Case study

Hereditary Spherocytosis In A Neonate with a new frameshift deletion-A Case Report

Keywords: Anaemia, Hereditary spherocytosis, Neonate, neonatal jaundice, Novel Mutations,

Abstract:

Introduction: Hemolytic anaemias often occur in neonates, often presenting with jaundice or encephalopathy. Hereditary spherocytosis is the most common cause, followed by glucose-6-phosphate-dehydrogenase deficiency and ABO isoimmunization. Early diagnosis and laboratory evaluation are crucial for effective interventions and preventing complications. This case report helps to recognise the clinical signs of hereditary spherocytosis early. And to emphasise the importance of the HS ratio in the diagnostic approach to hereditary spherocytosis. **Case Report:** A 20-day-old first-born female baby presented with progressive pallor and jaundice since 7 days of life. The baby was treated with phototherapy and discharged home. On the 20th day, the parents noticed increasing jaundice and pallor, leading to a provisional diagnosis of hemolytic anaemia with splenomegaly. The baby had anaemia and unconjugated hyperbilirubinemia with normal liver enzymes. Hemolysis was found, and the mother's blood group was A-positive. The baby had an HS Ratio of 0.43, suggesting hereditary spherocytosis. Clinical exome sequencing confirmed hereditary spherocytosis type 2. The baby is currently 9 months old and growing normally. **Conclusion:** The HS ratio is more useful to diagnose hereditary spherocytosis. This study further expanded the mutation spectrum of the SPTB gene. Reaffirms the diagnostic value of gene detection in neonatal HS type 2.

Introduction:

Hereditary spherocytosis (HS) is a common monogenic hemolytic anaemia disease characterised by spherical-shaped erythrocytes in peripheral blood. It is inherited in an autosomal dominant manner, with 75% of cases being autosomal dominant. HS occurs worldwide, with a prevalence of 1 in 1000 to 2000 births. [2] HS type 1 (HS1) is caused by ankyrin mutations, which are associated with both dominant and recessive HS. Exome sequencing could help detect pathogenic mutations in ANK1 and other genes, potentially

enabling an early diagnosis. This study contributes to understanding and diagnosing HS in neonates. and a simple, complete blood picture may be enough to suspect the HS.

Case report: A 20-day-old first-born female baby to a non-consanguinous married couple with an uneventful antenatal history, delivered at term gestation by Lower segment Cesarian section in view of foetal distress with a birth weight of 2.5 kg, was normal [Fig. 1]. After that, the baby presented with progressive pallor and jaundice for the first 7 days of life. The baby was treated with phototherapy for 2 days at an outside hospital, and as the jaundice reduced, he was discharged home. On the 20th day of life, parents noticed increasing jaundice and pallor and brought the baby to our hospital [Fig. 2]. There was no history of high-coloured urine, pale-coloured stools, or any bleeding manifestations. There are no similar complaints from other family members.

On examination, anthropometry was appropriate for age; the baby had severe pallor, icterus till the thighs, and spenomegaly. A provisional diagnosis of hemolytic anaemia with splenomegaly was made and started on phototherapy. On investigation, the baby had anaemia (Hb-5 g%) and unconjugated hyperbilirubinemia (TB-11, DB-1.1, IB-9.9). Liver enzymes were normal. The corrected reticulocyte count was elevated, and the peripheral smear showed microspherocytes, suggesting hemolysis. The mother's blood group was A positive, the baby's blood group was A positive, and the direct Coombs test was negative, so major and minor blood group incompatibilities (immune hemolysis) were ruled out.

On further evaluation for non-immune causes of hemolysis, glucose-6-phosphate dehydrogenase levels, thyroid function tests, and Hb electrophoresis were done, and the reports were normal. The incubated osmotic fragility test was inconclusive as it was done post-packed RBC transfusion. Usually neonatal RBC's osmolality was higher than that of adults. HS Ratio, i.e., MCHC:MCV, was 0.43 (> 0.36), suggesting hereditary spherocytosis. For confirmation, clinical exome sequencing was done, suggesting a SPTB gene frameshift deletion (SPTB c.4003delG), a heterozygous or autosomal dominant variety, as likely pathogenic for hereditary spherocytosis type 2.

During the hospital stay, the baby received PRBC transfusions twice and was discharged home with folic acid supplementation. The baby is currently 9 months old and developmentally normal, requiring blood transfusions once every 3 months with increasing intertransfusion duration.

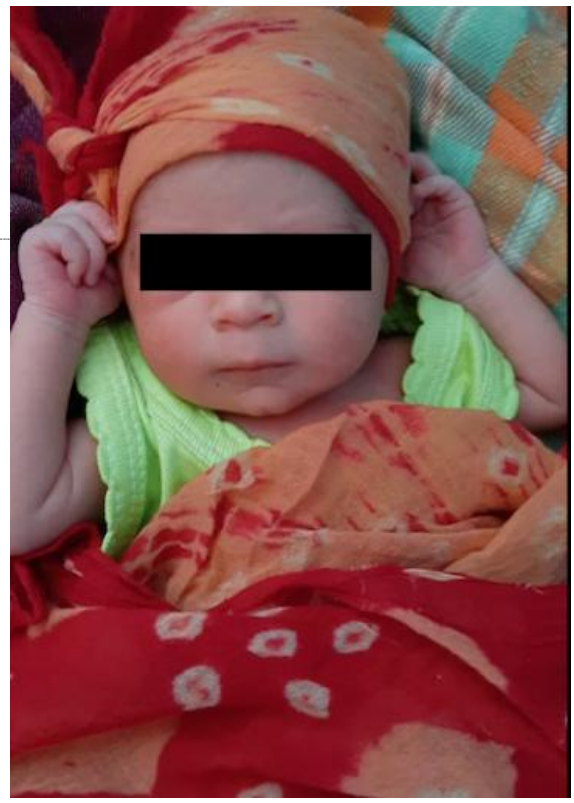

Fig:1 The baby was pink at birth

Fig:2 Baby at 20 days of life with pallor and jaundice

Discussion: Hereditary spherocytosis (HS) is a heterogeneous disorder in which abnormalities of RBC structural proteins (like ankyrin1, band 3, spectrin, and protein 4.2) lead to loss of erythrocyte membrane surface area, resulting in spherical, hyperdense, poorly deformable RBCs with a shortened life span (1). It occurs worldwide and affects individuals from all racial and ethnic groups.

The clinical spectrum ranges from foetal anaemia (hydrops) to asymptomatic neonates. Usually presents with anaemia and hyperbilirubinemia, but can also progress to encephalopathy and kernicterus (3). HS can also present with aplastic crises, gall stones, gout, splenic sequestration crises, folate deficiency, and cardiomyopathy. (4,5,6)

HS can be diagnosed by a peripheral smear showing microspherocytosis, reticulocytosis, an HS ratio of >0.36, an increased incubated osmotic fragility test, and decreased fluorescence intensity of EMA-tagged RBCs in the Eosin 5 Maleimide binding test. An MCHC of > or = 36.0 g/dL had 82% sensitivity and 98% specificity for identifying HS. DNA sequencing is confirmatory and usually done in babies with a negative family history and severe DCT-negative hemolysis. (7,8,9,10). In our case, the SPTB gene genomic position was Chr14:65249270, and the variant was c.4003delG/p. Glu1335fs*5, a Frameshift deletion with segment depth, was a 70x. Probable autosomal dominant sphenocytosis Type 2. This was a new variant not reported in any sources. We also planned a genetic test for parents, but they deferred it due to financial constraints.

Treatment includes blood transfusions for anaemia, phototherapy, exchange transfusions for hyperbilirubinemia, and encephalopathy. (11, 12) Folate supplementation to cope with increased erythropoiesis Darbopoeitin can be used as an adjunct to blood transfusions. (13) Splenectomy is rarely required in infancy (14). Xu C reported a neonatal case similar to our history in which he observed a novel frameshift mutation (p.Asp495fsTer78) in the STB gene. A mutation c.3737delA on the exon 16 of SPTB (14q23|NM_000347.5), leading to a mutation of p. (Lys1246fs) in the amino acid sequence, was identified in the exon 16. Additionally, the same mutation was identified in her father. (15) A novel gene mutation was discovered in a 26-day-old female who exhibited jaundice, anaemia, elevated reticulocyte and spherocyte counts, and an acidified glycerol hemolysis test. The patient and her father both have c.3737delA P. (Lys1246fs) in exon 16 of the SPTB (14q23 | NM_000347.5) gene. (16). The limitation of our case report is that we did not confirm the pathogenicity of the variant. Due to financial constraints.

Conclusion:The present study has enhanced the understanding of hereditary spherocytosis by exploring the HS ratio as a valuable diagnostic tool. Additionally, the study has extended our knowledge of the mutation spectrum of the SPTB gene. These findings further support the significance of gene detection in identifying neonatal HS type 2.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent:

As per international standard or university standard, Parent's written consent has been collected and preserved by the author(s).

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