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British Inherited Metabolic Disease Group

The British Inherited Metabolic Diseases Group (BIMDG) Annual Symposium

Trainee Session Abstract Booklet

Tuesday 17 - Wednesday 18 June 2025

Never underestimate a Neonate

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Background: An 11 day old, 2.1kg male, presented with jaundice, lethargy and decreased feeding. He had increased work of breathing and a low-grade fever, leading to sepsis screening with antibiotics and phototherapy for jaundice. Blood cultures were negative and cardiology review found no cause for tachypnoea. He deteriorated with poor suck and hypotonia despite treatment. This prompted broader investigations and an ammonia level was sent.

Results & Clinical course: An ammonia of >2000µmol/l, was phoned to the on-call paediatric registrar who notified the metabolic consultant. He was placed nil by mouth, started on a 10% dextrose infusion and transferred to PICU. Loading and maintenance IV nitrogen scavengers initiated alongside L-carnitine and L-arginine as per BIMDG guidelines and appropriate investigations sent. He was intubated and commenced continuous veno-venous haemofiltration (CVVH). Challenges encountered included low weight, hypotension, electrolyte imbalance and medicine calulations on a new IT system.

Urine organic acid analysis indicated high levels of 3-hydroxypropionic acid, propionylglycine, and methylcitrate, suggesting propionic acidaemia (PA). Therefore carglumic acid was trialled, leading to a rapid decrease in ammonia levels, which normalised over 48hours and CVVH was needed for just over 24hours. Medications were weaned and rationalised and enteral protein was gradually re-introduced.

An MRI brain showed no significant abnormalities, and an EEG was normal. Rapid trio exome analysis identified homozygosity for a PCCA splice site variant confirming the diagnosis of PA.

Conclusion: Our patient was discharged on NG supported feeds with appropriate protein restriction, maintenance levocarnitine and intermittent metronidazole. Maintenance carglumic acid was subsequently started to control ammonia levels though there have been no severe decompensations. Despite his precarious start in life he is developmentally normal at 8 months of age though we remain cautious about his long-term outcomes. Unfortunately he is not eligible for mRNA therapy trials but is under-going liver transplant assessment.

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.

Unveiling a Rare Case: Severe Pulmonary Hypertension and Neuroregression in an Infant with NFU1-Related Mitochondrial Dysfunction Syndrome

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Background: Pulmonary hypertension (PH) in infancy is often associated with cardiac or respiratory pathology, but neurometabolic disorders should be considered in cases with unexplained systemic involvement. We present a case of NFU1-related Multiple Mitochondrial Dysfunction Syndrome (MMDS1) highlighting the importance of early metabolic and genetic evaluation in critically ill infants.

Method: Our patient was a 4-month-old male who had symptoms with choking, apnoea, and neuroregression showing white matter changes in the MRI brain required intensive care unit admission. Eventually diagnosed with severe pulmonary hypertension, underwent extensive work up including molecular genetic testing.

Results: MMDS1 is a rare, autosomal recessive disorder leading to severe metabolic and neurological dysfunction. It should be considered in infants with PH, leukodystrophy-like MRI findings, and neurodevelopmental regression. PH in mitochondrial disorders remains poorly understood but may be secondary to endothelial dysfunction or metabolic derangements. This case highlights the need for early recognition and genetic testing in infants with unexplained multisystem disease, particularly in the cardiac intensive care setting.

Conclusion: This case highlights NFU1-related MMDS1 as a rare but important differential diagnosis for neonatal PH and neuroregression. The early intervention and extensive work up might yield the diagnosis, the prognosis remains poor. Multidisciplinary collaboration between cardiology, neurology, genetics, and metabolic teams is essential for diagnosis and care planning.

Keywords: Pulmonary hypertension, mitochondrial disease, NFU1, multiple mitochondrial dysfunction syndrome.

Natural history and diagnostic findings in an adult man diagnosed with attenuated Krabbe disease

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Background: Krabbe disease (KD), or globoid cell leukodystrophy, is a rare autosomal recessive lysosomal storage disorder caused by a deficiency in galactocerebrosidase (GALC). This enzymatic defect leads to the accumulation of psychosine, resulting in progressive demyelination and neurodegeneration. KD is typically classified into an infantile form with rapid progression and a late-onset form, which is more attenuated and often presents with spastic paraparesis. Diagnosis is challenging, requiring a high degree of clinical suspicion and confirmation through neuroimaging, biochemical assays, and genetic analysis.

Case: We report a 55-year-old male with progressive lower limb spasticity, gait disturbance, and mild cognitive impairment. Neurological examination revealed hyperreflexia, clonus, and bilateral lower limb weakness. MRI showed symmetrical T2 hyperintensities in the corticospinal tracts, suggestive of leukodystrophy. Cerebrospinal fluid (CSF) analysis demonstrated elevated protein levels without pleocytosis. Enzymatic assays confirmed reduced GALC activity, and genetic sequencing identified a novel pathogenic GALC variant. Psychosine quantification was borderline, aligning with the disease progression but not sufficient for a definitive diagnosis on its own.

Discussion: This case emphasises the need to consider KD in adults with progressive spastic paraparesis, particularly when MRI findings suggest leukodystrophy. The novel GALC mutation identified in this patient adds to the understanding of the genetic variation within the disease. While psychosine levels can provide valuable prognostic insights (along with MRS), their diagnostic reliability in attenuated disease remains uncertain, as demonstrated by this case, where the level overlapped with pseudo-deficiency, heterozygous carrier status, and normal controls. The case further underscores the importance of a multidisciplinary approach, including physiotherapy and genetic counselling, in management. Further research is essential to clarify the role of psychosine in both diagnosis and prognosis and to develop more refined diagnostic and therapeutic strategies for this rare disorder.

Eight years of trimethylamine analysis: Review of reference range

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Background: Sheffield Children's Hospital, part of South Yorkshire and Bassetlaw Pathology, provides a biochemical service for the diagnosis of trimethylaminuria, involving analysis of urinary trimethylamine (TMA) and trimethylamine-N-oxide (TMANO), and calculation of N-oxidation to provide an estimate of FMO3 enzyme activity.

In 2017 the assay was reconfigured on a new instrument, and reference ranges were adopted from the literature, based on limited data. This work aims to assess the validity of the free TMA reference range.

Methods: Analytical results from 2017-2025 were collated and the total number of samples along with the proportion of results above and below the reference ranges determined.

The 95th percentile of results from samples with normal N-oxidation was calculated. Comparison was made with the current reference range.

Results: 2661 patient samples were analysed. 385 (14%) had a free TMA above the current reference range. 497 (19%) had a free TMA above the calculated 95th percentile. 112 results (4%) lie between these values. The data are not from unique patients but include repeat and monitoring samples.

Conclusions: TMA is a product of bacterial metabolism, circulating levels are affected by diet, gut microbiota and enzyme activity, along with additional confounding factors making interpretation complex. Adopting the 95th percentile as a new reference range would classify more patients with normal enzyme activity as potentially positive. Adding an additional category of equivocal results with request for follow-up sample would be appropriate in these cases. Dietary loading with TMA precursors can help distinguish true positives from equivocal results. A protocol is available but further validation of this is needed.

Single gene analysis is not widely available, but FMO3 is part of the R98 panel. It would be useful to combine genetic with biochemical and clinical data, but these parts of the service are remote from one another.

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