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Hereditary Spherocytosis Masquerading under the Cloak of Recurrent Gallstones

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Abstract: ***Hereditary spherocytosis (HS) is a type of familial hemolytic anemia, in which heterogeneous alterations in one of the six genes that encode for proteins involved in vertical associations which tie the red blood cell (RBC) membrane skeleton to the lipid bilayer causes dysfunction or deficiency of cell membrane protein resulting in spherical - shaped, hyper - dense, and poorly deformable RBCs with a shortened life span. It has a wide spectrum of clinical features, ranging from an asymptomatic condition to a fulminant hemolytic anemia. Although Familial history increases the risk of HS, it may be sporadic in some cases. We report a case of 26year old female, who presented with Abdominal pain, vomiting and yellowish discoloration of skin. Under laboratory evaluation she was found to have anaemia with reticulocytosis, jaundice. In peripheral blood smear, spherocytes were moderately distributed. Direct, Indirect coomb's test was negative but osmotic fragility was high. Hence, she was confirmed as case of hereditary spherocytosis. She was vaccinated for Streptococcus Pneumonia and Neisseria meningitides, elective Laparoscopic splenectomy with cholecystectomy was done.***

Keywords: Hereditary Spherocytosis, spherocytes, osmotic fragility test, indirect hyperbilirubinemia.

1. Introduction

26 Year Female, housewife by occupation, was seen in the emergency with complaints of Abdominal Pain, Yellowish discolouration of skin, Vomiting and Fever.

Abdominal pain was since last 8 days which was restricted to Right Hypochondriac region and was of dull aching type which resolved with medication. Pain was not radiating to back or shoulder. No obvious visible lump seen. Vomiting since last 8 days and accompanied by fever since last 4 days.

No history of loose stools, constipation, outside food consumption, headache, chest pain, breathlessness, animal contact.

On general examination, she was conscious oriented obeying command with pulse of 112/min, BP of 108/66mmHg and respiratory rate of 20/min. Icterus was 4+. On systemic examination, Per abdomen tenderness was present in right hypochondriac region and Gross splenomegaly and moderate hepatomegaly was present. Rest all systemic examinations were within normal findings.

Past history of similar complains were present 6 months ago for which she underwent an Ultrasound of Abdomen & Pelvis which showed gall bladder calculi and mildly dilated common bile duct.

Contrast Enhanced CT abdomen done which was s/o Calculus in Terminal Common Bile Duct of 4mm size, Gall bladder being overtly distended with two calculi of 7mm and 6.8mm.

During the same admission she had Hyperbilirubinemia (20.4) with Direct (16.6) and indirect of (3.8). She underwent ERCP for the same and a stent was placed in CBD with evacuation of gall bladder calculi. Her hyperbilirubinemia had resolved then and fallen to 4.9 post stenting with indirect bilirubin being 4.7 and direct 0.2. She was planned for laparoscopic cholecystectomy but couldn't clear preanesthetic fitness because of indirect hyperbilirubinemia and then lost to follow up until now.

On day 1 of admission now, her haemoglobin levels was 8.6gm%, total leucocyte counts count raised to 15310 /cumm and Platelet count 2, 50, 000/cumm. Bilirubin of 10.8 (Direct - 4.9 and Indirect - 5.9) with ALP of 186. Renal parameters and serum electrolytes were within normal limits. A repeat CECT Abdomen was done which showed distended gall bladder but no evidence of calculi with mildly dilated common bile duct. Day 3, her abdominal pain and icterus had increased with TLC rising to 28380 and Bilirubin Total reaching 28.2 (Direct 20.2 and Indirect 7.6). Meanwhile we worked her up for indirect hyperbilirubinemia. Peripheral smear showed normocytic normochromic anaemia with mild anisopiokilocytiosis raised total leucocytes with marked neutropenia and no

evidence of abnormal cells. LDH was 247. Retic count was 13.8%.

Direct and indirect Coombs test were negative. Sickling test was negative. Haemoglobin electrophoresis didn't reveal any abnormal haemoglobin levels. Urine analysis didn't reveal any evidence of urobilirubinogen.

Serum Haptoglobin was below 10 indicating ongoing intravascular haemolysis. Viral markers for Hep A, B, C and E were negative. To rule out autoimmune aetiology ANA, ASMA AND IgG total were sent which were negative.

She underwent a repeat ERCP, where multiple gall stones were evacuated and CBD stent was replaced and CBD clearance was done. Her Bilirubin levels dropped in a jiffy overnight from 28.2 to 7.8 and stabilising to 4.1 on day 3 post ERCP.

Taking into consideration her age, no prior family history, history of recurrent gall stones at young age with general examination showing icterus and hepatosplenomegaly and laboratory evidence of normocytic anaemia with MCHC of >34 and RDW >14 and evidence of intravascular as well as extravascular haemolysis with low haptoglobin levels, repeat peripheral smear by senior haematologist was done keeping in mind a differential diagnosis of hereditary spherocytosis. Peripheral smear revealed Spherocytes 4+. To confirm our diagnosis we sent an Osmotic Fragility test which revealed that haemolysis begins with 0.65% NaCl, suggesting an increased osmotic fragility. Hence confirming our diagnosis of Hereditary spherocytosis.

With financial constrains we remain stuck with the hereditary pattern of inheritance and type of genetic defect involved.

She was vaccinated for capsulated organisms like Streptococcus Pneumonia and Neisseria meningitidis. Elective laparoscopic splenectomy along with cholecystectomy has been done in the same sitting.

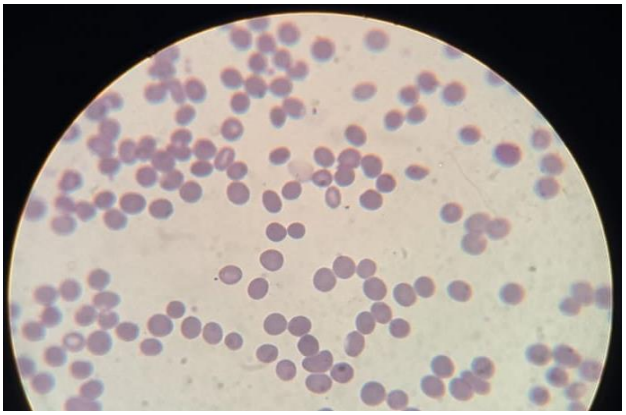

Figure 1: Peripheral smear depicting normocytic anaemia with spherocytes.

Table 1: Routine Laboratory investigations.

Parameter	Value	Normal Range
Haemoglobin	8.40gm %	12 - 15 gm%
Total Leucocyte Count	15, 310/cmm	4000 - 11, 000/cmm
Platelets	2, 50, 000/cumm	1, 50, 000 - 4, 50, 000/cumm
MCHC	37.10g/dl	31.5 - 34.5g/dl
RDW	18.60%	
LDH	247U/l	120 - 245 U/l
Retic Count	13.8%	0.5 – 2.5%
Haptoglobin	Below 10mg/dl	30 - 200mg/dl

Table 2: Special Investigations

Parameter	Result
Coombs Direct	Negative
Coombs Indirect	Negative
Sickling Test	Negative
ANA	Negative
ASMA	Negative
IgG total	Negative
Hep A IgM, Hep E IgM	Negative

Osmotic Fragility Test

(Heparin Whole Blood)

Investigation	Observed Value	Unit	Biological Reference Interval
Haemolysis begins in % Nacl.	0.65	%	0.45-0.5
Haemolysis completes in % Nacl	0.3	%	0.2-0.3
Median corpuscular fragility in % NaCl.	0.475	%	0.4-0.445
Impression	Increased.		

Comments :Advice : Molecular testing for definite opinion. Kindly correlate clinically.

Figure 2: Osmotic Fragility Test

Table 3: Serial Liver Function Test.

Parameters	Pre ERCP	Day of ERCP	Post ERCP Day1	Day of discharge
Total Bilirubin	10.8mg%	28.4 mg%	21.6mg%	4.1mg%
Direct Bilirubin	4.9mg%	7.8 mg%	18.5mg%	2.6mg%
Indirect Bilirubin	5.9 mg%	20.6 mg%	3.1mg%	1.5mg%
Alkaline Phosphatase	186U/L	247 U/L	163U/L	108U/L

2. Discussion

HS is a heterogeneous group of disorders caused by variants in certain genes that encode proteins of the red blood cell (RBC) membrane and cytoskeleton; specifically, HS is caused because of inadequate vertical linkages between the cytoskeleton and the lipid bilayer of the RBC membrane (1, 2). The loss of vertical linkages leads to loss of RBC membrane and a spherocytic (rather than biconcave disc) shape of HS RBCs, with decreased surface - to - volume ratio and decreased deformability that is essential to the normal RBC lifespan. HS is caused by quantitative deficiency of alpha - or beta - spectrin, ankyrin, protein 4.2, or band 3, encoded by the genes *SPTA1*, *SPTB*, *ANK1*, *EPB42*, and *SLC4A1*, respectively (2, 3). Thus it is a heterogenous disorder arising out of a variety of mutations from any one of the genes mentioned. It has been recognised that the inheritance pattern of hereditary spherocytosis is not always autosomal dominant; indeed, some of the most severe forms are instead autosomal recessive.

HS is seen in all populations but appears to be especially common in people of northern European ancestry. In these individuals, HS affects as many as 1 in 2000 to 1 in 5000 (prevalence, approximately 0.02 to 0.05 percent) (4, 5, 6, 7). HS can present at any age and with any severity, with case reports describing a range of presentations from hydrops fetalis in utero through diagnosis in the ninth decade of life (6, 8, 9).

The spectrum of clinical severity in hereditary spherocytosis is broad with main clinical findings being jaundice, splenomegaly, recurrent gallstones. It may be the finding of gallstones in a young person that triggers diagnostic investigation.

Mechanism of haemolysis include reduced deformability, which impairs passage through constricted regions of the microcirculation, haemolysis within the splenic microenvironment, and/or phagocytosis by the splenic red pulp macrophages, which may occur in response to splenic trapping (10, 11).

When there is a family history, it is usually easy to make a diagnosis based on features of HA and typical red cell morphology. However, family history may be negative for at least two reasons. First, the patient may have a de novo mutation, i. e., a mutation that has taken place in a germ cell of one of the patient's parents or early after zygote formation. Second, the patient may have a recessive form of HS. In such cases, more extensive laboratory investigations are required, including osmotic fragility, the acid glycerol lysis test, the eosin - 5' - maleimide (EMA) - binding test, and SDS - gel electrophoresis of membrane proteins; these tests are usually carried out in laboratories with special expertise in this area.

An increased MCHC (> 34) and increased RDW (>14%) with normal or subnormal MCV on an ordinary blood count should raise suspicion of Hereditary Spherocytosis.

Currently no way to correct the underlying genetic defect is available. Given the special role of spleen in hereditary spherocytosis, splenectomy is indicated in hereditary spherocytosis. Current recommendations are to proceed with splenectomy at the age of 4 - 6 years in severe cases, to delay splenectomy until puberty in moderate cases, and to avoid splenectomy in mild cases. Partial splenectomy can be considered in certain cases; and it is helpful to know about the outcome of splenectomy in the patient's affected relatives.

Before splenectomy, vaccination against encapsulated bacteria (Neisseria meningitidis and Streptococcus pneumonia) is imperative; penicillin prophylaxis after splenectomy is controversial. Along with splenectomy, chole - cystectomy should not be carried out automatically; but it should be carried out, usually by the laparoscopic approach, whenever it is clinically indicated.

For patients undergoing elective splenectomy, vaccinations should be given at least 14 days prior to the procedure and ideally 10 to 12 weeks prior. For patients undergoing emergency splenectomy, vaccine series should be started 14 days after splenectomy. For patients with nonsurgical asplenia or hypo - splenism, vaccinations should be given as soon as impaired splenic function is recognized.

References

[1] Lux SE 4th. Anatomy of the red cell membrane skeleton: unanswered questions. Blood.2016 Jan 14; 127 (2): 187 - 99. doi: 10.1182/blood - 2014 - 12 - 512772. Epub 2015 Nov 4. PMID: 26537302.

[2] Risinger M, Kalfa TA. Red cell membrane disorders: structure meets function. Blood.2020 Sep 10; 136 (11): 1250 - 1261. doi: 10.1182/blood.2019000946. PMID: 32702754; PMCID: PMC7483429.

[3] Eber S, Lux SE. Hereditary spherocytosis - - defects in proteins that connect the membrane skeleton to the lipid bilayer. Semin Hematol.2004 Apr; 41 (2): 118 - 41. doi: 10.1053/j. seminhematol.2004.01.002. PMID: 15071790.

[4] Mohandas N, Gallagher PG. Red cell membrane: past, present, and future. Blood.2008 Nov 15; 112 (10): 3939 - 48. doi: 10.1182/blood - 2008 - 07 - 161166. PMID: 18988878; PMCID: PMC2582001.

[5] Andolfo I, Russo R, Gambale A, Iolascon A. New insights on hereditary erythrocyte membrane defects. Haematologica.2016 Nov; 101 (11): 1284 - 1294. doi: 10.3324/haematol.2016.142463. Epub 2016 Oct 18. PMID: 27756835; PMCID: PMC5394881.

[6] Perrotta S, Gallagher PG, Mohandas N. Hereditary spherocytosis. Lancet.2008 Oct 18; 372 (9647): 1411 - 26. doi: 10.1016/S0140 - 6736 (08) 61588 - 3. PMID: 18940465.

[7] Eber SW, Pekrun A, Neufeldt A, Schröter W. Prevalence of increased osmotic fragility of erythrocytes in German blood donors: screening using a modified glycerol lysis test. Ann Hematol.1992 Feb; 64 (2): 88 - 92. doi: 10.1007/BF01715351. PMID: 1554800.

[8] Whitfield CF, Follweiler JB, Lopresti - Morrow L, Miller BA. Deficiency of alpha - spectrin synthesis in burst - forming units - erythroid in lethal hereditary

spherocytosis. Blood.1991 Dec 1; 78 (11): 3043 - 51. PMID: 1954389.

[9] Friedman EW, Williams JC, Van Hook L. Hereditary spherocytosis in the elderly. Am J Med.1988 Mar; 84 (3 Pt 1): 513 - 6. doi: 10.1016/0002 - 9343 (88) 90275 - 6. PMID: 3348251.

[10] Safeukui I, Buffet PA, Deplaine G, Perrot S, Brousse V, Ndour A, Nguyen M, Mercereau - Puijalon O, David PH, Milon G, Mohandas N. Quantitative assessment of sensing and sequestration of spherocytic erythrocytes by the human spleen. Blood.2012 Jul 12; 120 (2): 424 - 30. doi: 10.1182/blood - 2012 - 01 - 404103. Epub 2012 Apr 17. PMID: 22510876; PMCID: PMC3398764.

[11] Klei TRL, Dalimot J, Nota B, Veldthuis M, Mul FPJ, Rademakers T, Hoogenboezem M, Nagelkerke SQ, van IJcken WFJ, Oole E, Svendsen P, Moestrup SK, van Alphen FPJ, Meijer AB, Kuijpers TW, van Zwieten R, van Bruggen R. Hemolysis in the spleen drives erythrocyte turnover. Blood.2020 Oct 1; 136 (14): 1579 - 1589. doi: 10.1182/blood.2020005351. PMID: 32777816.