Submitted: 14.02.2022
Accepted: 07.03.2022
Early publication date: 27.07.2022

Endokrynologia Polska
DOI: 10.5603/EP.a2022.0064
ISSN 0423–104X, e-ISSN 2299–8306
Volume/Tom 73; Number/Numer 5/2022

Fructose-1,6-bisphosphatase deficiency

Cong Yi, Jian Xie*

Department of Paediatrics, Mianyang Central Hospital, School of Medicine, University of Electronics Science and Technology of China, Mianyang, China

Key words: *fructose-1,6-bisphosphatase (FBPase) deficiency; hypoglycaemia; hyperlactic acidaemia; acidosis*

Fructose-1,6-bisphosphatase (FBPase) deficiency is an autosomal recessive disorder. It is a liver deficiency/hypofunction resulting from mutations in the FBP1 gene on chromosome 9, long arm 2.2 (9q22), which results in a dysfunctional conversion of 1,6 fructose diphosphate to fructose 6 phosphate. The clinical manifestations are paroxysmal hypoglycaemia, hyperlactic acidaemia, metabolic acidosis, and ketosis; infection and a lack of food are common predisposing factors for this disease. Among the Dutch and French populations, for example, it has a prevalence of 1/350,000 and < 1/90,000, respectively [1, 2], but there are no statistics on its incidence in China. This paper aims to raise awareness of this disease by analysing the clinical manifestations of one genetically diagnosed case and reviewing the relevant current literature.

A Chinese female patient, aged four years and one month, was hospitalized in our hospital on 17 June 2020, having had a headache for one day, as well as 2 convulsions within 8 hours. Before her hospitalization, the patient had had a headache for one day, which was described as bearable and not severe. Eight hours before admission (04:00) the parents noticed that the child had a ring of phlegm in her throat, and for approximately one minute she maintained a blank stare, a pale complexion, clenched fists, and was unresponsive. The second such incident happened one hour later (05:00), with the same symptoms as the first, and lasted 20 minutes. When the patient came to, she was slightly pale and weak, but she had no prolonged hunger, no fever, and no coughing or coughing up of sputum; she was not nauseous and did not vomit. She also had no history of taking any specific medication or food prior to these spells.

A medical examination of the patient recorded the following data: weight 17 kg, height 102 cm, body temperature 36.5°C, respiratory rate 26 per minute, and heart rate 120 per minute. The child was lucid, with a slightly congested pharynx, and examinations of the heart, lung, abdomen, and nervous system were all normal.

An emergency department blood routine examination yielded the following results: white blood cell count: 27,000 /μL, C-reactive protein: < 5 mg/L, and blood glucose: 1.59 mmol/L (28.6 mg/dL). To hospital: blood glucose: 0.48 mmol/L (8.6mg/dL), blood gas analysis: pH 7.29, lactate (Lac): 8.1 mmol/L, HCO_3^-: 7.4 mmol/L, and anion gap: 30.9 mmol/L. The following results were also recorded: urine routine ketones ranged between (–) and (++), total cholesterol: 3.55 mmol/L, triglyceride: 6.13 mmol/L, uric acid: 861.4 μmol/L, insulin (fasting): 0.99 μU/mL, C-peptide, normal, and growth hormone (random): normal. The following laboratory findings were also normal: glycosylated combination, cortisol, adrenocorticotropic hormone, blood ammonia, thyroid function, electrolyte, liver and kidney function, myocardial marker, and immunoglobulin. Procalcitonin (1.32 μg/L), cerebrospinal fluid biochemical and acid-fast staining, and culture were also all normal, as were cranial magnetic resonance plain scan, electroencephalogram, and abdominal and adrenal ultrasound. An analysis of the serum acylcarnitine profile by tandem mass spectrometry indicated no specific result. Gas chromatography–mass spectrometry analysis of the urinary organic acids indicated that the heptanedioic, octanedioic, and azelaic acid levels were high.

Second-generation sequencing exon detection was conducted and detected 2 mutations of the *FBP1* gene, both located on chromosome 9. One was a guanine missense mutation to adenine at base 778 in exon 6, where the amino acid changed from glycine to arginine (c.778G>A, p.Gly260Arg) (Fig. 1A). This type of mutation was previously reported [3]. The other one was an adenine missense mutation to guanine at base

Jian Xie, Department of Paediatrics, Mianyang Central Hospital, NO.12 of Changjia Rord, Jingzhong Dstrict, Mianyang 621000, China, tel: +86 13778087780; e-mail: xiejianxj92@126.com

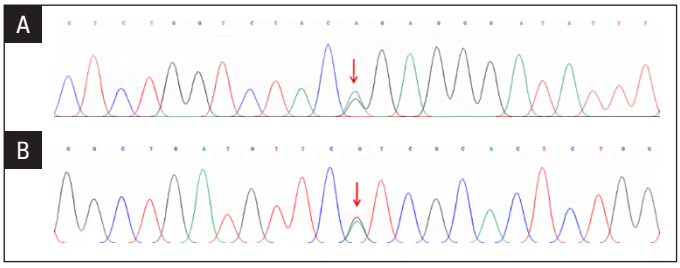

Figure 1. *Genetic mutation from the parents.* **A.** *Genetic mutation from the mother: c.778G>A, p.Gly260Arg;* **B.** *Genetic mutation from the father: c.761A>G, p.His254Arg*

761 in exon 6, the amino acid changing from histidine to arginine (c.761A>G, p.His254Arg) (Fig. 1B); this type had not previously been reported. The detection of the corresponding sites for the parents showed that the c.778G>A mutation was inherited from the patient's mother, and the c.761A>G had been inherited from the father. Accordingly, the child was diagnosed with FBPase deficiency.

Treatments such as fluid replacement, acid correction, and glucose injection (2 g/kg) were administered. The monitoring of blood glucose after admission showed a fluctuation from 4.0 to 8.8 mmol/L (72 to 158.4 mg/dL). All the indexes returned to normal within one week. During the following 14 months, a hypoglycaemia attack occurred only once, in August 2020, due to poor food intake. Her blood glucose was 2.6 mmol/L (46.8 mg/dL), but following glucose supplementation the blood glucose level recovered and no further discomfort was reported.

Fructose-1,6-bisphosphatase deficiency is a rare metabolic disease and a gluconeogenesis disorder. Because its clinical manifestations are atypical, if hypoglycaemia is not persistent and if the child's growth and development are normal, inexperienced clinicians may be prone to misdiagnose it. Nevertheless, the disease has a good prognosis after diagnosis and regular treatment; generally, it does not affect intelligence or motor system development [2, 4]. Therefore, it is necessary to raise clinical awareness of this disease so that it may be considered whenever recurrent hypoglycaemia and lactic acidosis are observed. Early genetic testing and a clear diagnosis could subsequently improve the prognosis and quality of life for children who inherit this condition.

References

1. Krishnamurthy V, Eschrich K, Boney A, et al. Three successful pregnancies through dietary management of fructose-1,6-bisphosphatase deficiency. J Inherit Metab Dis. 2007; 30(5): 819, doi: 10.1007/s10545-007-0606-y, indexed in Pubmed: 17705024.
2. Lebigot E, Brassier A, Zater M, et al. Fructose 1,6-bisphosphatase deficiency: clinical, biochemical and genetic features in French patients. J Inherit Metab Dis. 2015; 38(5): 881–887, doi: 10.1007/s10545-014-9804-6, indexed in Pubmed: 25601412.
3. Li N, Chang G, Xu Y, et al. Clinical and Molecular Characterization of Patients with Fructose 1,6-Bisphosphatase Deficiency. Int J Mol Sci. 2017; 18(4), doi: 10.3390/ijms18040857, indexed in Pubmed: 28420223.
4. Kato S, Nakajima Y, Awaya R, et al. Pitfall in the Diagnosis of Fructose-1,6-Bisphosphatase Deficiency: Difficulty in Detecting Glycerol-3-Phosphate with Solvent Extraction in Urinary GC/MS Analysis. Tohoku J Exp Med. 2015; 237(3): 235–239, doi: 10.1620/tjem.237.235, indexed in Pubmed: 26549536.