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Hereditary Spherocytosis with Beta Thalessemia—Study of two unique Rare Interesting Cases

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ABSTRACT:

Hereditary spherocytosis (HS), first described in 1871, is a familial haemolytic disorder with marked heterogeneity. Its clinical manifestations range from being asymptomatic to presenting as severe life-threatening haemolytic anaemia.

A 12-year-old male child presented to a tertiary care hospital in Navi Mumbai with complaints of icterus since 7-8 days and severe anaemia. On examination, patient had severe pallor a hemoglobin value of 4.3 gm/dl. Peripheral smear examination suggested presence of 25 per cent of spherocytes on smear. High Performance Liquid Chromatography (HPLC) was suggestive of Beta Thalassemia. Osmotic fragility showed hemolysis at 0.65 % of NaCl (Normal Range = 0.45- 0.5 %). Ultrasonograhy was suggestive of Hepatoslenomegaly.

HS is an inherited disorder of red blood cells and can be hereditarily transmitted from parents to children. Families with history of HS should be counselled since there exists up to 50 per cent of probability of each subsequent child having HS. Although genetic counselling is difficult to conduct in most developing countries due to the non-availability of resources and poor health infrastructure, it is most desirable part of clinical management of the condition. HS is a relatively uncomplicated clinical diagnosis of a genetic condition, which apart from diagnosis, needs genetic and general counseling of parents. This fact is underscored since parents have to receive counselling about the consequences of the diagnosis, the prognosis of the condition and the risk of another child being affected.

KEYWORDS: Hereditary spherocytosis (HS), familial haemolytic disorder, Beta Thalassemia, Osmotic fragility, High Performance Liquid Chromatography (HPLC), genetic counseling.

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INTRODUCTION

Hereditary spherocytosis (HS), described for the first time in the year 1871, is a familial disorder of red blood cells, which invariably leads to haemolytic anaemia. It occurs primarily due to plasma membrane structural defect. The plasma membrane structural defect is in the cytoskeleton of cell membrane of red blood corpuscles which occurs due to deficiency of specific proteins often known as spectrin[1,2] . The individuals affected by Hereditary spherocytosis may present with severe haemolytic anaemia with initial stages of the condition eliciting no remarkable clinical signs[1] . In majority of cases, Hereditary Spherocytosis inheritance is autosomal dominant and in few it is autosomal recessive type[1] .In people with Hereditary Spherocytosis, there is decreased deformability of the cell because of altered surface-to-volume ratio of erythreocytes leading to damage to cell membrane and hence, decrease in their lifespan[2] . The spherocytes, because of their characteristic spherical shape, are unable to assimilate absorbed hypo-osmotic fluid, making them osmotically fragile and thus, prone to hemolysis in the spleen[2]. The pathogenesis of Hereditary spherocytosis is in the genetic mutation of genes encoding for cytoskeletal protein molecules located on chromosome 17 that encode one or more plasma membrane proteins such as ankyrin, band 3 protein, α spectrin or β spectrin. The clinical severity differs between individuals with varying genetic mutations[2,3]. Hemolysis may be constant or occasional incident, induced by events such as post-infectious hypersplenism[2,3]. Un-diagnosed Hereditary Spherocytosis leads to kernicterus, a neurological complication, in adjunct to severe hemolytic anemia and gall stones. Thus, diagnosis of Hereditary Spherocytosis in early life is crucial in reducing the risk of complications in later life[3,4].

CASE HISTORY

12-year-old male came to the Mahatma Gandhi Medical College and Hospital with complaints of icterus since seven to eight days. Patient's hemoglobin was 3.4 gm/dl on his presentation at the hospital. Patient was given blood transfusion in view of low hemoglobin level. Though patient's hemoglobin level improved after blood transfusion, his status being icteric remained same (Table 1 and 2).

On examination, the patient's haematological parameters were within normal limits except for haemoglobin which had mildly increased after blood transfusion, though patient had evidence of haemolytic jaundice. Peripheral blood smear report showed presence of microspherocytes and variable number of spherocytes with general count being more than 25 per cent on smear (Figure 1). Reticulocyte count was increased along with few nucleated red blood cells and fragemented red blood cells, suggestive of Hereditary spherocytosis necessitating further investigations to rule out the same.

Other haematological investigations such as Osmotic fragility test showed hemolysis of red cells at 0.65% of sodium chloride [NaCl] (Normal: 0.45 – 0.5 %).

Red cell corpuscular fragility was increased to 0.48% (normal: 0.4- 0.445%).

Somehow, Red cells enzyme study using flow cytometric analysis of Eosin 5-maleimide was within normal limits. Glucose-6-phosphate dehydrogenase was within normal range.

On molecular studies, presence of red cell protein defect was observed, which was found to deficiency/structural abnormality in the cytotoskeletal proteins…

Hemoglobin electrophoresis showed presence of Beta thalessemia (Figure 2). Other ancillary clinical investigations such as Ultrasonography suggested presence of Hepato-splenomegaly with latent features of hypersplenism.

Patient underwent splenectomy in view of persistent and unrelenting haemolysis and splenomegaly. After splenectomy, patient's total bilirubin decreased with improvement in his overall general condition including being hemodynamically stable.

The results of all the above investigations were conclusively diagnostic of Hereditary Spherocytosis with Beta thalassemia.

As part of consultative protocol, examination of close family members of the patient for existence familial haemoglobinopathies was carried out, which revealed patient's younger sister was found to be suffering from HS with Beta thalassemia.

It was also found, on clinical investigations, that both parents of the patient are carriers of HS.

DISCUSSION

The clinical severity of HS varies from symptom-free carrier to severe haemolysis. Mild HS can be difficult to identify because individuals may have normal haemoglobin and bilirubin concentrations. The presence of spherocytes and a reticulocy- tosis will support the diagnosis. If there are no spherocytes seen on the film, no abnormalities in the red cell indices, and the reticulocyte count is normal, then a 'carrier' state cannot be excluded, but the individual is unlikely to have any clinical sequelae.

Hereditary spherocytosis is a haematological condition which includes a heterogeneous group of disorders with regard to clinical severity, defects in protein and inheritance mode. It is the most common inherited red cell membrane defect, though it is one of the rare disorders globally. It is associated with

hemolysis, the degree of which depends on correlation between the status of spleen and an intrinsic membrane defec[5,6].

The morphological abnormality in red blood cells that lead to shortened cell survival is due to deficiency or dysfunction in cytoskeletal components such as spectrin, ankyrin, band 3 and/or protein 4.2. Spectrin deficiency is the most commonly found defect in various studies[5,6,7,8]. Multiple mutations have been identified in genes harbouring these membrane proteins. Most cases of hereditary spherocytosis are heterozygous since homozygous states are not compatible with life and hence, lethal. An apparent correlation exists between clinical severity of hereditary spherocytosis [HS] and protein phenotypes. The clinical severity of HS varies from an uneventful carrier state to severe hemolysis[5,6]. Mild HS can be difficult to clinically identify because such individuals may have normal levels of hemoglobin and bilirubin. Generally, diagnosis of HS is often made in childhood and young adulthood, it is not seldom that the condition may be diagnosed at any age[5,6,7,8].

The mainstay of diagnosis of HS is dependent on clinical presentation, screening tests like extended complete blood counts, osmotic fragility or EMA test and plasma membrane electrophoresis[1,2]. Latest technological advances and introduction of modern automated haematological and biochemical analyzers have brought paradigm shift in laboratory analytical techniques with a consequent decrease undiagnosed or misdiagnosed cases of HS, which certainly bear significantly influence on short term and long-term prognostic consequences of the disease[1,2].

As far as clinical management of HS is concerned, splenectomy remains extremely effective in bringing down extravascular hemolysis with consequent furthering of lifespan of erythrocytes and is recommended step in clinical management of patients with severe HS[9,10]. If splenectomy is performed in a patient with symptomatic cholelithiasis, concomitant cholecystectomy should be done[9,10]. The time of splenectomy is mandated by clinical severity based on the degree of anemia, desirability blood transfusion and existence of cholelithiasis[5].

CONCLUSION

HS being rare among hemolytic anaemias worldwide, it often goes undiagnosed or misdiagnosed as it remains indolent in its milder form. Any evidence of hemolysis must be investigated thoroughly including summary exclusion of all differential diagnoses of various hemolytic anaemias inasmuch as even milder form of HS should be diagnosed in its early onset[5]. The diagnosis of HS should always be

considered as that of cholelithiasis and splenomegaly in adults as there may be a remarkable gap between its uneventful onset and ultimate diagnosis of the disease[5].

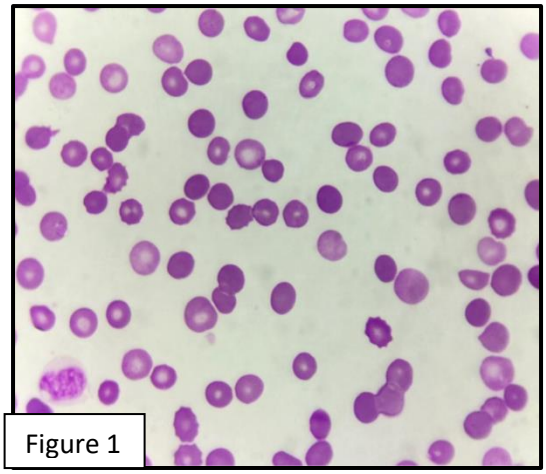

Figure1: Peripheral Smear showing Sherocytes.

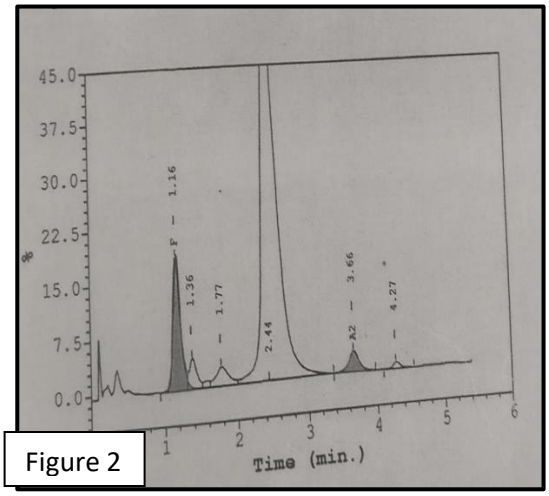

Figure2 : Hemoglobin electrophoresis report of the above mentioned patient showing Beta Thalessemia.

TABLE 1 : Blood indices of the patient during the course of hospital admission**.**

DATE	27/11	28/11	29/11	02/12	05/12	12/12	14/12	15/12	15/12	17/12	19/12
HB	4.3	8.9	7.3	7.0	6.4	8.4	12.6	11.1	11.9	10.3	11.3
PCV	13.7	35.7	27.3	21.8	18.4	24.9	35.7	34.5	35.3	30.4	3403
MCV	93.8	83.4	94.1	92.0	86.0	88.0	83.4	90.1	87.2	87.4	86.4
MCH	29.5	29.4	30.7	29.5	29.0	29.7	29.4	29.0	29.4	29.6	28.5
MCHC	31.4	35.3	32.6	32.1	34.8	33.7	35.3	32.2	33.7	33.9	32.9

TABLE 2 : Bilirubin values of the patient during the course of hospital admission.

DATE	05/12	12/12	19/12
TOTAL BILIRUBIN	3.74	2.79	0.78
DIRECT BILIRUBIN	0.77	0.63	0.23
INDIRECT BILIRUBIN	2.97	2.16	0.55

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