

Beta-ketothiolase deficiency brought with lethargy: Case report

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Abstract

Beta-ketothiolase deficiency is a rare autosomal recessive disorder of isoleucine and ketone body metabolism. This disorder is clinically characterized by ketoacidotic attacks. Ketoacidosis, vomiting, and dehydration, lethargy and coma may be seen during attacks. A 9-month-old girl was admitted to our hospital with acidosis and dehydration. The patient was lethargic. Ketoacidosis was suspected because of acetone odor on her breath. Her blood glucose level was 262 mg/dL and urine ketone was (++++). Branched chain amino acid levels were elevated in her blood sample. Organic acid analysis of urine revealed 2-methylacetoacetyl-CoA thiolase deficiency. This was reported because of rarity of the disease and we should consider it in the differential diagnosis of ketoacidotic episodes.

Keywords

beta-ketothiolase deficiency, ketoacidosis, coma

Introduction

The beta-ketothiolase enzyme (2-methylacetoacetyl-coenzyme A thiolase), a mitochondrial molecule, takes place through L-isoleucine catabolism and ketone bodies metabolisms. Beta-ketothiolase enzyme catalyzing, the last step in the isoleucine catabolism, has a major role in ketolysis as well as ketogenesis.^{1–3} A rare disease, only 50 cases of beta-ketothiolase deficiency have been reported in literature. Autosomal recessive inheriting congenital beta-ketothiolase enzyme deficiency or lack may cause life-threatening vomiting, dehydration, metabolic acidosis, lethargy, shock, and coma. However, it may be heterogeneous as a clinical finding. It varies from the coma table to the asymptomatic adult.⁴ In general, ketoacidotic attacks appear after triggers such as gastroenteritis, infections, and stress.^{4,5}

Diagnosis is acquired through testing for mild to severe ketoacidosis and urine organic acid directory, with increased 2-methyl 3-hydroxybutyric acid, tiglyl glycine, and 2-methyl acetoacetic acid and 2-butanon levels. There is only one case in literature that is reported along with hyperglycinemia.^{6,7} In this article, this case has been proposed although it is rare since it is a genetic disease that needs to be considered within diseases resulting in ketoacidosis and lethargy.

Case study

A 9-month-old girl was admitted to our clinic, with complaints including vomiting, somnolence, and excessive breathing. The patient was vomiting with fever for about 2 days, had taken less breast milk, vomited immediately after getting supplements, and lost 700 g; thus, she was brought to our pediatric emergency unit by her family. There was no similar disease with her personal or family history. She was not on any medication except Devit-3 drop. Upon physical examination, our case, the fourth child on her family of second grade consanguineous marriage, was determined to be 8.2 kg in weight (between 25 and 50).

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percentile), 70 cm in height (50. percentile), and 44 cm in head circumference (between 25 and 50. percentile). She appeared poor in general, dehydrated, and presented as lethargic. The patient had a 37.2°C axillary body temperature, 172/min peak heart rate, 75/35 mmHg blood pressure, 64/min respiratory rate, somnolence, dry mucosa, dry tongue, sunken eyeballs, sunken front fontanel, pale skin, decreased turgor and tonus, and respiratory acidosis. Acetone odor was found on her breath. Subcostal and intercostal retractions and rales in the long basal were determined, the liver was palpated at 3–4 cm on the midclavicular line, and bowel sounds were hypoactive. She was hypotonic and her responses were low to painful stimulations. No pathological reflex or meninx irritation findings were detected. In the full urine analysis, ketone was determined to be (++++), protein to be (+), leucocytes to be 10–12; in the full blood count, leucocytes: 21,000 (mm³), Hb: 12.1 g/dL, thrombocyte: 424.000/mm³, CRP: 18 mg/dL; in the peripheral blood smear, granulocyte 56%, lymphocyte 8%, basophil 34%, monocyte 2%; in addition, anisocytosis, poikilocytosis, hypochromia, and toxic granulation were found. In the blood gas analysis, pH was determined to be 7.19, pO₂ was 65 mmHg, pCO₂ to be 32 mmHg, and bicarbonate was 7 mEq/L. In the blood biochemistry, electrolytes, kidney, liver function, and lactate levels were normal. Glucose was determined as 262 mg/dL, and ammonia as 91 mcg/dL (31–123 mcg/dL). Ketone was positive in the blood. Urgent brain tomography and subsequent brain magnetic resonance imaging were assessed as normal. Organic acidemia was thought to be present in the patient. Treatment for metabolic acidosis was started with an appropriate liquid, bicarbonate treatment, and ceftriaxone 100 mg/kg/day for urinary tract infection. In the organic acid analysis of the urine sample taken during the attack before treatment, increased 3-hydroxybutyric acid and 2-methyl-3-hydroxybutyric acid values were observed (Table 1). In the acylcarnitine profile with Tandem Mass Spectrometry, increased C5-OH3-hydroxyisovaleric carnitine and C5-tiglyl carnitine levels were observed. In the blood spot sample, while free acyl-carnitine amino acid, free carnitine, and amino acid levels were found to be normal, 3-hydroxybutyryl carnitine, 3-hydroxy isovaleric carnitine, and tiglyl carnitine were high (Table 1). Clinical findings were found that comply with beta-ketothiolase enzyme deficiency when combined with the history and laboratory test results. Ketone in the urine was lost after 12 hours. After 24 hours

Table 1. Organic acid values of the patient with acute attack

Organic acids	Urine (μmol/mol creatine)
3-OH butyric acid	4171 (N: 0–11.1)
2 methyl 3-OH Butyric acid	108 (N: 3.2–26.6)
Organic acid	Blood (μmol/L)
3-hydroxybutyryl carnitine	1.64 (N: 0–0.5)
3-hydroxyisovaleryl carnitine	1.85 (N: 0–1)
Tiglyl carnitine	0.62 (N: 0–0.4)

Table 2. Urine organic acid values after 2 weeks from the acute attack

Organic acids	Urine (μmol/mol creatine)
Tiglylglycine	146 (N: 0)
2 methyl 3-OH butyric acid	372 (N: 3.2–26.6)
Organic acids	Blood (μmol/L)
3-hydroxy butyrylcarnitine	0.54 (N: 0–0.5)
3-hydroxy isovaleryl carnitine	1.46 (N: 0–1)

from application, blood gas values were within normal range. By examination at Hour 48 from her admission, her state of consciousness and other findings were back to normal. Two weeks after the acute attack, the urine organic acid assessment was repeated. We found 2-methyl 3-hydroxybutyric acid, and tiglyl glycine values to be high in accordance with the diagnosis of beta-ketothiolase deficiency (Table 2). Within the examination of free acyl carnitine and amino acid level in the blood collected 2 weeks after the attack, we determined 3-hydroxybutyryl carnitine and 3-hydroxy isovaleric carnitine values to be high (Table 2). Patient was started with L-carnitine 100 mg/kg/day, and a protein-limited (0.5–1 g/kg) low-fat diet was arranged. With a better general state and increased oral intake, the baby was discharged and referred to a medical center with pediatric endocrinology and metabolism department for follow-up.

Discussion

Beta-ketothiolase enzyme deficiency is a rare congenital metabolic disease with failed isoleucine catabolism and ketone body metabolism. Beta-ketothiolase in the mitochondrion irreversibly catalyzes propionyl coenzyme A formation from 2-methyl acetoacetyl coenzyme A in L-isoleucine catabolism. Acetoacetyl coenzyme A in cytosol reversibly catalyzes acetoacetyl coenzyme A formation from two acetyl coenzymes A in ketone body catabolism. Two completely different

diseases were reported, with congenital deficiency of both enzymes. The enzyme deficiency in cytosol is mostly in relation with mevalonic acinemia such as progressive growth retardation, hypotony, and choreoathetosis. Genetic abnormality was found with the long arm of chromosome 6. The gene related to beta-ketothiolase deficiency in the mitochondria was determined to be with the long arm of chromosome 11.⁸

Clinical findings may vary in beta-ketothiolase deficiency. Malnutrition in the newborn and infant periods may cause vomiting, diarrhea, ketoacidotic attacks, lethargy, and life-threatening metabolic coma; the symptoms may wait in silence until adulthood.^{3,9} In general, ketoacidotic attacks are triggered by gastroenteritis, upper respiratory tract infection, and factors causing physiologic ketosis in normal children, including fastening or stress, or increased protein intake. Central nerve system findings such as vomiting, dehydration, dyspnea, and lethargy to coma may be observed during the attacks.^{2,5} 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.³

Our patient had no complaint and had showed normal neuromotor development characteristics before the attack; however, she presented with rapid developing dehydration with shock and lethargy table. Since our patient's dehydration responded well to the metabolic acidosis fluid and bicarbonate treatment, no peritoneal dialysis was needed. Glucose metabolism defects may be seen in beta-ketothiolase deficiency. Our patient had hyperglycemia when presented, her hyperglycemia decreased to the rapid normoglycemic level, with appropriate fluid supplement, and she recovered from the acidosis.

High excretion of 2-methyl-3-hydroxybutyric acid tiglylglycine and 2-methylacetoacetate in urine was defined in literature by gas chromatography and mass spectrometry. The patient's urine, examined this way, found 2-methyl-3-hydroxybutyric acid and tiglylglycine levels were found to be normal. For the disease, severe metabolic acidosis is present in the blood gas analysis. Ammoniac is normal in general; however, rare cases have been reported with moderate levels.^{4,5} In our case, metabolic acidosis was present, but ammoniac levels were at normal levels. The distinguishing diagnosis of the disease includes all diseases causing ketoacidosis. Assessing blood gas, lactate, pyruvate, ammoniac, and urine organic acid analysis during the acute attack eliminates diabetic ketoacidosis, ketotic hypoglycemia, hormonal deficiency (such as growth

hormone, glucocorticoid), glucose and glycogen metabolism defects, congenital lactic acidosis, and other organic aciduria types. Salicylate poisoning should be taken into account.^{4,5} In our case, acylcarnitine analysis and urine organic acid levels complied with beta-ketothiolase deficiency. The purpose in the acute attack is to repress ketogenesis and to regulate acidosis. Acidosis should be treated carefully, and rapid alkalization should be avoided. Carnitine support should be started in terms of facilitating accumulated acyl CoA excretion.

The prognosis of beta-ketothiolase deficiency is good with early diagnosis and treatment; patients may live without any symptoms despite constant findings of increased metabolites in blood and urine. Sewell et al.¹⁰ have reported a case being followed-up since 8 years old with beta-ketothiolase deficiency diagnosis, with the patient having at 30 years old after an unproblematic pregnancy. Within the treatment approach, a diet with limited protein intake and a low level of isoleucine is advised. A diet rich in fats should be avoided since fats induce ketogenesis. Patients should avoid being hungry for long periods of time. In cases of low carnitine levels L-carnitine supplement (50 200 mg/kg/day) must be included.⁴ In our case, carnitine level assay could not be measured, but L-carnitine of 100 mg/kg/day was started to prevent secondary carnitine deficiency. Beta-ketothiolase deficiency is a disease passed through autosomal recessive inheritance and may be prenatally diagnosed.¹¹ With beta-ketothiolase deficient, it is important that other family members be scanned to prevent a possible ketoacidotic crisis. Our patient's family was advised to be scanned as well as followed up and monitored by the endocrinology and metabolism polyclinic. In our county, with common consanguineous marriages, beta-ketothiolase deficiency as a genetic disease should be considered in distinguishing the diagnosis of patients presenting with the attacks of changes in consciousness, acidosis, and blood sugar abnormalities corresponding to hyperketonemia.

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