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증 례

A Case of Short-chain Acyl-CoA Dehydrogenase Deficiency Detected by Newborn Screening

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Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is an autosomal recessive mitochondrial disorder of fatty acid oxidation associated with mutations in the *ACADS* gene. While patients diagnosed clinically have a variable clinical presentation, patients diagnosed by newborn screening are largely asymptomatic. We describe here the case of a 1-year-old male patient who was detected by newborn screening and diagnosed as SCAD deficiency. Spectrometric screening for inborn errors of metabolism at 72hrs after birth showed elevated butyrylcarnitine (C4) level of 1.69 mol/L (normal, 〈0.83 mol/L), C4/C2 ration of 0.26 (normal, 〈0.09), C5DC+C60H level of 39 mol/L (normal, 〈0.28 mol/L), and C5DC/C8 ration of 7.36 (normal, 〈4.45). The follow-up testing at 18 days of age were performed: liquid chromatography tandem mass spectrometry (LC-MS/MS), urine organic acids, and quantitative acylcarnitine profile. C4 carnitine was elevated as 0.91; urine organic acid analysis showed elevated ethylmalonic acid as 62.87 nmol/molCr (normal, 〈6.5), methylsuccinate 6.81 nmol/molCr (normal, not detected). Sequence analysis of *ACADS* revealed a homozygous missense mutation, c.164C〉T (p.Pro55Leu). He is growing well and no episodes of seizures or growth retardation had occurred.

Kew words: Short chain Acyl CoA dehydrogenase deficiency, SCAD, *ACADS* gene

Introduction

Short-chain acyl-CoA dehydrogenase (SCAD) deficiency is a rare, autosomal recessive disorder of mitochondrial fatty acid oxidation, first reported in 1987[1)]. Short chain acyl-CoA dehydrogenase (SCAD) is member of the acyl-CoA dehydrogenase (ACAD) family of mitochondrial enzymes involved in the beta-oxidation system. It catalyzes the first step in mitochondrial beta-oxidation of fatty acids 4 to 6 carbons in length[2)]. Short chain acyl-CoA dehydrogenase deficiency is an autosomal recessive metabolic disorder associated with mutations in the *ACADS* gene (Acyl-CoA Dehydrogenase, Short chain).

The neonatal features of SCAD deficiency reported clinically have included a broad range of symptoms, such as feeding difficulties[1)], hypo-

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tonia[3], lethargy[3], hypoglycemia[4], dysmorphic features[4], brain malformations with infantile spasms [5] and death. During later infancy and childhood, reported features have included failure to thrive[6], developmental delay[6], seizures[6], hepatomegaly and jaundice[7], and optic atrophy. While patients diagnosed clinically have a variable clinical presentation, patients diagnosed by newborn screening are largely asymptomatic[8]. Recently, with newborn screening by MS/MS, several metabolic disorders including SCAD deficiency are detected early in life, which allows immediate initiation of treatment and monitoring, particularly during times of illness. We describe here the case of a 1.2-year-old male patient who was detected by newborn screening and diagnosed as SCAD deficiency by genetic analysis.

Case Report

A male patient was born at the gestational age of 40+2 weeks by vaginal delivery, with body weight 3,855 g (78‰), height 51.3 cm (66‰), and head circumference 37.5 cm (96‰). Newborn screening testing was performed at 72 hrs after birth, resulted in elevated butyrylcarnitine (C4 carnitine) level of 1.69 mol/L (normal, <0.83 mol/L), C4/C2 ratio of 0.26 (normal, <0.09), C5DC+C60H level of 39 mol/L (normal, <0.28 mol/L), and C5DC/C8 ratio of 7.36 (normal, <4.45). The follow-up testing of C4, C4/C2, C5DC+C60H, and C5DC/C8 at 12 days of age showed elevated levels at 1.18, 0.26, 0.34, 8.45, respectively (Fig. 1). The following studies were performed at 18 days

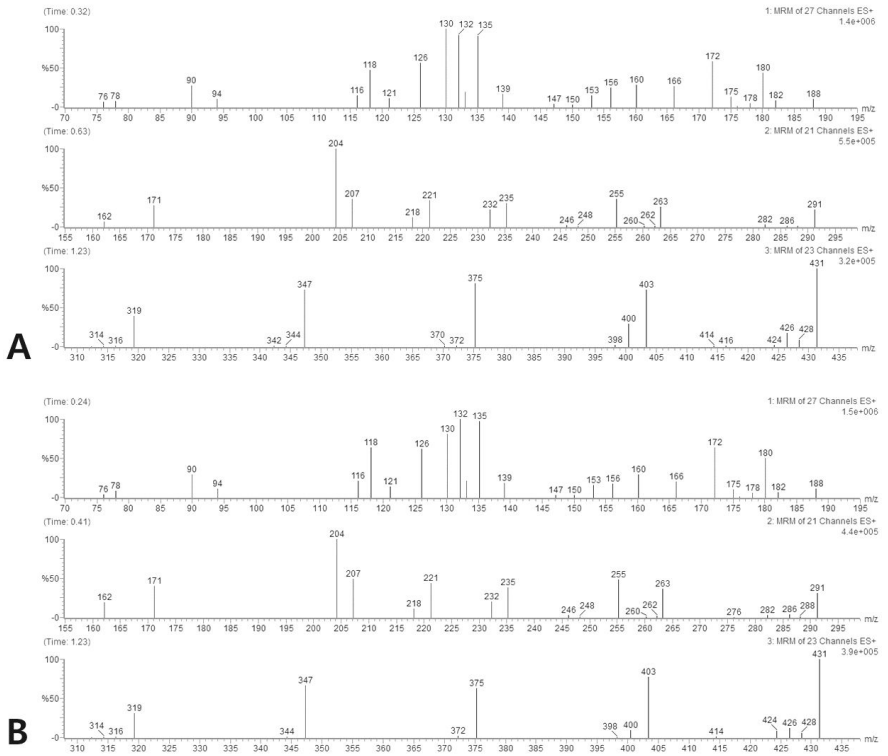

Fig. 1. Acylcarnitine profiling in the study patient. Elevated levels of C4 species are shown (A, B). C4 value is indicated as number 232.

of age: LC-MS/MS, urine organic acids, and quantitative acylcarnitine profile. C4 carnitine was elevated at 0.91; total acylcarnitine value was normal; urinary organic acid analysis showed elevated ethylmalonic acid at 62.87 nmol/molCr (normal, <6.5), and methylsuccinate at 6.81 nmol/molCr (normal, not detected). These biochemical findings suggested SCAD deficiency. To confirm the diagnosis of SCAD deficiency, all the coding exons of the *ACADS* gene and flanking introns were amplified by polymerase chain reaction and directly sequenced. Sequence analysis of *ACADS* revealed a homozygous missense mutation, c.164C>T (p.Pro55Leu). Both parents were heterozygous for this mutation. L-carnitine (100 mg/kg/d#2) and vitamin B1 (10 mg/kg/d#3) administration were initiated at 31 days of age. Avoidance of fasting and limitation of dietary fat were recommended to the patient. Follow-up ethylmalonic acid and methylsuccinate at 2 month old decreased slightly as 52.37 nmol/molCr (normal, <6.5) and 4.11 nmol/molCr (normal, not detected), respectively. Butyrylcarnitine was elevated to 1.32 μmol/L at the final follow-up when the patient was 6 month old. He is now 1.2 yrs with weight 12.9 kg (96 ‰), and height 81.6 cm (85‰). He had normal growth and development without metabolic crisis to date.

Discussion

SCAD deficiency is an autosomal recessive metabolic disorder of fatty acid beta-oxidation. Clinical features are variable: a severe form of the disorder can cause infantile onset of acidosis and neurologic impairment, whereas some patients develop myopathy alone. With the advent of screening for inborn errors of metabolism, patients with putative pathogenic mutations who remain asymptomatic have also been identified[9].

Because of the enzyme defect, increased level of C4-acylcarnitine in the plasma and increased level of ethylmalonic acid (EMA) in the urine are observed and suggest the diagnosis of SCAD deficiency. However, these findings are also found in individuals who carry one of two common polymorphisms identified in the SCAD coding region [10, 11]. Therefore, genetic analysis is helpful in the diagnosis.

The SCAD gene is located on chromosome 12q 22 and is approximately 13 kb long with 10 exons and 1,236 nucleotides in the coding sequence[12]. Several inactivating mutations in the *ACADS* gene have been identified in patients with SCAD deficiency. Overall, approximately 60 mutations in *ACADS* are known[13], with two common variants. The A 511C>T polymorphism located in exon 5 leads to substitution of tryptophan for arginine at position 171 of the mature enzyme (R171W; position 171 in the precursor); the A 625G>A variant in exon 6 substitutes serine for glycine at position 209 of the mature protein (G209S; position 209 in the precursor protein). Both *ACADS* sequence variants are relatively common in the healthy population[11]. In Korea, Kim et.[14] first reported that a female patient with no symptoms who was suspected as having SCAD deficiency as a result of MS/MS newborn screening had a novel homozygous mutation, c.1031A>G (p.E344G). A homozygous mutation, c.164C>T, detected in our case who showed normal growth and development without metabolic crisis is known as a mild phenotype[9].

There is no established treatment of SCAD deficiency. Our case has been treated with daily riboflavin, L-carnitine, and avoiding long time of

fasting. The administration of L-carnitine can help EMA be excreted by forming butyrylcarnitine. Despite there is still lack of evidence to support of clinical improvement, riboflavin and/or L-carnitine supplementation is considered as a treatment in SCAD deficiency.

In summary, a Korean male patient subjected to LC-MS/MS newborn screening, was suspected of SCAD deficiency. The diagnosis was confirmed by biochemical and genetic analyses. Further study is needed to understand the functional and structural changes of the proteins involved in this disorder and the associated clinical findings.

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