Fructose-1,6-Bisphosphatase Deficiency: A Pediatric Case Report

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Case report

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Abstract

Background: Fructose-1,6-bisphosphatase (FBPase) deficiency is a rare disorder of glucose metabolism, mainly revealed by hypoglycemia and lactic acidosis. The disease is caused by a mutation of *FBP1* gene, which is clustered in a 31-kb region on chromosome 9q22.

Case presentation: We described a two-and-half-year-old boy diagnosed as FBPase deficiency. The result of gene analysis showed that the patient had a compound heterozygote for the G164S and P308R, respectively inherited from his father and mother. To some degree, mutations are associated with activity of enzyme, which is corresponding to the level of glucose and extent of brain damage. Patients are advised to reduce intake of fructose and sucrose and avoid long-term fasting in order to reduce the risk of metabolic decompensation.

Conclusions: This report would like to provide profound insights of FBPase deficiency.

Background

Fructose-1,6-bisphosphatase (FBPase) deficiency is a rare autosomal recessive inherited disorder caused by mutations of *FBP1* gene. The most common onset symptoms are hypoglycemia and lactic acidosis, which manifesting as hyperventilation, coma and seizure. Acute crises are usually triggered by urgent episodes, such as infections, fasting, fever and vomiting[1]. The incidence of this disease is nearly 1:900000, 1:350000 and 1:1782.321 in France, Dutch and Southern Brazil, respectively[2,3]. Approximately more than 100 cases involved with dozens of variants in *FBP1* gene have been reported so far[4]. In this report, we described a novel mutation in *FBP1* gene and reviewed several original literatures to provide further insights of FBPase deficiency.

Case Presentation

A two-and-a-half-year-old boy presented to the pediatric emergency department with the symptoms of becoming groggy and unconscious. 5 days ago, he was vaccinated with pneumococcal conjugate vaccines (PCV). He felt faint for lack of food over 15 hours and was dysuria about 5 hours. He was starting to manifest as hyperventilation in relation to onset. His parents denied any accompanied signs, such as fever, cough, stomachache, headache seizures and apneic spells.

At the time of presentation, his physical examination revealed a temperature of 36.5℃, a heart rate of 98 beats per minute and a respiratory rate of 26 breathes per minutes. His oxyhemoglobin saturation was 98% in the supine posture. He had a very negative response to the painful stimuli. Pupil reaction to light was preserved in the lethargic boy and his lips were slightly dry. The cardiovascular physical examination focused on features of murmur, auscultation over the heart valves and assessment of peripheral perfusion. All findings on cardiac examination were normal. Absence of abnormalities on chest auscultation reduced the possibility of catching respiratory diseases. What's more, he exhibited negative symptoms of abdomen distends and bellyache. Normal bowel sounds were present at the same time.

Meanwhile, the abdominal examination reveal the normal size of liver and spleen. The neurologic examination, including Kernig sign, Brudzinski sign, Babinski sign, Gordon sign, Oppenheim sign and primitive reflexes, were normal as well.

He had been in recurrent low spirits for nearly one year and recovered after food feeding. However, it is the first record for him to manifest as coma. He was born with a normal history of pregnancy and delivery. There were no history of consanguineous marriage or chronic disease in his family. His six-year-old brother was also physical healthy. He received all childhood vacations, including hepatitis B vaccine, the Bacilli Calmette-Guerin (BCG) vaccine, polio vaccine, Diphtheria-Tetanus-Pertussis, measles vaccine, encephalitis vaccine and PCV. His parents denied history of hospitalization, traumatism and allergic reactions to drugs. Besides, he had normal growth and intellectual development.

Diagnostic Studies

Library tests included C-reactive protein (CRP), procalcitonin (PCT), glucose, blood ammonia, lactic acid and fasting insulin. Serum level of alanine aminotransferases (ALT) and aspartate aminotransferases (AST) were detect at the same time. All results were present in Table 1. Electrocardiograph (ECG) and echocardiography (UCG) were applied to evaluate cardiac structure and function. Other imaging examinations were also shown normal, such as ultrasound (abdomen) and brain magnetic resonance imaging (MRI) (Fig.1).

Genetic Analysis

After we received informed consent from his parents, blood samples of proband and his parents were collected to identify mutations in *FBP1* gene. His little brother didn't participate in the test. High-throughput sequencing (NGS) was adopted in this study. The results showed that G164S (c.490G>A) in exon 4 and P308R (c.923C>G) in exon 7, respectively detected from his father and mother, had a high risk of pathogenic potentiality. As both alleles of a diploid parent were different, his parents were all heterozygous at different loci. The child inherited G164S and P308R from each parent and then constituted a compound heterozygous mutation. Both mutations were caused by single-base substitution. All results of genetic analysis are shown in Table 2 and Fig 2.

Treatments

He put on a drip with glucose at a pace of 5 ml/kg/h. The patient received antibiotic therapies and liver-protecting drugs. 7 days later, abnormal levels in the blood returned to previous values. The level of glucose fluctuated from 4.5 mmol/L to 6.0 mmol/L when he discharged from hospital.

Follow-up

We suggested the little boy to reduce intake of fructose and sucrose and avoid prolonged fasting and febrile diseases, which could increase the risk of metabolic decompensation. He rarely manifests as

hypoglycemia. He is in kindergarten now. he could perform an astonishing variety of accomplishments, such as drawing, singing and even reciting.

Discussion

FBPase deficiency is a severe disorder of glucose metabolism, which is usually triggered by febrile diseases and prolonged fating. The defect prevents the endogenous formation of glucose and provokes an accumulation of lactate. Diagnosis of FBPase deficiency is eventually depended on genetic analysis and FBPase activity assay[5]. Since FBPase deficiency was first reported in 1970, several novel variations had been identified in different countries and regions[3,6]. However, it seems that no correction between genotype and phenotype has been convinced so far. Individuals with different variations may manifest as the similar clinical features, such as hypoglycemia, ketonuria, metabolic and lactic acidosis. Majority of the patients with FBPase deficiency experience normal growth and few with prolong brain damage and negative effects on mental abilities[7,8].

In this study, gene testing showed that a heterozygous C to G transition at nucleotide 923 of the coding sequence in exon 7, causing the exchange between proline and arginine, was a deleterious mutation. Without frequent convulsion and cerebral anoxia, this kind of variant seems to be harmless to the brain. What's more, the boy was brighter than average as his mother said. Mei et al[9] found a similar compound heterozygous variants (c.333+1_333+2delinsTC and c.490G>A) in *FBP1* gene. In contrast, the pitiful little boy had suffered from severe status epilepticus. Upon admission, patient experienced a lower level of glucose in the blood (0.3 mmol/L) compared to that (1.3 mmol/L) in our study. That is dangerous for cells of the central and peripheral nerve system and it would lead to irreversibly damages in cerebral tissue[10]. Meanwhile, a boy in Malaysia also presented with status epilepticus, which is different from other patients in the same study. He had experienced profound hypoglycemia (< 0.3mmol/L). As a result, less glucose was provide to the cerebral cells, which would lead to metabolic problems[8]. In Korean, a 4-year-old girl with hypoglycemia and hyperlactatemia was taken to the hospital. She experienced recurrent episodes of mental symptoms. At the same time, the level of glucose is too lower to be detect. Laboratory date showed that two mutations were identified in *FBP1* gene, including c.960-961insG and c.490G>A[11]. To some degree, there would be some connections between different mutations and level of glucose in the blood. In other words, some mutations may reduce the activity of enzyme, which is corresponding to lower level of glucose and causing brain damage. However, detrimental mutations, which were associated with the severity of FBPase deficiency, haven't been absolutely verified due to the limitations of the current level of detection.

The effective treatment of FBPase deficiency is similar to that of phenylketonuria. Dietary management is of critical importance. Preventing the disease attack is the most significant purpose, especially in young children. Children with FBPase deficiency are advised to reduce excessive intake of fructose and sucrose and avoid fasting more than 8 hours. What's more, exogenous glucose is extremely essential for patients when metabolic decompensation occurring[12].

Conclusion

In summary, this study identified two missense mutations associating with FBPase deficiency. c.923C>G is a novel mutation in *FBP1* gene, causing hypoglycemia and lactic acidosis. Mutations in *FBP1* gene are different from each other in the severity of disorder, which is associated with various level of glucose in the blood. Anyway, FBPase deficiency should be taken into consideration when patients manifest as hypoglycemia and lactic acidosis.

Declarations

Author contributions: Wrote the manuscript: JC; Contributed materials/analysis tools: JC and LX**;** Guided the writing of the manuscript and participated in research design: JP.

Disclosure Statement

The authors report no conflict of interests.

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Ethics approval statement

This study has been approved by the institutional review board of Anhui provincial hospital.

Consent for publication

Consent was obtained from the patient's parent for publication of this case report and any accompanying images.

Availability of data and materials

All valuable date had been shared in this submission.

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Tables

Table1 Summary of laboratory results of the child

Laboratory results	Prior treatment	posttreatment
Results of blood chemistry		
RBC (4.30-5.80×10^{12}/L)	4.33	3.96
Hemoglobin (130.0-175.0 g/L)	118.0	106.0
WBC (3.50-9.50×10^{9}/L)	11.71	4.71
Percent Neutrophils (40.0-75.0 %)	80.4	40.7
Percent Lymphocyte (20.0-50.0 %)	13.9	49.3
CRP (0.00-10.00 mg/L)	0.38	0.68
PCT (0.000-0.500 ng/ml)	0.851	0.312
Glucose (4.20-6.20 mmol/L)	1.30	4.55
CO2CP (22.00-29.00 mmol/L)	9.70	23.00
Blood ammonia (9.0-33.0 ummol/L)	39.6	43.2
Lactic acid (0.7-2.1 mmol/L)	10.6	2.6
Fasting Insulin (20.81-174.13 pmol/L)	23.85	(-)
ALT (5-50 U/L)	225.0	30.3
AST (15-45 U/L)	534.4	23.2
Other findings		
Ultrasound (abdomen)	Normal	Normal
Brain MRI	Normal	Normal
ECG	Normal	Normal
UCG	Normal	Normal

RBC: red blood cell; WBC: white blood cell; CRP: C-reactive protein; PCT: procalcitonin; CO2CP: carbon dioxide combining power; ALT: alanine aminotransferase; AST: aspartate aminotransferase; MRI: magnetic resonance imaging; ECG: electrocardiograph; UCG: echocardiography.

Table2 Annotations of the identified variations in *FBP1* gene

Gene	Number	Chromosomal position	Nucleotide change	Amino Acid change (NM_000507)	Exon position	Carrier
FBP1	1	chr9:97 372280	c.490G>A	p.G164S (p.Gly164Ser)	Exon 4	father
	2	chr9:97 365757	c.923C>G	p.P308R (p.Pro308Arg)	Exon 7	Mother

Figures

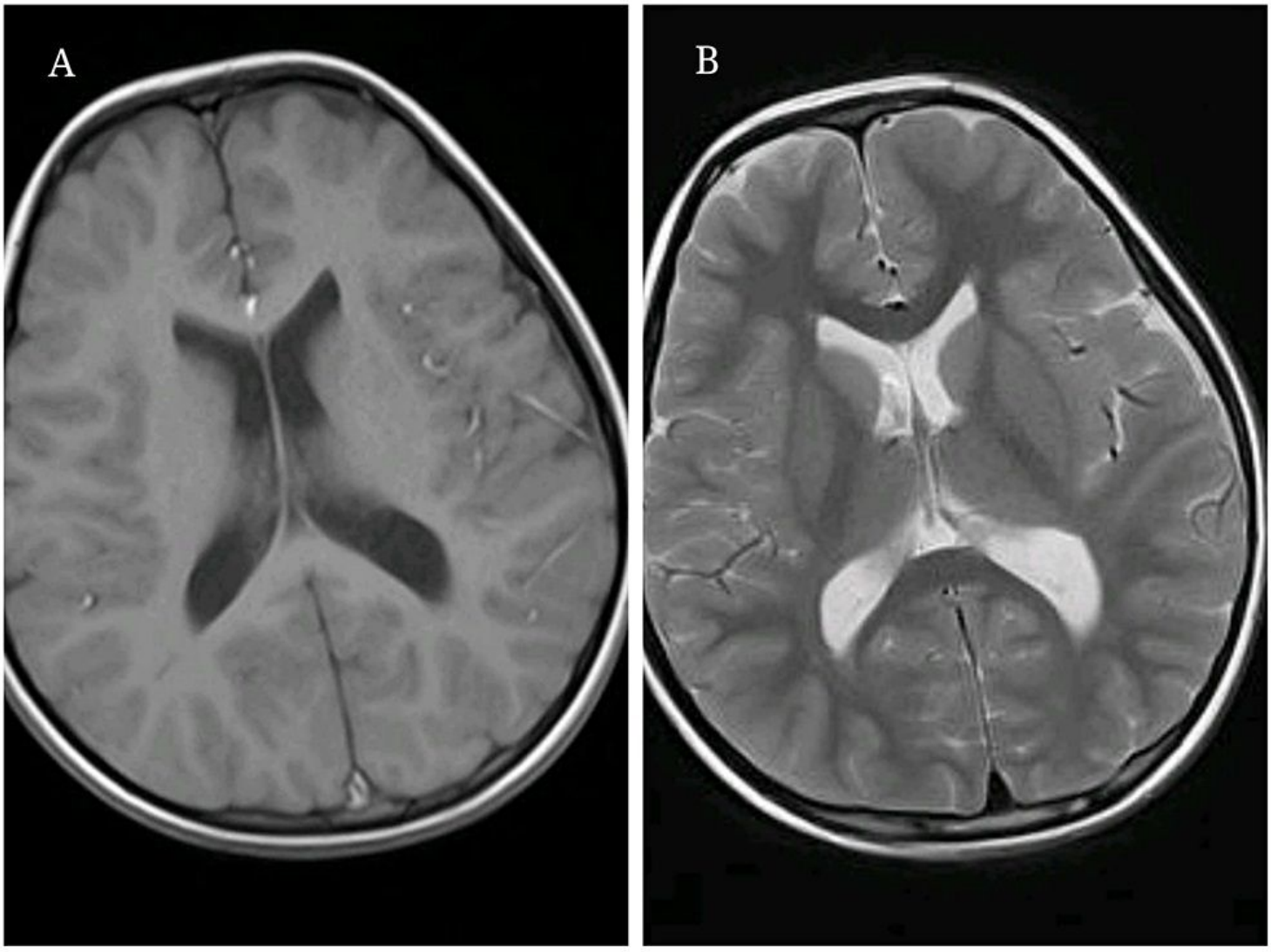

Figure 1

Diagnostic Studies Library tests included C-reactive protein (CRP), procalcitonin (PCT), glucose, blood ammonia, lactic acid and fasting insulin. Serum level of alanine aminotransferases (ALT) and aspartate aminotransferases (AST) were detect at the same time. All results were present in Table 1.

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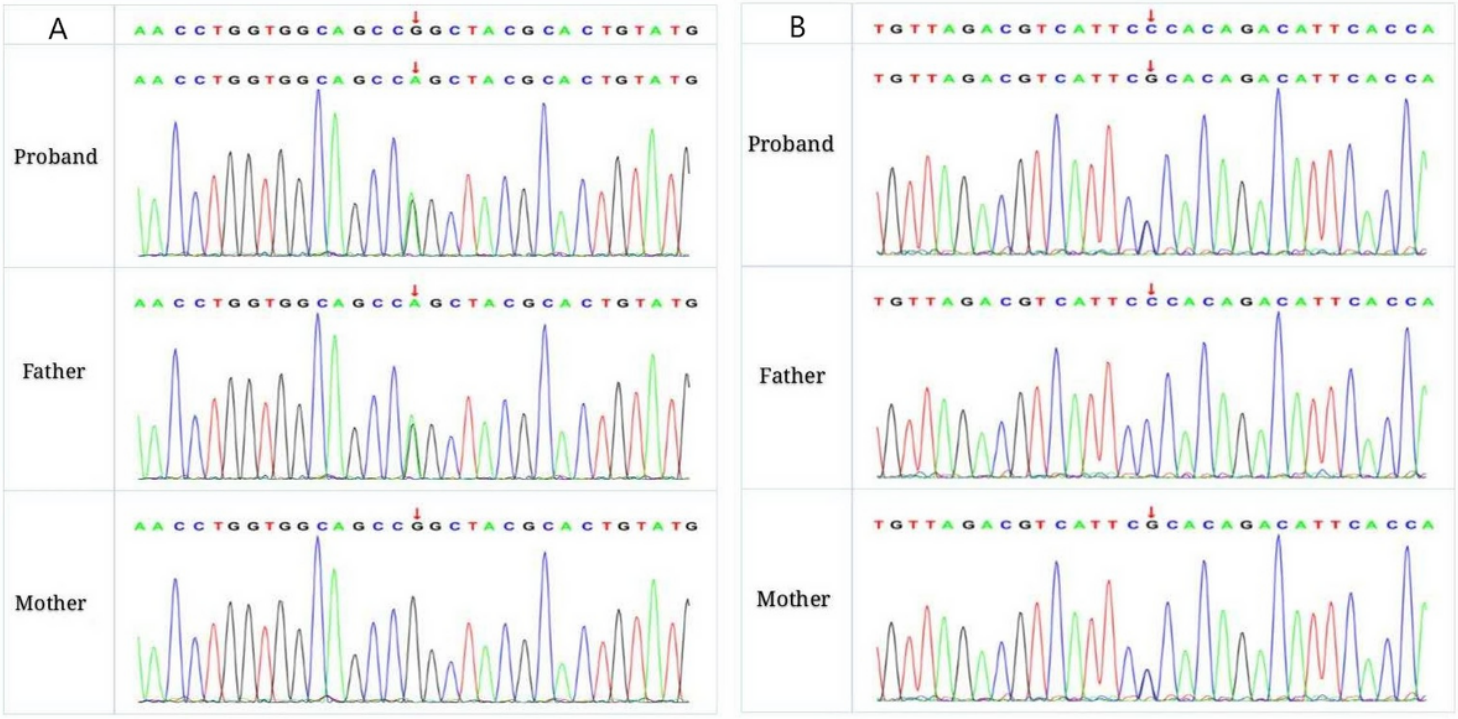

Figure 2

Genetic Analysis After we received informed consent from his parents, blood samples of proband and his parents were collected to identify mutations in FBP1 gene. His little brother didn't participate in the test. High-throughput sequencing (NGS) was adopted in this study. The results showed that G164S (c.490G>A) in exon 4 and P308R (c.923C>G) in exon 7, respectively detected from his father and mother, had a high risk of pathogenic potentiality. As both alleles of a diploid parent were different, his parents were all heterozygous at different loci. The child inherited G164S and P308R from each parent and then constituted a compound heterozygous mutation. Both mutations were caused by single-base substitution. All results of genetic analysis are shown in Table 2 and Fig 2.