Garrod Symposium 2018

Transplant in Inborn Errors of Metabolism

May 10 -12, 2018

SYMPOSIUM PROGRAM

THE GARROD ASSOCIATION

In cooperation with

THE UNIVERSITY OF BRITISH COLUMBIA

Interprofessional Continuing Education

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Sponsors

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Program

Please note: 25% of the scientific program will be interactive.

Thursday, May 10, 2018

Time	Session
12:00	Registration Open
12:30 – 14:30	CIMDRN Meeting (Invitation Only) (Room: Drawing Room)
14:30 – 16:00	Garrod Executive Committee Meeting (Invitation Only) (Room: Gazebo Room)
14:30 – 16:00	Nurse/ Genetic Counselor Webinar (Room: Drawing Room) Advances in Laboratory Diagnosis of Lysosomal Storage Disorders *Dr. Tim Wood*
14:30 – 16:00	Dieticians' Webinar (Room: Jasper Room) Dietary Management in MMA, PA and MSUD: Focus on Transplantation *Dr. Gregory Enns*
16:00 – 17:15	Plenary Session I: Bone Marrow Transplant (Room: Empire Ballroom) *Session Chair: Alicia Chan* Introduction and Welcome to the Meeting *Dr. Shailly Jain* Hematopoietic Cell Therapy for Lysosomal and Peroxisomal Disorders *Dr. Paul Orchard* Discussion
17:15 - 18:00	Platform Presentations (Selected Abstracts) Three abstracts (15 minutes each)
18:30 – 20:00	Welcome Reception (Mezzanine Level)

Friday, May 11, 2018

Time	Session
07:00 - 08:00	Registration Open & Breakfast (Provided) (Jasper Room & Drawing Room)
08:00 – 09:30	Plenary Session II: Liver Transplant (Empire Ballroom) *Session Chair: Shailly Jain* Liver Transplantation: The Modern Era *Dr. Patricia Kawada* Transplants in Patients with Inborn Errors of Metabolism *Dr. Aneal Khan* Discussion
09:30 – 10:00	Refreshment Break & Exhibitors & Posters (Mezzanine Level)
10:00 – 11:50	Plenary Session III: Liver Transplant in Urea Cycle Disorders (Empire Ballroom) *Session Chair: Shailly Jain* Liver transplant experience for Urea Cycle disorders in western Canada *Dr. Alicia Chan* The Toronto Experience in Liver Transplantation for Urea Cycle Disorders – Patient Selection and Outcome *Dr. Yaron Avitzur* Cognitive Outcomes in Liver Transplant *Dr. Shailly Jain* Discussion
11:50 – 12:30	Lunch (Provided) (Jasper Room & Drawing Room)
12:30 – 13:00	Dessert & Exhibits (provided) (Mezzanine Level)
13:00 – 14:30	Plenary Session IV: Liver Transplant for Organic Acid Disorders (Empire Ballroom) *Session Chair: Komudi Siriwardena* Liver Transplantation for Organic Acidemias *Dr. Gregory Enns* Discussion
14:30 – 15:00	Refreshment Break & Exhibitors & Posters (Mezzanine Level)

15:00 – 16:30 Plenary Session V: Liver Transplant for MSUD and Tyrosinemia (Empire Ballroom)
Session Chair: Iveta Sosova

Liver Transplant for Maple Syrup Urine Disease
Dr. Komudi Siriwardena

Tyrosinemia: Current situation and challenges
Dr. Fernando Alvarez

Discussion

16:30 – 17:45 Poster Walk & Exhibitors & Light Refreshments (Mezzanine Level)

17:45 Adjourn

Garrod Symposium Gala Dinner
Pioneer Award Presentation and Entertainment

Dinner & Entertainment at *The Muttart Conservatory (9626 96A Street, Edmonton, AB)*
Taxi vouchers will be provided for transportation to the Muttart Conservatory from the Fairmont Hotel Macdonald. Parking at the Conservatory is free.

19:00 Cocktail Reception & Access to Pyramids (available all night)
19:45 Dinner Buffet Opens
20:30 Performance #1 by the Ukrainian Cheremosh Society
20:40 Pioneer Award Presentation
20:50 Performance #2 by the Ukrainian Cheremosh Society
21:00 Dessert & Coffee
23:00 Adjourn

Saturday, May 12, 2018

Time	Session
07:30 – 08:15	Breakfast (Provided) (Jasper Room & Drawing Room)
08:15 – 10:25	Plenary Session VI: Cardiomyopathies and metabolic disorders (Empire Ballroom) *Session Chair: Alicia Chan* Pediatric Cardiomyopathies and Cardiac Transplantation in Metabolic Disorders *Dr. Jennifer Conway* Cardiomyopathies in Adults *Dr. Gavin Oudit* Mitochondrial respiratory chain disorders Cardiomyopathy *Dr. Komudi Siriwardena* Discussion
10:25 – 10:55	Refreshment Break & Exhibitors & Posters (Mezzanine Level)
10:55 – 11:30	Platform Presentations (Selected Abstracts) (Empire Ballroom) Two abstracts (15 minutes each) *Session Chair: Shailly Jain*
11:30 – 12:30	Garrod Association Membership Meeting (Empire Ballroom)
12:30 – 13:30	Lunch (Provided) (Jasper Room & Drawing Room)
13:30	Adjourn

Platform Presentation Schedule

Time	Title	Presenter	Abstract #	Page
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17:15	A case series study to optimize the hemodialysis prescription for the treatment of hyperammonemic patients with ornithine transcarbamylase deficiency	Christy Chong	1	18
17:30	Urea cycle disorders: Is fibrosis a common feature in all subtypes? A close look at liver cell injury from a Western Canadian Liver Transplantation Center	Shailly Jain	2	19
17:45	An innovative treatment trial of peroxisomal biogenesis disorders with anti-pexophagy agents	Neil Sondheimer	3	20
Saturday, May 12				
10:55	Kidney disease and organ transplantation in methylmalonic acidaemia	Chitra Prasad	4	21
11:10	Characteristics of a Canadian cohort of children with inherited metabolic diseases for which liver transplantation is a therapeutic option: Chart-reported findings from the Canadian Inherited Metabolic Diseases Research Network	Pranesh Chakraborty	5	22

Poster Abstract Listing

Title	Presenter	Poster #	Page
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Transient Plasma Methionine, Total Homocysteine, S-adenosylmethionine and S-adenosylhomocysteine elevations in a patient diagnosed with NGLY1 deficiency; a Congenital Disorder of eglycosylation	Caitlin Chang	2	24
Improving health care delivery for children diagnosed with rare metabolic diseases by learning from families and providers: protocol for phase I, a prospective cohort study of families' health care experiences	Andrea Chow	3	25
Carnitine uptake defect due to a 5'UTR mutation	Michael Geraghty	4	26
Case Report: Two siblings with type VII 3-methylglutaconic aciduria due to mutations in CLPB gene	Shailly Jain	5	27
MITO-FIND: Mitochondrial Functional and Integrative Next Generation Diagnostics	Marina Kerr	6	28
Plasma derived cell-free mitochondrial DNA (cf-mtDNA): A novel and non-invasive method to sequence intact mtDNA	Aneal Khan	7	29
Anesthetic Complications in patients with Niemann Pick C: Is there a higher risk?	Aneal Khan	8	30
Screening for Fabry cardiomyopathy using cardiac magnetic resonance imaging	Desmond Koo	9	31
Idiopathic chylous ascites in an adult patient with LRPPRC-associated Leigh syndrome: a coincidence or a rare clinical manifestation of mitochondrial dysfunction?	Alina Levtova	10	32
Expanding the Clinical Phenotype of NUS1-CDG, a rare Congenital Disorder of Glycosylation	Melissa MacPherson	11	33
Diagnostic challenges in a patient with global developmental delay, lipodystrophy, periventricular leukomalacia and spasticity	Melissa MacPherson	12	34
Review of C5OH as a newborn screening target	Janet Marcadier	13	35
Targeted Reduction in Pathogenic Heteroplasmy Through Binding of G-Quadruplex DNA	Mansur Naeem	14	36
Drug Approval System in Canada	Fadya Omar	15	37
Liver transplantation for inborn errors of metabolism: A survey of care practices and delivery in Canadian metabolic clinics	Kylie Tingley	16	38
D-2-hydroxyglutaric aciduria in a patient with speech delay due to a novel homozygous deletion in the D2HGDH gene	Eliza Phillips	17	39
Experiences with health care for children with inherited metabolic diseases in Canada: Updated findings from a multi-centre survey	Michael Pugliese	18	40
Establishing core outcome sets for phenylketonuria (PKU) and medium-chain Acyl-CoA dehydrogenase (MCAD) deficiency in children: rapid review findings	Michael Pugliese	19	41
Characterization of ocular changes in Gaucher disease: Case Report	Cheryl Rockman-Greenberg	20	42
Combined therapy trial of L-carnitine supplementation and L-valine restriction in a patient with 3-Hydroxyisobutyric aciduria due to a novel homozygous missense variant in the HIBADH gene	Florin Sasarman	21	43
The unexpected diagnosis: Case report of an atypical presentation of pyruvate dehydrogenase deficiency in an adult male	Angela Schinkinger	22	44
Medial rectus muscle and orbitofrontal region SUV measurements: a novel approach to detecting hypometabolism in mitochondrial disease (MD)	Roni Shanoada	23	45
Investigating in vivo bone architecture in hypophosphatasia using high-resolution peripheral computed tomography	Karamjot Sidhu	24	46

Importance of diet in treatment of mitochondrial respiratory chain disorders (RCDs)	Komudi Siriwardena	25	47
Evolution of GFM1 gene phenotype with age.	Komudi Siriwardena	26	48
Impaired mitochondrial fatty acid oxidation due to synergistic heterozygosity for ACADM/ETFA alleles in a child with Rett syndrome	Iveta Sosova	27	49
Utility of whey protein powder to establish dietary protein tolerance in young children with phenylketonuria	Rebecca Sparkes	28	50
Suboptimal metabolic control following liver transplantation in a young adult with maple syrup urine disease	Rebecca Sparkes	29	51
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Analysis of glutaric acid, 3-hydroxyglutaric acid and glutarylcarnitine in dried urine spots by liquid chromatography tandem mass spectrometry as possible biomarkers of catabolism in glutaric aciduria type 1	Andrea Yu	32	54

Executive Committee

Pierre Allard
Pranesh Chakraborty
Jo Nam
Andreas Schulze

Local Programming and Organizing Committee

Shailly Jain (Chair)
Alicia K.J. Chan
Clara Hung
Angela Schinkinger
Komudi Siriwardena
Sydney St. James
Iveta Sosova

Credits

This conference has been approved by the Canadian Association of Genetic Counsellors (CAGC) for 12.58 CECs.

This event has been approved by the Canadian Paediatric Society for a maximum of 13 credit hours as an Accredited Group Learning Activity (Section 1) as defined by the Maintenance of Certification program of The Royal College of Physicians and Surgeons of Canada. The specific opinions and content of this event are not necessarily those of the CPS, and are the responsibility of the organizer(s) alone.

Symposium Learning Objectives

By the end of the meeting participants will be able to:

- Understand and outline the indications for different types of transplants in inborn errors of metabolism
- List common metabolic conditions where transplant is considered a beneficial therapeutic option
- Describe expected benefits and change in management following a successful transplant in at least 5 metabolic conditions
- Understand the scope of transplant in metabolic cardiac disorders

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Session Learning Objectives:

Nurse/Genetic Counselor Webinar

Advances in Laboratory Diagnosis of Lysosomal Storage Disorders

Tim Wood, PhD, FACMG, Director, Metabolic Laboratory, Greenwood Genetic Center, Greenwood, SC, USA

1. Comprehend the general process of enzymatic assays commonly used for the diagnosis of LSDs
2. Recognize the limitations of urinary screening assays particularly for the MPS disorders
3. Compare an enzyme-first testing strategy with the classic screening strategies for identifying patients with a lysosomal storage disorder
4. Integrate molecular testing into testing for LSDs
5. Assess how novel urinary testing methods can improve/enhance treatment monitoring

Dieticians' Webinar

Dietary Management in MMA, PA and MSUD: Focus on Transplantation

Gregory Enns, MB, ChB, Director, Biochemical Genetics Program, Department of Pediatrics, Stanford University, Stanford, CA, USA

1. Discuss perioperative nutrition in liver transplantation for patients with MMA, PA, and MSUD
2. Describe natural and metabolic protein tolerance pre vs post-transplant in MMA, PA, and MSUD

Plenary Session I: Bone Marrow Transplant

Hematopoietic Cell Therapy for Lysosomal and Peroxisomal Disorders

Paul Orchard, MD, Medical Director, Inherited Metabolic & Storage Disease Bone Marrow Transplantation Program; Professor, Division of Pediatric Blood and Marrow Transplantation, Pediatric Blood & Marrow Transplantation Center, University of Minnesota, Minneapolis, MN, USA

1. Understand the rationale for the use of hematopoietic transplanataion for inborn errors
2. Recognize the risks and limitations of transplanatation
3. Have an appreciation for emerging issues related to newborn screening

Plenary Session II: Liver Transplant

Liver Transplantation: The Modern Era

Patricia Kawada, Clinical Lecturer, Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB

1. Review Indications for liver transplantation
2. Current liver transplantation listing and allocation in Canada
3. Surgical anatomy of liver transplantation
4. Outcomes of liver transplantation

Transplants in Patients with Inborn Errors of Metabolism

Aneal Khan, MD, MSc, FRCPC, FCCMG, Associate Professor, Department of Medical Genetics and Paediatrics, Alberta Children's Hospital Research Institute, Cumming School of Medicine, University of Calgary, Metabolic Diseases Clinic, Calgary, AB

1. To review new and developing technologies for cell transplant.
2. To provide an update on liver cell transplantation for urea cycle diseases.
3. To review the practical limitations to adopting new technologies.

Plenary Session III: Liver Transplant

Liver transplant experience for Urea Cycle disorders in western Canada

Alicia Chan, FRCP (C), FCCMG, Clinical Geneticist and Metabolics Specialist, Associate Professor, Edmonton Medical Genetics Clinic, University of Alberta, Edmonton, AB

1. Describe the experience of liver transplantation for Urea Cycle disorders in western Canada
2. Describe the changes in liver transplantation for Urea Cycle disorders in western Canada from past to the present

The Toronto Experience in Liver Transplantation for Urea Cycle Disorders – Patient Selection and Outcome

Yaron Avitzur, MD, Medical Director, Intestinal Rehabilitation and Transplantation, Gastroenterology, Hepatology and Nutrition; Director, Paediatric Gastroenterology Training Program, Gastroenterology, Hepatology and Nutrition; Staff Gastroenterologist, Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children; Associate Professor, Department of Paediatrics, Faculty of Medicine, University of Toronto, Toronto, ON

1. Describe the experience of liver transplantation for UCDs in Toronto
2. Describe the changes in liver transplantation for UCDs including patient selection and post-transplant outcomes

Cognitive Outcomes in Liver Transplant

Shailly Jain, MD, FRCPC, FCCMG, Clinical Geneticist & Metabolics Specialist, Associate Professor, Edmonton Medical Genetics Clinic, University of Alberta, Edmonton, AB

1. Describe the cognitive outcomes in pediatric patients following liver transplant.
2. Compare and contrast these outcomes when transplant is done due to an inborn error of metabolism.

Plenary Session IV: Liver Transplant for Organic Acid Disorders

Liver Transplantation for Organic Acidemias

Gregory Enns, MB, ChB, Director, Biochemical Genetics Program, Department of Pediatrics, Stanford University, Stanford, CA

1. List possible indications for liver transplantation in patient who have organic acidemias
2. Summarize potential risks and benefits of liver transplantation for organic acidemias
3. Discuss outcome data related to survival and neurological status post-transplantation

Plenary Session V: Liver Transplant for MSUD and Tyrosinemia

Liver Transplant for Maple Syrup Urine Disease

Komudi Siriwardena, MBChB (Otago), FRACP, FCCMG, Clinical Geneticist and Metabolics Specialist, Associate Professor, Edmonton Medical Genetics Clinic, University of Alberta, Edmonton, AB

1. Summarize current trends for liver transplantation in MSUD
2. Discuss the benefits of transplantation in MSUD

Tyrosinemia: Current situation and challenges

Fernando Alvarez, MD, Director, Liver Transplant Program, CHU Sainte-Justine; Professor, Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, Faculty of Medicine, University of Montreal, Montreal QC

1. Update challenges in the diagnosis of tyrosinemia
2. Summarize current results on the treatment of tyrosienmia
3. Discuss the indications and outcome of liver transplantation in Type I Tyrosinemia

Plenary Session VI: Cardiomyopathies and metabolic disorders

Pediatric Cardiomyopathies and Cardiac Transplantation in Metabolic Disorders

Jennifer Conway, MD, Assistant Professor, Division of Pediatric Cardiology, Department of Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB

1. Understand the impact of metabolic diseases on the heart in children
2. Discuss the outcomes of children with cardiac involvement
3. Discuss the role of advanced heart failure therapies in the management of children with metabolic condition

Cardiomyopathies in Adults

Gavin Oudit, MD, PhD, FRCPC, Director, Heart Failure Program, Canada Research Chair in Heart Failure; Clinician-Scientist, Mazankowski Alberta Heart Institute; Associate Professor, Department of Medicine, University of Alberta, Edmonton, AB

1. Describe the causes of cardiomyopathies in adults
2. Explain the pathophysiology of cardiomyopathies
3. Discuss the management of adult patients with cardiomyopathies: role of genome editing and precision medicine

Mitochondrial respiratory chain disorders Cardiomyopathy

Komudi Siriwardena, MBChB (Otago), FRACP, FCCMG, Clinical Geneticist and Metabolics Specialist, Associate Professor, Edmonton Medical Genetics Clinic, University of Alberta, Edmonton, AB

1. Explain common respiratory chain disorders associated with high risk of cardiomyopathy.
2. Discuss Cardiac transplantation for respiratory chain disorders in the literature.

Biographies

Tim Wood

Dr. Wood came to the Greenwood Genetic Center (GGC) as a clinical laboratory fellow in 2000. After completing fellowships in clinical molecular and clinical biochemical genetics, he was named assistant director of the biochemical genetics laboratory. In 2006 he was promoted to director. Dr. Wood is currently ABMG certified in both clinical molecular and clinical biochemical genetics.

Dr. Wood is a member of the Society of Inherited Metabolic Disease, the Society for the Study of Inborn Errors of Metabolism, the American Society of Human Genetics and is a fellow of the American College of Medical Genetics. Dr. Wood serves on the board of directors for the Southeastern Regional Genetics Group and is a member of the South Carolina Newborn Screening Advisory Committee.

Gregory Enns

Dr. Enns is a Professor of Pediatrics in the Division of Medical Genetics and has been Director of the Biochemical Genetics Program at Stanford University since 1998. As a clinician, he focuses on diagnosing and managing those who have mitochondrial disorders, organic acidemias, and other inborn errors of metabolism.

Paul Orchard

Dr. Paul Orchard is the Medical Director of the Inherited Metabolic & Storage Disease Program and a Professor in the Department of Pediatrics, Division of Blood and Marrow Transplantation at the University of Minnesota. He is interested in the use of hematopoietic stem cell transplantation (HSCT) and other cell therapies for inherited metabolic diseases, as well as combination therapy in order to improve outcomes.

Patricia Kawada

Dr. Patricia Kawada is currently appointed as Clinical Lecturer in the Department of Pediatrics in the Faculty of Medicine and Dentistry at the University of Alberta.

Aneal Khan

MSC in Nutrition – University of Toronto
MD – Queen's University
FRCPC – Pediatrics
FCCMG – Clinical Genetics
Dr. Khan's area of interest is Inborn Errors of Metabolism, and his profile is focused on mitochondrial, lysosomal storage, bone and cardiac diseases. His research work is in clinical trials. In addition, working with collaborators that do bench research, a number of his students have also performed work in laboratories looking at diagnostic and therapeutic methods for metabolic diseases.

Alicia Chan

Dr. Alicia Chan is currently appointed as Associate Professor in the Department of Medical Genetics in the Faculty of Medicine and Dentistry at the University of Alberta.

Yaron Avitzur

Dr. Avitzur is an Associate Professor at the University of Toronto, and the Medical Director of Intestine Rehabilitation and Transplantation at the Division of Gastroenterology, Hepatology and Nutrition at SickKids hospital. His clinical and research interest is at clinical outcomes and immune dysregulation post liver and intestine transplantation.

Shailly Jain

Shailly Jain completed medical education at the University of Western Ontario and the royal college residency in Medical Genetics at the University of Toronto. She did a CCMG fellowship in biochemical genetics at the University of Toronto. She joined the Edmonton Medical Genetics clinic in 2012 and is currently an associate professor at the University of Alberta. Her interests include newborn screening, lysosomal storage disorders and liver transplant for inborn errors of metabolism.

Komudi Siriwardena

Komudi Siriwardena is currently appointed as Associate Professor in the MED Medical Genetics - Non-Bud in the Faculty of Medicine and Dentistry at the University of Alberta. Research Interests include: cost benefit of molecular testing, neurocognitive outcome, phenylketonuria, quality assurance, and variability with plasma phenylalanine levels.

Fernando Alvarez

- Professor, Division of Gastroenterology, Hepatology and Nutrition, CHU Sainte-Justine, University of Montreal, 1999.
- Professor, Department of Pediatrics, University of Montreal, 1999.
- Director, Hepatic Transplantation Program, CHU Sainte-Justine, University of Montreal, 1995.
- Co-Director, Intercultural Pediatrics Unit (Medical Anthropology), CHU Sainte-Justine, University of Montreal, 2001.

Jennifer Conway

Dr. Jennifer Conway began her medical career by receiving her MD from the University of British Columbia in 2002. She subsequently went on to complete her pediatric and cardiology training at the IWK Health Center in Nova Scotia. Following, she underwent further subspecialty training at The Hospital for Sick Children in Toronto in pediatric heart transplant, heart function and mechanical support.

She continued on at the Hospital for Sick Children in Toronto until June 2013 and than joined the team at the Stollery Children's Hospital in Edmonton. Her subspecialty training, career to date and research interests, have been directed towards the care of children with end stage heart failure including mechanical assist devices and transplantation.

Gavin Oudit

Dr. Oudit is an associate professor, staff cardiologist and clinician-scientist at the Mazankowski Alberta Heart Institute, University of Alberta. He completed his BSc, MSc and MD studies at the University of Toronto followed by training in Internal Medicine, Clinician-Investigator Program (PhD), and Adult Cardiology. His clinical activity places a primary emphasis on heart failure and cardiomyopathies. He currently holds a Canada Research Chair in Heart Failure and is the Director of the Heart Failure program.

Conflict of Interest Disclosures

All speakers and committee members must disclose whether they do or do not have a relationship with a commercial entity such as a pharmaceutical organization, medical device company or a communications firm.

Committee Members

Shailly Jain
- I have had involvement in research sponsored by the company or participant in clinical studies concerning the use of the products manufactured by the company: Shire, Sanofi Genzyme (Clinical Trials and Registries)
- I have received/ am expecting to receive monetary support from the company: Shire, Sanofi Genzyme (honorariums for talks/ lectures)

Alicia Chan
- I have had involvement in research sponsored by the company or participant in clinical studies concerning the use of the products manufactured by the company: Shire, Sanofi Genzyme (Clinical Trials and Registries)
- I have received/ am expecting to receive monetary support from the company: Shire, Sanofi Genzyme (honorariums for talks/ lectures)

Clara Hung
- No affiliation

Jo Nam
- No affiliation

Angela Schinkinger
- No affiliation

Komudi Siriwardena
- I have had involvement in research sponsored by, or participation in clinical studies concerning the use of the products manufactured by Biomarin (PKU burden of PAH study) – local PI, no direct salary
- I have received/ expect monetary support from Biomarin (Honorarium for meeting – given to local chapters of rare disorders support group).

Sydney St. James
- No affiliation

Iveta Sosova
- No affiliation

Speakers

Gregory Enns
- I have involvement in clinical trials concerning the use of the products manufactured by Stealth Biotherapeutics and BioElectron
- I have received or expect monetary support received from: Biomarin / Audentes Therapeutics/ Amicus/ Regenxbio/ Neurovia (Data Safety Monitoring Board); Natera/ Horizon (Consultant)

Paul J Orchard
- I have involvement in clinical trial support with the following companies: Sanofi Genzyme, Bluebird Bio, Horizon

Patricia Kawada
- I have an involvement in research sponsored by or participation in clinical studies with AbbVie as a co-investigator on the HCU Pediatric Study.

Aneal Khan
- No affiliation

Alicia Chan
- I have had involvement in research sponsored by the company or participant in clinical studies concerning the use of the products manufactured by the company: Shire, Sanofi Genzyme (Clinical Trials and Registries)
- I have received/ am expecting to receive monetary support from the company: Shire, Sanofi Genzyme (honorariums for talks/ lectures)

Yaron Avitzur
- I have an involvement in research sponsored by or participation in clinical studies with Nutrina Ltd. on the medical advisory board, and as site PI.

Shailly Jain
- I have had involvement in research sponsored by the company or participant in clinical studies concerning the use of the products manufactured by the company: Shire, Sanofi Genzyme (Clinical Trials and Registries)
- I have received/ am expecting to receive monetary support from the company: Shire, Sanofi Genzyme (honorariums for talks/ lectures)

Komudi Siriwardena
- I have had involvement in research sponsored by, or participation in clinical studies concerning the use of the products manufactured by Biomarin (PKU burden of PAH study) – local PI, no direct salary
- I have received/ expect monetary support from Biomarin (Honorarium for meeting – given to local chapters of rare disorders support group).

Fernando Alvarez
- No affiliation

Jennifer Conway
- I have an involvement in research sponsored by or participation in clinical studies with Heartware (unrestricted research grant)

Gavin Y Oudit
- I have an involvement in research sponsored by Sanofi Genzyme in regards to biomarkers and heart disease in patients with Fabry Disease
- I have received or expect monetary support received from: Sanofi Genzyme, BristolMyersSquibb, Novartis, Selvier

Platform Presentation Abstracts

Platform Presentation Abstract 1

A case series study to optimize the hemodialysis prescription for the treatment of hyperammonemic patients with ornithine transcarbamylase deficiency

Chong C[1,2], Wade A[2,3], Khan A[2,3]
[1]Faculty of Science, University of Calgary, Calgary, AB, Canada, [2]Alberta Children's Hospital Research Institute, Calgary, AB, Canada, [3]Faculty of Medicine, University of Calgary, Calgary, AB, Canada

Objectives:

An early liver transplant is the key to the survival of infants born with Ornithine Transcarbamylase Deficiency (OTCD), a rare urea cycle disorder. If delayed, their hyperammonemia may cause permanent neurological damage or death. Hemodialysis (HD) is a lifesaving treatment that reduces their ammonia levels until they receive a transplant. However, the optimal dialysis parameters that efficiently decrease ammonia levels have not been identified. Optimal central venous access management procedures are also unknown.

Design and Methods:

This is a retrospective study of 7 male children with OTCD who received HD from 2010-2014. Ammonia levels and dialysis session sheets were collected for each dialytic session. We determined blood flow rate (Qb) in mL/kg/min, dialysate flow rate (Qd) as a factor of Qb, dialyzer size (m^2) as a percentage of body surface area, central venous access size and location, and session duration. Ammonia reduction half-life was calculated for each session.

Results:

Data from 172 dialysis sessions involving all 7 patients was collected. When blood flow rate (Qb) ranged from 7.0-9.0 mL/kg/min or when the dialyzer size was at least 1.2 times the body surface area (BSA), a half-life ranging from 0 to 60 min was observed. A multivariate regression analysis using Qb, Qd, dialyzer size and half-life will determine the optimal dialysis prescription.

Conclusions:

The main determinants of ammonia half-life using HD are Qb and the dialyzer size to BSA ratio and these can be optimized for the most effective ammonia reduction during hemodialysis.

Keywords:
Hemodialysis; Ornithine Transcarbamylase Deficiency; Hyperammonemia

Funding Acknowledgement (if applicable):
Alberta Children's Hospital Research Institute Summer Studentship

Platform Presentation Abstract 2

Urea cycle disorders: Is fibrosis a common feature in all subtypes? A close look at liver cell injury from a Western Canadian Liver Transplantation Center

Jain-Ghai S[1], Chan A[1], Siriwardena K[1], Khan A[4], Yap J[2], Sergi C[3]
[1]Department of Medical Genetics, University Of Alberta and Stollery Children's Hospital, Edmonton, Canada, [2]Department of Pediatrics, University of Alberta and Stollery Children's Hospital, Edmonton, Canada, [3]Department of Lab Medicine and Pathology, University of Alberta and Stollery Children's Hospital, Edmonton, Canada, [4]Medical Genetics and Pediatrics, University of Calgary, Alberta Children's Hospital, Calgary, Canada

Background:

Urea cycle disorders (UCD) are inborn errors of protein and nitrogen metabolism, presenting with hyperammonemia. The growing evidence of clinical liver dysfunction in UCDs raises the question whether our understanding of morphological changes should be updated in light of the new knowledge at cellular and subcellular level. Light and electron microscopy liver findings have been described in few publications, but comprehensive clinical-pathological correlations remain sparse.

Objective:

We present the histopathology of 19 patients with UCDs (7 ornithine transcarbamylase deficiency (OTCD), 7 argininosuccinate synthase deficiency (Citullinemia, ASSD), 3 carbamylphosphate synthase I deficiency (CPS-1D) and 2 argininosuccinate lyase deficiency (ASLD)).

Results:

We examined 21 specimens (3 liver biopsies, one autopsy and 17 explanted livers). Hydropic vacuolar degeneration (HVD), fibrosis, glycogenic islands (Gly-I) and glycogenated nuclei (GNN) were the most common findings in UCDs. Fibrosis is most common in OTCD cases (85%), CPS-1D (100%) and ASLD (100%), while least common in ASSD (30%). All cases with ASSD show presence of GNN, a finding that is only present in about 50% of all other UCDs.

Conclusion:

In our cohort, all cases had abnormal pathological findings. We speculate that GNN and fibrosis can possibly serve as differentiating factors between ASSD and other UCDs. We explore the role of glycogen and various urea cycle intermediates including ammonia in causing fibrosis and liver dysfunction.

Keywords:

Urea Cycle Disorder, Pathology

Platform Presentation Abstract 3

An innovative treatment trial of peroxisomal biogenesis disorders with anti-pexophagy agents

Sondheimer N[1, 3], Kim P[2]
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Objectives:

There are limited treatment options available for patients with peroxisomal biogenesis defects (PBDs). Preliminary studies in animal models and cell culture have suggested that PBDs caused by PEX1, PEX6 and PEX26 may act to amplify the turnover of peroxisomes rather than inhibiting their synthesis. Blocking the autophagic removal of peroxisomes (pexophagy) is a potential therapeutic strategy. In order to explore this possibility, we used a clinically approved medication (hydroxychloroquine sulfate – HCS) to inhibit pexophagy in two patients.

Design and Methods:

We received an "Innovative Drug Use" exception from our hospital to provide HCS to two patients with disease due to PEX1 and PEX6 mutations. Dosing was 4mg/kg/d div bid and the patients were monitored using very-long chain fatty acid levels in blood. Side effects were monitored by ophthalmological exams and liver function testing.

Results:

Although the trial was not designed to provide statistically evaluable results, the C26:C22 ratios was reduced in both patients. Ophthalmological examinations of the patients show no evidence of HCS associated retinopathy. Both families have elected to continue the use of HCS.

Conclusion:

In this study we observed modest improvements in a marker used for diagnosis of peroxisomal disease. Side effects were not observed. The use of HCS or other agents inhibiting pexophagy provides a rational means of improving peroxisomal number. We are exploring the possibility of a randomized control trial to provide evaluable data on the possibility of treatment.

Keywords:

Zellweger syndrome, peroxin, hydroxychloroquine

Platform Presentation Abstract 4

Kidney disease and organ transplantation in methylmalonic acidaemia

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Objectives:

Methylmalonic acidemia (MMA) is associated with chronic tubulointerstitial nephritis and a progressive decline in glomerular filtration rate (GFR). Optimal management of these children is uncertain, despite the establishment of organ transplantation. Our objectives are to document the pre-, peri- and post-transplant course of all children with MMA who underwent liver and/liver kidney transplant in our centers.

Design and Methods:

Retrospective chart review of all cases of MMA who underwent organ transplantation over the last 10 years.

Results:

Five children with MMA underwent liver transplant (4/5) and combined liver kidney transplant (1/5). Three were Mut0, two had cobalamin B disorder. All were transplanted between ages 3-5 years. Renal dysfunction prior to transplant was seen in 2/5 patients. For example patient 2 (liver transplant only) had impaired renal function pre transplant (GFR 54 ml/min/1.73m2), microalbuminuria, hypercalciuria and nephrocalcinosis.

Post-transplant at present she has microalbumin/creatinine ratio of 20.7 (0.0-2.8 mg/mmol creatinine) and Cystatin C eGFR of 46ml/min/1.73m2. Thus there has been slow decline in GFR. Serum MMA levels have decreased in all to < 300 micromol/L (0.10-0.40). Long-term follow up has shown slow progression of the renal disease albeit slow in 4/5. Four patients remain on low protein diet, carnitine, coenzyme Q and vitamin E post-transplant. 4/5 patients presented prior to newborn screening results.

Conclusion:

MMA is a complex metabolic disorder. Renal disease continues to progress post liver transplant. Close nephrology follow up, monitoring serum MMA levels, carnitine, protein restriction and addition of coenzyme Q and vitamin E may improve renal outcome.

Keywords:

Kidney, Methylmalonic acidemia, Hyperammonemia, eGFR

Platform Presentation Abstract 5

Characteristics of a Canadian cohort of children with inherited metabolic diseases for which liver transplantation is a therapeutic option: Chart-reported findings from the Canadian Inherited Metabolic Diseases Research Network

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Objectives:

The Canadian Inherited Metabolic Diseases Research Network (CIMDRN) collects baseline information regarding patient characteristics and diagnostic care for a cohort of Canadian children diagnosed with inherited metabolic diseases (IMD). Liver transplantation is a possible treatment for several of these IMD, including certain urea cycle defects (UCD), organic acidemias (OA), aminoacidemias (AA), and glycogen storage disease type 1 (GSD1). We describe this cohort as a potential platform for future studies of liver transplant care and outcomes.

Design and Methods:

Children diagnosed with a UCD, OA, AA, or GSD1, born 2006-2015, and receiving care at 1 of 13 participating metabolic clinics were eligible to participate. We extracted patient and clinical data from medical charts with parental consent.

Results:

From 71 participants to date, 38% were diagnosed with a UCD, 21% with an OA, 30% with an AA, and 11% with GSD1. 42% were symptomatic at the time of diagnosis; commonly documented symptoms included lethargy, vomiting, hyperammonemia, and metabolic decompensation. 13% were deceased at the time of their enrollment into the study with deaths occurring at a median age of 17 days. For those with data regarding initial treatment (n=54), drug therapy (65%) and diet therapy (72%) were frequently prescribed..

Conclusion:

CIMDRN collects cross-sectional diagnostic data for a cohort of children with IMD for which liver transplantation is a possible treatment. Most participating families consent to re-contact for future research, highlighting the potential of this platform for launching longitudinal studies to understand care and outcomes associated with liver transplantation in this population.

Keywords:

Liver transplant, rare disease, observational

Funding Acknowledgement: CIHR Emerging Team Grant, TR3-119195

Poster Abstracts

Poster Abstract 1

Controversies of jump analysis: squat jump is the optimal technique for use in clinical environments

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Background:

Jump performance is a quantitative measure to of lower body mobility. Two predominant styles of jump are countermovement-jump (CMJ), allowing a dip prior to jumping, and squat-jump (SJ), beginning from a bent position with as little dip as possible.

CMJ is favoured in existing research due to its focus on able-bodied subjects and athletes, who are capable of bending to create a countermovement. However, patients with weakness due to metabolic diseases may be unable to perform a CMJ or lose/gain the ability through disease course/treatment.

Objectives:

To determine if SJ yields statistically similar results to CMJ while retaining the abovementioned benefits.

Methods:

Thirteen healthy volunteer subjects performed 10 jumps in one day using BTS Bioengineering (model P4000, Novanta Padovana, Italy) force plates and accompanying SMART Motion Capture System (version 1.10.465.0) software. Subjects performed 5 CMJ's and 5 SJ's, alternating. Peak jump power was recorded, normalized to subject weight (watts/kilogram). The jumps will be repeated after 9 months to observe longer-term repeatability.

Results:

Jump power with CMJ (45.7 W/kg +12.5; mean+SD), exceeded jump power of the SJ (41.2 W/kg +9.07; mean+SD). Additionally, SJ produced a standard deviation of 9.07, lower than the 12.5 standard deviation of CMJ.

Conclusions:

SJ allows for a larger number of users to measure jumping power for clinical trials or monitoring patients without requiring programming or engineering alterations on force plate ergometers. SJ also produced lower variation, however, the 9-month follow-up is pending.

Keywords:
Jump, squat, countermovement, peak-power, weakness

Poster Abstract 2

Transient Plasma Methionine, Total Homocysteine, S-adenosylmethionine and S-adenosylhomocysteine elevations in a patient diagnosed with NGLY1 deficiency; a Congenital Disorder of Deglycosylation

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Objective:
To expand on the reported clinical and biochemical phenotype of NGLY1 deficiency; the only known Congenital Disorder of Deglycosylation (CDDG) in Humans.

Methods:
We report on a 4 year old female born to consanguineous parents, referred to the metabolics clinic for elevations in plasma methionine, total plasma homocysteine (tHcy), alpha-fetoprotein (AFP) and transaminases. She has global developmental delay, microcephaly, dysmorphic facial features, hypotonia, nystagmus and tremor in her upper extremities. She does not have seizures, lactic acidosis or hypolacrima. MRI brain demonstrated volume loss of the deep white matter of cerebral hemispheres, resulting in prominence of extra-axial CSF spaces, lateral and third ventricles. Thinning of the brainstem and absent anterior falx was noted. 1H-magnetic resonance spectroscopy of the brain was normal.

Results:
Metabolic investigations demonstrated consistent elevations in plasma methionine, tHcy, plasma S-adenosylmethionine (SAM) and plasma S-adenosylhomocysteine (SAH); with normal urine adenosine levels, over a period of one year. Sequencing of the ADK and AHCY genes was negative for variants. Plasma methionine, tHcy, AFP and transaminases normalized a year later but SAM and SAH continued to be elevated for six more months before normalization. Whole exome sequencing demonstrated a homozygous pathogenic variant; c.1405C>T (p.Arg469Ter); in exon 9 of the NGLY1 gene and the parents were heterozygous for this pathogenic variant.

Conclusion:
To our knowledge less than 20 patients have been reported with NGLY1 deficiency Worldwide and this case expands on the clinical and biochemical phenotype in this newly discovered inborn error of metabolism.

Keywords:
NGLY1, Congenital disorder of deglycosylation

Poster Abstract 3

Improving health care delivery for children diagnosed with rare metabolic diseases by learning from families and providers: protocol for phase I, a prospective cohort study of families' health care experiences

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Background:

Children with rare chronic diseases have diverse and disproportionately high needs for health services, but research regarding their health care experiences is sparse. In our multi-phase study, we will develop family-centered interventions that aim to sustainably improve health care experiences and both child and family outcomes for pediatric inherited metabolic diseases (IMD).

Towards this goal, phase I of our study will prospectively and comprehensively describe the health care experiences of families of children with IMD.

Methods:

We report the protocol for a single-group, prospective cohort study. Using purposive sampling, we will recruit 100 parents/guardians of children enrolled in the Canadian Inherited Metabolic Diseases Research Network through one of nine participating pediatric tertiary care centres across Canada. At baseline, participants will complete a survey and draw a visual map of their child's network of health care providers.

Over six months, participants will provide real-time perspectives on health care experiences using electronic diaries, supplemented by an in-depth interview. The diaries are informed by principles of patient-centered care: access, respect, coordination and continuity, communication, physical comfort, emotional support and family involvement. We will analyze the survey, diary, care map, and interview data using both quantitative (descriptive, social network, and regression analysis) and qualitative (thematic analysis) approaches as appropriate.

Conclusions:

Phase I of this study will describe the health care experiences of families of children with IMD. Later study phases will build upon this work, informing the development of family-centered interventions to improve care and outcomes for children with IMD and their families.

Keywords:

Family-centered care, pediatrics, rare diseases

Funding Acknowledgement:

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Poster Abstract 4

Carnitine uptake defect due to a 5'UTR mutation

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Abstract:

Carnitine Uptake Defect (CUD) is an autosomal recessive disorder due to mutations in the SLC22A5 gene. Classically patients presented in infancy with cardiomyopathy and characteristic EKG findings and associated skeletal muscle weakness. Later presentations include recurrent hypoketotic hypoglycemia, sudden death, rhabdomyolysis and/or recurrent muscle pain and weakness.

Newborn screening detects most of these clinical variants but in addition has identified maternal CUD often in asymptomatic women. We describe a family ascertained through 3 NBS positive infants found to be unaffected themselves but in whom the mothers (sisters) were affected. Subsequent investigations revealed 4 affected individuals within the pedigree.

Plasma carnitine was decreased and fractional excretion of free carnitine was increased (10.6-56%) in all affected individuals. Red cell uptake (S Olpin) showed a 37% reduction from the mean of normal controls (0.4; 1.08+/-0.24 pmol/mg protein/min). Analysis of the SLC22A5 gene in a commercial laboratory (Emory) by sequencing and del/dup analysis was normal. Whole exome analysis did not reveal a genetic cause and renal dysfunction was excluded by standard biochemical tests. Re- analysis on a Next Generation Sequencing panel specifically designed to fully cover newborn screening disease targets showed a homozygous change in the proband (SLC22A5;NM_003060:c.-149G>A; p.?). The gene encodes the carnitine transporter and the mutation is in the 5' UTR with a frequency within the gnomAd database of 0.001198.

While the effect of this variant has not been determined in vitro, the biochemical findings , reduced carnitine transport and the segregation within this large pedigree provides compelling evidence of causation.

Keywords:

Carnitine Uptake defect, 5'UTR mutation

Poster Abstract 5

Case Report: Two siblings with type VII 3-methylglutaconic aciduria due to mutations in CLPB gene

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Background:

3-methylglutaconic acidurias (3-MGA-urias) are unified by significant elevation in 3-methylglutaconic acid (3-MGA) in urine and plasma. Although rare in overall incidence, 3-MGA-urias type I, II, III and V are more common than types IV and VII. The clinical presentations of the subtypes have some overlap, but specific distinctive features exist.

Objective:

We report 2 siblings of African descent with molecularly proven type VII 3-MGA-uria due to caseinolytic peptidase B (CLPB) deficiency.

Results:

The index case presented at 15 months with bilateral cervical lymphadenitis, fever, and neutropenia (0.1 x 10^9/L) that improved with G-CSF. The patient was developing typically until 2 years of age when he showed regression of speech and cognitive skills, followed by gait abnormalities, progressive ataxia, dysarthria, global developmental delay, and cerebellar atrophy by 3.5 years of age.

Metabolic work-up revealed plasma 3-MGA of 2892 (103-384) and urine 3-MGA of 43 (1.9-9.1). Molecular testing confirmed the diagnosis with compound heterozygous mutations in the CLPB gene. Family history revealed an older sibling who died at 16 months of age following adenovirus pneumonitis. Given her combination of severe neutropenia, ataxia, brain atrophy, and elevated 3-MGA, CLPB deficiency was suspected.

Conclusion:

Autosomal recessive type VII 3-MGA-uria due to CLPB mutations is among the least common types of 3-MGA-urias, with less than 35 reported patients. We expand the phenotype by describing the presentations of two siblings, one of whom died at 16 months due to severe neutropenia. This case highlights the importance of genetic diagnosis to ensure appropriate follow-up for sequelae.

Keywords:

3-methylglutaconic aciduria, neutropenia, CLPB deficiency

Poster Abstract 6

MITO-FIND: Mitochondrial Functional and Integrative Next Generation Diagnostics

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Objectives:
The MITO-FIND project investigated which tests produce the highest diagnostic yield for mitochondrial disease (MD).

Methods:
We reviewed 296 cases (children and adults) referred to the Metabolic Clinic in Calgary since since 2004 for a mitochondrial disease. In medical records, after traditional testing, 70 cases were labeled as non-mitochondrial (NON-MITO), 106 cases as MD (MITO) and 120 cases as no diagnosis (NoDx). Patients in MITO (n=18) or NoDx (n=8) were recruited for nuclear gene exome sequencing (NGS) and Fischer's 2 tailed test used to compare the groups.

Results:
Muscle neuropathology (84.13%) had the highest sensitivity followed by muscle enzyme activity (66.67%), muscle mtDNA analysis (64.63%), and skin pathology (39.13%) ($p<0.05$). The sensitivity for brain MRI (40.91%), plasma 3-methyl glutaconic acid (32.43%) and NGS alone with a pathogenic mutation (16.67%) was not statistically significant.

2 cases in MITO had the diagnosis changed to NON-MITO. When NGS and muscle mtDNA analysis were both used, the combined sensitivity was 61.11% and specificity 87.5% ($p=0.04$) but NGS did not add any new diagnoses to the MITO group. In 5 cases in the MITO group, peripheral leukocyte DNA failed to detect the mtDNA mutation that was later found on muscle-extracted DNA.

Conclusion:
We conclude that a quality-controlled muscle biopsy protocol and NGS produced the highest yield for diagnosing a MD. A MD cannot be excluded without doing a muscle biopsy.

Keywords:
Mitochondrial disease, exome sequencing

Funding Acknowledgement (if applicable):
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Poster Abstract 7

Plasma derived cell-free mitochondrial DNA (cf-mtDNA): A novel and non-invasive method to sequence intact mtDNA

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Objectives:

We have observed that detecting mitochondrial DNA (mtDNA) mutations in using non-invasive methods (peripheral leukocytes or urine sediment) has lower sensitivity than muscle-extracted DNA. Research suggests that cellular apoptosis and cellular turnover release small 150-200 base pair fragments of DNA from hematopoietic and non-hematopoietic cell types, which can be extracted from plasma as cell-free DNA (cf-mtDNA).

Intact mtDNA has not been successfully identified from the cell free fraction previously. We suspected that the circular nature of mtDNA is protective, our objective was to develop a methodology to identify intact cf-mtDNA from plasma.

Methods:

Blood samples from patients with known mitochondrial disease (n=7) and healthy controls (n=7) were collected and their cf-mtDNA isolated. To demonstrate the presence of the mitochondrial genome within these samples, we amplified the isolated DNA using custom PCR primers specific to overlapping fragments of mtDNA. cf-mtDNA samples were then sequenced using the Illumina MiSeq sequencing platform.

Results:

We confirmed the presence of mtDNA, demonstrating that the full mitochondrial genome is in fact present within cfDNA isolates. Furthermore, sequencing positively matched the mitochondrial haplogroup obtained from a tissue specimen for each patient and control.

Conclusion:

We report the first successful method showing positive identification of cf-mtDNA by haplogroup analysis from plasma. This technique has the clinical applications of donor cell identification and identification of targets of mtDNA therapies.

Keywords:

Mitochondrial disease, cell free DNA

Funding Acknowledgement (if applicable):

Mito-Canada

Poster Abstract 8

Anesthetic Complications in patients with Niemann Pick C: Is there a higher risk?

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Objectives:

There are 230 million surgical procedures in the world every year with a mortality rate of 0.4/100 000 (World Health Organization). Because of the visceral and neurological organ involvement, we hypothesized that the risk of anesthetic complications was higher in NPC compared to the general population.

Methods:

We did 3 searches in PubMed for large studies in the general population e.g. circumcision (CONTROL), all papers in NPC patients (NPC), and all studies in other inborn errors of metabolism (IBEM). Papers had to describe the procedure, the general anesthetic used and complications that occurred.

There were 7/42 articles in CONTROL (without case reports), 3/27 in NPC and 7/362 in IBEM that met criteria. Adverse outcomes were compared between the groups using a 2-tailed Chi-squared analysis. We also reviewed 6 NPC patients in Calgary.

Results:

The complication rate in CONTROL was 145/661, NPC was 3/31, and IBEM 3/20 cases. There was no statistical difference between any 2 groups. In Calgary, 3/6 patients had a procedure with a general anesthetic and none had complications.

Overall, the most common anesthetic agents used in order of frequency were sevoflurane, propofol, nitrous oxide, ketamine and midazolam in CONTROL and IBEM. Propafol was used more frequently in NPC compared to the other 2 groups.

Conclusion:

There is a paucity of data from which anesthetic complications can be determined and lack of comparable control data in metabolic publications. A higher anesthetic risk in NPC versus the general population was not found with this analysis.

Keywords:

Niemann Pick C, anesthetic complications

Funding Acknowledgement (if applicable):

Alberta Innovates Heritage Youth Researcher Summer Program

Poster Abstract 9

Screening for Fabry cardiomyopathy using cardiac magnetic resonance imaging

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Objectives:

The prevalence of Fabry disease (FD) in patients with hypertrophic cardiomyopathy (HCM) has been reported to be 1 to 3 percent. Special applications of cardiac MRI (CMR), such as late gadolinium enhancement and noncontrast T1 mapping show potential for identifying FD during imaging with CMR.

The aim of this study is to prospectively evaluate the sensitivity and specificity of CMR in identifying FD in the background of genetic cardiomyopathies by next generation sequencing.

Methods:

A prospective case-control study using 3-Tesla CMR in patients with features of HCM on CMR with in whom the cause of cardiomyopathy is not known. DNA sequencing was performed on an Illumina MiSeq platform using a panel of 55 genes associated with HCM.

Results:

A total of 194 patients have been screened, 113 contacted that met eligibility criteria, 37 samples have been collected and 9 patients have been sequenced thus far. No case of FD has been found yet. Six patients had a pathological mutation for familial HCM, 2 patients likely have a rare pathogenic mutation and 1 patient was found to have a pseudogene mutation for MELAS. All patients had cardiac hypertrophy and late gadolinium enhancement. T1 mapping data is still under analysis.

Conclusion:

CMR labelled as HCM lead to identification of a genetic cause in 60% of cases with 2 additional cases likely. Two out of 3 negative cases had apical cardiomyopathy. No cases were falsely identified as Fabry cardiomyopathy. The study is currently open to recruitment and additional analyses are pending.

Keywords:

Fabry disease, magnetic resonance imaging

Funding Acknowledgement (if applicable):

Shire, Investigator Initiated Grant

Poster Abstract 10

Idiopathic chylous ascites in an adult patient with LRPPRC-associated Leigh syndrome: a coincidence or a rare clinical manifestation of mitochondrial dysfunction?

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Objectives:

To describe the occurrence of chylous ascites in an adult patient with LRPPRC deficiency. Mitochondrial disease is said to be capable of causing "any symptom, in any organ, at any age", and the full phenotypic spectrum of mitochondriopathies is yet unknown. Idiopathic chylous ascites is a rare and poorly understood condition that has never, to our knowledge, been reported in association with an inborn error of metabolism.

Design and Methods:

Case report, review of pediatric and adult charts, Pubmed search for instances of co-occurrence of idiopathic chylous ascites and mitochondrial disease.

Results:

We describe an adult patient with an LRPPRC-associated Leigh syndrome caused by novel biallelic LRPPRC mutations - c.515A>G (p.Y172C) and c.2805+5G>C - distinct from the French-Canadian founder mutation. At the age of twenty-five, he developed massive chylous ascites, for which no cause could be identified despite extensive radiological investigation and intestinal biopsy.

In retrospect, very mild ascites had been present intermittently since childhood. After repeated drainage of the initial fluid, the patient responded well to dietary long-chain fatty acid restriction with medium-chain triglyceride supplementation.

Conclusions:

To our knowledge, this is the first case report of idiopathic chylous ascites in a patient with primary mitochondrial disease. The association may be coincidental. We note, however, that the metabolically active nature of lymphatic transport, as well as the fact that a distinct morphotype has been reported in LRPPRC deficiency and other mitochondriopathies, make a causal link plausible.

Keywords:

mitochondrial disease, LRPPRC, chylous ascites

Poster Abstract 11

Expanding the Clinical Phenotype of NUS1-CDG, a rare Congenital Disorder of Glycosylation

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Objective:

To expand on the reported clinical phenotype of NUS1-CDG, a rare Congenital Disorder of Glycosylation (CDG).

Methods:

We report on a 15 year old female born to non-consanguineous parents, followed in the Metabolics clinic for a type 1 pattern CDG (unknown subtype) diagnosed by transferrin isoelectric focusing (TIEF). The type I CDG pattern was also confirmed by mass spectrometry analysis of carbohydrate deficient transferrin.

Clinically the patient has severe global developmental delay, speech delay, epilepsy, severe myopia, truncal ataxia, bilateral hand tremor, hypotonia and idiopathic thrombocytopenia purpura.

Results:

Molecular genetic testing identified homozygous variants of unknown significance in the NUS1 gene at c.803C>A (p.Ser268Tyr), classified as likely pathogenic. N-glycan analysis demonstrated mildly increased Man5 and reduced Man9 and complexed N-disialo-glycan. The N-linked Man5/Man9 ratio is at 5.10 (normal <3.54) consistent with a potential deficiency of dolichol-linked mannose and consistent with NUS1-CDG.

Conclusion:

To our knowledge our patient is the oldest patient reported in the literature with NUS1-CDG and this case expands on the published clinical phenotype. Furthermore, as the N-Glycan analysis analyzes glycans released from all glycoproteins, it can detect abnormalities of N-glycan types that are not present on transferrin molecules e.g. N-linked high mannose glycans etc., but there is an under-recognition that many subtypes of type I CDG may not be detected by transferrin analysis but instead would be detected by N-glycan analysis. Thus this case demonstrates the importance of performing N-glycan analysis over/ in conjunction with TIEF for elucidating and differentiating the subtypes of CDG.

Keywords:

NUS1-CDG, CDG, NUS1, N-Glycan, TIEF

Poster Abstract 12

Diagnostic challenges in a patient with global developmental delay, lipodystrophy, periventricular leukomalacia and spasticity

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Objective:

Present diagnostic challenges encountered in a consanguineous patient with a complex phenotype, followed in Metabolics clinic.

Methods:

We report a 4 year old male born to consanguineous parents followed for developmental delay, nystagmus, seizures, spasticity, lipodystrophy and failure to thrive. MRI brain showed bilateral patchy periventricular white matter abnormalities and volume loss with normal 1H-magnetic resonance spectroscopy.

Results:

Metabolic workup including creatine kinase and transferrin isoelectric focusing (TIEF) were negative. A novel homozygous likely pathogenic variant in NOTCH3 (c.5677C>T; p.Arg1893*) was identified but deemed not sufficient to explain the phenotype, so whole exome sequencing (WES) was pursued and revealed in addition to the NOTCH3 variant, novel homozygous missense variants in ISPD (c.733C>G; p.Leu245Val) and in PMM2 (c.657G>C; p.Glu219Asp), both predicted deleterious by in silico tools and classified as variants of uncertain significance (VUS).

Despite the normal TIEF, the variants in PMM2 warrant further investigation with N-glycan analysis as many subtypes of CDG are missed by TIEF alone. Similarly further investigations of the ISPD variant is needed given the recent suggestion that supplementation with ribitol is therapeutic.

Conclusion:

This case 1. Highlights the emerging concept of multiple diagnoses in a single patient and hence the value of early WES in complex phenotypes, especially in consanguineous families; 2. Emphasizes the utility of N-glycan analysis over TIEF to diagnose CDG; 3. Demonstrates the emerging idea of recessive versions of dominant disorders associated with phenotypic expansion; 4. Illustrates challenges in effectively diagnosing patients with rare diseases, especially if there is potential for therapeutics.

Keywords:

PMM2, ISPD, NOTCH3, TIEF, Glycan

Poster Abstract 13

Review of C5OH as a newborn screening target

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Introduction:

Newborn Screening Ontario (NSO) is the provincial screening program in Ontario, Canada. The NSO Advisory Council provides guidance and advice to NSO and periodically reviews the existing targets of screening.

Objective: Based on the high number of false positives and diagnostic/medical uncertainty related to 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency, the screening algorithm for C5OH-related targets and the diseases themselves were nominated for a formal review.

Method:

The performance of the newborn screen was reviewed between 2006-2014, in addition an extensive literature review and survey of the provincial treatment centres was conducted to ascertain the clinical status of the patients identified as having a C5OH-related target.

Results:

There were 1,153,673 infants screened in the time period. The sensitivity was 100% and the positive predictive value 5.8%. The survey of the treatment centres highlighted the high number of asymptomatic individuals with 3-MCC deficiency (22/22 newborns and 19/19 maternal cases) identified through screening. The cases of beta-ketothiolase and holocarboxylase deficiencies were not asymptomatic. Incorporating C6DC, C5:1, C3 and C3/C2 acylcarnitine results into the screening algorithm with more conservative cutoffs decreased the number of screen positives by >80% with no reported cases of false negatives; the PPV improved to 25%.

Conclusions:

The combination of false positives, low penetrance of 3-MCC deficiency, maternal cases, low numbers of symptomatic target diseases and lack of proven benefit of screening for the conditions led to the recommendation to remove all C5OH-related targets from the newborn screening panel. This was implemented in December 2017.

Keywords:

Newborn screening, C5OH-related targets

Poster Abstract 14

Targeted Reduction in Pathogenic Heteroplasmy Through Binding of G-Quadruplex DNA

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Background:

Diseases due to mitochondrial DNA (mtDNA) mutations are lethal and few therapeutic options are available. Because most mutations exist in a state of heteroplasmy, the coexistence of wild type and mutated mtDNA, strategies that can alter this ratio in favor of wild-type mtDNA ("heteroplasmy shifting") may be therapeutically useful.

We sought to explore whether the natural tendency of mtDNA to form G-quadruplex structures (GQs) could be exploited to induce heteroplasmy shift.

Methods:

We identified all confirmed pathogenic mtDNA mutations in MitoMAP database that increased the potential for mtDNA to form GQ in silico. We evaluated GQ formation by circular dichroism (CD) and ultraviolet melting spectra (UV-Melting).

To investigate the effect of GQ and GQ-binding agents on DNA polymerase, we used a modified Taq primer extension assay. Patient-derived fibroblasts were treated with candidate GQ binding agents (GQBA) and the cells were evaluated for mtDNA quantity and genotype.

Results:

We elected to study the Leigh Syndrome (LS) associated mt.10191T>C mutation. In vitro GQ formation was evaluated by CD spectra. UV-melting showed an increase in melting temperature and stabilization by GQBA. The m.10191C mutation leads to a decrease in the processivity of polymerase compared to either non-GQ containing sequence or mt.10191T. Cyclical treatment of patient derived cells with mt.10191T>C with GQBA resulted in heteroplasmy shift.

Conclusions:

Heteroplasmy shifting presents potential therapy for patients with disease due to mtDNA mutations. Here we demonstrate a significant and reproducible decrease in heteroplasmy level using small molecule approach based upon differential stabilization of GQ forming region.

Keywords:

mtDNA, heteroplasmy, mitochondrial disease, therapeutics

Funding Acknowledgement (if applicable):

We acknowledge The Centre for Genetic Medicine and Restracomp at The Hospital for Sick Children.

Poster Abstract 15

Drug Approval System in Canada

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Objectives:

There is limited literature outlining the approval process in Canada for new drugs. Additionally, there appears to be no obvious legal framework under which a drug is approved on provincial formulary after approval from Canadian Agency for Drugs and Technologies in Health (CADTH). Our objective was to identify what regulatory process is followed in Canada for new drugs for metabolic disease.

Design and Methods:

We reviewed publications from Health Canada, The Canadian Legal Information Institute, and Pubmed covering the Canadian drug approval process and how many drugs were processed.

Results:

The drug approval process in Canada is multi-faceted and regulations weren't clear. There's a 300 calendar day service standard for Health Canada to review a standard New Drug Submission (NDS). In the 2016/17 fiscal year, the average time to approve a NDS in Biologics and Genetic Therapies Directorate was 366 days.

The pan-Canadian Pharmaceutical Alliance (pCPA), advised by CADTH, is responsible for negotiating drug prices with manufacturers, however not all drugs approved by Health Canada are negotiated by pCPA. As of December 27, 2017, the pCPA made the decision not to negotiate 57 drugs - 3 being metabolic treatments. Unfortunately, patients with the diseases those drugs were intended for remain untreated.

Conclusions:

We were able to identify a general workflow, but found that some of the steps of drug approval did not have regulatory framework or guidelines that could be monitored. We also couldn't identify who is accountable when patients with rare diseases don't get access to their therapy.

Keywords:

Drug Approval, Drug Review

Poster Abstract 16

Liver transplantation for inborn errors of metabolism: A survey of care practices and delivery in Canadian metabolic clinics

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Objective:

Liver transplantation has been established as an effective intervention for many inherited metabolic diseases (IMD). However, care practices related to liver transplantation for IMD are not yet well-characterized.

Our objective is to better understand health service delivery and outcomes related to liver transplants for eligible IMD (amino acid disorders, urea cycle disorders, organic acid disorders, and hepatic glycogen disorders) in patients followed by metabolic clinics in Canada.

Design and Methods:

Currently, there are 14 pediatric metabolic disease treatment centres across Canada participating in the Canadian Inherited Metabolic Diseases Research Network (CIMDRN). Physicians representing each of these treatment centres have been invited by email to participate in an online questionnaire, which was developed by the research team. The questionnaire addresses the following topics: centres' protocols and usual care practices for IMD patients referred for liver transplantation; types of liver transplantation or donors used for patients followed at the centres; and expected and actual outcomes for patients following transplantation.

Results:

Data collection is underway; complete results will be ready for presentation at the meeting. These data will provide an atlas of patients for whom IMD physicians are considering liver transplantation, insight into practice variation, and parameters that IMD physicians consider important in considering liver transplantation for their patients.

Conclusions:

The findings of this study will be used to understand the nature of care related to liver transplantation for IMD patients in Canada, and ultimately to establish priorities for future research to improve clinical care and outcomes for this patient population.

Keywords

Inherited metabolic diseases, liver transplantation

Poster Abstract 17

D-2-hydroxyglutaric aciduria in a patient with speech delay due to a novel homozygous deletion in the D2HGDH gene

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Objective:

D-2-hydroxyglutaric aciduria (D-2HGA) is a rare autosomal recessive neurometabolic disorder with a variable clinical spectrum. The severe phenotype is characterized by epileptic encephalopathy, hypotonia, cardiomyopathy and facial dysmorphisms, while the mild phenotype can present with hypotonia and developmental delay. Here we report on a novel homozygous deletion in the D2HGDH gene; encoding D-2-hydroxyglutarate dehydrogenase, in a patient with D-2HGA and speech delay.

Methods:

The proband is a 5 year old male born to consanguineous parents, referred to the Metabolics clinic for elevated urine 2-hydroxyglutaric acid (2-HGA) levels on two occasions; 1348 mmol/mol Cr and 1497 mmol/mol Cr (normal <20 mmol/mol) respectively. Clinically the patient is non-dysmorphic but has moderate expressive speech delay, mild fine motor delay and mild hypotonia. Brain MRI and in vivo 1H-Magnetic resonance spectroscopy were normal.

Results:

Molecular testing identified a novel homozygous deletion of exons 3-10 in the D2HGDH gene (encompassing 75% of the protein), predicted to result in a truncated protein and classified as pathogenic.

Conclusion:

This case expands on the reported clinical phenotype of D-2HGA due to D2HGDH variants, with speech delay being the most prominent clinical finding. Interestingly, despite identifying a deletion in D2HGDH predicted to severely impact protein function, our patient is on the milder end of the phenotypic spectrum of D-2HGA.

Keywords:

D-2-hydroxyglutaric aciduria, D2HGDH, 2-hydroxyglutaric acid

Poster Abstract 18

Experiences with health care for children with inherited metabolic diseases in Canada: Updated findings from a multi-centre survey

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Objectives:

To describe parents' perspectives on experiences with health care for Canadian children with inherited metabolic diseases (IMD).

Methods:

We conducted a cross-sectional mailed survey of parents/guardians of children (<12 years) with an IMD enrolled in the Canadian Inherited Metabolic Diseases Research Network (n>660). Participants reported: (i) satisfaction with care in five health system settings; (ii) experiences with family-centred care within the metabolic clinic, measured using the Measure of Processes of Care (MPOC-20); and (iii) care coordination, based on items from the Family Experiences with Coordination of Care.

Results:

Among 126 responses to date, most participants (86%) were mothers of children with IMDs and 54% identified metabolic clinic staff as their child's main care provider. While >70% of participants were satisfied with care from the metabolic clinic, emergency department, blood laboratory, inpatient services, and pharmacy, 6-19% reported a notable negative experience at these settings.

Median MPOC scores indicated child and family needs were met to a "fairly great" or "great" extent within the metabolic clinic, with the exception of the provision of general information and connection to community resources, where needs were met to a "moderate" extent.

A minority of participants received written visit summaries (28%). Of those whose children used multiple health services, 59% received help with care coordination.

Conclusion:

While most participants were satisfied with the care their children received, some reported gaps in care related to information provision and coordination across services. Further analyses will explore the relationship between experiences with care and child quality of life.

Keywords:

Family-centred care, rare disease, survey

Funding Acknowledgement (if applicable):

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Poster Abstract 19

Establishing core outcome sets for phenylketonuria (PKU) and medium-chain Acyl-CoA dehydrogenase (MCAD) deficiency in children: rapid review findings

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Objectives:

This study aims to establish core outcome sets (COS) for phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) deficiency that can be incorporated into future clinical trials. The objective of the first phase of the study, presented here, is to identify a comprehensive list of outcomes reported in past studies of PKU and MCAD deficiency.

Design and Methods:

A rapid review was performed following established methods for knowledge synthesis. A comprehensive peer-reviewed search strategy identified citations which were then screened for inclusion/exclusion by two independent reviewers using specific criteria. Relevant data elements were extracted from eligible studies, including details of reported outcomes and outcome measurement instruments.

Results:

Database searching identified 6073 records; 575 studies were deemed eligible following two-stage screening. Of these, 507 reported outcomes of PKU, 53 of MCAD deficiency, four of both PKU and MCAD deficiency, and 11 of newborn screening in general. The PKU outcomes reported in these studies included blood phenylalanine, bone mineral density, dietary intake, growth rate, quality of life, and intellectual ability. MCAD deficiency outcomes included metabolic decompensation, mortality, morbidity, blood glucose, hospitalization, and plasma free carnitine.

Conclusions:

Comprehensive lists of candidate outcomes for PKU and for MCAD deficiency have been developed from the rapid review. These outcomes will be presented to patients/carers, health professionals, and policy makers in a Delphi survey to establish COS for these two conditions. COS ultimately will serve to establish a Canadian registry and conduct registry-based clinical trials that will establish evidence for treatments of these rare diseases.

Keywords:

Core-outcome-sets; Delphi; Inherited-metabolic-diseases; MCAD-deficiency; PKU

Funding Acknowledgement (if applicable):

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Poster Abstract 20

Characterization of ocular changes in Gaucher disease: Case Report

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Objectives:

Gaucher disease (GD) progression is well documented despite treatment with enzyme replacement therapy (ERT) or substrate reduction therapy (SRT). These are attributed to antibody formation, lack of penetration of enzyme or natural history of disease. We now report progressive ocular involvement in one of two siblings with type 3 GD treated with ERT and SRT.

Design and Methods:

Siblings on both ERT and SRT with mild neurologic impairment were previously reported when protein-losing enteropathy 2° calcified mesenteric lymphadenopathy developed in the male. Total parenteral nutrition including lipid (20% soybean oil emulsion) was initiated.

Visual examination showed normal fundi. Brain MRI was normal. Bilateral vitreous and pre-retinal deposits were identified on presentation 2 years later with a history of "floaters and orbs". Ocular findings progressed requiring bilateral vitrectomies. Vitreous fluid was analysed for Glucosylceramide (GluCer) and Galactosylceramide (GalCer) isoforms by ultra-performance liquid chromatography – tandem mass spectrometry. Cholesterol and triglyceride content were also studied.

Results:

A marked increase of 12 GluCer isoforms including two methylated isoforms was identified in this GD patient compared to a control. GalCer, cholesterol, and triglycerides were not detected. Residual deposits continue to clear, now ~1 year postoperatively.

Conclusions:

This is the first documentation that the white vitreous and preretinal deposits seen in our patient with GD type 3 and reported in other GD patients reflect the accumulation of GluCer substrate seen in this storage disease. The origin of the GluCer is uncertain as is the reason for the discordance in expression from his affected sister.

Keywords:

Gaucher, mass spectrometry, ocular involvement

Poster Abstract 21

Combined therapy trial of L-carnitine supplementation and L-valine restriction in a patient with 3-Hydroxyisobutyric aciduria due to a novel homozygous missense variant in the HIBADH gene

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Objectives:

Determine efficacy of the combination therapy of L-carnitine supplementation and L-valine restriction in a patient with failure to thrive, hypotonia and 3-Hydroxyisobutyric aciduria (3OHIB). 3OHIB was initially described as a disorder of valine metabolism but is now thought to represent a heterogeneous group of disorders with different underlying mechanisms including respiratory chain defects, and with a wide phenotypic spectrum.

Methods:

We report on 15-month-old female born to consanguineous parents, diagnosed with 3OHIB biochemically at 3 months and found to have, by whole exome sequencing, a novel homozygous missense variant in the HIBADH gene encoding 3-Hydroxyisobutyrate Dehydrogenase; c.302C>G (p.Thr101Arg); predicted to be deleterious. This novel variant occurs in a highly-conserved threonine residue in close proximity to the NAD binding site of the enzyme and therefore is expected to disrupt the enzymatic function.

Results:

The patient was initially started on L-carnitine at 4 months followed by a combined therapy trial of L-carnitine and L-valine restriction at 8 months. Pretreatment plasma L-3OHIB levels were 638 uM (normal reference range: 4.1-11.7 uM), and after L-carnitine supplementation, the levels dropped to 389 uM at 8 months before L-valine restriction. At 11 months on the combined therapy of L-carnitine and L-valine restricted diet, 3OHIB was 84 uM. Clinically the patient gained weight and has improved tone centrally and peripherally.

Conclusion:

This is the second case report to our knowledge to show improvement in metabolic and clinical parameters in a patient with 3OHIB due to a novel variant in the HIBADH gene.

Keywords:

3-Hydroxyisobutyric aciduria, HIBADH, Valine, Carnitin

Poster Abstract 22

The unexpected diagnosis: Case report of an atypical presentation of pyruvate dehydrogenase deficiency in an adult male

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Objective:

We report on an atypical presentation of pyruvate dehydrogenase (PDH) deficiency in adulthood without elevated lactate on magnetic resonance spectroscopy (MRS), plasma or urine to illustrate the variable presentation of this disease.

Design and Methods:

The 34-year-old male presented with progressive cognitive and motor deterioration over one year with history of an acute episode of confusion that self-resolved at 27 years of age. Apart from a history of migraines, the patient had been a healthy adult who was a professional baker.

On presentation, he had increased lower limb spasticity without dystonic posturing and cognitive slowing with difficulty retrieving words and problem solving which led to loss of employment and independence. Serial MRIs showed volume loss and scattered calcification in cerebral hemispheres with calcification of the pons. Otherwise investigations for toxic, infective, immune mediated and vascular causes of neurodegeneration were negative. Panel testing for genetic and metabolic causes of neurodegeneration was done.

Results:

A likely pathogenic mutation, c.406G>A, was identified in the PDHA1 gene. A fibroblast sample was analyzed for PDH enzyme activity and was found to be deficient, showing less than 10% activity. The c.406G>A mutation was previously reported in a child with developmental delay, mild dysmorphisms and mildly elevated serum lactate (N Engl J Med 2012; 367:1921-1929); to our knowledge, enzyme activity analysis was not performed.

Conclusion:

We discuss the presentation, diagnostic investigations and course of disease for this patient to highlight the expanding phenotype of PDH deficiency and demonstrate the usefulness of panel genetic testing.

Keywords

Atypical pyruvate dehydrogenase deficiency, PDHA1

Poster Abstract 23

Medial rectus muscle and orbitofrontal region SUV measurements: a novel approach to detecting hypometabolism in mitochondrial disease (MD)

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Introduction:

L-arginine has reported to increase cerebral perfusion and has been used in patients with MD. Papers reporting reduction in stroke-like episodes do not present quantitative data or sufficient controls. We found that MD patients show areas of cerebral hypoperfusion using positron emission tomography-computed tomography (PET-CT), which may represent areas of impaired energy production to monitor therapeutic effects of L-arginine.

Methods:

This retrospective case series included eight patients with MD, five (2 MELAS, 2 mitochondrial DNA deletion, and one Leigh syndrome) fit our inclusion criteria: minimum two brain PET-CT using 18F-fluorodeoxyglucose (FDG), record of blood arginine levels and clinical outcomes before and after L-arginine free base (~500 mg/kg/day/6 month period). PET-CT images were compared to 62 controls (32 from Calgary with no known orbitofrontal pathology via brain MRI and 30 from Hermes FDG reference database for PET-CT).

Results:

In the medial ocular muscles, all MD patients had lower SUV compared to controls (mean=0.37 ± 0.21 vs. 0.54 ± 0.23; $p<0.0001$) but not in the orbitofrontal region (0.85 ± 0.32 vs. 0.84 ± 0.27; NS). Changes in the cerebrum were standardized to changes in the medial ocular muscles.

Cerebral hypoperfusion improved in two patients after arginine levels increased and improved in two patients despite a decrease. One saw no improvement after a near doubling of arginine. No patient reported clinical improvement.

Conclusion:

Despite studies showing changes in cerebral perfusion with L-arginine, we found at the current dose (~$300/month), there was no demonstrable relationship between L-arginine supplementation, brain perfusion, or clinical improvement.

Keywords:

arginine, PET-CT, mitochondrial, disease, hypometabolism

Poster Abstract 24

Investigating in vivo bone architecture in hypophosphatasia using high-resolution peripheral computed tomography

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Objective:

Hypophosphatasia (HPP; OMIM# 171760) is a rare autosomal recessive inborn error of metabolism characterized by low serum tissue non-specific isoenzyme of alkaline phosphate (TNSALP) activity. TNSALP plays an important role in the mineralization of bone. Without appropriate TNSALP levels, HPP patients present with progressive worsening of bone health making them more vulnerable to fractures. Architecture, in addition to bone mineral content, plays an important role in determining overall bone strength.

The objective was to pilot the use high-resolution peripheral quantitative computed tomography (HR-pQCT) in the study of bone density and architecture in subjects with HPP disease in assessing their bone quality.

Design and Methods:

A retrospective cohort study was conducted. Five subjects diagnosed with HPP were observed during the normal course of their disease management. The subjects varied in age of onset of disease, treatment status with asfotase alfa, use of anti-resorptive therapy, mobility and weight-bearing status.

Results:

Our observations were that HR-pQCT can measure trends in mineral density and architecture over a long period of observation and may be an early indicator of the response to interventional therapies. Decreased loading forces led to continued declines in bone density and architecture in peripheral limbs of the subjects, and this pattern was not reversed with the application of enzyme replacement therapy, vitamin D, and in some cases, oral bisphosphonates. Applying increased loading forces by weight-bearing and maintaining mobility may reverse these trends.

Conclusion:

We conclude that HR-pQCT can serve as a valuable tool to monitor bone health in HPP patients.

Keywords:

Hypophosphatasia, computed tomography, bone health

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Poster Abstract 25

Importance of diet in treatment of mitochondrial respiratory chain disorders (RCDs)

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Objective:

We present an infant with Leigh syndrome due to m.13513G>A mutation in the ND5 gene who dramatically improved in growth in response to dietary intervention.

Design and Methods:

The 8 month old female infant with pre-existing growth failure and developmental delay presented with acute emesis, dehydration, central hypotonia, and lethargy. Change in glucose infusion rate from 3.1 to 6.2mg/kg/min resulted in rapid deterioration in neurological status and an increase in lactate from 3.4 to 15mmol/L with apnea, bradycardia and hypotension requiring ventilatory and inotropic support.

Following metabolic consultation, alteration of parenteral nutrition to 70% of calories from fat resulted in rapid improvement. Patient was maintained on a high lipid diet of breast milk and solids, supplemented with Lipistart (gradually decreased to provide 40% of daily calories from fat) and Beneprotein (to provide 2 to 2.5g/kg/day of protein) with improved growth and progression of developmental milestones. Patient moved out of province at 20 months of age.

Results:

Her weight at birth, at 2, 8 and 20 months of age plotted at 18, 1.8, 0.9 and 21.8% centiles. The length and head circumference improved from 0.4% to 40.1%, and 2.8% to 15.3% at 8 and 20 months respectively.

Conclusion:

As demonstrated by our case, diet is integral to clinical progression in RCDs but is poorly referenced in medical literature when discussing phenotype and treatment. This case also highlights the importance of input from an appropriately trained dietitian in management of children with RCDs

Keywords:

Leigh syndrome, lactic acidosis, diet

Poster Abstract 26

Evolution of GFM1 gene phenotype with age

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Objective:

We describe a male, 28 years of age with biallelic GFM1 mutations to understand the evolution of phenotype with age. GFM1 encodes for mitochondrial elongation factor G 1, part of the mitochondrial translation system, and is associated with progressive hepatoencephalomyopathy. Fewer than 15 patients with GFM1 mutations have been described with the oldest aged 5 ½ years.

Method:

Our patient had acidosis, poor feeding and hypotonia in first week of life followed by delayed development. A clinical diagnosis of mitochondrial respiratory chain disorder was made at 2 years of age following onset of seizures, severe regression and lactic acidosis, and confirmed by reduced cytochrome oxidase activity in muscle. Patient regained milestones to baseline following Initiation of gastrostomy tube feeds, anticonvulsant and antioxidant therapy.

Despite moderately severe cognitive disability and mild spasticity of limbs, patient remains independent for all self-care with no further regression. There was normalization of lactic acidosis and stability of basal ganglia changes on cranial MRIs with clinical stability. Following negative testing for mitochondrial DNA abnormalities, repeat needle muscle biopsy at 20 years showed COX negative fibres and ultrastructural abnormalities consistent with original clinical diagnosis. Recent panel testing for nuclear genes showed one known (c.910A>G) and one likely (c.1297_1300delGACA) pathogenic variants in the GFM1 gene consistent with the phenotype.

Conclusion:

The stability of clinical status and cranial MRI imaging accompanied by normalization of plasma lactic acidosis in our patient demonstrate the possibility of disease stabilization for those that survive early childhood in milder variants of GFM1.

Keywords:

GFM1, hepatoencephalomyopathy, mitochondrial

Poster Abstract 27

Impaired mitochondrial fatty acid oxidation due to synergistic heterozygosity for ACADM/ETFA alleles in a child with Rett syndrome

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Background:

Patients with more than one genetic diagnosis contributing to their overall phenotype are increasingly being identified. We report an 11 year old with Rett syndrome with an additional biochemical impairment of mitochondrial fatty acid oxidation.

Case Report:

A female term infant was diagnosed with Rett syndrome at 3 years of age. Her newborn metabolic screen (NMS) results were normal; however, she was born before expanded tandem mass-spectrometry-based NMS. At 10 years of age, as a part of a neurological investigation of dystonia in the left leg, a dried blood spot (DBS) acylcarnitine profile showed abnormalities suggestive of medium-chain acyl-CoA dehydrogenase deficiency (MCADD).

Follow-up urine acylglycine profile revealed elevated hexanoyl- and suberylglycine, with slight elevations of octanoyl- and heptanoylglycines, the values of which were lower than typically seen in classic cases of MCADD, but higher than expected for heterozygotes. Repeat analyses of DBS, plasma acylcarnitine, and urine acylglycine profiles showed a "hybrid" MCADD/Glutaric Aciduria II pattern. Urine organic acid profiles showed marginally elevated excretion of glutaric acid, 3-methylglutaric acid, and relatively minor amounts of hexanoylglycine and suberylglycine. Molecular analysis revealed heterozygosity for the common ACADM variant (c.985>A) and an in-frame deletion in ETFA gene (c.809_811delTAG, p.Val270del).

Clinically, there is no history of hypoglycemia, decompensation or weakness. The patient has tolerated illnesses and prolonged fasting without any concerns.

Conclusions:

The biochemical and molecular findings in this patient are compatible with a double heterozygous ACADM/ETFA genotype, leading to a phenomenon referred to as "synergestic heterozygosity" which explains the biochemical phenotype.

Keywords:

Fatty acid oxidation, Synergestic heterozygosity

Poster Abstract 28

Utility of whey protein powder to establish dietary protein tolerance in young children with phenylketonuria

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Objectives:

In patients with phenylketonuria (PKU), establishing the maximum amount of natural protein/phenylalanine (Phe) that can be consumed while maintaining good metabolic control can be challenging. Young children may not accept changes in taste or texture if cow's milk and other higher protein foods are introduced, and parents may be reluctant to introduce new foods that may later be withdrawn. We aimed to determine the utility of tasteless whey protein powder for establishing dietary protein tolerance.

Design and Methods:

Six children (aged 1 to 4 years) with well-controlled PKU on diet treatment were challenged with progressive addition of whey protein powder to their diets, both on and off sapropterin dihydrochloride, while monitoring phenylalanine levels once or twice per week.

Results:

All children were found to tolerate more natural protein compared to their baseline diets. Sapropterin further increased protein/Phe tolerance, leading to relaxation of dietary restrictions; one child has transitioned to a full, unrestricted diet with no metabolic formula. No adverse effects of whey powder were noted and parents were satisfied with the approach.

Conclusions:

Whey protein powder is a useful tool for establishing the upper limit of dietary tolerance for natural protein/Phe in children with PKU, without altering the taste or composition of their medical diets. This strategy can be used prior to, during and after sapropterin responsiveness testing, and can be used to inform liberalization of the diet in a safe and systematic way.

Keywords:

phenylketonuria, PKU, diet, protein, sapropterin

Poster Abstract 29

Suboptimal metabolic control following liver transplantation in a young adult with maple syrup urine disease

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Case Report:

A 22 year old male with maple syrup urine disease (MSUD) had good metabolic control on dietary treatment. From adolescence, progressively worsening mental health and behavioral disturbances presented increasing challenges for nutrition management of MSUD. Although he was not considered at high risk for acute decompensation, his parents advocated strongly for liver transplantation to ease the caregiver burden.

Plasma branched chain amino acid levels in the postoperative period were within control range, but five months following liver transplantation, on an unrestricted diet, leucine had increased to 400-600 mcmol/L, higher than expected compared to a cohort of transplanted MSUD patients. Plasma concentration ratios of leucine/isoleucine and leucine/valine were similar to the transplanted cohort, suggesting normalization of branched chain ketoacid dehydrogenase enzyme regulation.

Possible explanations for this suboptimal response to transplantation were explored. Portosystemic shunt and insulin resistance were excluded. Medication effects and coincidental heterozygosity of the donor liver for a pathogenic mutation in BCKDHA, BCKDHB or DBT were considered unlikely and logistically challenging to exclude. Modest dietary protein restriction and metabolic formula were reintroduced.

This case illustrates an atypical metabolic response to liver transplantation in MSUD, and an approach to evaluating increased branched chain amino acid levels in patients following transplant.

Keywords:

MSUD, liver transplantation, leucine

Poster Abstract 30

Case report: Improved creatine kinase with decreased simple and supplemental carbohydrate intake in two siblings with Glycogen Storage Disease type IIIa.

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Objective:

We describe two siblings with Glycogen Storage Disease IIIa (GSD IIIa) with a significant improvement of creatine kinase (CK) following a decrease in simple and supplemental carbohydrate intake.

Design and Methods:

Two male siblings (age 13 and 8 years) were diagnosed with GSD IIIa. The older sibling was diagnosed at 4 years and the younger sibling after birth. Both siblings developed increased CK levels greater than 2500mmol/L. The younger sibling also developed hypertrophic cardiomyopathy at 5 years and was started on cardiac medications.

Over 29 months, treatment included decreasing simple and supplemental carbohydrate while maintaining euglycemia; a high protein diet was continued. Significant reduction in simple carbohydrate intake was confirmed by food record analysis. The older sibling completely eliminated supplemental cornstarch. The younger sibling eliminated daytime cornstarch however required 0.6g/kg of Glycosade to maintain euglycemia overnight.

Results:

In both siblings, CK levels decreased significantly. The older sibling's CK decreased from 2955mmol/L to 334mmol/L. The younger sibling's CK decreased from 3507 mmol/L to 427mmol/L. The younger sibling's recent echocardiogram showed stabilization of his hypertrophic obstructive cardiomyopathy.

Conclusion:

We present two siblings with GSD IIIa who benefited from a decrease in simple and supplemental carbohydrate intake. This was demonstrated by a decrease in CK levels and no adverse effects were observed. Of note, their previous high protein diet did not result in a decrease in CK. Further follow-up will determine if this intervention also had a positive effect on the younger sibling's cardiomyopathy and their risk for myopathy.

Keywords:

GSD, CK, carbohydrate, myopathy, cardiomyopathy

Poster Abstract 31

HSD10 disease and p.Leu122Val variant: mild clinical phenotype and probable founder effect in French-Canadian patients from Quebec

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Background:

HSD10 disease, originally described as 2-methyl-3-hydroxybutyryl-CoA dehydrogenase (MHBD) deficiency, is a rare X-linked disorder of a moonlighting protein encoded by the HSD17B10 gene. Biochemical diagnosis is based on elevated isoleucine degradation metabolites, although pathogenesis is now known to reflect other functions of the HSD10 protein. The typical phenotype in males is an infantile-onset progressive neurodegenerative disorder associated with severe mitochondrial dysfunction (J Inherit Metab Dis 2012;35:81-89).

Index patients:

We identified three index patients (two males, one female) with HSD10 disease. Each was independently investigated in infancy or childhood because of neurological concerns (spasticity, choreoathetosis) and/or developmental concerns. All had persistent, moderate elevations of urinary 2-methyl-3-hydroxybutyric acid and tiglylglycine. Analysis of HSD17B10 identified a single missense variant, c.364C>G, p.Leu122Val, in each case. This variant, considered pathogenic based on functional studies, was previously reported in one Dutch patient and is rare according to the ExAC database (1/88 000 alleles).

Family studies:

Cascade testing of family members identified adult relatives with similar biochemical profiles and the same genetic variant, including an apparently asymptomatic hemizygous male. All three families originate from the same region of Québec (Montmagny/Beauce). Genealogical studies and haplotype studies (SNP array) are underway.

Conclusions and future directions:

We report patients from three families with HSD10 disease, caused by p.Leu122Val in HSD17B10, probably reflecting a founder effect. Evaluation thus far suggests that the associated clinical phenotype is attenuated and not rapidly progressive, but long-term surveillance will be essential. Vigilance and proactive steps to identify additional affected individuals will also be necessary.

Keywords:

HSD10 disease; MHBD deficiency; HSD17B10.

Poster Abstract 32

Analysis of glutaric acid, 3-hydroxyglutaric acid and glutarylcarnitine in dried urine spots by liquid chromatography tandem mass spectrometry as possible biomarkers of catabolism in glutaric aciduria type 1

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Background:

Glutaric Aciduria type 1 (GA1) is caused by a deficiency of glutaryl-coenzyme A (CoA) dehydrogenase in the metabolic pathway of lysine, hydroxylysine and tryptophan, resulting in accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3OHGA), and glutarylcarnitine (C5DC).

Currently, analysis of GA and 3OHGA concentrations are not recommended for use in treatment monitoring because it is believed that they do not correlate with clinical parameters. However, variation of these compounds over time as possible biomarkers of disease status has not been systematically studied.

Methods:

Our patient is a 3-year-old girl who was identified by a positive newborn screen for GA1. She has compound heterozygous mutations in GCDH (c.877G>A [p.A293T]; c.701G>A [p.R234Q]), and her glutaryl-CoA dehydrogenase activity in fibroblasts was in the affected range.

We have followed her from birth with periodic monitoring of GA and 3OHGA levels using the method reported by Al-Dirbashi et al (2011). C5DC levels were measured in the same dried urine spot using a different method. Her biochemical parameters were correlated with her clinical status.

Results:

Urinary 3OHGA levels were elevated at the time of diagnosis and during illness but were occasionally normal when the patient was clinically well (maximum = 22.5 micromol/L, minimum = 4.2 micromol/L, reference range 0-7.1 micromol/L). Urinary GA levels were in the normal range. C5DC/C5 and C5DC/C5OH ratios were only above the cutoff at diagnosis.

Conclusions:

Urinary 3OHGA appears to be a possible biomarker of catabolism. More studies will be needed to determine whether it is a predictor of clinical outcome.

Keywords:
Glutaric aciduria

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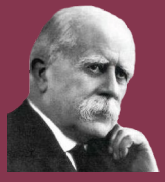

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