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Platform Presentation

Late-onset ornithine transcarbamylase deficiency: biochemical, clinical, and functional consequences of a novel regulatory region variant

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Objective:

Ornithine transcarbamylase (OTC) deficiency (OMIM #311250) can present during the neonatal period, infancy, or adulthood. A late onset phenotype is influenced by the enzymatic activity of OTC and *OTC* expression levels. The objective of this study is to review the pathogenicity of a novel promoter region variant, c.-106C>A.

Design and Methods:

This study was conducted among 3 independent pedigrees who have the c.-106C>A variant. Retrospective chart reviews were performed on 37 individuals, and biochemical and clinical data were abstracted. Functional OTC enzyme data was obtained from the liver biopsy of two probands.

Results:

The mean age of diagnosis for all symptomatic males was 20.8 years. All heterozygous females are asymptomatic. Out of 14 affected males, 7 of them experienced at least one episode of hyperammonemia. The proband for family A presented at age 55, with a maximum ammonia level of 694 micromol/L. The proband for family B presented at age 15 with a maximum ammonia level of 1568 micromol/L and subsequently died from cerebral encephalopathy. Their liver biopsy OTC enzyme activity level was 2.2 micromol·g liver^{-1}·min^{-1} (control was 73.2). The proband for family C presented at age 24 with hyperammonemia and died of cerebral encephalopathy. Their liver biopsy OTC enzyme activity level was 0 micromol/hr/gram tissue (control was 1500-9000). Ammonia scavenger therapy has been effective to date for most of the males included in the study.

Conclusion:

The functional data indicates that the c.-106C>A OTC promoter region variant is pathogenic, when paired with the biochemical and clinical data.

Long term follow-up and treatment outcome of primary biopterin deficiencies. Vancouver experience

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Objectives:

To evaluate long-term follow up, treatment and outcomes in eight patients with BH_4 (tetrahydrobiopterin) defects. To introduce The International Working Group on Neurotransmitter related Disorders (iNTD), the first international network focusing on the study of primary and secondary neurotransmitter disorders to Canadian metabolic centres.

Methods:

Retrospective chart review on patients with BH_4 deficiencies followed for the last 20 years in the pediatric and adult metabolic clinics. Age of presentation and diagnosis, presenting symptoms, biochemical abnormalities, molecular results, treatment, clinical, cognitive and behavioural symptoms were recorded.

Results:

Three patients with autosomal recessive (AR), two patients with autosomal dominant (AD) guanosine triphosphate cyclohydrolase (GTPCH) deficiency, and three patients with 6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency were reviewed. Current ages are between 9 and 38 years. Age at presentation varied between newborn and 6 years. Diagnosis was made between newborn to 8 years. Treatment for the AR forms included L-dopa/Carbidopa (10:4), 5-hydorxytryptophan and Tetrahydrobiopterin (Kuvan). The AD form was treated with L-dopa/carbidopa. Monitoring of treatment was done with serum prolactin level. Motor symptoms and development improved in all on treatment. Most patients had intellectual disability, ranging from mild to moderate, or learning disabilities, except for one patient with AD GTPCH deficiency. Behavioural and psychiatric symptoms were common.

Conclusion:

This study demonstrates largely favourable long-term outcome of patients with BH_4 deficiencies in our centre. Their data has been introduced to the iNTD registry, which was founded with the aim to foster exchange and improve knowledge in the field of these rare diseases.

Efficacy and safety of the recommended pegvaliase dosing regimen in adults with phenylketonuria in the phase 3 PRISM studies

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Objectives:

Pegvaliase is a blood phenylalanine (Phe)-lowering enzyme substitution therapy approved for adults with phenylketonuria and uncontrolled Phe (>600micromol/L) on existing management. Here we present the efficacy population in the updated US label.

Design and Methods:

In PRISM-1, pegvaliase-naïve patients with blood Phe >600micromol/L were randomized 1:1 to 20 or 40mg/day pegvaliase maintenance dose. Participants continued pegvaliase in PRISM-2 part 4 at 5-60mg/day at investigator discretion. This subgroup analysis includes patients randomized to and treated with ≥1 dose of pegvaliase 20mg/day (n=118).

Results:

Most patients achieved Phe ≤600micromol/L (91 patients, 77%) and ≤360micromol/L (86, 73%) by 36 months at <20-60mg/day. Most patients achieved Phe ≤600micromol/L by 24 weeks at 20mg/day (36/44 patients, 82%), 16 weeks at 40mg/day (18/26, 69%), and 16 weeks at 60mg/day (8/12, 67%). Phe ≤600, ≤360, and ≤120micromol/L was achieved by 48%, 42%, and 32% of patients, respectively, at 12 months (n=97), 76%, 66%, and 50% at 24 months (n=86), and 75%, 66%, and 48% at 36 months (n=77). Among 285 patients exposed to a pegvaliase induction/titration/maintenance regimen, common AEs included arthralgia (77%), injection site reaction (66%), injection site erythema (51%), and headache (55%); 44 patients discontinued treatment due to an AE. Non-IgE-mediated anaphylactic AEs occurred in 29 patients; 6/21 patients rechallenged had a recurrence of anaphylaxis. Types and rates of adverse reactions during maintenance were similar with 20, 40, and 60mg/day.

Conclusions:

Pegvaliase demonstrated sustained and substantial Phe reduction related to treatment duration and dose. Long-term pegvaliase treatment had a manageable safety profile for most patients.

Elucidating the role of sphingolipids in the pathogenesis of hepatocellular adenoma linked to GSD Ia

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The etiology of hepatocellular adenoma (HCA), a common inflammatory complication in glycogen storage diseases (GSD), still remains elusive. However recent studies have linked the occurrence of HCA with ectopic toxic lipid accumulation. Sphingolipids are signaling molecules that regulate diverse cellular processes including senescence and apoptosis, which are underlying mechanisms in the pathogenesis of HCA.

We studied the profile of sphingolipids in GSD Ia mice model and quantified 21 analytes from five families of sphingolipid species to investigate their role in the development of chronic liver inflammation. A targeted sphingolipidomic method was established based on Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) to evaluate Ceramide (Cer), Glucosylceramide (GlcCer), Lactosylceramide (LacCer), Sphingomyelin (SM), and Ceramide-1-phosphates (C1P) in biological samples (plasma and liver).

We successfully applied this method to determine the composition of endogenous sphingolipids in the plasma and liver of GSD Ia mice. The plasma concentrations of Cer (25 to 106-fold), GlcCer (18 to 36-fold), LacCer (7 to 40-fold), and SM (1.7 to 8.6-fold) were significantly elevated in GSD Ia mice compared to the controls. These results may imply that the disturbed homeostasis of sphingolipids is associated with the pathogenesis of HCA in GSD, and has a great potential as a new biomarker and therapeutic target. To certify the clinical relevance of our method, we will extend the analysis to the GSD I patients and assess the changes of endogenous levels of sphingolipid metabolites after the treatment.

Effect of Creatine Supplementation on AGAT Expression and Metabolic Intermediates in GAMT-Deficient mice

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Investigation of creatine (CT) supplementation on the expression of AGAT and on CT metabolites in a GAMT-deficient mouse model. 12-weeks old mice were fed with CT-free or CT enriched (2% or 4%) mouse chow for 10 weeks. Urine was collected weekly, brain, kidney, liver, heart, and skeletal muscle were harvested after 10 weeks.

In urine, CT increased in all mice treated with 2% and 4% CT. Guanidinoacetate (GAA) decreased by ~80% and ~90% in wildtype and mutants, respectively.

Creatine: In kidney and liver, CT increased in wildtype and mutants. There was no CT change in brain and muscle in wildtype; but increase of CT in mutants. In mutant brain and muscle, CT increased from 1,000 to 7,500 (2% and 4%) and from 300 to 21,000 (2% and 4%), respectively. There was a slight decrease in CT in wildtype heart, while CT increased in mutant heart.

GAA: In all organs of wildtype mice but muscle, GAA decreased by ~50%. In mutants, GAA decreased by 60% (kidney), 99% (heart), 90% (brain), and 99% (muscle), but appeared to rise in liver (needs to be confirmed).

Quantitative PCR and Western blot revealed marked decrease in AGAT mRNA and protein by ~50% (2% and 4%) in wildtype and mutants.

In summary, CT metabolites in urine and organ homogenates confirm the efficacy of CT supplementation in GAMT deficiency through marked increase of CT and persistent reduction in GAA (except liver). The effect on GAA is likely caused by the CT mediated suppression of AGAT.

Triheptanoin for the Treatment of Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD): Final Results of an Open-Label, Long-Term Extension Study

Jerry Vockley, Barbara Burton, Gerard Berry, Nicola Longo, John Phillips, Amarilis Sanchez-Valle, Kimberly A. Chapman, Pranoot Tanpaiboon, Stephanie Grunewald, Elaine Murphy, Xiaoxiao Lu, Syeda Rahman, Kathryn Ray, Antonio Nino Ramirez.

Objectives:

In study UX007-CL202 (NCT02214160), triheptanoin provided sustained reduction in the rate and duration of major clinical events (MCE) in patients with LC-FAOD who were previously treated with triheptanoin or were triheptanoin-naïve.

Methods:

As of February 18, 2020, 94 patients enrolled: 24 rolled over from study UX007-CL201, 33 were triheptanoin-naïve, and 37 were from investigator studies or early access program (IST/EAP).

Results:

Among triheptanoin-naïve patients, there was an 86.5% reduction in the median MCE rate from 2.00 events/patient/year in the pre-triheptanoin period (median follow-up, 18.0 months) to 0.28 events/patient/year (n=33; P=0.0343) in the triheptanoin period (median follow-up, 21.9 months). The extension study showed sustained efficacy, with a 46% reduction from 1.69 events/patient/year in the pre-triheptanoin period (mean follow-up, 17.3 months) to 0.91 events/patient/year (integrated analysis, n=29; P=0.0245) in the triheptanoin period (mean follow-up, 55.0 months). Pretreatment data were unavailable for IST/EAP patients. Safety was assessed for 99 patients, including five from UX007-CL201 who did not roll over. Frequent treatment-related related adverse events (AEs) included diarrhea, abdominal pain/discomfort, and vomiting; most were mild/moderate in severity.

Seventy (71%) patients had serious AEs; five had seven treatment-related serious AEs per the investigators (rhabdomyolysis [n=2], diverticulitis, ileus, acute pancreatitis, chronic gastritis, and gastroesophageal reflux disease), all of which resolved. Five patients had fatal AEs due to underlying disease or intercurrent infection that were not treatment-related.

Conclusions:

Treatment with triheptanoin resulted in sustained reduction in the rate and duration of MCEs in patients with LC-FAOD. Long-term safety was consistent with the established safety profile of triheptanoin.

Youth and family engagement in clinical trials about phenylketonuria, spinal muscular atrophy, and mucopolysaccharidoses

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Objectives:
Youth and family partners are increasingly collaborating with research teams to improve the relevance of research to patient values and clinical care. The INFORM RARE network is developing three clinical trials about pediatric phenylketonuria (PKU), spinal muscular atrophy (SMA), and mucopolysaccharidoses (MPS). Our aim was to create two separate advisory groups of youth and families with lived experience in these conditions to add their perspectives to the patient and family member partners already involved as co-investigators in co-conducting our research.

Design and methods:
In March 2021, youth (aged 12-18 years) and family members (parents, caregivers) with experience of PKU, SMA or MPS were invited through patient organizations and social media to apply to join the advisory groups. We selected advisors based on age, clinical condition, and geographical location to ensure a breadth of perspectives were represented.

Results:
Eleven youth and 9 family members were recruited and have provided their perspectives, guidance, and feedback at key points during the research process via virtual meetings and email communications. We have provided compensation to advisors in recognition of their contributions. Advisory group members have shown enthusiasm and commitment to their roles and provided insightful feedback, such as suggestions about the content and layout of an online survey, meaningful trial outcomes, and features of a video game intervention.

Conclusions:
We established youth and family advisory groups for clinical trials about PKU, SMA and MPS, which are providing vital information about the relevance and feasibility of our research.

First report of type 2 diabetes mellitus in an adult with HMG-CoA lyase deficiency: A case report

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Background
3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) lyase deficiency is an autosomal recessive disorder, resulting in a lack of ketogenesis and leucine catabolism. Hallmarks of decompensation include hypoglycemia without ketosis (or hypoketosis), metabolic acidosis, and hyperammonemia. Management includes avoiding fasting and restricting dietary protein and fat, often translating to a high carbohydrate diet. Conversely, type II diabetes mellitus (T2DM) requires carbohydrate restriction and/or anti-hyperglycemic agents; thus, managing these co-existing disorders is challenging.

Case Presentation
A 36-year-old male with HMG-CoA lyase deficiency, metabolic syndrome, and a recent diagnosis of T2DM (HbA1c 7.9%) presented with confusion. His BMI was 34.3 and acanthosis nigricans was present on exam. Family history was negative for T2DM. Blood work revealed pH 6.97, glucose 32 mmol/L, ammonia 235 umol/L, bicarbonate 4 mmol/L, and beta-hydroxybutyrate 0.4 mmol/L. He was diagnosed with hyperosmolar non-ketotic hyperglycemia and hyperammonemia secondary to HMG-CoA lyase metabolic decompensation requiring ICU admission. Hyperammonemia management was challenging because alternative calories with IV dextrose (due to hyperosomolar non-ketotic hyperglycemia) and IV lipids (due to HMG-COA lyase deficiency) couldn't be provided. Thus, he was started on hemodialysis and IV insulin with marked improvement.

Conclusion

We hypothesize that HMG-CoA lyase deficient patients are at increased risk for T2DM due to avoidance of fasting and carbohydrate supplementation. His T2DM diagnosis may have been a key factor in his presentation, impairing cellular glucose uptake and producing a state similar to hypoglycemia, despite being profoundly hyperglycemic. Managing T2DM and HMG-CoA lyase deficiency warrants special considerations because of the potential for hypoglycemia leading to metabolic decompensation.

Biochemical and genetic profile of pediatric patients referred to the metabolic service for ketotic hypoglycemia at The Hospital for Sick Children - A retrospective chart review

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Objective:

1. To compare the carrier frequency in hypoglycemia genes in KH patients with a control group of patients that had testing with WES/WGS done for other indications but did not present with hypoglycemia. We hypothesized patients with KH have higher carrier rates compared to patients that did not experience hypoglycemia.

2. To describe biochemical parameters and genetic findings in KH patients over 10 years.

Design and methods:

A retrospective chart review of all patients evaluated in the Metabolic Genetics clinic at the Hospital for Sick Children for KH and had metabolic hypoglycemia panel, WES/WGS between 2010-2020.

Results:

29 charts were analyzed. The median age of presentation was 3 years. The most common presenting symptom was lethargy in the context of gastrointestinal symptoms.

The most common biochemical findings were high free fatty acid (93%), high anion gap metabolic acidosis (40%), elevated CK, ALT, AST (20%), and lactate (10%). Specialized metabolic tests yield nonspecific results.

Genetic testing confirmed metabolic conditions in 5 patients including glycogen storage disease type IX (3 siblings) and type 0 (1), fructose-1,6-bisphosphatase deficiency (1). Only 2 patients were heterozygous for a pathogenic variant in ACADM & HMGCL.

Conclusions:

1. Biochemical evaluation is important in KH. Specialized metabolic & genetic tests should be tailored based on critical sample results and in our cohort led to the diagnosis of 3 metabolic conditions.

2. As we did not find a high carrier number for pathogenic mutations in hypoglycemia genes, comparison to the control group was not conducted.

Long-term follow-up of primary neurotransmitter disorders - single centre experience (2004-2021)

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Objective:
Primary pediatric genetic neurotransmitter disorders mimic common neurological conditions; disorders of movement, tone, intellectual disability, epilepsy and cerebral palsy. The objective of this case series was to evaluate the clinical experience, natural history, diagnostic tests employed, progression as well as outcomes of five pediatric patients.

Design and Methods:
Five pediatric patients with primary neurotransmitter defects were identified in the genetics database (London, ON, CA) between 2004-2021. Data on investigations, diagnosis, management and long-term outcomes was extracted.

Results:
Three of five patients [6-pyruvoyl-tetrahydropterin synthase deficiency (2 patients), pyridoxine dependent epilepsy (1)] presented to the clinic in the neonatal period. Two children showed normal development trajectories, while one is developmentally delayed. Two of five patients were born outside Canada, [Succinic Semialdehyde Dehydrogenase (SSADH) deficiency (1) and Amino Acid Decarboxylase (AADC) deficiency (1)]. Both were diagnosed in later life, one diagnosed with cerebral palsy was subsequently diagnosed with SSADH deficiency at age 13. The other presented at age 7 with gross developmental and motor delays, AADC deficiency was confirmed via genetic testing, reduced AADC enzyme activity, and relatively normal CSF neurotransmitter assays.

Conclusions:
Early detection and diagnosis of neurotransmitter deficiencies can carry a significant impact on long term outcomes such as motor function and cognitive ability in selected situations. Molecular genetics, newborn screening for inborn errors of metabolism and biochemical investigations (blood, urine, CSF) are critical to establishing early diagnosis and providing potential treatment. Genetic counselling is an important aspect of management.

Gene variant and neuromuscular findings from a Long-Chain Fatty Acid Oxidation Disorder gene panel program

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Peter Baker II, Omid Khazaie Japalaghi, Nicola Longo, Deborah Marsden Heather McLaughlin, Kate Simmons, Jillian Yong, Nicole Miller

Background:
Long-chain fatty acid oxidation disorders (LC-FAOD) are rare, life-threatening, autosomal recessive conditions that can be diagnosed clinically with plasma acylcarnitine analysis and molecular testing. Undiagnosed LC-FAOD may present with hypoglycemia, cardiomyopathy, cardiac arrhythmias, and neuromuscular symptoms.

Methods:
Patients with a clinical diagnosis or suspicion of LC-FAOD are eligible for this no-charge NGS gene panel which includes 6 genes associated with LC-FAOD plus 18 genes associated with disorders that cause abnormal acylcarnitine profiles.

Results:
As of 28 October 2021, LC-FAOD gene variants were identified in 153 (37%) of 417 patients tested, including 83 variants of uncertain significance (VUS), 8 likely pathogenic (LP), and 102 pathogenic (P) variants. Twenty-three patients had positive (2 P/LP) LC-FAOD results and 19 had potential positive (2 variants, at least 1 VUS) results. VUS resolution analysis led to the reclassification of 6 variants from VUS to LP or P. Five patients had variants in two or more LC-FAOD genes and 22 had variants in one LC-FAOD gene and one or more non-LC-FAOD genes. Fifty-one patients had only one LC-FAOD gene variant identified.

The most common neuromuscular symptoms among patients ages ?13 (76 reported) were myopathy (42), elevated creatine kinase (36), and rhabdomyolysis (30), and among patients <13 years (83 reported) were elevated creatine kinase (22), and myopathy (12).

Conclusions:
Program results demonstrate the diverse composition of gene variants in patients referred for LC-FAOD genetic testing. Approaches to resolve VUS and identify previously undetected variants in patients with suspected LC-FAOD are important and necessary.

Mitochondrial long chain fatty acid oxidation and carnitine defects in a single Canadian metabolic genetics clinic

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Objectives:
Mitochondrial long-chain fatty acid oxidation (LCFAOD) and carnitine defects are inherited metabolic disorders. Their estimated incidence is 1/5,000–10,000 births. We performed a retrospective review study (REB-ID#Pro00108842) to report phenotypes, genotypes, and treatment outcomes of these disorders.

Design and Methods:
We included all patients with LCFAOD and carnitine defects and reviewed their charts.

Results:
Thirty-nine patients included: carnitine uptake deficiency (CUD) (n=15), carnitine palmitoyl transferase I (CPT1) (n=11) and II (CPTII) (n=2) deficiencies, carnitine-acylcarnitine translocase (CACT) (n=3)**,** very long-chain acyl-CoA dehydrogenase (VLCAD) (n=4), long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) (n=3), and multiple acyl-CoA dehydrogenase (MAD) (n=1) deficiencies. Mean age was 20.4□17.6 years (range 3 months- 55 years: 21 children (<18 years) and 18 adults. Seven patients had hypoglycemia: CPT1 (n=3), VLCAD (n=1), CACT (n=2) and MAD (n=1) deficiencies. Six patients had episodes of rhabdomyolysis: CPT1 (n=1), CPT2 (n=2), LCHAD (n=3) deficiencies. Five patients had history of myalgia: CPT1 (n=1), CPT2 (n=1), CUD (n=1) and VLCAD (n=2). Fatigue was reported in five patients with CUD. Retinopathy and peripheral neuropathy (n=1) were present in one patient with LCHAD deficiency. One patient with VLCAD deficiency had cardiomyopathy. One patient with CACT deficiency died due to arrythmia and cardiac arrest. All patients were diagnosed by biochemical and/or molecular genetic investigations of candidate genes. There were 9 patients on the long-chain fat restricted diet: CPTII (n=2), LCHAD (n=3), VLCAD (n=4) deficiencies.

Conclusion:
The prevalence of LCFAOD and carnitine defects was 4.75% and 23% of those patients had diet management for LCFAOD.

A new patient with phosphatidylinositol glycan anchor biosynthesis class O (PIGO) protein deficiency identified by exome sequencing

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Objectives:
To report a new patient with PIGO deficiency involved in the glycosylphosphatidylinositol (GPI) biosynthesis for the phenotype and genotype.

Design and Methods:
We reviewed patient chart and reported clinical, biochemical, and molecular genetic investigation results. We reviewed the literature for previously published cases.

Results:
This five-year-old female was born with the history of intra-uterine growth retardation after an induction of labor at 37 weeks' gestation via vaginal delivery. Her global developmental delay was recognized from the first year of life. She had generalized seizures characterized by being scared, opening her eyes, screaming, and drooling at the age of one year. She has history of strabismus. She has ingrown and curved toenails with color discoloration and absent finger- and toenails on her 5th fingers and toes bilaterally.
Her current developmental age is between 9-12 months. Her exome sequencing revealed biallelic variants [(c.3103C>G; p.Arg1035Gly (maternal)/c.1688_1691del; p.Asp536Valfs*4 (paternal)] in *PIGO.* She had characteristic dysmorphic features including hypertelorism, long palpebral fissures, short nose, broad nasal bridge, broad nasal tip, tented mouth, brachytelephalangy, broad halluces, and hypoplastic/absent nails. She had marginally elevated alkaline phosphatase (478 U/L; reference range 130-430). Brain magnetic resonance imaging was normal. There were less than 15 patients with PIGO deficiency reported in the literature.

Conclusion:
Exome sequencing allowed the diagnosis of PIGO deficiency in this patient. Despite early infantile onset symptoms, diagnosis was delayed for about 5 years. Exome sequencing will allow metabolic geneticist to diagnosis patients earlier in the absence of the specific biomarker.

Short-term clinical and biochemical outcome of a patient with pyridoxine-dependent epilepsy due to biallelic variants in ALDH7A1

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Objectives:
To report short-term treatment outcome of patient with pyridoxine-dependent epilepsy (PDE) due to biallelic variants in *ALDH7A1* (PDE-ALDH7A1)

Design and Methods:
We reviewed patient chart and reported clinical, biochemical, molecular genetics and treatment outcome of the patient with PDE-ALDH7A1.

Results:
This 18-month-old boy presented with febrile seizures after his sixth-month vaccination. His seizure was characterized by stiffening with a fixed left-sided gaze. He had two episodes of status epilepticus, apnea and hypoxia. Electroencephalography was normal. His development was reported to be normal until 6 months of age. Markedly elevated urine alpha-aminoadipic semialdehyde (AASA) (45.96 mmol/mol creatinine; reference range <1) and biallelic variants in *ALDH7A1* [(c.1279G>C; p.(Glu427Gln) (paternal)/c.212C>T; p.(Pro71Leu) (maternal)] confirmed the diagnosis of PDE-ALDH7A1 at age 7 months. Pyridoxine (200 mg/day), arginine (400mg/kg/day) and lysine-restricted diet (50-60mg/kg/day). Urine AASA was significantly improved (1.8mmol/mol creatinine; reference range <0.5). Interestingly plasma pipecolic acid was marginally elevated (4.57micromol/L; reference range<4.2) and repeat was normal. Brain magnetic resonance imaging was normal. On the current therapy, he has been seizure free. At age 18 months, he does not have unsupported walk or any words yet. His current developmental age is at 7-9 months.

Conclusion:
Despite early initiation of therapy and good treatment compliance as well as improvements in his biomarkers, his developmental milestones did not improve since treatment start. It seems that new treatments are needed to improve neurodevelopmental outcomes.

Corpus Callosum Dysgenesis as a Presenting Feature of NDUFAF8-related Leigh Syndrome

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Leigh Syndrome caused by NDUFAF8 loss of function mutations has been rarely described in the literature. We present three familial cases with homozygous alleles of variant c.161A>C, p. (Glu54Ala), that was originally classified as a variant of uncertain significance (VUS). Two of the children have displayed characteristic phenotypes of fatal Leigh disease, with rapid developmental regression followed by encephalopathy and eventual death. Mitochondrial testing in one individual confirmed a complex I deficiency. While largely clinically unaffected to this date, the third child demonstrated severe dysgenesis of the corpus callosum on fetal MRI. This case report will describe these three siblings' history while including selected imaging to highlight this intracranial anomaly. The study will suggest that the NDUFAF8 gene be considered by clinicians in the future when seeking a monogenic etiology for Leigh Disease. It will also provide additional evidence for the importance of early imaging prior to the onset of symptoms in individuals with family history. Finally, the information presented will add to existing body of literature on Leigh Syndrome to further highlight its genotypic variability.

Treatment outcome of neurotransmitter replacement therapy in secondary biogenic amine deficiencies

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Objectives:
To assess motor and non-motor response to neurotransmitter replacement therapy in secondary biogenic amine deficiencies. Hypotheses were generated to expand our views from uni-, and bi-dimensional pathways and signaling cascades to tri-dimensional models where proteins, enzymes, ion molecules and structural scaffolding all have their spatial and temporal relationship, to give us further insight into the mechanism of secondary neurotransmitter disorders.

Methods:
Twelve patients with secondary biogenic amine deficiencies were given a trial of treatment with Levodopa/Carbidopa and 5-Hydroxytryoptophan, including one rigorously designed and approved N=1 trial. Results of responses in motor and non-motor symptoms were followed over a period of minimum 12 months.

Results:
Response in motor symptoms, such as movement disorders and strength were favourable in all patients. The N=1 trial outcome was evaluated with standardized testing and video-recording. Non-motor symptoms that improved included: self-injury, seizures, anxiety, sleep and behaviour. A diagram representing the complex presynaptic synthesis, storage, transport and exocytosis was developed, with interactions between ion channels and cytoskeleton and neurotransmitter effect on postsynaptic receptors.

Conclusion:
This study demonstrates the potential of secondary neurotransmitter deficiencies to serve as novel therapeutic targets. As there was a largely favourable response to therapy in our case series, a careful trial of neurotransmitter replacement therapy may be considered in patients with cerebrospinal fluid (CSF) monoamines below reference range.

Vestronidase alfa for the treatment of mucopolysaccharidosis VII (MPSVII): updated results from a novel, longitudinal, multicenter Disease Monitoring Program (DMP)

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Objectives:
Vestronidase alfa (recombinant human beta-glucuronidase [GUS]) enzyme replacement therapy is approved in the United States, Europe, and parts of Latin America for the treatment of MPSVII, an ultra-rare, autosomal recessive, debilitating, progressive lysosomal storage disease caused by GUS enzyme deficiency.

Methods:
The DMP is an ongoing, multicenter observational study collecting standardized real-world data from patients with MPSVII (N?35 planned) treated with vestronidase alfa or any other management approach. Data will be collected for up to 10 years and include demographics, clinical history, clinical characteristics, cognition, mobility, skeletal disease, pulmonary function, patient/caregiver-reported health-related quality of life, and long-term vestronidase alfa safety and effectiveness. Data are monitored and recorded in compliance with Good Clinical Practice guidelines. Annual individual patient reports will be provided to patients and caregivers.

Results:
As of 31 May 2021, 20 patients are enrolled: 19 in the treated group and one untreated. Seven patients (35%) had a history of non?immune hydrops fetalis. Three patients who reached two years of treatment in the DMP had an 88% reduction from baseline in the original (parent) clinical study in dermatan sulfate uGAG excretion. Four serious adverse events (SAEs) in two patients were reported. One SAE, intermittent hypotension, was assessed as an infusion-associated reaction to vestronidase alfa; this SAE did not meet hypersensitivity criteria, and the patient continues vestronidase alfa. No deaths were reported.

Conclusions:
Reductions in uGAG demonstrate ongoing effectiveness of vestronidase alfa at DMP Year 2. No new safety concerns were identified, and all patients continue on study. Enrollment is ongoing.

Improvement in left ventricular ejection fraction in patients treated with triheptanoin for long-chain fatty acid oxidation disorders (LC-FAOD)

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Objectives:
In situations of energy crises or fasting, the inability to convert long-chain fats into energy can cause unpredictable, life-threatening, cardiomyopathic events in people with long-chain fatty acid oxidation disorders (LC-FAOD). Triheptanoin, a seven carbon, medium-chain triglyceride (MCT) approved in the United States, Canada and Brazil as a source of calories and fatty acids for the treatment of LC-FAOD, demonstrated increases in left ventricular ejection fraction (LVEF) in a double-blind, randomized clinical trial (RCT). Here, the effect of triheptanoin treatment is assessed in patients who present with low LVEF in four completed studies.

Methods:
Data from the double-blind RCT (NCT01379625), two open-label trials (NCT01886378 and NCT02214160), and a retrospective study in critically ill patients (NCT03768817) provided an opportunity to compare triheptanoin treatment with even-carbon MCT in a subgroup of LC-FAOD patients presenting with LVEF ≤55%.

Results:
In each of the four studies, patients with baseline LVEF ≤55% treated with triheptanoin demonstrated a change towards the normal LVEF range compared with controls (N=25 in total). In the RCT, patients randomized to triheptanoin experienced a 5.8% increase in mean LVEF after four months of treatment compared with even-carbon MCT (n=5; p=0.1050). LVEF increased by 6.4% (n=5; p=0.0453) and 6.1% (n=9; p=0.0078) after triheptanoin initiation in the open-label studies, respectively. In the retrospective study, patients treated with triheptanoin as rescue therapy experienced a mean improvement of 13.5% (n=8; p=0.040) in LVEF.

Conclusions:
These results suggest that triheptanoin leads to improvement of left ventricle function in LC-FAOD patients who present with LVEF ≤55%.

High dose alglucosidase alfa (rhGAA) in the treatment of infantile onset Pompe disease: A single center experience

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Infantile onset Pompe disease (IOPD) is a lysosomal storage disorder. Accumulation of glycogen in the lysosome leads to severe involvement of cardiac, respiratory and skeletal muscles. Alglucosidase alfa (rhGAA) has been the only approved therapy for IOPD and if started early, has shown significant improvement in the cardiac phenotype. However, the approved dose of 20mg/kg/every other week (qOW) has in general been ineffective in reversing the progressive neuromuscular phenotype. Recent literature has shown growing evidence of higher dose of therapy leading to improved outcomes.

We present two cases of IOPD who transitioned to the higher dose of alglucosidase alfa due to clinical deterioration or suboptimal cardiac response. Patient one has CRIM positive IOPD and was gradually titrated to 40mg/kg/every week due to muscular weakness and prolonged intubation following a lower respiratory infection. Patient two has CRIM negative IOPD and was transitioned to 40mg/kg/qOW due to suboptimal cardiac response.

Results show clinical improvement in both patients. Biomarkers [creatine kinase, AST, ALT, uHex4 (glucose tetrasaccharide)] fluctuated based on clinical course rather than a linear trajectory with dosing of alglucosidase alfa. Both patients tolerated the higher dose without need for additional pre-medications, steroids or additional immunomodulation.

Conclusion:
IOPD is a severe disorder and current dosing of 20mg/kg/qOW has not been effective in halting the progression of disease. Here, we provide additional evidence in support of higher alglucosidase alfa dose and show clinical improvement
and acceptable safety profile in two children with IOPD.

Cerebrotendinous xanthomatosis in an adult identified by targeted next generation sequencing panel for hereditary spastic paraparesis

Tara Dzwiniel, Tripthi Sugumar, Oksana Suchowersky, **Saadet Mercimek-Andrews**

Objectives:
To report a new patient with cerebrotendinous xanthomatosis (CTX), and to expand the spectrum of phenotype and genotype

Design and Methods:
We reviewed patient chart for clinical, biochemical, and molecular genetic investigation results.

Results:
This 35-year-old male was born at term of non-consanguineous parents. Early developmental milestones in infancy and childhood were normal. He developed bilateral juvenile-onset cataracts and had cataract surgery at age 19 years. There was no history of childhood diarrhea, seizures or dysarthria. He developed a lower-limb spasticity at the age of 29 years which was slowly progressive. His initial neurological exam was performed in the neurogenetic clinic at the age of 35 years and showed increased muscle stretch reflexes (upper and lower extremities), upgoing plantars, impaired vibration at toes, impaired joint position below ankles, mild intention tremor on the left, and spastic gait. There was mild swelling on his achilles tendon. Brain magnetic resonance imaging revealed increased T2 signals in the dentate nuclei and bilateral posterolateral spinal cord. Targeted next generation sequencing panel for hereditary spastic paraparesis (75 genes) revealed two pathogenic variants in trans (c.379C>T; p.Arg127Trp/c.1072C>T; p.Gln358*) in *CYP27A1*and confirmed the diagnosis of CTX.

Conclusion:
Our patient with CTX presented with juvenile onset cataract and young adult-onset spasticity and tendon xanthomas. CTX is one of the treatable inherited metabolic disorders that chenodeoxycholic acid improves or prevent clinical features, if started early. For this reason, early diagnosis of CTX, even in the absence of the classical triad, is important in this treatable neurometabolic disease.

A multi-case report evaluation of the NDUFV1 p.E214K variant and its association with Leigh syndrome in Low-German speaking Mennonites in Southwestern Ontario

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Objective:
Leigh syndrome is a progressive neurometabolic disease that causes lesions in the midbrain and brainstem and is characterized by early onset rapid neurodegeneration. Pathological variants in over 80 nuclear encoded genes have been identified as causing Leigh syndrome, usually involving coding regions of proteins in mitochondrial metabolism. Our objective is to describe the clinical presentations of five patients from two families of a common Low-German Speaking (LGS) Mennonite background, each diagnosed with Leigh syndrome and identified as carrying the same NDUFV1 p.E214K gene variant. Furthermore, we present our clinical findings in conjunction with in-silico analysis and review of existing literature to suggest that this variant found in patients from a Southwestern Ontario Mennonite population is deleterious and associated with Leigh syndrome features.

Design & Methods:
Gene sequencing was performed on DNA and fibroblast samples of affected patients from both families. Clinical and laboratory records were reviewed to collect data on affected individuals in both families. Databases and in silico analysis tools PROVEAN, ClinVar, gnomAD, PolyPhen-2 and DynaMut were used to evaluate protein structure, population genetics and predict the pathogenicity of the mutation.

Results:
Next generation gene sequencing confirmed existence of the NDUFV1 p.E214K variant in patients of the same Southwestern Ontario Mennonite population. Of the five patients described in the study, one patient is still alive while four are deceased.

Conclusions:
The clinical data of patients with shared ancestry, review of functional studies in yeast models and in silico analysis all suggest that this variant should be categorized as pathogenic.

Baseline demographics and clinical characteristics of patients enrolled in the followME Fabry Pathfinders registry

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Objectives:
The followME Fabry Pathfinders registry (EUPAS20599) evaluates real-world safety, effectiveness, and patient-reported outcomes for current Fabry disease (FD) treatments. We present baseline patient demographics and clinical characteristics as of August 2021.

Design & Methods:
Patients aged ≥16 years with a confirmed FD diagnosis and estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2 were enrolled into one of three groups: migalastat-amenable *GLA* variants receiving migalastat; any *GLA* variant receiving enzyme replacement therapy (ERT); migalastat-amenable *GLA* variants not receiving FD-specific therapy (untreated).

Results:,
374 patients were enrolled: migalastat group (n=168 [44.9%]; median [range] age at enrollment, 56.0 [16–78] years; female, 45.8%); ERT group (n=68 [18.2%]; 46.0 [20–70] years; female, 52.9%); untreated group (n=138 [36.9%]; 44.0 [16-82] years; female, 79.0%). Proteinuria was present in 21.7% of patients and 40.6% had an eGFR ≤90 mL/min/1.73m^2. Median [range] eGFR was 86.1 [30.5-139.7], 95.6 [39.6-139.7], and 101.03 [49.5-139.7] mL/min/1.73m^2 in the migalastat, ERT, and untreated groups, respectively. Median [range] left ventricular mass index (g/m^2) was: migalastat group (overall, 98.0 [18.0–289.0]; females, 73.5 [18.0-195.8]; males, 115.3 [31.7–289.0]); ERT group (93.5 [28.2–341.0]; 98.9 [47.4–169.3]; 91.2 [28.2–341.0]); untreated group (74.8 [51.0–168.3], 73.5 [51.0–139.8]; 78.0 [70.0–168.3]. Prior cardiac events (before treatment initiation or enrollment for untreated) were reported in 7.1%, 2.9%, and 5.1% of patients, respectively; none had prior renal events.

Conclusions: The baseline data in the followME registry, the largest real-world cohort of migalastat-treated patients, provides the basis for understanding real-world treatment patterns.

Supported by Amicus Therapeutics.

Continuous glucose monitoring (CGM) to alter nutrition management of patients with glycogen storage disease (GSD) type 1 with suboptimal glucose monitoring: 3 case reports

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Objectives:
The use of CGMs in the management of GSD has become standard in many metabolic centers but given the cost and lack of coverage, is currently not used routinely in Canada. We report 3 CGM trials in GSD type 1 patients who lack adequate glucose monitoring to illustrate how safe and significant advancements in nutrition management plans were possible.

Design and methods:
2 adults with GSDIb and 1 teenager with GSDIa were monitored between 10 to 35 days using the Dexcom G6. Indications for CGM trials were: 1. significant weight gain, 2. recurrent episodes of asymptomatic hypoglycemia with multiple complex comorbidities, and 3. recurrent episodes of asymptomatic hypoglycemia with biochemical evidence of poor chronic metabolic control.

Results:
Case 1: 39yo female with goal to skip one hour of continuous enteral feeds if eating. Achieved up to 2 hours of fasting time with intake from a prescribed food portion list. Case 2: 51yo female with goal to prevent hypoglycemic episodes. Altered glycosade dosing and timing according to trends of hypoglycemia to significantly improve morning and afternoon hypoglycemia. Case 3: 13yo male with goal to extend fasting time beyond 3 hours and improve GSD control. Increased fasting time by 30 minutes and improved GSD biochemistries.

Conclusions:
CGM allowed nutrition changes that otherwise would not have been possible due to safety concerns with inadequate blood sugar monitoring. CGM is a tool to improve metabolic control. Metabolic clinics should consider advocating for coverage of CGM monitors for GSD patients as standard of care.

Development and validation of method for quantitating cystine in mixed leukocytes by HILIC-Z chromatography tandem mass spectrometry: comparison with C18 chromatography

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Objectives:
To determine whether chromatographic separation of cystine in mixed leukocytes by HILIC chromatography can reduce ion suppression and overall increase sensitivity, when compared to an existing C18 chromatographic method.

Design and methods:
Based on an application note from Agilent technologies (5) for analyzing 20 amino acids including cystine by HILIC-Z chromatography, we determined that the limit of detection for cystine had to be improved by a factor 100. Sample preparation, chromatography and mass spectrometry parameters where optimized.

Results:
A chromatographic gradient was adapted for cystine only, resulting in a 10-minute total run time. Addition of 1% formic acid to the mobile phase buffers were critical to improving peak shape and maximizing signal intensity. Acidification of samples with 50mM HCl combined with the use of plastic vials also resulted in improved peak shape and increased signal intensity. Globally, when analyzing pure cystine solutions, the signal intensity was similar in HILIC and C18. However, as we observed no ion suppression in HILIC, the signal intensity was 5x higher with mixed leukocytes extracts. Both methods agreed well when analyzing mixed leucocytes samples spiked with cystine, and performance using ERNDIM external quality control samples were within one standard deviation of the target values. Preliminary work to measure cystine from granulocytes isolated by immunoaffinity, showed the potential for decreasing the volume of blood needed and would have the advantage of increased sample stability.

Conclusion:
The HILIC and C18 chromatography are both sensitive and reproducible, allowing accurate diagnosis and follow up of patients with cystinosis.

Reduction in plasma phenylalanine levels in patients with phenylketonuria with live biotherapeutic SYNB1618: interim analysis from an ongoing phase 2 study

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Objectives:
Phenylketonuria (PKU) is a metabolic disease characterized by an inability to degrade phenylalanine (Phe), causing neurotoxicity. SYNB1618, a live, modified strain of the probiotic bacterium E. coli Nissle was engineered to consume Phe in the gastrointestinal tract (GI) through expression of the enzymes phenylalanine ammonia lyase (PAL) and L-amino acid deaminase (LAAD). SYNB1618 metabolizes Phe to harmless compounds excreted in urine.

Methods:
SynPheny-1 is an open-label study in adult PKU patients with Phe >600 micromol/L. Patients followed individualized study diets reflecting baseline Phe intake from 7 days prior to dosing to 2 weeks after the last dose. The dose of SYNB1618 was gradually increased: 1x1011 livecells for the first 3 days, 3x1011 on days 4-6, then 1x1012 TID on days 7-13. A D5-Phe tracer studywas conducted at baseline and on Day 14 at the 2x1012 dose. Key outcomes were change from baseline in D5-Phe AUC0-24h and fasting blood Phe.

Results:
Interim analysis of 9 PKU patients showed a 40.0% (95% CI 64.9, -2.7) decrease in D5-Phe AUC0-24h compared to baseline. Change from baseline in fasting blood Phe level was -14.5% (CI-27.9, 2.2) on Day 7 after the dose-ramp and at the 3x1011 dose, -19.5% (CI -32.3, -4.3) on Day 14 at the 1x1012 dose, and +18.7% (CI -2.4, 44.3) after cessation of dosing. The most common AEs were mild to moderate GI symptoms. No SAEs or deaths were observed.

Conclusion:
SYNB1618 is a promising novel oral treatment option for PKU, and further clinical development is warranted.

The mitochondrial MT-TW m.5537_5538insT variant presents with significant intra-familial clinical variability

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Objectives:
Mitochondrial disorders can present with a wide range of phenotypes. Those due to mitochondrial DNA variants may be influenced by heteroplasmy and the same variant may result in different clinical phenotypes. We demonstrate this phenomenon by describing the family below.

Design and Methods:
We present a family in which multiple family members carry a rare, pathogenic mitochondrial variant (m.5537_5538insT, MT-TW gene) with differing levels of heteroplasmy and clinical features.

Results:
The proband presented in infancy with febrile seizures. She later developed treatment resistant seizures and epilepsia partialis continua, memory loss, loss of mobility, cognitive decline, migraines, optic atrophy, cardiomyopathy, and hyperlactatemia. She had a stroke resulting in her death at 21 years of age. Brain MRI was in keeping with MELAS syndrome and she was found to carry the variant at 97% heteroplasmy in muscle. Her mother has MELAS syndrome with small size, easy fatiguability, myoclonus, tremor, optic neuropathy, renal impairment, gait instability, cardiac hypertrophy, and progressive white matter T2-hyperintense lesions on brain MRI. The variant is homoplasmic in urinary epithelial cells. Another family member presented in infancy with tremors, motor regression, global developmental delay, axial hypotonia, and failure to thrive. She's had continued clinical deterioration, including feeding issues, irritability, worsening hypotonia, dystonia, seizures, and lactic acidemia. Brain MRI is in keeping with Leigh syndrome. The variant to is homoplasmic in blood. Her mother has hearing loss and carries the variant at ~50% heteroplasmy.

Conclusions:

We demonstrate that this variant is associated with a variety of phenotypes ranging from asymptomatic to mild mitochondrial symptoms to classic MELAS and Leigh syndrome.

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Poster

Quantitative succinylacetone measurement by gas chromatography-tandem mass spectrometry (GC-MS/MS): a valuable tool for diagnosis, monitoring and characterization of tyrosinemia type I and other hypersuccinylacetonemias

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Background and Objectives:
Tyrosinemia type 1, due to deficient activity of fumarylacetoacetate hydrolase (FAH), causes accumulation of succinylacetone (SA). SA concentrations in plasma and urine of untreated patients are typically several thousand-fold higher than normal (nanomolar) concentrations, therefore are easily measurable. As quantitation of SA in the nanomolar range became important for monitoring patients treated with nitisinone, our group established a GC-MS assay (J Chromatogr B 2006;832:24-9). This later led to identification of milder forms of hypersuccinylacetonemia and their genetic causes, notably maleylacetoacetate isomerase (MAAI) deficiency (J Med Genet 2017;54:241-247). It also fostered other research collaborations related to tyrosinemia. We recently acquired a new, more sensitive triple quadrupole technology
(GC-MS/MS), and sought to apply this to improve and streamline SA analysis.

Methods and Results:
A stable isotope dilution process is used, with sample treatment consisting of an oximation step followed by a single liquid-liquid extraction then trimethylsilyl derivatization.
Quantitation is based on intensities of the ion transitions m/z 620 --> 181 for SA and 625--> 186 for the internal standard. Method validation demonstrated enhanced analytical specificity and sensitivity, with good precision and accuracy. Using GC-MS/MS instead of GC-MS allowed a limit of quantitation in the low nanomolar range while decreasing the specimen volumes required, as well as reducing the number of sample processing steps, chromatographic run time, and instrument maintenance.

Conclusions:
This assay is well suited for diagnosis and monitoring of tyrosinemia type 1 in the clinical laboratory; also, for identification of mild hypersuccinylacetonemias and for relevant research applications.

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Poster

Designing patient-oriented longitudinal disease registries for children with rare metabolic diseases in Canada

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Objectives

High-quality disease registries that collect meaningful longitudinal data on patient outcomes can facilitate research both on natural history and on intervention effectiveness. INFORM RARE is a multidisciplinary research network of patients/families, clinicians, methodologists, ethicists and policymakers established to design and conduct registry-based trials toward improved care for children with rare diseases. We aimed to design and implement two robust, patient-oriented, longitudinal Canadian registries for mucopolysaccharidoses (MPS) and phenylketonuria (PKU), respectively.

Design and methods

Facilitating a shared research agenda and sustainable vision, we co-designed the two new disease registries in partnership with the Canadian MPS Society and Canadian PKU & Allied Disorders, Inc. Both registries will be hosted on the National Organization for Rare Disorders (NORD) IAMRARE™ Platform. All partner organizations collaborate to establish a governance structure, policies and procedures for the collection, access, and sharing of registry data for efficient observational and intervention research; ethical and legal responsibilities; funding and sustainability.

Results

Initial eligibility criteria include: a diagnosis of MPS or PKU, age 18 years or younger, and receiving healthcare in Canada. With participant consent, the registries will collect and store patient-, caregiver- and clinician-reported data informed by core outcome sets for each disease. Participants will own their own registry data and have the option to be contacted to partner and participate in research and/or share their data with researchers meeting prescribed criteria.

Conclusions

Two collaboratively established patient-oriented longitudinal registries are designed to efficiently conduct innovative observational and intervention research, which will ultimately improve health care and outcomes for patients.

Towards a core outcome set for mucopolysaccharidoses (MPS) in children: a rapid review of outcomes in intervention studies and guidelines

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Objectives:
To inform the development of a core outcome set (COS) for children with mucopolysaccharidoses (MPS), we aimed to identify all outcomes measured in recent intervention studies or recommended to measure in guidelines for this population.

Design and methods:
Using a comprehensive search strategy, we identified English-language intervention studies and guidelines published between 2011-2021. Trials and guidelines specific to children with MPS were eligible. Following two stages of screening by two independent reviewers, data were extracted by a single reviewer and verified by another. Details pertaining to the study design, patient (sub)population, intervention, and comparator were extracted, along with verbatim outcomes and associated outcome measurement tools. Outcomes were grouped into the following *a priori* core areas: life impact, pathophysiological manifestations, growth and development, resource use, and death.

Results:
We identified 2555 unique intervention studies and guidelines, of which 73 met inclusion criteria. All MPS subtypes except MPS IVB and MPS IX were addressed in at least one article. Of 84 unique outcomes reported, 13 (15.5%) were reported by only one article. The median (Q1-Q3) number of unique outcomes per article was 10 (6-15). The most frequently reported outcomes were general adverse events (61.6% of articles), urinary glycosaminoglycans (57.5%), and immune-related adverse events (57.5%). Most outcomes were in the pathophysiological manifestations and life impact core areas.

Conclusions:
Outcomes reported in intervention studies and guidelines for MPS in children vary considerably, supporting the need for a COS to standardize the selection and measurement of outcomes for future studies.

Family-centred care interventions for children with ongoing, elevated healthcare needs: a scoping review

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Objectives:
To identify and characterize family-centred care interventions for children with ongoing, elevated healthcare needs and their families.

Design and methods:
In this scoping review, we searched Medline, Embase, PsycInfo, and Cochrane databases and the grey literature for articles on family-centred care interventions for families of children aged <=12 years with ongoing, elevated healthcare needs. We analyzed characteristics of included interventions, including dimensions of family-centred care, based on the Picker Principles of Patient-Centred Care. We summarized results descriptively.

Results:
We identified 2,882 unique, potentially eligible articles. Of these, 64 articles describing 62 unique interventions were included. Quasi-experimental studies (n=19) and randomized controlled trials (n=11) were most commonly used to examine interventions, followed by qualitative and mixed methods studies (n=9 each). More than half of the interventions (n=32) addressed 3 or 4 family-centred care principles. The principle most frequently addressed was information sharing, communication and education (n=50), through interventions such as: information meetings with care providers; informational tools or resources; and online platforms facilitating information sharing and communication with providers. The next most frequently addressed principles were: family involvement in care (n=42); respect for patient/family preferences (n=33); and access to care (n=32). All but two interventions directly targeted families. Interventions were commonly delivered in person (n=22), virtually (n=12), or using both approaches (n=20).

Conclusion:
We identified family-centred care interventions that can be further examined, adopted, and/or adapted by future researchers, health care providers, and administrators interested in improving healthcare for children with chronic illness, including inherited metabolic diseases, and their families.

Workforce survey of metabolic physicians and laboratory clinicians demonstrates urgent need to improve access to human and infrastructure resources

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Objective:

To understand current working conditions and barriers to optimal provision of inherited metabolic diseases (IMD) service

Design and Methods:
We developed a 25-question survey using Research Electronic Data Capture (REDCap) and invited all IMD physicians and clinical laboratory scientists in Canada to complete this questionnaire.

Results:
Survey respondents included 11 clinical laboratory scientists and 18 IMD physicians. 48% of respondents were older than 50 years. 38% of IMD physicians provided consultative services to 2 or more provinces. 90% of survey respondents are working full time but only 35% work full time caring for IMD patients with the rest having competing demands on their time. 45% of respondents had on-call responsibilities 1 night in 3 or more often. 35% of IMD physicians had waiting lists longer than 6 months. All respondents indicated that care was available for adults with IMD in their primary province of work, but 44% indicated that care was only provided for adults within pediatric institutions. The most common barriers to optimal care included access to allied health care professionals (44%), timely metabolic and molecular genetic testing (41%), access to medications for the treatment of IMD (37%) and care for adults with IMD (31%).

Conclusions:
The number of patients with IMD who require expert care is increasing due to advances in diagnostic and therapeutic tools. Major shortages already exist in the IMD workforce. Significant investments in infrastructure for clinical care and training will be required to meet the needs of the expanding patient population.

Caregiver perspectives on family management of care for children with inherited metabolic diseases: results from a cross-sectional survey

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Objective:
To describe family experiences with managing healthcare for children with inherited metabolic diseases (IMDs), as families are important partners in the management of pediatric IMDs.

Design and methods:
We conducted a cross-sectional online survey of parents or guardians ("caregivers") of children <=12 years with IMDs receiving care at and recruited through one of 11 Canadian pediatric metabolic clinics. Using a purposive, maximum variation sampling approach, we sought sample diversity on variables we anticipated to be associated with healthcare management: treatment centre, residential proximity to specialty care, child age, sex, IMD, and typical clinical course trajectory of the IMD, classified as (a) chronic and non-progressive; (b) acute, episodic; or (c) multi-system and progressive. We collected data on family experiences with IMD management, including: family time and financial contributions; degree of difficulty in managing care and accessing care requirements; caregiver quality of life; and family experiences with support services. We will use descriptive statistics (e.g., medians, proportions) to summarize the data.

Results:
Recruitment will end in March 2022. Forty-one participants have completed the questionnaire to date. Eighteen IMDs are represented. Thirteen children have an IMD with typical clinical trajectory (a); eighteen with trajectory (b); and ten with trajectory (c). Twenty children (48.8%) are younger than three years; nineteen (46.3%) are female. We will present full results on family experiences for the whole sample.

Conclusion:
We will identify important family contributions and impacts of IMD care and highlight potential areas of support for families that may be addressed by future interventions.

Parents' perceptions of health care networks of young children with inherited metabolic diseases (IMD): a mixed methods study

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Objectives:
We sought to understand parents' perceptions of the health care networks of children with inherited metabolic diseases (IMD). Methods: This mixed methods study is embedded in an ongoing prospective cohort study. Parents/guardians of children <= 12 years with IMD were enrolled from one of 11 Canadian metabolic clinics. Parents created a 'care map' depicting their perceptions of their child's network of care providers and connections between providers. We used social network analysis to describe network size, interconnectedness (density: ratio of perceived vs possible connections among providers, 0-1) and centralization (degree to which connections in a network centre around one provider, 0-1). A subset of participants participated in a semi-structured interview about their care map. We analyzed interviews thematically and integrated quantitative and qualitative results narratively. Results: To date, we have analyzed 27 care maps from 58 participants and conducted eight interviews. In preliminary social network analysis, participants identified a median of 16 (interquartile range 10-19) providers in their children's networks. Networks were not highly interconnected (median density, 0.06) nor highly centralized (median centralization, 0.21). We identified qualitative themes within three domains: (i) parents' experiences with managing their children's care networks; (ii) relationships with providers, including the importance of mutual trust; and iii) providers as part of a dynamic network. Conclusions: Our findings highlight the complexity of care for children with IMD, the importance of positive relationships with providers, and gaps in care coordination that place high demands on parents. These results can inform the design of interventions to improve care.

A good news story: Two cases of citrin deficiency presenting with neonatal cholestasis

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Objectives:
We describe two cases of citrin deficiency (citrullinemia II) who presented with conjugated hyperbilirubinemia. We highlight this rare diagnostic entity in the differential diagnosis for conjugated hyperbilirubinemia and discuss the highly favourable clinical and biochemical outcomes achieved.

Design and Methods:
This is a retrospective case review of two patients from our centre, since 2019.

Results:
Two healthy term infants, patients A (5 weeks) and B (8 weeks), presented with conjugated hyperbilirubinemia [patient A total bilirubin 144.1 and patient B 100 (normal 3.4-17.1 umol/L), patient A direct bilirubin 54.9 and patient B 72 (normal 0.0-5.0) umol/L)]. Biliary atresia was ruled out. RBC galactose-1-phosphate was elevated at 210 (patient A) and 351 (patient B) (normal 0-50 ug/g Hb). Amino acid profile demonstrated elevated citrulline, arginine, threonine and threonine/serine ratio in both patients. Genetic testing identified homozygous c.1769 C>A p.(Ser590*) likely pathogenic mutations in patient A. Patient B has a heterozygous variant of unknown significance, c.1233A> C in *SLC25A13.* This variant has been described as a loss of function splice mutation associated with elevated citrulline levels in heterozygous individuals (PMID: 27453504). Both patients were started on soy infant formula, with normalization of liver studies and improvement in amino acid profile over approximately four months. They are clinically well with normal growth and development.

Conclusion:
Citrin deficiency is a rare metabolic disorder that can present with conjugated hyperbilirubinemia in infancy and should be considered in the differential diagnosis. Both patients have shown excellent clinical and biochemical outcomes with galactose-free and carbohydrate-restricted diets.

Caregiver perceptions of effects of the COVID-19 pandemic on health care access and management for children with inherited metabolic diseases: a cohort analysis

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Objective:
To describe the impact of the COVID-19 pandemic on health care access and management for children with inherited metabolic diseases (IMDs).

Design / methods:
We recruited parents/guardians ("caregivers") of children <=12 years with IMD to participate in a cohort study on family healthcare experiences through 11 participating Canadian pediatric metabolic clinics.
Following enrollment, we invited participants to complete one cross-sectional, online, intake questionnaire which included questions on COVID-19 diagnoses, family well-being, in-person and virtual healthcare experiences, and pandemic effects on access to care, child health, and family IMD management. All measures were caregiver-reported. We will analyze data using descriptive statistics (e.g., medians, proportions). **Results:** Forty-one participants across eight provinces/territories and ten treatment centres have completed the questionnaire. The survey will be administered December 2020 – April 2022. Thirty-three (80.5%) caregivers reported >=1 healthcare appointment changed from in-person to virtual and 24 (58.5%) reported >=1 appointment delayed or cancelled over the past six months due to the pandemic. We will present full results on the pandemic's effects on healthcare for the whole cohort.

Conclusion:
The pandemic has exacerbated existing healthcare challenges for children with chronic illness across Canada and will likely continue to affect healthcare delivery in the future. This study, collecting data from participants experiencing a variety of provincial/territorial pandemic-related policies, across a timespan encompassing multiple pandemic waves, will help to elucidate caregiver perspectives on changes to healthcare delivery for children with IMDs and their impacts. These perspectives should be considered in the design of healthcare interventions for this population.

Primary Carnitine Deficiency in Association with BBOX1 Variants

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Background:
Carnitine is essential for long-chain fatty acid beta oxidation in the mitochondrion. Primary or secondary carnitine deficiencies cause multisystemic defect in energy metabolism. 75% of carnitine pool is derived from diet and the remaining is biosynthesized endogenously. The physiological relevance of endogenous carnitine biosynthesis is unclear.

Objectives:
To investigate carnitine biosynthesis in patients with primary carnitine deficiency.

Design:
Clinical and laboratory findings of patients with suspected primary carnitine deficiency were reviewed.

Results:
Three patients from two independent families were referred to our service for persistently low total and free plasma carnitine levels. One patient had developmental delay, and all presented with myopathy, and exercise intolerance. One adult patient developed acute psychosis. Unlike carnitine transporter deficiency, fractional urine excretion of carnitine was normal (< 5%). We measured carnitine biosynthesis intermediates. Plasma levels of γ-butyrobetaine were elevated, consistent with a possible defect in γ-butyrobetaine dioxygenase. Molecular testing revealed bialleleic variants of BBOX1.

Conclusions:
Patients with biallelic variants of BBOX1 may present with primary carnitine deficiency and a specific clinical picture.

The mechanism of creatine mediated downregulation of AGAT expression

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The rate limiting step in creatine biosynthesis is carried out by the enzyme arginine:glycine amidino transferase (AGAT). Walker in the late 1950's demonstrated end-product inhibition of dietary creatine in rats by repression of AGAT activity in a non-enzyme kinetic manner. Not until the mid 1980's did Van Pilsum provide evidence that creatine acts at the pre-translational level to control AGAT expression. We used different cell models to further delineate the mechanism of creatine mediated downregulation of AGAT expression.

Following 24h treatment of HeLa, HepaRG, RH30, and HAP1 cells with 50 mM creatine, a two- to three-fold decrease in AGAT mRNA and protein levels is observed using qPCR and Western blotting. Ethynyl-Uridine labelled endogenous nascent AGAT RNA levels in HepaRG cells in pulse-chase experiments directly showed that the stability of AGAT mRNA is decreased 50% by 50 mM creatine. We have generated AGAT-c-terminal Nanoluc Luciferase reporter HAP1 cell line by CRISPR that continues to respond to CT. Treatment with actinomycin D (ActD), a transcriptional inhibitor, in combination with creatine for 6 hrs resulted in a further 30% decrease in luciferase activity compared to cells treated solely with ActD or creatine. Furthermore, responsiveness to CT can also be largely recapitulated using a luciferase reporter consisting solely of the coding region of AGAT fused in-frame to Nanoluc luciferase driven by a heterologous CMV promoter. The combined results strongly suggest creatine treatment decreases the stability of AGAT mRNA, pointing to the importance of a post-transcriptional and transcriptional regulatory mechanism.

Phenotypic variability and impact of newborn screening on patients with severe Biotinidase Deficiency Tyr210Cys (Y210C) in Southwestern Ontario

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Objectives:
Biotinidase Deficiency (BD) is an autosomal recessive metabolic disease caused by impaired biotin recycling, which may cause hypotonia, seizures, developmental delay, optic atrophy, and hearing loss. Our objective is to describe the phenotypic variability and impact of newborn screening (NBS) on patients with severe BD with the *Tyr210Cys* variant.

Methods:
We conducted a retrospective chart review comparing BD *Tyr210Cys* patients diagnosed through NBS to those diagnosed upon clinical presentation at a tertiary hospital in Southwestern Ontario.

Results:
Two brothers with BD were diagnosed prior to NBS. The brothers presented at ages 3 and 4 with acute onset of weakness, ataxia, spasticity, severe visual impairment, and elevated urinary 3-hydroxyisovaleric acid. Following initiation of biotin therapy, both brothers experienced dramatic improvement in motor function and respiratory distress. However, visual and hearing impairments persisted, with optic atrophy in one brother and bilateral hearing loss in the other. Additionally, one continued to experience lower limb and gait abnormalities. With NBS, three individuals were identified with profound BD *Tyr210Cys* (two *Tyr210Cys/Tyr210Cys* , one *Tyr210Cys/Asp444His*) and started on biotin supplementation. They are growing well with no development of BD symptoms and are developmentally age-appropriate.

Conclusions:
Individuals with untreated severe BD *Tyr210Cys* may exhibit severe motor, visual, and hearing loss, despite biotin supplementation. The two brothers from our centre illustrate the phenotypic variability of the Tyr210Cys variant in severity and long-term outcomes. Early diagnosis with NBS and prompt biotin supplementation has changed the clinical course and prevents subsequent development of neurological complications.

Culturally sensitive provision of rapid biochemical and molecular diagnosis at birth in children at risk for Maple Syrup Urine Disease in Southwestern Ontario

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Objectives:

Maple Syrup Urine Disease (MSUD) is an autosomal recessive metabolic disorder and is common in the Old Order Mennonite (OOM) population of Southwestern Ontario where 10% of the population carry the *p.Tyr438Asn BCKDHA* variant. While prenatal diagnosis is available for pregnancies at 25% risk, most OOM women decline invasive testing. Patients may present before newborn screening (NBS) results with encephalopathy and clinical decompensation. We aimed to compare patients diagnosed with MSUD within 24 hours of life through rapid biochemical and molecular testing to those diagnosed upon clinical presentation.

Design and Methods:
We conducted a retrospective chart review comparing MSUD patients diagnosed through rapid testing (the newborn nurses for the first 15hr of life; at 15hr, a blood specimen is collected for amino acid analysis) to those who presented symptomatically.

Results:
Of 20 patients who received rapid testing, 5 were diagnosed with MSUD and had mean leucine levels of 320 micromol/L compared to 84 micromol/L of the 15 non-MSUD infants. Three infants presented clinically with leucine levels of 2468 micromol/L. The rapidly diagnosed infants continued ketonex formula, did not require hospitalization, and are growing well with age-appropriate neurological development, while the 3 infants presenting clinically had prolonged hospitalization of more than 10 days and required hemodialysis for elevated leucine levels.

Conclusions:
Patients with MSUD can present in the first week of life prior to provincial NBS results. Rapid biochemical and molecular testing at our centre provided prompt diagnosis and treatment for families who declined prenatal diagnosis.

The Canadian Prairie Metabolic Network (CPMN): A Collaborative Approach to Diagnosing Inborn Errors of Metabolism (IEMs)

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Next-generation sequencing (NGS) has revolutionized clinical medicine. Should NGS be integrated early in the diagnostic work-up of patients suspected to have IEMs? With a rapid turnaround time, this "OMICS First" approach may improve patient care and reduce the burden on the healthcare system by identifying a diagnosis sooner than the traditional approach to IEMs.

Objectives:
The CPMN aims to build a network of metabolic teams across the Prairies that will use an NGS-based approach to diagnose metabolic disorders, while enriching the knowledge base of genomic variants in Canadians as part of Genome Canada's All for One initiative. By partnering with Discovery DNA, Inc., the CPMN will offer rapid exome and genome sequencing, as well as mitochondrial DNA and pharmacogenomic sequencing.

Design & Methods:
The CPMN currently accepts referrals for Manitoba patients suspected to have an IEM. Consented participants are reviewed and those deemed eligible have a buccal swab collected. We plan to expand to the other Prairie provinces in years 2 and 3.

Results:
To date, 37 participants were approved for NGS and 19 results were reported: 2 positive (pathogenic/likely pathogenic), 12 VUS, and 5 negative/uninformative, with 2 medically-actionable incidental findings. The average turnaround time for WES was 13.4 +/- 3.6 days.

Conclusions:
The CPMN relies on collaborations between clinical, academic, and private sectors across the Prairies. This unique approach addresses human resource gaps and provides metabolic patients with access to timely and comprehensive genomic testing. Future evaluations will include a health economic assessment and exploration of the patient experience.

Dietary treatment of branched-chain keto-acid dehydrogenase kinase deficiency in four Hutterite siblings

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Objectives:

Branched-chain keto-acid dehydrogenase kinase (BCKDK) deficiency is a rare, potentially treatable metabolic cause of intellectual disability and autism first recognized in 2012. We describe four Hutterite siblings with BCKDK deficiency; ages 2 months, 3 years, 5 years, and 11 years. They presented with neurodevelopmental phenotypes including microcephaly, global developmental delay, autism, and seizures. All four siblings had low branched chain amino acid (BCAA) levels and were homozygous for a likely pathogenic variant, BCKDK c.347T>A, p.(Ile116Asn). Dietary treatment was introduced via protein and/or BCAA supplementation with the biochemical target of normalizing BCAA levels and the clinical goal of improving development and optimizing neurologic outcomes.

Design and Methods:

Baseline clinical evaluations, food records, and plasma amino acid levels were collected before initiating dietary treatment. Protein intake was supplemented using a nutritional whey protein supplement, as well as L-leucine, L-isoleucine, and L-valine powders to target normalization of plasma BCAA levels.

Results:

The volume, taste and texture of the supplements resulted in oral refusal amongst the eldest three siblings despite trialling various administration methods. Normalization of BCAA levels was not achieved, and the clinical course remained unchanged for these siblings. The infant continues to receive protein supplementation and close clinical follow-up, with improvement in BCAA levels.

Conclusions:

These cases offer the first description of BCKDK deficiency in the Hutterite population. Although protein supplementation was not accepted by the oldest three siblings, ongoing dietary treatment and clinical follow-up of the infant will be critical in better understanding the clinical course of this rare, potentially treatable neurodevelopmental disorder.

Gender dysphoria in patients with inborn errors of metabolism

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Patients with inborn errors of metabolism (IEM) require lifelong treatment typically from infancy through adulthood. We describe four patients with IEMs who are experiencing significant amount of psychosocial stress and gender dysphoria (GD) due to their underlying sexual identity and related problems. Two patients with phenylketonuria (PKU), one transgender and the other one bisexual and transgender, one female transgender patient with 3-hydroxy-3-methylglutaryl-CoA lyase deficiency (HMG-CoA Lyase deficiency), and one male transgender patient with ornithine transcarbamylase (OTC) deficiency are reported herein. A potential relationship between the psychopathology of transgender related issues and metabolic diseases has not been previously described.

Biallelic hydroxymethylbilane synthase (HMBS) deficiency causes a rare leukoencephalopathy with mitochondrial dysfunction in siblings

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Objectives:
Heterozygous pathogenic variants in *HMBS* cause acute intermittent porphyria, while biallelic inheritance results in a severe leukoencephalopathy. Thirteen cases of
biallelic *HMBS* deficiency have been reported in the literature. The majority show severe motor delay, developmental regression, dystonia, ataxia, and characteristic MRI abnormalities, with death typically occurring in childhood. We report 2 additional cases of *HMBS* deficiency in siblings with leukoencephalopathy and features of mitochondrial dysfunction.

Methods:
A 7 month old girl presented with motor delay, macrocephaly, status epilepticus, and hypotonia. MRI was significant for diffuse symmetric white matter T2 hyperintensities, with sparing of the corpus callosum and grey matter. She had persistent mild hyperlactatemia and hyperalaninemia. Her teeth fluoresced red under Woods lamp examination. Her older brother had died at 3 years of age with similar clinical features, as well as progressive cortical blindness and developmental regression. Brain MRI was nearly identical. He also had persistent mild hyperlactatemia and hyperalaninemia, with respiratory chain dysfunction on muscle biopsy. Despite extensive biochemical workup he remained undiagnosed at the time of death.

Results:
Trio whole exome sequencing of the siblings and their father identified biallelic variants
in *HMBS,* which were present in trans in both siblings. Urine porphyrins in the girl showed elevated ALA and PBG.

Conclusions:
These additional cases of *HMBS* deficiency showed evidence of mitochondrial dysfunction, consistent with recent functional studies of this disorder in the literature. In addition, both siblings had refractory seizures, which has previously not been reported as a significant feature in the literature.

Further Delineation of the Phenotype Associated with Ribose-5-phosphate isomerase

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Objective:
Ribose-5-phosphate isomerase deficiency (RPID) is a rare inborn error of the pentose phosphate pathway, characterized by progressive leukoencephalopathy, psychomotor retardation, epilepsy, optic atrophy, sensorimotor neuropathy, cerebellar ataxia, and increased excretion of ribitol and arabitol in urine. To date only four affected individuals have been reported.

Design and Methods:
A 22-year-old man with previous diagnoses of cerebral palsy, global developmental delay, deafness, and retinal abnormalities provisionally consistent with Leber Congenital Amaurosis underwent clinical exome sequencing.

Results:
Whole exome sequencing identified a novel homozygous missense variant in RPIA (c.785T>C, p.(Phe262Ser)). Analysis of urine polyols showed markedly increased excretion of arabinitol and ribitol, confirming the diagnosis of RPID. The patient had a pattern of bilateral retinitis pigmentosa and optic atrophy. He exhibited previously documented white matter disease but with sparing the sub-cortical fibres instead of involvement. His magnetic resonance spectroscopy, retinal involvement, EEG abnormalities, developmental delay and male gender are consistent in previous reports with variable reports of hearing involvement and infantile onset.

Conclusions:
This report adds to the literature by documenting a further case of this exceptionally rare disorder, including a characteristic MRS suggestive of polyols in the CSF, presence of elevated polyols in the urine, and relative sparing of (as opposed to predilection for) the subcortical white matter. We will review and expand the pertinent literature, particularly as it relates to the ocular and CNS manifestations of this rare inborn error. This report also reinforces the importance of genome wide sequencing in patients identified as having ‘cerebral palsy’.

An unusual case of a DNA damage repair disorder presenting with infantile hypermethioninemia

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DNA damage repair disorders are a group of inherited conditions caused by deficiency of the nuclear proteins responsible for repairing acquired genome damage. These conditions have pleiotropic features including growth failure, predisposition to malignancy, photosensitivity, multiorgan dysfunction and neurocognitive impairment. Hypermethioninemia can be caused by inborn errors of the transsulfuration pathway and liver disease.

We report a 2-month-old male infant who was referred to the Alberta Children's Hospital Metabolics Clinic with hypermethioninemia, cholestasis and failure to thrive. Biochemical investigations showed elevated methionine, homocysteine and demethylation intermediates. A pyridoxine trial failed to normalize the biochemical abnormalities. Restriction of dietary methionine rapidly normalized the methionine and homocysteine, which persisted after liberalization of the diet. Known heritable causes of hypermethioninemia were excluded via gene panel. The infant's grown remained poor and his development was delayed. He also developed a severe, blistering sunburn despite adequate UV protection.

Exome sequencing identified a likely pathogenic homozygous variant in *ERCC1* (NM_202001.3): c.466C>T (p.Arg156Trp). *ERCC1* encodes a component of the nucleotide excision repair pathway. Very few patients with ERCC1 deficiency have been reported to date. The spectrum of severity ranges from childhood lethal cerebrooculofacioskeletal syndrome (OMIM 610758) to a syndrome of short stature, photosensitivity, liver dysfunction and renal tubulopathy with survival beyond childhood.

The patient's prognosis remains unclear in this rare and poorly delineated syndrome. The etiology and frequency of hypermethioninemia remains unknown in this group of disorders. Whether it is an intrinsic feature of this condition or related to underlying liver disease is unexplored in the literature.

Clinical application of atmospheric pressure chemical ionization gas chromatography mass spectroscopy in multi-reaction monitoring mode for the quantification of urine organic acid metabolites

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Objectives:
Urine organic acid (UOA) analysis is a key diagnostic tool when assessing patients for inborn errors of metabolism (IEMs). As an alternative to the current gold standard for qualitative clinical UOA testing through GC-EI-MS (Gas Chromatography-Electron Impact-Mass Spectroscopy), the Agilent 7890 GC in tandem with the Waters' Xevo TQ-S MS contains an easily interchangeable LC-ESI (liquid chromatography-electrospray Ionization) and GC-APCI (Atmospheric Pressure Chemical Ionization) instrument set-up. This project aims to develop and validate a novel quantitative UOA method for clinical use.

Design and Methods:
Patient urine samples and quality control (QC) specimens were spiked with internal standard, extracted via a liquid-liquid ether extraction, reacted with BSTFA to form trimethylsilyl derivatives, and then run-in full scan and multiple-reaction monitoring (MRM) mode. Elution times and ion mass spectra profiles of UOA metabolites of interest were determined.

Results:
Successful GC separation of key isobaric UOAs was achieved. Following instrument optimization, 34 organic acids of high clinical interest were evaluated in patient and QC samples. MRM parameters were developed, and clinical validation is in progress for methyl malonic acid quantification. Initial results show acceptable limit of detection and linearity. Other organic acids of clinical interest are also in the process of quantitative method development.

Conclusion:
This instrument offers promising GC separation of UOA metabolites coupled with APCI-MS detection. With clear paths for future work, the APCI technique presents great benefits for the field of biochemical genetic screening with the ability to perform LC and GC analysis on a single instrument.