

## CASE REPORT

# Hereditary Elliptocytosis

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## ABSTRACT

Hereditary elliptocytosis (HE) is a group of disorders characterized by the presence of elliptical-shaped erythrocytes on peripheral blood smear. Hereditary elliptocytosis and its related disorders are characterized by clinical, biochemical, and genetic heterogeneity. Manifestations range from the asymptomatic carrier state to severe, transfusion dependent hemolytic anemia. Abnormalities of various membrane protein defects contribute to mechanical defects of the erythrocyte membrane skeleton. We present a rare case of HE, an incidental finding without any clinical symptoms related to it. We also discuss on pathophysiology and being.

**Keywords:** Elliptocytes, Erythrocyte, Hemolysis.

**How to cite this article:** Sharmila PS, Kannupriya, Paul MF. Hereditary Elliptocytosis. J Med Sci 2015;1(2):41-43.

**Source of support:** Nil

**Conflict of interest:** None

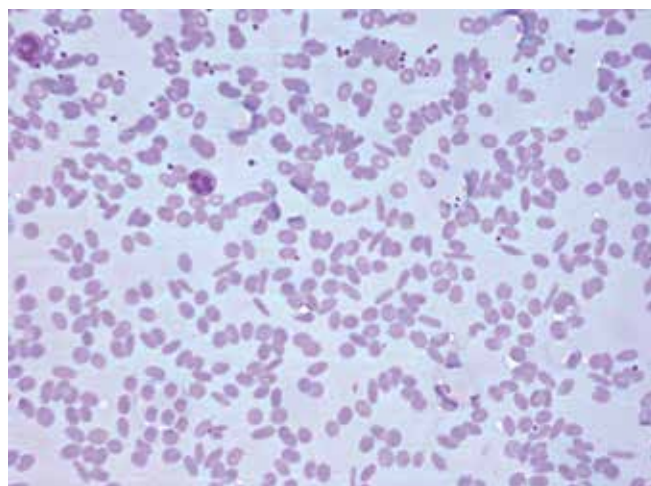
## INTRODUCTION

Hereditary elliptocytosis (HE) and its variants are congenital hemolytic disorders in which erythrocytes are either elongated into a cigar or oval-shaped or are poikilocytic and bizarrely-shaped.<sup>1</sup> The presence of at least more than 25% of cells which have an elliptocyte morphology has been suggested as a criterion to diagnose HE.<sup>2</sup> However, the prevalence of elliptocyte cells in the peripheral blood smear can vary from 0 to 100. The frequency of this disorder ranges from 1/5000 to 1/10,000 population among Caucasians. Worldwide, the incidence is estimated to be 1/2000 to 4000 individuals.<sup>3</sup> It is more common in regions where malaria is endemic; the prevalence in West Africa approaches 6/1000.<sup>3</sup> The true incidence is unknown because the clinical severity of HE is heterogeneous, and many patients are asymptomatic. The incidence of an elliptocytosis variant known as Southeast Asian ovalocytosis, ranges from 5 to 25% in Melanesia, Philippines, Indonesia, and Southern

Thailand.<sup>4</sup> Inheritance of HE is autosomal dominant. However, *de novo* mutations have been reported in rare cases.

## CASE REPORT

A 72 years old male presented to our hospital with history of abdominal pain and loss of appetite for 1 week. There was no significant past or family history. He was a non-alcoholic, vegetarian. No history of any drug therapy. On clinical examination, patient had tenderness at renal, angle. Ultrasonography (USG) examination of abdomen and pelvis revealed right-sided mild hydronephrosis and a small calculus in lower one-third of right ureter. Thus with these clinical findings, the diagnosis of right hydroureteronephrosis with ureteric calculus was made and patient underwent for lithotripsy for ureteric stone. Laboratory investigations included complete hemogram, renal function test and liver function test, preoperatively and postoperatively. Which were within normal range except hematological findings. Peripheral smear showed 40% elliptocytes along with occasional tear drop cells (Figs 1 and 2). No polychromatophilic or nucleated erythrocyte or red cell inclusions were seen. Osmotic fragility test was done to rule out spherocytosis. Indirect and direct Coombs' test was also done to rule out autoimmune hemolysis. Postoperatively, patient made uneventful recovery and discharged home. However as peripheral smear showed 40% elliptocytes, a diagnosis of asymptomatic HE was made since HE is an inherited

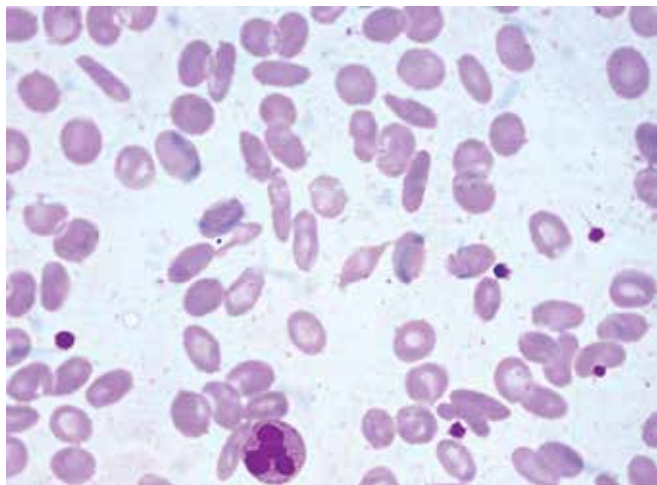


**Fig. 1:** Photomicrograph of HE shows elliptocytes (Giemsa stain: 40x)

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**Fig. 2:** Photomicrograph of HE shows elliptocytes (Giemsa stain: 100x)

disorders, the patients offspring are also counseled and examined, their peripheral smear examination showed up to 15% elliptocytes.

### PATHOPHYSIOLOGY

The primary defect in HE lies in the protein scaffolding that constitutes the membrane skeleton of red blood cells (RBCs). The quantity of spectrin, the major cytoskeletal protein in the RBC membrane from individuals with HE is normal, but it is structurally abnormal. More than 90% of the spectrin derived from normal RBCs exists in a tetrameric form or as a combination of higher order oligomers. In contrast, the major portion of spectrin molecules extracted from RBCs from individuals with HE exists as dimers. The defect in RBC membrane stability observed in elliptocytes from these individuals is due to the failure of proper spectrin dimer-tetramer association.<sup>4</sup> There are four molecular defects that can cause this, each associated with an abnormality or defect in spectrin or proteins required for proper association of spectrin molecules: (1) abnormalities in the  $\alpha$ -chain of spectrin, (2) abnormalities in the  $\beta$ -chain of spectrin, (3) a defective protein 4.1, and (4) a defective protein.<sup>3</sup>

Abnormalities in the  $\alpha$ -chain of spectrin occur in 25% to 30% of cases of HE, and several such abnormalities have been identified. In such cases, normal and abnormal spectrins are present in approximately equal amounts in tetrameric and dimeric forms respectively. Variant spectrins are designated by a superscript identifier that indicates the abnormal domain I of the alpha chain, a region at the head of the spectrin molecule involved in spectrin dimer-dimer interaction. Other  $\alpha$ -chain spectrin variants seen in RBCs from individuals with HE including Sp $\alpha$ 1/78, Sp $\alpha$ 1/65, Sp $\alpha$ 1/61, Sp $\alpha$ 1/46 and Sp $\alpha$ 1/43.

Two truncated variants of the  $\beta$ -chain of spectrin (Sp $\beta$  220/216 and Sp $\beta$  220/214) have been described

which demonstrate defective dimer self-association. Both of the spectrin variants fail to undergo enzymatic phosphorylation. Moreover, the structurally altered  $\beta$ -chain in these spectrin variants is also responsible for defective binding of spectrin to ankyrin, another important component of the RBC cytoskeleton. A defective protein 4.1 is seen in one-third of patients with HE. This defect is seen most commonly in inhabitants of southern France and North Africa. Last, fewer patients exhibit an abnormal protein 3 molecule compared to the other three types of cytoskeletal protein abnormalities discussed above the mutation of a gene on the X chromosome can give rise to elliptocytosis associated with Alport's syndrome.

The mortality and morbidity in these disorders depend on the frequency and degree of hemolytic anemia. The clinical phenotype ranges from asymptomatic carrier status to severe transfusion-dependent, and even fatal, hemolytic anemia. Individuals with chronic hemolysis may have complications, such as jaundice, splenomegaly, and early gallbladder disease. Mortality is rare. Most patients have normal physical examination findings, but should be evaluated for signs of cardiovascular compromise. Patients undergoing hemolysis may have pallor, jaundice or splenomegaly. In rare cases, transient pure red blood cell aplasia can be the initial clinical presentation.<sup>5</sup>

In addition to the hereditary causes of elliptocytosis, it is important to consider the nonhereditary or acquired causes of elliptocytosis.<sup>2</sup> There are a multitude of acquired hematological disorders which can lead to elliptocyte forms in the peripheral blood smear. These include iron deficiency anemia, thalassemia, megaloblastic anemia, myelofibrosis, myelophthisic anemia, myelodysplastic syndrome and pyruvate kinase deficiency. These causes must be ruled out before investigating hereditary causes of elliptocytosis.

### DISCUSSION

Elliptocytosis was first described by Dresbach in the year 1904 and first recognized as a hereditary condition in the year 1932 by Hunter. The incidence of HE is hard to determine because more than 90% of the people with elliptocytosis are asymptomatic.

Most patients are clinically asymptomatic, and the diagnosis is usually made incidentally when a blood smear is examined. Asymptomatic patients are heterozygous for the disease and are classified as having mild or common HE. Approximately, 10% of patients have moderate to severe anemia, with intermittent episodes of acute hemolysis with jaundice and splenomegaly. There are three main forms of HE as follows:<sup>1</sup>

- *Common hereditary elliptocytosis*: Common HE is rarely symptomatic in the neonatal period. Severe hemolytic anemia with poikilocytosis and jaundice almost never occur. Typically, elliptocytes do not appear in the blood until the patient is aged 4 to 6 months. Even when neonatal hemolysis is severe, the symptoms usually resolve by the time the patient is aged 6 to 12 months, and the anemia improves. In children and adults, common HE is usually asymptomatic or associated with mild hemolytic anemia, although moderate or even severe hemolysis occasionally occurs. The degree of hemolysis does not correlate with the percentage of elliptocytes seen in the blood. The severity of hemolysis in common HE varies not only among different kindreds but also within given families.
- *Spherocytic elliptocytosis*: This form of HE is seen mainly in Europeans. The peripheral blood smear shows an abundance of spherocytes admixed with elliptocytes. The genetic defect is not well-characterized in these cases.<sup>1</sup>
- *Southeast Asian ovalocytosis*: Southeast Asian ovalocytosis (stomatocytic elliptocytosis) is a benign disorder in which erythrocytes have a broad oval-shaped. Stomatocytes are occasionally present. However, the disorder appears to decrease the risk of malaria parasitemia and the clinical severity of malaria. This condition occurs in as many as 15% of the indigenous population of Malaysia and Papua, New Guinea.

## LABORATORY INVESTIGATIONS AND DIAGNOSIS<sup>1</sup>

The primary approach to diagnosis is based on clinical suspicion. As mentioned before, cases are usually discovered during a routine peripheral blood examination for other causes. These disorders are suspected in patients with unexplained hemolysis, particularly if splenomegaly or a family history are present, or abnormal RBC indices are identified. Because RBCs are spheroidal and the mean corpuscular volume (MCV) is normal, the mean corpuscular diameter is below normal, and RBCs resemble microspherocytes. Mean corpuscular hemoglobin concentration (MCHC) is increased. Reticulocytosis of 15 to 30% and leukocytosis are common.

If these disorders are suspected, the RBC osmotic fragility test (which mixes RBCs with varying concentrations of saline) and the RBC autohemolysis test

(measuring the amount of spontaneous hemolysis after 48 hours of sterile incubation) can be performed. In addition, direct antiglobulin (Coombs') test may be done to rule out spherocytosis due to autoimmune hemolytic anemia. Red blood cell fragility is characteristically increased but, in mild cases, it may be normal. Red blood cell autohemolysis is increased and can be corrected by the addition of glucose. Demonstration of the molecular defect in the spectrin molecule confirms the diagnosis; however, the methods (i.e. isolation, enzymatic digestion, and electrophoretic analysis) used for this purpose are not routinely available in most clinical laboratories.<sup>2</sup>

Genetic counseling should be offered to parents with this condition to explain the risks regarding the transmission of the condition.<sup>4</sup>

## CONCLUSION

Hereditary elliptocytosis is an asymptomatic condition with rare presentation as hemolytic anemia. Most patients are clinically asymptomatic, and the diagnosis is usually made incidentally when a blood smear is examined. Asymptomatic patients are heterozygous for the disease and are classified as having mild or common HE. Approximately, 10% of patients have moderate to severe anemia, with intermittent episodes of acute hemolysis with jaundice and splenomegaly.

Our patient was diagnosed as a rare case of HE, an incidental finding without any clinical symptoms related to it.

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