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Research Article

Case Of Congenital Hemolytic Anemia - Hexokinase Deficiency In An Infant

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ABSTRACT

Hexokinase deficiency is a rare autosomal recessive disorder that causes congenital haemolytic anaemia. It affects the initial glycolytic enzymes, causing premature haemolysis of blood cells, leading to severe and chronic nonspherocytic haemolytic anaemia, often accompanied by jaundice. This condition was less frequent and did not reveal spherocytosis. Here, we present the case of an infant with a 4-month history of progressive pallor and jaundice accompanied by hepatosplenomegaly. Thorough investigations have ruled out conditions such as thalassaemia, hereditary spherocytosis, and autoimmune haemolytic anaemia. Whole exome sequencing was eventually performed as a last resort to identify the possibility of an inherited defect presenting with complaints, and a final diagnosis of haemolytic anaemia due to hexokinase 1 deficiency was arrived at, with homozygosity for the defect located on exon 16 and the variant c.2252G>C (p.Gly751Ala).

Keywords: Hexokinase deficiency, Haemolytic anaemia, Jaundice, Pallor

INTRODUCTION

Hexokinase deficiency is an exceptionally rare autosomal recessive disorder that leads to congenital haemolytic anaemia. Here, it primarily affects the initial enzyme in the glycolytic pathway, which is responsible for catalysing glucose phosphorylation. This enzyme plays a crucial role in the sole metabolic pathway that is capable of providing ATP to red blood cells. This condition is characterised by a deficiency of essential enzymes crucial for glycolysis and red blood cell (RBC) nucleotide metabolism, resulting in congenital haemolytic anaemia, accompanied by jaundice as the major clinical manifestation. Notably, peripheral smears do not reveal spherocytosis, and laboratory assessments exclude abnormalities in haemoglobin levels.

Hexokinase deficiency is among the less frequent hereditary defects in glycolysis associated with nonspherocytic haemolytic anaemia.[1] The deficiency of this enzyme results in premature haemolysis of blood cells, causing severe and chronic nonspherocytic haemolytic anaemia, which is the most prevalent clinical manifestation. Jaundice often accompanies this condition.[1] According to existing literature, one of the earliest reported cases of hexokinase deficiency dates back to 1967 when an adult presented with anaemia which upon detailed investigation led to the discovery of the first reported case of hexokinase deficiency.[2] In 1967, a study identified an association between hexokinase deficiency in human erythrocytes and hereditary nonspherocytic haemolytic anaemia.[3] The hexokinase activity in the erythrocytes of affected individuals was initially only slightly reduced. Nevertheless, considering the extent of reticulocytosis, a notable decrease in hexokinase activity was evident.

CASE REPORT

Case history:

A 4-month-old male, first born to parents in a third-degree consanguineous marriage, presented with complaints of progressive pallor observed since birth, accompanied by jaundice. Although there were no antenatal complications, it was during the postnatal period that the infant was admitted to the neonatal intensive care unit because of hyperbilirubinemia noted on day 1 of life, with initial indirect bilirubin levels reaching 18 mg/dl. The infant underwent intensive phototherapy until day 8, which resulted in bilirubin levels that returned to the normal range. TORCH and ABO incompatibility tests were performed and found to be

negative. Further investigation revealed anaemia (haemoglobin level of 10 mg/dl), leading to transfusion of packed red blood cells and fresh-frozen plasma due to suspected coagulation defects. However, subsequent blood examinations revealed normal haemoglobin levels. Workups for sepsis, inborn errors of metabolism, and organic acids were also investigated and were found to be negative. As the infant showed symptomatic improvement, he was discharged with the advice of follow-up in case of recurring symptoms of pallor and jaundice.

At 4 months of age, the infant returned with similar complaints of progressive pallor and jaundice accompanied by hepatosplenomegaly, with both organs extending 4 cm below the right and left costal margins. A repeat blood workup revealed a haemoglobin level of 5.7 mg/dl, and a peripheral smear displayed microcytic hypochromic red blood cells with anisopoikilocytosis and polychromatophils, along with normal white blood cell and platelet counts. Thorough investigations have ruled out conditions such as thalassaemia, hereditary spherocytosis, and autoimmune haemolytic anaemia. Whole exome sequencing was eventually performed as a last resort to identify the possibility of an inherited defect presenting with the abovementioned complaints, and a final diagnosis of haemolytic anaemia due to hexokinase 1 deficiency was arrived at, with homozygosity for the defect located on exon 16 and the variant c.2252G>C (p.Gly751Ala).

DISCUSSION

The hexokinase enzyme plays a very important role in the generation of ATP in erythrocytes, and it is also one of the rate-limiting steps in the glycolytic pathway within erythrocytes. This condition is usually inherited as autosomal recessive, and alteration in the red blood cell count due to a lack of this enzyme results in a haemolytic blood picture; usually, no inclusion bodies are noted on the peripheral blood smears of the affected individuals. Non-spherocytic haemolytic anaemia which occurs as a result of hexokinase deficiency, results from hexokinase 1 (HK1) deficiency which is extremely rare.

Hexokinase deficiency can occur as a result of a broad spectrum of mutations, including missense, nonsense, deletion, and intronic mutations. Children with this condition can present with haemolysis which commences as early as infancy. As mentioned in our case, children present with progressive pallor, fatigue, jaundice due to hyperbilirubinemia, and dark-yellow urine. In most cases, while working up the patient, autoimmune causes of haemolytic anaemia are ruled out when the Coomb's test is negative. Affected children often exhibit normal haemoglobin structure and stability. Various other enzyme deficiencies have been reported to be associated with this condition, such as pyruvate kinase deficiency, pyrimidine 5'nucleotidase deficiency, and homozygous glucose phosphate isomerase (GPI) deficiency. Under all these conditions, there is a decrease in the levels of adenosine triphosphate (ATP), leading to premature RBC death and haemolysis.

Individuals affected by this condition can also present during adulthood with an insidious onset of pallor and jaundice. Rijksen et al. reported a 19-year-old woman who presented with anaemia since birth with marked reticulocytosis and hyperbilirubinemia which was identified and worked up only during adulthood.[4] Treatment for this condition primarily involved symptomatic care, and patients were advised to avoid potential triggers for haemolysis, such as specific drugs, stress, or certain foods. In our case, recovery was uneventful following appropriate management of anaemia and associated symptoms.

This enzyme plays a pivotal role in the chemical processes that facilitate the breakdown of sugar molecules (glycolysis) and serves as a crucial source of energy for red blood cells (RBCs). When an enzyme is defective at any stage of these processes, the proper functioning of red blood cells is compromised, leading to haemolysis and subsequent anaemia.[2] According to the available literature, recently in the year 2020, Dongerdiye et al. reported a case in India where a four-and-a-half-year-old female child inherited the defect as autosomal recessive. (5) On genetic testing, she was found to have a novel pathogenic variant in the Hexokinase 1 gene which resulted in severe haemolytic anaemia and developmental delay.[3]

CONCLUSION

Hexokinase deficiency is not the most common cause of haemolytic anaemia in an infant, but it is very important to rule out if the most common causes, such as haemoglobinopathies and enzyme deficiencies (such as glucose 6 phosphate dehydrogenase deficiency and pyruvate kinase deficiency) do not fit the clinical picture or if the laboratory parameters are not a match. In addition to pallor and jaundice, cases of HK1 gene mutations can also present with features such as developmental delay and neurological defects. Depending on the severity of the disease follow-up of these patients is planned as it is important long term, as some may require repeated blood transfusion and conservative management while others in later stages may require bone marrow transplantation.

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