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The Prevalence of Hereditary Elliptocytosis in Iraq-Kerbala

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Abstract

Background: Hereditary elliptocytosis is a well-known red cell membrane disorder that is usually asymptomatic with difficulty to determine the actual incidence. Aim: This work aims to assess the prevalence of hereditary elliptocytosis in Iraq-Kerbala. Materials and methods: In this cross-sectional prospective study 10000 persons were examined by hematologist during the period from January 2014 to March 2022 in a specialized legal private laboratory for hematological investigations in Iraq/Kerbala through doing full blood count and blood film. Uncorrected reticulocyte count, serum total bilirubin and indirect bilirubin were done only for cases that are detected to have hereditary elliptocytosis with daily record for the presence or absence of hereditary elliptocytosis. Cases of hereditary elliptocytosis are defined when there are elliptocytes or ovalocytes that constitute 25%-100% of total red cells in stained blood film when other causes of elliptocytosis are excluded. All visitors (males and females, any age) from Iraq-Kerbala who were coming for that private laboratory during the period of study who need complete blood count and blood film for general checking or referred from medical clinics or hospitals for diagnosis or follow up of certain disease were selected for the study.Results: Three cases out of 10000 are discovered to have hereditary elliptocytosis (3/10000). 1/3 cases were discovered incidentally during general checking while the other 2/3 cases had disorders (presented for treatment of another diseases, namely chronic renal failure and urinary tract infection). 1/3 of cases had Anemia while the other 2/3 cases had normal Hb levels. 2/3 of cases (66.66%) had slightly raised uncorrected reticulocyte count, slightly raised serum total bilirubin and serum indirect bilirubin, reflecting the presence of mild hemolysis. Conclusion: The prevalence of hereditary elliptocytosis in Iraq-Kerbala is 3.0/10000 of population.

Keywords

Hereditary Elliptocytosis, Red Cell Membrane Disorders.

Hereditary elliptocytosis (HE) is an autosomal dominant red cell membrane disorder that is characterized by the presence of elliptical or oval red cells in the peripheral blood film[1] with a frequency ranging from 1/5000 to 1/10000 of Caucasian population while the worldwide incidence is estimated at 1/2000 to 4000 individuals, being more common in regions endemic in malaria probably because elliptocytes exert some resistance to malaria. The prevalence in West Africa approaches 6 per 1000 individuals[2]. The actual incidence is unknown because most patients are asymptomatic[3]. No studies were found in Iraq to determine the prevalence or incidence of HE.

The major defect in HE is weakness or fragility of the red cell cytoskeleton resulting from horizontal connections of membrane skeleton, mainly spectrin dimer-dimer interactions and spectrin-actin-protein 4.1 at the junctional complex[4]. Hereditary elliptocytosis is an asymptomatic condition with rare presentation as hemolytic anemia, hence the diagnosis is usually made incidentally when a blood smear is examined[5].

The hallmark of HE is the presence of elliptocytes in the peripheral blood film. These elliptocytes may number from few to 100%; the degree of hemolysis does not correlate with the number of peripheral blood film elliptocytes. The presence of at least 25% of elliptocytes or ovalocytes in the peripheral blood film suggests hereditary elliptocytosis[6].

The osmotic fragility is generally normal or slightly reduced. Other laboratory findings in HE are similar to those found in other hemolytic anemias and usually reflect slightly reduced red cell survival with a rare incidence of anemia[7]

Southeast Asian ovalocytosis (SAO) is a dominantly inherited variant of HE in the aboriginal peoples from Papua New Guinea, Indonesia, Malaysia, the Philippines and southern Thailand, in areas where malaria is endemic, with prevalence varying between 5% and 25%[8]. Rounded rather than elongated elliptocytes, are found on peripheral blood smear. Most SAO patients are asymptomatic, although a few experiences mild hemolysis including neonatal hemolytic anemia that require phototherapy[9].

Morphologically, elliptocytes are red blood cells that are cigar or pencil shaped with parallel sides and an area of pallor while ovalocytes are oval or egg shaped red cells[10,11].

Hereditary pyropoikilocytosis (HPP) is a rare cause of severe hemolytic anemia characterized by erythrocyte morphology resembling that in patients after a thermal burn. Many HPP patients experience severe hemolytic anemia in childhood that evolves into typical HE later in life[12].

Recently, HPP is described as a severe form of HE that both of them might present in one family. In HPP, both spectrin deficiency plus relative deficiency of spectrin tetramers are inherited due to co-inheritance of low expression allele for alpha spectrin, compound heterozygosity or homozygosity for two HE alleles or in a number of families mutated protein 4.1 gene resulting in failure to produce protein, the heterozygous states produce HE without hemolysis while the homozygous states produce severe hemolysis with extensive red cell fragmentation[13].

Materials and methods

A prospective cross sectional descriptive study was designed for a total number of 10000 individuals during the period from January 2014 to March 2022 in a specialized legal private laboratory for hematological investigations in Iraq/Kerbala through doing complete blood count (CBC) and blood film for all laboratory visitors including healthy individuals who need to do such investigations for general checking including pre-marriage checking and individuals who were referred from medical clinics and hospitals to do such investigations for diagnosis or follow up of certain diseases regardless age and gender, but the area of living of Individuals was necessarily Iraq-Kerbala. A written signed consent was taken from every individual or from his/her parents (for individuals less than 18 years old). Definition of cases of hereditary elliptocytosis includes the presence of 25% or more of elliptocytes or ovalocytes under the microscope in the absence of other causes of elliptocytosis (iron deficiency anemia, megaloblastic anemia and thalassemia). Exclusion criteria include individuals who were investigated by CBC and blood film before and already included in the study to prevent double involvement of the same individual, individuals who were living outside Iraq or outside Kerbala city and the presence of less than 25% of elliptocytes or ovalocytes in the stained peripheral blood film. Initial medical history includes the age, gender, mobile number and area of living. Extended medical history (through mobile call) for the cases of hereditary elliptocytosis includes history of consanguinity of their parents, previous history of yellowish discoloration of skin or sclera, previous history of anemia or blood transfusion and previous history of diagnosis of hereditary elliptocytosis. Method was done by doing complete blood count (CBC) by automated machine (Abbott cell-dyn, Ruby) and blood film using leishman stain with examination under the microscope by hematologist. Uncorrected reticulocyte count (automated count by Abbott cell-dyn, Ruby by using reticulocyte reagent 3.7 ml ready for use tubes), serum total bilirubin and indirect bilirubin (by using Architect c4000 Abbott analyzer, the last Total bilirubin and direct bilirubin kits were G96045R01 and G95978R02, respectively, manufactured for Abbott laboratories, Product of Canada), serum iron, total iron

binding capacity (TIBC), and serum ferritin (by using Architect c4000 Abbott analyzer) and Hb electrophoresis (by D10, Bio-Rad) were done only for cases that were diagnosed to have hereditary elliptocytosis. Anemia was defined as Hb level of less than 11.5 g/dl for adult females and less than 12.5 g/dl for adult males. Normal uncorrected reticulocyte count was defined as 0.2-2%. The normal serum total bilirubin and serum indirect bilirubin were 0.1-1.2 mg/dl and 0.3-0.8 mg/dl, respectively. There was a daily record for the presence or absence of hereditary elliptocytosis. The study is descriptive and analyzed by calculating the prevalence per 10000 individuals.

Results

Results of the study are shown in table 1 and 2. The total number of participants was 10000 individuals. Females were 6817/10000 (68.17%) while males were 3183/10000 (31.83%). Age ranges between 3 days and 80 years. Three cases out of 10000 are discovered to have hereditary elliptocytosis (3/10000). 2/3 of cases of hereditary elliptocytosis (66.66%) were females while 1/3 of cases (33.33%) was male. 2/3 of cases of hereditary elliptocytosis (66.66%) showed the presence of consanguinity between their parents while 1/3 of cases (33.33%) showed unrelated parents. Unfortunately, we could not do peripheral blood film for parents, brothers and sisters of cases of hereditary elliptocytosis because they were died, unable or refused to come for doing the test. 1/3 of cases showed previous investigations (previous evidence) for the presence of anemia without hemolysis while 2/3 of cases showed no previous history of anemia. No one of cases was treated previously by blood transfusion. No one was diagnosed previously to have HE (from medical history or previous investigations for the cases when available). No one of these 3 cases was having history of yellowish discoloration of skin or sclera since childhood.

All cases (100%) showed morphologically elongated, but not rounded elliptocytes in the peripheral blood film. 2/3 of cases (66.66%) showed a percentage of elliptocytes of 70% in blood film while 1/3 of cases (33.33%) showed a percentage of elliptocytes of 80%. One out of 3 cases was healthy female, aged 31 years presented for general checking while the other 2 out of 3 cases were referred from other clinics for diagnosis or follow up of diseases (48 years old male patient had chronic renal failure and 18 years old female patient had urinary tract infection). 1/3 of cases showed anemia (Hb: 9.2 g/dl) due to chronic renal failure (with medical reports of recent diagnosis of chronic renal failure with anemia, low MCV, low serum iron, low TIBC, high serum ferritin, high ESR and high CRP) while the other 2/3 of cases showed normal Hb levels (12.6 g/dl and 12.1 g/dl). 2/3 of cases showed high uncorrected reticulocyte count (2.6% and 2.8%) while 1/3 of cases (the case of chronic renal failure) showed normal reticulocyte count (1.8%). 2/3 of cases (66.66%) showed slightly raised serum total bilirubin and slightly raised serum indirect bilirubin. Results of serum total bilirubin and serum indirect bilirubin for cases were: (1.7 and 1.0 mg/dl), (1.9 and 1.1 mg/dl) and (0.9 and 0.4 mg/dl), respectively, reflecting the presence of mild hemolysis in 2/3 of cases. 2/3 of cases showed normal serum iron, normal TIBC and normal serum ferritin while 1/3 showed changes of chronic renal failure (low serum iron, low TIBC and high serum ferritin). 100% of cases showed normal Hb electrophoresis. Individuals who showed elliptocytes or ovalocytes of less than 25% with or without anemia were excluded from the study.

Table 1. Medical history of individuals who were diagnosed to have hereditary elliptocytosis (HE).

Number of HE per 10000	Previous history of anemia (previous CBC)	Previous history of blood transfusion	Previous history of diagnosis of HE	History of consanguinity of their parents
3	1/3, (33.33%)	0/3, (0.0%)	0/3, (0.0%)	2/3, (66.66%)

Table 2. Laboratory findings of individuals who were diagnosed to have hereditary elliptocytosis (HE).

Number of HE per 10000	Anemia at presentation	Reticulocytosis	High serum total bilirubin	High serum indirect bilirubin
3	1/3, (33.33%)	2/3, (66.66%)	2/3, (66.66%)	2/3, (66.66%)

Discussion

Results showed that three cases out of 10000 had hereditary elliptocytosis. The Prevalence of hereditary elliptocytosis is 3.0/10000 in Kerbala city-Iraq which is similar figure to that of United States in which the prevalence is 2.5-5 per 10000 and consistent with the overall worldwide incidence of HE which is estimated at 1/2000 to 4000 individuals[2]. The actual incidence is unknown because most patients are asymptomatic. No studies were found in Iraq to determine the prevalence or incidence of HE. Elliptocytes may number from few to 100%; the degree of hemolysis does not correlate with the number of peripheral blood film elliptocytes. In this study hereditary elliptocytosis is defined as the presence of 25% or more of elliptocytes or ovalocytes in the peripheral blood film[6]. All cases of HE showed a percentage of 70% or more of elliptocytes in blood smears (2/3 of cases (66.66%) showed a percentage of elliptocytes of 70% in blood film while 1/3 of cases (33.33%) showed a percentage of elliptocytes of 80%).

Such cases are likely to be heterozygous, but unfortunately we could not do peripheral blood film for parents and other family members (brothers and sisters) for cases with hereditary elliptocytosis because they were died or unable to come for doing the test. We expected that one parent for every case had hereditary elliptocytosis. Consanguinity of parents was present in 2/3 of cases; however, no case of hereditary pyropoikilocytosis was found among these three cases. All cases show morphologically elongated, but not rounded elliptocytes in the peripheral blood film, indicating that the subtype of hereditary elliptocytosis is the common hereditary elliptocytosis rather than the other two subtypes which include the spherocytic subtype that is common in European populations and show spherocytes and elliptocytes in the peripheral blood film and the South east Asian ovalocytosis subtype that is common in South east Asia that shows morphologically rounded, but not elongated elliptocyte in the peripheral blood film.

1/3 cases showed anemia without hemolysis, but previous CBC showed anemia due to chronic renal failure while the other 2/3 cases showed normal Hb levels. Moreover, 2/3 of case showed mild hemolysis (Compensated hemolysis, reflected by high serum total and indirect bilirubin) that is consistent with other areas throughout the world that describe HE as asymptomatic disorder[5]. 2/3 of cases showed reticulocytosis as another indicator for hemolysis without anemia while 1/3 of cases showed upper normal value of reticulocyte count (1.8%) which might reflect inability of the bone marrow to raise this count due to chronic renal failure. However, this patient had high serum total and indirect bilirubin as indicators for red cell hemolysis. In patients with chronic renal failure, many factors can participate for the development of anemia including low erythropoietin level, bone marrow suppression by inflammatory cytokines, mild hemolysis and other causes. So that additional factor for the development of anemia in patients with chronic renal failure will be the presence of coexisting hereditary hemolysis like hereditary elliptocytosis in which the body will be unable to compensate for red cell hemolysis.

Individuals who showed elliptocytes or ovalocytes of less than 25% of the total red cells in the peripheral blood film were excluded from the study. The presence of at least 25% of elliptocytes or ovalocytes in the peripheral blood film suggests[6], but not prove the presence of hereditary elliptocytosis. So that such cases need exclusion of other causes of elliptocytosis which include iron deficiency anemia, megaloblastic anemia and thalassemia. In this study, there was no case of acquired elliptocytosis that had 25% of elliptocytes or more. We recommended that CBC and blood film should be added throughout the world as simple investigations for checking before marriage of couples to prevent much more severe form of HE i.e HPP despite the fact that HPP is a rare disorder.

Conclusion

The prevalence of cases of hereditary elliptocytosis in Iraq-Karbala is 3.0 per 10000 of population.

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