INTRODUCTION:

N-acetylglutamate synthase (NAGS) deficiency (OMIM #237310) is an ultra-rare autosomal recessive disorder, which results in the inability to activate the key urea cycle enzyme carbamoylphosphate synthetase 1 (CPS1). Patients often suffer life-threatening episodes of hyperammonaemia, both in the neonatal period and also at subsequent times of catastrophic stress.

We report a four-day-old neonate who was noted to have 3-methylglutaconic aciduria at the time of significant hyperammonaemia and lactic acidosis. Low plasma citrulline and minimal ornithine aciduria were additional findings that suggested a proximal urea cycle disorder. Subsequent molecular testing identified bi-allelic pathogenic variants in NAGS.

MOLECULAR ANALYSIS:

Next generation sequencing of 10 genes associated with urea cycle disorders (invitae):

NAGS (NM_153006.3)

Variant 1: c.622C>T | p.Arg208*

Variant 2: c.1368_1369delT | p. Gly457Alafs*110

DISCUSSION:

3-methylglutaconic aciduria (3-MGA) occurs in a variety of conditions (see Table 1).1,2 Aside from 3-MGA Type I, a defect in 3-methylglutaryl-CoA hydratase, the aetiology underlying the 3-MGA in each condition is unclear. It has been proposed that either the mevalonate shunt (activated by increased isoprenoid intermediates) can increase production of 3-methylglutaconic acid,3 or that increased acetyl-CoA accumulation due to mitochondrial dysfunction is converted back (through the reversible steps of leucine catabolism) into 3-methylglutaconic acid.4

This is the first patient to our knowledge in the literature with the combination of NAGS deficiency and 3-methylglutaconic aciduria.1 As such, this condition should also be considered within the differential diagnosis for patients with 3-MGA where a proximal urea cycle disorder is suspected, and a trial of carmacinic acid initiated if the treatment focus is still active management.

There are also other known conditions that can cause the combination of hyperammonaemia, lactic acidosis and 3-methylglutaconic aciduria, specifically SERAC2 deficiency (OMIM #614739) and TME70 deficiency (OMIM #614052).5 These disorders have key phenotypic findings, of hypoglycaemia and liver failure in the former,6 and cardiomyopathy in the latter, though these features are not always present. Confirmation of the diagnosis on clinical, biochemical and molecular grounds is crucial in order to ensure tailored treatment.

CONCLUSION:

We report the first patient in the literature with NAGS deficiency and 3-methylglutaconic aciduria at the time of diagnosis. This patient presented with severe neonatal-onset hyperammonaemia, with associated persistent elevation in lactate, suggesting that the 3-MGA is more indicative of secondary mitochondrial dysfunction, rather than a disease-specific finding. Further study in other patients with confirmed NAGS deficiency is required to establish whether 3-MGA may be used as a biomarker of severe metabolic decompensation.

References: