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A case of recurrent hyperammonaemia

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Ammonia

- Produced by amino acid metabolism in liver, muscle & kidney; and by action of gut bacteria
- Neurotoxic
- "Untreated hyperammonaemia can cause irreversible brain damage and death at any age. Therefore it is essential to measure ammonia in every sick patient in which a metabolic disease may be the underlying diagnosis"
- "Any ammonia >150 µmol/L in children, or >200 µmol/L in neonates and >100 µmol/L in adults requires immediate attention."

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Table 2 – Causes of Hyperammonaemia

DEFECTS OF THE UREA CYCLE	OTHER METABOLIC DISORDERS
Inherited Deficiencies of : - N-Acetyl glutamate synthase (NAGS) - Carbamoyl phosphate synthase (CPS) - Ornithine transcarbamylase (OTC) - Argininosuccinate synthase (citrullinaemia) - Argininosuccinate lyase (argininosuccinic aciduria) - Arginase (argininaemia) - Carbonic anhydrase VA deficiency	Organic Acidurias e.g Propionic aciduria, Methylmalonic aciduria, Isovaleric aciduria Disorders of Fatty Acid Oxidation e.g Medium chain acyl-CoA dehydrogenase deficiency Carnitine palmitoyltransferase II deficiency Others - HHH syndrome - Lysinuric protein intolerance (LPI) - Hyperinsulinaemic hyperammonaemia - Ornithine aminotransferase deficiency (OAT) (neonatal form) - Mitochondrial respiratory chain defects - Pyruvate dehydrogenase deficiency - Citrin deficiency (citrullinaemia type II) - Congenital lactic acidosis
ACQUIRED	OTHER
• Liver failure / impairment • Urinary tract infection • GI bacterial overgrowth • Drugs e.g. valproate, chemotherapy • Total parenteral nutrition • Severe illness e.g. asphyxia, sepsis • Reyes syndrome • Systemic herpes simplex	• Artefactual increase - poor specimen quality / haemolysis - difficult venepuncture - skin contamination - contaminated tube - delayed analysis / protein breakdown • Transient hyperammonaemia of the Newborn

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MetBioNet :

Guidelines for investigation of hyperammonaemia

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Carbonic anhydrase VA deficiency

- Described as an inherited cause of hyperammonaemia in 2014
- Autosomal recessive condition

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Carbonic anhydrase VA (CAVA)

$$CO_2 + H_2O \overset{CAVA}{\rightleftharpoons} HCO_3^-$$

- Provides bicarbonate for 4 mitochondrial enzymes -

*Carbamoyl phosphate synthetase 1	Urea cycle	
*Propionyl CoA carboxylase	BCAA catabolism	Biotin dependent
*Pyruvate carboxylase	Glycolysis/Krebs cycle	Biotin dependent
3-Methylcrotonyl CoA carboxylase	Leucine catabolism	Biotin dependent

- *Deficiencies associated with hyperammonaemia

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Biochemical features of CAVA deficiency

- Hyperammonaemia with hyperlactataemia & ketonuria a consistent finding
- Hyperlactataemia & ketonuria likely due to inhibition of pyruvate carboxylase
- Markers of propionyl CoA carboxylase & 3-methylcrotonyl CoA carboxylase def seen in some patients
- ~65% of cases remain stable after initial crisis

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References

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- Diez-Fernandez C et al. Defective hepatic bicarbonate production due to carbonic anhydrase VA deficiency leads to early-onset life-threatening metabolic crisis. Genet Med 2016;18:991-1000.

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