Hereditary spherocytosis (HS) is the most frequent form of red blood cell membrane disorder and the most common cause of chronic hereditary hemolytic anemia. The etiology of the disease is a deficiency in the membrane proteins which results in instability of the cytoskeleton. The case is presented of a 32-year-old man who was admitted with pain in the right hypochondrium, jaundice and hyperpigmentation of the urine. HS due to protein-3 deficiency was diagnosed and the clinical syndrome at admission was attributed to bile duct obstruction. The laboratory methods which determine the diagnosis of HS are discussed and reference is made to the therapeutic management of the patients. The search for HS should not be omitted in the investigation of chronic hemolysis, because of the variety of clinical manifestations of the disease, which may remain asymptomatic and undetected even in old age.
Five days after admission, spontaneous improvement was observed; the jaundice and the abdominal pain improved progressively. Laboratory data showed total bilirubin 7 mg/dL, direct bilirubin 6 mg/dL. Ultrasound (US) of the abdomen demonstrated hepatomegaly (maximum diameter 19.1 cm), splenomegaly (maximum diameter 20.2 cm) and the gallbladder was full of gallstones and sludge, without dilatation of the biliary duct. Following these findings, the clinical signs and laboratory abnormalities were ascribed to a temporary obstruction of the bile duct. On discharge, the patient was vaccinated against S. pneumoniae, H. influenzae and N. meningitidis, and one month later he underwent cholecystectomy and splenectomy laparoscopically and was advised to take 1 mg folic acid per day.

The laboratory findings immediately before operation were: WBC 10×10^3 cells/μL, Hb 11.3 g/dL, Ht 30.7%, PLT 150×10^3/μL, total bilirubin 6.23 mg/dL, direct bilirubin 0.46 mg/dL, LDH 291 U/L, AST 22 IU/L, ALT 11 IU/L, ALP 63 IU/L, γGT 9 IU/L, total cholesterol 71 mg/dL, HDL 26 mg/dL, LDL 9 mg/dL. The peripheral blood smear showed spherocytes, microspherocytes, polychromasia and RET about 15%. After the operation, mild reactive thrombocytosis was observed. G6PD assay was repeated and was normal. He was monitored as an outpatient and clinical improvement was observed.

**DISCUSSION**

Hereditary spherocytosis comprises of a heterogeneous group of disorders with regard to clinical severity, protein defects and mode of inheritance. It is the commonest inherited red cell membrane disorder, although it is generally a rare disease worldwide. This disorder is associated with increased hemolysis, the degree of which depends on the interplay between an intact spleen and an intrinsic membrane protein defect. The abnormal morphology and the shorter lifespan of the red cells in hereditary spherocytosis are attributable to a deficiency or dysfunction of one of the constituents of the red cell cytoskeleton, the role of which is to maintain the shape, deformability and elasticity of the red cell. Hemolysis is primarily confined to the spleen and therefore is extravascular.

The abnormal red cell morphology, which results in shortened cell survival, is due to a deficiency of, or a dysfunction in, spectrin, ankyrin, band 3 and or protein 4.2. Spectrin deficiency is the most common defect. A variety of mutations have been noted in genes encoding these membrane proteins. The genes responsible are localized on chromosomes 1, 2, 8, 15 and 17 for membrane proteins. Most cases of hereditary spherocytosis are heterozygous because homozygous states are lethal. In pedigrees that have a dominant defect, affected family members tend to have similar degrees of hemolysis and clinical severity. Severe hemolytic anemia is often associated with a greater reduction of the affected membrane protein(s). There
is an apparent correlation between clinical and protein phenotypes. The clinical severity of HS varies from a symptom-free carrier state to severe hemolysis. Mild HS can be difficult to identify because individuals may have normal levels of hemoglobin and bilirubin. Although the diagnosis of HS is often made in childhood and young adulthood, it may be diagnosed at any age.

The peripheral blood smear shows numerous spherocytes. Larger bluish cells (polychromasia) also may be seen. The complete blood count (CBC) and reticulocyte count reveal a low hemoglobin concentration and elevated reticulocyte count. The MCHC is usually high, with levels greater than 35 g/dL. The MCV may be low, or high if there is substantial reticulocytosis. Hematology analysers using the principle of flow cytometry (i.e. dual angle laser light scattering method) produce a more accurate determination of red cell volume (MCV) and hemoglobin concentration (MCHC) than blood cell analysers using the principle of electrical aperture impedance. These automated red cell parameters can be used to predict or identify hereditary spherocytosis with a typical clinical presentation during the routine CBC without requiring additional laboratory tests (such as osmotic fragility or the EMA binding test) to confirm the diagnosis. The test of osmotic fragility can be useful in establishing the diagnosis of HS. A normal osmotic fragility result does not exclude the diagnosis of HS and may occur in 10–20% of cases of HS. The test may also be normal in the presence of iron deficiency, obstructive jaundice, and in the recovery phase from an aplastic crisis when the reticulocyte count is increased. Cell dehydration occurring in the spherocytes of a patient with HS can be one of the causes of normal osmotic fragility that results in non-splenectomized patients. A positive osmotic fragility result may also be obtained in patients with hereditary elliptocytosis (HE) and hemolysis. The cryohemolysis test, the osmotic gradient ektacytometry and the EMA binding test have a higher predictive value in the diagnosis of HS because there have been no reports of positive results in immune or non-membrane-associated disorders. Identification of a deficiency in a membrane protein associated with erythrocyte cytoskeleton confirms the diagnosis of HS. Quantification of membrane proteins by SDS-PAGE is, however, not necessary for the majority of cases because a definitive diagnosis can be made on the basis of red cell indices, the clinical/family history and a positive result from a screening test. Co-inheritance of other hematological disorders, such as beta thalassemia trait or sickle cell disease, can lead to confusion in the diagnosis. Iron, folate or vitamin B12 deficiencies can mask the laboratory features. Obstructive jaundice alters the lipid composition of the red cell membrane, masking the film appearances and reducing the hemolysis.

The patient presented had moderately severe hemolysis, as was evidenced by low hemoglobin, persistent reticulocytosis, jaundice, hepatosplenomegaly, hypocholesterolemia. Hereditary spherocytosis was suggested by the following findings: Hyperdense red cells, reticulocytosis and reticulocyte indices (MCSV-MCV) and increased osmotic fragility. The direct antiglobulin test was negative. The diagnosis was confirmed by partial reduction of band 3 protein (found by SDS-PAGE of red blood cell membrane proteins).

The molecular pathology of HS is heterogeneous and total absence of band 3 has been reported in few cases. Band 3 reductions can be detected in 10–20% of patients with the benign, dominantly inherited pattern. As a result, it may be diagnosed at an older age, even after the age of 50 years. Spectrin deficiency is more frequently diagnosed in childhood and band 3 deficiency in adulthood. The Hb is slightly lower, and spherocyte numbers and hemolysis markers higher in spectrin deficiency than in band 3 deficiency as well. In addition, splenomegaly and gallstones are more frequent in band 3 deficient patients whereas anemia, neonatal jaundice and transfusion requirement is more common in those with spectrin or ankyrin deficiency.

The complication of common jaundice, which was noted in this patient on admission, was ascribed to a temporary obstruction of bile duct. Hypocholesterolemia observed was ascribed to chronic anemia with increased erythropoietic activity. The exact etiology of hypocholesterolemia in these patients is not known and the data are insufficient, but it is thought to be due to increased cholesterol requirements of the proliferating erythroid cells.

The clinical diagnosis in a typical case of HS is usually straightforward and a family history is very important, found in nearly 75% of cases. A family study could not be carried out in this case since the patient's family resides in another country, but he denied a similar history in any member of the family. Thus, this case may be either recessively inherited, or sporadic as occurs in 25% of cases or a silent carrier state, as it has been suggested to occur in 1.4% of the population. It is important to ask for a family history of jaundice and or splenectomy, as families may not realize that the cause for such events involves their red blood cells.

HS in this case report was characterized as moderate and the patient underwent concurrent cholecystectomy
Η κληρονομική σφαιροκυττάρωση αποτελεί την πιο συχνή κληρονομική μορφή διαταραχής της ερυθροκυτταρικής μεμβράνης και το συχνότερο αίτιο χρόνιας κληρονομικής αιμολυτικής αναιμίας. Οφείλεται σε ελλείψεις πρωτεϊνών μεμβράνης που έχουν ως αποτέλεσμα την εμφάνιση αστάθειας του κυτταροσκελετού. Παρουσιάζεται ενδιαφέρον περιστατικό που αφορά σε ένα νεαρό άνδρα, ηλικίας 32 ετών, ο οποίος εισήχθη στην κλινική λόγω άλγους στο δεξιό υποχόνδριο, ίκτερο και υπέρχορωση των ούρων. Στον ασθενή τέθηκε η διάγνωση της κληρονομικής σφαιροκυττάρωσης από έλλειψη πρωτεΐνης 3, ενώ το κλινικό σύνδρομο της εισαγωγής αποδόθηκε σε αποφρακτικό επεισόδιο του χολεδόχου πόρου. Στο παρόν άρθρο συζητούνται οι εργαστηριακές μέθοδοι που καθορίζουν τη διάγνωση και γίνεται αναφορά στους θεραπευτικούς χειρισμούς των ασθενών με κληρονομική σφαιροκυττάρωση. Η αναζήτηση της κληρονομικής σφαιροκυττάρωσης δεν πρέπει να παραλείπεται στη διερεύνηση της χρόνιας αιμόλυσης, αφού λόγω της ποικιλίας των κλινικών εκδηλώσεων της νόσου μπορεί να παραμένει ασυμπτωματική και αδιάγνωστη, ακόμη και σε μεγάλες ηλικίες.

Λέξεις ευρετηρίου: Αιμολυτική αναιμία, Πρωτεΐνη 3, Σφαιροκυττάρωση, Υπερχολερυθριναιμία, Χολολιθίαση

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