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Leucine levels in maple syrup urine disease (MSUD) from a single centre in the United Kingdom

Gribben J [1], Billmore K [1], Slabbert A [1], Champion M P [2], Lemonde H [2], Mundy H [2]

[1]Dietetics Dept, St Thomas' Hosp, London, United Kingdom, [2]Ctr Inh Met Dis, Evelina Children's Hosp, London, United Kingdom

Background: Optimal control of leucine concentrations in MSUD disease is essential for maximising neurocognitive outcomes. In 2014 Frazier et al. published guidelines recommending lowering the leucine treatment range to 75–200 μmol/L for patients ≤5 years and 75–300 μmol/L for >5 years. In 2013, the UK Expanded Newborn Screening (ENBS) guidelines recommended the range 200–400 μmol. In 2015, this was later reduced to 150–300 μmol/L and reported the typical leucine intake for classical MSUD as 300 mg/day (6 × 50 mg leucine exchanges). We have adopted these guidelines for our MSUD patients aged 5 years and under.
Aim: To audit leucine monitoring results to determine if the lower treatment range was achievable.
Methods: A 12 month retrospective review of all blood spot leucine levels (including during illness), number of 50 mg leucine exchanges per day and frequency of samples. All classical MSUD patients 5 years and under were included.
Results: Six patients were identified (median age 4.75 years, range 0.7–8 years). All diagnosed in the neonatal period (median age 13 days, range 7–17 days), median screening level 3635 (range 1153–4600 μmol/L). The mean of each patient's 12 month leucine monitoring results was determined (median 210, range 178–290 μmol/L). The proportion of leucine concentrations below 300 μmol/L for each patient was also determined (median 75 %, range 60–92 %). The median number of samples per patient received in 52 weeks was 64 (range 37–76). The median number of mean 50 mg leucine exchanges per day for each patient was 7 (range 5–13). The median peak leucine level during illness was 765 (range 554–895 μmol/L).
Discussion: Our data shows that the UK ENBS lower treatment range of 150–300 μmol/L is achievable without having to overly restrict leucine exchanges.

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A case of maleylacetoacetate isomerase deficiency

Preece M A [1], Hardy C [1], Hutchin T [1], Santra S [2], Vijay S [2], Antoniadi T [3], McMullan D [3]

[1]Biochem Genetics, Children's Hospital, Birmingham, United Kingdom, [2]Clinical IMD, Children's Hospital, Birmingham, United Kingdom, [3]Regional Genetics, Womens Hospital, Birmingham, United Kingdom

Background: Maleic aciduria leading to a diagnosis of maleylacetoacetate isomerase (MAAI) deficiency.
Case Report: An 18 month old girl with developmental delay, difficult behaviour, irritability and autistic features.
Results: Urine organic acids showed hydroxyketoheptanoate, diketoheptanoate and a trace of succinylacetone (SA). Further investigation for tyrosinaemia type 1 showed normal amino acids, liver function tests and coagulation. AFP was slightly increased (21kU/L: normal < 10) but lectin reactive-AFP was normal. Liver and brain MRI showed no significant findings. Plasma SA and urine 5-aminolevulinic acid were slightly increased (2.20umol/L; ref range < 0.1 & 22.1umol/mmol creat; ref range < 5.2 respectively). Apart from SA and metabolites, urine organic acids showed no phenolic acids but maleic acid was increased. Fibroblast fumaryl acetoacetase and sequencing of the *FAH* gene were normal. Treatment with low dose nitisinone (0.15 mg/kg/day) and a low tyrosine diet were commenced. The biochemical abnormalities resolved except AFP which remained slightly increased.
The biochemical findings suggested MAAI deficiency due to a defect in the GSTZ1 gene. The Illumina HiSeq platform was used to sequence the gene captured by the TruSight One Panel target enrichment system (Illumina). Analysis was performed with an in-house pipeline. Quality analysis of coverage data revealed a pattern consistent with a homozygous deletion of exons 3, 4, 5 and 6. This was confirmed by targeted microarray analysis (Affymetrix CytoScan HD array). This deletion has not been previously described in the literature or in any database; as it removes a big part of the gene it is likely to be pathogenic.
Discussion: Although it is not clear whether MAAI deficiency has caused the neurodevelopmental problems, this case adds to our knowledge of the phenotype of MAAI deficiency.

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Hyperprolinemia as a clue in the diagnosis of a patient with a psychiatric disorder

Duarte M [4], Moreira A [3], Antunes D [1], Ferreira C [5], Correia H [5], Sequeira S [2], Marques M [4]

[1]Genetic Dept, Hosp Dona Estefania, Lisbon, Portugal, [2]Metab Unit, Ped Dept, Hosp D Estefania, Lisbon, Portugal, [3]Neuroped Dept, Hosp Dona Estefania, Lisbon, Portugal, [4]Child and Adol Psy Dep, Hosp D Estefania, Lisbon, Portugal, [5]Unit Cyto Hum Gen Dept, INSA, Lisbon, Portugal

Background: Over the last few years, microdeletions of the 22q11.2 region responsible for DiGeorge syndrome, or velocardiofacial syndrome, have been increasingly related to neuropsychiatric disorders including schizophrenia and bipolar disorders. These signs seem to be related to certain genes located in the hemideleted region as the proline dehydrogenase (PRODH) and the catechol-o-methyltransferase (COMT) genes. The PRODH or proline oxidase deficiency is responsible for hyperprolinemia type 1 (HPI) also causing psychiatric manifestations.
Case Report: We describe a 17 year old boy with previous mild psychomotor and speech delay, mild cognitive impairment, and obsessive behaviours who started his adolescent psychiatric care presenting irritable mood and aggressive behaviour with schizophrenia symptoms that scored a "severely ill" level PANSS assessment. Symptoms got worse when he was treated with valproic acid and plasma aminoacids showing increase in alanine and proline, suggested a mitochondrial involvement of the proline metabolic pathway.
Results: Mild dysmorphia suggested a possible 22q11.2 deletion genetically confirmed involving both the PRODH and COMT regions. HPI that can present with psychiatric features is however a recessive disorder and therefore the symptoms could not be solely explained by this genetic deletion. Additional investigations also showed disclosed a p.L289m (c.1865 T > A) mutation in the PRODH gene.
Discussion: We believe that the association of this mutation together with the 22q11.2 deletion would lead to a decrease of functional protein. Although it may be difficult to diagnosis chromosomal abnormalities in patients with no clear malformations and mild dysmorphic features as in this patient we emphasize need to investigate the aetiology in patients with psychiatric symptoms, especially if they have other systemic manifestations such as developmental delay or psychotic symptoms, as it may be important in the management of the patients.

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A novel *BCAT2* mutation causes hypervalinaemia/hyperleucine-isoleucinaemia in a boy with a developmental disorder with autism

Knerr I [1], Urquhart J [2], Hughes J [1], Rogers Y [1], Jones S [2], Lynch S A [3], Treacy E [1], Mayne P D [4], Banka S [2], Olpin S [5]

[1]Nat Centr Inher Met Dis TSCUH, Dublin, Ireland, [2]Centre for Genomic Medicine, Manchester, United Kingdom, [3]Genetics Department TSCUH,