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Hereditary Elliptocytosis- A Case Report

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Abstract
Hereditary elliptocytosis is a rare genetically determined erythrocytic disorder with elliptical red cells on peripheral blood smear. We present a case of a 12-year-old male who presented with a history of easy fatigability accompanied by breathlessness for 6 months and fever on and off for 5 days. On examination, he had severe pallor with mild icterus, mild hepatomegaly and moderate splenomegaly. Hematological investigation showed severe anemia with Hemoglobin of 3.9g/dl. Peripheral smear revealed numerous elliptocytes. Further investigations pointed towards a final diagnosis of hereditary elliptocytosis.
Hereditary elliptocytosis is mostly clinically silent, sometimes presenting with hemolysis. The most prominent peripheral blood finding is the presence of elliptocytes which should not be missed as it plays an important role in the diagnosis. The mostly clinically silent nature and the numerous differential diagnosis of elliptocytes makes it diagnostically challenging.

Keywords: Hereditary elliptocytosis, Elliptocytes, Erythrocyte membrane, Anemia, Hemolysis

Introduction
The frequency of hereditary elliptocytosis (HE) is 1 in 3,000 to 5,000 in United States. [1] Worldwide incidence among different ethnic/racial groups is varied with incidence as high as 1% in some parts of Central Africa. [2] Although no such data is available for Indian population, it is not rare. [3,4]. Most HEs are clinically silent (90%) and so discovered incidentally; while some presents with hemolytic disease. [5] Given the high incidence of this entity in other populations and its clinically silent nature, this finding is probably often missed or misinterpreted in the routine laboratory.

Case report: A 12-year-old male presented with a history of easy fatigability accompanied by breathlessness on exertion for 6 months and fever for 5 days. He gave a past history of 2 blood transfusions. His 21 years old sister had history of anemia with icterus. His father had expired after an episode of severe jaundice around 10 years back.
On examination, he was poorly built, had severe pallor with mild icterus, mild hepatomegaly and moderate splenomegaly. There was no evidence of clubbing, edema or lymphadenopathy.
His Complete Blood Count showed Haemoglobin of 3.9g/dl, Mean Corpuscular Volume 94.7 fl, Mean Corpuscular Haemoglobin 28.9 pg, Mean Corpuscular Haemoglobin Concentration 30.5 g/dl, Total Leukocyte count 8,300 cells/cu.mm and Platelet Count 2.3lakhs/cu.mm. Corrected Reticulocyte count was raised to 10%. Peripheral smear examination (PS) revealed moderate anisopoikilocytosis with about 90% elliptocytes, few microelliptocytes, few tear drop cells and reticulocytosis. [Fig.I & II] Total leukocyte count was in the normal range with normal morphology of WBCs and platelets. Sickling test was negative. Osmotic fragility test was normal with fresh red cells, but abnormal (increased) with red cells incubated for 24 hours at 37 degree Celsius. Liver function test showed increased levels of both conjugated and unconjugated bilirubin with normal AST and ALT levels and mild hypoproteinemia. Ultrasonography showed moderate splenomegaly.
Peripheral smear of sister also showed >50% elliptocytes.
In view of family history of anemia, past history of blood transfusions and more than 90% elliptocytes on PS, a diagnosis of hereditary elliptocytosis (hemolytic variant) was made and ancillary tests advised.

Discussion: Hereditary Elliptocytosis Syndromes are a family of genetically determined erythrocyte disorders characterized by elliptical red cells on PS. Elliptocytosis was first described by Dresbach in the year 1904 and was recognized as a hereditary condition in 1932 by Hunter. HE is inherited as an autosomal dominant trait except for hemolytic HE and HPP. Both sexes are equally affected.

HE is usually discovered as an incidental finding during blood smear examination in which a percentage of red blood cells are elliptical. The most consistent and characteristic laboratory findings in all variants of HE is the presence of more than 25 % elliptocytes on PS and usually more than 60%. [6]

It is caused due to disruption of horizontal protein-protein interaction i.e. defect in self association of αß spectrin heterodimer to form tetramer (most common) and defect in Junctional complex protein–protein interaction (Protein4.1R,GlycophorinC). This membrane instability leads to altered membrane deformability and mechanical properties leading to elliptocytosis. [1, 7, 8] Approximately 65% of cases of hereditary elliptocytosis are the result of mutations of alpha spectrin, 30% are the result of mutations of beta spectrin, and 5% are the result of mutations of protein 4.1. [9]

Normal RBCs can regain their discoid shape because of their elastic recoil after they pass through the microcirculation, the RBC in HE fail to regain their normal biconcave shape. This failure eventually produces the fixed characteristic morphology of elliptocytes with a decreased surface to volume ratio. These elliptocytes are less deformable and are eventually trapped and removed by the spleen.

Hereditary Elliptocytosis syndromes are classified into several groups; common hereditary elliptocytosis (HE), hemolytic hereditary elliptocytosis, hereditary pyropiokilocytosis (HPP), spherocytic hereditary elliptocytosis and South East Asian Ovalocytosis (SAO). They are characterized by clinical, biochemical and genetic heterogeneity.

There are five main forms of HE.

A) Common HE:

This variant is typically discovered incidentally since it is asymptomatic except during acute or chronic illness. PS shows 15-100% elliptocytes. In infants it presents as infantile pyropoikilocytosis which presents with moderate to severe hemolytic anemia with hyperbilirubinemia and marked red cell fragmentation.

B) Hemolytic HE:

This variant shows variable severity of chronic hemolytic anemia with splenomegaly. On PS, poikilocytosis, elliptocytosis, microelliptocytosis and RBC fragmentation are seen. More severe hemolytic anemia is seen during infections.

C) Hereditary pyropoikilocytosis:

This variant presents in infancy or early childhood with moderate to severe hemolytic anemia, requiring intermittent transfusion, overlapping with severe hemolytic HE. Splenomegaly and growth retardation are present. PS shows extreme poikilocytosis, elliptocytosis, microspherocytosis, microelliptocytosis, membrane budding and cell fragments. RBCs show thermal instability at 46ºC.

D) Spherocyticovalocytosis:

Two population of cells on seen on PS i.e. elliptocyte like and microspherocytes. These patients have mild anemia with predisposition to aplastic crisis.

E) Southeast Asian ovalocytosis:

PS shows plump rounded elliptocytes, many having one or more transverse ridges. These patients are usually asymptomatic although they maybe symptomatic in neonates.

Pseudoelliptocytosis is a common artefact of PS preparation. This is ruled out since in pseudoelliptocytosis the blood cells appear stretched and lined up in parallel; this finding is in contrast to true elliptocytosis in which the cells are oriented in different directions. [10]

Differential diagnosis includes megaloblastic anemia, iron deficiency anemia, leukemia, myelofibrosis, myelodysplastic syndromes, myelophthisic anemias, polycythemia, sickle cell disease, and thalassemia and pyruvate kinase deficiency. These disorders show elliptocytes in variable percentages but rarely cross 60%. Therefore the older criteria based on percentage of elliptocytes is not applicable. Positive family history is the most reliable differentiation of HIM. [7]

Biochemical studies for membrane protein quality and quantity gives definite diagnosis. [2] Other studies include functional studies for spectrin self-association, triptic mapping and genetic studies. [1]

Conclusion

Diagnosis of HE is challenging because it is mostly clinically silent and differentials for elliptocytes are numerous. The presence of elliptocytes on PS should not be missed as it is important for diagnosis. Family studies help in ruling out other differentials which can mimic this entity.

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Figures

1. FIG I Peripheral Smear, Wright Stain 400X showing moderate anisopoikilocytosis, numerous elliptocytes, few microelliptocytes and reticulocytosis. Two lymphocytes in the background are also seen.
2. FIG II Peripheral Smear, Wright stain 1000X. Showing moderate anisopoikilocytosis, numerous elliptocytes and few microelliptocytes.