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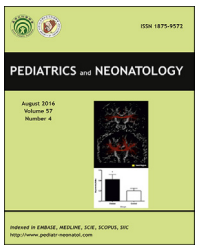

Original Article

Fructose-1,6-bisphosphatase deficiency as a cause of recurrent hypoglycemia and metabolic acidosis: Clinical and molecular findings in Malaysian patients

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Key Words
Fructose-1, 6-bisphosphatase; FBPase deficiency; *FBP1* gene mutation

Abstract *Background:* Fructose-1,6-bisphosphatase (FBPase) deficiency is a rare autosomal recessive inborn error of gluconeogenesis. We reported the clinical findings and molecular genetic data in seven Malaysian patients with FBPase deficiency.
Methods: All patients diagnosed with FBPase deficiency from 2010 to 2015 were included in this study. Their clinical and laboratory data were collected retrospectively.
Results: All the patients presented with recurrent episodes of hypoglycemia, metabolic acidosis, hyperlactacidemia and hepatomegaly. All of them had the first metabolic decompensation prior to 2 years old. The common triggering factors were vomiting and infection. Biallelic mutations in *FBP1* gene (MIM*611570) were identified in all seven patients confirming the diagnosis of FBPase deficiency. In four patients, genetic study was prompted by detection of glycerol or glycerol-3-phosphate in urine organic acids analysis. One patient also had pseudo-hypertriglyceridemia. Seven different mutations were identified in *FBP1*, among them four mutations were new: three point deletions (c.392delT, c.603delG and c.704delC) and one splice site mutation (c.568-2A > C). All four new mutations were predicted to be damaging by *in silico* analysis. One patient presented in the neonatal period and succumbed due to sepsis and multi-organ failure. Among six survivors (current age ranged from 4 to 27 years), four have normal growth and cognitive development. One patient had short stature and another had neurological deficit following status epilepticus due to profound hypoglycemia.

Abbreviations: FBPase, fructose-1,6-bisphosphatase; HGMD, Human Gene Mutation Database; Polyphen, Polymorphism Phenotyping; SIFT, Sorting Intolerant From Tolerant; ExAC, Exome Aggregation Consortium.

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Conclusion: FBPase deficiency needs to be considered in any children with recurrent hypoglycemia and metabolic acidosis. Our study expands the spectrum of *FBP1* gene mutations.
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1. Introduction

Fructose-1,6-bisphosphatase (FBPase) deficiency (OMIM #229700) is a rare autosomal recessive inborn error of gluconeogenesis. FBPase is a critical regulatory enzyme in gluconeogenesis that catalyzes the removal of 1-phosphate from fructose 1,6-bisphosphate to form fructose 6-phosphate, which permits endogenous glucose production from gluconeogenic amino acids (e.g., alanine and glycine), glycerol, or pyruvate/lactate. Patients with FBPase deficiency rely on intake of glucose and breakdown of glycogen to maintain normoglycemia. Hence hypoglycemia is likely to occur when glycogen reserves are limited (in newborn) or exhausted (during fasting). Hypoglycemia may also follow ingestion of large amounts of fructose.[1]

Most of the patients with FBPase deficiency present before 6 months of age. Neonatal presentation is characterized by hyperventilation, hepatomegaly, hypoglycemia, severe metabolic acidosis and hyperlactacidemia. Subsequent episodes usually follow fasting and are often precipitated by intercurrent infections. These acute episodes usually respond well to vigorous therapy with intravenous glucose and sodium bicarbonate. Once diagnosis is established, prognosis is excellent with avoidance of fasting and children do not usually have psychomotor delay. However, if undiagnosed, patients are at risk of severe and prolonged hypoglycemia which may result in significant morbidity and mortality.[1,2]

FBPase deficiency may be suspected by detecting elevated urinary excretion of glycerol or glycerol-3-phosphate.[3,4] Direct enzymatic assay of hepatic FBPase activity remains the most specific diagnostic test for FBPase deficiency, but this is only performed by a handful of reference laboratories. Molecular study is increasingly performed to confirm the diagnosis. FBPase is encoded by the *FBP1* gene (MIM*611570), which spans over 31 kb and consists of seven exons. It is located at chromosome bands 9q22.2-q22.3.[4] Currently, about 35 mutations in the *FBP1* gene have been reported and the majority are private mutations. The notable exceptions are c.959dupG and c.-24-26_170 + 5192del, which are recurring among Caucasians and Japanese, and patients from Turkey and Armenia, respectively.[5–10]

In the present study, we report the clinical findings, laboratory data, and molecular genetic analysis in seven patients with FBPase deficiency. This is the first report of FBPase deficiency in Malaysia.

2. Materials and methods

2.1. Subjects

All patients diagnosed with FBPase deficiency from 2010 to 2015 were included in this study. Their clinical and laboratory data were collected retrospectively. Urinary organic acids were analyzed by gas chromatography/mass spectrometry (GC/MS).

2.2. Molecular study

Written informed consent was obtained from the patients or legally authorized representative before approximately 2.5 ml of peripheral blood was withdrawn and collected in standard ethylenediaminetetraacetic acid (EDTA) tube. Genomic DNA was extracted from patients and their parents as well as healthy control individuals using a commercial QIAamp DNA Blood Mini Qiacube Kit (QIAGEN, Hilden, Germany). Bidirectional sequencing of all seven *FBP1* exons plus approximately 50 base pairs of flanking non-coding intronic DNA on either side of each exon was performed using genomic DNA.

The sequencing results were compared with the genomic reference of *FBP1* using SeqScape software version 2.5 (Applied Biosystems, Foster City, CA). Small insertion or deletion mutation was reconfirmed by Mutation Surveyor software (Softgenetics, State College, PA). All single nucleotide variants (SNVs) or indels were reported by following the recommendation of Human Genome Variation Society (HGVS) (http://www.hgvs.org/mutnomen). All mutations identified were annotated against publicly available database such as the Human Genome Mutation Database (HGMD) (http://www.hgmd.cf.ac.uk/ac/index.php) and 1000 Genome Browser (http://www.1000genomes.org). The new mutations were also analyzed in 50 local healthy individuals as control group to determine if they were local polymorphism. The pathogenicity and functional effects of the new *FBP1* mutations were evaluated by PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org/) and MutationTaster (http://www.mutationtaster.org/). Mutations detected were also compared with HomoloGene (NCBI) database (https://www.ncbi.nlm.nih.gov) to evaluate the percentage of conservation among eukaryote species.

This study was approved by the Institutional Medical Research & Ethics Committee and conducted in accordance with the Declaration of Helsinki.

3. Results

3.1. Clinical findings

There were seven patients (3 males, 4 females) from six families diagnosed with FBPase deficiency. All of them had recurrent hypoglycemia and ketoacidosis. Two patients had first episodes of hypoglycemia during the neonatal period, while the remaining 5 patients were symptomatic prior to 2 years old. Parental consanguinity was reported in 3 families. The main

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