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Review

BETA-KETOTHIOLASE DEFICIENCY IN AN INFANT: A RARE CASE REPORT

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ABSTRACT

Beta ketothiolase deficiency is a rare autosomal recessive disorder of isoleucine and ketone body metabolism characterised by unexplained episodes of ketoacidosis which is often triggered by infections, prolonged fasting and large protein load. A 6 months old boy was admitted to our hospital with history of convulsions, lethargy and loss of consciousness, dehydration with metabolic acidosis, hypoglycemia and ketonuria. β- ketothiolase deficiency was confirmed by urine Gas Chromatography –Mass Spectrometry. This case is being reported because of rarity of the disease and should be considered as a differential diagnosis in ketoacidotic episodes.

INTRODUCTION

Beta-ketothiolase (3-oxothiolase) aka mitochondrial acetoacetyl-coA thiolase (T2) is a reversible mitochondrial enzyme involved in final steps of isoleucine catabolism and ketolysis. The hallmark of this disorder is ketoacidosis, often triggered by infections, prolonged fasting and large protein load. Clinical manifestations are quite variable, ranging from mild cases showing normal development to severe episodes of acidosis and cognitive impairment. Mild to moderate hyperammonemia may also be present during attacks. Both hypoglycemia and hyperglycemia have been reported in isolated cases. Diagnosis is made by urine organic acid assay which reveals large amounts of 2-methylacetoacetate and its decarboxylated products butanone, 2-methyl-3-hydroxybutyr ate, and tiglylglycine. β- ketothiolase deficiency is inherited as an autosomal recessive trait and may be more prevalent than previously appreciated. The gene ACAT-1 for this enzyme is located on chromosome 11q22.3. Diagnosis is confirmed by molecular analysis of ACAT-1 gene or using enzyme assay of leucocytes or cultured fibroblasts.[1] Prenatal diagnosis can be made by measurement of enzyme activity in cultured amniocytes and chorionic villous cells.[2]

Treatment of this disorder includes hydration and infusion of bicarbonate to correct metabolic acidosis. A 10% glucose solution with appropriate electrolyte and intravenous lipid may be used to minimize catabolic state. Restriction of protein intake to 1-2 gm/kg/day is recommended for long term therapy. L-carnitine should be given to prevent secondary carnitine deficiency. Vitamin B-complex is also recommended. Long term prognosis for achieving normal life seems favourable. Thus early diagnosis of this disorder has good prognosis.[3]

CASE STUDY

A 6 months old male child, weighing 5.9 kg, product of a consanguineous marriage, presented to our hospital with complaints of dullness, lethargy, abnormal body movements and loss of consciousness and rapid breathing since 3 days. He was delivered after a full term pregnancy, had a history of neonatal convulsions. Also, there was a history of death of two siblings earlier after similar illness. There was no neck holding, no cooing or social smile. He has been on exclusive breastfeeding since birth. He was not on any medications.

On physical examination, child appeared dull, lethargic and dehydrated. The axillary temperature was 101.8°F, heart rate was 168/min with weak peripheral pulses and delayed CRT respiratory rate was 56/min, dry mucosa, sunken eyes, depressed anterior fontanel, pale skin, decreased skin turgor and acidotic breathing. Subcostal retractions were present, the liver palpable at 2-3 cm below costal margin in the midclavicular line. On neurological examination, GCS was found to be 5/15, hypotonic, deep tendon reflexes exaggerated and planter reflex bilaterally extensor. No cranial nerve abnormalities or signs of meningeal irritation were detected.

Laboratory investigations revealed a haemoglobin of 8.3 g/dL (hematocrit: 23.1%), platelet count 4, 65,000/mm 3, leucocytes: 20,100 mm 3, differential counts being neutronph ills 70.4% and lymphocytes 17.20%; CRP: 40.87 mg/L. An arterial blood gas analysis revealed pH 6.908, PaCO2 16.1mm Hg, PaO2 of 121 mmHg, HCO3- 3.2 mmol/L, anion

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gap 41.0 mmol/L and lactate 0.3 mmol/L, suggestive of a high anion gap metabolic acidosis. His blood glucose was 51 mg/dl, renal functions were normal on admission, liver functions appeared to be moderately deranged with total serum bilirubin levels 1.71 mg/dl, SGOT 140.6 IU/L, SGPT 137.6 IU/L , alkaline phosphatase levels 353 IU/L, serum total protein and albumin levels were normal. On urine analysis ketones were (++++), proteins (++), erythrocytes (+++). Urine tested negative for reducing substances. Serum ammonia levels were found to be 39µmol/L while serum acetone levels were 80mg/dL. For further evaluation, urine GCMS was done which revealed increased excretion of 2-Methyl-3-hydroxybutyric acid, 3-Hydroxybutyric acid, 3-Hydroxyisovaleric acid, 3-Hydroxypropionic acid and Adipic acid, suggestive of β-ketothiolase deficiency. He was started on intravenous fluids, antibiotics and bicarbonate therapy but the child did not respond well to treatment and developed acute renal failure along with shock. Despite treatment for the same, unfortunately the child could not be saved.

DISCUSSION

Beta-ketothiolase enzyme deficiency is a rare congenital metabolic disease with failed isoleucine catabolism and ketone body metabolism. Beta-ketothiolase in the mitochondrium irreversibly catalyzes propionyl coenzyme-A formation from 2-methyl acetoacetyl coenzyme-A in L-isoleucine catabolism. The gene related to beta-ketothiolase deficiency in the mitochondria was determined to be with the long arm of chromosome 11.[4] This patient had history of convulsions, was found to have an altered mental status, hypoglycemia, ketonemia, ketonuria and severe metabolic acidosis but ammonia levels were normal.

Monastiri et al. reported that the disease was characterised by consanguinity and a history of sibling death with a similar clinical picture in all cases, and by frequent neurological symptoms.[5] This patient also was a product of a second degree consanguineous marriage with a history of death of two siblings after similar clinical manifestations. Peritoneal dialysis was required for deep acidosis and kidney failure in two of four cases reported by Monastiri et al., and both cases ended with death.[5] In this case, acidosis didn't improve despite hydration and bicarbonate therapy. The renal functions kept on declining after admission and finally resulted into a complete renal shut down and ultimately resulted into death.

A typical organic acid profile of an acute episode is massive excretion of 2-methylacetoacetate, 2-methyl-3-hydroxybutyrate, and tigylglycine with massive excretion of ketone bodies and dicarboxylic acids.[2] In our case, urine GCMS showed an increased excretion of 2-Methyl-3-hydroxybutyric acid, 3-Hydroxybutyric acid, 3-Hydroxyisovaleric acid, 3-Hydroxypropionic acid and Adipic acid.

Our patient presented with severe dehydration, shock and a poor GCS along with hypoglycemia, ketoacidosis, declining renal functions; was treated with IV fluids, bicarbonate therapy, antibiotics, ionotropes as well as mechanical ventilation but he didn't respond well to treatment and unfortunately died. This disorder being an autosomal recessive trait could be asymptomatic amongst the carriers thereby screening of other family members was adviced.

CONCLUSION

In infants presenting with episodes of acidosis, changes in consciousness and abnormal blood sugar levels, β-ketothiolase deficiency should be considered as a differential diagnosis and such children must be investigated for same. Screening of other family members should be considered in such cases as it is an autosomal recessive condition.

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