Fructose 1,6-bisphosphatase Deficiency Causing Cerebral Hypoxic Ischemic Injury in a Pediatric Patient

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Abstract
Fructose 1,6-bisphosphatase (FBPase) deficiency is a rare inborn error of metabolism (FBPase) deficiency is a rare inborn error of metabolism. FBPase is a key enzyme in the gluconeogenic pathway and its deficiency can result in severe hypoglycemia, ketonuria and metabolic acidosis [1]. It may manifest as early as the neonatal period or take a few years for the symptoms to appear. The attacks are precipitated by prolonged fasting, infections or ingestion of fructose containing formulas. The following is a case report of a 7-year old boy with FBPase deficiency who presented with stroke-like symptoms in the setting of severe hypoglycemia. To our knowledge this is the first case published describing FBPase deficiency causing cerebral hypoxic-ischemic injury.

Keywords: Fructose 1,6-bisphosphatase; Cerebral Hypoxic Ischemic Injury

Introduction
Fructose 1,6-bisphosphatase (FBPase) deficiency is a rare inborn error of metabolism. FBPase is a key enzyme in the gluconeogenic pathway and its deficiency can result in severe hypoglycemia, ketonuria and metabolic acidosis [1]. It may manifest as early as the neonatal period or take a few years for the symptoms to appear. The attacks are precipitated by prolonged fasting, infections or ingestion of fructose containing formulas. The following is a case report of a 7-year old boy with a history of FBPase deficiency who presented with altered mental status, right-sided hemiparesis, focal weakness, dysarthria, ataxia and hypoglycemia. MRI brain showed restricted diffusion indicating acute and subacute changes bilaterally consistent with hypoxic injury.

Our literature search on PubMed, Cochrane and Google with terms including “fructose 1,6-bisphosphate deficiency,” “stroke,” “hemiparesis” and “neurological,” indicates no cases reported for FBPase deficiency having a stroke-like presentation.

Case Presentation
A 7-year old boy of Arabic descent, was diagnosed with FBPase deficiency at 11 months of age after an episode of hypoglycemia. He had presented with seizures multiple times since then mainly due to repeated hypoglycemia. He now presented to the Emergency Department with altered mental status. Four days prior, he had complained that his tongue felt “heavy” and later developed unbalanced gait and dysarthria. The mother called his genetics counselor who instructed her to give him glucose gel, which she administered twice but showed no improvement. She had been maintaining his blood sugar records which ranged from 67 to 118 mg/dl. She denied seizures, fever, vomiting, diarrhea, cough, sick contacts or decreased oral intake. The patient had been discharged from the hospital 6 days prior, after a recovery to baseline post-seizure secondary to severe hypoglycemia.

On evaluation upon admission, he was noted to be afebrile, and with normal vital signs. Neurological examination was significant for altered mental status, right-sided hemiparesis, marked dysarthria and a hemi-paretic gait with poor balance. Blood work was within normal limits, and the blood glucose level was 110 mg/dl. MRI of the brain (Figures 1a and 1b) revealed bilateral and symmetrical restricted diffusion affecting the caudate nuclei, putamen and to a lesser extent, the globus pallidus. In addition, small patchy areas of restricted diffusion were seen in the frontal and temporal regions bilaterally. These findings were consistent with severe hypoxic injury.

He received intravenous (IV) glucose replacement and glucose levels were maintained between 100 and 200 mg/dl. Almost immediately after the glucose replacement was initiated, he began to show signs of improvement in his mental status. This was followed by a slowly progressive improvement in his speech and hemiparesis. His oral glucose replacement therapy consisted of two tablespoons of cornstarch in milk three times a day. As the patient improved clinically, his IV glucose replacement was weaned. The patient made a remarkable clinical improvement throughout his admission and at the time of discharge his imbalance had improved and he was able to walk without support. His right-sided weakness as well as impaired fine motor control remained but had improved significantly. He continued to have difficulty with fine motor control, including difficulty buttoning shirt buttons and difficulty grasping a pen. His handwriting still showed noticeable impairment, both

Figure 1a: Diffusion weighted image (DWI), Figure 1b: Apparent diffusion coefficient (ADC).

There is bilateral and symmetrical restricted diffusion (figure 1a) with corresponding ADC changes (figure 1b) affecting the caudate nuclei, putamen and to lesser extent the globus pallidus.

1a 1b
with observational decreased fluidity of movement as well as with legibility. At worst, his speech was 40-50% intelligible but now had improved to 60-70% intelligible. He remained seizure-free throughout admission.

Discussion

FBPase is a key enzyme in gluconeogenesis that converts Fructose 1,6-bisphosphate to Fructose 6-phosphate and inorganic phosphate. FBPase deficient persons may present with profound hypoglycemia, ketonuria, elevated blood lactate and alanine levels, and metabolic acidosis. FBPase deficiency is an autosomal recessive inherited disorder. The enzyme is encoded from the FBP1 gene on chromosome 9q22.2-q22.3. [1,2], another gene, FBP2, encodes the enzyme in muscles. Up to 17 different mutations in individuals with FBPase deficiency have been described including missense, deletion, insertion and nonsense mutation types [1–3].

FBPase deficiency usually manifests in the neonatal period but may take up to a few years to appear. Typically an FBPase deficient individual may suffer hypoglycemic attack due to prolonged fasting, febrile illness or consumption of fructose containing formulas. This will manifest as irritability, vomiting, hyperventilation and may be followed by muscular hypotonia, dyspnea, tachycardia, seizures, somnolence or coma. These hypoglycemic episodes are treated with IV or oral glucose. Maintenance therapy includes frequent feeds, usage of slowly absorbed carbohydrates such as cornstarch and avoiding fasting as well as ingestion of sucrose, sorbitol and fructose [4].

Our patient’s stroke-like presentation and altered mental status along with his past medical history of FBPase deficiency is quite concerning. His MRI brain images indicating restricted diffusion adds to the probability of FBPase deficiency resulting in stroke-like symptoms. FBPase has been shown to exert substantial therapeutic effect in a variety of shock states and in tissue ischemia. It enhances anaerobic carbohydrate utilization and ATP production and inhibits the generation of oxygen free radicals during ischemia or hypoperfusion and during post-ischemic reperfusion. Oxygen free radicals are considered an important contributor of brain edema and irreversible ischemic brain injury [5]. Therefore, FBPase deficient individuals would be more prone to hypoxic ischemic injury in the brain. Farias et al. [5] described how rabbits subjected to ischemic-hypoxic brain injury showed a fast EEG recovery to baseline after FBPase administration. This is explained by the ability of FBPase to sustain glycolysis and increase ATP production in an oxygen-deficient environment. Although this warrants more studies and investigation, the brain of FBPase sufficient persons could be expected to tolerate an ischemic-hypoxic insult better.

Previous studies have shown that hypoglycemic insults predominantly affect cerebral gray matter [6,7]. A study conducted to investigate sequential neuro-radiological changes in brains of patients after hypoglycemic coma revealed that MRI showed bilateral lesions in the basal ganglia, hippocampus and cerebral cortex [7]. Thirty minutes post-hypoglycemia in rats, the ATP level is low particularly in the cerebral cortex, the striatum and hippocampus as compared to other areas of the brain [7,8]. This suggests the particular vulnerability of individual areas of the brain to hypoglycemia. It has been proven that severe glucose deprivation may lead to brain energy failure and membrane ionic pump failure [9,10]. The basal ganglia require high energy input for motor control and may be selectively damaged by systemic processes that decrease cerebral metabolism [11].

Patient Course

Upon follow up in the neurology clinic at 1, 2 and 3 months after discharge, he continued to show a progressive improvement, however he had not fully returned to his baseline. The right sided weakness is markedly improved with only a mild weakness in his lower extremity. This is noted mainly when running. His speech is now 80-90% back to his baseline, with persisting mild difficulty with speech articulation. His fine motor impairment persists, but is noticeably improved since discharge. He continues to receive physical, occupational and speech therapies, which have aided with his neurological improvement. Moreover, staying compliant with the advised diet will help prevent further hypoglycemic episodes.

Conclusion

FBPase deficiency is known to cause hypoglycemia, ketonuria and metabolic acidosis, precipitated by prolonged fasting, infections and intercurrent illness. Prolonged glucose deprivation may lead to brain energy failure; hence hypoglycemia-induced hypoxic-ischemic injury can lead to a stroke-like presentation. This presents as focal weakness, gait disturbance and dysarthria and requires emergent glucose replacement therapy. In order to avoid such severe consequences of hypoglycemia, it is best to avoid any periods of prolonged fasting especially during febrile illnesses. To our knowledge this is the first case published describing FBPase deficiency causing cerebral hypoxic-ischemic injury.

References


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