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Case Report

A rare case of fructose-1, 6-bisphosphatase deficiency: Clinical features in a pediatric patient

Shami Pokhrel, Subha Sainju, Prasanna Lamsal, Uma Devi Chhetri

Department of Pediatrics, Lumbini Medical College, Palpa, Nepal

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ABSTRACT

Fructose-1, 6- bisphosphatase deficiency is a rare autosomal recessive inborn error of fructose metabolism which mainly affects gluconeogenesis. It often presents with ketotic hypoglycemia and lactic acidosis, with hyperventilation. The disease has a high mortality rate when undiagnosed.

Here we report a case of this rare disorder, referred to our hospital in Western Nepal, diagnosed originally as pneumonia. The patient presented in respiratory distress with severe metabolic acidosis and dehydration. She also demonstrated hypoglycemia, hypernatremia, coagulation dysfunction and albuminuria, all of which gradually improved, though her lactate remained consistently elevated. This led to investigation of urinary ketones which were positive suggesting a defect in the metabolism of carbohydrates. Urine organic acid profile and whole exome sequencing finally confirmed the diagnosis of Fructose-1, 6- bisphosphatase deficiency. To our knowledge this is the first case report of this disease diagnosed in Nepal.

1. Introduction

Fructose-1, 6-bisphosphatase deficiency is a heritable autosomal recessive disease which is caused by the pathogenic variants in the FBP1 gene, [1] with an incidence between 1/350,000 and 1/900,000 making it one of the rarest diseases. [2] It has a very high mortality, as failure of timely management causes worsening symptoms, leading to multiorgan failure and sepsis-like presentation. [3] As symptoms of the disease lack specificity, one must have a high index of suspicion for an inborn error of metabolism. Furthermore, it must be distinguished from glycogen storage and mitochondrial diseases, which are also characterized by hypoglycemia and lactic acidemia. Since it is not possible to diagnose the disease solely on clinical grounds, genetic testing is required to provide a definitive diagnosis. [4]

2. Case report

A 28 months old female child presented to our emergency department with symptoms of acute respiratory distress and lethargy. She had fever the day before, followed by multiple episodes of non-bilious vomiting the next morning. She then developed sudden onset of fast and difficult breathing. There was no history of cyanosis, skin rashes, loss of consciousness, abnormal body movements, abdominal pain, jaundice, diarrhea, ear and eye redness and discharge, possible toxin ingestions or rhinorrhea. There was no significant past medical history. She was born term via emergency cesarean section for meconium stained fluids, weight appropriate for gestational age with an unremarkable post natal period. There was no family history of chronic disease or consanguineous marriage. Her 8 year old sibling was in good health born via normal delivery. Mother denied any prior hospitalization, trauma or allergic reaction to drugs. Her growth and developmental milestones were normal and she received immunizations as per the National schedule. There was no history of particular food aversion or preferences.

At the time of presentation, she had temperature of 97.6 °F, heart rate of 160/min, respiratory rate of 52/min with increased work of breathing. Her oxygen saturation in room air was 85 % and blood pressure was 80/56 mmHg. She was pale and lethargic with a modified Glasgow Coma Scale score 14/15 with bilateral pupils reactive to light. On neurologic examination, Kernig and Brudzinski signs were absent. She was moving all her limbs equally. There was no deviation of eyes or face. She had pallor, dry oral mucosa and was lethargic. No particular odor was noted. Her lungs fields were clear. Her cardiovascular examination was normal. Her abdominal examination revealed hepatomegaly of firm consistency with regular border with span of 12 cm. Her spine showed no abnormality. She had no rashes on her body.

E-mail address: shamipokhrel@hotmail.com (S. Pokhrel).

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3. Initial laboratory test showed the following

The total leukocyte count was 42,800 × 10^9/L (4–10.5), the percentage of neutrophils and lymphocytes was 80 % and 17 %, respectively. The red blood cell count was 4.01 × 10^{12}/L (3.5–5.5), hemoglobin was 110 g/L (120–150), total platelet count was 725 × 10^9/L (150–450), C-reactive protein was 96 mg/L (0–5). Blood biochemical tests showed that alanine aminotransferase was 23.0 U/L (8–40), aspartate aminotransferase was 37 U/L (5–40), urea was 68 mg/dl (15–45), creatinine was 0.5 mg/dl (0.5–1.4), and glucose was 50 mg/dl (60–140). The coagulation function showed that the prothrombin time was >2 min (11–13 s), activated partial thromboplastin time was 209 s (20–25), D-dimer was 0.573. Arterial Blood Gas showed pH 6.84 (reference range 7.35–7.45), partial pressure of carbon dioxide (PCO_2) <10 mmHg, partial pressure of oxygen (PO_2) 113 mmHg, bicarbonate (HCO_3) 1.3 mmol/L (22–26) and lactate was 9.80 mmol/L. Electrolytes tests were sodium 152 mmol/L (130–150), potassium 5.5 mmol/L (3.5–5.5), chloride 131 mmol/L (98–106), ionized calcium 1.54 mmol/L (1.20–1.38) and magnesium 3.4 mg/dl.

The child was immediately intubated and managed as septic shock with intravenous (IV) antibiotics, IV inotropes after fluid challenges, IV sodium bicarbonate infusions, IV dextrose to maintain blood glucose and multiple transfusions of Fresh Frozen Plasma and Packed Red Blood Cells, after which the child improved slowly on the following days. She was planned for extubation on seventh day of her admission and started on dexamethasone a day earlier. However, while weaning her off ventilator, she developed seizures and high blood pressure, for which antiepileptic medication and mannitol were started, after which seizures and her condition improved. She was extubated the next day, on the eighth day of her admission. After extubation, she was taken for Computed Tomography (CT) scan of the head, which showed, a likely intracranial bleed (Fig. 1) along with features of cerebral edema and mild atrophy (Fig. 1B). Her abdominal ultrasonography reported no other significant abnormality except hepatomegaly. Her echocardiography was normal. Her endotracheal tube culture grew *Pseudomonas Aeruginosa* and antibiotics were adjusted accordingly. She was gradually fed by orogastric tube. Her overall health improved, though, she had persistently high lactate level with positive urine ketones. Samples were collected for urine for organic acids and whole exome sequencing in view of inborn errors of metabolism. She was advised to avoid prolonged fasting, and eat frequent small meals. On the twentieth day, she was discharged home on levetiracetam.

4. Diagnostic work up

We suspected an inborn error of metabolism, as gluconeogenesis disorders cause hypoglycemic attacks with lactic acidosis, and further examinations were performed to establish a definitive diagnosis. The urinary organic acid profile showed significantly elevated glycerol and lactate, indicating a possible Fructose-1, 6- bisphosphatase deficiency. Test results were as following: Lactic acid 44.17 (6.70 %), glycerol 21.27 (2.72 %), urine acetoacetic acid 1.59 (0.10 %). Whole exome sequencing revealed a homozygous variant in FBP1 gene, c.778G > A (p.Gly260Arg) fulfilling the pathogenicity criteria, PS4, PM2, PP3 and classified as likely pathogenic according to American College of Medical Genetics and Genomics (ACMG) guidelines set in 2015. On follow up, the patient is doing well with no neurological deficits and normal behavior as per her peer group. Her parents have been advised to seek genetic counselling.

5. Discussion

Fructose-1, 6-Biphosphatase deficiency (FBP1) was first described by Baker and Winegrad in 1970. The worldwide incidence is estimated to be between 1/350,000 and 1/900,000 [2] Exact incidence in Nepal is unclear. However, a publication in 2018 described 18 patients from the Indian subcontinent, two of whom were from Nepal. [5] It has been described more commonly in females and our case is consistent with that as our proband is female. [6] The disease usually presents as sepsis, which could also be because sepsis triggers the disease manifestations. [3] Our case was managed initially as sepsis, though persistence of an elevated blood lactate level and urine ketones prompted us to investigate further. The diagnosis of FBP1 is usually provided by genetic analysis of the *FBP1* gene, which is located on chromosome 9q22.32. There are 59 described pathogenic variants. [1] In our case, the mutation 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), similar to previously described mutations. [7] We advised the mother that the child should not fast for more than 8 h, [8] and should avoid excessive intake of fructose and sucrose as per Dietary Guidelines for Hereditary Fructose Intolerance (HFI). [9]

Fructose-1, 6-bisphosphatase deficiency is a rare disease. To our belief, this is a first case detected and diagnosed in Nepal. Ketotic hypoglycemia with lactic acidosis should raise the suspicion of this disease. Therefore, it is necessary to raise clinical awareness of this disease which will help in prompt investigation and prevention of next episodes.

CRediT authorship contribution statement

Shami Pokhrel: Writing – original draft, Visualization, Supervision, Data curation, Conceptualization.

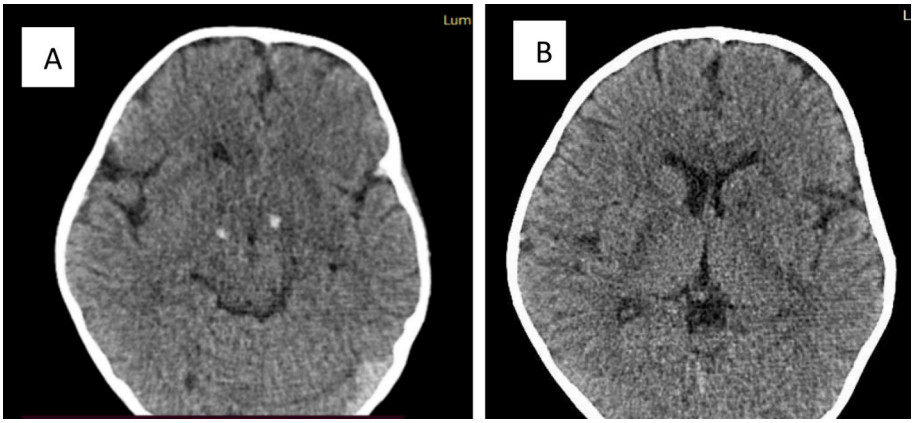

Fig. 1. A. Multiple hyperdense foci of similar size at bilateral hypothalamic region with surrounding mild hypodensity, a likely intracranial bleed. B. Ill-defined hypodensities involving bilateral corona radiata, internal capsule and head of left caudate nucleus with partial effacement of bilateral basal ganglia and compression of frontal horn of left ventricle, demonstrating likely edema with mild cerebral atrophy.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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