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RESEARCH ARTICLE

GLUOSE 6-PHOSPHATE ISOMERASE DEFICIENCY: A RARE ENTITY

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Abstract

A young male presented to us with the chief complaints of jaundice, non-bilious vomiting and intermittent high-grade fever in the background of past history of recurrent blood transfusions.On examination, he had pallor, icterus with a massive non tender splenomegaly and his laboratory parameters were suggestive of indirect hyperbilirubinemia with low haptoglobin and elevated lactate dehydrogenase levels with reticulocytosis and erythroid hyperplasia on bone marrow aspiration. His Direct and indirect coombs test were negative.To rule out hemoglobinopathies, his hemoglobin electrophoresis was sent, which turned out to be normal. Hence, red blood cell membrane and enzyme studies were carried out which revealed Glucose-6-phosphate isomerase deficiency.

Introduction:-

Erythrocyte metabolism is mainly dependent on the glycolytic pathway and enzyme deficiencies of these pathways manifest as hemolytic anemia. One such enzymopathy is Glucose 6-phosphate isomerase deficiency which leads to non-spherocytic hemolytic anemia, a rare autosomal recessive disorder.

A young male presented with the chief complaints of jaundice, non-bilious vomiting and intermittent high-grade fever. He had no associated complaints of abdominal pain, obstipation, constipation, bone pain, chest pain or any evidence of respiratory distress.

He had a significant past history of recurrent blood transfusions with a frequency of 3-4 times/year since the age of 6 years. There was no significant family history of recurrent jaundice or any blood transfusion. No history of consanguineous marriage in the family.

On general and systemic examination, he had a normal built with a Body mass index of 21 kg/m^2, tachycardia with a resting pulse rate of 118/minute and no evidence of hypotension or signs of respiratory distress.

He had severe pallor, icterus and per abdominal examination revealed a massive non-tender splenomegaly extending beyond the umbilicus (18 centimeter from the left costal margin towards the right iliac fossa).

Investigations
His basic laboratory parameters were as following as noted in **Table 1**:

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Table 1:- Laboratory Investigations of patient during his ward stay.

Hemoglobin: (12-16g/dl)	3.3 g/dl
Total leucocyte count(4000-11000/microlitre)	18000/microlitre
Platelet count (150k-450k)	345k/microlitre
Mean corpuscular volume (80-100 fL)	132 fL
Mean corpuscular hemoglobin (27.5-33.2 pg)	36.4 pg
Mean corpuscular hemoglobin concentration (33.4-35.5g/dL)	27.5 g/dL
Reticulocyte count (0.5-2,5%)	44.75%
ReticulocyteProduction index (0.5-2.5%)	10%
Immature reticulocyte fraction (1.5-12.1%)	42.8 %
Total bilirubin levels (0.3-1.3 mg/dl)	12.6 mg/dl
Direct bilirubin levels (0.1-0.3 mg/dl)	1.6 mg/dL
Serum vitamin B12 levels (190-950 pg/ml)	218 pg/ml
Lactate dehydrogenase	2000 U/L
Serum haptoglobin	10 mg/dl

Peripheral smear examination showed macrocytosis, mild anisocytosis, target cells, and a few spherocytes with basophilic stippling.

Differential Diagnosis

In the background of fever, all preliminary investigations were carried out to rule out infectious diseases like malaria, dengue, leptospirosis and typhoid which could have precipitated hemolysis. A routine screen for hepatitis B, C and human immunodeficiency virus was found to be negative. Aerobic and anaerobic blood and urine culture showed no growth. A low serum haptoglobin and an elevated lactate dehydrogenase was recorded which pointed towards intravascular hemolysis. His glucose 6-phosphate dehydrogenase levels were normal. Other causes of congenital indirect hyperbilirubinemia like Crigler-najjar syndrome or Gilberts syndrome in presence of severe hemolysis could not be accounted for raised indirect bilirubin levels.

Thereby to rule out autoimmune hemolytic anemia, Direct and indirect coombs test were performed which were negative. Bone marrow aspirate and examination showed an erythroid hyperplasia supporting the diagnosis of hemolytic anemia. In view of anemia with elevated lactate dehydrogenase levels and low serum haptoglobin levels with reticulocytosis, erythroid hyperplasia on bone marrow and indirect hyperbilirubinemia, in the background of recurrent blood transfusions, a hemoglobin electrophoresis by high performance liquid chromatography was carried out. However, the screen for hemoglobinopathies turned out to be negative.

Red blood cell enzyme assay and red blood cell membrane defect study was performed on a pre-transfusion sample, which revealed a rare enzymopathy: Glucose 6-phosphate isomerase enzyme deficiency. The levels were found to be 21.7 IU/gram of hemoglobin (normal range: 45-75 IU/g Hb)

Treatment

Our patient was admitted and underwent laparoscopic splenectomy with cholecystectomy after adequate vaccination prior to surgery and after optimization of hemoglobin levels and giving broad spectrum antibiotics.

He was started on penicillin prophylaxis and aspirin (75 mg/day) post-procedure.

Outcome And Follow-Up

He responded well to therapy as the patient is on a regular follow up currently since past 2 years on an outpatient basis and has not required any blood transfusion. His LDH levels decreased. However, indirect hyperbilirubinemia is still persistent without drop in hemoglobin.

Discussion:-

Glucose-6-phosphate isomerase is an enzyme that catalyzes the second step of Embden Meyerhof pathway (Glycolytic pathway) i.e., isomerization of glucose 6 phosphate to fructose 6 phosphate which is a rate limiting step of glycolysis.[(1)]Mutation in glucose phosphate isomerase gene, located on chromosome 19q.13.1, leads to impairment of glycolytic pathway.

There is an accumulation of glucose-6-phosphate which leads to activation of negative feedback and there is lysis of red blood cells. It is a rare disorder with only few cases been reported so far worldwide. The spectrum of clinical manifestations includes a non-spherocytic hemolytic anemia,however, can include muscle weakness, cerebellar ataxia and mental retardation rarely.[1][2] Diagnosis can be established with the help of red cell enzyme assay afterruling out other common causes of hemolytic anemias such as autoimmune hemolytic anemia, hemoglobinopathies, red blood cell membrane defects like hereditary spherocytosis, red cell enzyme defectslike glucose-6-phosphate deficiencies and pyruvate kinase deficiency. It is difficult to obtainlevels of glucose-6-phosphate isomerase levels, however a high index of suspicion should be kept after other causes of intravascular hemolysis are ruled out. No treatment guidelines have so far been studied in this field, splenectomy proves to be a helpful measure in decreasing the bloodtransfusion frequency and thereby improving the quality of life.[3,4]

Learning Points

1. Glucose 6-phosphate isomerase deficiency is a rare enzymopathy leading to non-spherocytic hemolytic anemia
2. A possibility of underlying enzymopathy must be kept in mind during evaluation of patients with intravascular hemolysis.
3. Splenectomy proves to be useful measure in treatment of G6PI deficiency hemolytic anemia.

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