INTRODUCTION:
3-Methylglutaryl-CoA hydratase (3-MGCH), encoded by the AUH gene, catalyzes one of the key steps in the breakdown of leucine. Bi-allelic pathogenic variants in AUH impair function of this enzyme, causing 3-MGCH deficiency (OMIM 606529). This results in elevations of 3-methylglutaconic aciduria, with or without 3-hydroxyisovaleric aciduria and elevated plasma 3-hydroxyisovaleryl carnitine (CSOH).

Due to the limited number of reported cases in the literature (less than 40), the clinical consequences of these urinary abnormalities are unclear. Initial case reports described varying clinical features including encephalopathy, developmental delay, extrapyramidal symptoms, cardiomyopathy and pyruvic ketosis1,2, whilst others suggested this may be an asymptomatic condition in childhood3. More recent reports indicate that some patients may develop late-onset leukoencephalopathy4,5.

We report a case series of six Australian patients with 3-methylglutaryl-CoA hydratase deficiency, four of whom were diagnosed on newborn screening.

Case 1
Age at Diagnosis: 2 weeks
Gender: Male
Detected via Newborn Screening: Yes
Plasma C5OH: 2.5 µmol/L (RR <1.5)
Not elevated (not elevated
Gross elevation (gross on
Not elevated (not elevated on repeat
Lack of duplication (not elevated
Aware of 3-MGCH deficiency
Asymptomatic. Active Lifestyle
Atopy
Autism Spectrum Disorder

Case 2 (Sister of Case 1)
Age at Diagnosis: 2 weeks
Gender: Female
Detected via Newborn Screening: Yes
Plasma C5OH: 1.6 µmol/L (RR <1.5)
Gross elevation (gross on repeat)
Lack of duplication (not elevated
Aware of 3-MGCH deficiency
Asymptomatic. Active Lifestyle
Atopy
Autism Spectrum Disorder

Case 3
Age at Diagnosis: 6 days
Gender: Male
Detected via Newborn Screening: Yes
Plasma C5OH: 1.7 µmol/L (RR <1.5)
Gross elevation (gross on repeat)
Lack of duplication (not elevated on repeat
Aware of 3-MGCH deficiency
Asymptomatic. No concerns regarding growth or development

Case 4
Age at Diagnosis: 2 weeks
Gender: Female
Detected via Newborn Screening: Yes
Plasma C5OH: 2.34 µmol/L (RR <1.13)
Gross elevation (gross on repeat)
Lack of duplication (not elevated on repeat
Aware of 3-MGCH deficiency
Asymptomatic. No concerns regarding growth or development

Case 5
Age at Diagnosis: 2 weeks
Gender: Female
Detected via Newborn Screening: Yes
Plasma C5OH: 0.63 µmol/L (RR <0.1)
Lack of duplication (not elevated
Aware of 3-MGCH deficiency
Asymptomatic. No concerns regarding growth or development

Case 6 (Sister of Case 5)
Age at Diagnosis: 2 weeks
Gender: Male
Detected via Newborn Screening: Yes
Plasma C5OH: 0.15 µmol/L (RR 0.1)
Lack of duplication (not elevated
Aware of 3-MGCH deficiency
Asymptomatic. No concerns regarding growth or development

DISCUSSION:
3-Methylglutaryl acidaemia (3-MGAs) are both a clinically and genetically heterogeneous group of disorders that include 3-MGA Type I (3-MGCH deficiency), Type II (Barth Syndrome), Type III (Costeff optic atrophy), Type V (dilated cardiomyopathy with ataxia), Type VI (MEGDEL Syndrome), Type VII (CLPB deficiency), Type VIII (HTRA2 deficiency), and Type IX (TIMM50 deficiency). 3-MGA also occurs in conditions associated with secondary mitochondrial dysfunction. Whilst 3-methylglutaryl acidaemia is observed in these disorders, it may be that this metabolite does not exert toxic effects in and of itself. Rat models suggest that the accumulation of 3-MGA may inhibit Na+,K+-ATPase activity and affect the basal potential membrane required for normal neurotransmission, potentially contributing to encephalopathy particularly during periods of metabolic crises16. Rat models also show evidence that elevations in 3-MGA, 3-methylglutarate, and 3-hydroxyisovalerate induce lipid and protein oxidative damage10.

It is unclear whether the potential for toxicity in 3-MGCH deficiency translates into a clinical phenotype in humans. Most patients in our case series are still asymptomatic as young adults (including case 1) and none are receiving treatment. The clinical features reported that cases 5 and 6 may or may not be related to their biochemical diagnosis as there is also sibling with autism without 3-MGA. Our case series adds to the limited literature regarding patients diagnosed with 3-MGCH deficiency on newborn screening and further supports that the clinical features identified previously in childhood are related to ascertainment bias and if patients identified on newborn screening will have symptoms in adulthood.

References:
1 C. Coman et al. (2020). Leucine regulates autophagy via acetylation of the mTORC1 component receptor. EMBO Molecular Medicine; 12: 1-12.
3 C. Coman et al. (2022). Leucine regulates autophagy via acetylation of the mTORC1 component receptor in young rats. EMBO Molecular Medicine; 14: 1-14.

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Poster: