Short Chain Acyl-CoA Dehydrogenase Deficiency

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Short chain Acyl-CoA dehydrogenase deficiency (SCADD) is a rare fatty acid oxidative disorder (FAOD) inherited as an autosomal recessive pattern. Patients could present with a variety of symptoms, such as hypoglycemia, metabolic acidosis, cyclical vomiting, myopathy and developmental delay or asymptomatic individual. Since the introduction neonatal screening programs, it has been found that majority of the patients with SCADD are asymptomatic at the time of diagnosis.

We present this atypical, yet symptomatic case of a patient with confirmed SCADD who presented at the age of 11 months with recurrent chest infections, vomiting and cyanotic episodes. The diagnosis was confirmed with increased ethylmalonic acid (EMA) in urine and molecular genetic analysis, which identified a pathogenic variant c.529T>C (p. Trp177Arg) in axon 5 of ACADS gene (OMIM 606885; chromosome 12q24.31). The patient was managed with dietary modifications and referral to a metabolic specialist. Parents were referred for genetic counseling regarding future conception.

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Short chain Acyl-CoA dehydrogenase deficiency (SCADD) is a fatty acid oxidative disorder inherited in autosomal recessive pattern[1]. Acyl-CoA dehydrogenase reductase is a co-enzyme responsible for converting fats to fuel that can be used by the body; this step is essential during fasting and metabolic stress[2]. Deficiency in the enzyme leads to accumulation of butyrylcarnitine and ethylmalonic acid in blood and urine[3].

Clinical phenotype and biochemical conditions vary. After the introduction of newborn screening for metabolic disorders by tandem mass spectrometry (TMS), many asymptomatic infants with SCADD had been identified. Severe features of SCADD includes dysmorphic facial features, feeding difficulty, failure to thrive, metabolic acidosis, ketotic hypoglycemia, lethargy, developmental delay, seizure, hypotonia and myopathy[4]. The symptoms usually aggravated during physiological stress such as fasting and illness. Because most identified cases are asymptomatic during newborn screening, clinical manifestation of SCADD remains questionable[3].

The aim of this report is to present a rare case of severe SCADD, which is the first to be reported in Bahrain.

THE CASE

An eleven-month-old Yemeni female with developmental delay presented with a history of difficulty in breathing associated with cyanosis, vomiting and choking during feeding. Perinatal history revealed that the patient was born at full-term via spontaneous vaginal delivery, no NICU admission at birth and no maternal illnesses or infections.

The patient did not receive any vaccine in Yemen and was exclusively breastfed; she was not yet weaned to soft food. Her parents are first degree cousins. The mother gave a history of two infantile deaths, one neonatal death, one abortion and one intrauterine fetal death (IUFD), and our case is the only living child of the couple.

The patient's symptoms and past medical history raised suspicion of an inborn error of metabolism (IEM).

Physical examination revealed coarse facial features, frontal bossing and a flat nasal bridge, grade 2/6 systolic murmur, bilateral rhonchi, crepitation over the right lung and hepatosplenomegaly. The patient was hypotonic with brisk reflex and clonus and had a global developmental delay (GDD). She was unable to sit without support, did not develop mature pincer grip, babbles but does not say mama or papa.

Clinical features were consistent with an IEM. The diagnosis was made based on the molecular analysis of ACADS gene. An EDTA blood sample was sent to BIOSCIENTIA Human Genetics in Germany. They have extracted the patient DNA and amplified it by polymerase chain reaction (PCR) and analyzed it by direct sequencing. The resulting sequencing data were

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compared with the reference sequence NM-000017.3. Urine test revealed increased excretion of ethylmalonic acid (EMA) and tiglylglycine, as well as traces of methylsuccinic acid and isovalerylglycine. L-Carnitine profile was normal. Molecular genetic of ACADS gene detected pathogenic variant c.529T>C (p. Trp177Arg) in axon 5 of ACADS gene in heterozygous state, see figure 1. U&E, LFT, RFT, CK, and CKMB were all within normal range.

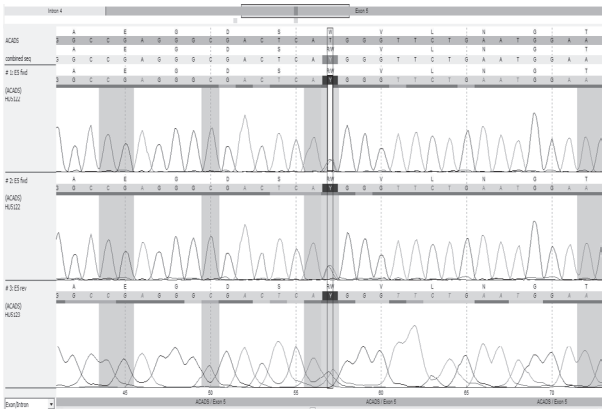

Figure 1: Short Chain Acyl-CoA Dehydrogenase Gene

The patient was admitted with bronchopneumonia and suspicion of IEM. The acute infection was treated accordingly.

The diagnosis of SCADD was confirmed, and the patient was started on a high-carbohydrate and low-fat diet. A dietician prescribed her low-fat formula milk and advised the mother to feed her high-carbohydrate food with a small meal before bedtime to avoid hypoglycemia. As part of her management, the patient was referred to a metabolic specialist. We continued to follow her for two years and still has the clinical features with progressive myopathy.

The patient is doing well; however, she is still developmentally delayed, and continues to have recurrent infections and aspiration pneumonia.

DISCUSSION

SCADD is a rare fatty acid oxidative disorder; the clinical signs and symptoms vary widely, and most diagnosed patients remain asymptomatic. Hence, it is essential to recognize individuals with severe forms of SCADD that have a typical clinical manifestation of the disease. Even after the diagnosis of SCADD, a physician must perform other investigations to exclude other metabolic disorders because the relationship between clinical features and SCADD remains uncertain. Long-term evaluation of the asymptomatic patient is necessary to identify the relationship between biochemical and clinical features of the disease.

Clinical features of SCADD varies from severe to asymptomatic myopathy[5]. Since the introduction of neonatal screening, SCADD has been identified in many cases, yet, most remain asymptomatic[4].

Two distinct clinical phenotypes of SCADD have been recognized. One is in infants with acute acidosis and muscle weakness, the other in middle-aged patients with chronic myopathy[6]. Our patient fits into the first category. Furthermore, neonatal-onset could have different clinical features that may include: metabolic acidosis, failure to thrive, developmental delay, seizures and myopathy.

Contes et al described a case of a two-year-old female with SCADD that presented in early postnatal period with poor feeding, emesis, and failure to thrive. She also had progressive muscle weakness and developmental delay[7]. Tein et al reported 10 cases in Ashkenazi Jew with variable phenotype expression of SCADD[8]. Common clinical features include hypotonia, developmental delay, speech delay, myopathy, lethargy and feeding difficulties. Muscle biopsy was performed in 3 patients and 2 revealed features of multiminicore myopathy and one with lipid storage disease[8]. Urine ethylmalonic and methylsuccinic aciduria were elevated, normal to reduced free carnitines and inconsistently abnormal acylcarnitine profile[8].

The diagnosis of SCADD can be made by increased excretion of ethylmalonic acid and methylsuccinic acid in urine[5]. Muscle fibroblast will demonstrate low to intermediate activity towards butyryl-CoA. Molecular diagnosis by whole-genome sequencing can identify mutation in ACADS gene, as well as southern or northern plot analysis for the specific mutation[9]. Although most studies state that SCADD is harmless and treatment is unnecessary, some patients have severe forms of SCADD; therefore, identification of symptomatic cases are vital. Management along with parental counseling is crucial to prevent long-term complications for the patient and to prevent recurrence in future pregnancy[5].

CONCLUSION

The management for symptomatic patients is by maintaining a high-carbohydrate and low-fat diet, avoidance of fasting and an annual check-up to assess growth and development.

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