalance in the number of severe intraventricular hemorrhage events by study group was observed at the first interim analysis; enrollment was stopped based on recommendations from the data and safety monitoring board. The planned noninferiority analysis could not be conducted and a post hoc comparison was performed instead. Final date of follow-up was December 2018.

INTERVENTIONS Participants were randomized to umbilical cord milking (n = 236) or delayed umbilical cord clamping (n = 238).

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of death or severe intraventricular hemorrhage to determine noninferiority of umbilical cord milking with a 1% noninferiority margin.

RESULTS Among 540 infants randomized, 474 (88%) were enrolled and completed the trial (mean gestational age of 28 weeks; 46% female). Twelve percent (29/236) of the umbilical cord milking group died or developed severe intraventricular hemorrhage compared with 8% (20/238) of the delayed umbilical cord clamping group (risk difference, 4% [95% CI, −2% to 9%]; P = .16). Although there was no statistically significant difference in death, severe intraventricular hemorrhage was statistically significantly higher in the umbilical cord milking group than in the delayed umbilical cord clamping group (8% [20/236] vs 3% [8/238], respectively, risk difference, 5% [95% CI, 1% to 9%]; P = .02). The test for interaction between gestational age strata and treatment group was significant for severe intraventricular hemorrhage only (P = .003); among infants born at 23 to 27 weeks’ gestation, severe intraventricular hemorrhage was statistically significantly higher with umbilical cord milking than with delayed umbilical cord clamping (22% [20/93] vs 6% [5/89], respectively, risk difference, 16% [95% CI, 6% to 26%]; P = .002).

CONCLUSIONS AND RELEVANCE In this post hoc analysis of a prematurely terminated randomized clinical trial of umbilical cord milking vs delayed umbilical cord clamping among preterm infants born at less than 32 weeks’ gestation, there was no statistically significant difference in the rate of a composite outcome of death or severe intraventricular hemorrhage, but there was a statistically significantly higher rate of severe intraventricular hemorrhage in the umbilical cord milking group. The early study termination and resulting post hoc nature of the analyses preclude definitive conclusions.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT03019367


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Author Affiliations: Author affiliations are listed at the end of this article.
Corresponding Author: Anup Katheria, MD, Neonatal Research Institute, Sharp Mary Birch Hospital for Women & Newborns, 3003 Health Center Dr, San Diego, CA 92123 (anup.katheria@sharp.com).

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Musculoskeletal Pain, Physical Function, and Quality of Life After Bariatric Surgery

Sharon Bout-Tabaku, MD, MSCE,a,b Resmi Gupta, MS, MA,c Todd M. Jenkins, PhD,c Justin R. Ryder, PhD,d Amy E. Baughcum, PhD,e Rebecca D. Jackson, MD,f Thomas H. Inge, MD, PhD,g,h John B. Dixon, MBBS, PhD,i Michael A. Helmrath, MD,c Anita P. Courcoulas, MD,j James E. Mitchell, MD,k Carroll M. Harmon, MD, PhD,l,m Changchun Xie, PhD,n Marc P. Michalsky, MD,e,f TEEN-LABS CONSORTIUM

OBJECTIVES: To evaluate the longitudinal effects of metabolic and bariatric surgery (MBS) on the prevalence of musculoskeletal and lower extremity (LE) pain, physical function, and health-related quality of life.

METHODS: The Teen Longitudinal Assessment of Bariatric Surgery study (NCT00474318) prospectively collected data on 242 adolescents undergoing MBS at 5 centers over a 3-year follow-up. Joint pain and physical function outcomes were assessed by using the Health Assessment Questionnaire Disability Index, Impact of Weight on Quality of Life – Kids, and the Short Form 36 Health Survey. Adolescents with Blount disease (n = 9) were excluded.

RESULTS: Prevalent musculoskeletal and LE pain were reduced by 40% within 12 months and persisted over 3 years. Adjusted models revealed a 6% lower odds of having musculoskeletal pain (odds ratio = 0.94, 95% confidence interval: 0.92–0.99) and a 10% lower odds of having LE pain (odds ratio = 0.90, 95% confidence interval: 0.86–0.95) per 10% reduction of BMI. The prevalence of poor physical function (Health Assessment Questionnaire Disability Index score >0) declined from 49% to <20% at 6 months (P < .05). Physical comfort and the physical component scores, measured by the Impact of Weight on Quality of Life – Kids and the Short Form 36 Health Survey, improved at 6 months postsurgery and beyond (P < .01). Poor physical function predicted persistent joint pain after MBS.

CONCLUSIONS: Joint pain, impaired physical function, and impaired health-related quality of life significantly improve after MBS. These benefits in patient-reported outcomes support the use of MBS in adolescents with severe obesity and musculoskeletal pain and suggest that MBS in adolescence may reverse and reduce multiple risk factors for future joint disease.

WHAT’S KNOWN ON THIS SUBJECT: Adolescents with severe obesity have chronic musculoskeletal pain, which limits their physical function and quality of life. They are at high risk for early knee osteoarthritis and worsening obesity, which will significantly impact public health.

WHAT THIS STUDY ADDS: There are large, sustained decreases in prevalent musculoskeletal pain and improvements in physical function after bariatric surgery. Poor physical function and clinical depressive symptoms predict musculoskeletal pain and should be addressed early in weight loss programs to ensure joint health.


Drs Bout-Tabaku, Gupta, Jenkins, and Michalsky conceptualized and designed the study, acquired, analyzed, and interpreted the data, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript critically for important intellectual content; Drs Ryder, Baughcum, Jackson, and Inge assisted with conceptualizing and designing the study, analyzed and interpreted the data, and reviewed and revised the manuscript critically for important intellectual content; Dr Xie assisted with data acquisition, analyzed and interpreted the data, and reviewed and revised the manuscript critically for important intellectual content; Drs Dixon, Helmrath, Courcoulas, Mitchell, and Harmon analyzed and interpreted the data and (Continued)
AUTISM SPECTRUM DISORDER (ASD) IS A COMPLEX NEUROLOGICAL DISORDER THAT AFFECTS AN INDIVIDUAL'S DEVELOPMENT BY IMPAIRING SOCIAL INTERACTION AND COMMUNICATION AND CAUSES STEREOTYPICAL BEHAVIORS THAT DISRUPT THE ANATOMY AND FUNCTIONAL CONNECTIVITY IN THE BRAIN. MOST COMMON PSYCHIATRIC COMORBIDITIES FOUND TO BE ASSOCIATED WITH AUTISM INCLUDE ANXIETY AND INTELLECTUAL DISABILITY. INDIVIDUALS WITH AUTISM HAVE IMPAIRED SPEECH \[1, 2\] AND TEND TO HAVE LIMITED SOCIAL INTERACTION MOSTLY DUE TO THEIR OWN LIMITATION OF SOCIAL SKILLS AND DUE TO THEIR FAILURE TO UNDERSTAND SELF-INNER MENTAL STATES \[3\]. THE IMPAIRMENT OF SPEECH IN AFFECTED INDIVIDUALS DEPENDS ON THE SEVERITY OF THE AUTISM DISORDER AS AUTISTIC INDIVIDUALS TEND TO REPEAT CERTAIN WORDS OR PHRASES THEY HEAR OTHERS SAY, THEIR SPEECH MIGHT SOUND MORE FORMAL AND THEY EXHIBIT REPETITIVE BEHAVIORS \[4\]. THE PREVALENCE OF AUTISM IS ON THE RISE AND THE GLOBAL PREVALENCE OF ASD HAS BEEN REPORTED TO BE 1 IN 160 PERSONS, ACCORDING TO THE WORLD HEALTH ORGANIZATION (WHO) (2014). BASED ON A PARENT SURVEY, THE RECENT PREVALENCE OF ASD IN THE U.S. IS REPORTED TO BE 1 IN 45 CHILDREN \[5\]. A STUDY CONDUCTED IN 2006 IN THE UNITED KINGDOM REPORTED AN ASD PREVALENCE OF 38.9/10,000 IN 9 TO 10-YEAR-OLDS \[6\], WHILE ANOTHER STUDY CONDUCTED BY THE NATIONAL AUTISTIC SOCIETY (2014) REPORTED THAT 1/100 CHILDREN ARE AFFECTED WITH ASD. IN GULF COOPERATION COUNCIL (GCC) COUNTRIES, THE

ASSOCIATION OF GENES WITH PHENOTYPE IN AUTISM SPECTRUM DISORDER

Sabah Nisar1, Sheema Hashem1, Ajaz A. Bhat1, Najeeb Syed1, Santosh Yadav1, Muhammad Waqar Azeem2,3, Shahab Uddin4, Puneet Bagga5, Ravinder Reddy5, Mohammad Haris1,6

1Research Branch, Sidra Medicine, Doha, Qatar
2Department of Psychiatry, Sidra Medicine, Doha, Qatar
3Weill Cornell Medicine, Doha, Qatar
4Translational Research Institute, Hamad Medical Corporation, Doha, Qatar
5Center for Magnetic Resonance and Optical Imaging, Department of Radiology, Perelman School of Medicine at The University of Pennsylvania, Philadelphia, PA 19104, USA
6Laboratory Animal Research Center, Qatar University, Doha, Qatar

Correspondence to: Mohammad Haris; email: mharis@sidra.org, harissgpgi@gmail.com
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ABSTRACT

Autism spectrum disorder (ASD) is a genetic heterogeneous neurodevelopmental disorder that is characterized by impairments in social interaction and speech development and is accompanied by stereotypical behaviors such as body rocking, hand flapping, spinning objects, sniffing and restricted behaviors. The considerable significance of the genetics associated with autism has led to the identification of many risk genes for ASD used for the probing of ASD specificity and shared cognitive features over the past few decades. Identification of ASD risk genes helps to unravel various genetic variants and signaling pathways which are involved in ASD. This review highlights the role of ASD risk genes in gene transcription and translation regulation processes, as well as neuronal activity modulation, synaptic plasticity, disrupted key biological signaling pathways, and the novel candidate genes that play a significant role in the pathophysiology of ASD. The current emphasis on autism spectrum disorders has generated new opportunities in the field of neuroscience, and further advancements in the identification of different biomarkers, risk genes, and genetic pathways can help in the early diagnosis and development of new clinical and pharmacological treatments for ASD.
Targeted Resequencing of Wetland Sediment as a Tool for Avian Influenza Virus Surveillance

Chelsea G Himsworth 1,2,3, Jun Duan 4, Natalie Prystajecky 4,5, Michelle Coombe 1,2,3, Waren Baticados 4, Agatha N Jassem 4,5, Patrick Tang 6, Eric Sanders 7, William Hsiao 4,5

Abstract

Surveillance methods for avian influenza virus (AIV) based upon collecting and testing samples from individual wild birds have several significant limitations primarily related to the difficulties associated with obtaining samples. Because AIVs are shed in waterfowl feces, the use of environmental substrates where waterfowl feces accumulate may overcome some of these limitations. However, these substrates are difficult to analyze using traditional diagnostic techniques, such as virus culture and PCR, because of virus
inactivation, RNA degradation, low concentration of target RNA, microbial complexity, presence of inhibitory substances, and other factors. We investigated the use of a genomics-based approach called targeted resequencing to detect and characterize AIVs in wetland sediments during the 2014-15 North American highly pathogenic avian influenza outbreak. We identified AIV in 20.6% (71/345) sediment samples obtained from wetlands (n=15) and outdoor waterbodies on AIV-infected poultry farms (n=10) in British Columbia, Canada (the first area affected during the outbreak). Thirteen hemagglutinin (HA) and nine neuraminidase (NA) subtypes were detected, including H5, N1, and N8 sequences that clustered with other sequences associated with the North American outbreak. Additionally, as many as eight HA and eight NA subtypes could be detected in a single sediment sample. This proof-of-concept study shows the potential utility of sediment sampling coupled with genomics-based analysis as a tool for AIV surveillance.

**Keywords:** Anseriformes; avian influenza; genomics; next generation sequencing; sediment; surveillance; waterfowl; wetlands.
Transcatheter ductus arteriosus stenting in paediatric cardiology: Indications, results and perspectives

Stenting du canal artériel par cathétérisme en cardiologie pédiatrique : indications, résultats et perspectives

Estibaliz Valdeomillos, Zakaria Jalal, Younes Boudjemline, Jean-Benoit Thambo, for the Filiale de cardiologie pédiatrique et congénitale de la Société française de cardiologie

Department of Paediatric and Adult Congenital Cardiology, Bordeaux University Hospital (CHU), avenue Magellan, 33600 Pessac, France
IHU Liryc, Electrophysiology and Heart Modelling Institute, fondation Bordeaux université, 33600 Pessac, France
U1045, Inserm, centre de recherche cardio-thoracique de Bordeaux, 33000 Bordeaux, France
Heart Center, Sidra Medicine, Doha, Qatar

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KEYWORDS
Stents;
Ductal stenting;
Blalock-Taussig shunt;
Hybrid palliation;
Norwood procedure

Summary
Stenting the arterial duct emerged in the early 1990s as an alternative to a variety of surgical interventions in neonates with a duct-dependent pulmonary or systemic circulation complex defect. Furthermore, palliative ductal stenting has been applied in older children with severe suprasystemic pulmonary arterial hypertension, as an alternative to surgical shunts, such as Potts anastomosis. Early results of this technique were discouraging, but by learning from the failures of the past, ductal stenting has become a reliable palliative therapy. In this review, we aim to describe the historical evolution of ductal stenting, its different clinical applications and outcomes, and future perspectives for this strategy in congenital cardiac catheterization.

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Abbreviations: BTS, Blalock-Taussig Shunt; HLHS, hypoplastic Left Heart Syndrome; PA, pulmonary Artery; PAH, Pulmonary Arterial Hypertension; PDA, Patent Ductus Arteriosus.
* Corresponding author: Department of Paediatric and Adult Congenital Cardiology, Bordeaux University Hospital (CHU), avenue Magellan, 33600 Pessac, France.
E-mail address: estibaliz.valdeomillos@gmail.com (E. Valdeomillos).

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European Society of Paediatric Radiology abdominal imaging task force: recommendations for contrast-enhanced ultrasound and diffusion-weighted imaging in focal renal lesions in children

M. Beatrice Damasio 1, Lil-Soile Ording Müller 2, Thomas A. Augdal 3, Fred E. Avni 4, Luca Basso 1, Costanza Bruno 5, Damjana Klučevšek 6, Annemiek S. Littouij 7,8, Stéphanie Franchi-Abella 9, Luisa M. Lobo 10, Hans-Joachim Mentzel 11, Marcello Napolitano 12, Alkaterini Ntoulla 13, Michael Riccabona 14, Samuel Stafrace 15, M. Magdalena M. Wozniak 16, Philippe Petit 17

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Abstract
Contrast-enhanced ultrasound (CEUS) and diffusion-weighted imaging (DWI) are safe, repeatable imaging techniques. The aim of this paper is to discuss the advantages, technical factors and possible clinical applications of these imaging tools in focal renal lesions in children.

Keywords Children · Contrast-enhanced ultrasound · Diffusion-weighted imaging · Kidney · Magnetic resonance imaging · Recommendations · Tumour · Ultrasound

Introduction
Paediatric focal renal lesions include a wide spectrum of pathological entities, such as congenital malformations and dysplasia, inflammatory processes, neoplastic diseases and traumatic injuries. In assessing and evaluating focal renal pathologies, imaging plays a crucial role. Especially in the paediatric field, contrast-enhanced ultrasound (CEUS) and diffusion-weighted imaging (DWI) are considered emerging and useful tools, being radiation-free and thus safe and repeatable. The aim of this

1 Department of Radiology, IRCCS, Istituto Giannina Gaslini, Via Gaslini 5, 16147 Genova, Italy
2 Division of Radiology and Nuclear Medicine, Department of Paediatric Radiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway
3 Department of Radiology, University Hospital of North Norway, Tromsø, Norway
4 Department of Pediatric Radiology, Jeanne de Flandre Hospital, CHRU de Lille, Lille, France
5 Radiology Institute, Department of Radiology, AOUI, Verona, Italy
6 Department of Radiology, University Children’s Hospital, Ljubljana, Slovenia
7 Department of Radiology, Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands
8 Department of Radiology, University Medical Center, Utrecht, the Netherlands
9 Service de Radiopédiatrie, Hôpital Bicêtre - Hôpitaux Universitaires Paris-Sud, Paris, France
10 Serviço de Imagiologia Geral, Centro Hospitalar Universitário Lisboa Norte (CHULN), Lisbon, Portugal
11 Section of Pediatric Radiology, Institute of Diagnostic and Interventional Radiology, University Hospital Jena, Jena, Germany
12 Department of Paediatric Radiology and Neuroradiology, V. Buzzi Children’s Hospital, Milan, Italy
13 Department of Radiology, Poole Hospital NHS Foundation Trust, Poole, UK
14 Department of Radiology, Division of Pediatric Radiology, University Hospital Medical University, Graz, Austria
15 Department of Diagnostic Imaging, Sidra Medicine, Doha, Qatar
16 Department of Paediatric Radiology, Medical University of Lublin, Lublin, Poland
17 Service d’Imagerie Pédiatrique et Prénatale, Hôpital Timone Enfants, Marseille, France

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Incidence Of Clostridium difficile Infection And Associated Risk Factors Among Hospitalized Children In Qatar

Ahmed Khalil 1
Mohamed A Hendaus 2
Asmaa Mohamed 1
Anand Deshmukh 3
Ahmed Elmasoudi 1

1 Department of Pharmacy, Hamad General Hospital, Doha, Qatar; 2 Department of Pediatrics, Hamad Medical Corporation, Sidra Medicine, Weill Cornell Medicine, Doha, Qatar; 3 Microbiology Laboratory, Hamad General Hospital, Doha, Qatar

Background: Clostridium difficile infection (CDI) is the single most common cause of nosocomial diarrhea in both adults and children. There is a deficiency in the literature regarding the incidence and associated risk factors in hospitalized children. This study aimed to determine the incidence of CDI and its associated risk factors.

Methods: A retrospective study was conducted among 200 pediatric patients admitted to the pediatric ward at Hamad General Hospital (HGH) in Qatar. The study collected data from January 1, 2015 till December 2015. Univariate and multivariate logistic regression methods were used to assess each risk factor of CDI.

Results: Among the 200 patients, 23 were diagnosed with CDI (incidence: 5.9 per 1000 inpatient admission cases). The mean patient age (±SD) was 6.4 ± 3.4 years. The incidence of antibiotic exposure (22.5; 95% CI: 15.0–38.7; P <0.001), prolonged hospitalization (28.9; 95% CI: 17.1–43.3; P <0.001), and enteral feeding (33.3; 95% CI: 15.9–55.1; P <0.001) were significant risk factors for CDI.

Conclusion: Antibiotics exposure, prolonged hospitalization, and enteral feeding were significant risk factors of CDI in hospitalized children; thus, emphasizing the importance of antimicrobial stewardship programs in the prevention of hospital-associated infection. Further prospective studies are needed to assess the trend in incidence and to identify other risk factors of CDI.

Keywords: antimicrobial stewardship, Clostridium difficile infection (CDI), hospital acquired, hospitalized pediatric patients, risk factors

Introduction

Clostridium difficile (C. difficile) is an anaerobic, gram-positive bacillus, endospore-forming bacteria and can cause infection through environmental or oral-fecal routes. The first C. difficile infection was described in 1935.1 C. difficile was first detected in stool samples of healthy neonates, leading to its classification as normal gut flora, and was not a major cause of disease until 1978.2,3 Clostridium difficile infection (CDI) ranges from self-limiting diarrhea to severe pseudo-membranous colitis, and is considered as one of the most common causes of nosocomial diarrhea in both adults and children.4–6

Latest studies have implied that CDI is emerging as a culprit of diarrhea in infants and children.7–9 This growing incidence has been insinuated, in part, to the augmented antibiotic prescriptions, the advent of a hyper-virulent strain of C. difficile, new and sensitive techniques to detect CDI, and increased attentiveness of CDI among clinicians.10,11
COMMENTARY

Why Are Children With Bronchiolitis At Risk Of Urinary Tract Infections?

Mohamed A Hendaus 1,2
1Department of Pediatrics, Section of Academic General Pediatrics, Sidra Medicine, Doha, Qatar; 2Department of Clinical Pediatrics, Weill-Cornell Medicine, Doha, Qatar

Abstract: Viral respiratory infections are frequently eliminated from human bodies without any sequelae. Secondary serious bacterial infection (SBI) in children with acute bronchiolitis has been an apprehension expressed by health care providers. Several published studies have shown an association between acute bronchiolitis and secondary bacterial infection, including urinary tract infections (UTI). However, the proposed mechanism by which a virus can induce UTIs is not yet known. The aim of this commentary is to update the current evidence of risk of UTI in children with bronchiolitis. 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 viral respiratory illness.

Keywords: bronchiolitis, infection, urine

Review Of The Literature

Viral respiratory infections are frequently eliminated from human bodies without any sequelae. Nevertheless, in some occasions viruses can evade the immune reaction of the airways, leading to austere respiratory diseases.1 Potent mechanical and immunosuppressive methods protect the lungs against external infections, but a solitary respiratory tract infection can change immunity and pathology.2 Secondary serious bacterial infection (SBI) in children with acute bronchiolitis has been an apprehension expressed by health care providers.3 Several published studies have shown an association between acute bronchiolitis and secondary bacterial infection, including urinary tract infections (UTI).4–13 However, the proposed mechanism by which a virus can induce UTIs is not yet known.

In a review of the literature, the percentage of patients with fever with positive urine cultures ranged from 4.2% to 20.0% in infants <3 months of age and 0% to 7.4% in older children (3 to 36 months of age).14 Ralston et al3 conducted a systematic review delineating the risk of occult SBI in young febrile infants presenting with either "clinical bronchiolitis" or "proven RSV infection". The review included 11 studies.4–7,9–13,15,16 The rate of urinary tract infections in the 11 studies analyzed was 3.3% (95% confidence interval, 1.9–5.7%). The authors concluded the rate of urine cultures positive for bacteria was noteworthy, though asymptomatic bacteriuria may have muddled the results. Recently, McDaniel et al17 conducted a systematic review and meta-analysis exploring the prevalence of UTI in infants and young children with bronchiolitis when positive urinalysis (UA) results being incorporated into the UTI definition. The investigators included 18 studies,4–7,9,11–13,15,16,18–25 seven of which had UA information.4,11,16,18,20–22 The definition of positive UA varied among the studies. Some considered positive UA as...
A Systematic Review of Childhood Diabetes Research in the Middle East Region

Saras Saraswathi1†, Sara Al-Khawaga1,2†, Naser Elkum3 and Khalid Hussain1*

1 Division of Endocrinology, Department of Pediatrics, Sidra Medicine, Doha, Qatar, 2 College of Health & Life Sciences, Hamad Bin Khalifa University, Qatar Foundation, Education City, Doha, Qatar, 3 Biostatistics Section, Clinical Research Center, Research Services, Sidra Medicine, Doha, Qatar

Background: Diabetes mellitus (DM) is a common chronic disorder in children and is caused by absolute or relative insulin deficiency, with or without insulin resistance. There are several different forms of childhood DM. Children can suffer from neonatal diabetes mellitus (NDM), type 1 diabetes (T1DM), type 2 diabetes (T2DM), Maturity Onset Diabetes of the Young (MODY), autoimmune monogenic, mitochondrial, syndromic and as yet unclassified forms of DM. The Middle East has one of the highest incidences of several types of DM in children; however, it is unclear whether pediatric diabetes is an active area of research in the Middle East and if ongoing, which research areas are of priority for DM in children.

Objectives: To review the literature on childhood DM related to research in the Middle East, summarize results, identify opportunities for research and make observations and recommendations for collaborative studies in pediatric DM.

Methods: We conducted a thorough and systematic literature review by adhering to a list recommended by PRISMA. We retrieved original papers written in English that focus on childhood DM research, using electronic bibliographic databases containing publications from the year 2000 until October 2018. For our final assessment, we retrieved 429 full-text articles and selected 95 articles, based on our inclusion and exclusion criteria.

Results: Our literature review suggests that childhood DM research undertaken in the Middle East has focused mainly on reporting retrospective review of case notes, a few prospective case studies, systemic reviews, questionnaire-based studies, and case reports. These reported studies have focused mostly on the incidence/prevalence of different types of DM in childhood. No studies report on the establishment of National Childhood Diabetes Registries. There is a lack of consolidated studies focusing on national epidemiology data of different types of childhood DM (such as NDM, T1DM, T2DM, MODY, and syndromic forms) and no studies reporting on clinical trials in children with DM.

Conclusions: Investing in and funding basic and translational childhood diabetes research and encouraging collaborative studies, will bring enormous benefits financially, economically, and socially for the whole of the Middle East region.

Keywords: T1DM, Middle-East, childhood, MODY, insulin-resistance, prevention, epidemiology, registry
Determination of Pathogenicity of Breast Cancer 1 Gene Variants using the American College of Medical Genetics and Genomics and the Association for Molecular Pathology Guidelines

Angela Brown, Mansour Zamapoor, Donald R. Love, Debra O. Prosser

ABSTRACT: Objectives: Molecular diagnostic laboratories screen for mutations in disease-causing genes in order to confirm a clinical diagnosis. The classification of DNA variants as ‘pathogenic’ or ‘likely pathogenic’ mutations creates a workflow bottleneck, which becomes increasingly challenging as greater number of genes are screened. The classification challenge is also acute if there are conflicting reports regarding pathogenicity and differing classification criteria between laboratories. This study aimed to compare two procedures for the classification of variants in the breast cancer (BRCA1) gene. Methods: This bioinformatic study was conducted at LabPLUS, Auckland, New Zealand, from February to June 2017. DNA was extracted from peripheral blood samples of 30 patients and gene library construction was carried out using a commercially available targeted panel for the BRCA1 and BRCA2 genes. The genes were subsequently sequenced and the sequence data analysed. The guidelines published by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/Amp) provides a comprehensive framework for the interpretation of variants in genes that are associated with Mendelian disorders. The use of these guidelines were compared to the variant classifications that were achieved by reference to those reported in the BRCA Exchange database. Results: The results showed concordance between the two classification protocols for a panel of 30 BRCA1 gene variants, although the transparency in following the ACMG/Amp guidelines provides a diagnostic laboratory with a generalisable approach that allows laboratory-directed revisions to be undertaken in light of new information. Conclusion: The ACMG/Amp-based guidelines were applied to a cohort of patients with BRCA1 gene variants. The use of these guidelines provides a system which creates consistency in variant interpretation and supports subsequent clinical management.

Keywords: BRCA1 Gene; Bioinformatics; DNA Sequencing; Nonsense Codon; Splice Donor Site; New Zealand.
The Diagnostic use of Magnetic Resonance Imaging for Acute Abdominal and Pelvic Pain in Pregnancy

Asma Tarannum, Haifa Sheikh, Kwabena Appiah-Sakyi, Stephen W. Lindow

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The Diagnostic use of Magnetic Resonance Imaging for Acute Abdominal and Pelvic Pain in Pregnancy

Asma Tarannum ¹ Specialist in Obstetrics and Gynaecology

Haifa Sheikh ¹ Specialist in Obstetrics and Gynaecology

Kwabena Appiah-Sakyi ¹,² Consultant in Obstetrics and Gynaecology

Stephen W. Lindow ¹,² Consultant in Obstetrics and Gynaecology

Womens Wellness and Research Centre. Hamad Medical Corporation. Doha. Qatar

Sidra Medicine. Doha. Qatar

Correspondence to;

Dr Asma Tarannum

• ATARANUM@hamad.qa
Abstract:

**Objectives**: Acute abdomino-pelvic pain in pregnancy represents a diagnostic challenge. In many cases, radiological and laparoscopic diagnostic modalities are hazardous or contraindicated. Magnetic Resonance Imaging (MRI) is not commonly used for this indication and the results are not widely published.

**Design and Setting**: A single-center retrospective observational study.

**Population**: 34 cases of pregnant women with abdomino-pelvic pain who underwent MRI as an additional modality when clinical, laboratory and ultrasound (USS) findings were indeterminate.

**Methods**: Case notes were reviewed where pregnant women underwent a MRI investigation for abdominal-pelvic pain. Primary Obstetric indications for an MRI eg placenta accreta were excluded.

**Main outcome measures**: The differential diagnosis after; 1) history and physical examination and 2) with the addition of USS and 3) with the further addition of an MRI were all individually compared to the eventual diagnosis.

Results: The diagnoses reached by MRI corresponded with the final diagnosis in 22 out of 23 cases. In the remaining 11 cases MRI accurately ruled out presence of pathology. MRI was inaccurate in 1 case.
Effects of Vasoactive Medications and Maternal Positioning During Cesarean Delivery on Maternal Hemodynamics and Neonatal Acid–Base Status

Allison Lee, MD, MS,*, Warwick Ngan Kee, BHB, MBChB, MD, FANZCA, FHKCA, FHKAM (Anaesthesiology)

INTRODUCTION

Acute events during the peripartum period and their management during anesthesia can significantly contribute to the neonate’s acid-base status at birth. Maternal hemodynamics, fluid management, choice of vasopressor, maternal positioning and

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* Corresponding author.

E-mail address: al3196@cumc.columbia.edu


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Editorial

Noradrenaline for haemodynamic control in obstetric anaesthesia: Is it now a suitable alternative to phenylephrine?

Single-shot spinal anaesthesia (SA) is the neuraxial technique used most often for routine elective caesarean section (CS), as it is easier, quicker and less costly than combined spinal-epidural anaesthesia (CSE). It is also more reliable than epidural anaesthesia (EA) for providing effective sensory block. However, compared with CSE or EA, SA has the disadvantage of inducing a rapid onset dense sympathetic block that almost inevitably results in hypotension that may be severe if not adequately prevented; this in turn may lead to adverse maternal and neonatal consequences [1,2]. The search for the optimal management of hypotension in this setting has therefore become one of the most active areas of research in obstetric anaesthesia.

In this issue, Anaesthesia Critical Care & Pain Medicine is publishing a randomised controlled study comparing noradrenaline (norepinephrine) (NA) versus phenylephrine (PE) infusion for prophylaxis of spinal hypotension during elective CS [3]. There are now many studies published on NA use in this context, with related recent meta-analyses and systematic reviews [4]. However, this is the first randomised controlled double-blind trial (RCTDBT) that compares NA versus PE, as it will be most often administered in clinical practice, i.e. as a manually titrated infusion (in an adequate 1:1.5 approximately equipotent ratio); while also using a standard intrathecal dose (hyperbaric bupivacaine 10 mg + fentanyl 10 μg) and a recommended rapid co-load infusion of lactated Ringer’s solution (15 mL/kg) [5]. The main findings were similar effectiveness of NA versus PE to maintain maternal blood pressure, with lower number of physician interventions and possibly lower incidence of reactive hypertension and bradycardia. It is therefore a useful addition to the growing evidence that NA is a suitable, and possibly superior, alternative to PE (discussed below).

However, it should be acknowledged that some aspects of the study design are unclear or suboptimal, which may make it difficult to draw clear conclusions from the results; therefore, they should be viewed as exploratory rather than firm evidence. First, based on the declared primary outcome and power analysis, this study was designed to determine superiority between groups for the incidence of hypotension. Today, this may no longer be the optimal primary outcome to choose because, given that PE and NE are both potent vasoconstrictors, it is not clear why one would expect a 30% difference in efficacy between them. Further, any difference that did occur would be most likely attributable to differences in relative dosage regimen rather than any inherent difference in vasopressor effectiveness. The primary outcome was indeed not different between groups. From a methodological point of view, this finding also needs to be interpreted carefully, as a non-significant test for superiority does not show equivalence, but merely that no difference was detected. Second, given the (unsurprising) lack of difference for the primary outcome, the discussion and conclusions focus on the secondary outcomes, including number of physician interventions, bradycardia and reactive hypertension incidences. The authors state that “post-hoc pairwise comparison was performed using Bonferroni test”, but there were in fact a large number of other secondary outcomes included, and it is unclear if Bonferroni corrections was applied to account for the total number of these secondary outcomes. In other words, there is concern for inflated risk of type 1 error. Third, the treatment of hypotension in both groups included a bolus of PE or even ephedrine (if heart rate < 75 bpm), whereas it would have been more logical to keep on using NA as rescue boluses in the NA group to have a “cleaner” comparison between the two vasopressors studied and a better potential to detect differences between them.

Where are we nowadays?

The RCTDBT by Nigan Kee et al. [6] proposed NA use in 2015 as a potential alternative to PE, which is the vasopressor widely accepted today as the recommended first-line agent. Since then, all the subsequent trials have confirmed that NA and PE are similarly effective for maintaining maternal blood pressure provided that they are used in an equipotent ratio (ranging from 1:1.3 to 1:1.6). The current study by Hasain et al. [3] is in agreement with these other recent studies and further strengthens them by confirming...
the findings in a clinical practice setting based on a manually titrated NA infusion.

The remaining issues are whether there are potential advantages of using NA over PE and if so, whether they are clinically relevant and not counterbalanced by potential risks or disadvantages for the mother and/or the neonate. First, maternal bradycardia is much less likely to occur using NA than PE. This has been consistently shown in most studies adequately powered for this outcome (the current study by Hasanin et al. [3] also showed a trend towards less bradycardia with NA but this was not statistically significant because of insufficient power), although additional studies are still needed to quantify more clearly the magnitude of this effect. Of clinical relevance, NA may not only lessen the incidence of bradycardia but may also reduce its severity, compared with PE. This is quite obvious when actually using the drug. Of note, there are rare cases of maternal collapse reported during onset of SA for CS that are preceded by maternal bradycardia, so a such decrease in venous return rather than the bradycardic effect of PE itself. Nonetheless, given the severity of this rare complication, using a vasopressor such as NA that does not add baroreflex bradycardia seems intuitively advantageous. Second, maternal cardiac output has been shown to be on average 10% higher with NA versus PE during prophylactic infusion [4,6]. Whether this is a clinical benefit remains uncertain given the recent shown that cardiac output increases initially after induction of SA and tends to simply return to baseline value during PE prophylactic infusion [7]. However, when a high rate of PE infusion is used (≥ 100 mcg/min), cardiac output may decrease by up to ~20% from baseline value [8]; as pointed out by Hasanin et al. [3], further studies are thus specifically needed in high-risk pregnancies to determine whether NA may prevent this decrease and produce potential beneficial effects for the mother and/or the neonate. Third, NA may possibly better protect the mother from reactive hypertension compared with PE because of quicker offset when the infusion is reduced or stopped [3.9]. The above may explain why Hasanin et al. [3] found less physician interventions were required with NA versus PE. Fourth, it might be expected that NA would produce less nausea and/or vomiting than PE, as a result of the higher maternal cardiac output with similar blood pressure. This hypothesis is not supported by all studies published so far [4]. This suggests that this much disturbing maternal side effect is mainly related to pressure-dependent effects rather than flow-dependent effects.

The potential risks and disadvantages of NA over PE remain a subject of debate. The concern for maternal tissue ischaemia during NA extravasation from peripheral veins when using a dilution solution of 5–10 mg/ml is no different than when an equipotent concentration of PE is used. This was nicely addressed in the editorial by Vallejo et al. [10].

Importantly, care must be taken when assessing publications to identify which NA preparation has been used (i.e., brand name and manufacturer) and most importantly if the NA concentration is expressed as NA base or NA bitartrate, since base is twice as potent as bitartrate formulation (i.e., 5 mcg/ml of NA base = 10 mcg/ml of NA bitartrate) [11]. The vast majority of countries worldwide uses NA base, which is the pharmacologically active part of the vasopressor, to express the NA concentration as required by their national agency. However, this is not the case in France where NA bitartrate formulation is used to express the NA concentration as per French agency request (ANSM) [11]. This may also occur in some other countries (e.g., in Africa and Asia) that import NA from the manufacturer (Aguettant) in France. In the current study of Hasanin et al. [3], one assumes that the NA concentration of 4 mcg/ml is expressed as NA base, but this remains unclear as it was not explicitly stated.

The last issue is whether NA provides better [6], identical [12] or worse neonatal outcome [13] compared with PE, as assessed with surrogate markers such as umbilical arterial pH (UA pH), lactate, oxygen content, and catecholamines. This cannot be fully detailed here. Cooper [13] raised concerns about cases of foetal acidosis that occurred in a dose-finding study of intermittent boluses of NA [14] with no obvious explanation provided, although it is unclear whether ephedrine was used as a rescue vasopressor. Most other RCDBTs comparing NA and PE did not find or did not report differences in neonatal outcomes, except the initial study by Ngn Kee et al. [6] that found that neonates in the NA group versus the PE group had slight but statistically significant better UA pH, UA oxygen content and lower UA catecholamines (adrenaline and noradrenaline). A recent large randomised, double-blind, pragmatic non-inferiority trial, presented in part at the Obstetric Anaesthetists’ Association (OAA) meeting in May 2019, of 533 elective and 135 non-elective patients found no difference in UA pH (NA vs. PE: 7.289 ± 0.049 vs. 7.287 ± 0.046) nor in UA base excess (–4.8 ± 2.8 vs. –4.9 ± 2.8 mmol/l) [12]. Although reassuring, more research is still needed to fully understand these unclear discrepancies among studies.

In conclusion, as NA use is relatively new for haemodynamic control during caesarean section performed under SA, accumulation of more evidence is still necessary. The study of Hasanin et al. [3] is an interesting opportunity to expand our knowledge on this hot topic. In line with previous studies, it suggests that NA is as effective as PE when infused for maintenance of maternal blood pressure with no greater side effects. Nonetheless, more information is still needed about the comparative effects of NA and PE, particularly regarding maternal nausea and neonatal outcomes. The advantages of NA over PE likely include less maternal bradycardia and greater cardiac output. NA might also allow a more precise and easier titration around the targeted blood pressure, because of quicker offset of action that could result in less reactive hypertension. Thus, provided that one pays attention to prevent drug dilution errors, NA can now be considered a reasonable alternative to PE for routine use. The current dynamic international research on this topic will tell us in the near future if NA can be further recommended to actually replace PE as first-line vasopressor in obstetrics: a nice perspective...

Disclosure of interest

F.J. Mercier: honoraria received from Aguettant Company for lectures and consulting. The other authors declare that they have no competing interest.

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Frédéric J. Mercier*,” Mickaël Soued3, Estelle Morau1, Warwick D. Ngan Keea

aDépartement d’Anesthésie, Hôpital Antoine Béclère - Hôpitaux Universitaires Paris-Sud - Assistance Publique-Hôpitaux de Paris (AP-HP) & Université Paris-Sud, 92141 Clamart-Cedex, France

bDépartement d’Anesthésie Réanimation, Centre Hospitalier Narbonne, 11100 Narbonne, France

cDepartment of Anaesthesiology, Sidra Medicine, Doha, Qatar

*Corresponding author
E-mail address: frederic.mercier@aphp.fr (F.J. Mercier).
Controversies related to vitamin D deficiency effect on the maternal and feto-placental unit – an update

Shabnum Sibtain\textsuperscript{a}, Prabha Sinha\textsuperscript{b}, Madhavi Manoharan\textsuperscript{c} and Aaleen Azeez\textsuperscript{d}

\textsuperscript{a}Azra Naheed Medical College, Lahore, Pakistan; \textsuperscript{b}Oman Medical College, National University, College of Medical Science and Technology, Muscat, Oman; \textsuperscript{c}Sidra Medicine, Doha, Qatar; \textsuperscript{d}Azra Naheed Medical College, Lahore, Pakistan

\textbf{ABSTRACT}

Vitamin D deficiency (Vit D deficiency) is a global health concern and a common occurrence especially among pregnant women. It has been suggested that Vit D deficiency has implications on both the mother and the foetus. Vitamin D deficiency is the most under-diagnosed nutritional deficiency in the world, affecting the majority of individuals, irrespective of their geography, gender, age or race. Vitamin D deficiency is also linked with several diseases (autoimmune diseases, cancer, cardiovascular, dementia and musculoskeletal diseases). Therefore, appropriate supplementation is required in a deficient population. A diagnosis can be missed as symptoms associated with pregnancy are also seen in vitamin D-deficient women. A timely diagnosis and treatment can be beneficial as these disorders can cause maternal and foetal morbidity. Vitamin D status during pregnancy has been associated with maternal and foetal morbidity, but reported findings are inconsistent.

\textbf{KEYWORDS}

vitamin D; preeclampsia; birth weight; fetal growth; preterm pregnancy; assisted conception; fertility

\section*{Introduction}

The deficiency of Vitamin D is the most under-diagnosed nutritional deficiency in the world affecting the majority of individuals, irrespective of their geography, gender, age or race. The deficiency is also linked with several diseases (autoimmune disease, cancer, cardiovascular disease, dementia, musculoskeletal disease, etc.). Therefore, appropriate supplementation is required in a deficient population.

\section*{Methods}

A systematic review of articles, case-controlled studies, cohorts and meta-analysis of randomised controlled trials published in PubMed and in the Cochrane Database in the last ten years. Case Reports, Letters, and Editorial papers were excluded.

There is a high prevalence of Vitamin D deficiency worldwide, more so during pregnancy (Palacios and Gonzalez 2014). There is evidence that Vitamin D causes an increased sensitivity to insulin, glucose tolerance, calcium metabolism and bone development and can influence many factors in the mother and the developing foetus (Shahgheibi et al. 2016). Vitamin D deficiency is associated with an increased risk of developing preeclampsia, preterm labour, gestational diabetes, small for gestational age, low birthweight, an increased rate of caesarean section and infertility (Barrett and McElduff 2010).

This review highlights and examines the effect of Vitamin D deficiency on the mother and feto-placental unit. A systematic review of articles, case-controlled studies, cohorts and meta-analysis of randomised controlled trials published in PubMed and the Cochrane Database in the last ten years was studied. As mentioned before, Case Reports, Letters, and Editorial work were excluded from this study.

\section*{Physiology}

Vit D is mainly synthesised in the skin from exposure to sunlight as the main source where synthesis is facilitated by ultraviolet B (UV-B) radiation that converts 7-dehydrocholesterol (found in plasma membranes of the epidermis and dermis) to the provitamin cholecalciferol. Cholecalciferol (Vitamin D3) is derived from animal-based foods and ergocalciferol (Vitamin D2) from plants which are biologically inert. There is little Vitamin D in animal food resources, which include fatty fish, fish liver oil, and egg yolk, in the form of Vitamin D3. Vitamin D2 is obtained from vegetable sources such as sun-exposed yeast and mushrooms.

Vitamin D binding protein (DBP) takes Vitamin D3 in the blood to the liver. There are two enzymatic hydroxylations in the body for its activation. The first takes place in the liver, mediated by the 25-hydroxylase which forms 25-hydroxyvitamin D (25OH). The second reaction takes place in the kidney, mediated by 1\textalpha\textsuperscript{-}hydroxylase, which converts 25OH to the biologically active hormone, calcitriol (1,25-dihydroxyvitamin D (1,25(OH)\textsubscript{2} D) and inactive 24,25-dihydroxycholecalciferol. After synthesis of calcitriol in the kidneys, it binds to DBP and transports to the target organs. This dissociates
Effects of consanguinity in a cohort of subjects with certain genetic disorders in Qatar

Tawfeg Ben-Omran1,2,3 | Kaltham Al Ghanim4 | Tarunashree Yavarna1 | Maha El Akoum1 | Muthanna Samara5 | Prem Chandra6 | Nader Al-Dewik1,7,8

1Section of Clinical and Metabolic Genetics, Department of pediatrics, Hamad Medical Corporation, Doha, Qatar
2Department of Pediatric, Weill Cornell Medical College, Doha, Qatar
3Division of Genetic & Genomics Medicine, Sidra Medicine, Doha, Qatar
4Department of Social Sciences, Qatar University, Doha, Qatar
5Department of Psychology, Kingston University London, London, UK
6Medical Research Centre, Hamad Medical Corporation, Doha, Qatar
7College of Health and Life Sciences, Hamad Bin Khalifa University (HBKU), Doha, Qatar
8Department of Pediatrics, Women’s Wellness and Research Centre (WWRC), Hamad Medical Corporation, Doha, Qatar

Correspondence
Tawfeg Ben-Omran, Section of Clinical and Metabolic Genetics, Department of Pediatrics, Hamad Medical Corporation, Doha, Qatar. Email: tomran@hamad.qa

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Abstract

Background: Consanguineous marriages are common in the Middle East including the Gulf countries. The rate of consanguinity in Qatar is approximately 54%, which are mainly first cousins’ marriages. Previous studies showed that consanguinity increases the prevalence of birth defects and other genetic disorders. Thus, we studied the effects of consanguinity in a cohort of subjects with certain genetic disorders in Qatar.

Methods: This cross-sectional study was conducted at two centers in Qatar (Hamad Medical Corporation “HMC” and Shafallah “SC”) including 599 Qatari families with certain types of genetic and nongenetic anomalies.

Results: Consanguineous marriages were seen in 397 of 599 (66.2%) Qatari families and first cousin group counts for 65% in Qatari population. In the total cohort and at HMC, all consanguineous marriages had a significantly higher risk of Autosomal Recessive disorders than nonconsanguineous marriages (total cohort: odds ratio (OR) = 1.72; 95% CI: 1.10, 2.71; p = .02; HMC: OR = 2.98; 95% CI: 1.37, 6.09; p = .005). On the other hand, at HMC, nonconsanguinity was significantly related to chromosomal abnormality (OR = 6.36; 95% CI: 1.13, 35.85; p = .036).

Conclusion: Our data suggest a significant role of parental consanguinity in increasing the prevalence of genetic disorders; mainly Autosomal Recessive disorders than nonconsanguineous marriages (total cohort: odds ratio (OR) = 1.72; 95% CI: 1.10, 2.71; p = .02; HMC: OR = 2.98; 95% CI: 1.37, 6.09; p = .005). On the other hand, at HMC, nonconsanguinity was significantly related to chromosomal abnormality (OR = 6.36; 95% CI: 1.13, 35.85; p = .036).

KEYWORDS
Arab, Autosomal Recessive, consanguinity, genetic disorders, Qatar

INTRODUCTION

Consanguinity and endogamy are high in the Middle East including the Gulf countries and range between 20% and 50% (Al-Gazali et al., 1997; Al-Gazali et al., 1999; Hamamy et al., 2011; Tadmouri et al., 2009; Teebi & El-Shanti, 2006). In many Middle Eastern countries, consanguineous marriages are culturally favored with longstanding traditions (Hamamy,
Vasopressor drugs for the prevention and treatment of hypotension during neuraxial anaesthesia for Caesarean delivery: a Bayesian network meta-analysis of fetal and maternal outcomes

Preet M. Singh 1,*, Narinder P. Singh 2, Matthew Reschke 3, Warwick D. Ngan Kee 4, Arvind Palanisamy 1 and David T. Monks 1

1Department of Anesthesiology, Washington University in St. Louis, St. Louis, MO, USA, 2Department of Anesthesiology, MM Super Specialty Hospital, Mullana, Ambala, Haryana, India, 3Department of Anesthesia, Johns Hopkins University, Baltimore, MD, USA and 4Department of Anesthesiology, Sidra Medicine, Doha, Qatar

*Corresponding author. E-mail: singh.p@wustl.edu

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Abstract

Background: The optimal choice of vasopressor drugs for managing hypotension during neuraxial anaesthesia for Caesarean delivery is unclear. Although phenylephrine was recently recommended as a consensus choice, direct comparison of phenylephrine with vasopressors used in other healthcare settings is largely lacking. Therefore, we assessed this indirectly by collating data from relevant studies in this comprehensive network meta-analysis. Here, we provide the possible rank orders for these vasopressor agents in relation to clinically important fetal and maternal outcomes.

Methods: RCTs were independently searched in MEDLINE, Web of Science, Embase, The Cochrane Central Register of Controlled Trials, and clinicaltrials.gov (updated January 31, 2019). The primary outcome assessed was umbilical arterial base excess. Secondary fetal outcomes were umbilical arterial pH and \( P_{CO_2} \). Maternal outcomes were incidences of nausea, vomiting, and bradycardia.

Results: We included 52 RCTs with a total of 4126 patients. Our Bayesian network meta-analysis showed the likelihood that norepinephrine, metaraminol, and mephentermine had the lowest probability of adversely affecting the fetal acid-base status as assessed by their effect on umbilical arterial base excess (probability rank order: norepinephrine > mephentermine > metaraminol > phenylephrine > ephedrine). This rank order largely held true for umbilical arterial pH and \( P_{CO_2} \). With the exception of maternal bradycardia, ephedrine had the highest probability of being the worst agent for all assessed outcomes. Because of the inherent imprecision when collating direct/indirect comparisons, the rank orders suggested are possibilities rather than absolute ranks.

Conclusion: Our analysis suggests the possibility that norepinephrine and metaraminol are less likely than phenylephrine to be associated with adverse fetal acid-base status during Caesarean delivery. Our results, therefore, lay the scientific foundation for focused trials to enable direct comparisons between these agents and phenylephrine.

Keywords: maternal outcomes, hypotension; network meta-analysis, vasopressors; Caesarean section, fetal outcomes; spinal anaesthesia
Expression and Function of the Endocannabinoid Modulating Enzymes Fatty Acid Amide Hydrolase and N-Acylphosphatidylethanolamine-Specific Phospholipase D in Endometrial Carcinoma

Thangesweran Ayakannu 1,2, Anthony H. Taylor 1,3, Monica Bari 4, Nicoletta Mastrangelo 5, Mauro Maccarrone 5† and Justin C. Konje 1,6,7 * †

1 Endocannabinoid Research Group, Reproductive Sciences Section, Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, United Kingdom, 2 Gynaecology Oncology Cancer Centre, Liverpool Women’s NHS Foundation Trust, Liverpool Women’s Hospital, Liverpool, United Kingdom, 3 Department of Molecular and Cell Biology, University of Leicester, Leicester, United Kingdom, 4 Department of Experimental Medicine and Surgery, Tor Vergata University of Rome, Rome, Italy, 5 Department of Medicine, Campus Bio-Medico University of Rome, Rome, Italy, 6 Department of Obstetrics and Gynaecology, Sidra Medicine, Doha, Qatar, 7 Women’s Wellness and Research Center, Hamad Medical Corporation, Doha, Qatar

Background: The concentrations of three N-acylethanolamines (NAEs), anandamide (AEA), N-oleylethanolamide (OEA), and N-palmitylethanolamide (PEA) are increased in the endometria of women with endometrial cancer (EC). It is widely accepted that plasma levels of these three NAEs are regulated by the actions of the rate-limiting enzymes N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and fatty acid amide hydrolase (FAAH), which are synthesizing and degradative, respectively. The expression and activity of these enzymes have not previously been studied in EC.

Methods: FAAH activity in peripheral blood lymphocytes, and transcript and protein expression for FAAH and NAPE-PLD in EC tissues were measured using enzyme, quantitative RT-PCR, and histomorphometry (of immunoreactive tissue sections), respectively. Samples were from 6 post-menopausal women with atrophic endometria (controls) and 34 women with histologically diagnosed EC. Concentrations of the three NAEs also measured in plasma and tissues were correlated with lymphocytic FAAH activity and the NAPE-PLD and FAAH transcript and protein levels.

Results: Peripheral lymphocyte FAAH activity was unaffected in women with EC compared to controls. The FAAH transcript expression level was significantly (p < 0.0001) 75% lower in EC whilst NAPE-PLD levels were not significantly (p = 0.798) increased. In line with the transcript data, a significant (p < 0.0001) tumor type-dependent 70–90% decrease in FAAH protein and significant 4- to 14-fold increase in NAPE-PLD protein (p < 0.0001) was observed in the malignant tissue with more advanced disease.
Letter to the Editor

From Multiple Daily Injections to Hybrid Closed-Loop System in Ten Days, Utilizing a Structured Initiation Protocol

Goran Petrovski, MD, MSc, PhD, Fawziya Al Khalaf, MD, Judith Campbell, Hannah Fisher, Fareeda Umer, and Khalid Hussain, MD

Keywords
Hybrid Closed Loop System, multiple daily injections, protocol, type 1 diabetes

The pivotal studies in MiniMed 670G Hybrid Closed Loop (HCL) system included participants experienced with insulin pump therapy, assuming that the success of HCL systems depends on prior use of technology. However, there is no evidence for the superior glycemic control achieved by patients with prior experience with advanced technologies over those on multiple daily injections (MDI). For this end, the following standardized protocol to initiate HCL system in individuals on MDI was created: two days, HCL system assessment; five days, HCL system training (two-hour sessions in five consecutive days with groups of three to five participants); three days, Manual Mode use of HCL system, cumulating in ten days from MDI to Auto Mode activation.

The aim of the study was to evaluate this ten-day initiation protocol for MiniMed 670G HCL system in people with diabetes (PWD) type 1 on MDI in achieving desirable glycemic control.

An open-label single-arm, single-center study was performed in 30 children (age 10.24 ± 2.6 years; duration of diabetes 2.8 ± 1.7 years) on MDI following the structured protocol for ten days and followed for 84 days. The participants used the sensor for a median of 92% of the time and spent a median of 89% in Auto Mode. 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 = .017) and sensor glucose levels decreased from 193 ± 41 mg/dL to 142 ± 12 mg/dL (P = .001), accordingly.

Time in range (TIR; 70-180 mg/dL) continuously improved over time from 46.9% ± 18.5% at baseline, reaching a plateau after one month, to 75.6% ± 7.1% in the third month of Auto Mode (as shown in Figure 1). This was achieved without any severe hypoglycemia or diabetic ketoacidosis.

Insulin-to-carbohydrate ratio (ICR) was initially made more aggressive regardless of the meal period from a median of 15 g/unit at the beginning to 12 g/unit at the end of the study (P = .002). Total daily insulin of 0.8 ± 0.3 U/(kg/d) at baseline increased to 0.9 ± 0.2 U/(kg/d) at the end of the study (P = .020).

The reductions in HbA1c and in the sensor glucose in our study are greater than those previously reported in children and adolescents, and similar to adults. The median TIR (70-180 mg/dL) achieved in Auto Mode was 74.8% ± 7.1%, which is similar to the previously reported medians of 73.5% and 74.9% (2-19) in adults, but significantly higher than 68.8% in adolescents and 64.6% in children. The clinical outcomes were most probably driven by the high sensor and auto mode use and possible specific initiation protocol.

The total number of Auto Mode exits significantly decreased from 8.4 ± 1.8 in the first two weeks to 4.2 ± 0.9 events per week in the third month after enabling Auto Mode (P = .016).

Modifying ICR by increasing the meal bolus dose by almost 20% during the first month of Auto Mode use is similar to previously reported findings.

We conclude that PWD type 1 on MDI therapy can successfully initiate the HCL system, using a short structured
ten-day protocol. Further investigation on more varied population and ages should be performed to confirm these findings.

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ORCID iD
Goran Petrovski https://orcid.org/0000-0002-8622-2186

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Figure 1. Time in ranges at baseline, during Manual Mode and Auto Mode periods. Values are shown as percentage spent in ranges during the interval. CGM, continuous glucose monitoring; MDI, multiple daily injections. Glucose values <50 mg/dL are not shown on the graph: 0.3% in Manual Mode and Auto Mode period day 57-84, 0.4% in all other periods.
Anthropometric correlation with hamstring graft size in anterior cruciate ligament reconstruction among males

Isam Moghamis, Yousef Abuodeh, Ali Darwiche, Talal Ibrahim, Mohammad Al Ateeq Al Dosari, Ghalib Ahmed

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Abstract
Purpose Pre-operative knowledge of hamstring graft size for anterior cruciate ligament reconstruction (ACL) is of clinical importance and useful in making appropriate decisions about graft choice. This study investigated if there is any correlation between anthropometric measurements such as height, weight, body mass index, thigh length, and circumference with the size of hamstring tendon graft in anterior cruciate ligament reconstruction.

Methods The anthropometric data of 50 consecutive adult males, who underwent primary ACL reconstruction using quadruple hamstring autograft, were collected prospectively. Data analysis using Pearson’s correlation test was performed and multiple logistic regression analysis was used to investigate any correlation not detected by Pearson’s test and to eliminate confounders.

Results Patient’s height and thigh length demonstrated a positive correlation with gracilis graft length ($r = .464$, $P = .001$, $r = .56$, $P = .001$, respectively) and semitendinosus graft length ($r = .545$, $P = .001$, $r = .78$, $P = .000$, respectively). While the patient’s age was the only independent factor which had a positive correlation with the quadrupled hamstring graft diameter ($r = .412$, $P = .004$), multiple regression analysis showed abdominal girth had a significant negative correlation with gracilis ($P = .04$) and semitendinosus ($P = .006$) graft thickness.

Conclusion This study demonstrated that some anthropometric measurements had a positive correlation with the hamstring graft length and diameter in male patients. Hence, these results provide preliminary support for the use of some anthropometric measurements in the preoperative planning and prediction of the hamstring graft length and diameter in anterior cruciate ligament reconstruction.

Keywords Anterior cruciate ligament · Hamstring graft size · Anthropometric measurements

Introduction

Rupture of the anterior cruciate ligament (ACL) is one of the most common encountered knee injuries [1]. Deficiency of this ligament can be severely detrimental to high-level athletes or individuals participating in sports [2].

The aim of an ACL reconstruction is to restore the function and biomechanics of the native ligament. Various grafts available for use in the reconstruction of the ACL and the hamstring is one of the most commonly utilized autograft [3, 4]. A graft diameter greater than 8 mm has been recommended by many authors in order to reduce the risk of graft failure [5–7]. There are considerable variations in the size of hamstring tendons between individuals, and hence graft diameter is often unpredictable.

Pre-operative knowledge of the hamstring graft length and diameter is of clinical importance and may assist surgeons in making appropriate and informed decisions about the graft choices which may increase surgeon’s confidence and enhance patient’s evaluation and counseling regarding graft choice [8–10].

Various studies exist in the literature regarding prediction of graft size. However, no consensus has been reached due to differences in results between the studies [11–13].

This study investigated if there is any correlation between anthropometric measurements such as height, weight, body mass index, thigh length, and thigh circumference with the
Long-term outcome of LRBA deficiency in 76 patients after various treatment modalities as evaluated by the immune deficiency and dysregulation activity (IDDA) score

Victoria Katharina Tesch, MD, Hassan Abolhassani, MD PhD, Bella Shadur, MD, Joachim Zobel, MD, Yuliya Mareika, MD, Svetlana Sharapova, PhD, Elif Karakoc-Aydiner, MD, Jacques G. Rivière, MD, Marina Garcia-Prat, MSc, Nicolette Moes, MD PhD, Filomeen Haerynck, MD PhD, Luis I. Gonzalez-Granado, MD, Juan Luis Santos Pérez, MD PhD, Anna Mukhina, MD, Anna Shcherbina, MD PhD, Asghar Aghamohammadi, MD, PhD, Lennart Hammarström, MD PhD, Figen Dogu, MD, Sule Haskoglu, MD, Aydan İ. İkincioğulları, MD, Sevgi Köstel Bal, MD PhD, Safa Baris, MD, Sara Sebnem Kilic, Neslihan Edeer Karaca, MD, Necil Kutukculer, MD, Hermann Girschick, MD, Antonios Kolios, MD, Sevgi Keles, Vedat Uygun, MD, Polina Stepensky, MD, Austen Worth, MD, Joris M. van Montfrans, MD PhD, Anke M.J. Peters, MD, Isabelle Meyts, MD, Mehdi Adeli, MD, Antonio Marzollo, MD PhD, Nurcicek Padem, MD, Amer M. Khojah, MD, Zahra Chavoshzadeh, MD, Magdalena Avbelj Stefanija, MD PhD, Shahrzad Bakhtiar, MD, Benoit Florkin, MD, Marie Meeths, MD, Laura Gamez, PhD, Bodo Grimbacher, MD, Mikko RJ. Seppänen, MD PhD, Arjan Lankester, MD, Andrew R. Gennery, MD, Markus G. Seidel, MD, for the Inborn Errors, Clinical, and Registry Working Parties of the European Society for Blood and Marrow Transplantation (EBMT) and the European Society of Immunodeficiencies (ESID)

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2. Abstract

**Background.** Recent findings strongly support hematopoietic stem cell transplantation (HSCT) in patients with severe presentations of lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency, but long-term follow-up and survival data for non-transplanted patients beyond previous patient reports or meta-reviews are scarce.

**Objective.** This international, retrospective study was conducted to elucidate the longitudinal clinical course of transplanted and non-transplanted LRBA-deficient patients.

**Methods.** We assessed disease burden and treatment responses with a specially developed immune deficiency and dysregulation activity (IDDA) score, reflecting the sum and severity of organ involvement and infections, days of hospitalization, supportive care requirements, and performance indices.

**Results.** Twenty-four of 76 LRBA-deficient patients from 29 centers (10 years median follow-up, range: 1–52) underwent HSCT from 2005 to 2019. Overall survival after HSCT (median follow-up 20 months) was 70.8% (17/24 patients); all deaths were due to non-specific, early, transplant-related mortality. Currently, 82.7% (43/52) of non-transplanted patients (aged 3–69 years) are alive. Of 17 HSCT survivors, seven are in complete and five in good partial remission without treatment (12/17, 70.6%). Only five of 43 non-transplanted patients (11.6%) are without immunosuppression. IDDA scores were significantly lower in patients who survived HSCT than in those receiving conventional treatment ($P=0.005$) or in patients who received abatacept or sirolimus as compared to other therapies, and in patients with residual LRBA expression. Higher disease burden, longer duration before HSCT, and lung involvement were associated with poor outcome.

**Conclusions.** The life-long disease activity, implying a need for immunosuppression and risk of malignancy, must be weighed against the risks of HSCT.
Effect of gender on childhood maltreatment in the state of Qatar: Retrospective study

Mansoura Salem\textsuperscript{a}, Soha R. Dargham\textsuperscript{b}, Madeeha Kamal\textsuperscript{c}, Nehal Eldeeb\textsuperscript{b}, Khalid A. Alyafei\textsuperscript{d}, Margaret A. Lynch\textsuperscript{d}, Marcellina Mian\textsuperscript{b}, Ziyad R. Mahfoud\textsuperscript{b,}\textsuperscript{*}

\textsuperscript{a} Suez Canal University, Egypt & Primary Health Care Corporation, Doha, Qatar
\textsuperscript{b} Weill Cornell Medicine-Qatar, Doha, Qatar
\textsuperscript{c} Sidra Medicine, Doha, Qatar
\textsuperscript{d} Kings College, London, United Kingdom

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\textbf{ABSTRACT}

\textbf{Background:} International maltreatment studies show a range of results for overall rates of child maltreatment and gender differences. The ISPCAN Child Abuse Screening Tools (ICAST) were designed to reduce variability in data collection.

\textbf{Objective:} To investigate the influence of gender on the experiences of discipline and maltreatment in childhood among young people in Qatar, informing practice and policy development.

\textbf{Participants and Setting:} A representative sample of Qatari youth aged between 18 and 24 years were identified using a cross sectional random household survey. The total number of subjects was 697 of whom 46.8\% were male.

\textbf{Methods:} Participants self-administered the ICAST-R (retrospective), which includes questions about exposure below the age of 18 to potentially abusive physical, psychological and sexual behaviors. Verbal consent was obtained following an introductory explanation and assurance of confidentiality.

\textbf{Results:} At least one form of physical abuse was reported by 22.1\% of participants and was significantly higher among males (28.2\%) than females (16.7\%) \( p < 0.001 \). A trend for greater abuse was identified among boys aged over 5 which become statistically significant between 10 - 13 years \( p = 0.001 \). For psychological abuse the overall rates were very similar, 16.2\% for girls and 15.0\% for boys. Only 17 (2.5\%) of participants reported sexual abuse, with no statistically significant gender difference.

\textbf{Conclusions:} Physical, psychological and sexual abuse all occur in Qatar. This study demonstrates the importance of identifying the role of gender and age when exploring the extent and nature of maltreatment in a population. It allows for better targeting of preventative action.

1. Introduction

Child abuse or child maltreatment is defined by the World Health Organization (WHO) as "all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment or commercial or other exploitation, resulting in actual or potential harm to the child's health, survival, development or dignity in the context of a relationship of responsibility, trust or power" (World Health Organization, 1999). The WHO points out that the prevalence of child maltreatment varies according to how it is defined, the type of...