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A case of severe acidosis in a 12-month-old: Succinyl-CoA:3-ketoacid-CoA transferase deficiency with *OXCT1* gene mutations

Navjot Dhammi, Jenna Essakow, Renata Gallagher and Cynthia Gaw

Abstract

Succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency is a rare autosomal recessive disorder that results in severe ketoacidosis due to a defect in ketone utilization. We describe a case of a 12-month-old infant presenting with severe metabolic acidosis, ketosis, and hyperammonemia, a combination of symptoms suggestive of an inborn error of metabolism. Genetic testing found our patient had a homozygous variant in the *OXCT1* gene, c.1543A>G (p.Met515Val). This was the first identified case of SCOT deficiency at our institution. We share our acute management strategies for initial stabilization in the intensive care unit, as well as our approach to preventing morning ketosis after discharge using uncooked cornstarch.

Keywords

Organic acidemia, inborn errors of metabolism, metabolic acidosis, succinyl-CoA:3-ketoacid CoA transferase deficiency

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Introduction

Certain inborn errors of metabolism often present early in the neonatal period while others are seen later in infancy and require prompt diagnosis and management, as acute presentations can result in severe neurological deficits.[1] Succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency is a rare autosomal recessive (OMIM #245050) ketone utilization defect that presents with recurrent or episodic ketoacidosis in later infancy.[2] Common presentation is a high anion gap acidosis secondary to ketone use disorder.

Ketone bodies (acetoacetate and 3-hydroxybutyrate) are alternate substrates of energy in fasting states, formed from fatty acid oxidation and ketogenesis in hepatocytes and transferred via the bloodstream to non-hepatocyte mitochondria, where they are used as substrates for the tricarboxylic acid cycle.[1] Patients with SCOT deficiency have a defect in ketolysis producing an accumulation of ketone bodies with resultant ketoacidosis.[4]

We report a case of a 12-month-old infant with SCOT deficiency who presented twice with severe acidosis requiring intensive care and careful discharge planning.

Case report

Our patient is a 12-month-old male with mild motor delay and no other significant medical history admitted after presenting to the emergency department with a 4 day history of upper respiratory symptoms, 1 day of diarrhea, and worsening mental status changes. At baseline, the patient was nonverbal, unable to roll over, sit up unassisted, or pull to stand. The infant was born at 39 weeks via spontaneous vaginal delivery to a G1P1 mother. Prenatal history was notable for severe pre-eclampsia in the third trimester and insufficient prenatal care in the second trimester.

The mother of the patient initially brought him to an outside emergency room the day prior to admission for ongoing respiratory symptoms, most significantly tachypnea. He was diagnosed with bronchiolitis and sent home. On the day of admission, the family returned to the hospital as the patient had worsening symptoms and was difficult to arouse.

Initial laboratory findings identified a severe metabolic acidosis with pH 6.87 (NmL 7.31–7.47 pH), pCo2 21 mm Hg (NmL 30–50 mm Hg), bicarbonate 3 mmol/L (NmL 18.0–23.0 mmol/L), anion gap 30 mEq/L (NmL 3–10 mEq/L), and markedly elevated serum ketones (Table 1), initially

Department of Pediatrics, UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA

Corresponding Author:
Navjot Dhammi, Department of Pediatrics, UCSF Benioff Children's Hospital Oakland, 747 52nd Street, Oakland, CA 94609-1809, USA.
Email: nav.dhammi92@gmail.com

Table 1. Laboratory values at presentation, transfer, and readmission.

	Initial presentation – Santa Rosa Memorial	Upon transfer – Children's Hospital Oakland	Readmission – Santa Rosa Memorial	Readmission – Children's Hospital Oakland	Reference range
pH	6.87	7.04	7.2	7.16	7.31–7.47
HCO_3- (mmol/L)	3	3	9	5	18.0–23.0 mmol/L
Anion gap (mEq/L)	30	30	23	33	3–10 mEq/L
Serum ketones (mmol/L)	>4.5	8.41	–	2.91	0.2–0.27 mmol/L
Urine ketones	–	2+	–	2+	Negative
Ammonia (µmol/L)	–	115	–	40	29.0–59.0 µmol/L
Serum glucose (mg/dL)	194–230	130	75	41	54–117 mg/dL
WBC (Th/mm^3)	30.3	35.6	14.2	14.9	5.0–15.0 Th/mm^3
Platelets (Th/mm^3)	764	684	739	526	150–400 Th/mm^3
Predisposing factor	Rhinovirus infection		Emesis		

concerning for possible diabetic ketoacidosis or toxic ingestion.

Upon transfer to the pediatric intensive care unit, the patient was afebrile, tachycardic, and tachypneic with a Kussmaul breathing pattern. He was minimally responsive to stimulation, only opening his eyes or moving with painful stimuli. Repeat labs were significant for a similar blood gas with a severe anion gap metabolic acidosis, glucose levels >200 mg/dL (NmL 54–117 mg/dL), and serum beta-hydroxybutyrate greater than 4.5 mmol/L (NmL 0.02–0.27 mmol/L). Additional concerning labs included ammonia of 115 µmol/L (NmL 29–59 µmol/L), leukocytosis of 35 Th/mm^3 (NmL 5.0–15.0 Th/mm^3), and thrombocytosis of 684 Th/mm^3 (NmL 150–400 Th/mm^3) (Table 1). His respiratory viral panel was positive for rhinovirus/enterovirus. His HgBA1C was 5.1% (NmL < 5.7%). An EEG did not identify any seizure activity. Urine toxicology screen, salicylate levels, alcohol levels, and acetaminophen levels were all within normal ranges.

The constellation of severe anion gap metabolic acidosis, ketosis, and hyperammonemia was concerning for an inborn error of metabolism.

In order to limit precursors of a possibly blocked metabolic pathway (protein or fat), the patient was not started on any feeds. He was given parenteral fluids with dextrose 10% at one and a half times maintenance to help reverse the catabolic state. The fluids contained 75 mEq of sodium acetate to correct the severe acidosis. Insulin was initiated at (0.1 units/kg/h) for elevated serum glucose levels in the 300–400 mg/dL. In order to address the hyperammonemia, he was loaded with an enteral ammonia scavenging agent, sodium phenylbutyrate (250 mg/kg), and then received maintenance doses (150 mg/kg) every 6h. Co-factor supplementation with carnitine (60 mg/kg per day divided twice a day), for a possible organic acidemia and secondary carnitine deficiency, and thiamine (50 mg) for possible B1 responsiveness was also initiated. The patient had been started on empiric antibiotics prior to transfer, which were continued during the initial evaluation. After 36 h on this regimen, his lab abnormalities resolved. He was subsequently transitioned to a normal calorie infant formula and transferred to acute care pediatrics, where he continued to improve. He remained on an oral ad lib diet in the general wards, which he tolerated well, although his solid food intake remained low. He was stable prior to discharge, very well-appearing, and without any significant illness symptoms.

The patient was discharged home on a regular diet including formula and baby foods, puree as well as levocarnitine (30 mg/kg twice daily). During this admission, the genetics team was consulted and aided with management and recommended metabolic screening laboratories including, plasma amino acids, urine organic acids, total and free carnitine, and an acylcarnitine profile, along with gene sequencing studies (Invitae Ketolysis Disorders and Hyperammonemia panel). Given the hyperammonemia, hypoglycemia, and ketosis the presumed diagnosis was organic aciduria. However, urine organic acids showed high ketones only, with no other abnormal, or abnormally elevated organic acids. The concern at discharge was then for SCOT deficiency, or a newly described disorder of bicarbonate metabolism, carbonic anhydrase VA deficiency that results in hyperammonemia and ketosis.

Readmission

The patient was readmitted to the ICU less than 1 day after discharge. The mother reported that immediately after discharge, the patient was acting normally and eating well. On the night of re-admission, his mother fed him a new formula because her local store was out of their usual formula. The patient had emesis after the first feeding with the new formula and continued to have poor intake. He developed increased work of breathing similar to his first presentation, prompting the family to return to the emergency department approximately 9 h after discharge. He arrived somnolent and hypoglycemic with a high anion-gap metabolic acidosis (Table 1). His ammonia levels and lactate were normal. Following a dextrose bolus, he was placed on dextrose and acetate-containing fluids and recovered quickly.

After 24 h in the intensive care unit, he was discharged to the general wards for monitoring of acidosis and safe discharge planning. After his rapid readmission, it was important to have a home discharge plan that focused on a manageable feeding schedule. During this admission, his genetic testing returned and was indicative of SCOT deficiency. Our patient's sequencing showed a homozygous variant *c.1543A>G (p.Met515Val)* in the *OXCT1* gene. On day 7 of hospitalization, he underwent a controlled overnight fast to assess the safe duration of fasting overnight. After approximately 8 h of fasting, he again developed metabolic acidosis (pH 7.33, bicarbonate 12.3 mmol/L), elevated beta-hydroxybutyrate 6.08 mmol/L, and low blood glucose (glucose 64 mg/dL). His acidosis was again corrected with dextrose and acetate-containing fluids.

The patient was on ad-lib Similac infant formula (similar to his home formula). However, as a 12-month-old, he needed high volumes to meet his goal caloric needs. As he struggled to meet his volume goals, he was switched to a higher caloric density formula to decrease his total goal volume. Due to insurance authorization issues, the family was unable to obtain the higher calorie formula. Given how quickly he entered a ketotic state after his overnight fast it was essential to find an accessible and affordable solution that would permit the patient to sleep through the night and prevent ketosis in states of stress. Uncooked cornstarch was introduced to his overnight formula as a way to promote sustained glucose release. He received 0.5 g/kg of cornstarch nightly which was titrated to 1 g/kg prior to discharge. He tolerated the cornstarch addition very well. Given the known side effects of abdominal discomfort with cornstarch, he was also started on simethicone (2 mg/kg per dose). In the 48 h prior to discharge, the patient tolerated 1 g/kg cornstarch nightly, with serum bicarbonate consistently between 20 and 24 mmol/L, serum beta-hydroxybutyrate 0.5 mmol/L, and negative urine ketones after fasting for up to 9 h. He was discharged on supplemental cornstarch 1 g/kg nightly, urine ketone strips for home, and an emergency letter for future ED visits.

At his 1 month follow-up visit with metabolic genetics, he remained on nightly cornstarch without morning ketonuria. Five months after discharge he was receiving occupational therapy services for his baseline motor delay and growing well. Parents declined further genetic testing.

Discussion

The first case of SCOT deficiency was reported in the literature in 1972 after post-mortem tissue of a 6-month-old infant was examined for enzymatic activity and found to have no measurable SCOT activity.[3] SCOT catalyzes the first rate-limiting step of ketone body utilization by mitochondria. It transfers the CoA from succinyl-CoA to acetoacetate to form acetoacetyl-CoA which can be used for the tricarboxylic acid cycle.[1,5] The SCOT enzyme is encoded by the *OXCT1* gene which maps to chromosome 5p13 and contains 17 exons.[6] There are approximately 29 known mutations reported of the *OXCT1* gene associated with SCOT deficiency.[10] This variant was reported by Erdol et al.[7] in a Turkish infant with SCOT deficiency.

SCOT deficiency is not detected on our newborn screen by tandem mass spectrometry as there is no characteristic acylcarnitine elevated on the acylcarnitine profile. Age of onset is variable. Patients presenting acutely are managed by always first ensuring ABCs (airway, breathing, and circulation) are appropriate. It is then essential to appropriately fluid resuscitate the patient, taking into account acid/base status, presence of hyper/hypoglycemia, and electrolyte derangements. The primary goal of initial management is to correct any imbalances slowly to prevent any excessive electrolyte shifts. Also important is the correction of hyperammonemia with scavengers, as well as the prevention of protein catabolism. Not seen in this patient, but permanent ketosis can be present in this disorder even when patients are asymptomatic between episodes.[11] An initial set of laboratory studies on presentation including but not limited to serum glucose, venous blood gas, electrolytes, lactate, serum ammonia, serum ketones (beta-hydroxybutyrate), urine ketones, and urinalysis are recommended. Empiric antibiotic treatment should be initiated, as children with inborn errors may experience a crisis with infection. Further, sepsis can mimic metabolic disease.[8]

Once stabilized, patients should avoid prolonged fasting to prevent mobilization of fatty acids and ketogenesis. Any high energy/stress state (fever, exercise, fasting, etc.) can cause patients to enter ketosis and in the presence of a ketolysis defect can cause profound ketoacidosis, as in the patient presented here. Given the acute presentation of this patient and then the readmission, we strove to create a reasonable home plan that would avoid nighttime awakening for overnight formula feeds or supplemental feeds via nasogastric or G-tube as we knew prolonged fasting-induced ketosis. There was limited information on the management of SCOT deficiency and prevention of ketosis during prolonged fasting. Based on their experiences with cornstarch in other metabolic disorders, the metabolic team recommended QHS cornstarch therapy and guided the provision of this. An accessible intervention, uncooked cornstarch can be found easily. Furthermore, it is a simple yet effective method to maintain blood glucose and prevent severe illness and hospitalization in patients similar to ours. Cornstarch is commonly used in liver glycogen storage diseases to maintain euglycemia and in idiopathic ketotic hypoglycemia. In SCOT deficiency, it can be used to maintain normal blood glucose overnight. Cornstarch is a slow-release starch (i.e., a carbohydrate that is slowly broken down in the intestines as its structure is less accessible to degradation) with a low glycemic index often used in patients at risk for hypoglycemia.[9] The steady release of glucose allows more stable blood glucose levels over longer periods of time and maintains euglycemia longer than other dietary carbohydrates.[9] It can't be started after 6 months of age due to the infant's immature

amylase activity. Amylase is the enzyme used to break down cornstarch and is not fully developed until about 2 years of age. The starting dose is often 0.5–1 g cornstarch/kg body weight and can be titrated up based on gastrointestinal tolerance to a higher daily dose (most common side effects include bloating, and diarrhea). There are limited published guidelines or data on cornstarch dosing in SCOT deficiency. We started our patient at 0.5 g/kg and titrated up for effect. We used ARGO cornstarch as it's best tasting and has the longest sustainability. It is also pure cornstarch and affordable. Patients remain on cornstarch until they can fast overnight and still maintain their blood sugars.

In 12 months follow-up, our patient reported compliance with nightly cornstarch and had no repeat intensive care unit admissions. The DNA testing and metabolic testing did not identify another cause for the hyperammonemia and motor delay present in this patient. We have not ruled out another disorder, but it is most likely both the hyperammonemia and delay are due to SCOT deficiency. We don't always have an explanation for hyperammonemia for inborn errors of metabolism which is a secondary phenomenon.

Conclusion

In summary, SCOT deficiency is a rare ketone utilization defect. Patients usually present in extremis and require rapid resuscitation. Inpatient patient management involves prompt correction of acidosis and metabolic derangements managed by fluid resuscitation and metabolic support. Once stabilized, the focus should be on maintaining a non-fasting state during the day and night for which overnight cornstarch can be helpful.

Author's note

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