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Case Report

Succinyl-CoA:3-ketoacid CoA transferase deficiency presenting as recurrent refractory ketoacidosis in an infant

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ABSTRACT

Succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency is a rare disorder of ketone body utilization caused by impairment of the *OXCT1* gene, leading to recurrent life-threatening ketoacidosis despite preserved glycemia. We report an 8-month-old female infant with recurrent episodes of severe high anion gap metabolic acidosis with marked ketosis and preserved blood glucose requiring peritoneal dialysis and mechanical ventilation. Metabolic investigations demonstrated isolated ketone body accumulation and whole exome sequencing identified a homozygous variant of uncertain significance (VUS) in *OXCT1*, ultimately confirming SCOT deficiency in the appropriate biochemical and clinical context. This case highlights the importance of considering ketolysis defects in infants with recurrent ketoacidosis and preserved glycemia, and demonstrates the utility of extracorporeal therapy in refractory metabolic crises.

Keywords: Succinyl-CoA:3-ketoacid CoA transferase deficiency, SCOT deficiency, OXCT1, Ketoacidosis, Ketolysis disorder

INTRODUCTION

Succinyl-CoA:3-ketoacid CoA transferase deficiency (SCOTD) is an autosomal recessive inborn error of ketone body utilization caused by dysfunction of succinyl-CoA:3-ketoacid CoA transferase (SCOT), encoded by the OXCT1 gene. This enzyme catalyzes the conversion of acetoacetate to acetoacetyl-CoA, a critical step in peripheral ketone utilization during fasting or catabolic stress; and its deficiency results in accumulation of ketone bodies. Patients present in infancy or early childhood with recurrent episodes of ketoacidosis and ketonuria, and are otherwise asymptomatic. Due to lack of a biochemical blueprint, the diagnosis of this disorder is frequently delayed, and molecular confirmation is achieved through mutation analysis of the *OXCT1* gene.[1]

In this case, the patient harbored a VUS, which, in conjunction with characteristic biochemical findings and clinical phenotype, supported the diagnosis of SCOTD.

CASE REPORT

An 8-month-old female infant was referred to our pediatric intensive care unit (PICU) for evaluation of recurrent episodes of severe metabolic decompensation. She was the third child of parents with fourth-degree consanguinity, born at term with a birth weight of 2.4 kg, with normal birth history and growth and age-appropriate developmental milestones prior to illness onset, and there was no family history of unexplained infant deaths, neurological disorders, or inherited metabolic disease. Over the preceding four weeks, she was admitted thrice to the hospital for recurrent ketoacidosis without an identifiable precipitating factor. These episodes were not associated with any hyperammonemia, hypo/hyperglycemia or organ dysfunction (Table 1). The child improved with supportive therapy and bicarbonate supplementation and returned to her baseline activity and feeding between episodes, although the interval between episodes progressively shortened.

Two days after discharge from her third hospitalization, she developed tachypnea and progressive drowsiness and was referred to our institution. On arrival, she was drowsy with a Glasgow Coma Scale (GCS) score of 13/15. Her heart rate was 170 beats/min, respiratory rate 80 breaths/min, blood pressure 92/60 mmHg, oxygen saturation 98% on room air, and capillary refill time was 2 seconds. Clinical examination revealed sunken eyes and dry oral mucosa suggestive of dehydration. While mild hepatomegaly was present, the remainder of the systemic examination was unremarkable.Initial investigations in the emergency department demonstrated severe high-anion-gap ketoacidosis with pH 7.07, pCO_2 17.6 mmHg, bicarbonate 5 mmol/L, lactate of 2.4, anion gap of 25, serum β-hydroxybutyrate 5.7 mmol/L, with initial elevated levels of blood glucose (195 mg/dL) and ammonia (195 µmol/L).

In the PICU, she was started on rehydration with dextrose containing intravenous fluids with a glucose infusion rate (GIR) of 6 mg/kg/min and bicarbonate supplementation (9 mEq/kg/day). A metabolic cofactor cocktail comprising thiamine, biotin, riboflavin, pyridoxine, folinic acid, vitamin C, and carnitine was administered empirically. Investigations at admission showed a hemoglobin was 8.1 g/dL, total leukocyte count 15,300/mm³, and platelet count 7.12×10^5/mm³. Renal and liver function, as well as serum electrolytes (sodium, potassium, chloride, serum calcium, magnesium, and phosphate) were within normal limits. Urinalysis demonstrated ketonuria, 1+ proteinuria, and 1+ glycosuria.

Over the next 12 hours, the GIR was progressively increased to 12 mg/kg/min with continuous insulin infusion at 0.1 U/kg/hour while maintaining euglycemia and suppressing ketogenesis. However, while her hydration improved and urine output normalized, severe metabolic acidosis and ketonemia persisted, with bicarbonate levels remaining below 7 mmol/L at 18 hours post admission. Peritoneal dialysis was initiated approximately 22 hours after admission and optimized according to the patient's metabolic response.

Six hours following initiation of peritoneal dialysis, she developed respiratory fatigue requiring endotracheal intubation and mechanical ventilation. However, her ventilatory requirements remained minimal, and she continued to remain hemodynamically stable throughout the remainder of her PICU stay. Serial biochemical monitoring demonstrated progressive correction of ketoacidosis, following initiation of peritoneal dialysis (Figure 1). Peritoneal dialysis was discontinued after approximately 36 hours, sedation was omitted, the child was given a spontaneous breathing trial, and successfully extubated a day later.

A comprehensive metabolic evaluation was performed at admission, and the principal biochemical and molecular findings are summarized in Table 1. The metabolic profile suggested a differential diagnosis of disorders of ketolysis, fructose-1,6-bisphosphatase deficiency, and ketotic organic acidemias. Pending confirmatory investigations, the child was empirically commenced on lactose-free formula (Zerolac) because fructose-1,6-bisphosphatase deficiency remained an important differential diagnosis. However, the absence of recurrent hypoglycemia together with normal serum uric acid and total cholesterol concentrations made this diagnosis less likely. The overall clinico-biochemical picture favoured a ketolysis defect, and whole exome sequencing was performed for molecular confirmation. The child was subsequently transferred to the ward and discharged on two-hourly feeds, oral sodium bicarbonate, and L-carnitine supplementation, with advice for close follow-up pending genetic results.

On follow-up, the child was active and clinically stable. Whole exome sequencing identified a homozygous missense variant of uncertain significance in *OXCT1* gene c.487A>G, p.Thr163Ala. This variant was a warm VUS, which is novel as per gnomAD and with a medium impact of this variant on protein as predicted by REVEL (0.95) and CADD-PHRED (27.3) scores. Some in silico prediction tools have predicted a possible pathogenic effect and a decreased protein stability because of this variant. This supported a diagnosis of SCOT deficiency in the appropriate clinical and biochemical context. Fructose restriction was discontinued, and the parents were counselled regarding long-term dietary management, including continuation of frequent feeds, addition of complex carbohydrates with nocturnal uncooked corn starch supplementation, and ongoing sodium bicarbonate and carnitine therapy.

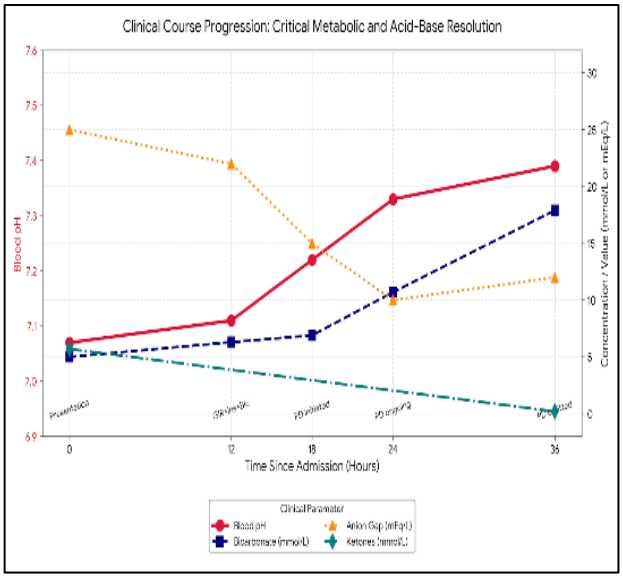

Figure 1: Serial biochemical response during acute metabolic decompensation.

Progressive improvement in arterial pH, bicarbonate concentration, anion gap and ketone concentration following escalation of glucose infusion, insulin therapy, bicarbonate supplementation, and initiation of peritoneal dialysis.

Table 1: Summary of diagnostic biochemical and genetic investigations.

Investigations	Findings
Initial metabolic evaluation	Severe high-anion-gap metabolic acidosis (pH 7.07, HCO_3^- 5 mmol/L, AG 25) with marked ketonemia (β-hydroxybutyrate 5.7 mmol/L), normal lactate (2.4 mmol/L), hyperglycemia (195 mg/dl), transient hyperammonemia (195 µmol/L), and normal uric acid (4.6 mg/dl) and total cholesterol (101 mg/dL).
Urine GCMS	Markedly elevated 3-hydroxybutyric acid and acetoacetic acid
Tandem mass spectrometry (MS/MS)	Elevated total and free carnitine Total carnitine 248.05 umol/l (NR- 20-80) Free Carnitine 202 umol/l (NR- 24-66) Raised C0/(C16+C18 ratio) 117 (NR<100) Mildly elevated C2 and C4OH acylcarnitines
Plasma amino acids/ acylcarnitine profile	Mild glycine elevation, other amino acids- normal levels
Whole exome sequencing	Homozygous *OXCT1* variant (NM_000436.4:c.487A>G; p.Thr163Ala), classified as a Variant of Uncertain Significance (VUS)

DISCUSSION

Ketone bodies (acetoacetate and β-hydroxybutyrate) are synthesized in hepatic mitochondria from acetyl-CoA generated during fatty acid β-oxidation, particularly during fasting and other catabolic states. They serve as an important alternative energy substrate for extrahepatic tissues, especially the brain. Peripheral utilization of ketone bodies depends on the SCOT enzyme, encoded by OXCT1, which catalyses the conversion of acetoacetate to acetoacetyl-CoA. Deficiency of this enzyme impairs ketolysis despite preserved hepatic ketogenesis, resulting in accumulation of ketone bodies and recurrent episodes of severe ketoacidosis.[1,2]

SCOT deficiency is a rare autosomal recessive inborn error of ketone body metabolism that typically presents during infancy with recurrent episodes of high-anion-gap metabolic ketoacidosis, often precipitated by fasting or intercurrent illness. Although persistent ketosis has traditionally been regarded as a hallmark of the disorder, several genetically confirmed patients have been reported without permanent ketosis.[1,3] The clinical presentation is heterogeneous and frequently overlaps with more common disorders including diabetic ketoacidosis, organic acidemias, fatty acid oxidation defects, and disorders of gluconeogenesis, making early diagnosis challenging.[4] Definitive diagnosis therefore relies on molecular genetic testing or demonstration of reduced SCOT enzyme activity in conjunction with the clinical and biochemical phenotype.[5]

Acute management of SCOTD aims to suppress ketogenesis by providing adequate carbohydrate substrate, reversing catabolism, and correcting the metabolic acidosis.[4,6] Accordingly, our patient was treated with progressively increasing glucose infusion rates, bicarbonate supplementation, insulin infusion, and intensive supportive care. A notable feature of our patient was the difficulty in suppressing ketogenesis despite conventional metabolic therapy. Unlike disorders of excessive ketone production, SCOT deficiency results from impaired peripheral ketone utilization. Consequently, ketone bodies continue to accumulate despite attempts to suppress hepatic ketogenesis, which may explain why some patients require substantially higher glucose infusion rates and insulin therapy to suppress lipolysis and hepatic ketogenesis, and, in severe cases, renal replacement therapy to facilitate correction of refractory metabolic acidosis.[1,7-9] Our patient required both mechanical ventilation and continuous renal replacement therapy before satisfactory metabolic control was achieved, reflecting the severity of the metabolic derangement.

This case also illustrates the diagnostic challenges associated with SCOT deficiency. Although recurrent ketosis with preserved or near-normal lactate concentrations is characteristic, blood glucose concentrations may vary considerably, and episodes may mimic diabetic ketoacidosis, organic acidemias, or disorders of gluconeogenesis. The absence of significant hyperlactataemia, despite profound metabolic acidosis, is an important clue suggesting a ketolysis defect rather than a primary disorder of pyruvate metabolism or gluconeogenesis. Definitive diagnosis therefore relies on integration of the clinical presentation with biochemical investigations and molecular confirmation.[4,5,8]

SCOTD should therefore be considered in any infant presenting with recurrent high-anion-gap ketoacidosis, particularly when marked ketosis occurs in the absence of significant hyperlactatemia or disease-specific organic acid accumulation. Early recognition allows timely institution of appropriate metabolic therapy, prevents unnecessary dietary restrictions instituted for alternative metabolic diagnoses, and facilitates early escalation to intensive care interventions-including high glucose infusion rates, insulin therapy, and renal replacement therapy when conventional treatment fails-to minimise morbidity and prevent neurological injury.

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