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CASE REPORT

SCOT DEFICIENCY MIMICKING SEPSIS: AN UNUSUAL CAUSE OF INCREASED ANION GAP METABOLIC ACIDOSIS

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ABSTRACT

Introduction: Succinyl-CoA:3-oxoacid CoA transferase (SCOT, EC 2.8.3.5) deficiency is a rare autosomal recessive inborn error of metabolism (IEM). We report here an infant admitted to intensive care unit with the diagnosis of sepsis.
Case Presentation: A five-month-old female patient was admitted to the intensive care unit with lethargy and respiratory distress. She had severe high anion gap metabolic acidosis. The IEM was screened by plasma amino acid analysis, showing no abnormalities, and by acylcarnitine analysis, showing low-normal levels of free carnitine. Urine organic acid analysis revealed massive ketonuria and elevated levels of dicarboxylic acids. Fatty acid oxidation disorder-targeted gene panel revealed a homozygous splice site variant (c.78+1_78+6 del) in the OXCT1 gene.
Discussion and Conclusion: SCOT deficiency should be considered when massive ketosis is detected in increased anion gap metabolic acidosis with sepsis-like manifestation. Supportive therapy should be initiated quickly to prevent irreversible neurological damage.

Keywords: Metabolic acidosis, *SCOT* deficiency, anion gap

INTRODUCTION

SCOT deficiency (OMIM#245050) is an autosomal recessive inborn error of ketone metabolism, caused by mutations in the OXCT1 gene on chromosome 5p13. There are less than 50 patients reported to date (1). Ketone bodies are produced in the liver by fatty acid oxidation or by catabolism of small amounts of ketogenic amino acids (2). When there is a shortage of glucose as an energy source, tissues, and the brain in particular, utilize ketone bodies(KB) to supply energy. Succinyl-CoA:3-oxoacid CoA transferase (SCOT;EC 2.8.3.5), the deficient enzyme in SCOT deficiency, is involved in the first step of ketone body utilization and catalyzes reversible transfer of CoA from succinyl-CoA to acetoacetate (3). In cases of an increased need for energy such as starvation, infection, and surgery, glucose is insufficient to provide energy and needs ketone support. In the patients with SCOT-deficient; KBs cannot be utilized and accumulates in the body.

Table 1. The acylcarnitines profile and urine organic acid analysis for the patient with SCOT deficiency.

	Unit	Value	Reference range
DBS carnitine			
Free carnitine	(µmol/L)	11.9	8–60
C3-DC/C4-OH	(µmol/L)	0.55	< 3.03
Total carnitine	(µmol/L)	28.33	
C2	(µmol/L)	11.01	5–80
C3+C16	(µmol/L)	**1.62**	> 2.0
PHE/C3+C16	(µmol/L)	**19.75**	< 20
Urine organic acid			
Acetoacetic acid	(mmol/mol Crn)	**63.4**	< 19
Adipic acid	(mmol/mol Crn)	**1796**	< 22
2-methylacetoacetic acid	(mmol/mol Crn)	**-**	< 24
3-Hydroxyisovaleric acid	(mmol/mol Crn)	**778.4**	< 24
3-hydroxybutyrate	(mmol/mol Crn)	**9288**	< 63
3-hydroxy-2-methylbutyric acid	(mmol/mol Crn)	**-**	< 10
Suberic acid	(mmol/mol Crn)	**51.1**	< 10

Inborn errors of metabolism (IEM) can present with non-specific symptoms such as vomiting, poor feeding, and lethargy. Clinicians first consider sepsis due to these findings and initiate the treatment. Presentation with neurological deterioration such as sudden coma, and lethargy following an uneventful history is a characteristic of IEM (4). This paper will present an infant with SCOT deficiency that and was diagnosed upon the clue of increased anion gap metabolic acidosis revealed by laboratory examinations.

CASE REPORT

A five-months-old female patient was admitted to the intensive care unit with lethargy and respiratory distress. The patient was born uneventfully at gestational age of 40 weeks and with birth weight of 2010g. Her parents were consanguineous. Her developmental skills were appropriate to age. She started receiving complementary foods one week before the admission and the mealtime started to get longer. On evaluation, body temperature was 36.7°C, blood pressure was 94/52 mmHg, heart rate was 164/min, respiratory rate was 80/min, and Glasgow coma score was 7 (E2V2M3). She had hypotonia, tachycardia, and decreased response to pain. Laboratory analyses revealed metabolic acidosis (pH: 7.10; pCO2: 15 mmHg; HCO3: 4.6 mmol/L; base excess: 23.1) with normoglycemia (6.3 mmol/L) and anion gap of 25.4 mmol/L (Na: 143 mmol/L; Cl: 113 mmol/L). Blood lactate (0.065 mmol/L) and ammonia (69 µmol/L) were within the normal range. Urine ketones were highly positive (++++). There were no laboratory findings suggestive of infection.

We initiated treatment with intravenous fluids containing high dextrose, sodium bicarbonate and vitamin cocktail due to the suspected IEM. Parental administration of sodium bicarbonate resulted in resolution of acidosis over 12 hours. To screen the IEM, we investigated acylcarnitine, plasma amino acids, and urine organic acids. The plasma amino acid analysis showed no abnormalities, while acylcarnitine showed low- normal levels of free carnitine. Urine organic acid analysis revealed massive ketonuria and elevated levels of dicarboxylic acids, (Table 1), and thus SCOT deficiency was diagnosed.

The infant was discharged at day 10 of admission under carnitine therapy and advised to avoid prolonged fasting. Fatty acid oxidation disorder-targeted gene panel (Illumina, MiniSeq®,USA) revealed a homozygous splice site variant (c.78+1_78+6 del) in the OXCT1 (ENST00000196371) gene. The parents were identified as carriers for the same mutation by Sanger Sequencing (Table-1). The patient is currently one year old, growing well, and no further metabolic decompensation has occurred.

DISCUSSION

SCOT deficiency is a rare disease; patients are completely normal in the non-metabolic crisis period (1). In IEMs presenting with metabolic crises with high morbidity, early diagnosis and rapid intervention can prevent irreversible damage (5). Due to their rarity, these diseases are not considered. Capturing the clues of IEM with a comprehensive assessment enables clinicians to reach a diagnosis. Consanguinity is the first clue in the history for IEM

(6). Disorders with a reduced fasting tolerance including fatty acid oxidation and ketogenesis typically present during periods of reduced food intake and/or increased energy need such as prolonged fasting or metabolic stress (7). The onset of patient's complaints after receiving complementary foods, especially the reduced number of meals, was another clue in the history.

Generally, the amount of unmeasured anion increases in circulation due to reasons such as diabetic ketoacidosis, uremia, and salicylate intoxication. When increased anion gap metabolic acidosis is detected, basic tests such as glucose, electrolytes, liver function tests, lactate, ammonia and ketones are used secondarily to reduce the disorders in the differential diagnosis (5). On clinical picture of anion gap metabolic acidosis with neurological deterioration; organic acidemias such as isovaleric acidemia, methylmalonic acidemia, propionic acidemia, or pyruvate metabolism disorders are considered (4). The findings of hyperammonemia in patients with organic acidemia is helpful in differential diagnosis (8). Anion gap metabolic acidosis can also be detected in pyruvate metabolism disorders, but it can be differentiated from inborn errors of ketone metabolism by the normal lactate level. Another clue in the present patient was that a mild symptom such as loss of appetite could turn into a severe clinical picture such as coma during day, which could improve within hours with only hydration therapy. SCOT-deficient patients usually respond to hydration therapy (9) and rarely need dialysis (10). When metabolic screening is examined, low carnitine may cause false negative results in acylcarnitine analysis due to insufficient saturation of acylcarnitine. The second important issue is that if the patient has high level of excretion (due to kidney function, or overhydration or drug use), the diagnostic value of the ACCRN profile would be low (11,12). The patient was diagnosed with SCOT deficiency by the massive ketonuria and elevated levels of dicarboxylic acids in the sample collected in the non-fasting period, detected in the urine organic acid profile. Since 3-hydroxy-2-methylbutyric acid and 2-methylacetoacetic acid were not detected in urine organic acid analysis, 2-Methylacetoacetyl CoA thiolase deficiency, a member of the ketone body utilization disorders, was not considered in this patient (2).

Mutations in the OXCT1 gene have been reported in 38 patients to date (1). The splice site mutation identified in our patient (c.78+1_78+6 del) was previously reported in a 16-month-old female patient of Turkish origin. Similarly, the SCOT activity in the fibroblasts was measured 15% less in the patient who presented with ketoacidosis attack (13). In the present case, functional enzyme analysis could not be performed in our laboratory due to reasons such as financial burden. However, the clinical, biochemical and molecular findings support SCOT deficiency.

In conclusion, SCOT deficiency should be considered in patients with increased anion gap metabolic acidosis. Supportive therapy should be initiated quickly to prevent irreversible neurological damage.

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