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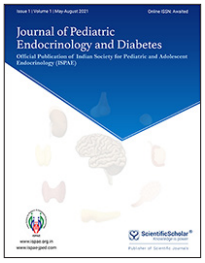

Case Report

A rare case of β-ketothiolase deficiency presenting as mimicker of diabetic ketoacidosis

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ABSTRACT

β-ketothiolase (3-oxothiolase, BKT), also called mitochondrial acetoacetyl-coenzyme-A thiolase (T2), is a mitochondrial enzyme involved in isoleucine catabolism and ketone metabolism. BKT or T2 deficiency is inherited as an autosomal recessive trait and results in a rare inborn error of metabolism called alpha-acetoacetic aciduria. Patients with this disorder usually present with intermittent attacks of ketoacidosis. Here, we report a case of BKT deficiency that mimicked diabetic ketoacidosis (DKA) at presentation and discuss the clinical profile and interpretation of laboratory findings. An 8-month-old male child presented with seizures, coma, hyperglycemia, shock, and high anion gap metabolic acidosis with normal serum lactate and negative urinary ketone requiring correction with sodium bicarbonate, management of shock and sepsis, and mechanical ventilation. During his stay in the hospital, he developed ketonuria and episodes of hypoglycemia on a glucose insulin infusion with persistent metabolic acidosis which prompted us to look for an inborn error of metabolism, as hemoglobin A1C (HbA1C) and C-peptide levels were normal. Both tandem mass spectrometry (TMS) and urinary gas chromatography mass spectrometry (GCMS) were confirmatory. Diagnosis of BKT deficiency was further confirmed with genetic testing which revealed a novel homozygous mutation in the acetyl-CoA acetyltransferase 1 (*ACAT1*) gene. In infants manifesting with clinical features of diabetic ketoacidosis (DKA), cautious interpretation of laboratory findings and consideration of inborn errors of metabolism including the rare BKT deficiency are needed for a favorable outcome and prediction of prognosis.

Keywords: Diabetic ketoacidosis, Beta-ketothiolase, High anion gap acidosis, Methyl malonic aciduria, Organic acidemias

INTRODUCTION

β-ketothiolase (BKT), also called mitochondrial acetoacetyl-coenzyme-A thiolase (T2), is a reversible mitochondrial enzyme involved in the catabolism of the amino acid isoleucine and in ketone metabolism. BKT deficiency is a rare form of inborn error of metabolism, inherited as an autosomal recessive trait. The gene for T2 enzyme, acetyl-coenzyme-A acetyltransferase -1 (ACAT1), is located on chromosome 11q22.3-23.1 and includes 12 exons. 2-methyl acetoacetyl-CoA thiolase deficiency was first reported in 1971 and 250 cases have been reported worldwide.[1,2] The usual age of presentation is between 6 and 18 months with intermittent episodes of ketoacidosis. The disease has a favorable long-term prognosis if identified and managed early in the course of the disease with protein restriction and supplementation with carnitine.[3] Here, we report an interesting case of T2 deficiency with unusual presentation mimicking diabetic ketoacidosis (DKA) at presentation.

CASE REPORT

An 8-month-old developmentally normal male child presented with three episodes of tonic seizures and altered sensorium. There was a history of one episode of fever spike, 2 days before presentation. The patient was a small for gestational age baby with a history of hyperbilirubinemia and documented hypoglycemia (29 mg/dL) at birth with a history of neonatal intensive care unit stay for a duration of 5 days. Family history was not significant, he being the only child born out of a non-consanguineous marriage. The patient was immunized for age. The patient was referred from a secondary care center with documented hyperglycemia (524 mg/dL) and severe metabolic acidosis (pH 6.9, bicarbonate [HCO_3] 3.6 mmol/L) after receiving normal saline fluid boluses and HCO_3 correction.

The patient was received in our emergency in shock and severe respiratory distress. His weight was 6 kg and his length was 64 cm. The Z-score for weight for length was between −1 SD and −2 SD. His head circumference was 41 cm (−1 to −2 SD). Blood glucose was high (471 mg/dL) and arterial blood gas was suggestive of severe metabolic acidosis (pH 6.99, normal lactate, high anion gap of 22.7, and HCO_3 of 3.7 mmol/L), but urine dipstick was negative for ketone. A fluid bolus was given, and HCO_3 correction was continued. The patient was intubated and transferred to the pediatric intensive care unit (PICU). In PICU, the child was put on a mechanical ventilator where a urine sample for ketones came out to be positive (Dipstick ketone: ++). Insulin infusion was started with a diagnosis of DKA. However, hemoglobin A1C (HbA1C) was normal (3.4%). Urine ketone became negative after starting insulin infusion. The patient had a fluctuating course of hyperglycemia and hypoglycemia, requiring insulin intermittently. Repeat HbA1C was 5.4% (3.5–6.0%) and C-peptide levels (0.8 ng/mL, range: 0.85–3.85 ng/mL) were normal.

In view of persisting high anion gap metabolic acidosis with varying episodes of hypo- and hyperglycemia, a differential of high anion gap acidosis other than DKA was considered. As kidney function tests (urea: 74 mg/dL and creatinine: 0.7 mg/dL), liver function tests (serum glutamic-pyruvic transaminase/serum glutamic-oxaloacetic transaminase: 31/30 IU/dL), and serum lactate level (1.5 mmol/L) were normal, causes of inborn errors of metabolism (IEMs) such as organic acidemia (methyl malonyl aciduria and propionic acidemia) were considered and metabolic workup was done. Samples for tandem mass spectrometry (TMS) and gas chromatography and mass spectroscopy (GCMS) were sent on day 2 of the PICU stay. Mega doses of vitamins (doses per day: thiamine 50 mg, riboflavin 50 mg, pyridoxine 100 mg, methylcobalamine 500 mg, and biotin 10 mg) and oral carnitine (100 mg/kg/day) were added. Acidosis started improving by day 3 of the illness. The child showed clinical improvement and was extubated.

Serum ammonia levels (98 and 123 μmol/dL) and serum lactate (3.7 and 5.3 mmol/L) were slightly elevated. Serum B12 level (642 μg/dL) and serum homocysteine level (8 mmol/L) were normal. TMS and GCMS reports received on D4 of illness were confirmatory. In TMS, there was a rise in malonyl carnitine (C3-DC) level with a corresponding increase in the secondary level markers with a C3-DC/C5-DC (glutaryl carnitine) ratio (34.6; cutoff: 10). Increased excretion of 2-methyl 3-hydroxybutyric acid, 3-hydroxybutyric acid, acetoacetic acid, and ethyl hydra acrylic acid was noted in the urinary GCMS. Patient's whole exome sequencing was done which detected homozygous *ACAT1* mutation (c.833T>C, p. Val278Ala) in exon 9 on chromosome 11 suggestive of alpha-methyl acetoacetic aciduria.

The child was put on mild protein restriction and L-carnitine supplementation was continued. The patient was discharged with parental education and advice to avoid prolonged fasting and recognize the danger signs of decompensation and sickness management. Parents were counseled about the inheritance of this genetic mutation and its implications for future offspring. Magnetic resonance imaging done on follow-up was normal and the child is keeping well with no lag in neuromotor development.

DISCUSSION

BKT (mitochondrial acetoacetyl-CoA thiolase, T2) deficiency is a rare metabolic disorder that affects the metabolism of ketone bodies and catabolism of amino acid isoleucine. T2 plays an important role in ketone body metabolism. It synthesizes acetoacetyl-CoA from acetyl-CoA in the liver (ketogenesis) and catalyzes acetoacetyl-CoA to acetyl-CoAs in the last step of ketolysis in extrahepatic tissue. T1 (mitochondrial 3-ketoacyl-CoA thiolase) can compensate for T2 deficiency in ketogenesis but to a lesser extent in ketolysis. As a result, T2 deficiency results in ketosis. T2 is the only known enzyme that catalyzes the last step in the isoleucine degradation. It cleaves 2-methyl-acetoacetyl-CoA into propionyl-CoA and acetyl-CoA. Deficiency of this enzyme results in 2-methyl acetoacetic aciduria. Accumulation of amino acid catabolic intermediates 2-methyl acetoacetyl-CoA in blood and its excretion as 2-methyl acetoacetic aciduria is quite characteristic of BKT deficiency and differentiates this disorder from other causes of high anion gap metabolic acidosis (e.g. salicylate poisoning), organic acidemias with blood glucose variation (e.g. hypo-, normo- or hyperglycemia) such as methylmalonic aciduria, propionic academia, and DKA (hyperglycemia, ketosis, and ketonuria).[4,5]

Our patient presented with severe metabolic acidosis with hyperglycemia (471 mg/dL) requiring insulin infusion initially. However, non-resolution of high anion gap metabolic acidosis even with insulin and HCO_3 therapy, varying glycemic records, normal HbA1C, and C-peptide levels necessitated a workup for an inborn error of

metabolism (IEM). Increased malonyl carnitine level and a rise in the secondary markers (C3-DC/C5-DC ratio: 34. 6, cut off 10) in the TMS report suggested methylmalonic aciduria. However, normal complete blood counts, serum B12 and homocysteine levels, and absence of excretion of methylmalonic acid in the urine excluded its diagnosis. Increased urinary excretion of 2-methyl 3-hydroxybutyric acid in addition to acetoacetate, and beta-hydroxybutyric acid suggested the involvement of isoleucine catabolism and ketolytic pathway. Methyl-hydroxyl-butyryl-CoA dehydrogenase (MHBD) deficiency in the isoleucine catabolic pathway also results in the accumulation and excretion of 2-methyl 3-hydroxybutyric acid in urine. However, MHBD deficiency presents as a neurodegenerative disease and does not cause ketosis. Clinical exome sequencing of the patient detected homozygous mutation of exon-9 of chromosome 11 proving the diagnosis of alpha-methyl acetoacetic aciduria and BKT deficiency.

The diagnosis of BKT deficiency is made by urinary organic acid and blood acylcarnitine analysis during acute metabolic decompensation. Increased urinary excretion of 2-methyl acetoacetate, 2-methyl 3-hydroxybutyrate, and tiglylglycine is a hallmark of the disease. Confirmatory tests for diagnosing T2 deficiency are enzyme assay in cultured cells and DNA sequence analysis which shows *ACAT1* gene mutation. Timely suspicion, diagnosis, and management of T2 deficiency carry a very favorable prognosis without any residual sequelae.[6]

Patients with T2 deficiency present with ketoacidotic episodes. The age at onset of symptoms is usually between 6 and 36 months with peak onset at 6–11 months of age. Seizures, altered sensorium, dehydration, tachypnea with metabolic acidosis, ketonuria, and variable glycemia (hyperglycemia and hypoglycemia) are usual during acute metabolic decompensation in these children. However, neurological complications, such as extrapyramidal symptoms, ataxia, and developmental delay can occur as a sequelae of severe metabolic crisis, often with basal ganglia involvement.[7]

Riudor *et al*. have reported metabolic coma with ketoacidosis and hyperglycemia in 2-methyl acetoacetyl-CoA thiolase (T2) deficiency.[8] However, hyperglycemia mimicking DKA is quite an unusual presentation in these children. Al-Hakami *et al*. from Saudi Arabia reported a case of a 2-year-old male child presenting initially with type 1 diabetes mellitus with DKA, requiring insulin infusion and discharged on subcutaneous insulin. During the second admission, the child presented with severe acidosis and hypoglycemia, and the diagnosis of T2 deficiency was made.[9]

The mutations of the *ACAT1* gene are highly diverse. To date, 105 *ACAT1* variants associated with T2 deficiency have been reported in 149 patients. The most frequent variant is c.622C >T (p.Arg208*) accounting for 66% of all *ACAT1* variant alleles identified in Vietnamese patients with T2 deficiency. The second most common disease-associated *ACAT1* variant is c.1006–1G>C which has been identified in 13 families, most of which are Vietnamese in origin. The third most common disease-associated *ACAT1* variant and the most common missense variant is c.578T>G (p.Met193Arg) which has been detected in eight families, most of which are from India. In our case, a novel mutation, homozygous *ACAT1* mutation (c.833T>C, p. Val278Ala) in exon 9, has been noted.[10]

Even though a considerable proportion of symptomatic T2 deficient patients present with severe ketoacidosis with encephalopathy and hemodynamic collapse, hyperglycemia and ketonuria mimicking DKA are not uncommon presentations. Awareness of mimickers of DKA and appropriate management in these children can prevent death or permanent neurological complications as has been observed in our patient. The management of T2 deficiency can be divided into that for acute crisis and during the asymptomatic period. Management of acute ketoacidotic episodes includes intravenous glucose, electrolytes, and insulin infusion, and sodium HCO_3 correction with frequent glucose monitoring, and supportive care with mechanical ventilation and dialysis when required. During the asymptomatic period, patient needs mild protein (1.5–2.0 g/kg/day) restriction, avoids fasting and excess fat intake. During sickness, sufficient oral intake of glucose and electrolyte solution needs to be taken and infection needs to be promptly treated. L-carnitine supplementation is also given especially in those with low carnitine levels.

CONCLUSION

DKA and high anion gap acidosis are not uncommon pediatric emergencies. Awareness of DKA mimickers such as sepsis and IEM needs to be borne in mind while managing these patients. Appropriate workup and treatment of these conditions are required for a favorable outcome.

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Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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