BIMDG

British Inherited Metabolic Disease Group

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Abstract Booklet

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Contents

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Ferroptosis in the Pathology of Mitochondrial Diseases

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Background: Mitochondria are the central metabolic hubs of the cell and host fundamental energy transformation processes such as TCA cycle, OXPHOS and iron-sulphur cluster biogenesis. Mitochondrial diseases are some of the most common inherited neurometabolic disorders affecting an estimated 1 in 5,000 live births. They typically arise from primary defects in oxidative phosphorylation (OXPHOS), usually affecting the brain, muscles and heart but can be a combination of any tissue, with any kind of symptom, at any age of human life. Unfortunately, we still don't understand the disease mechanisms and there are no available treatment options. When mitochondria fail, they start to leak out "fumes" such as oxidative radicals (ROS), which can damage lipids, proteins, and DNA. Extensive ROS accumulation can lead to the activation of cell death such as ferroptosis, defined by iron-dependent accumulation of lipid peroxidation. In this project, we map the tissue-specific metabolic responses and ferroptosis susceptibility upon OXPHOS dysfunction. This project aims to study if the oxidative damage and the cellular responses to these radicals can explain the disease variability and identify new treatment targets.

Methods: We have employed a mouse model for mitochondrial cardiomyopathy and investigated the ferroptotic landscape of cardiac and skeletal muscle. We have mapped the oxidative stress responses and damage in tissues and cellular models of mitochondrial dysfunction. By using advanced metabolome, proteome, and RNA sequencing techniques we have identified novel metabolic and transcriptional programs that are activated in mitochondrial disease.

Conclusions: Our results provide strong in vivo evidence supporting the role of ferroptosis in mitochondrial cardiomyopathies, reinforcing its emerging significance in cardiovascular diseases. These findings open new avenues for future research to investigate the molecular mechanisms underlying mitochondrial diseases and offer potential targets for novel therapeutic strategies aimed at preserving tissue function and extending health span.

Mind the Gap: Futureproofing Lysosomal Labs for the Next Generation

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Lysosomal storage disorders (LSDs) are an expanding and highly specialized area of metabolic biochemistry. Despite significant expertise across UK laboratories, service provision is uneven, and diagnostic methodologies can vary. To address these challenges, we have undertaken a comprehensive gap analysis to identify and document current testing provisions, workforce and training needs, and emerging technologies.

By surveying labs nationwide, we will explore access to reagents, standardization of testing protocols, and the integration of biochemical and genetic data. This effort also aims to reveal perceived barriers—such as resistance to harmonization—and propose solutions to foster inter-laboratory comparability. The findings will be synthesized into a strategic plan, outlining short- and long-term goals for a potential lysosomal lab network.

We hope to form a forum for peer-to-peer knowledge exchange, hosting discussions on new technologies, complex cases and quality assurance. Regular engagement would nurture collaboration among clinical and technical staff, thereby improving staff retention and enhancing training opportunities. This structure could

also facilitate centralized data collection, enabling the development of multiplex diagnostic assays and shared diagnostic algorithms.

Key outputs will include a roadmap for diagnostic provision over the next 10–20 years, identified points of contact across labs (including trainees), and a pilot phase to evaluate the network's efficacy.

This initiative ultimately aims to future-proof LSD diagnostics by promoting uniform testing practices, facilitating innovation, and fostering a supportive community of experts dedicated to delivering equitable, high-quality services for patients across the UK.

Effectiveness and Tolerability of Migalastat in Adult Fabry Disease: A Single Regional Centre Experience

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Background: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficient α-galactosidase A (α-Gal) activity. Migalastat provides an oral treatment option for patients with amenable mutations. We evaluate its effectiveness and tolerability in our patients.

Methods: Eighty-seven adult Caucasian patients (55 males, 32 females) with amenable mutations were included. Baseline characteristics, biochemical markers, and outcomes were assessed. A comparative analysis was conducted by splitting the cohort into two groups based on migalastat treatment (treatment naïve (TN) and treatment switch (TS) from enzyme replacement therapy (ERT)). Differences were assessed using the Chi-square and Mann-Whitney U test. Non-fatal cardiovascular events (NFCVE) rates were calculated per 1,000 person-years.

Results: Of the 87 patients, 48 (55.2%) were TN and 39 (44.8%) TS. The TN group (including one cardiac transplant recipient) were older (57 vs 47 years; p=0.002),had less males (56 vs 72%), a higher median heart rate (68 vs 62 beats/min, p=0.012) and urine protein creatinine ratio (12 vs 9 mg/mmol, p=0.04). The rest of the characteristics were similar between groups. Molecular analysis identified 14% classical, 67% late-onset, and 19% not categorised mutations (can present as either). Baseline lysoGb3 levels were comparable between groups at baseline and declined at 12 months by 43% in TN and 46% in TS. NFCVE rates were 0.08 and 0.04 per 1,000 person-years in TN and TS group respectively. Three patients (3.4%) reverted to ERT (2 TN and 1 TS), with one death in the TS group. Follow-up was longer in the TS group (median 11.8 vs 3.6 years, p<0.001).

Conclusion: Migalastat effectively reduces lysoGb3 and is generally well tolerated in a cohort predominantly consisting of late-onset mutations. Identifying patients who require reverting to ERT remains crucial. Notably, favourable efficacy and tolerability were observed in a treatment-naïve cardiac transplant recipient.

Continued treatment efficacy despite recurrent hypersensitivity reactions to enzyme replacement therapies in infantile-onset Pompe disease: use of rapid drug desensitisation guided by intradermal drug testing.

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Background: Enzyme replacement therapy (ERT) permits long-term survival of patients with infantile onset Pompe disease (IOPD), however infusion associated reactions (IARs) of varying severity are commonly reported. IARs can usually be addressed with premedication and infusion rate adjustment, but may require additional approaches. Rapid drug desensitisation (RDD) entails ERT micro-dilution with additional low drug rate (mg/kg/hour) infusion steps while achieving target dose administration.

Methods: A 3-year-old boy had been diagnosed at 2 months with CRIM-positive IOPD and commenced therapy with alglucosidase alfa without immunomodulation. There was a positive treatment response with resolution of cardiomyopathy and good motor developmental progress. He had, however, recurrent mild IARs requiring adjustment of premedications to include steroids, antipyretic and antihistamine. He developed moderately raised anti-drug IgG antibodies. Therapy was switched to avalglucosidase alfa, but with continued occurrence of IARs consistent with an early type 1 hypersensitivity pattern. IARs occurred consistently after 3-6mg of infusion and included variable cough, desaturation and dermal flushing. Skin prick (SPT) and intradermal (IDT) testing of alglucosidase, avalglucosidase and cipaglucosidase with saline and histamine controls was used to assess baseline response and after implementation of a rapid drug desensitisation infusion schedule.

Results: Drug-specific IgE was negative. Baseline SPT was negative with positive IDT reaction to alglucosidase and avalglucosidase. Subsequent RDD protocol was implemented with first infusion tolerated without reaction. Repeat SPT/IDT after 7 day was negative to alglucosidase, avalglucosidase and cipaglucosidase indicating maintained tolerance, however subsequent standard infusion schedule was associated again with IAR. RDD schedule is continuing to be implemented.

Despite recurrent IAR, the patient continues to maintain positive treatment response across cardiac, respiratory and motor outcome domains and has low-moderate titre anti-drug IgG levels.

Conclusion: Evaluation of IARs to ERT in IOPD patients and use of novel tolerance approaches including rapid drug desensitisation can permit ongoing efficacious treatment.

Marathon training in Ornithine Transcarbamylase deficiency- how far is too far?

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Introduction: Urea Cycle Disorders carry a risk of acute decompensation due to energy expenditure/protein turnover associated with intensive exercise. The limits of safe exercise tolerance, and the magnitude of biochemical effect from breaching this, is not defined.

Methods/Case History: A 26 year old Male with Ornithine Transcarbamylase (OTC) deficiency, diagnosed and treated from infancy, underwent training for a marathon in January-February 2025. Pre-training management:

Arginine 1500mg BD, Glycerol Phenylbutyrate 4ml BD. Pre-training protein intake using 0.83g/kg bodyweight fluctuated between 55-70g yielded plasma Ammonia 40-65µmol/L, with one outlier of 113µmol/L (normal <50µmol/L). During training, plasma Ammonia and nutritional intake was monitored to observe the effect of increased distance and intensity.

Results: Protein intake at training outset - 63g/day. Plasma Ammonia (with corresponding nutritional intake) changed from 43µmol/L following a 10mile run (67g protein, 396g carbohydrate) to 138µmol/L following 18miles over 3 days (72g protein, 320g carbohydrate) to 177µmol/L following 17miles over 4 days (70g protein/day, carbohydrate unknown). Glycerol Phenylbutyrate was then increased to 5ml BD. Despite this, a plasma Ammonia of 196µmol/L occurred following an 8mile run in a single day/21miles over the preceding week (62g protein, 424g carbohydrate). Ammonia dropped to 38µmol/L following rest days and utilisation of oral emergency regimen. A joint patient-MDT decision was made to stop marathon training.

Conclusion: Endurance athlete's protein requirements are typically 1.1-1.2g/kg bodyweight – clearly at odds with safe protein limits for UCDs as defined by best practice guidelines. Protein restrictions can be difficult to maintain with increasing carbohydrate demands as endurance athletes require 6-10g/kg bodyweight. The effects of increased distance, protein intake and intensity contributed to hyperammonaemia for our patient. Further research in a controlled environment could establish safe limits of exercise and corresponding carbohydrate and protein intakes. The extent of increasing Glycerol Phenylbutyrate to support extended training could also be considered.

Never Mind the Peanuts...Lysosphingolipid biomarker C26:0-lyso-phosphatidylcholine (C26:0-LPC) overcomes false positive Very Long Chain Fatty Acids and has a favourable pre-analytical profile

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Background: Very Long Chain Fatty Acid (VLCFA) analysis has been a critical tool for the laboratory diagnosis of disorders of peroxisomal metabolism for decades. Pre-analytical (e.g. haemolysis) influences are known, as are dietary influences, most notably peanuts. The lysosphingolipid biomarker C26:0-lysophosphatidylcholine (C26:0-LPC) is employed internationally as a newborn screening tool for X-ALD; analysis is both faster and simpler than VLCFAs. C26:0-LPC has also been used effectively as part of symptomatic screening for peroxisomal disorders. Published data suggests enhanced sensitivity and specificity versus VLCFAs, hinting that pre-analytical and dietary factors are less influential for C26:0-LPC. We evaluate these factors herein.

Methods: 6 volunteers were VLCFA-loaded with whole nut peanut butter (90g). Samples were collected pre-dose and then at 3 post-dose intervals. VLCFA analysis was performed on each sample by stable-isotope dilution GC-MS. C26:0-LPC was measured in each sample by LC-MS/MS.

Of 517 unaffected control samples analysed during evaluation of C26:0-LPC in our laboratory, 94 were haemolysed and 15 lipaemic. C26:0-LPC results from visibly haemolysed or lipaemic samples were compared against those without evidence of pre-analytical changes.

Finally, C26:0-LPC was measured in plasma samples from subjects (n = 5) with deranged VLCFAs which had subsequently normalised.

Results: VLCFA levels in all 6 subjects were deranged at 3 hours post-dose. This derangement was variable, in agreement with previously published data, persisting for at least 7 hours. By contrast, there was no significant change in C26:0-LPC across samples.

Haemolysis and lipaemia demonstrated no significant effect on the level of C26:0-LPC.
Plasma with deranged VLCFAs which had normalised on repeat always demonstrated C26:0-LPC within the normal distribution of results in both initial and repeat samples.

Conclusions: C26:0-LPC is not influenced by haemolysis, lipaemia or dietary intake of VLCFAs; this likely underpins the improved clinical specificity and sensitivity of this biomarker in comparison to VLCFAs.

Hepatic outcomes in adult patients with glycogen storage disease type III (GSD 3)

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Background: Glycogen storage disease type III (GSD 3) is an inborn error of glycogen degradation caused by a deficiency of the glycogen debrancher enzyme. Many patients live well into adulthood with specialist dietary intervention, however long-term hepatic complications such as liver cirrhosis and hepatocellular carcinoma (HCC) are increasingly being recognised. We aim to describe the hepatic outcomes of our centre's GSD 3 cohort.

Methods: A retrospective analysis of clinical records was undertaken of all adult patients (alive and deceased) with GSD 3 at the Mark Holland Metabolic Unit.

Results: A total of 19 patients with GSD 3 (58% male) were identified with a median age of 33 years. The cohort had a median body mass index of 31.9kg/m2 [IQR 25.6 – 40.8kg/m2]. 47% of the cohort had a diagnosis of cirrhosis and 2 patients (11%) developed HCC. Both patients were male, aged 29 and 49 years and had Child-Pugh A cirrhosis. They were both diagnosed with early-stage HCC and managed with curative intent with surgical resection. Both subsequently died due to complications of HCC recurrence with survival times of 49 and 48 months respectively. The HCC incidence was calculated as 6.06 per 1,000 person-years at risk and 9.57 per 1,000 person-years among only those patients with cirrhosis. Uptake of fibrosis assessment locally was low at only 11%.

Conclusion: The cohort had a high lifetime risk of developing both cirrhosis and HCC. The majority of patients were overweight or obese providing a metabolic risk-factor for cirrhosis. Existing literature also implicates the progressive accumulation of abnormal glycogen in the pathogenesis of cirrhosis in GSD 3. However, despite the potential combined effects of these factors, the observed HCC incidence in cirrhotic patients with GSD 3 is similar to rates reported in metabolic dysfunction-associated steatotic liver disease (MASLD) cirrhosis (10-15 per 1,000 patient years).

Paediatric Homozygous Familial Hypercholesterolaemia: a single centre's experience

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Background: Homozygous Familial Hypercholesterolaemia (HoFH) is a rare disorder of cholesterol metabolism (1 in 250-360,000) with profound elevation of low-density lipoprotein cholesterol (LDLC) and very early atherosclerotic cardiovascular disease (ASCVD). Untreated, median age at death is 18 years. Reduction of LDLC below 2.0mmol/l can reverse atheromatous plaque formation prompting increasingly challenging

treatment target LDLC levels for children/adolescents: <3.0 mmol/l or <1.8 mmol/l if ASCVD present (European Atherosclerosis Society 2023). Patients often have negligible LDL-receptor activity limiting response to conventional agents such as statins, ezetimibe and PCSK9 inhibitors. Evinacumab, recently approved by NICE, and lipoprotein apheresis (LA) reduce LDLC independent of LDL-receptor activity. The aim of this study was to review clinical features, management and LDLC reduction achieved in our centre.

Method: Clinical notes review of HoFH patients managed at Evelina London Children's Hospital.

Results: 14 patients were identified with median follow up 4.2 years (range 0.3-14.3). At diagnosis: median age 4.2 years (range 0.1-9.3), median LDLC 21.8 mmol/l (range 16.3-28.1), xanthomata n=14, LDLR gene variants n=14, ASCVD n=9 (2 aortic valve, 5 aorta, 3 carotid). No patients had coronary artery involvement on CT angiography. Management: low saturated fat/cholesterol diet and statin in all (5 Atorvastatin, 9 Rosuvastatin), Ezetimibe n=13, Evolocumab n=1, LA n=7, Evinacumab n=8. Sequential introduction of therapies resulted in median LDLC with diet, statin +/- Ezetimibe 15.9mmol/l (range 7.8-25), reducing to 4.9mmol/l (range 3.8-6.7) with LA, and to 2.5 mmol/l (range 1.5-5.5) following Evinacumab. Median reduction on Evinacumab was 65% (range 44-73). Only patients on LA and Evinacumab achieved LDLC <3.0 mmol/l 5/8 (63%), LDLC <1.8 mmol/l 2/8 (25%).

Conclusion: Achieving target LDLC in Paediatric HoFH remains challenging, even with combination therapy, however, target LDLC is now possible with the addition of Evinacumab.

Think Ammonia: The Survey

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Background: Hyperammonaemia is a life-threatening condition associated with inherited metabolic disorders (IMDs) and requires urgent recognition and intervention. Delays in diagnosis and treatment can result in severe long-term consequences, including neurological damage and death. The "Think Ammonia!" campaign, launched by Metabolic Support UK (MSUK), aims to improve awareness, advocate for best practices, and support earlier diagnosis and treatment.

Methods: MSUK conducted an online survey to gather insights from individuals with IMDs and their caregivers regarding their experiences with hyperammonaemia diagnosis and treatment. The survey was distributed via social media, the MSUK website, and direct outreach. Questions were focused on staff awareness, testing timelines, communication, and long-term health impacts. Data was analysed by the MSUK team.

Results: The survey included 34 respondents (85% caregivers, 15% individuals with IMDs). A total of 92% reported inadequate staff awareness of hyperammonaemia signs, 62% experienced delays in ammonia level testing, and 65% reported long-term physical effects from delayed treatment, with 92% of these being neurological. Additionally, 43% didn't felt listened to by healthcare professionals, highlighting significant communication barriers.

Conclusions: These findings demonstrate critical gaps in hyperammonaemia management, reinforcing the need for improved clinician training, earlier testing, and clearer communication. The "Think Ammonia!" campaign provides healthcare professionals with essential resources to address these challenges. Implementing targeted education and awareness initiatives could improve early recognition and treatment, reducing long-term complications.

Healthcare provision and patient's outcomes in adolescents with Phenylketonuria: A UK centre experience

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Background: In any adolescent, the brain is undergoing anatomical and physiological maturation processes with changes to cognitive development. However, in adolescents with phenylketonuria (PKU), executive function and mental health is adversely affected by high blood phenylalanine (Phe) levels. We aim to describe clinical outcomes in adolescents with PKU.

Methods: Cross-sectional questionnaires were performed about quality of life (EuroQol "EQ-5D-5L" questionnaire), anxiety and depression (Hospital Anxiety and Depression Scale- HADS) and food neophobia in a single PKU centre. Retrospective data on metabolic control (previous 12 months), and current data on anthropometry, dietary treatment, medical history and comorbidities were collected. Questionnaires were self-completed by n=25/33(76%) adolescents.

Results: 33 adolescents with PKU participated with a mean age of 13.1±1.3y (16 boys,17 girls). All were on a Phe restricted diet, with 3 also prescribed sapropterin. A mean of 36±26 blood Phe spots were performed over 12 months. There was a mean of 83% blood Phe <600 µmol/L and 49% <360 µmol/L. Thirty nine percent

(n=13/33) of adolescents were overweight/obese, 18% (n=6/33) overweight and 21% (n=7/33) obese. Medical history documented mental health disorders (anxiety/depression) in 7 cases, low mood/suicidal thoughts/self-harming in 5, and neuro diversity in 3 (autism and/or attention-deficit/hyperactivity disorder (ADHD). In the HADS questionnaire, 12% (n=3/25) of adolescents scored borderline abnormal for depression. Mean anxiety scores for females were almost twice as high compared to males. No food neophobia was identified.

Conclusions: Adolescents with PKU presented with high levels of depression and anxiety. Long term studies focusing on quality of life and neurocognition even when achieving the PKU European guidelines are necessary. Different therapeutic options are needed to improve the outcome of patients with PKU.

Development of patient education/support for patients with Hereditary Fructose Intolerance (HFI) under the Addenbrooke's Metabolic Service

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Background: HFI is an autosomal recessive disorder of fructose metabolism due to aldolase B deficiency. Presentation includes hypoglycaemia, abdominal symptoms and acute liver injury after ingestion of fructose, sucrose or sorbitol. Management is strict dietary avoidance. Lower numbers of adult HFI patients are under UK metabolic services than expected given prevalence, however over recent years we have experienced increased self-referrals from older adults (>60yrs). They cite concerns about long term impacts of HFI, and anxiety around ongoing dietary challenges. Group education has been found beneficial in supporting those with rare diseases.

Methods: An electronic questionnaire was sent to our HFI patient cohort (n=15) to see whether group education/support would be of interest and what topics would be preferred.

Results: 6/15 responded suggesting scientific updates, help with recipes/diet, coping with anxiety, guidance on educating others about HFI and chance to share experiences.

We therefore planned a programme with shared experience from our oldest (87years) HFI patient, a scientific update, an anxiety management workshop from our clinical psychologist, groupwork around communicating about HFI, and launched our new HFI recipe book (developed by our dietetic team with patient input).

Attendance was excellent with 12/15 attending. Average age attendees was 68years (range 52-87). 9/12 of the attendees self-referred to our service as older adults having not had metabolic reviews since childhood. Interestingly no younger transition patients attended. Feedback indicated that all patients found the sessions useful.

Conclusions: Our increasing cohort of self-referred patients with HFI appear very engaged with their health and keen for support. There are high levels of anxiety amongst the group. MDT input including medical, nursing, dietetic and psychologist support is essential to manage the needs of this population. Two of the cohort who attended are now establishing a patient association to reflect growing support demands (www.hfisupport.org.uk).

Adult Refsum Disease: Dietary management is more than only restricting phytanic acid intake

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Background: Adult Refsum disease (ARD) is an autosomal recessive condition, resulting in phytanic acid (PA) accumulation in plasma and tissue. A PA-restricted diet is the mainstay of treatment. The importance of adequate energy and carbohydrate provision to reduce PA mobilisation from adipose tissues is highlighted in this case series.

Case report: Four patients diagnosed with ARD >10 years ago, experienced a rapid rise in circulating PA levels despite adherence to a low PA diet. A 72-year-old male lost 5kg in weight over 3 months. PA increased from 200-300µmol/L to 557µmol/L. After optimising calorie intake, PA levels reduced by 84% within 7 weeks to 91µmol/L. A 39-year-old female self-initiated a low carbohydrate diet and daily exercise resulting in 3.7kg weight loss over 3 weeks. PA increased from 340 to 1078µmol/L. Implementing regular meals and increasing carbohydrates reduced PA levels by 59% in 4 months. In a 49-year-old female with low appetite and weight loss of 4kg in five months, PA increased to 1363 µmol/L, but reduced by 54% in 5 months with initiating regular meals, adequate carbohydrates and weight regain. A 63-year-old male self-initiated a low carbohydrate diet to improve HbA1c. PA increased from 124 µmol/L to 891 µmol/L. Implementing low GI diet with adequate carbohydrates reduced PA by 47% in 4 months and improved HbA1c. All cases were managed as outpatients.

Conclusion: These cases demonstrate that an adequate energy and carbohydrate intake are important in optimising circulating PA levels and preventing metabolic crisis. Baldwin et al (2010) demonstrated that the time required for circulating PA levels to halve was 22 days with acute inpatient management and 44±16 months in the outpatient setting in patients' adherent with chronic low PA diet. This case series highlights that weight and carbohydrate management have integral roles, alongside a low PA diet, in ARD.

Does sertraline cause symptomatic non-genetic MADD?

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Background: A significant number of adult patients presenting with muscle symptoms and abnormal acylcarnitine profiles suggestive of multiple acyl-CoA dehydrogenase deficiency (MADD) do not have a genetic diagnosis in clinical practice. Emerging literature has explored a potential association between sertraline use and late-onset MADD.

Our study aimed to review clinical and laboratory findings in patients with the biochemical profile of MADD and to assess any differences between those on sertraline and those not receiving the medication.

Methods: A single-site, retrospective cohort study. We reviewed the medical records including clinical features, anti-depressant use, genetic testing and muscle biopsy findings of adult patients with biochemical MADD between 2016 and 2024.

Results: Thirty patients were identified with a mean age of 40 years (range: 18–70) and 56% were female. The most common clinical presentations were muscle pain, muscle weakness, and exercise intolerance. Three patients (10%) had a confirmatory genetic diagnosis. Seventeen patients (17/27; 63%) were on sertraline with

the mean daily dose of 140 mg (50 – 250 mg) and mean duration of 4.6 years (1 month – 10 years). Patients on sertraline had higher serum creatine kinase than those not on the drug: 120 U/L (29 – 2344) median (range) compared with 74U/L (50-206) p=0.02. Elevated plasma lactate was found in 25% of sertraline users and 18% of non-sertraline users. Amongst those who underwent muscle biopsy (n=8), 50% of patients on sertraline showed lipid aggregation, compared to 25% in the non-sertraline group.

Conclusions: Sertraline use was found in 63% of adult patients with symptomatic, non-genetic MADD. Our findings suggest that their clinical picture and muscle biopsy findings are indistinguishable compared to those cases with genetic MADD. Further work is required to determine the prevalence of non-genetic MADD in the general population and how sertraline causes impaired fatty oxidation and mitochondrial dysfunction.

Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) and sleeve gastrectomy for weight management

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Introduction: We report the first known case of a patient with attenuated VLCADD who underwent successful bariatric surgery.

Case report: The patient is a female aged 67 with attenuated VLCADD causing episodic metabolic decompensation, obesity (peak weight 140kg, BMI 47kg/m2), type 2 diabetes, hypertension, dyslipidaemia, and osteoarthritis (four previous uncomplicated orthopaedic operations). Bariatric surgery was considered after successful 10kg weight loss with diet and required collaboration between the bariatric and metabolic teams to minimise the risk of metabolic decompensation.

Special considerations: (1) sleeve gastrectomy was chosen over gastric bypass to avoid dumping syndrome if high glucose polymer was required for VLCADD emergency management; (2) 2-week pre-operative liquid 'liver shrinkage' diet provided 1100 kcal, 70g protein (compared with standard 850 kcal) to minimise the risk of decompensation from calorie deficit; (3) peri-operative management with IV 10% glucose.

The liver shrinkage diet did not cause metabolic decompensation. Surgery was uncomplicated and she was discharged home after a week with a liquid meal plan providing 1100kcal, 70g protein.

A week later she was readmitted with dehydration, high CK, acute kidney injury and not meeting calorie requirements (estimated <800 kcal/day). She was managed with a supervised calorie intake of 1000-1200 kcal, >60g protein spread over 3 meals and a snack before bed. Dietary restrictions were relaxed to allow faster progression through textures to increase variety and overcome taste fatigue. After discharge continued support at home included regular phone calls to encourage adherence to the diet plan. There was no further metabolic decompensation.

At 4 months post-surgery weight was 118kg (BMI 41kg/m2), excess weight loss 22%, which has since plateaued.

Conclusion: Successful bariatric surgery and post-operative care is possible in patients with attenuated VLCADD. Close pre- and post-operative collaboration between the bariatric and IMD teams is essential to minimise risks.

Multisystem Involvement and Hypoalbuminemia in N-linked Congenital Disorder of Glycosylation (CDG): A Case Series

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Background: This study aims to elucidate the diverse clinical spectrum of N-linked CDG, specifically exploring the implications and management of associated hypoalbuminemia.

Methods: Retrospective case study of children with confirmed diagnosis of N linked glycosylation disorders.

Results: This study analysed four children (three Caucasian, one Asian) with PMM2, ALG1, ALG3, and ALG8 CDG, presenting at a median age of 1.5 months (0-5 months). Common features included IUGR, hypotonia, feeding difficulties, and hypoalbuminemia.

PMM2 CDG was associated with seizures, behavioural issues, cerebellar hypoplasia, transaminitis, coagulopathy, genitourinary problems, pericardial effusion requiring fenestration surgery, breath-holding spells, multiple line related thrombosis and hypothyroidism.

ALG1 CDG presented with cerebellar hypoplasia, cardiac defects (multiple VSD), respiratory distress, and low protein C levels.

ALG3 CDG manifested with severe cardiac defects (Severe pulmonary stenosis with cardiomyopathy), respiratory failure, and atypical facial features.

ALG8 CDG featured cataracts, transaminitis, genitourinary abnormalities, pericardial effusion and breath-holding spells.

Abnormal transferrin glycoforms (type 1 pattern) was found in PMM2, ALG1, and ALG8. Hypoalbuminemia and elevated urine protein were universal. ALG8-CDG showed elevated D-dimer.

Severe hypoalbuminemia, despite albumin transfusions was a common finding, proved challenging. Endothelial leak, not solely proteinuria or protein losing enteropathy or hepatic dysfunction, was implicated. D-dimer, protein levels, and protein C emerged as potential biomarkers; Endothelial barrier support therapy (EBST) is being explored.

Two children (PMM2 and ALG8) survived, while two (ALG1 and ALG3) died in the neonatal period.

Conclusion: This case series illustrates the wide spectrum of clinical presentations and substantial multisystem involvement in children with N-linked CDG subtypes. The management of hypoalbuminemia poses a significant challenge, particularly during acute illness. While endothelial barrier support therapy shows promise, further research is imperative to validate its efficacy and establish optimal treatment protocols.

Late-onset argininosuccinic aciduria unmasked by sodium valproate

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Background: Argininosuccinic aciduria (ASA) is a urea cycle disorder caused by argininosuccinate lyase (ASL) deficiency. Classically, ASA presents with neonatal hyperammonaemia, lethargy, poor feeding, vomiting and encephalopathy. Late-onset presentations can be milder although neurocognitive disturbance, seizures and encephalopathy are described. Despite increasing awareness of adverse effects, sodium valproate (VPA) remains widely used to treat epilepsy, psychiatric disorders and migraine, and is known to cause hyperammonaemia.

Methods: A 20-year old male presented with generalised tonic-clonic seizures preceded by a viral illness. Post-ictal recovery was poor, remaining encephalopathic despite weaning of sedation. Background included idiopathic generalised epilepsy, diagnosed age 18, managed with levetiracetam and VPA. Age 2 years, investigations for developmental delay were normal.

Results: Brain MRI upon presentation was unremarkable. EEG demonstrated diffuse delta slowing out of proportion to sedation. VPA was increased to a daily dose of 1800 mg. Plasma ammonia was 652 µmol/L, with a urea cycle disorder suspected. Repeat MRI brain showed restricted diffusion in frontal/temporal/parietal cortices without significant oedema. VPA and protein intake were stopped, commencing haemodialysis, nitrogen scavengers, intravenous glucose and arginine, resulting in rapid normalisation of ammonia. Amino acids and organic acid analysis revealed elevated glutamine, citrulline, and argininosuccinic acid, with low arginine and elevated urinary orotate. Pathogenic variants were detected in ASL gene, confirming the diagnosis of ASA. Gradual improvement followed over subsequent weeks, with occasional breakthrough seizures and residual cognitive impairment.

Conclusions: We present a case of late-onset ASA unmasked by VPA therapy for epilepsy, highlighting apparent normal development until crisis presentation. Seizures may persist despite normalisation of hyperammonaemia, due to the underlying pathophysiology of ASA and the role of ASL in nitric oxide homeostasis. Given the ease of measurement, checking plasma ammonia in patients exposed to VPA, may detect otherwise undiagnosed urea cycle disorders, offering an opportunity for intervention.

Adjusting Dietary Therapy using Continuous Glucose Monitoring and Proposed Glycaemic Targets in Glycogen Storage Disease Type Ia: A Case Study

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Background: Overnight hyperglycaemia was noted in our Glycogen Storage Disease Type Ia (GSDIa) adult case study and our aim was to improve this using dietary modification and evaluating continuous glucose monitoring (CGM) data. Management of GSDIa aims to maintain euglycaemia through dietary treatment and a prospective study in GSDIa provides guidance on using and interpreting CGM data; suggesting glycaemic targets for CGM-derived outcomes (Rossi et al., 2022).

Methods: Baseline 10-day CGM data were collected from our case to evaluate current dietary management efficacy for overnight feeding and subsequent changes, such as the addition of fibre and/or protein to their overnight glucose polymer feed; repeating the 10-day CGM after a wash-in period of two weeks. CGM data were analysed using Rossi et al.'s (2022) guidance and compared to evaluate the effect of the dietary management changes.

Results: When compared to standard overnight (01:00 – 05:00) treatment (25% glucose polymer, providing 0.18 g carbohydrate/Kg/hr) the addition of 22 g protein and 12 g soluble fibre demonstrated: a reduction in mean (from 7.9 to 6.6 mmol/L), median (from 7.5 to 6.6 mmol/L) and range (from 3.8 – 11.4 to 3.4 – 10.0 mmol/L) of glucose; a reduction in "time-above-range" (>10.0 mmol/L [from 8% to <1%], an increase in "time-in-range" (≥3.9 and ≤10.0 mmol/L [from 92% to 98%]), and "time-under-range" (Level 1 hypoglycaemia: ≥3.0 and <3.9 mmol/L [from 0.2% to 1.5%]); there was no Level 2 hypoglycaemia (<3.0 mmol/L) observed. All results were within Rossi et al.'s (2022) suggested reference ranges.

Conclusion: The addition of protein and fibre to overnight feeding reduced overnight hyperglycaemia. The use of Rossi et al.'s (2022) guidance and suggested glycaemic targets for continuous glucose monitoring in glycogen storage disease Ia provide objective analyses to allow effective comparison of dietary interventions. The suggested reference glycaemic targets warrant critical discussion.

Insights into aging among adults affected with Inherited Metabolic Diseases-one tertiary centre experience

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Introduction: Inherited metabolic diseases (IMDs) are commonly thought of as diseases of childhood and much of the care orientated towards children and young adults. As diagnosis and treatment of IMDs improves, there is an increasing cohort of older people with IMDs who may have two or more long-term conditions (multi-morbidity) and/or frailty. Here we present the data from one adult centre on the prevalence of IMDs in a cohort of patients aged 50 and over.

Methods: A retrospective review was completed of electronic clinical records of adult IMD patients, who were 50 and above years old. Extracted data included: date of birth, sex and metabolic condition, age at diagnosis and frailty associated data.

Results: Over 40% of patients with lysosomal storage diseases and 16% of patients with general metabolic diseases were aged 50 and over. 1 in 10 patients was diagnosed with late onset/attenuated form of an IMD. Most patients were diagnosed with an IMD in childhood and developed long-term complications related to their underlying condition. Their increased risk of frailty was associated with progressive neurocognitive decline and/or decline in mobility (20.6% of LSDs and 31.8% of general metabolic IMDs required physiotherapy input in the last 3 years).

Conclusions: The aging population of patients with IMDs has increased over the last decade. Increased life expectancy is accompanied by increases in age-related and IMD-related complications. The pathomechanisms of aging in IMDs are not well understood and warrant further research.

This also highlights the urgent need for service development and new models of care to meet the needs of older people with IMD, who may have multi-morbidity and/or frailty, as well as frailty related syndromes such as cognitive impairment and falls. This population also provides insights into the evolving natural history of IMDs with improvements in early diagnosis and available treatments.

Navigating Eliglustat Drug-Drug Interactions Through a Pharmacist-Led MDT Approach

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Background: Eliglustat is used in the treatment of Gaucher Disease. At supratherapeutic plasma concentrations, eliglustat is predicted to prolong the QT interval on an electrocardiogram (ECG), potentially leading to dangerous arrhythmias. It is metabolised by cytochrome P450 enzymes CYP2D6 and CYP3A4, but CYP2D6 activity varies considerably necessitating genotyping. When neither enzyme is available due to drug-drug interactions (DDI) or poor metaboliser status, eliglustat can accumulate, risking QT interval prolongation. At our centre, a pharmacist-led multi-disciplinary team meeting (MDT) reviews DDIs and assesses the risk of QT interval prolongation; we reviewed this process.

Methods: We reviewed all patients prescribed eliglustat, excluding those without both baseline and on-treatment ECGs. DDI reviews, MDT interventions and ECGs were analysed retrospectively from electronic patient records. QT intervals were corrected using the Fridericia formula (QTcF). Significant QTcF prolongation was defined as >480ms or a change of >60ms from baseline.

Results: In total 38 patients were included; 81 MDT referrals took place and 256 potential DDIs assessed. No patients experienced significantly prolonged QTcF, and the mean change in QTcF from baseline was -0.1±18.1ms. Seventeen patients (44.7%) required MDT intervention to safely initiate eliglustat. One patient developed heart block on eliglustat without QTcF prolongation.

Conclusions: These findings highlight the effectiveness of our pharmacist-led MDT model in preventing dangerous DDIs with eliglustat and maintaining therapeutic drug concentrations, reducing the risk of QT interval prolongation. Our results align with prior data confirming that eliglustat does not prolong the QT interval at therapeutic concentrations. This review underscores the pharmacist's role in optimising medication safety. The patient who developed heart block had eliglustat withdrawn, but the condition persisted. A pacemaker

was implanted several years later, and no evidence suggested eliglustat contributed. Centres prescribing eliglustat or other drugs requiring CYP enzyme genotyping could adapt this model to enhance patient safety.

Shaping Phenylketonuria research through patient and public involvement

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Background: Patient and Public Involvement and Engagement (PPIE) is essential in research to ensure studies address priorities meaningful to affected communities. This study describes PPIE activities that informed doctoral research on sapropterin treatment for phenylketonuria (PKU) in England.

Methods: A comprehensive PPIE strategy was implemented between September 2022 and November 2024. Initial engagement began at the National Society for PKU conference in 2022, followed by an online questionnaire developed with PKU experts, including healthcare professionals, patient representatives, and caregivers. The questionnaire explored views about the proposed research design and implementation, and was distributed through patient and professional associations, networks, and social media. Responses were analysed using descriptive statistics and qualitative analysis.

Results: Sixty-one responses were received: 20 (33%) from people with PKU, 24 (39%) from family members/caregivers, and 17 (28%) from healthcare professionals. Key themes identified included treatment experience variability, psychological impact of sapropterin response testing and dietary changes, healthcare system variations, and research priorities. Twenty participants volunteered as PPIE advisors. Findings led to research design modifications, including: ensuring diverse representation of treatment experiences, developing multiple data collection methods to improve accessibility, integrating psychological support considerations, implementing strategies to reach underserved populations, and establishing clear feedback mechanisms.

Conclusion: This PPIE work represents an important milestone in engaging those affected by PKU in research design and development. The study has shaped PKU research by capturing crucial insights about sapropterin treatment experiences and identifying potential barriers to research participation for this rare disease community. The strong response demonstrates the PKU community's commitment to research involvement and the importance of their perspective in developing patient-centred research. The findings provide a valuable model for meaningful community engagement in rare disease research.

A prolonged release compared to an amino acid protein substitute in classical PKU effect on morning phenylalanine and tyrosine concentrations

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Background: Physiomimic technology applied to L-amino acids (PM-AA) impacts their absorption slowing down their gastrointestinal release, providing a more physiological effect. No work has been completed on PM-AA compared to F-AAs in patients with phenylketonuria (PKU).

Aim: To compare the effect of PM-AA v F-AA on blood phenylalanine (Phe), tyrosine (Tyr) concentrations after an overnight fast in children with classical PKU.

Methodology: A randomised non blinded 2 arm controlled cross over study was carried out over 28 days. Patients were randomised to receive either PM-AA or F-AAs as their last protein substitute of the day for 7 days. On the last two days of each study arm days 6 and 7 and 27 and 28 blood spots were collected at 5, 6 and 7 am measuring Phe /Tyr. Each arm was separated by a 14-day washout period.

Results: A total of n=13 out of 16 children completed the study, mean age 11.8 y (range 7-15). There was a statistically significant difference in morning Phe concentrations in the PM-AA compared to the F-AA group when compared to baseline: PM-AA; -17.8% (p-0.048) compared to F-AAs; +27.6% (p=0.006). For Tyr there was a statistically significant increase in the PM-AA compared to baseline +33.8% (p=0.0008) while no change was noted for the F-AA. Comparing Phe and Tyr at the end of each treatment arm after completing PM-AA or F-AA a statistically significant difference was observed for Phe and Tyr, being lower after taking PM-AA v F-AA , Phe µmol/L (330.3 v 389.6) p= 0.0002 and higher for Tyr µmol/L PM-AA v F-AA (54.1 v 48.2) p-0.011.

Conclusion: A physiomimic protein substitute given as the final substitute of the day significantly lowers blood morning Phe and increases Tyr, demonstrating improved metabolic control reducing overnight catabolism and likely muscle breakdown compared to the F-AA group.

Attention to Sapropterin Administration: Can it Bring Clinical Advantage?

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Background: In patients with mild or moderate PKU, sapropterin dihydrochloride therapy may lower blood Phe and enhance Phe tolerance. Attention to its administration, particularly the timing, giving with food (with appropriate macronutrient composition) is important.

Methods: We describe two boys with PKU who demonstrate the clinical impact of adjusting sapropterin administration.

Case 1, a 7y boy with mild PKU had a 40%reduction in blood Phe when given a 30-day trial with sapropterin (20mg/kg/day). He was treated with sapropterin (20mg/kg) once daily dissolved in water with breakfast. Protein tolerance increased from 26g to 50g/day, and protein equivalent reduced to 20g/day. Median blood Phe was 230µmol/L (range:130-300). After six months, the same dose was administered twice daily (breakfast and evening meal), but remained dissolved in water. Natural protein tolerance increased to 60g/day, with a median blood Phe of 130µmol/l (range:80-220). By 8y, he swallowed the sapropterin tablets whole, twice-daily with meals. He ate an unrestricted protein intake (estimated 80g/day) and the protein substitute was stopped. Median blood Phe was lowered to 100µmol/L (range:80-150).

Case 2, a 4.9y boy with mild PKU had a 33%reduction in blood Phe when given a 30-day trial with sapropterin (20mg/kg/day). He was then treated with sapropterin (20mg/kg) once daily dissolved in water with breakfast. Protein tolerance increased from 14g to 55g/day and protein equivalent reduced to 20g/day. Median blood Phe was 240µmol/L (range:120-320). At 6.9y, he changed to twice-daily sapropterin (breakfast and evening meal), and it was swallowed whole with food. Median blood Phe lowered to 130µmol/L (range:100-130), and he no longer followed protein restriction or takes protein substitute.

Conclusion: These case study showed clinical and dietary benefit when sapropterin administration was changed. It is unclear if advantage was gained from twicedaily administration, attention to meal time composition or taking the tablets intact. Further research is necessary.

Familial Hypercholesteremia in the Northwest of England: is it diagnosed too late?

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Background: Familial hypercholesterolaemia (FH), an inherited dyslipidaemia disorder, affects 1 in 250 people in the UK (UK). For people aged 20-39, FH represents a 100-fold risk of cardiovascular death. Untreated, the chances of suffering a myocardial infarction are 50% for men by age 50 and 30% for women by age 60. Evidence suggests early diagnosis and treatment of FH in childhood effectively mitigates the risk of death.

There is no national FH screening programme in the UK, despite evidence that this would be highly cost-effective. Diagnosis depends on routine NHS health checks and cascade testing following a cardiac event in an index patient.

Aim: To report age and sex of people referred for genetic testing in the Northwest of England

Methods: Retrospective evaluation of genetic testing data from the Northwest of England between 2018 and 2023.

Results: 2959 people (64% female), median age 53 years (range 1-88) were tested, of whom 95% were adults (≥16 years). The median age at testing for paediatric patients was 11 years, and 54 for adults, and was higher in females than males [57 years (range16-87) versus 48 (range16-88), p=<0.001].

Conclusion: The data analysis is limited by using age at testing as a proxy, as genetics testing may take place much later than the actual date of diagnosis. However, using age at testing as a proxy for the age of diagnosis, the data shows that on average, FH diagnosis in the Northwest occurs very late, leaving patients untreated and at higher risk of cardiovascular disease and death. Despite males being at greater risk of cardiac events, they were tested much less than females.

These data indicate that reliance on NHS health checks and cascade testing delays diagnosis, strengthening the case for a national screening programme in childhood or young adult life.

Review of Patients Diagnosed with Biotin Thiamine Responsive Basal Ganglia disease in our centre

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Background: Case series of patients who were diagnosed with Biotin-Thiamine response Basal Ganglia disease (BTRBGD) in our centre (2020-2025). The aim of the review was to assess the age of onset of symptoms in patients, when our team were called for advice, time of commencement of medications and outcomes of patients.

Methods: Review of patient's hospital electronic notes for clinical information, MRI images and examination details.

Results: Five patients were referred to our service who were subsequently diagnosed with BTRBGD over the 5-year period. Four patients presented to their local hospital between the ages of 3 weeks and 2 years old. For the 4 patients that presented clinically, it was at least the second presentation for all patients that prompted investigations and referral to our team. One patient was a prospectively treated known sibling. All symptomatic patients had high lactate, poor feeding, and abnormal neurology at times of referral.

All symptomatic presenting children were treated with high dose Thiamine (40mg/kg/day) and Biotin (5-10mg/kg/day) based on clinical symptoms and MRI findings. Patients spent 12-72hours in their local hospital before our team were called for metabolic opinion. Genetic confirmation for all patients was returned, but no treatment was held for any patient awaiting genetic confirmation.

All symptomatic patients showed improvement within days of starting treatment, and none have had any future acute metabolic decompensations since commencement of vitamin supplementation.

All patients who presented clinically continue to have neurological symptoms and developmental delay. The prospectively treated patients has normal development for age and is thriving.

Conclusion: BTRBG disease is a treatable cause of Leigh syndrome. The initiation of treatment in symptomatic patients leads to metabolic stability, but a variety of neurodevelopmental issues remain for these patients. Patients who were started on treatment after a period of acute decompensation continue to have neurological deficits.

Nutritional management of a successful multifetal PKU Pregnancy

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Background: International evidence and guidelines for nutritional requirements in multifetal pregnancies are limited and not well described within the IMD community. We present the nutritional management of a twin pregnancy in PKU.

Methods/Case history: A 35-year-old woman living with classical PKU (non-responder to Sapropterin and genetic diagnosis of 2 null variants: c.912+1G>A, c.1315+1G>A) underwent a dichorionic diamnotic pregnancy in 2024. This was preceded 18 months prior by a singleton pregnancy ending in stillbirth at 34+5/40 (presumed due to intrahepatic cholestasis of pregnancy [IHCP] - total bile acids peak = 222µmol/L [normal <10 µmol/L]).

IHCP carries 70-90% risk of recurrence, higher for multifetal pregnancy and influenced timing of delivery for this pregnancy. Psychology input facilitated patient compliance. Gestational nutritional goals: avoidance of maternal PKU syndrome, optimal growth of both foetuses, optimal weight gain for mother with pre-conception BMI>30kg/m2, mitigation of IHCP risk.

Nutritional management followed international guidelines utilising data from foetal growth scanning, nutritional biochemistry, dietary assessment and maternal anthropometry.

Results: Both twins delivered successfully by c-section at 33+6/40. Maternal mean (±Standard deviation) bloodspot phenylalanine during 1st, 2nd, and 3rd trimester: 268±85µmol/L,170±65µmol/L and 181±27µmol/L respectively (target 120 - 250µmol/L). Maternal TBA peak = 16µmol/L. Total protein intake

1.05-1.65g/kg/day (synthetic amino acids >=75% protein intake) using pre-gestation weight. Maternal weight change by delivery was +20.5kg.

Both twins required NICU admission but without specific organ support/prolonged enteral feeding, both "not suspected" on day 5 newborn screening sample for PKU.

Post-partum, maternal bloodspot phenylalanine increased 10-fold reflecting uterine involution and collagen resorption (peak bloodspot phenylalanine = 1452µmol/L).

Conclusion: Supporting this individual required intensified dietetic input, with support from a multi-professional team, including specialist maternal medicine colleagues. Our case highlights one of the first published cases of a successful multifetal pregnancy for an individual living with PKU.

MADDening Results Secondary to Sertraline

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Background: Multiple acyl CoA dehydrogenase deficiency (MADD) is a clinically heterogenous disorder which may present in adulthood, typically in the riboflavin-responsive form caused by mutations in the ETFDH gene.

Biochemically, MADD is characterised by a pattern of elevated medium and long chain acylcarnitines. There is a growing awareness of secondary factors causing a "MADD-like" pattern of acylcarnitine results, including nutritional deficiencies and certain medications such as sertraline, a commonly prescribed selective serotonin reuptake inhibitor (SSRI).

We report a case of 23-year old male identical twins under evaluation for a possible metabolic condition, which has so far eluded genetic characterisation. They shared a very similar clinical course and ate a balanced diet. Only one brother had been prescribed sertraline (for clinical purposes).

Methods: Plasma acylcarnitine analysis was performed in both brothers on the same day. In addition, we reviewed the records of other patients reviewed in our service with "MADD-like" acylcarnitines, and a literature review was undertaken of other cases linking "MADD-like" acylcarnitines and sertraline use.

Results: Brother 1 (not on sertraline): no abnormalities on acylcarnitine profile.

Brother 2 (on sertraline): Free carnitine 31 umol/L [15-53]; C6 0.17 umol/L [<0.12]; C8 0.78 umol/L [<0.22]; C10 1.44 umol/L [<0.30]; C5-DC 0.11 umol/L [<0.10]; C12 0.25 umol/L [<0.10]; C14:1 0.20 umol/L [<0.18]. For both brothers, a urine organic acid profile was normal.

Analysis and interpretation performed by Sheffield Children's colleagues (for which many thanks).

8 papers (case reports, case series and poster abstracts) were found describing gene negative riboflavin-responsive MADD in patients on sertraline. Sertraline has been linked with a lipid-storage myopathy, and decreased activity of ETF proteins.

Conclusion: Sertraline is increasingly being recognised to cause an acylcarnitine profile which may mimic MADD. Further research should focus on outcomes in such patients and what therapies - such as riboflavin supplementation- may be beneficial.

Post-baseline outcomes of the UK Early Access to Medicines Scheme registry for cipaglucosidase alfa plus miglustat in late-onset Pompe disease

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Background: Late-onset Pompe disease (LOPD) is a rare disorder characterised by progressive loss of muscle and respiratory function due to acid α-glucosidase deficiency. Cipaglucosidase alfa plus miglustat (cipa+mig), a two-component therapy, was accepted into the UK Early Access to Medicines Scheme (EAMS; 50636/0001) in 2021, providing patients early access to an innovative LOPD therapy pending marketing authorisation. A prospective observational registry under the EAMS evaluated the real-world safety and effectiveness of cipa+mig in adults with LOPD who had ≥2 years of enzyme replacement therapy (ERT) experience.

Methods: Data from standard-of-care clinical monitoring assessments were extracted from patient medical records where available; no additional measures were mandated.

Results: Of 45 patients who received cipa+mig under the EAMS, 36 consented to registry participation. For patients with available data, baseline (BL) median (range) 6-minute walk distance (6MWD; n=19) was 260.0 m (10.0–630.0); sitting % predicted forced vital capacity (FVC; n=22) was 61.5% (15.3–100.5); Fatigue Severity Score (FSS; n=15) was 53.0 (36.0–63.0). For patients with available data, post-BL visit 1 median (range) 6MWD (n=15) was 397.0 m (63.0–656.0); sitting % predicted FVC (n=16) was 60.0% (15.0–90.0); FSS (n=13) was 46.0 (14.0–63.0). For patients with available BL and post-BL data, time between BL and post-BL visit 1 varied from 82 to 1401 days. Shielding during the COVID-19 pandemic limited clinical assessments. Pre-EAMS, 20 patients had falls and three had infusion-associated reactions with previous ERT.

Conclusion: This is the first real-world description of an adult cohort selected by their clinician for change of therapy to cipaglucosidase alfa plus miglustat. Limited available data and variable times between baseline and post-baseline assessments made statistical analyses and conclusions challenging. This highlights the need to improve monitoring frequency and consistency for patients with late-onset Pompe disease. Supported by Amicus Therapeutics, Inc.

5,10-Methenyltetrahydrofolate synthetase deficiency (MTHFS deficiency): expanding the clinical and biochemical phenotype

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Background: 5,10-methenyltetrahydrofolate synthetase (MTHFS) deficiency is an ultra-rare folate metabolism disorder with only eleven cases previously reported. It is characterised by microcephaly, developmental delay, seizures, feeding difficulties and short stature. MRI brain typically shows hypomyelination. Biochemistry is variable with low or low-normal 5-methyltetrahydrofolate (5-MTHF) in serum and/or CSF and normal or elevated homocysteine levels in plasma. Treatment success with 5-MTHF is variable.

Case report: We present a new case of MTHFS deficiency with a milder phenotype. This 12 year old female presented with developmental delay at 4-6 months with lack of head control. She walked supported from 4 years, and independently from 7 with a broad-based gait and truncal hypotonia. She has microcephaly, but no seizures and continues with slow developmental progress. MRI brain at 3 and 11 years showed delayed myelination. CT head showed calcification in the bilateral pallido-nigral tract, described in cerebral folate deficiency. CSF 5-MTHF was low normal 63 mmol/L (46-160), whilst taking folinic acid. Serum folate, total homocysteine, plasma amino acids, urine organic acids and lactate were normal. Whole genome sequencing showed compound heterozygous variants of uncertain significance in MTHFS gene with biparental inheritance. We compared CSF 5-formyltetrahydrofolate (5-FTHF) in our patient and control patients taking folinic acid. Her CSF 5-FTHF levels were 4 times higher and 5MTHF:5FTHF ratio 10 times lower. Cultured skin fibroblasts showed reduced activity of 5,10 MTHFS consistent with MTHFS deficiency. Treatment was changed to calcium mefolinate.

Discussion: MTHFS deficiency is an ultra-rare disorder which presents with varying degrees of severity and variability in diagnostic biomarkers. Our case demonstrates a mild phenotype whereby genetics supported by low MTHFS activity in fibroblasts confirmed diagnosis. Although not routinely measured, CSF 5-FTHF may be a useful diagnostic biomarker in this condition. Further research of this compound should be undertaken and results interpreted with caution.

Miglustat: a first-in-class enzyme stabiliser for late-onset Pompe disease

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Background: In late-onset Pompe disease (LOPD), deficiency of acid α-glucosidase (GAA) causes progressive loss of muscle and respiratory function. Cipaglucosidase alfa (cipa) is a recombinant human GAA (rhGAA) enriched with natural bis-mannose-6-phosphate to improve uptake into muscle. A key challenge with rhGAA therapy is inactivation at the near-neutral pH of blood. To address this challenge, intravenous cipa is delivered

as a two-component therapy with oral miglustat (mig), an enzyme stabiliser that competitively and reversibly binds to cipa in blood. We present preclinical and clinical data to further clarify the efficacy and safety benefits of two-component therapy with cipa+mig in patients with LOPD.

Methods: In dose-finding studies with Gaa knockout mice, muscle glycogen levels and grip strength were evaluated for cipa (20mg/kg) with and without mig (10mg/kg; equivalent human dose 260mg).

Results: Glycogen reduction in quadriceps muscle was greater for cipa+mig than cipa alone. Grip strength improved at a greater rate for cipa+mig than cipa alone and approached levels not statistically different from wild-type mice after 5 months of treatment. In human patients with LOPD (n=11), mig (260mg) increased cipa area under the curve in plasma by 28.5% versus cipa (20mg/kg) alone. Patients treated with cipa alone showed dose-dependent decreases in urine hexose tetrasaccharide levels (surrogate glycogen storage marker) by up to ~15% from baseline that decreased by a further ~10% when mig (260mg) was added. In a head-to-head study, cipa+mig had a similar safety profile to alglucosidase alfa. Of 151 patients treated with cipa+mig in three clinical trials, 21 (13.9%) had 68 adverse events related to mig only, none of which were serious.

Conclusions: Stabilisation of cipaglucosidase alfa by miglustat in the circulation improved cipaglucosidase alfa exposure, further reduced hexose tetrasaccharide levels, and was well tolerated in clinical studies in patients with late-onset Pompe disease. Supported by Amicus Therapeutics, Inc.

True Faces of Rare: Preferences for authentic imagery in disorder-specific materials by people living with rare diseases and their communities

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Background: Rare disease awareness and educational materials often feature stock images of individuals who may or may not have the condition in question. While these visuals aim to be inclusive, they may feel generic and fail to resonate with people living with rare diseases. Given the potential role of visual representation in fostering connection and understanding, this study assessed the importance that people living with rare diseases place on seeing authentic images in disorder-specific materials.

Methods: A two-question digital survey was conducted from September 17 to October 15, 2024, via Microsoft Office Forms. The survey included a Likert scale question (1 = not important, 10 = very important) measuring the importance of authentic imagery in disorder-specific materials and an open-ended question exploring the reasons behind respondents' ratings. The survey was disseminated by Metabolic Support UK and the Ectodermal Dysplasia Society. Data were analysed using Microsoft Excel.

Results: The survey (n = 50) revealed a strong preference for authentic imagery, with an average importance rating of 8.2/10. The majority (80%) rated the importance between 8 and 10, indicating a strong desire for genuine representation. Key qualitative themes included:

- Authenticity and connection: Respondents valued real images for enhancing relatability and reducing isolation.
- Raising awareness and normalising appearances: Authentic visuals helped educate the public and healthcare professionals, increasing awareness and acceptance.
- Concerns of stereotyping: While many valued authenticity, some cautioned against visuals that might create misleading or fixed impressions of rare diseases.

Conclusions: People living with rare diseases highly value authentic imagery in disorder-specific materials, associating it with greater emotional support, increased awareness, and enhanced engagement. However,

diversity in representation is crucial to avoid reinforcing stereotypes. These findings highlight the need for patient-centred approaches in developing rare disease educational materials, ensuring that visuals foster connection while accurately reflecting diverse experiences.

Distinctive phenotype associated with Mitochondrial ATAD3 gene cluster duplication: a case series

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Background: Phenotypical presentation with corneal clouding, hydrops foetalis and multi-system involvement raises a diagnostic suspicion of lysosomal storage disorder [LSD]. We report a case series of three neonates who presented with these features along with profound lactic acidosis and multi-organ failure leading to death. ATAD3 gene cluster duplication was confirmed in all three cases.

Methods: A retrospective review of case notes of patients under our care confirmed to have mitochondrial ATAD3 gene cluster duplication.

Results: 3 neonates [2 males and 1 female] known to our service since 2019, from unrelated pedigrees, were identified to have ATAD3 gene cluster duplication. All neonates presented soon after birth with encephalopathy and seizures and had burst suppression on CFAM [cerebral function analysing monitor]. All three had hydrops, cloudy corneas, no organomegaly, severe biventricular cardiomyopathy and methylglutaconic aciduria. They had multiorgan failure needing ventilatory, inotropic support and renal replacement therapy. Sodium bicarbonate infusion and enteral sodium dichloroacetate were trialled for profound lactic acidosis in all three neonates, with no response. White cell enzyme analysis in them for possible lysosomal storage disorder was normal. Reorientation of care given the refractory multiorgan failure led to death within the first week of life, in all three neonates.

Trio rapid genome sequencing in neonates 1&2 and nuclear mitochondrial gene panel sequencing in neonate 3, identified a de novo heterozygous pathogenic duplication involving the mitochondrial ATAD3 gene cluster. This resulted in perturbed mitochondrial biogenesis and cholesterol metabolism explaining the unique phenotype combining that of an LSD and a mitochondrial disorder.

Conclusion: Our experience highlights the importance of considering a genetic diagnosis of ATAD3 gene cluster duplication when faced with a phenotypical presentation which makes one suspect LSD as well as a mitochondrial disorder.

Decompensating Inherited Metabolic Disorders and the Oral Emergency Regimen. The Adult Patient Experience in Bristol

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Background: The Emergency Regimen (ER) is a key treatment for decompensating or intoxication type Inherited Metabolic Disorders (IMDs). Patients attending our IMD clinic will have been given verbal and written information on their ER, and supply organised. Following recent acute admissions, it became apparent that enhanced patient education is indicated. The adult IMD caseload who need ER includes patients with learning difficulties, and ageing patients accessing clinical interventions requiring starvation. This survey aims to inform

future patient education and thus reduce admissions and improve clinical outcomes by exploring adult ER use including during work and travel.

Methods: A questionnaire was emailed to all relevant patients consisting of twelve questions, eight of which were multiple choice and four being free text. A dietetic assistant external to the IMD team, helped patients access the survey to ensure representative and diverse responses e.g. those with visual impairments.

Interim results: All respondents so far know the name of their ER product and said they had stock at home, but there was variability in stock availability away from the home/during travel. Results show that unwell patients do not commence the ER soon enough and do not take enough of the product for long enough. There was also uncertainty on what their ER consisted of and how to manage running out of product

Conclusion: Written and verbal information may be insufficient in ER education. Accessible and engaging information in various formats could lead to improved ER use. Frequent reminders are required on the importance of the ER product, with content to include the quantity and frequency of product required.

Elevation of branched chain amino acids due to Branched Chain Amino Acid Transferase 2 deficiency (BCAT2): to treat or not to treat?

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Introduction: BCAT2 is a vitamin B6-dependent enzyme involved in the first step of the catabolic pathway of BCAA. BCAT2 deficiency causes a recognisable biochemical profile with raised BCAA and undetectable alloisoleucine. The clinical phenotype is variable from asymptomatic patients to those with autistic features and developmental delay. Treatment options include dietary BCAA restriction and/or pyridoxine supplementation which can improve the biochemical profile.

Methods: We performed a retrospective review of the genetic, clinical and biochemical features in five previously unreported patients with mutations in BCAT2 gene. Four patients were identified through Newborn Screening and one following investigations for early developmental delay and features of leukodystrophy. Genetic results in 4/5 patients revealed compound heterozygous missense variant in one patient and homozygous nonsense mutation in BCAT2 gene in three patients.

Biochemical testing at diagnosis confirmed elevated BCAA in all patients with undetectable alloisoleucine in two cases. Pyridoxine was commenced in three patients and BCAA restricted diet was adopted in two of them, and combined treatment in one. BCAA levels measured on a weekly-monthly basis. Treatment with B6 and or diet achieved a reduction without normalisation of BCAA levels. Alloisoleucine levels became detectable in patients started on B6 in two patients.

Neurological profile demonstrated significant diversity, ranging from normal neurodevelopment in three patients to speech delay and behavioral disorders in two. MRI scans in latter ones revealed white matter abnormalities on T2-weighted images. None of these patients experienced encephalopathic crises despite elevated BCAA.

Discussion: BCAT2 deficiency is an ultra-rare condition in which further research and understanding is required to determine human pathogenicity. Our case expands the clinical and biochemical phenotype of this disease demonstrating its potentially mild presentation despite significant elevation in BCAA. Prompt intervention with diet/pyridoxine may improve the biochemical profile however further studies are required to determine clinical effects in these patients

Difficulties in diagnosing mild peroxisomal biogenesis disorders – a case example

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Background: This patient was 31 years old when she received a diagnosis of a peroxisomal biogenesis disorder (PBD) from Whole Genome Sequencing (WGS).

Past history included developmental delay and progressive, multi-systemic complications throughout childhood including sensorineural hearing loss, and in later years amelogenesis imperfecta, optic atrophy, retinitis pigmentosa.

Routine metabolic investigations were undertaken at 14 years-of-age which were essentially unremarkable, including normal phytanate and pristanate (however no evidence that straight chain VLCFAs were measured).

Methods & Results: WGS revealed homozygous pathogenic variants in PEX1 (c.2528G>A p), associated with a mild PBD with similar presentations in the literature.

VLCFAs were analysed in view of the genetic findings. C26 was marginally increased at 1.58 µmol/L (ref. < 1.5) with borderline C26/C22 ratio (0.029 ref. < 0.030) and slightly raised C24/C22 ratio (1.09 ref. < 0.97). Phytanate and pristanate were again normal. Fortunately, clinical details including the genetics were provided to aid interpretation, and these subtle biochemical findings were deemed consistent with a milder PBD and reported as such. Bile acids and pipecolate testing were added to further characterise the biochemical phenotype. Pipecolate was significantly raised (40.6 µmol/L - ref. < 2.46). Bile acids analysis did not show the abnormal intermediates that relate to PBDs, however absence of these was not inconsistent to the diagnosis, given our own experience and literature evidence that show these are not always detected in milder PBDs.

Conclusion: This case illustrates the importance of testing the full peroxisomal biochemical repertoire in patients with a progressive history of multisystemic issues, as well as the power of WGS in identifying mild PBDs that are more difficult to diagnose biochemically. We expect further mild/attenuated cases to be identified in the future as WGS panels are more widely requested. These are providing greater insights into the phenotypic and biochemical variability of PBDs.

KS-462-282: An alternative Krabbe Disease biomarker with excellent diagnostic potential

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Background: Biomarkers for Krabbe Disease have the potential to improve efficiency of clinical and laboratory pathways for the diagnosis of this rare disease of sphingolipid metabolism, whilst improving the patient experience. Having also demonstrated great potential of the biomarker galactosyl-sphingosine (psychosine) when employed as a second-tier test following a broader lysosomal enzyme screen, we examined the potential of an alternative biomarker of unknown identity. This species has been previously described anecdotally as undergoing the same MRM mass transition (462>282) as total hexosyl (galactosyl+glucosyl)-sphingosine in LC-MS/MS lyso-sphingolipid analysis; crucially it is chromatographically resolved under simple reversed-phase conditions.

Methods: KS 462-282 was measured in Krabbe Disease positive patient samples (early infantile (n=11), late infantile (n=28), juvenile (n=6), adult (n=2), pseudodeficiency (n=27)) and unaffected controls (n=285). Sample preparation consisted of simple protein precipitation. Subsequent analysis was performed by UPLC-MS/MS; calibration with the surrogate reference material glucosyl-sphingosine was facilitated by the stable isotope internal standard D5-glucosylsphingosine.

Results: Initial results from this relatively large cohort show equivalent clinical sensitivity (100%) to that of psychosine. Clinical specificity of KS-462-282 (98.5%) is also very good, but marginally inferior to psychosine (99.5%). These performance indicators are impressive, considering this is a semi-quantitation of an unknown species. This biomarker successfully differentiated paediatric Krabbe disease from unaffected patients and those with a pseudodeficiency. Adult-onset patients were not reliably differentiated. Additionally, the relative degree of increase in the presence of this species showed a significant correlation with severity of disease phenotype.

Conclusion: We propose that structural characterisation of this biomarker (KS-462-282) and synthesis of authentic reference materials and stable isotope internal standards could prove transformative to the use of biomarkers in diagnostic pathways for Krabbe Disease; largely through simplification of the analytical process.

Evaluating Reference Intervals for Galactose-1-Phosphate Uridyl Transferase: Integrating Biochemical and Genetic Data

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Background: Classic galactosaemia is a life-threatening disease which occurs due to an inborn error of galactose metabolism. Determination of galactose-1-phosphate uridyl transferase (GALT) activity is integral to early diagnosis, and recommended in the GalNet Guideline (Welling et al. 2017). The Synnovis Biochemical Genetics laboratory is a key referral centre for GALT testing, utilising a fluorometric enzymatic method developed in-house, based on the Beutler methodology (Beutler and Baluda 1966). Our GALT reports include a reference interval (RI) derived using unaffected patients (n=495), and a heterozygote RI derived using confirmed carriers of the pathogenic GALT variant (n=14).

There was a need to review in-use RIs, and to establish a cut-off for galactosaemia rule-in, to improve the quality of GALT reports. Periodic review of in-use RIs is also necessary to comply with the ISO 15189:2022 standard. Additionally, comparing GALT activities across a broader range of heterozygote genotypes, would further refine GALT reporting.

Methods: A RI was calculated directly from unaffected patient (n=774) GALT activities sourced from the LIMS (GeneWorks) by the nonparametric method, as recommended in CLSI EP28-A3. GALT activities in patients (n=86) who received genetic follow-up testing (Sanger sequencing in-house, or obtained from external genetic reports) were also compared.

Results: The unaffected RI was 20.0 – 45.1 µmol/hr/g Hb (90% confidence-interval 19.3–20.7 and 43.7–45.9). Within the population of individuals who received follow-up genetic analysis, the assay demonstrated highest Youden's index (0.953) for classic galactosaemia at 3.0 µmol/hr/g Hb (positive-predictive value = 98%, negative-predictive value = 98%). Box-plot analysis demonstrated significant variations in GALT activity between numerous variant types, including pathogenic GALT carriers and Duarte variants.

Conclusions: Utilising individuals who had undergone follow-up genetic testing, enabled us to better define expected GALT activities in homozygote and heterozygote populations, improving reporting where sample sizes were otherwise insufficient for CLSI-compliant RI generation.

The Efficacy of Liquid Valine and Isoleucine Supplements in MSUD

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Background: In maple syrup urine disease (MSUD), dietary treatment consists of natural protein restriction, limiting intake of leucine (Leu), valine (Val), and isoleucine (Ile), together with branched chain amino acid (BCAA)-free formula to support anabolism. Additional Val and Ile supplements are commonly required to promote anabolism, accelerating blood Leu reduction and preventing Val and Ile deficiency. Existing Val and Ile supplements are powders requiring reconstitution with water (or are mixed with other powders) and contain carbohydrate. The aim was to evaluate the acceptability of ready to use (RTU) Val (50mg/ml) and Ile (25mg/ml) oral solutions in the dietary management of MSUD.

Methods: A prospective, open-label acceptability study in 4 children with MSUD aged 3 to 14 years conducted over 56 days (28 days on valine, 28 days on isoleucine). Data was collected by questionnaires on: gastro-intestinal tolerance, acceptability, tolerance, ease of use and adherence with liquid Val and Iso supplements. Weekly blood Val, Ile, and Leu levels were conducted.

Results: The liquid Val start dose was a mean of 163 mg/day (range 150-200), and Ile 225 mg/day (range 150-300). At the study end, overall dose of liquid supplements decreased by 37% for Val (median dose, 133 mg/day, range 50-140) and 23% for Ile (median dose, 175 mg/day, range 150-300) compared with powdered supplements. Blood Leu (mean 226 µmol/L, range 88-442) was well controlled. The natural protein and protein equivalent intake from protein substitute was unchanged. All patients reported better palatability, overall acceptability, ease of use and good gastro-intestinal tolerance with the RTU liquid supplements.

Conclusion: The RTU, liquid Val and Ile supplements required minimal dietetic calculation. For patients, they were convenient, easy to administer, palatable, well tolerated, lessened burden, and overall had improved adherence.

Elevated 4-methylsterol and 4,4-dimethylsterol in microcephaly, congenital cataract and psoriasiform dermatitis syndrome due to methylsterol monooxygenase 1 (MSMO1) deficiency provides diagnostic and treatment response biomarker

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Background: MSMO1 encodes methylsterol monooxygenase 1 which demethylates 4,4-dimethylsterols to 4-methyl,4-carboxy-sterols and 4-methyl sterols to zymosterone in the cholesterol biosynthesis pathway. Deficiency of MSMO1 is associated with a syndrome of microcephaly, congenital cataract, and psoriasiform dermatitis, with pathogenesis due to effects of the elevated methyl- and dimethylsterols and deficiency of cholesterol products. Targeted systemic and topical therapy with hydroxymethylglutaryl-CoA reductase

inhibition and cholesterol replacement may be effective. There is a need for a disease-specific biomarker to support diagnosis and treatment evaluation.

Methods: An 11-year-old girl had progressive treatment-refractory psoriasiform dermatitis from 6 months of age, with subsequent developmental delay and learning difficulties, and bilateral cataracts noted at 3 years requiring lensectomy. Molecular genetic testing identified biallelic likely pathogenic MSMO1 variants; RNA studies suggested exon-skipping for one of the variants. Cholesterol (4.3mmol/L), very long chain fatty acids and liver function tests were normal. Plasma sterols were analysed by GC-MS following hydrolysis of sterol esters.

Results: Plasma sterol analysis identified a peak at 42.9 minutes on a SIM chromatogram for m/z 472 present in the patient but not in the control consistent with 4alpha-methyl-5alpha(H)-cholest-8(9)-en-3 beta-ol TMS ether or 4alpha-methyl-5alpha(H)-cholest-7(8)-en-3 beta-ol TMS ether, and a peak at 44.7 minutes for m/z 484 present in the patient but not in the control consistent with 4,4'-dimethyl-cholesta-8(9),24-cholestadien-3beta-ol, thus providing evidence of elevated 4-methylsterols and 4,4-dimethylsterols as a disease-specific biomarker.

Therapy with simvastatin to inhibit upstream hydroxymethylglutaryl-CoA reductase and thereby decrease accumulation of these metabolites, together with downstream cholesterol supplementation, provided by combined oral and topical routes, has been initiated.

Conclusion: Successful identification of elevated plasma 4-methylsterol and 4,4-dimethylsterol in the patient provided biochemical confirmation of diagnosis, supporting the MSMO1 molecular genetic findings. Serial measurement of the methyl- and dimethylsterols will be assessed to review impact of therapy in conjunction with serial clinical and dermatological outcome measures.

Evaluation of neurodevelopmental outcome after haematopoietic stem cell transplant (HSCT) in a patient with Triosephosphate isomerase deficiency (TPI-D)

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Background: TPI-D is a rare glycolytic defect associated with haemolytic anaemia, cardiomyopathy, neuro-regression, increased infection susceptibility and death in early childhood. Neuro-regression has a significant impact on function and quality of life. There is a paucity of robust developmental outcome measures reported in TPI-D. There are no standard disease-modifying therapies; HSCT is a novel therapy although without published neurodevelopmental outcomes.

Method: A standardised developmental assessment (ASQ®-3) was completed in a TPI-D patient (E105D homozygous) on ketogenic diet who underwent HSCT. This tool provides data regarding communication, gross and fine motor, problem solving and personal/ social aspects of development and compares this to age-matched norms. The assessment was completed every 3-4 months from age 4-18 months encompassing HSCT treatment period (age 4-6 months). A gross motor tracking tool (Alberta Infant Motor Score) compared sitting skills against documented cases of E105D TPI-D not treated with HSCT.

Results: Significant progression was demonstrated in communication, fine motor, problem solving and social skills. Scores were 1-16 points above the threshold for typical development at 9 months and 4-17 points above at 18 months. Progress also continues with gross motor skills however, slower than age typical. There was a positive divergence between skills observed in this patient and available untreated cases who scored a

maximum of 1/12 for sitting skills, achieving sitting with support, whereas our post-HSCT patient scored 12/12 progressing to independent sitting and transitions into crawling.

Conclusion: Developmental surveillance and use of relevant outcome measures is a useful tool in measuring the effectiveness of novel therapies such as HSCT in rare disorders. The patient continues to make progress compared to reported cases who demonstrate skill plateau/ regression. Ongoing review is essential to continue to track progress and to offer insights into the potential impact of novel therapies on neurodevelopment in this disorder.

An unusual case of argininosuccinic aciduria highlighting the challenges and importance of identification of argininosuccinic acid in amino acid analysis

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Background: A 17-month-old male was referred to general paediatrics for poor weight gain and growth. Samples for plasma and urine amino acids and urine organic acids were sent to the Metabolic laboratory at UHS.

Methods: Amino acid analysis was undertaken by IEC Chromatography (Biochrom 30+). Organic acid analysis was undertaken by GCMS.

Results: Plasma amino acids were unremarkable except an increased plasma citrulline (60 µmol/L, RR 6-34 µmol/L). Urine amino acids demonstrated an apparent very large increase in isoleucine. Given plasma isoleucine was normal, this was concluded to be argininosuccinic acid (ASA). No clear peaks of ASA or ASA anhydrides were noted in plasma. Urine organic acids were normal with no orotic acid detected. Plasma ammonia was normal. A diagnosis of argininosuccinic aciduria (ASA lyase deficiency) was suspected and the patient was referred to the Paediatric Metabolic team in Bristol.

Plasma amino acids at UHBW showed a normal plasma citrulline 38 µmol/L (RR 10-51 µmol/L) with a small clear ASA and small broad possible ASA anhydride peaks. Urine amino acids demonstrated prominent ASA and ASA anhydride peaks. No significant orotic acid was detected on organic acids and this was confirmed quantitatively (1.8 µmol/mmol, ref. <3.5).

Conclusion: Argininosuccinic aciduria can be diagnostically challenging as key pathognomonic metabolites can co-elute in IEC amino acid methods. ASA is unstable and readily converts to ASA anhydrides in vitro. In this case the ASA anhydrides were less clear in plasma than in urine. A recent review of our analytical performance at identifying ASA in EQA samples prompted a reoptimisation of our amino acid analytical programme and procedures for monitoring performance for identifying ASA consistently. We have since introduced a monthly performance check (ASA QC) to ensure our method is reliable for ASA detection.
Genetic confirmation of ASA lyase deficiency in this case is awaited.

FollowME Fabry Pathfinders registry: patient-reported outcomes in a cohort of patients on migalastat treatment for median 4 years

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Background: The observational followME Fabry Pathfinders registry (EUPAS20599) is evaluating real-world safety, incidence of Fabry-associated clinical events (FACEs), effectiveness and patient-reported outcomes (PROs) for patients with Fabry disease (FD) enrolled in one of three groups: migalastat-amenable GLA variants receiving migalastat, any GLA variant receiving enzyme replacement therapy, and migalastat-amenable GLA variants not receiving FD-specific treatment. We aimed to prospectively analyse PROs to better understand the perspective of patients being treated with migalastat.

Methods: Included patients had been treated with migalastat for ≥2 years, enrolled in the electronic (e)PRO platform, and had two or more ePRO measurements over ≥2 years. ePROs collected were the Brief Pain Inventory (BPI), FABry disease PRO-GastroIntestinal (FABPRO-GI) and Treatment Satisfaction Questionnaire for Medication-9 (TSQM). Outcomes were investigated in the overall population and the subgroup of patients who initiated migalastat within 30 days of completing the first ePRO assessment (representing a true baseline).

Results: The overall population included 86 patients, and the true baseline subgroup included 25 patients. In the overall population and the true baseline subgroup, respectively, median (interquartile range) duration of migalastat treatment from first ePRO assessment was 4.0 (3.4, 4.3) years and 3.8 (3.5, 4.3) years, median age at enrolment was 54 and 51 years, and 46.5% and 68.0% of patients were female. BPI scores for pain and pain interference remained low and stable in the overall population and true baseline subgroup over 36 months of follow-up. Types and frequency of bowel movements according to the FABPRO-GI also remained generally stable over 36 months in the overall population and true baseline subgroup. TSQM effectiveness and global satisfaction scores for the true baseline subgroup increased over 24 months, while convenience remained high and stable.

Conclusions: In this real-world registry, patients had stable levels of pain and gastrointestinal symptoms and high levels of treatment satisfaction.

Retrospective Analysis of Vitamin B12 Dose Optimization in Methylmalonic acidaemias and Cobalamin Deficiency-Related Disorders: Insights from a Tertiary Metabolic Centre in the UK

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Background: Methylmalonic acidemias (MMA) encompass disorders of methylmalonate and cobalamin (vitamin B12) metabolism, manifesting as isolated MMA or combined MMA and homocystinuria (MMA-Hcy). Some forms are responsive to vitamin B12, and parenteral hydroxocobalamin is a mainstay of treatment, but dosing recommendations vary.

Aims and Methods: A single-centre retrospective review of patients with MMA and MMA-Hcy disorders treated with hydroxocobalamin was undertaken aiming to document current dosing practice and evaluate the impact of higher vitamin B12 schedules on plasma MMA, homocysteine and methionine, and urinary MMA levels.

Results: 31 patients were included: 16 with MMA (including MMA Mut type) and 14 with other cobalamin-related disorders.

Hydroxocobalamin total weekly doses ranged from 0-20mg/week, with 19.4% receiving 5-10mg/week. Dosing patterns varied included 1mg daily, 1mg three/week, up to 10mg once/week.
The mean plasma MMA concentration was 75.7 µmol/L, significantly higher than the normal range (0.00-0.28 µmol/L). Plasma and urinary MMA levels were analysed based on dose variations, revealing that higher doses of vitamin B12 (e.g., 10 mg/week, 20 mg/week) were associated with lower MMA levels.

Conclusions: The analysis suggests that higher doses of vitamin B12 up to 20mg/week improved the plasma and urinary MMA concentrations in MMA and MMA-Hcy disorders. Further analysis of the clinical impact (frequency of decompensations, growth, and development) is planned.

Keywords: Methylmalonic acidemia, Vitamin B12, Plasma methylmalonic acid, Urinary methylmalonic acid.

Continuous Glucose Monitoring in the GSD cohort of Addenbrooke's Metabolic Service

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Background: CGM is increasingly recognized as a monitoring modality for hepatic GSD patients. It has been shown that CGM can uncover nocturnal hypoglycaemia and can uncover glycaemic variation in individual hepatic GSD patients. There is good concordance between CGM and glucose self-monitoring.

We aimed to summarise CGM data from our GSD cohort and gather information of time in range (TIR), time above range (TAR) and time below range (TBR) as well as hypoglycaemia unawareness. We also present case studies for three individual patients.

Methods: Retrospective data pooling of CGM traces and clinical information gathering from patient's clinical notes. Statistical figures of blood glucose levels were gathered from either Libre View or Dexcom depending on the patient's sensor. We analysed each patient's information separately to highlight any unique opportunities for tailored treatment but also as a cohort for all of the GSD cohort.

Results: 46% of our patient cohort (6/13) have trialed a CGM. 4/6 remain on CGM as funding has been obtained for exceptional circumstances. Data analysis for the whole cohort showed good accordance to finger prick testing. Summarized TAR for the whole GSD cohort was 8.8%, TBR was 25% and TIR was 86%. Three of the patients have hypoglycaemia unawareness. We have additionally summarized three individual cases of the patients in more detail, including information on their CGM funding and their dietetic management.

Conclusions: Half of our glycogen storage disease patients on continuous glucose monitoring had hypoglycaemia unawareness meaning that they are reliant on these devices as an early warning system for impending hypoglycaemia. In addition it proves a useful tool for education on blood glucose level fluctuations and dietary adjustments. Continuous glucose monitoring gives an opportunity for personalized dietetic treatment of this patient cohort.

Barriers and facilitators to clinical trial participation: improving accessibility, logistics, and awareness

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Background: Fabry disease is a rare, life-limiting genetic disorder. Current treatments include Fabry-specific therapies and symptom management. However, further advancements depend on clinical trial participation. The low prevalence and dispersed nature of rare disease populations make participation difficult, with patients facing logistical hurdles such as long-distance travel.

Methods: During the MPS Society's 2024 Fabry Matters Conference (UK), insights were gathered from Fabry patients and caregivers attending the event. Fifty-one respondents completed a survey. Descriptive statistics and the Behavioural Change Wheel were used to analyse responses.

Results: Responses were provided by 36 female and 15 male patients with a median age of 51.1 years (mean 49.7±13.6, range 14.1–72.3). Of the 51 respondents, 65% (n=33) were unaware of clinical trials taking place, most did not know where to find information (88%, n=29), 9% (n=3) were not interested in trials and 3% (n=1) were awaiting diagnosis confirmation. Among those who had participated in trials (n=19), key factors in improving their experience were, regular trial updates (74%, n=14), flexible schedules (47%, n=9), and emotional or financial support (26%, n=5). When asked what would encourage patients to take part in clinical trials, 84% (n=43) hoped for better management of their condition. However, concerns about side effects (84%, n=43) and travel demands (63%, n=32) were the most common barriers to participation. Seventy-five percent (n=38) of patients were more inclined to participate if travel arrangements were provided.

Based on the results from the behaviour change analysis, several interventions are suggested to improve participation rates, including clear educational materials on side effects, remote or nearby trial locations, reframing travel as an investment in health and offering logistical and emotional support.

Conclusions: Implementing these strategies can help patient organisations, pharmaceutical companies and clinical trial logistics vendors encourage participation in trials for patients with Fabry and other rare diseases.

Primary and secondary multiple acyl-coA dehydrogenase deficiency (MADD): clinical insights and treatment response

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Introduction: Multiple acyl-CoA dehydrogenase deficiency (MADD) is an autosomal recessive disorder caused by mutations in ETFA, ETFB, or ETFDH. The riboflavin-responsive subtype (rrMADD) is typically linked to ETFDH mutations, though some patients show biochemical abnormalities without classical clinical features or pathogenic variants, suggesting a acquired or secondary form possibly influenced by medications (e.g. sertraline) or nutritional deficiencies. We aimed to review our cases of MADD-like biochemical profiles to identify potential secondary cases.

Methods: A retrospective analysis of 13 adult patients with acylcarnitine profile consistent with MADD was conducted. Patients were classified as primary rrMADD (ETFDH mutations) or secondary MADD (no confirmed genetic cause, with possible contributory factors). Clinical, biochemical, genetic data, and riboflavin response were analysed.

Results: Three patients were diagnosed with primary rrMADD (ETFDH mutations), while 10 lacked mutations, or other classical features. Plasma acylcarnitine levels were significantly elevated in primary rrMADD cases in comparison to secondary (C6, C8, C10 and C12). Riboflavin supplementation resulted in both symptomatic and biochemical improvement in all primary cases, but only 10% of secondary cases. Secondary MADD patients exhibited intermittent biochemical abnormalities (80%), with 70% showing micronutrient deficiencies and 80% using sertraline, of whom 50% had both risk factors. Muscle biopsy was performed in 50% of secondary MADD cases, with only one showing lipid storage myopathy (LSM). Fibroblast studies were performed in 20% of secondary cases (all normal).

Conclusion: A riboflavin trial may aid diagnosis while awaiting genetic testing or muscle biopsy in a patient presenting with myopathy, acylcarnitine profile and organic acid findings consistent with MADD. Non-responders and those with negative genetic findings should undergo medication and nutritional review to correct potentially secondary causes.

Limitations: This study is observational, limiting the ability to infer causality. The associations between secondary MADD, medication use, and micronutrient deficiencies require further investigation to elucidate mechanism.

Role of tele monitoring in rare disease management

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Background: The European Guidelines for the Management of Phenylketonuria (PKU) recommend monthly PKUF blood monitoring. This allows phenylalanine levels to be tracked, dietary adjustments made and promotes self-management.

Audit of the Northern Ireland (NI) adult PKU cohort, against guidelines, showed 9% of patients achieved these recommendations, with 53% of patients sending no PKUF cards.

A Quality Improvement (QI) project was designed to identify barriers to testing and seek patient involvement in improving engagement.

Patient, Public Involvement (PPI) identified that remembering to send a PKUF card was the biggest barrier to uptake (83%). 89% felt a text reminder service would help.

Florence (FLO), a text reminder service was implemented as a QI initiative with the aim of increased engagement with testing.

Method: FLO was offered to all patients with PKU, within the service, initially for 6 months with option to continue on completion. Patient satisfaction was captured via questionnaire.

Re-audit was then undertaken, analysing 12 months of data, with the aim of identifying differences between those patients availing of FLO and those who did not. Audit focused on frequency of PKUF testing; phenylalanine levels and testing issues. Patient demographics were also collated.

Results: Results showed 41% of the clinic population availed of FLO. Average card frequency was improved, 3.46 (non-FLO) to 5.13 (FLO). FLO supported attainment of improved control (levels <600umol) compared to non-FLO, 64% v's 36% respectively. Card issues were significantly decreased with FLO.

Patient satisfaction showed 100% found FLO useful, easy to use and would recommend.

Conclusion: FLO was positively received by patients and not only increased engagement with testing and card frequency but also supported reduction in card issues and improved blood Phenylalanine control.

A text reminder service is a useful patient engagement tool and has potential for expansion into other areas of adult metabolic services.

Phenylketonuria (PKU) - A Transition Model for Rare Disease

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Background: Phenylketonuria (PKU) is a rare inherited metabolic disorder, where specialised diet is the corner stone of treatment. Patients remain under the care of the specialist multidisciplinary team (MDT) for life.

Baseline audit showed high rates of disengagement at transition stage: 65% of patients did not attend (DNA) their first adult appointment; 46% DNA all subsequent appointments (>80% were female). A patient survey showed elevated rates of anxiety around transition.

The project aim was to develop and implement a service user led, patient centred transition process seeking to improve engagement with adult IMD services.

Methods: In collaboration with the paediatric MDT, and patients, a new model for transition was developed. Commencing at 16 years, this model focused on identified patient priorities including developing relationships with the adult IMD team, practical dietary education and peer interaction. Dedicated transition clinics were initiated, comprising a combination of individual appointments and group education based on structured patient curriculums. Curriculums were bespoke for the group, authored and delivered by the adult MDT.

Outcomes were captured through recorded attendance; evaluation forms and knowledge questionnaires.

Results: High attendance seen at dedicated group education sessions and individual appointments (80-100% in first cohort). Patient questionnaires illustrated improved knowledge, which was maintained at 18 months.

Evaluation forms provided positive feedback. Patients actively participated in group sessions, looked forward to returning and noted positive impact of peer interaction.

Conclusion: This model is improving engagement with adult services and empowering through knowledge, which will promote self-care among patients at transition stage.

Anxiety around transition is evident. This project has reduced this through education and development of relationships with the adult team.

Within the regional metabolic service in Northern Ireland, the phenylketonuria transition model is being adapted for other metabolic disorders such as galactosaemia. Pathways for rarer conditions are under development.

Glycogen Storage Disease type 3 & Ketogenic Diet Therapy – Case Report

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Background: Glycogen storage disease type 3 (GSD 3) is an inborn error of metabolism caused by a deficiency of the glycogen debranching enzyme. Complications of the condition include recurrent hypoglycaemia, faltering growth, liver adenomas, myopathy, cardiomyopathy, and osteoporosis.

The aim of dietary treatment is to ensure euglycemia, achieve normal growth, improve muscle strength, and prevent cardiomyopathy. Standard dietary management is to provide a regular source of carbohydrate (food, uncooked cornstarch, enteral tube feed), and high protein (2-3g of protein per kilogram of bodyweight). There is emerging evidence that the ketogenic diet therapy (KDT) in conjunction with oral ketone supplementation is an effective option in the management of GSD 3a.

Clinical case: An eight-year-old girl, with GSD 3a, on standard dietary management presented with worsening hypertrophic cardiomyopathy. It was decided to trial D,L-3-hydroxybutyrate, KDT and high-protein diet. The MCT KDT was used as it would allow the diet to contain more carbohydrate and protein.

Monitoring targets for glucose levels were set between 4-7mmol/L and ketone levels between 1-2mmol/L. Dietary management targets: 20% carbohydrate, 60% fat (45%MCT/15%LCT) and 20% protein (3-4g/kg/d). D,L-3-hydroxybutyrate was introduced in a stepwise fashion with electrolyte and plasma 3-OH-butyrate monitoring 3months after the dietary change.

Results: After 9months on the new treatment; BMI improved from 21.5kg/m2 (98th centile) to 19.5kg/m2 (75th-91st centile), creatine kinase reduced from 1630U/L to 660U/L and improvements in energy level and exercise tolerance were reported. This has corresponded to improvement of her cardiomyopathy (data will be available for poster presentation).
Conclusion: The patient had severe progressive cardiomyopathy on standard dietetic (high protein, uncooked cornstarch) and pharmacological (beta-blocker) management. With the new diet we report improvement in growth parameters, clinical status, and cardiomyopathy with the corresponding biochemical and echocardiographic findings.

Disorder or distraction: Considering the significance of an ACADSB gene variant in a young person with developmental delay

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Introduction: Short/branched-chain acyl-CoA dehydrogenase (SBCAD) deficiency is a rare inborn error of metabolism due to mutations in the ACADSB gene. Diagnostic biomarkers include C5-Carnitine elevation and increased urinary excretion of 2-methylbutyrylglycine (2MBG). There is uncertainty about the clinical relevance of this diagnosis.

Case presentation: A 5-year-old boy, born to consanguineous parents, underwent genetic testing for developmental delay, autism, two café au lait spots, and periventricular white matter hyperdensities. He had previously reported homozygous c.443C>T variants in the ACADSB gene and follow-up biochemistry revealed mildly elevated C5-carnitine on blood spot and increased 2MBG in the urine.

The proband had two brothers and a sister. Both boys had EHCPs but were in mainstream education; his sister is fit and well. His parents were heterozygous for the familial variant with one brother confirmed as a carrier (sister untested); all three siblings had no 2MBG in the urine.

Discussion: A literature review reveals a mixed picture in patients with ACADSB gene variants. 13 ‘symptomatic’ patients have been described presenting between 3 days to 6 years of age with seizures, developmental delay, hypotonia, and failure to thrive. Management includes carnitine supplementation, an emergency plan, and protein restriction in some instances. One affected individual had an asymptomatic sibling with the same gene change. Over 100 asymptomatic patients have been reported after detection on newborn screening with the majority receiving no treatment.

Conclusion: Given the concerns raised about the proband’s brothers and the other aspects of his phenotype, this challenges the significance of an ACADSB gene variant in this young person. The expanding availability of whole genome analysis for developmental delay will likely lead to an increased pressure on metabolic services and genetic departments to unravel these ambiguous cases.

How good is blood Phe control in Maternal PKU in Europe: results from 102 pregnancies

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Background: In phenylketonuria (PKU), high blood phenylalanine (Phe) levels during pregnancy negatively influences foetal organogenesis and growth leading to maternal PKU syndrome. Pregnancies must be carefully planned, in order to control blood Phe levels ≤ 360 µmol/L pre-conception and throughout pregnancy. Our aim was to study metabolic control in PKU pregnancies throughout Europe.

Methods: 11 centres managing PKU participated. Data was collected retrospectively between 2012-2018 from dietetic records from pregnancies on blood Phe (µmol/L), natural protein (NP) intake (g/day), protein substitute (PS) intake (g/day) and maternal weight (kg).

Results: 84 female patients with PKU with a total of 102 pregnancies (mean age:30.4±4.8y) participated. 7 were hyperphenylalaninemia (HPA), 25 mild PKU, 56 classical PKU and 14 were unclassified. Sapropterin was prescribed in 2 pregnancies. Only 27% (8/102) of patients successfully achieved consistent blood phe levels ≤360µmol/L at least 2 weeks pre-conception. During pregnancy, 88% of blood Phe levels were ≤360µmol/L, with a mean Phe of 229±65. The mean number of blood Phe samples was 60 (1.5 per week) per pregnancy.

In general pre-pregnancy, 35% of blood Phe levels were ≤360µmol/L. 61% and 43% were <600µmol/L pre/post pregnancy with mean blood Phe 462±226 and 724±230 respectively. 25% (25/102) had no levels performed post-pregnancy (>2.8y) compared to 7% (7/102) pre-pregnancy (>2.9y).

Mean prescribed Phe intake pre/during/post pregnancy was 810±720 vs. 787±551 vs. 1110±722mg. NP intake was 17±15 vs. 17±11 vs. 23±15 g/day. Protein equivalent from PS was 57±21 vs. 66±16 vs. 50±23 g/day and total protein 73±14 vs. 83±14 vs. 73±18 g/day (1.1±0.3 vs. 1.1±0.4 vs. 1.0±0.4 g/kg)

Conclusions: Although a high level of metabolic control is maintained during pregnancy, <30% achieved consistent levels of ≤360µmol/L prior to conception with minimal monitoring post pregnancy. The long-term impact on the offspring needs intensive study.

Are Cystatin-C measurements useful for the surveillance of chronic kidney disease in Paediatric MMA patients?

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Background: Chronic kidney disease (CKD) is a well-known complication of Methylmalonic Acidaemia (MMA) and can lead to renal replacement therapy and renal transplantation. In our centre annual surveillance for CKD is undertaken in MMA patients from the age of 2 years involving isotopic glomerular filtration rate (iGRF) measurements. Cystatin C is a small protein produced by all nucleated cells and an important biomarker of kidney function. It is freely filtered by the glomeruli and almost entirely reabsorbed by renal tubular cells making it a useful indicator of GFR. It can be measured in a single blood test and levels are unaffected by age and muscle mass. The aim of this study is to determine if Cystatin C measurements can be used to screen for CKD in MMA patients.

Methods: Prospective collection of paired iGFR and cystatin C measurements in MMA patients at GOSH from December 2021-March 2025. A cut off GFR <60ml/m2/1.73m2 is used to consider referral to Nephrology for monitoring and management. Cystatin C >1mg/L is considered abnormal.

Results: Fifteen patients underwent routine annual surveillance with paired iGFR and cystatin C measurements. A total of 22 paired measurements were obtained. All GFR <60ml/m2/1.73m2 were detected with a cystatin C of >1mg/L with a sensitivity of 100%, but a specificity of 33%. All GFR <60ml/m2/1.73m2 are detected with a cystatin C >2mg/L with a sensitivity and specificity of 100%.

Conclusion: A cystatin C >2mg/L in MMA patients may indicate a GFR <60ml/m2/1.73m2, prompting appropriate and timely referral to Nephrology. Cystatin C measurements have a high sensitivity but variable specificity; cystatin C >1mg/L may not always reflect an abnormal GFR. This study was limited by the small numbers in this cohort and further studies should be undertaken to determine the usefulness of measuring cystatin C in MMA patients.

Managing the untreatable - the broader role of rapid whole genome sequencing in neurological regression

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Background: Rapid agnostic Whole Genome Sequencing (WGS) has traditionally been used in the paediatric and neonatal intensive care setting when suspecting a likely monogenic diagnosis. However, in cases of neurological regression, it is available to patients requiring ward level care or potentially those in the community.

Method/Results: Here we report the case of an infant for whom developmental delay became regression and agnostic WGS was completed. This process identified an ultra-rare cause for our patient's presentation (homozygous mutations in SLC25A46 - a gene known to be associated with Leigh syndrome presentations), which sadly is not treatable. However, by sharing information from existing literature and other case reports, we were able to take the family through both the cause of their child's problems and help inform shared decision making regarding the prognosis and direction of care. Additionally, we present a summary of information known to date regarding the spectrum of phenotypes associated with changes in SLC25A46.

Conclusion: Whilst always hoping to find a treatable cause, this case highlights the wider benefits of rapid agnostic WGS - being able to share a diagnosis with family and the positive effect this can have on understanding, clinician-family relationships and advanced care planning. By sharing this case, we hope to improve awareness not only of this particular genetic phenotype, but also of the importance of rapid genetic testing even where no treatable diagnosis can be established and the benefits for families in these circumstances.

Optimising Ketogenic Therapy in Multiple Acyl-CoA Dehydrogenase Deficiency: A Case Report

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Background: Multiple acyl-CoA dehydrogenase deficiency (MADD) is a rare autosomal recessive metabolic disorder affecting fatty acid β-oxidation. Management focuses on avoiding prolonged fasting and following a low-fat, low-protein, high-carbohydrate diet. Exogenous ketone bodies have been explored as an alternative energy source for patients with fatty acid oxidation disorders.

Case Report: We describe a 24-year-old male diagnosed with neonatal-onset MADD from Qatar initially following a low-fat vegetarian diet. At age 14 he suffered a cardiac arrest, resulting in significant neuro-disability and requirement of an implantable cardioverter-defibrillator. Following transfer of care to London, he was managed with Nutri-Align-BHB salts and butane-1,3-diol liquid in addition to riboflavin, levocarnitine, coenzyme Q10 and walnut oil. Due to an international shortage of Nutri-Align-BHB salts, he was electively admitted for cardiac and electrolyte monitoring while transitioning to NHS101 and up-titration of butane-1,3-diol. Capillary ketone levels were monitored at multiple time points throughout the day (upon waking, pre-dose, 1, 2, and 3 hours post-dose and at bedtime) to assess response.

Pre-admission daily ketone intake was 38g (0.466g/kg) and capillary ketones remained between <0.1 to 0.2mmol/L for approximately 19/24 hours on the initial regime. The high calcium and sodium load of NHS101 led to higher butane-1,3-diol doses to meet ketone requirements. This combination increased daily ketones to 73.2g (0.897g/kg) and demonstrated a favourable ketogenic response. Capillary ketones stabilised at 0.3 to 0.7mmol/L for 16/24 hours with the greatest responses occurring later after 18:00hrs. Notably, ALT levels improved from 176 to 81U/L by discharge. His cardiac and renal function remained stable.

Conclusion: This case demonstrates that NHS101 and butane-1,3-diol can effectively enhance ketosis in a MADD patient without compromising metabolic stability. Further studies are needed to optimise dosing strategies and assess long-term safety in this patient population.

Optimising Peripheral Intravenous Catheter Insertion and Management in Out-of-Hospital Settings: Addressing Patient and Technical Factors, Enhancing Nurse Competency, and Promoting Evidence-Based Practices for Improved Outcomes

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Background: Peripheral intravenous catheter (PIVC) insertion is a critical component of patient care in out-of-hospital settings, with its use becoming routine for a wide array of therapies. However, repeated failed attempts at catheter insertion are both a source of patient distress and a contributing factor to suboptimal clinical and economic outcomes.

Method: This study examines the challenges associated with PIVC placement in out of hospital settings, specifically within Lloyds Clinical, where a diverse group of patients receives intravenous therapies, including lysosomal storage disorders, oncology medications, antibiotics, and treatments for rare disorders. This retrospective observational study was conducted over a 17-month period, from July 2023 to November 2024 and analysed 16,872 nursing visits, identifying cases of sub optimal PIVC insertion and exploring the causes behind these instances.

Results: Of these 16,872 visits, there were 140 instances where the first-attempt success rate for PIVC placement was not achieved. This indicates that, in these cases (0.81%), the nurse was unable to successfully place the PIVC on the first attempt. While the overall first-stick success rate remains high, these incidents provide valuable insight into potential areas for improvement in patient education, insertion technique or nurse training and highlights the importance of continuing education and support to ensure the best possible outcomes for our patients.

Conclusion: Findings suggest that patient-related anatomical and physiological factors, such as vein visibility and previous medical interventions, account for the majority of failed insertions. The review of current literature further emphasises the importance of addressing variability in nursing practices, enhancing educational frameworks, and adopting evidence-based guidelines to optimize PIVC insertion and management. Additionally, the study suggests strategies such as patient education, localised warming techniques, and targeted nurse retraining to improve

Discrepant urine biochemistry in a paediatric patient with Alkaptonuria

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Alkaptonuria is a rare inborn error of phenylalanine metabolism that typically presents in adulthood with ochronotic pigmentation of skin, osteoarthropathy and urine that darkens upon standing. The clinical features are caused by accumulation of homogentisic acid (HGA) within the blood and urine, which forms a dark melanin-like pigment when oxidised or alkalinised. The presence of this pigment within biological fluid is known to cause interference in various biochemical assays, as described herein.

We describe a 6-year-old patient who presented to the paediatric renal clinic with unexplained gross proteinuria (420 – 2260 mg/mmol) and dark urine, but no protein on urine dipstick. Nephrotic syndrome and infection were excluded and all blood biochemistry, including renal function parameters, were normal. Renal ultrasound was unremarkable and genetics for Lowe's and Dent's disease were negative. The only other abnormalities identified were a low urine creatinine, occasional high urine albumin and calcium to creatinine

ratios (ACR/CCR), and a generalised aminoaciduria. Organic acid analysis would later identify a large peak of HGA, which is a well-documented interferent in urine protein and creatinine analysis.

The HGA was turning this patient's urine black when combined with the alkaline buffer used in the benzethonium chloride method, resulting in positive interference in the turbidimetric measurement of urine protein. Similarly, in the enzymatic creatinine method, it was consuming most of the peroxidase available for the colourimetric measurement of creatinine, causing negative interference. This suggests the elevated protein to creatinine ratios were false positives, explaining the patient's otherwise unremarkable biochemistry and imaging. It was thought the occasionally elevated ACR/CCR and generalised aminoaciduria were also the result of the low creatinine skewing these ratios.

Alkaptonuria patient's urine contains large quantities of HGA, which is known to cause interference in the measurement of urine protein and creatinine using the benzethonium chloride and enzymatic methods, respectively

A Rare cause of rhabdomyolysis in a 12 year old girl

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We present the case of 12 year old girl previous fit and well, who developed sudden pain in the backs of her legs resulting in difficulty to walk and fall. On presentation at local Hospital creatine kinase was 189,000 U/L with no evidence of viral symptoms or weakness in upper limbs. The patient was able to pass urine however this was bright red in colour, the only other results of note was a full blood count suggestive of a haemolytic anaemia. A diagnosis of fatty acid oxidation defect was initial suspected however this was excluded by blood spot and plasma acylcarnitine analysis. Since the initial presentation the patient was only able to exercise for 2 minutes before experiencing muscle weakness. In the end a diagnosis of glycogen storage disease type XII (aldolase A deficiency) was achieved through a combination of genetics and a novel red cell enzyme assay.

A case of X-linked form of combined Methylmalonic aciduria and Homocysteinemia - Cbl X

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Background: methylmalonic aciduria and homocystinemia type cblX (MAHCX) prevalence according to orphanet data: <1/1,000,000, caused by a violation of the transcription coregulator - HCFC1 (OMIM#309541), which regulates the expression of the MMACHC gene.

Case report: We report a case of X-linked combined methylmalonic aciduria and homocysteinemia - Cbl X, which was diagnosed in a 6-month-old boy based on clinical, biochemical, and molecular genetic changes. The child was born at 39 weeks gestation, with a normal weight and height and 8/9 Apgar score. The disease manifests at the age of 2 months with epi syndrome (severe partial seizures, clonus), hyperkinesis (choreoathetosis), loss of stato-motor skills, and hypotension.

The metabolic profile at the diagnosis was: C3 -7.5 mmol (0.2 - 5.25); C3/C2-0.228 (0-0.2); C3/C16-2.86 (0-2); Hcy 24,8 μM/l (5-12); MMA 163,8 mM/M CRE (≤2); 3-OH-isobutirate 17,9 mM/M CRE (≤2); folic acid 34,2 μM/l (34,8).

Molecular genetic analysis: the uncertain significance mutation c.218C>T(p.Ala 73Val) in the hemizygous state was detected in the HCFC1 gene (all in silico tests were in favour of pathogenic), which is associated with X-linked recessive methylmalonic aciduria and homocysteinemia of the CblX type.

At the age of 6 months, therapy was started: hydroxicobalamin (1 mg/day), betaine hydrochloride (250 mg/kg/day), L-carnitin (100 mg/kg/day), antiepileptic drugs.

Discussion: It is advisable to use the C3/C2 acylcarnitine ratios to avoid false-negative results when cobalamin metabolism is suspected, since C3 is not a sufficiently specific marker.

HCFC1 mutation analysis should be part of the molecular genetic screening in patients with suspected CblC-type cobalamin metabolism disorder, because genetic testing of the MMACHC gene in some cases does not detect rearrangements, even in the presence of relevant clinical manifestations and biochemical changes.

BIMDG

British Inherited Metabolic Disease Group