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Beta-Ketothiolase Deficiency: A Case Presentation and Literature Review

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Introduction:

Beta-ketothiolase deficiency is a rare autosomal recessive disease of isoleucine catabolism and ketone body utilization.(1) We present the case of a patient with this condition, its pathology, diagnosis, and management.

Case Presentation:

A 3 year old boy, 2nd child to consanguineous parent, presented to the emergency department with intermittent abdominal pain and vomiting. He was treated for a presumed UTI and discharged on oral Cefalexine once tolerating oral fluids.

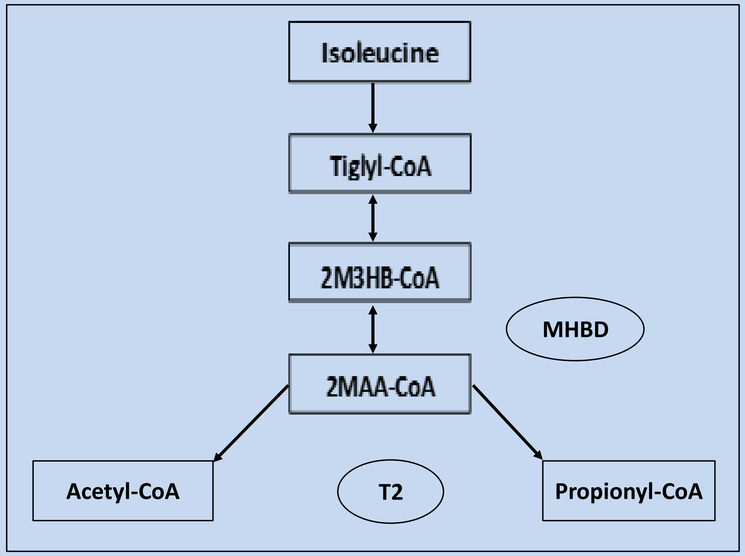
He re-presented after 24 hours as his symptoms had not improved. He was discharged home again with the advice to continue the antibiotics.

He was brought back a third time by his parents after a further 18 hours with severe vomiting and appeared short of breath. On examination he was tachycardic and tachypnoeic. His blood glucose was 3.8mmol/L and urinalysis showed high concentrations of ketones. A capillary blood gas showed a severe metabolic acidosis with partial respiratory compensation.

After discussion with a specialist centre further investigation were arranged. Urinary organic acids assay showed increased excretion of acetoacetate and 3OH-n-butyric acid. Genetic testing confirmed a homozygous mutation c.473A>G of the ACAT1 gene.

Pathology:

Beta-ketothiolase deficiency is caused by a mutation in the ACAT1 gene leading to a deficiency of mitochondrial acetoacetyl-CoA thiolase (T2) enzyme. T2 catalyses the breakdown of 2-methylacetoacetyl-CoA into acetyl-CoA and propionyl-CoA.(2) Deficiency of this enzyme leads to an accumulation of ketone bodies leading to ketoacidosis.



The catabolism of isoleucine. T2 catalyses the reaction to form acetyl-CoA.(3)

Clinical presentation:

Patients typical first present between 6 and 18 months of life, with symptoms occuring during times of physiological stress (e.g. febrile illness). Symptoms include vomiting, dystonia, choreic movements, nystagmus, convulsion, and respiratory distress. If untreated it can cause neurodevelopmental delay, coma, and death.(3,4)

Diagnosis and Management:

During the ketotic crisis blood sampling will show a severe metabolic acidosis. Usually patients will be normoglycaemic, however blood glucose can be higher or lower than normal.

Definitive diagnosis is acheived by enzymatic assay to confirm deficiency of the T2 enzyme.(1) Other investigations may suggest the diagnosis including Urine organic acid analysis which will show increased excretion of 2-methylacetoacetyl-CoA, tiglylglycine, and 2-methyl-3-hydroxybutyryl. Additionally acylcarnitine analysis of blood or urine may show the presence of tiglylcarnitine and

2-methyl-3-hydroxybutyrylcarnitine.(3)

The main stay of treatment involves avoiding prolonged fasting. A diet low in isoleucine and carnitine supplementation may also be beneficial.

During crisises patients should be treated with glucose infusion to suppress ketogenesis.(3)

Conclusion & perspectives:

Beta-ketothiolase deficiency is treatable, with a favourable outcome if diagnosed early. Emergency medicine doctors and paediatricians should suspect metabolic disease in any child presenting with ketoacidosis. Particular attention should be paid to patients presenting with recurrent episodes, with a similar presentation in a family member, or an unexplained sibling death in the family.

(1) Fukao et al. Ketone body metabolism and its defects. J Inherit Metab Dis. 2014 (2) Abdelkreem et al. Beta-ketothiolase deficiency: resolving challenges in diagnosis. J Inborn Errors Metab Screen. 2016. (3) Fukao T. Beta-ketothiolase deficiency. Orphanet encyclopaedia. 2004. (4) Hillman RE, Keating JP. Beta-ketothiolase deficiency as a cause of the "ketotic hyperglycinaemia syndrome". Pediatrics. 1974. (5) Hori et al. Inborn errors of ketone body utilization. Pediatr Int. 2015.