

Succinyl-CoA: 3-Ketoacid CoA-Transferase Deficiency in a Saudi Girl

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ABSTRACT

Objective: Succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency is a rare genetic disorder of ketone utilization and isoleucine catabolism caused by mutations in the OXCT1 gene,

Case: A Saudi girl case of SCOT deficiency confirmed by genetic analysis has been reported in this study. A 5-year-old girl presented to the emergency with the first episode of severe metabolic ketoacidosis after a febrile illness. On admission, she was drowsy lethargic, and severely dehydrated needs to admit in a highly dependent area. Initial investigations were done during the crisis showed refractory severe metabolic acidosis (pH of 7.18, HCO₃⁻ of 7.4 mmol/L), normal ammonia, lactic acidosis, and urine organic acid profile revealed elevations in 3-hydroxybutyrate and acetoacetate. Genetic analysis was done by CentoMito Comprehensive (Large extended screening panel), sequencing of OXCT1 gene revealed that the proband is homozygous for the missense likely pathogenic variant c.1402C>T p.(Arg468Cys) confirming the diagnosis of SCOT deficiency.

Conclusion: This is the first Saudi child with succinyl-CoA:3-ketoacid CoA transferase (SCOT) deficiency case report as searched in the literature. This case highlights the importance of suspecting SCOT deficiency in the differential diagnosis of pediatric metabolic ketoacidosis in preventing life-threatening of severe Metabolic ketoacidosis

Keywords: Ketoacidosis, OXCT1, Succinyl-CoA: 3-oxoacid CoA transferase deficiency, ketone

INTRODUCTION

Succinyl-CoA:3-ketoacid CoA transferase (SCOT) is an enzyme needed for ketone body utilization (1). SCOT deficiency is a rare autosomal recessive disorder with an incidence of less than one per 1,000,000 newborns (2). Delayed on diagnosis and lack of awareness, many cases have been missed during their initial presentation (2). It usually manifests with acute, recurrent ketoacidosis episodes triggered by ketogenic stress, infection (3). The neonatal presentation has been reported in the first days of life and the other patients usually manifesting the disease within the first two years (4). Patients are typically asymptomatic the intervals between episodes of metabolic ketoacidosis. The laboratory finding is the nonspecific pattern of an anion gap metabolic acidosis with the elevation of urine organic acids; analysis reveals high concentrations of 3-hydroxybutyrate and acetoacetate but patients with a mild mutation do not (4) and no abnormalities in ammonia, lactate, and amino acid.

To date approximately 37 affected individual and 24 different mutations of the OXCT1 have been reported as causative for SCOT since the first case was reported in 1972 (5).

In this study, we report on the Saudi child case as of SCOT deficiency confirmed by molecular analysis and characterize a missense mutation in OXCT1 gene.

CASE

A 5-year-old girl who is the fourth child of healthy, Saudi, consanguineous parents, there was no family history of similar or metabolic diseases. presented to the emergency room with a two days' history of vomiting, lethargy, tachypnea, and tachycardia no fever has been documented. She has been previously well with uneventful birth and neonatal periods and She had normal growth and development prior to the recent crisis.

Case Report

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She was drowsy, unresponsive to painful stimuli and had decreased reflexes. A febrile, no skin rash, no meningeal sign and she had acidotic breathing. Laboratory investigations showed severe high anion gap metabolic acidosis (pH 7.13, pCO₂ 10.6 mmHg, HCO₃ 7.2 mmol/L). Plasma glucose was normal, Ammonia 56 (mcg/dl), Lactic acid 3.1 (mmol/L) and with 3+ ketonuria. Septic screening workup including blood culture, urinalysis and culture were unremarkable. Radiographic imaging of the chest and abdomen was unremarkable. She has required intubation and was managed with intravenous fluids, repeated doses of intravenous bicarbonate therapy, inotropes, and broad-spectrum antibiotics. Further investigation was requested by the metabolic team tandem mass spectrometry, urine organic acid analysis. GC/MS analysis revealed the presence of acetoacetate and 3-hydroxybutyrate. Normal serum and urine amino acid. To confirm the diagnosis, CentoMito Comprehensive (Large extended screening panel), was sent and revealed a homozygous pathogenic variant was identified in the OXCT1 gene. The test was performed on dried blood spots on a filter paper at Centogene AG, Germany. The child was homozygous for a missense variant c.1402C>T p. (Arg468Cys) causes an amino acid change from Arg to Cys at position 468. According to HGMD Professional 2018.4, this variant has previously been described as a disease-causing for 3-oxoacid CoA transferase deficiency (6). The patient was bound to ventilation for 48 hours and ketoacidosis improved, and she was weaned off mechanical ventilation and discharged on day 7 days in her normal state of health

Table 1: Biochemical parameters of the patient

Investigations	Result of patient ^c
Plasma glucose	Normal
VBG	Severe high anion gap metabolic acidosis (pH 7.13, pCO ₂ 10.6 mmHg, HCO ₃ 7.2 mmol/L).
Serum and urine amino acid	Unremarkable
Urine organic acid analysis. GC/MS	Acetoacetate and 3-hydroxybutyrate
Metabolic tandem mass spectrometry	Unremarkable
Urine dipstick	3+ ketonuria
Blood and urine cultures	Normal
Lactic acid	3.1 (mmol/L)
Radiographic imaging of the chest and abdomen	Unremarkable

MATERIAL and METHOD

Peripheral blood samples (5 ml) were collected in EDTA tubes from the patient. Written informed consent was obtained before the samples' collection. CentoMito Comprehensive (Large extended screening panel), was performed by Centogene using Next Generation Sequencing

Technologies. The entire coding region of nuclear genes including 10 bp of intronic flanking sequences were amplified and sequenced. Raw sequence data analysis, including base calling, demultiplexing, alignment to the hg19 human reference genome (Genome Reference Consortium GRCh37) and variant calling were performed using validated in-house software.

Due to the limitations of the method, the target sequences of the requested panel might not be covered 100%.

For mitochondrial genome analysis, the genes were amplified and sequenced, and raw sequence data analysis, including base calling, demultiplexing, alignment to the Revised Cambridge Reference Sequence (rCRS) of the Human Mitochondrial DNA (NC_012920), and variant calling were also performed using validated in-house software.

Following the base calling and primary filtering of low-quality reads, a standard Bioinformatics pipeline was implemented to annotate detected variants and to filter out

probable artifacts. The pipeline confidently detects heteroplasmy levels down to 15%. All identified variants are evaluated with respect to their pathogenicity and causality, and these are categorized into classes 1 - 5.

All variants related to the phenotype of the patient, except benign or likely benign variants are reported. Variants of relevance identified by NGS are continuously and individually in-house validated for quality aspects: those variants which meet our internal QC criteria (based on extensive validation processes) are not validated by Sanger. CentoMito Comprehensive (Large extended screening panel), the list of analyzed genes (nuclear and mitochondrial) Analysis does not include copy number variations (CNV) or large deletion/duplications.

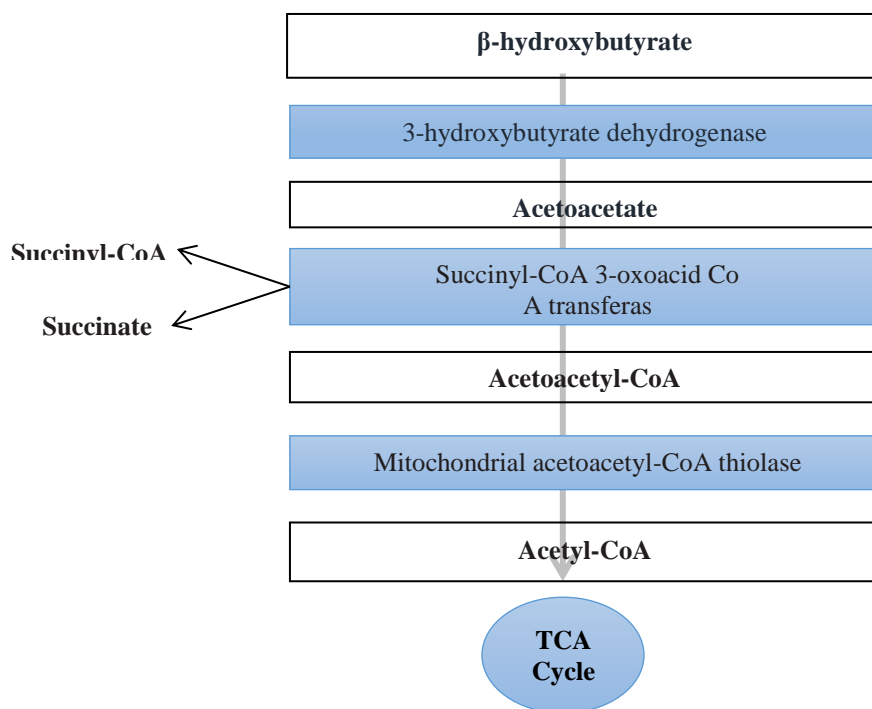
RESULT and DISCUSSION

SCOT protein is a homodimer of the 56.2-Kd subunit (7). SCOT protein is found in the tissue of the brain, heart, and kidney except for the liver (8). Human SCOT cDNA is about 3.2 kb and encodes for 520 amino acids (7). The OXCT1 gene is located on chromosome 5p12-p13 and spans more than 100 kb, includes 17 exons (9). This gene is a member of the CoA transferase family I, which has a role in catalyzing the transfer of CoA between carboxylic acid groups (10)

SCOT catalyzes the first, step in ketosis by transferring the CoA from succinyl-CoA to acetoacetate, to produce acetoacetyl-CoA. Then acetoacetyl-CoA converted by mitochondrial acetoacetyl-CoA thiolase into acetyl-CoA,

Acetyl-CoA is then entering the tricarboxylic acid TCA cycle to generate the energy so (succinyl-CoA:3-ketoacid-CoA transferase, is the key reaction that enables ketone body utilization as energy during starvation (**Fig. 1**))

The typical presentation is in early childhood, with vomiting, hyperpnea, drowsiness, lethargy and in severe cases coma evoked by ketogenic stress such as fasting, infection and physical exertion. Though rare, neonates can present with vomiting, poor suckling, and lethargy. Episode intensity and frequency is variable and severe attacks are fatal. All clinical presentation of SCOT due to Permanent ketosis or persistent ketonuria which is pathognomonic feature of SCOT deficiency (11). SCOT deficiency may mimic diabetic ketoacidosis if associated with hyperglycemia; or even organic acidemia such as propionic, methylmalonic acidemias, congenital lactic acidosis, salicylate and mitochondrial acetoacetyl-CoA thiolase deficiency (12).

Figure 1: Pathway of Succinyl-CoA 3-oxoacid CoA transferase

Individuals with mitochondrial acetoacetyl-CoA thiolase, T2 deficiency, can mimic attacks of succinyl CoA:3-oxoacid CoA transferase SCOT deficiency but owing to specific finding in urinary organic acid profile revealed high levels of tiglylglycine (TIG) 2 methylacetoacetic acid (2MAA) and 3-OH-2-methyl-butyric acid (2M3HB). was effectively excluded. In SCOT deficiency, a blood acylcarnitine profile by tandem mass spectrometry unremarkable only elevated levels of ketone bodies in the blood and urine, patients which is considered a pathognomonic feature of SCOT deficiency (11)

Patients are reported to be healthy between episodes, even if the initial episode or crisis was severing which has been documented (14). Most patients make a full recovery following episodes of acidosis with a good prognosis and tend to decrease in ketoacidosis episodes after mid-age (15). But in some patients with SCOT deficiency may develop Cardiomegaly or congestive heart failure (16) and the cases of neurological deficit and mortality are rare (18).

Definitive diagnosis of SCOT deficiency is by molecular genetic studies. And enzyme assays on lymphocytes or cultured fibroblasts. But we proceed to genetic test and no enzyme assay was done for our patient SCOT-deficient patients either have a residual activity or no will have the same the of clinical presentation severity and frequency of metabolic ketoacidosis crises (13) but the patient with residual enzyme or mild mutation may have no permanent ketosis (11).

The proband was homozygous for the c.1402C>T p.(Arg468Cys) causes an amino acid change from Arg to Cys at position 468. According to HGMD Professional 2018.4, this variant has previously been described as disease-causing for 3-oxoacid CoA transferase deficiency by Fukao et al., 2011(11), and Sulaiman et al., 2018 (17)).

It is classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG

Homozygous or compound heterozygous pathogenic variants in the OXCT1 gene have been associated with succinyl-CoA:3-oxoacid-CoA transferase deficiency (SCOTD), an autosomal recessive disorder (OMIM® 245050).

There are no data about the presence of common Mutations of OXCT1 gene and there has been no obvious relation between the severity of the disease and the genotype.

The family members screening is crucial to identify asymptomatic individuals and genetic counseling should be provided.

The management of an acute crisis includes hydration with normal saline and dextrose, intravenous sodium bicarbonate bolus to corrected acidosis followed by infusion if needed, and avoid rapid correction and hypernatremia correcting hypoglycemia and peritoneal dialysis in severe acidosis Treated underlying infection with broad-spectrum antibiotic and further septic workup.

CONCLUSION

SCOT deficiency should be suspected in patients presenting with severe metabolic ketoacidosis with or high anion gap metabolic acidosis preceded by an acute infection or fasting. And have non-specific laboratory findings. The patients have favorable outcomes with time

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