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HbH Disease: An Under Diagnosed Disease in Eastern India: A Case Report

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Abstract: ***Introduction: Alpha Thalassemia is the most common single gene disorder, an autosomal recessive inheritance caused by large deletions and point mutations in the α globin genes. resulting in the reduction or complete absence of α-globin chain synthesis. A 33-year-old male patient came to the OPD with chief complaints of fever, dyspepsia, vomiting and extreme weakness. On examination he had moderate to severe pallor and mild Icterus. Materials and methods: He was detected to have HbH disease and on supravital stain he had beta chain tetramer. He also had features of haemolysis as evidenced by doing routine haematological parameters. The patient was treated with 2 units of PRBC transfusion, antibiotics, antipyretics and Ursodeoxycholic acid and referred to surgeon for opinion of treatment of his obstructive jaundice due to pigment stones present in gall bladder. Conclusion: The prognosis of HbH disease varies greatly depending upon the degree of Hb affection, haemolytic anaemia and the complications arising due to it. Prompt diagnosis and treatment is required to avoid complications any be during premarital genetic counselling or prenatal diagnosis.***

Keywords: alpha thalassemia, haemolysis, anaemia

1. Introduction

Globally, Alpha Thalassemia is the most common single gene disorder, an autosomal recessive inheritance caused by large deletions and point mutations in the α globin genes. resulting in the reduction or complete absence of α-globin chain synthesis. The Indian subcontinent shows a range of prevalence from 1% to 18% in non-tribal populations to over 90% in some tribal groups. (1) Though mechanism is still not known, it has been evidenced that like the other hemoglobin related disorders, α-thalassemia is selected because carriers are better protected against the devastations of falciparum malaria.[1]

A healthy person has four functional α-globin genes (α2 and α1) linked on each chromosome 16 and is designated as αα/αα. Individuals may be affected with variable degree of alpha globin chain defect, either a non-deletional mutation or deletion of loci affecting one α-globin gene on a single chromosome, associated with mild anemia presenting as 'silent' α-thalassemia or α-thalassemia trait (when two genes are involved), may be compound heterozygotes (affecting both gene of same chromosome) or homozygotes (affecting one gene each of both the chromosome) expressing moderate to severe haemolytic anemia with associated ineffective erythropoiesis.(2,3) Such individuals are known to have HbH disease. The excess of β-like globin chains synthesized form non-functional β chain tetramers called HbH (β_4 tetramers) in adults and γ chain tetramers called Hb Bart's (γ_4 tetramers) in utero. The affected foetus develops the most severe form of α-thalassemia with no expression of α-genes called the Hb Bart's Hydrops Fetalis Syndrome.(4)

In this article, we are reporting a case of HBH disease in a 33 year old male patient which indicates the under diagnosis of such cases in the Indian Subcontinent though not rare.The diagnosis is important not only for the affected patients but also from the public health point of view as these hereditary disorders needs awareness, better education, diagnosis, treatment, and research to decrease the disease burden on the country's health.

2. The Case

A 33-year-old male patient came to the OPD of college of Medicine and Sagore Dutta Hospital with chief complaints of fever, dyspepsia, vomiting and extreme weakness. On examination he had moderate to severe pallor and mild Icterus. The patient had weight of 35 Kg and height 5 feet. Pulse rate was 116/m and BP was 90/70 mm of Hg. On examination he had palpable liver and tenderness in right hypochondrium and epigastrium. Abdominal ultrasonography confirmed the presence of acute cholecystitis associated with multiple gall bladder calculi with thickening of gall bladder wall.

He had no history of alcoholism. But he gave history of repeated chest infections and fever since his 12 years of age. 5 years ago, he was hospitalised in his nearby rural hospital for extreme weakness and jaundice, where he received 2 units of whole blood transfusion for anemia and treated as a case of haemolytic jaundice. He also had poor performances in school and he has been school drop-out since 11th standard.

This time the patient was treated with 2 units of PRBC transfusion, antibiotics, antipyretics and Ursodeoxycholic acid and referred to surgeon for opinion of treatment of his obstructive jaundice

3. Materials and Methods

On 2nd follow up as per our suggestion he underwent haemoglobin typing from our laboratory (BIORAD Variant II Beta thalassemia short Program Method: High Performance Liquid Chromatography). which confirmed the presence of HBH in his hemogram (haemoglobin Barts) (figure 1).

We also processed the sample with supravital stain (New methylene blue) for demonstration of the precipitated beta chain tetramers (HBH Inclusions) within the red blood cells. 2 volumes of EDTA –blood was mixed with 1 % New methylene blue stain and incubated for 1 hour at 37®C. After incubation, the cells are resuspended and a thin blood smear is spread over glass slide. The smear is dried and examined under the oil immersion objective. The inclusion bodies appear as multiple greenish blue spherical dots on the RBC, like pitted pattern of golf ball. They can be readily distinguished from reticulocytes, which appear as darker staining, irregular reticulofilamentous material or infrequent fine dots. [5]

The patient was also evaluated for the routine haematological and biochemical parameters. Bone marrow examination were suggested but refused by the family members for being an invasive procedure

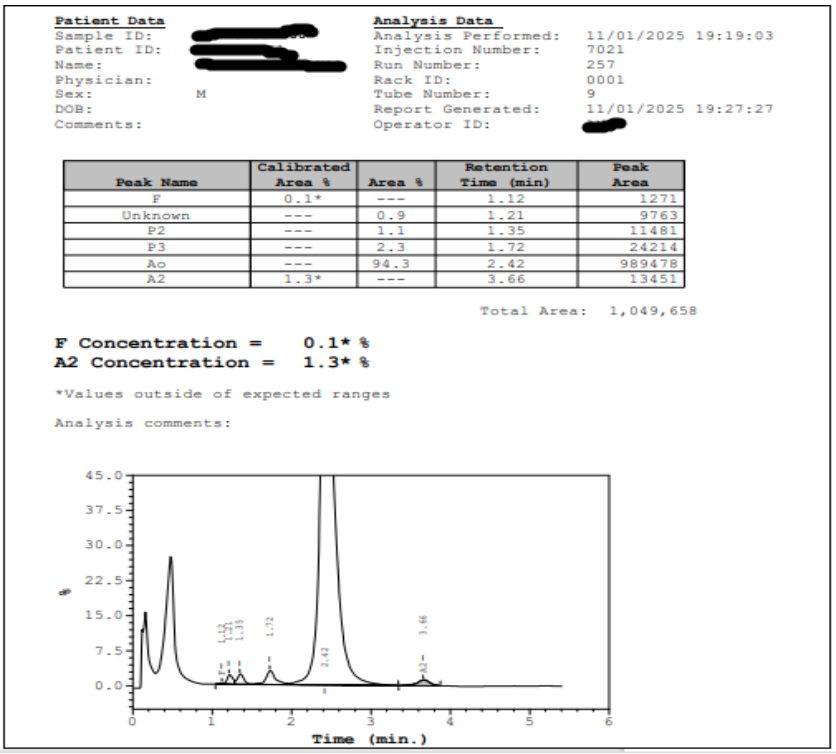

Figure 1: Haemoglobin Typing (HPLC)

Table 1: Laboratory Parameters

Parameter	Value	Biological Reference Interval	Units
Hemoglobin	7.6	13-17	g/dl
RBC	4.85	4.5- 5.5	* 10^6/µl
WBC	3.57	4-10	*10^3/µl
PCV	36.3	40-50	%
MCV	74.9	83-101	fl
MCH	21.6	27-32	pg
Peripheral blood picture	Anisocytosis, fragmented RBC, tear drop cells		
RDW	16.9	11.6-14	%
Iron	73	30-160	µg/dl
TIBC	268	250-425	µg/dl
Ferritin	89	22-322	ng/ml
Bilirubin (Total)	3.8	0.3-1.2	mg/dl
Bilirubin (Direct)	1.9	0.1 to 0.3	mg/dl
ALT	23.6	7-56	U/L
AST	18.4	8-33	U/L
ALP	190.7	44-147	IU/L
Total Protein	5.6	6-8.3	g/dl
Albumin	3.9	3.5-5.5	g/dl
Amylase	32.9	30-110	U/L
Lipase	41.2	0-160	U/L
TSH	4.1	0.4-4	mIU/L
fT4	1.6	0.8-1.9	Ng/dl

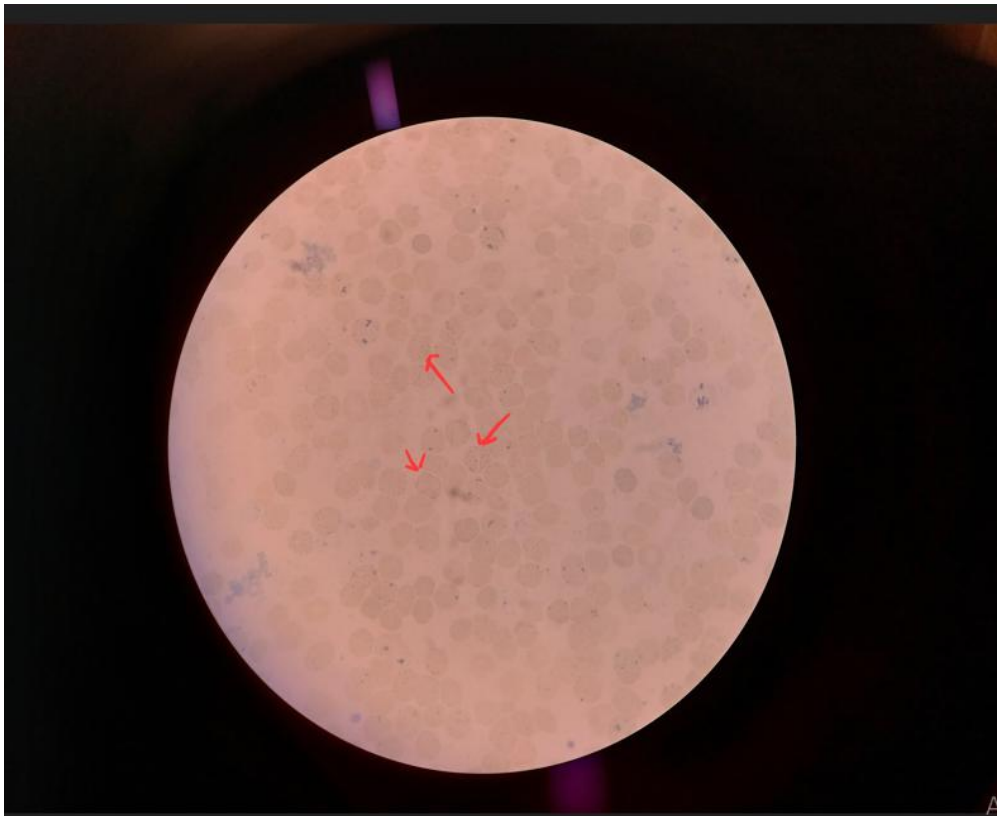

Figure 2: Supravital stained peripheral blood smear showing numerous Haemoglobin H inclusions note: the golf ball –like appearance of the red blood cells.

4. Discussion

Hemoglobin H is formed when only one normal alpha gene has been inherited. This causes significantly impaired alpha globin production. In the neonatal period, this will cause an excess of gamma, and in adults, excess of beta-globin chains. Free alpha chains are insoluble. Both gamma and beta chains are soluble and they make homotetramers. Hemoglobin H is made of four beta chains, and HbBarts is made of four gamma chains. They are unstable and easily precipitate within the cell. HbH in adults can make up to 40% of circulating hemoglobin in affected individuals. This hemoglobin is more susceptible to oxidant injury and has poor oxygen-carrying capacity. Its affinity is 10 times more than HbA. It has an abnormal oxyhemoglobin dissociation curve. This means that it can bind to oxygen but does not deliver it to tissues normally.[6]

Hemoglobin H can cause both chronic hypochromic microcytic anemia and hemolytic anemia, which can worsen in periods of oxidant stress. This can be effectively broken down as ineffective erythropoiesis and increased hemolysis. The microcytic hypochromic anemia can occur due to impaired hemoglobin production due to decreased alpha chain synthesis and hyperhydration of the cell. Though the cause of the hyperhydration in alpha thalassemia is not clear it may be due to the premature closure of K-Cl cotransporter, which may prevent the usual loss of K-Cl and water that is part of the red blood cell remodelling process.[7]

Hemoglobin H cannot servive in the circulation for a long time, this may be due to two main factors: abnormal red blood cell membrane with increased rigidity and increased inclusion bodies. [7]

The peripheral blood film in HbH disease shows hypochromia and microcytosis with inclusion bodies. Inclusion bodies are better visualized with a supravital dye such as methyl violet or brilliant cresyl blue. In the bone marrow examination, there may be erythroid hyperplasia with poorly hemoglobinized erythroblasts carrying inclusion bodies. Hemoglobin electrophoretic or chromatographic techniques can demonstrate HbH. DNA-based genotyping can also be done to diagnose more precisely.[8]

The present case also shows the features of jaundice and haemolytic anemia. The Hb typing showed the HbH pattern. The supravital staining method also confirmed the same. The liver enzymes are within normal limit which excludes any possibility of hepatitis or liver injury. The presence of pigment stone may be the due to excess hemolysis and bilirubin formation. The patients recovered with the conservative management and after 2 months he underwent laparoscopic cholecystectomy.

5. Conclusion

The prognosis of HbH disease varies greatly depending upon the degree of Hb affection, haemolytic anemia and the complications arising due to it. Prompt diagnosis and treatment is required to avoid complications any be during premarital genetic counselling or prenatal diagnosis

6. Limitation

Patient and his family (parents and siblings) were suggested to undergo haemoglobin typing for screening and DNA analysis. Post operative gall bladder calculi chemical nature

(? pigment stone) analysis by Fourier Transform Infrared (FTIR) spectroscopy was proposed. However, due to financial constraints these could not be executed.

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