Case study

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

Abstract:

Hemolytic anaemias are not infrequently encountered in the neonatal period and present as anaemia with jaundice. Severe cases may present as encephalopathy or kernicterus. Hereditary spherocytosis (HS) is the most common cause of nonimmune hemolytic anaemia and the third most common cause of kernicterus after glucose-6-phosphate-dehydrogenase deficiency and ABO isoimmunization. Therefore, it's important to be aware of the constellation of symptoms and signs, and the laboratory evaluation that is necessary to diagnose early and to start early effective interventions, thereby preventing complications. This article presents a case of non-immune Hemolytic anaemia with splenomegaly.this case report help to recognize the clinical signs of hereditary spherocytosis early. And to emphasize the importance of HS ratio in diagnostic approach of hereditary spherocytosis,

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 LSCS with a birth weight of 2.5 Kg was normal [Fig:1]after that baby presented with progressive pallor and jaundice since 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 (4%) 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 reports were normal. The incubated osmotic fragility test was inconclusive as it was done post-packed RBC transfusion. 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.

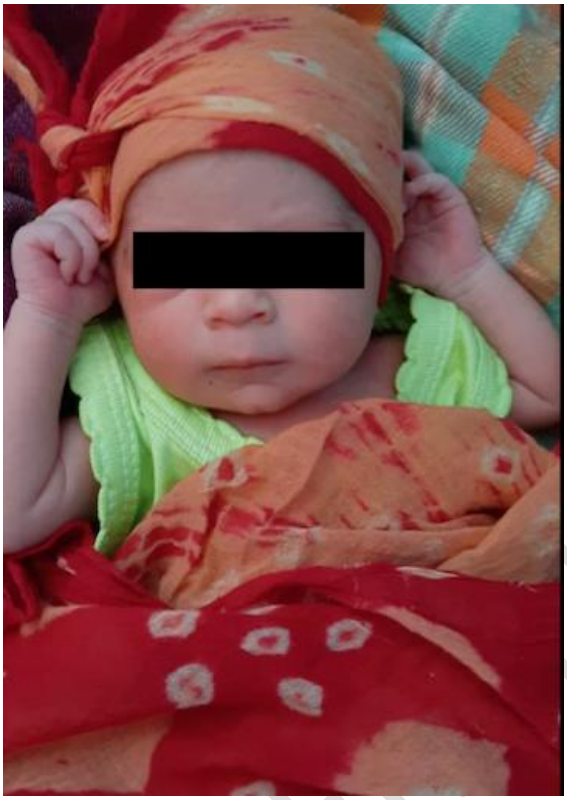

Fig:1 Baby at birth

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,α/βspectrin,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.

Clinical spectrum ranges from fetal anemia /hydrops to asymptomatic neonate. Usually presents with anemia and hyperbilirubinemia ,can also progress to encephalopathy and kernicterus (3).HS can also present with aplastic crisis, gall stones, gout, splenic sequestration crisis, folate deficiency, cardiomyopathy.(4,5,6)

HS can be diagnosed by peripheral smear showing microspherocytosis, reticulocytosis, HS ratio of >0.36, increased incubated osmotic fragility test, decreased fluorescence intensity of EMA tagged RBCs in 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, usually done in babies with 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 planed genetic test for parents also but they deferred due o financial constraints.

Treatment constitutes blood transfusions for anemia, phototherapy, exchange transfusions for hyperbilirubinemia and encephalopathy.(11,12) Folate supplementation to cope up 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 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 mutation of p.(Lys1246fs) in 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 we did not confirm he pathogenicity of the varient. Due to financial constraints.

Conclusion:

HS ratio is more useful to diagnose the hereditary spherocytosis present study further expanded the mutation spectrum of the SPTB gene. Reaffirms the diagnostic value of gene detection in neonatal HS type 2.

References:

1)ChasisJA,AgreP,MohandasN.Decreasedmembrane mechanical stability and in vivo loss of surface area reflect spectrin deficiencies in hereditary spherocytosis. JClinInvest. 1988;82(2):617–623

2) Guitton C, Garçon L, Cynober T, et al. [Hereditary spherocytosis: guidelines for the diagnosis and management in children]. Arch Pediatr. 2008;15(9):1464–1473

3)Berardi A, Lugli L, Ferrari F, et al. Kernicterus associated with hereditary spherocytosis and UGT1A1 promoter polymorphism. Biol Neonate. 2006;90(4):243–246

4) Krueger HC, Burgert EO. Hereditary spherocytosis in 100 children. Mayo Clin Proc. 1966 Dec;41(12):821-3

5)Tamary H, Aviner S, Freud E, Miskin H, Krasnov T, Schwarz M, Yaniv I. High incidence of early cholelithiasis detected by ultrasonography in children and young adults with hereditary spherocytosis. J Pediatr Hematol Oncol. 2003 Dec;25(12):952-4.

6)Kobayashi Y, Hatta Y, Ishiwatari Y, Kanno H, Takei M. Human parvovirus B19-induced aplastic crisis in an adult patient with hereditary spherocytosis: a case report and review of the literature. BMC Res Notes. 2014 Mar 11;7:137.

7)YaishHM,ChristensenRD,HenryE,BaerVL,BennettST.Asimple method of screening newborn infants for hereditary spherocytosis. J Applied Hematol. 2013;4:27–32

8) King MJ, Smythe JS, Mushens R. Eosin-5-maleimide binding to band3andRh-relatedproteinsformsthebasisofascreeningtestfor hereditary spherocytosis. Br J Haematol. 2004;124(1):106–113

9)Dacie JV, Lewis SM, Luzatto L. Investigation of the hereditary haemolytic anaemias: membrane and enzyme abnormalities. In: Dacie JV, Lewis SM, eds. Practical Haematology. London, England: Churchill Livingstone; 1991;195–225

10)Won DI, Suh JS. Flow cytometric detection of erythrocyte osmotic fragility. Cytometry B Clin Cytom. 2009;76(2):135–141

11)AmericanAcademyofPediatricsSubcommitteeonHyperbilirubinemia Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297–316

12) FlahermanVJ,KuzniewiczMW,EscobarGJ,NewmanTB.Totalserum bilirubin exceeding exchange transfusion thresholds in the setting of universal screening. JPediatr.2012;160(5):796–800.e1

13) Tchernia G, Delhommeau F, Perrotta S, et al. Recombinant erythropoietin therapy as an alternative to blood transfusions in infants with hereditary spherocytosis. Hematol J. 2000;1(3):146–152

(14)Bolton-Maggs PH, Langer JC, Iolascon A, et al. Guidelines for the diagnosis and management of hereditary spherocytosis–2011 update. Br J Haematol. 2012;156(1):37–49

(15)Xu C, Wu Y, Wang D, Zhang X, Wang N. Novel SPTB frameshift mutation in a Chinese neonatal case of hereditary spherocytosis type 2: A case report. Exp Ther Med. 2022 Jul 28;24(3):600. doi: 10.3892/etm.2022.11537. PMID: 35949318; PMCID: PMC9353470.

(16)Yang Liu, Li Song, Jianbo Shu et al. A novel SPTB gene mutation in neonatal hereditary spherocytosis: a case report and literature review, 28 August 2019, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.2.10866/v1]