The Indian Journal of Pediatrics (May 2021) 88(5):505
https://doi.org/10.1007/s12098-021-03694-9

SCIENTIFIC LETTER

Novel Mutation with Fructose-1,6-Bisphosphatase Deficiency

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Received: 2 December 2020 / Accepted: 4 February 2021 / Published online: 12 February 2021

To the Editor: Genetic studies in fructose-1, 6-bisphosphatase deficiency (FBP1D) are scarce [1, 2]. We report a novel mutation in a developmentally normal, 2-y-old girl, born of a nonconsanguineous marriage, presenting with fever, vomiting, drowsiness, hepatomegaly, hypoglycemia, severe metabolic acidosis, hyperlactatemia (10.2 mmol/L), normal ammonia, and ketonuria. Neonatal period was unremarkable. One year back, she had a similar illness requiring dextrose and bicarbonate infusion. Tandem mass spectrometry (TMS) was normal. Clinical exome sequencing revealed a homozygous 3 base pair deletion in exon 3 of the *FBP1* gene (chr9:g.94620363_94620365del; Depth: 156x) resulting in an in-frame deletion of amino acids (p.Glu99del; ENST00000415431.5). The *FBP1* gene spans approx. 31 kb on chromosome 9q22.2-q22.3 and consists of 8 exons [1]. The observed variation was in the fructose-1-6-bisphosphatase N-terminal domain of the FBP1 protein, in the nonrepeated region. The p.Glu99del variant has not been reported in the 1000 genomes or in the genome aggregation database (gnomAD). Common variants in the Indian population are missense mutations - c.841G>A (p.Glu281Lys) in exon 8 and c.472C>T (p.Arg158Trp) in exon 6 [3]. Intragenic deletions in *FBP1* are rare [2, 4].

FBP1D presents with episodic lactic acidosis and ketotic hypoglycemia, manifesting as hyperventilation, seizures, or coma. Triggers include fever, fasting, vomiting, infections, and excessive fructose ingestion. Half of children have hypoglycemia in the neonatal period, but mostly normal development [1]. Early, prolonged hypoglycemia may cause intellectual disability. Diagnosis is confirmed by identifying biallelic *FBP1* pathogenic variants on molecular genetic testing *or* deficient FBP1 activity in liver or mononuclear white blood cells, the latter not widely available [1].

FBP1D should be suspected in children with episodic hypoglycemia, lactic acidosis, and ketosis. TMS is normal; elevated glycerol-3-phosphate in urine organic acid analysis is suggestive [1]. Molecular diagnosis helps in timely and accurate diagnosis of this rare but treatable disorder. Simple measures (avoiding triggers, timely admission, and dextrose infusion) can ensure a normal life for the child.

Declarations

Conflict of Interest None.

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