Case Report

Short-chain enoyl-CoA hydratase deficiency causes prominent ketoacidosis with normal plasma lactate levels: A case report

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ABSTRACT

We report a case of a 7-month-old boy with Short-chain enoyl-CoA hydratase (ECHS1) deficiency concomitant with prominent ketoacidosis, and no elevation in plasma lactate levels. He suddenly became unconscious, after he had a lot of defecation. He was referred to our hospital by a local doctor because of a right conjugate deviation and hypotonia. Initial investigations revealed severe anion gap metabolic acidosis, hyperuricemia, hyperketonemia, and normal lactate levels in the blood and cerebrospinal fluid. Magnetic resonance imaging of the brain showed abnormal signals in the bilateral caudate nucleus and globus pallidus, suggesting the possibility of inborn errors of metabolism. Thus, analysis of acylcarnitine analysis and urine organic acid was performed but could not help diagnose his condition. We then performed mutation analysis using a DNA panel. We found the following heterozygous mutations in *ECHS1*: c.5C > T (p. Ala2Val) and c.176 A > G (p. Asn59Ser), leading to the diagnosis of Leigh encephalopathy. This case report expands our understanding of the multiple symptoms of ECHS1 deficiency and emphasizes the importance of genetic testing for inborn errors of metabolism, such as ECHS1 deficiency, to initiate early treatment.

1. Introduction

Short-chain enoyl-CoA hydratase (ECHS1) deficiency is a rare congenital metabolic disorder with autosomal recessive inheritance (OMIM 616277). ECHS1 deficiency was first reported as Leigh syndrome by Peters [1]. Characteristic symptoms include severely delayed psychomotor development, nystagmus, hyperlactatemia, and brain lesions in the basal ganglia. The symptoms and severity of ECHS1 deficiency may vary. However, the incidence of ECHS1 deficiency is rare.

Herein, we report a 7-month-old boy with ECHS1 deficiency presenting with conjugate deviation, hypotonia and prominent ketoacidosis, without elevation of lactate levels.

2. Case presentation

The patient was born uneventfully at a gestational age of 40 weeks and 2 days. His weight, length, and circumference of the head at birth were 3178 g (+0.14 standard deviation [SD]), 48.0 cm (−0.89SD) and 32.0 cm (−1.12SD), respectively. There were no abnormalities in newborn screening for inborn errors of metabolism. His parents were

non-consanguineous and there was no family history of an inborn errors of metabolism. Before onset of the disease, he was able to roll over, but was unable to sit steadily or crawl. His mother had fever 3 days before his hospitalization, but he had no signs of infection. On the day of hospitalization, he was not lively in the morning. He had constipation for 5 days prior to hospitalization. After having a lot of defecation, the patient became unconscious. His parents took him to a nearby doctor. He was then referred to our hospital after exhibiting right conjugate deviation and hypotonia.

The weight and height of the patient was 6.4 kg (−2.15SD) and 64.2 cm (−2.08SD), respectively. His body temperature, blood pressure, and pulse rate were 37.7 °C, 86/50 mmHg, and 132 beats per minute, respectively. He manifested with tachypnea (56 per minutes). His Glasgow coma scale score was 10 (E4V1M5). His general condition was poor, and a ketone odor was detected. He exhibited right conjugate deviation with a normal light reflex. He was hypotonic and had decreased reflexes.

Initial investigations revealed severe high anion gap metabolic acidosis (pH 7.249, pCO2 12.7 mmHg, HCO_3^- 5.6 mmol/L) with mild hypoglycemia (3.1 mmol/L). The patient showed elevated levels of uric

acid (59.5 μmol/L), β-hydroxybutyric acid (8242 μmol/L) and aceto-acetic acid (4183 μmol/L; Table 1). Blood ammonia, liver and kidney function, and electrolytes were within the normal range. There were no laboratory findings suggestive of infection. Blood and cerebrospinal lactate and pyruvate levels were also normal. Brain magnetic resonance imaging showed abnormal signals in the bilateral caudate nucleus and globus pallidus (Fig. 1), suggesting the possibility of inborn errors of metabolism. Thus, we initiated treatment with intravenous fluids containing glucose and vitamin cocktail. On the 3rd day of hospitalization, lactate and CPK levels tended to increase and peaked on day 7 of hospitalization. Neurological findings gradually improved, and muscle tension and tendon reflex became almost normal on day 7 of hospitalization. To analyze the inborn errors of metabolism, we evaluated the acylcarnitine and urine organic acid levels. Acylcarnitine analysis was normal, and urine organic acid analysis showed a slight increase in 2-methyl-3-OH-butyrate, but not tiglylglycine. These results were not in accordance with beta-ketothiolase deficiency. However, the ratio of free fatty acid/total ketone body was less than 0.3, that suggested inborn errors of ketolysis, such as beta-ketothiolase deficiency [2]. Urinary organic acid analysis also showed an increase in lactate and pyruvate, suggestive of congenital lactic acidosis, such as mitochondrial disease, and transient hypoxia. We then performed mutation analysis using a DNA panel consisting of 59 genes that may be involved in inborn errors of metabolism, such as fatty acid oxidation, ketone body metabolism and transport, and glycogen storage diseases using the MiSeq Sequencing System (Illumina, San Diego, CA) at the Kazusa DNA Research Institute, as previously described [3]. Genomic polymerase chain reaction followed by direct sequencing of ECHS1 were also performed as previously reported. There were heterozygous mutations in ECHS1, as previously reported: c.5C > T (p. Ala2Val) and c.176A > G (p.Asn59Ser). Direct sequencing confirmed that these mutations were inherited from his father and mother, respectively. Thus, he was diagnosed with Leigh syndrome due to ECHS1 deficiency. Based on the genetic testing, we reanalyzed the urine organic acid analysis, 2,3-dihydroxy-2-methylbutyric acid was detected.

3. Discussion

ECHS1 is a mitochondrial enzyme that catalyzes reactions in multiple metabolic pathways, such as fatty acid ß oxidation and degradation of branched-chain amino acids (valine, leucine, and isoleucine). ECHS1 deficiency was first reported in Leigh syndrome by Peters in 2014 [1]. Since then, ~50 cases of ECHS1 deficiency have been reported. The symptoms and findings of ECHS1 deficiency vary and the frequency of ECHS1 deficiency is rare. Even patients with identical genotypes have different symptoms. The main pathophysiology of ECHS1 deficiency

involves the accumulation of toxic intermediate metabolites, such as methacrylyl-CoA, in the mitochondria in the valine catabolic pathway. Patients with ECHS1 deficiency have characteristic symptoms, such as severely delayed psychomotor development, nystagmus, hyper-lactatemia, and brain lesions in the basal ganglia, with metabolic acidosis and variable ketosis. This case report is based on a 7-month-old boy with ECHS1 deficiency and chief complaints of conjugate deviation and hypotonia. The findings upon examination of the patient were: 1) remarkable ketoacidosis and 2) normal levels of lactate in the blood and cerebrospinal fluid.

The 3-hydroxyisobutyryl-CoA hydrolase gene (HIBCH) is located downstream of ECHS1 in the valine metabolic pathway. Thus, patients with ECHS1 deficiency show symptoms similar to those in patients with a deficiency of HIBCH. Patients with HIBCH deficiency exhibit marked ketoacidosis during stress conditions, such as fever. This can be attributed to the enhanced supply of ATP to the brain owing to fatty acid ß oxidation. In contrast, ketoacidosis is not always observed with patients with ECHS1 deficiency. Some patients with ECHS1 deficiency have ketoacidosis [4], but some patients with ECHS1 deficiency do not present with prominent ketoacidosis due to the impairment of short-chain fatty acid ß oxidation and inability to produce ketone bodies [5]. It has recently been reported that ECHS1 is less involved in isoleucine metabolism and fatty acid ß oxidation [7]. There were no abnormalities in the acylcarnitine profile in the patient, suggesting normal fatty acid ß oxidation.

Patients with ECHS1 deficiency usually have elevated levels of lactate and pyruvate with preserved ratio in plasma. Elevation in the levels of lactate and pyruvate in patients with ECHS1 deficiency results from impaired pyruvate dehydrogenase activity [1]. The mutations in the present case are common to the Japanese patients with ECHS1 deficiency. The patients with these mutations have increased lactate levels in the acute phase, not in the non-acute phase [5,6], suggesting that it is important to measure lactate levels in the acute phase. Interestingly, this patient showed no elevation of lactate and pyruvate in the blood or cerebrospinal fluid, likely due to preserved pyruvate dehydrogenase activity, at least during the onset. This suggests mitochondria function and pyruvate dehydrogenase activity was retained, especially in the liver. The pathology of ECHS1 deficiency involves the accumulation of methacrylyl-CoA, which leads to the impairment in ATP production [7]. Thus, we speculate that methacrylyl-CoA accumulated in the brain to induce the onset of disease, compared to the liver that is an essential metabolic organ, in the present case. More interestingly, urinary pyruvate and lactate were elevated. The discrepancy between urine and plasma results suggests the importance of measuring lactate and pyruvate in both samples.

Due to diversity of clinical manifestations, mitochondrial diseases

Table 1
Laboratory findings.

Blood gas (venous blood)			Biochemistry						cerebrospinal fluid		
pH	7.249		TP	6.4	g/dL	BS	55	mg/dL	WBC	2	/μL
pCO$_2$	12.7	mmHg	Alb	4.5	g/dL	NH$_3$	35	μg/dL	Lymph	100	%
HCO$_3^-$	5.6	mmol/L	BUN	9.4	mg/dL	FFA	2.15	mEq/L	Protein	22	mg/dL
BE	−2.2	mmol/L	Cre	0.22	mg/dL	AcAc	4183	μmol/L	Sugar	95	mg/dL
AG	26.4	mmol/L	Na	138	mmol/L	3-OHBA	8242	μmol/L	Lactate	23.5	mg/dL
			K	4.1	mmol/L	Lactate	13.8	mg/dL	Pyruvate	2.36	mg/dL
Hematology			Cl	106	mmol/L	Pyruvate	1.17	mg/dL	MBP	<40	pg/mL
WBC	13,100	/μL	AST	46	IU/L	total carnitine	63.1	μmol/L	OB	none	
Band	6	%	ALT	33	IU/L	free carnitine	15.0	μmol/L			
Seg	38	%	LDH	238	IU/L	acylcarnitine	48.1	μmol/L			
Lymph	51	%	CPK	92	IU/L						
Hb	13.7	g/dL	UA	11.2	mg/dL						
Plt	38.8	10^4/μL	CRP	0.0	mg/dL						

BE, base excess; AG, anion gap; WBC, white blood cell; Band, blood band cell; Seg, segmented cell; Lymph, lymphocyte; Hb, hemoglobin; Plt, platelets; TP, total protein; Alb, albumin; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Cl, chloride; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase; UA, uric acid; CRP, C-reactive protein; BS, blood sugar; NH$_3$, ammonia; FFA, free fatty acid; AcAc, acetoacetic acid; 3-OHBA, 3-hydroxybutyric acid; MBP, myelin basic protein; OB, oligoclonal band.
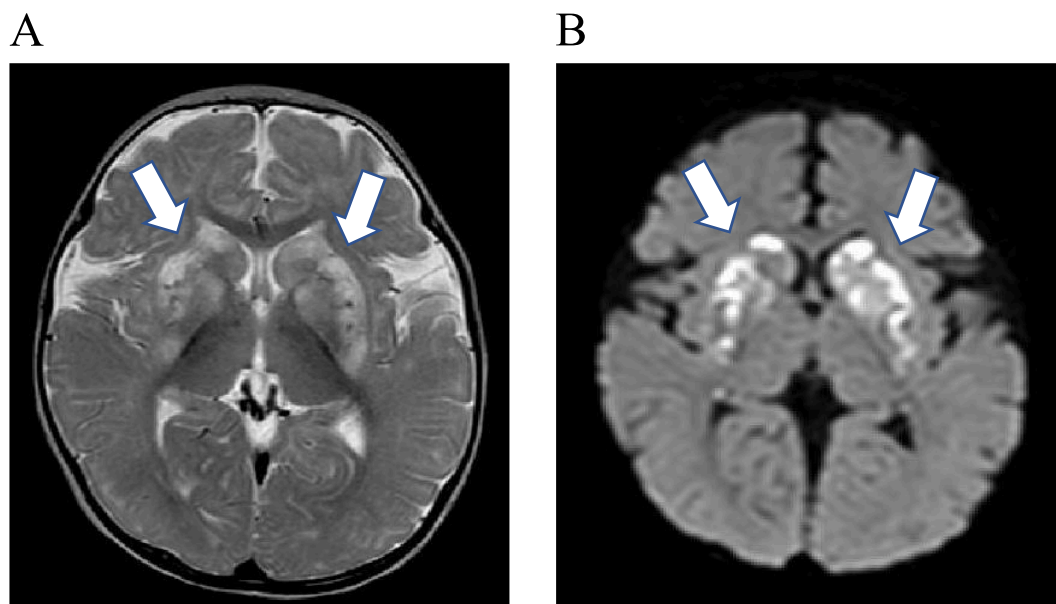
A

B

Fig. 1. Brain magnetic resonance imaging on admission showed bilateral abnormal signals in bilateral caudate nucleus and globus pallidus (as shown by the arrow; A. T2 Axial; B. Diffusion-weighted imaging).

often have a long delay to diagnosis [8]. This patient was suspected to possess inborn errors of ketolysis, but was diagnosed with ECHS1 deficiency upon genetic testing without measuring enzyme assay. Genetic tests, such as targeted next-generation sequencing and whole exome sequencing, are useful for diagnosing inborn errors of metabolism, including those involved with mitochondrial diseases [9–11]. Early interventions, such as valine-restricted diets and *N*-acetylcysteine supplementation, might be effective for patients with ECHS1 deficiency [7]. Thus, genetic testing is useful in detecting the deficiency and initiating treatment early. However, enzyme assay is still important methods for diagnosis, as they can diagnose properly and genetic testing cannot detect underlying mutations in all patients [5,12].

In conclusion, we report a case of ECHS1 deficiency concomitant with conjugate deviation, hypotonia, prominent ketoacidosis and no elevation in lactate levels in a 7-month-old boy. The patient is likely to have no impairment in the rate of short-chain fatty acid β oxidation and pyruvate dehydrogenase activity. The findings of this patient expand our understanding of ECHS1 deficiency. Analyzing the biology and findings of more patients with ECHS1 deficiency is necessary to further understand the clinical characteristics of this disease. Furthermore, genetic tests, such as targeted next-generation sequencing and whole exome sequencing, will prove useful for the early diagnosis of inborn errors of metabolism that can be treated, such as ECHS1 deficiency.

4. Ethics approval

This is an observational retrospective patient report that did not involve any research-based intervention. All interventions were intended to diagnose and treat the patient. No aspect of the case report is in contradiction with the Helsinki Declaration of 1975, as revised in 2000.

5. Submission declaration and verification

This report has not been published previously and is not under consideration for publication elsewhere. Publication of this report is approved by all authors.

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Patient consent

Written informed consent for the present study was obtained from the patient's parents.

Author contributions

M.U., J.M., S.F., N.F., T.O., K.I. and T.O. were involved in clinical management of patients. H.S. and K.M. performed mutation analysis. H. H. supervised this study, reviewed the manuscript. M.U.wrote the first draft. J.M. revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors confirm the absence of previous similar or simultaneous publications.

Declaration of Competing Interest

None.

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