Case report

Annals of Clinical and Medical Case Reports

Late Diagnosis OfFructose 1,6 Bis-Phosphatase Deficiency In A Child With Altered Sensorium And Metabolic Acidosis: A Case Report

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Received Date: 26 Aug 2024
Accepted Date: 11 Sep 2024
Published Date: 16 Sep 2024

Citation:
Poonam Agrawal. Late Diagnosis OfFructose 1,6 Bis-Phosphatase Deficiency In A Child With Altered Sensorium And Metabolic Acidosis: A Case Report. Annals of Clinical and Medical Case Reports 2024.

1. Abstract

Fructose 1,6 bis-phosphatase is one of the key enzyme in the process of gluconeogenesis which converts fructose 1,6 bisphosphate to fructose 6 phosphate. We are reporting one such case of Fructose 1,6 bis-phosphatase, which remained undiagnosed for many years before it came to our notice. Three and half-year-old girl presented to the paediatric emergency department with seizures and altered sensorium after prolonged fasting. Suspicion of gluconeogenic enzyme deficiency was suspected based on Rothera's test (for urinary ketone body), seliwanoff's test (for reducing keto sugar), benedict's test (for reducing carbohydrates), blood glucose assessment, arterial blood gas analysis etc and genetic analysis was done to confirm the diagnosis. Genetic test report showed FBP(-) (ENST00000415431.5) at Exon 5 c.494A>G(p.Tyr165Cys) homozygous "Fructose 1,6-bisphosphonate deficiency" of autosomal recessive inheritance , pathogenic variant.

We conclude that inborn error of metabolism should always be suspected in patients presenting with nonspecific sign and symptoms related to carbohydrate, lipid metabolism. Easy bed side test like Rothera's test, seliwanoff's test, benedict's test, blood glucose assessment, arterial blood gas analysis give crucial information regarding possibility of such enzyme deficiency facilitating early initiation of therapeutic measures till more definitive diagnostic results like enzyme assay, gene mutation analysis reports are made available.

2. Keyword:
Fructose 1,6 bis-phosphatase, Gluconeogenesis, Rothera's test, Seliwanoff's test, Inborn error of metabolism

3. Introduction

Fructose 1,6 bis-phosphatase (F1,6 BP) is one of the key enzyme in the process of gluconeogenesis which converts fructose 1,6 bisphosphate to fructose 6 phosphate by removing inorganic phosphate from substrate. This enzyme is competitively inhibited by fructose 2,6 bisphosphate and allosterically inhibited by AMP. Fructose 1,6 bis-phosphatase (F1,6 BP) is tetrameric protein in most of the species except in yeast. This enzyme is also known as fructose diphosphate and is represented as EC 3.3.1.11[1, 2]. Deficiency of this enzyme is inherited as autosomal recessive disorder which means if both the parents are carrier/heterozygous the 25 % siblings will be symptomatic, 25% will be asymptomatic and remaining 50% will be carrier. More than 35 mutations have been described in various literatures including mutations like frameshift mutation, deletion mutation, splice donor variance and missense mutation have been found associated with this disease [3]. Deficiency of Fructose 1,6 bis-phosphatase (F1,6 BP) (OMIM#229700) is rare with the incidence ranging from 1/350000 to 1/900000 [4]. We are reporting one such case of Fructose 1,6 bis-phosphatase, which remained undiagnosed for many years before it came to our notice.

4. Case Report

Three and half-year-old girl presented to the paediatric emergency department with seizures and altered sensorium. Her mother gave the history of two episodes of vomiting previous night followed by almost nine hours of fasting. Baby had three more similar episodes of seizures and altered sensorium since the time of birth. Every time it was precipitated during sickness and prolonged fasting for which she was admitted in local hospitals and was managed conservatively. As per history given by parents, the child was treated symptomatically and was discharged in healthy condition but no definitive diagnosis was made in this regard. This baby was the only child to parents from nonconsanguineous marriage. Antenatal period was uneventful and she was born as full term normal vaginal delivery. On examination baby was lethargic, pale and irritable. Liver and spleen were not palpable. Fundus examination was normal.
Baby was thoroughly investigated and various investigations revealed many significant findings which are given in table below:

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Table:

Day since admission	parameter	values	Normal range
D-1	pH	7.15	7.35-7.45
D-1	PaO2	91 mmHg	75-100 mmHg
D-1	PaCO2	32 mmHg	35-45 mmHg
D-1	bicarbonate	18 mEq/L	22-26 mEq/L
D-1	lactate	1.4 mmol/L	2.0-4.0 mmol/L
D-1	cholesterol	220mg/dl	desired <200 mg/dl
D-1	Triglyceride	160mg/dl	desired <150 mg/dl
D-1	Total bilirubin	1.3mg/dl	
D-1	Direct bilirubin	0.4mg/dl	
D-1	Indirect bilirubin	0.9 mg/dl	
D-1	SGOT(AST)	15U/L	
D-1	SGPT(ALT)	22U/L	
D-1	Total protein	6.8 g/dl	
D-1	Albumin	4g/dl	
D-1	Globulin	2.8 g/dl	
D-1	Random blood sugar	55 mg/dl	
D-1	Hb	11.3g/dl	
D-1	TLC	6200/mm3 with 60% neutrophils,	
D-1	platelets	2.2 lakhs	
D-1	Fasting insulin	4pIU/ml	(Insulin sufficiency in prepubertal children >10 pIU/ml)
D-2	. Random cortisol	10micro gram/dl	10 to 20 micrograms per dl (mcg/dL)
D-2	. Growth hormone	25ng/ml.	5-23 ng/ml
D-2	. Urine was positive for keto sugar	Seliwanoff's test was found positive).	

Liver biopsy, MRI brain, CSF analysis, EEG were normal.

In view the finding of profound hypoglycemia, hyper-triacylglyceredemia, metabolic acidosis and positive seliwanoff's test for keto sugar in the urine, the inborn error of carbohydrate metabolism was suspected. Keeping in mind the rare finding of positive seliwanoffs, the differential diagnosis made was either error in fructose metabolism causing fructosuria, or the defect in gluconeogenic pathway resulting in excretion of keto sugar in the urine. Genetic evaluation of the child was done after counselling the parents. Her genetic test report showed FBP(-)(ENST00000415431.5) at Exon 5 c.494A>G(p.Tyr165Cys) homozygous "Fructose 1,6-bisphosphonate deficiency" of autosomal recessive inheritance , pathogenic variant.

With the above findings diagnosis of deficiency of "fructose 1,6 bis-phosphatase" enzyme was made and she was managed with IV fluids. She was discharged after 5 days in stable condition and parents were advised to feed her complex carbohydrate rich diet at frequent interval and avoid long duration of fasting. She is currently 6 years old, clinically stable with developmentally normal for her age. There is no neurological deficit and is being managed on with frequent meals avoiding the fructose and sucrose intake. Her recent MRI done showed gliotic changes in the bilateral occipital lobes and adjacent periventricular white matter which are likely sequelae of old hypoglycaemic events.

5. Discussion

Fructose 1,6 bis-phosphatase (F1,6 BP) is the gluconeogenic enzyme responsible for conversion of fructose 1,6 bisphosphate to fructose 6 phosphate, a key step during gluconeogenesis from various gluconeogenic precursors. Deficiency of this enzyme results inneuro metabolic disorder, where clinical hallmark of the disease is lethargy, hyperventilation, vomiting, irritability, somnolence up to stage of coma and muscular hypotonia [5]. These symptoms get precipitated due to illness, vomiting, prolonged fasting, excess consumption of fructose etc. Biochemically hypoglycaemia, hyper lactic-acidaemia, ketoacidosis, hyperuricemia, metabolic acidosis are frequently associated [6]. Children are asymptomatic between the episodes and most of these children have normal intellectual and physical development. Very few children are afflicted with intellectual disability possibly due to early and prolonged hypoglycemic episodes. Most of the cases the clinical signs and symptoms in this deficiency are nonspecific and overlaps with various other metabolic disorder like hereditary fructose intolerance (Aldolase B deficiency), Glucose 6 phosphatase deficiency, Phospho-enol-pyruvate carboxy kinase deficiency, Pyruvate carboxylase deficiency, HMG Co A lyase deficiency etc [7].

High degree of suspicion of Fructose 1,6 bis-phosphatase (F1,6 BP) is essential in babies presenting with such manifestation as the delay in treatment may result in irreparable loss. There are few published reports on this enzyme deficiency in children at global platform but in India this enzyme deficiency is rarely reported. It is mostly reported in younger children though deficiency of fructose 1, 6 bis-phosphatase in adult patient is rarely reported [8]. Some of the studies have reported positive Seliwanoff's test in urine of such children suffering with F1,6 BP deficiency stating this condition as "fructosuria'7 We wish to emphasize on the fact that Seliwanoff's test is the qualitative test to assess the presence of keto sugar in the urine and in our opinion positive seliwanoff test in such babies may be due to excretion of dihydroxyacetone phosphate (DHAP) and fructose 1,6 bisphosphate which are reducing keto sugar. DHAP and fructose 1,6 bisphosphate remain unutilized during Fructose 1,6 bis-phosphatase deficiency and they get excreted in urine giving Seliwanoff test positive.

It is important to understand that fructose metabolism as such is not defective in Fructose 1,6 bis-phosphatase (F1,6 BP) deficiency as this enzyme belongs to gluconeogenic pathway and not the fructose

metabolism, hence chances of excretion of frank fructose in the urine is negligible. Our suggestion supports the finding of lack of fructose in a case reported by Kamate M. et al [7]. In some cases, glycerol is found in the urine of such babies suffering with deficiency of fructose 1,6 bis-phosphatase [9]. Finding of glycerol in the urine during hypoglycemic attack with associated manifestation is an important clue to the diagnosis of fructose 1, 6 bis phosphatase enzyme deficiency. This may be due to non utilization of glycerol in the process of gluconeogenesis as the whole process of gluconeogenesis is defective in such case. There are reports which have found the association of fructose 1,6 bisphosphatase deficiency with hepatic dysfunction [10] Treatment modality involves avoidance of fasting by advising frequent meal with diet rich in glucose. Restriction of sucrose and fructose is advised along with administration of uncooked corn starch 2 gram per kilogram mixed with water at midnight. This helps in sustaining blood glucose for longer duration and avoid hypoglycemicspells[11] Restriction of sucrose and fructose is done for simple reason that fructose metabolism in liver produces dihydroxy acetone phosphate (DHAP) and glyceraldehyde. DHAP is either used in aerobic/anaerobic glycolysis to generate pyruvate or lactate as the case may be, of it may get converted to glucose by various gluconeogenic enzymes, F16BPase being one of them.

On the other hand, glyceraldehyde produced has three different fates
a. Oxidized by aldehyde dehydrogenase
b. Reduced by alcohol dehydrogenase
c. Phosphorylated by kinase to produce glyceraldehyde 3 phosphate which either enter in glycolytic route or is utilized in gluconeogenesis

Many reports on this disease have mentioned the hyper triacyl-glyceredemia in such babies [12,13]. Even this baby had marginally higher level of triacyl glyceride in the blood which may be a case of pseudo hypertriglyceridemia. In pseudo hypertriglyceridemia, the raise to tricycle glycerol level is due to increased glycerol level (due to its non utilization during gluconeogenesis)and not actual increase of triacylglycerol [14]. Glycerol blanking method can be used to measure true level of triacyl glyceride in such babies. This highlight the importance of careful interpretation of hypertriacyl glyceredemia in babies suffering with this rare metabolic error.

Long term follow up of the patient is required to monitor the development milestone and assess the quality of life Parents should be counselled and must be explained regarding the prognosis of the disease. They must be educated regarding importance of avoiding hypoglycaemic spells. It's important to prevent though repeated infections so patient must be vaccinated influenza annual basis to reduce the risk of infection. Dietary management includes restriction of food items containing fructose,sucrose, glycerol and sorbitol. Treatment mainly consists of parental education, which needsstrong emphasis on the importance of avoidance of fasting especiallyduring infections along with avoiding fructose containingfoods and glycerol.Our report emphasizes the fact that urinary organic acid analysisshould be performed in patients with hypoglycaemia andlactic acidosis not only to exclude amino acid defects, but alsoto identify disorders of gluconeogenesis, because glycerol excretionon fasting or during acidosis is of diagnostic importance infructose 1,6 bis phosphatase deficiency. Urinary organic acid analysis should be performed in patients with hypoglycaemia and lactic acidosis, not only to exclude amino acid defects but also to identify disorders of gluconeogenesis.

6. Conclusion

Inborn error of metabolism (IEM) though rare are often encountered in hospital settings. Most of the time the diagnosis is missed and patients are send home after giving symptomatic treatments which adversely affect the quality of life in long run. Most specific diagnostic test in fructose 1,6 bis phosphatase enzyme deficiency is assessment of this enzyme in hepatic cell which can be done only in few selected reference diagnostic labs and most of the time it is not within the reach.

Easily available biochemical test like Seliwanoff's test (for reducing keto sugar), benedict's test (for reducing carbohydrates), blood glucose assessment, arterial blood gas analysis gave crucial information regarding possibility of this enzyme deficiency facilitating early initiation of therapeutic measures till more definitive diagnostic results like enzyme assay, gene mutation analysis reports are made available. We wish to conclude that inborn error of metabolism should always be suspected in patients presenting with nonspecific sign and symptoms related to carbohydrate, lipid metabolism. High degree of suspicion is important for timely diagnosis and initiating therapeutic measures at very early stage of life in such conditions to minimize the damage and improve the quality of life of such children.

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