Fructose-1,6-bisphosphatase deficiency with confirmed molecular diagnosis. An important cause of hypoglycemia in children

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ABSTRACT

Objectives: To draw attention towards fructose-1,6-bisphosphatase (FBPase) deficiency as an important cause of hypoglycemia and lactic acidosis and to implement preventive strategies.

Methods: This observational, cross-sectional study was conducted on 7 Saudi patients with genetically confirmed FBPase deficiency from 2008 to 2018 at Prince Sultan Military Medical City, Riyadh, Saudi Arabia.

Results: Participants ranged in age from 1-10 years, and all presented with recurrent hypoglycemia. All but one had associated severe metabolic acidosis, and 3 patients (42.9%) presented with hypoglycemia and severe acidosis since birth. The mean duration from presentation to diagnosis was 39.4 months, as other diagnoses, like glycogen storage diseases and mitochondrial diseases needed to be ruled out. Development was normal apart from speech delay in one patient with a novel variant of the FBP1 gene. All patients have homozygous variants in the FBP1 gene.

Conclusion: Fructose-1,6-bisphosphatase is an important cause of hypoglycemia and acidosis; therefore, it is important to offer early molecular diagnostics in any child presenting with these symptoms. Molecular diagnostics should always be undertaken to confirm the diagnosis and for further preventive strategies.

Keywords: Fructose-1,6-bisphosphatase, FBPase, FBP1 gene, fructose, hypoglycemia.


Deficiency of hepatic fructose-1,6-bisphosphatase (FBPase) is an autosomal recessive disorder with impaired gluconeogenesis leading to hypoglycemia and lactic acidosis. It was first described in 1970.¹ Fructose-1,6-bisphosphatase¹ gene is composed of 8 exons located on chromosome 9q22.2-q22.3.² Fructose-1,6-bisphosphatase enzyme is crucial for the conversion of FBP to fructose 6-phosphate and inorganic phosphate.³ Patients could develop seizures and coma.³ The metabolic decompensation usually occurs with fasting, infections, and stress. Fructose-1,6-bisphosphatase deficiency is also associated with impaired purine catabolism and this is the cause of hyperuricemia in these patients.⁴ Other derangements with metabolic decompensations include increased liver enzymes and increased urinary ketones.

With early diagnosis and strict management, the long-term prognosis for FBPase deficiency is excellent which highlights the importance of early molecular confirmation.⁵,⁶ The aim of this study was to draw the attention of pediatricians towards FBPase deficiency as an important cause of recurrent hypoglycemia and lactic acidosis and to emphasize the importance of molecular diagnostics to confirm the diagnosis.

Methods. This study was observational, cross-sectional, according to principles of Helsinki Declaration, carried out in Prince Sultan Military Medical City, Riyadh, Saudi Arabia, on October 2018 by reviewing medical records of 7 Saudi patients with genetically confirmed FBPase deficiency from 2008-2018.

All patients presenting with hypoglycemia or acidosis with confirmed molecular diagnosis of FBPase deficiency were recruited in the study. A total of 7 patients with genetically confirmed diagnosis were included. Those without molecular confirmation were excluded. Data were collected from medical records, including scheduled outpatient clinics and inpatient admission records. Ethical approval from our Institutional Review Board was obtained before starting this study.

Statistical analysis. The data were analyzed using Statistical Package for Social Science, version 20 (IBM Corp, Armonk, NY, USA). Qualitative data were presented in numbers and percentages. PubMed search was used to find prior related researches.

Results. Case 1. A female patient was a product of first-degree cousin marriage, presenting on the 1st day of life with respiratory distress, hypoglycemia, and acidosis. Sepsis was excluded. Systemic examination was unremarkable apart from laryngomalacia. She had normal development. Investigations revealed blood glucose of 0.8 mmol/l (3.3-8), lactate 12.6 mmol/l (0.5-2.2), PH 7.18 (7.35-7.45), carbonate (HCO₃⁻) 9.9 mmol/l (22-26), and high uric acid level 728 umol/l (110-390). Ammonia, creatine phosphokinase (CK), lipid profile, hepatic profile, Tandem mass spectrometry (MS), and urine organic acids were normal. At first
the suspected diagnosis was glycogen storage disease (GSD) and mitochondrial disease (MD), which were excluded by molecular studies. Then the diagnosis was confirmed by whole exome sequence (WES) at the age of 41 months, homozygous for FBP1 gene: c.114-115insCTGCAC (p.L38delinsLCT).7

**Case 2.** The male patient is the brother of case 1 and he had the same presentation as his sister with normal systemic examination. His blood glucose 2.2 mmol/l, PH 7.23, HCO3 11 mmol/l, and lactate 14.4 mmol/l. Ammonia, CK, lipid profile, and Tandem MS were normal. Hepatic profile showed slightly increased gamma-glutamyl transferase level 88 U/L (7-32 U/L) other liver enzymes were normal. Urine organic acid showed highly elevated lactic acid, pyruvic acid, moderately elevated 3-hydroxybutyric acid, and 2-hydroxybutyric acid. Mitochondrial disease was excluded. The final diagnosis was confirmed at the age of 18 months by WES revealing same variant as his sister.

**Case 3.** The female patient was an outcome of consanguinous marriage, she presented on the first day of life with hypoglycemia and severe metabolic acidosis. System examination showed just palpable liver. Her development was normal. Her blood glucose 2.2 mmol/l, PH 7.09, sodium bicarbonate 5.4 mmol/l, lactate 13.4mmol/l, CK 377 U/L (50-170 U/L). Urate, lipid profile, liver enzymes, ammonia, and Tandem MS were all normal. Urine organic acids revealed increased lactic acid, 3 hydroxybutyric acid and 2 hydroxybutyric acid. Genetic study for GSD comprehensive panel by massively parallel sequencing at the age of 34 months revealed homozygous variant (c.959dupG) which is predicted to result in translational frame shift and premature protein termination (p.Ser321Lefs*13). This variant has alternately been described in the literature using designations such as 8-10

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**Discussion.** Although several reports in the literature about FBPase deficiency, including reports from the Kingdom of Saudi Arabia, 4-11 this diagnosis...
still not entertained by the pediatricians, which makes
delay in the management of patients. In this study
although number of patients is limited, the delineation
of genomic variants has helped in reaching the
diagnosis and in future preventive strategies including
pre-implantation genetic diagnosis for the families and
carrier screening for other family members.
This study was positive familial history for the
condition in 5 of our patients (71.4%), which could
be explained by the high rate of consanguinity among
Saudi population.
Three of the patients (42.9%) presented at birth with
respiratory distress, severe acidosis, and hypoglycemia.
In a study of 4 patients with FBPase deficiency carried
out by Niu Li et al,\textsuperscript{3} 2 patients (50%) presented on day
1 and 3 with symptoms.
The mean duration from the patients' presentation
until diagnosis was 39.4 months. The earliest age
at diagnosis was 1.5 years, whereas the latest age of
diagnosis was 9 years and 5 months (Table 1). Diagnosis
was made late due to the limited molecular testing
facilities available in our institute 8 years back and
because MD or GSD were first suspected in other
institutions. Once negative, they were referred to us,
with FBPase deficiency having remained unsuspected as
a possible cause in the other institutions.
In all patients, the diagnosis was confirmed by
molecular testing, as shown in Table 2. Homozygous
mutation in \textit{FBPI} gene with duplication of 2 amino
acids (c.114-115 ins CTGCAC) was documented in 4
patients, namely, case 1, 2, 3, and 5. This mutation was
reported before by Faiyaz-Ul-Haque et al.\textsuperscript{7} One of our
patients had a novel mutation of \textit{FBPI} gene (c. 334-2
A\textsuperscript{T}). The mutation site was in intron 3; this variant
change the invariant splice site and is thus categorized
as likely pathogenic.\textsuperscript{12} This novel variant needs further
molecular and functional studies.
All patients were managed on fructose, sucrose free
diet with added cornstarch and frequent feeding, with
glucose monitoring at home with excellent prognosis.
Families offered PGD in order to prevent disease
recurrence. Pinto et al,\textsuperscript{11} studied the international
practices in the dietary management of patients with
FBPase deficiency and concluded that in emergencies
all agreed upon restriction of sucrose and fructose, but
the use of cornstarch varied widely especially in older
patients where it may not be necessary.
In conclusion, fructose-1,6-bisphosphatase
deficiency is an overlooked cause of hypoglycemia and
acidosis in our community, since GSD and MD were
initially suspected, which led to a delay in the diagnosis
averaging approximately 3 years in duration in this
study. It would be important to consider this diagnosis
early for any child with recurrent hypoglycemia and
acidosis, and to increase the awareness of general
pediatricians towards this disease as it is easy to treat

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient's age</th>
<th>Age at presentation</th>
<th>Age at diagnosis</th>
<th>Blood glucose (3.3-8 mmol/l)</th>
<th>HCO3 (22-26mmol/l)</th>
<th>Lactate (0.5-2.2mmol/l)</th>
<th>Urate (210-430umol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48 M</td>
<td>Day 1</td>
<td>41 M</td>
<td>0.8</td>
<td>9.9</td>
<td>12.6</td>
<td>728</td>
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<tr>
<td>2</td>
<td>24 M</td>
<td>Day 1</td>
<td>18 M</td>
<td>2.2</td>
<td>11</td>
<td>14.4</td>
<td>432</td>
</tr>
<tr>
<td>3</td>
<td>45 M</td>
<td>Day 1</td>
<td>34 M</td>
<td>2.2</td>
<td>5.4</td>
<td>13.4</td>
<td>330</td>
</tr>
<tr>
<td>4</td>
<td>36 M</td>
<td>12 M</td>
<td>33 M</td>
<td>1.3</td>
<td>10</td>
<td>7.8</td>
<td>689</td>
</tr>
<tr>
<td>5</td>
<td>122 M</td>
<td>12 M</td>
<td>113 M</td>
<td>1</td>
<td>14.3</td>
<td>10.8</td>
<td>214</td>
</tr>
<tr>
<td>6</td>
<td>43 M</td>
<td>5 M</td>
<td>42 M</td>
<td>1.6</td>
<td>No acidosis</td>
<td>1.8</td>
<td>NA</td>
</tr>
<tr>
<td>7</td>
<td>55 M</td>
<td>24 M</td>
<td>48 M</td>
<td>2.3</td>
<td>21.7</td>
<td>5.2</td>
<td>NA</td>
</tr>
</tbody>
</table>

HCO3: carbonate, M: month, NA: not available

<table>
<thead>
<tr>
<th>Case</th>
<th>\textit{FBPI} gene transcript</th>
<th>cDNA</th>
<th>Protein</th>
<th>Zygosity</th>
<th>PMID references</th>
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<tbody>
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<td>1</td>
<td>(NM_000507.3) c.114_119dup</td>
<td>p.C39_T40dup</td>
<td>Hom\textsuperscript{'}</td>
<td>Faiyaz-Ul-Haque et al,\textsuperscript{7}</td>
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<tr>
<td>2</td>
<td>(NM_000507.3) c.114_119dup</td>
<td>p.C39_T40dup</td>
<td>Hom\textsuperscript{'}</td>
<td>Faiyaz-Ul-Haque et al,\textsuperscript{7}</td>
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</tr>
<tr>
<td>3</td>
<td>(NM_000507.3) c.114_119dup</td>
<td>p.C39_T40dup</td>
<td>Hom\textsuperscript{'}</td>
<td>Faiyaz-Ul-Haque et al,\textsuperscript{7}</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(NM_001127628.1) c.841G&gt;T</td>
<td>p.Glu281\textsuperscript{*}</td>
<td>Hom\textsuperscript{'}</td>
<td>Faiyaz-Ul-Haque et al,\textsuperscript{7}</td>
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</tr>
<tr>
<td>5</td>
<td>(NM_000507.3) c.114_119dup</td>
<td>p.C39_T40dup</td>
<td>Hom\textsuperscript{'}</td>
<td>Faiyaz-Ul-Haque et al,\textsuperscript{7}</td>
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<tr>
<td>6</td>
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<td>Splice mutation</td>
<td>Hom\textsuperscript{'}</td>
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<tr>
<td>7</td>
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<td>p.(Ser321Valfs*13)</td>
<td>Hom\textsuperscript{'}</td>
<td>Kikawa et al,\textsuperscript{8} 1995</td>
<td></td>
</tr>
</tbody>
</table>

\textit{FBPI}: fructose-1,6-bisphosphatase-1, cDNA: complementary deoxyribonucleic acid, Hom: homozygous.
with good prognosis. It is important to offer early molecular diagnostics particularly for implementing preventive strategy like PGD.

Furthermore, the wide variation of the clinical presentation needs to be elaborated with further research, including the search for any correlations between genotype and phenotype with further functional studies specially for the novel variants.

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