A Case of Succinyl-CoA:3-Oxoacid CoA Transferase Deficiency Presenting with Severe Acidosis in a 14-Month-Old Female: Evidence for Pathogenicity of a Point Mutation in the *OXCT1* Gene

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Abstract

Keywords

- ▶ succinyl-coA: 3-oxoacid CoA transferase deficiency
- ▶ *OXCT1* gene
- ▶ ketoacidosis

We describe a case of succinyl-CoA:3-oxoacid CoA transferase (SCOT) deficiency in an otherwise healthy 14 month-old female. She presented with lethargy, tachypnea, and hyperpnea with hypoglycemia and a severe anion gap metabolic acidosis. Early management included correction of the acidosis and metabolic support with dextrose and insulin. Inborn errors of metabolism are rare outside the neonatal period. However, SCOT deficiency may present at older ages. Maintaining a high index of suspicion, immediate transfer to a pediatric intensive care unit, and prompt metabolic support are key to achieving a favorable outcome.

Introduction

Succinyl-CoA:3-oxoacid CoA transferase (SCOT, EC 2.8.3.5) deficiency is a rare autosomal recessive inborn error of ketone metabolism caused by mutation of the *OXCT1* gene.^{1,2} SCOT is an important enzyme in ketolysis that allows for the activation of acetoacetate to acetoacetyl-CoA in extrahepatic mitochondria, a necessary step in the utilization of ketones for energy in the citric acid cycle.³ Individuals who are totally deficient in this enzyme are prone to develop ketoacidosis during stress states and periods of fasting because of the propensity of ketone bodies to accumulate in the liver and subsequently in the blood when they cannot be converted to energy.⁴ The severe form of this disorder is rare, with approximately 30 to 40 cases reported worldwide since it was first described in 1972.^{5–28}

The age of onset for SCOT deficiency appears to be variable, with more than half of all cases presenting in the neonatal period.⁴ Patients are typically asymptomatic in the intervals between episodes of severe acidosis. Patients

who present acutely later in childhood pose significant diagnostic challenges. It is also difficult to diagnose SCOT because there are no characteristic metabolites apart from a nonspecific pattern of an anion gap metabolic acidosis with ketone bodies on laboratory testing.⁴

With this report, we discuss the diagnosis and critical care management of a previously healthy 14-month-old female who presented acutely with refractory metabolic acidosis and was eventually found to have a single nucleotide variation of newly determined significance leading to SCOT deficiency.

Patient Presentation

A previously healthy 14-month-old Hispanic female was presented to an outside emergency department with lethargy, tachypnea, hyperpnea, and tachycardia with normal blood pressure, worsening over the last day in the setting of recently spacing out her infant feeds. She notably had no symptoms of antecedent illness (e.g., viral respiratory infection) and had been fasting for 12 hours. Her initial laboratories were

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significant for blood glucose level of 31 mg/dL, arterial pH of 7.01, lactate of 1.1 mmol/L, and anion gap greater than 40. She received a dextrose bolus, 20 mL/kg normal saline, and was placed on a maintenance 5% dextrose infusion while being transferred to our pediatric intensive care unit from the outside hospital. The glucose infusion rate was maintained at a minimum of 4.6 mg/kg/minute with titration according to the patient's blood sugar.

On arrival, she was found to have a worsening high anion gap acidosis with pH 6.70, unmeasurable (less than -30 meq/L) base deficit, and lactate of 0.3 mmol/L. Initial stabilization included intubation, central line placement, multiple doses of sodium bicarbonate, and infusions of 10% dextrose, sodium bicarbonate, and insulin. Her pH slowly improved from 6.90 to 7.20 over 16 hours of aggressive therapy. At that point, her anion gap had decreased to 18 and her pH normalized. As her sodium bicarbonate infusion was weaned, her anion gap rose to 31 with a pH of 7.35, and bicarbonate was added back to her maintenance fluids. She was maintained on sodium bicarbonate maintenance fluids for an additional 14 hours. During this time, extensive toxicology, nephrology, and endocrinology work-up did not reveal an underlying etiology. ►Table 1 details the patient's acid-base status over the first 50 hours of treatment.

Evaluation for an inborn error of metabolism sent at admission included plasma amino acids, urine organic acids, plasma acylcarnitine, plasma (total, free, and esterified carnitine), methylmalonic acid level, uric acid, and lipid profile. These revealed a severe catabolic state with a nonspecific pattern of ketosis that was elevated well beyond the normal range, suggestive of a primary ketolysis disorder. ►Table 2 details these abnormal findings. While urinary lactate was elevated, potentially raising concern for other enzymopathies, the serum lactate was never abnormal and follow-up genetic testing helped clarify the diagnosis.²⁹ The fatty acid profile was not sent in the acute decompensation, but in follow-up, the patient was noted to have an essentially normal fatty acid profile with the exception of persistently elevated docosahexaenoic acid (200 nmol/mL, normal range: 30–160 nmol/mL).

Focused whole exome sequencing revealed a homozygous missense single nucleotide variation in a highly conserved region of exon 8 of the *OXCT1* gene on chromosome 5 (c.733G > T:p.V245F). The noted variation is a change of a single guanine to thymine in the DNA leading to an amino acid change from valine to phenylalanine (V245F). This mutation was not observed in the Exome Aggregation Consortium (ExAC) database consisting of more than 60,000 individuals of all ethnicities.³⁰ Parents denied consanguinity, and a three-generation pedigree revealed no relatives with similar disease or unexpected death (►Fig. 1).

The patient was extubated on hospital day 5 and discharged on day 9 in her normal state of health. She was given a strict meal schedule and calorie counts to ensure that she would not exceed 10 hours of fasting. Her parents were instructed to routinely check her urine for ketonuria with home test strips. At her last clinic visit, 8 months after discharge, she has not had persistent ketonuria and has resumed her normal development.

Discussion

Severe metabolic acidosis with an elevated anion gap, low glucose, and normal lactate in a child is concerning for toxic ingestion versus inborn error of metabolism. Presentation outside the newborn period lessens but does not eliminate the probability of an inborn error of metabolism as an etiology. SCOT deficiency, the eventual diagnosis, may present acutely in children up to several years old. ►Table 3 summarizes the published SCOT cases with age of onset and mutation, if known. This case highlights the importance of maintaining a high index of suspicion for an inborn error of metabolism even in previously healthy, normally developing children.

Our patient was found to have SCOT deficiency after laboratory testing revealed a nonspecific pattern of ketosis and a point mutation V245F was identified in the *OXCT1* gene. This point mutation had previously been classified as a variant of unknown significance in three individuals in 2014.³¹ Our patient's presentation presents compelling evidence for pathogenicity of

Table 1 Acid-base status and management over the first 50 hours of treatment

Time	pH	Base excess	Anion gap	Fluid management
Day 1, 13:06	6.70	−28		Sodium bicarbonate bolus 4 meq/kg
Day 1, 13:37	6.99	−20		Sodium bicarbonate bolus 2 meq/kg
Day 1, 15:16	6.91	−22		Sodium bicarbonate bolus 4 meq/kg
Day 1, 22:08	7.06	−21	37	Sodium bicarbonate bolus 9 meq and sodium bicarbonate infusion started
Day 2, 03:54	7.16	−10	23	
Day 2, 10:03	7.29	+4	18	Infusions stopped
Day 2, 15:50	7.46	+6	20	
Day 3, 02:45	7.34	−9	29	Bicarbonate added to maintenance fluids
Day 3, 05:54	7.37		24	
Day 3, 11:55			17	
Day 3, 17:52	7.51		14	Bicarbonate removed from fluids

Table 2 Abnormal laboratory testing for inborn error of metabolism

Test	Patient's result	Normal range
Serum β -hydroxybutyrate	8.62 mmol/L	0.02–0.27 mmol/L
Urinary 3-hydroxybutyric acid	>20,000 mmol/mol creatinine	0–4 mmol/mol creatinine
Urinary acetoacetic acid	>40,000 mmol/mol creatinine	0–5 mmol/mol creatinine
Urinary lactic acid	1,291 mmol/mol creatinine	0–150 mmol/mol creatinine
Urinary pyruvic acid	49 mmol/mol creatinine	0–30 mmol/mol creatinine
Urinary 2-keto-3-methylvaleric acid	28 mmol/mol creatinine	0–10 mmol/mol creatinine
Urinary 2-ketoisocaproic acid	16 mmol/mol creatinine	0–4 mmol/mol creatinine
Urinary 2-ketoisovaleric acid	33 mmol/mol creatinine	0–4 mmol/mol creatinine

Fig. 1 Three-generation pedigree as assessed by clinical history. Arrow signifies patient described in this report.

this variant. More than 20 mutations in the *OXCT1* gene have previously been identified in SCOT deficient patients and structurally mapped by Shafqat et al.³² Based on this paper and structure analysis using Chimera molecular modeling system (University of California, San Francisco), it appears that our patient's mutated residue falls in close proximity to known pathogenic mutations in a highly conserved hydrophobic pocket important for protein dimerization.^{32,33} Introduction of a larger but still hydrophobic residue would likely inhibit but not eliminate SCOT dimerization, providing a theoretical mechanism for protein dysfunction in this case.

The nonspecific pattern of ketosis on urine organic analysis is helpful in distinguishing the disorder from mitochondrial acetoacetyl-CoA thiolase (T2) deficiency, a similar autosomal recessive disorder of ketolysis that has more specific metabolites on laboratory tests.⁴ T2 deficiency can present identically to SCOT deficiency with an acute ketoacidotic attack in a child between 5 months and 2 years of age, often triggered by infection or starvation.⁴ Hori et al published general guidelines for the diagnosis of ketone body utilization disorders including SCOT deficiency and T2 deficiency in 2015.⁴ These guidelines maintain that ketone body utilization disorders should be suspected in patients with more severe ketosis than expected with a clinical history of fasting and/or febrile condition. It ought to be noted that this clinical history of fasting may be fairly mild and, in our patient, may have otherwise been missed given that this fasting was consistent with normal development. The patient's mother had only been spacing out infant feeds in the

context of longer continuous periods of sleep. There was no preceding viral prodrome or any symptoms suggestive of ingestion or another triggering stress state.

This report must be interpreted within the context of certain limitations. No functional enzyme analysis was performed (e.g., with patient fibroblasts) as this test is not readily available through our laboratory and is not common practice for our geneticists. However, the patient's clinical and biochemical presentation strongly supports a diagnosis of SCOT deficiency. Familial analysis was deferred for the patient's parents due to the family's financial concerns. Recognizing that homozygosity for a rare variant is unusual in nonconsanguineous parents, we cannot exclude the possibility of a large deletion on one allele giving the appearance of homozygosity.

Conclusion

We present a unique case of delayed but severe onset of SCOT deficiency associated with spacing out enteral feeds. This case is associated with a point mutation of SCOT, V245F, which had previously been classified as a variant of unknown significance. Despite our patient's extremely low pH and slow correction, she recovered with no deficits. Our case emphasizes the importance of rapid transfer to a pediatric critical care unit with aggressive supportive care and early metabolic support. If a pediatric critical care unit is not readily available, intravenous dextrose and insulin are the critical steps to reverse ongoing ketosis and may provide

Table 3 Age at presentation and identified mutations in all reported cases of succinyl-CoA:3-oxoacid CoA transferase deficiency

Report	Age at presentation	Mutation
Perez-Cerda et al 1992 ⁸	26 h	S283X (homozygous) ^a
Snyderman et al, 1998 ^{1,2}	38 h	Unknown
Fukao et al 2010 ²⁵	2 d	Paternal T435N; maternal c.658–666dupAACGTGATT p.N220_I222dup
Yamada et al 2007 ²⁶	2 d	671G > A, which is a single-base substitution at the last nucleotide of exon 6
Fukao et al 2011 ¹⁷	3 d	Paternal E273X; Maternal V404F
Pretorius et al 1996 ⁷	3 d	Two siblings, R268H (homozygous) ^a
Niezen-Koning et al 1997 ¹⁰	3 d	Unknown
Berry et al 2001 ¹⁹	4 d	G324E (homozygous)
Middleton et al 1987 ¹⁴	>30 d	Unknown
Tildon et al 1972 ⁵	51 d	Unknown
Barić et al 2001 ¹⁶	6 mo	L327P (homozygous) ^a
Sakazaki et al 1995 ⁶	6 mo	Unknown
Hori et al 2013 ²⁷	7 mo	Homozygosity for a G to A mutation at the fifth nucleotide of intron 13
Longo et al 2004 ²²	8 mo	R217X (homozygous)
Middleton et al 1987 ¹⁴	10 mo	Unknown
Fukao et al ¹⁷ 2004	10 mo	Two brothers, both with T435N (homozygous)
Present case	14 mo	V245F (homozygous)
Fukao et al 2006 ²³	16 mo	6 bp deletion at the splice donor site of intron 1
Fukao et al ¹⁷ 2004	17 mo	T435N (homozygous)
Rolland et al 1998 ¹¹	17 mo	S405P ^a
Fukao et al 2011 ¹⁷	19 mo	R468C (homozygous)
Merron et al 2009 ²⁰	22 mo	Unknown
Fukao et al 2011 ¹⁷	3 y	Paternal A215V; maternal S226N
Erdol et al 2016 ²⁸	8 mo	Paternal M515V; maternal K173E

^aCase reports where the causative mutation is identified in a subsequent study.

enough benefit to stabilize a patient without escalating interventions. We conclude that inborn errors of metabolism in children with severe refractory metabolic acidosis must be considered even in the absence of other medical history for prompt diagnosis and good outcomes.

Note

All procedures were conducted in compliance with the policies of the Yale Institutional Review Board.

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