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Fructose-1,6-bisphosphatase deficiency presented with complex febrile convulsion

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Abstract

Fructose-1,6-bisphosphatase (FBPase) deficiency is a rare inborn error of metabolism affecting gluconeogenesis caused by *FBP1* gene mutations. It could be more fatal to infants and children when glycogen reserves are insufficient. A 4-year-old girl was admitted with complex febrile convulsion. Initial laboratory results showed hypoglycemia, metabolic acidosis, and hyperlactatemia. Plasma amino acid and urine organic acid analyses showed increased levels of alanine and tricarboxylic acid cycle intermediates. However, she had similar clinical features, including confusion under severe hypoglycemia, two additional times over 6 months. Correct diagnosis could not be made because of nonspecific symptoms, and mitochondrial disorder was initially suspected. Clinical exome sequencing was performed, and compound heterozygous mutations of c.960_961insG and c.490G>A (p. Ser321ValfsTer13 and p. Gly164Ser) in the *FBP1* gene were identified. This is the first Korean pediatric case of FBPase deficiency that initially presented with neurologic clinical features. Despite its very low prevalence in Far-East Asian countries, FBPase deficiency should be considered in children with repeated clinical features of metabolic acidosis with hypoglycemia.

CASE REPORT

INTRODUCTION

FBPase is a key enzyme in gluconeogenesis that converts fructose 1,6-bisphosphate to fructose 6-phosphate and inorganic phosphate. FBPase deficiency (OMIM #229700) is caused by mutations of the *FBP1* gene in an autosomal recessive manner (Baker & Winegrad, 1970). This disorder may cause life-threatening episodes of severe metabolic acidosis and hypoglycemia. Episodes are triggered by fasting, illness, and fever. The symptoms of affected individuals are nonspecific and easily misdiagnosed as mitochondrial disorders or other metabolic diseases (Kikawa *et al.* 1997; Santer *et al.* 2016).

The patient presented with neurologic features described in this report had repeated episodes of hypoglycemia and metabolic acidosis. Clinical exome sequencing (CES) was performed to determine the cause of metabolic conditions, and compound heterozygous mutations in the *FBP1* gene were identified.

CASE REPORT

A 4-year-old girl was admitted for complex febrile convulsions with hypoglycemia and metabolic acidosis. She was born at term after an uneventful pregnancy and delivery. At the time of admission, her blood sugar was too low to be checked, and she was in a semi-comatose state. Her insulin level was low, and acylcarnitine was within the normal limit. Her initial laboratory results indicated metabolic acidosis, hypoglycemia, hyperlactatemia, and hyperuricemia. Serum amino acid analysis showed an increased alanine level, and urine organic acid analysis revealed elevated tricarboxylic acid cycle intermediate levels. In addition, the blood lactate-to-pyruvate molar ratio (lactate, 6.3 mmol/L: pyruvate, 0.2 mmol/L; 31>25) increased, as often shown in impaired oxygen phosphorylation. She experienced three more episodes of febrile convulsions within 1 day and was given antiepileptic therapy. Electroencephalography (EEG) initially showed more increased spike discharge and decreased frequency with slow background on the right hemisphere. After initiation of glucose infusion, her blood sugar returned to normal. EEG normalization was reported, and her neurologic symptoms were favorable. Brain magnetic resonance imaging showed no abnormal findings.

After several months, she presented abdominal pain with fever after more than 8 hours of fasting. Abdominal examination revealed no hepatomegaly as shown in glycogen storage disorder. Eating candies containing sorbitol caused her vomiting to worsen. Along with metabolic acidosis (pH, 7.176; base excess, −18.5 mmol/L) and hypoglycemia, she had severe gastroenteritis symptoms that caused lethargy and mental change. Clinical and laboratory data are presented in Table 1.

CES was performed to confirm the diagnosis of repeated metabolic ketoacidosis, and compound heterozygous mutations of c.960_961insG and c.490G>A (p. Ser321ValfsTer13 and p. Gly164Ser) in the FBP1

Tab. 1. Clinical and laboratory information for each attack.

	1st event	2nd event	3rd event	4th event
Age at each event	4yr 5month	4yr 9month	4yr 11month	5yr 2month
Symptoms for hospitalization due to hypoglycemia	Mental change (semicoma), Seizure, Fever, Vomiting	Fasting status, Fever, Vomiting, Abdominal pain	Fever, Vomiting, Abdominal pain	Mental change (Drowsiness), Vomiting
Blood gas analysis				
pH (7.32~7.38)	7.264	7.176	7.179	7.254
pCO2 (38~50mmHg)	33.0	19.0	28.8	27.3
HCO3 (22~29mM)	15.1	7.1	10.8	12.2
BE (-5~3mM)	-10.2	-18.5	-15.5	-12.8
Biochemical evaluation				
Glucose (70-110mg/dL)	Low (uncheckable)	Low (uncheckable)	<7	8
Urea (7~17mg/dL)	15.6	51.9	16.1	22.3
Creatine(0.21~0.53mg/dL)	0.34	0.69	0.43	0.35
Uric acid (2.5~5.9mg/dL)	8.4	18.7	10.5	10.0
AST (13.0~34.0IU/L)	162	71	45	60
ALT (5.0~46.0IU/L)	67	72	18	22
Albumin (3.8~5.4 g/dL)	4.4	4.8	4.8	4.8
Hormone evaluation				
Insulin (1.0~10.7uU/mL)	<0.20		<0.20	<0.20
Cortisol (6.7~22.6ug/dL)	37.0		37.5	34.3
Growth hormone (0~9.5ng/mL)	0.62		1.90	1.00
IGF-1 (30.1~252.2ng/mL)	61.4		68.7	88.0
Metabolic evaluation				
Lactate (0.5~2.2mmol/L)	6.3	4.2	5.1	7.2
Ketone(urine)	2+	3+	2+	2+

gene were identified. Variants were verified by Sanger sequencing (Figure 1). After the diagnosis of FBPase deficiency, the patient was instructed to avoid prolonged fasting and to restrict her dietary intake of fructose and sucrose. She did not experience any clinical episodes during the follow-up period.

DISCUSSION AND CONCLUSION

The estimated incidence of FBPase deficiency is less than 1 in 900,000 individuals; so far, only one case of an adult who had a compound heterozygote for G164S and 838delT has been reported in Korea (Moon *et al.* 2011; Santer *et al.* 2016).

Previous studies have shown that prolonged hypoglycemia can lead to energy failure and interruptions of many critical cellular activities. The brain utilizes 25% of the body's glucose owing to its high metabolic rate, and it requires a continuous supply of glucose because it does not produce glucose intrinsically and only contains a very limited store of glycogen. During hypoglycemia, glutamate and aspartate increase in the tissue because of truncation of the tricarboxylic acid cycle and initially affects sodium and water influx, which causes cellular edema (Neil & Hemmen, 2011). The hypoglycemia can manifest as seizures, stroke-like episodes, cognitive dysfunction, and coma.

Because FBPase deficiency is very rare, nonspecific symptoms of the disease can be easily misdiagnosed as other metabolic diseases such as respiratory chain disorders or glycogen storage diseases causing hypoglycemia and lactic acidosis (Lebigot *et al.* 2015; Li *et al.* 2017). Our patient's neurological clinical features and increased blood lactate-to-pyruvate molar ratio initially caused suspicion of mitochondrial disease. Most FBPase deficiency patients initially present during the first 2 years of life. However, some patients show accompanying neurologic symptoms after a period of clinical silence, especially infants or young children who are first referred to the neurology clinic and are often suspected of other disorders.

The diagnosis of FBPase deficiency is established by mutation analysis of the *FBP1* gene and measurement of FBPase activity. The sensitivity of FBPase activity measurement remains relatively low, and this diagnostic procedure is generally considered invasive because of the use of liver biopsy (Asberg *et al.* 2010; Li *et al.* 2017). However, CES using a next-generation sequencing technique is non-invasive and particularly useful for molecular diagnosis of complex metabolic diseases and other rare genetic conditions at the same time.

Hypoglycemia in patients with FBPase deficiency should be treated properly by glucose infusion. Glucagon injections may be ineffective and provoke the accumulation of gluconeogenic substrates such as lactate, alanine, and glycerol. Intravenous administration of glycerol or fructose solution for treatment of brain edema should not be used in any patients with hypoglycemia-induced neurologic symptom before evaluation of FBPase deficiency (Hasegawa *et al.* 2003). Therefore, an accurate diagnosis is important for proper management and prevention of complications of the disease. Early diagnosis of FBPase deficiency and simple interventional measures such as avoidance of prolonged fasting in febrile illness and restriction of dietary fructose and sucrose could reduce the risk of metabolic decompensation.

Each variant identified in this patient had been previously reported as a pathogenic allele (Kikawa *et al.* 1997; Li *et al.* 2017). The frameshift mutation (c.960_961insG) was known as the most common mutation in Japan and was identified in a Korean patient for the first time (Herzog *et al.* 2001; Kikawa *et al.* 1997). Because of the small number of patients, it is difficult to suggest that any ethnic background has a high prevalence of this mutation. However, a recent study indicated that ethnicity might affect the spectrum of mutations (Herzog *et al.* 2001; Santer *et al.* 2016). In addition, another missense mutation, c.490G>A, has also been previously described in Asian patients (Santer *et al.* 2016).

In summary, we reported the first pediatric case of FBPase deficiency diagnosed using CES in a 4-year-old Korean girl who presented with initial symptom of complex febrile convulsions. Because of the rarity of FBPase deficiency, it can be easily misdiagnosed and can lead to unfavorable outcomes. FBPase deficiency should be in the differential diagnosis when infants and children have repeated clinical features of metabolic acidosis with hypoglycemia. It would be interesting to determine whether FBPase mutations have a founder effect among Asian populations.

FINANCIAL DISCLOSURE

Authors have no financial interests in this manuscript and no affiliations (relationships) to disclose.

ETHICS STATEMENT

The present study was approved by the Institutional Review Board of the Yonsei University Health System (IRB, 4-2016-1035).

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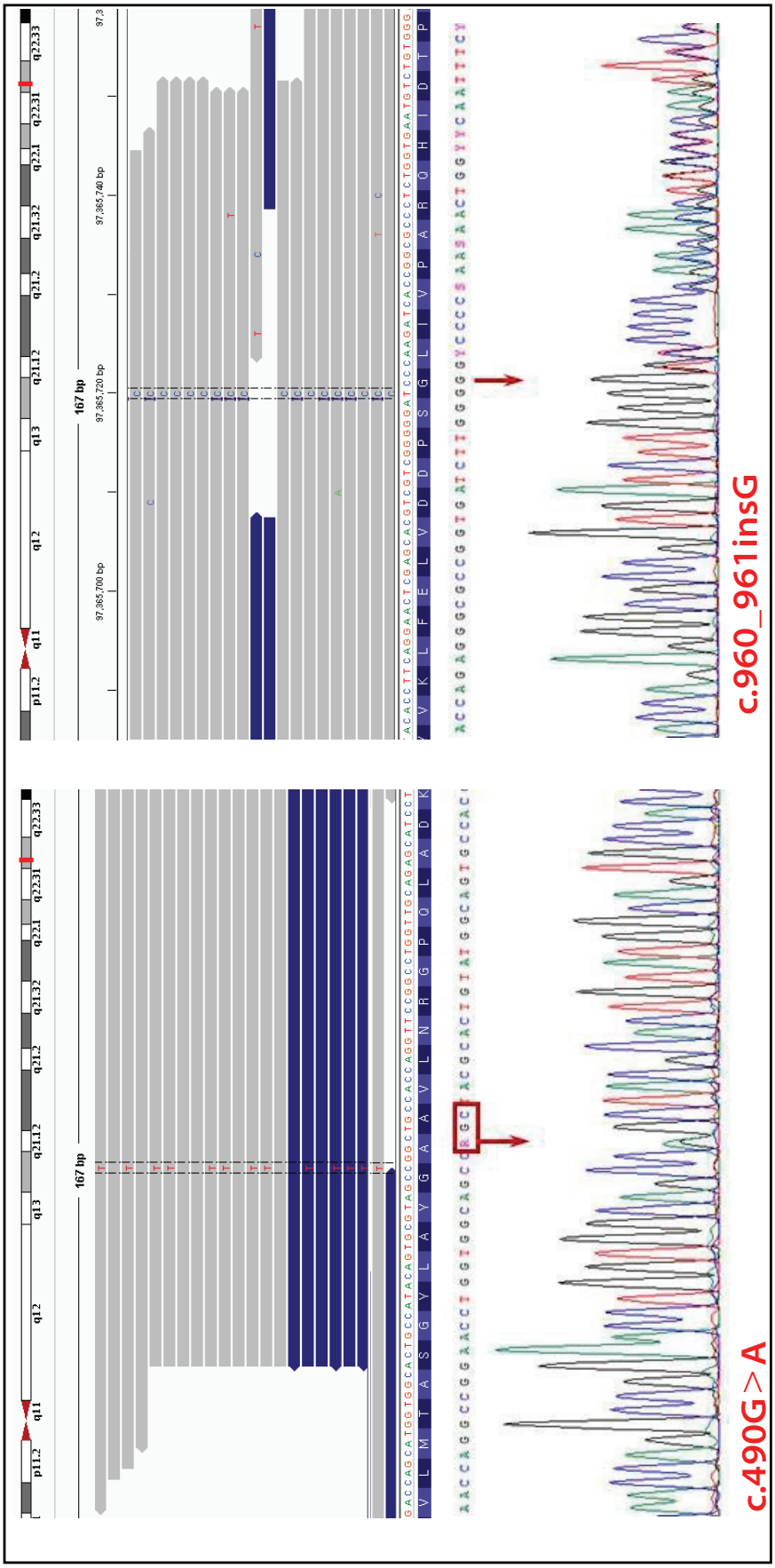

Fig. 1. Missense mutation c.490G>A in exon 4 predictably leading to the exchange of glycine with serine at codon 164, and insertion mutation 960_961insG predictably leading to frame shift and termination of protein translation (top). Both mutations were confirmed by Sanger sequencing (bottom).

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