CLINICAL VIGNETTE

Hereditary Spherocytosis – as a Cause of Hemolytic Anemia

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Case

A 26-year-old Asian male presented to Primary Care after a visit to the Emergency Department (ED) for nausea, vomiting, dizziness, and decreased hearing. He had been diagnosed in the ED with peripheral vertigo thought to be related to labyrinthitis. Labs drawn during his ED visit were remarkable for a total bilirubin of 9.2 mg/dL, with normal alkaline phosphatase, alanine transaminase (ALT), and aspartate transaminase (AST). The patient denied any significant health issues. His past medical history was significant for high indirect bilirubin dating back to his time in the military. He was told that this was 'normal'. His exam was significant for jaundice however he stated that his skin and eyes had always been yellow. Remote labs revealed prior total bilirubins of 5.6 and 8.6 mg/dL. Fractionation had shown the bilirubin to be almost entirely indirect bilirubin.

Additional tests were done at the time of his clinic visit. Repeat total bilirubin was 12.5 mg/dL, with a direct bilirubin of 0.4 mg/dL. Lactate dehydrogenase (LDH) was slightly elevated at 206 U/L and haptoglobin was low at < 6 mg/dL. Hemoglobin was normal at 14.0 g/dL, mean corpuscular hemoglobin concentration (MCHC) was elevated at 36.8, and reticulocyte count was elevated at 4.89%. Coombs test was negative and peripheral smear was unremarkable. Abdominal ultrasound revealed normal liver and spleen. The lab values were collectively suggestive of low grade hemolysis and the patient was referred to Hematology.

Family history obtained by Hematology revealed that the patient had a brother who had similar symptoms, for which he underwent splenectomy with resolution of symptoms. Osmotic fragility testing was ordered, which returned abnormal and he was diagnosed with hereditary spherocytosis (HS). He underwent splenectomy. Subsequent labs revealed gradual improvement in his total bilirubin to 2.4 mg/dL.

Discussion

HS is the most common disorder of a group of inherited disorders that cause structural defects in the red cell membrane. Other disorders in this group include hereditary elliptocytosis and hereditary stomatocytosis. HS is most common in those from northern Europe and North America, where its incidence is reported to be around 1:2000.[1] The incidence of HS is higher if better screening methods are used, allowing for the detection of the disease in asymptomatic individuals. Modern double beam laser technique applied in routine hematology revealed incidence of 1:150 men and 1:800 women.[2]

HS is caused by different types of genetic mutations in one (or possibly more) of several red cell membrane proteins. Three-fourths of the time, the mutations behave in an autosomal dominant pattern, so a single mutation is enough to cause the disease. In some cases, inheritance occurs in an autosomal recessive pattern. De novo mutations also occur in a small percentage of cases. HS has been characterized according to the severity of anemia and hemolysis. In HS trait, hemoglobin, reticulocyte count, and bilirubin are normal. In mild HS, hemoglobin is 11-15 g/dL, reticulocyte count is 3-6%, and bilirubin is 1-2 mg/dL. In moderate HS, hemoglobin is 8-12 g/dL, reticulocyte count is >6%, and bilirubin is >2 mg/dL. In severe HS, hemoglobin is 6-8 g/dL, reticulocyte count is >10%, and bilirubin is >3 mg/dL.[3]

The variability in clinical presentation is mainly due to the different underlying genetic defects that cause the disease. Individuals with HS may present at any age, ranging from the newborn to the older adult. Diagnosis of HS usually occurs in the neonatal period to young adult life. During the first few months of life, most newborns with HS present with icterus, as well as pallor and/or dyspnea due to anemia.[4] In a study of 402 severely jaundiced newborns, four were eventually diagnosed as HS.[5]

Individuals who are not diagnosed in infancy may present with incidental finding of spherocytes on blood smear or symptoms related to complications of chronic hemolysis, like jaundice, anemia, splenomegaly, or pigment gallstone. The most common presentation is jaundice with mild to moderate hemolysis or hemolytic anemia. A family history of HS makes HS a likely diagnosis on the differential.

Initial evaluation starts with complete blood count (CBC), peripheral smear, reticulocyte count, liver function tests (LFT) and tests for hemolysis. CBC will reveal the hemoglobin count and the degree of anemia. Mean corpuscular hemoglobin concentration (MCHC) may be increased (>36 g/dL) suggesting the presence of spherocytes. Peripheral smear should be done to look for spherocytes. Reticulocyte count will be elevated. LFTs will reveal the elevated bilirubin count.

Hemolysis testing may reveal increased indirect bilirubin and lactate dehydrogenase (LDH), as well as low haptoglobin. Coombs testing will be negative, ruling out autoimmune hemolytic anemia.

According to the 2011 guidelines on HS, additional diagnostic testing is not indicated in individuals with a family history of HS who have classic clinical features (like jaundice and splenomegaly) and typical laboratory results (like spherocytes, elevated MCHC, and elevated reticulocyte count). If the diagnosis is not clear from the presentation, then additional testing is needed. Cryohemolysis test and EMA binding are recommended screening tests. The osmotic fragility test is not recommended for routine use due to poor sensitivity. Gel electrophoresis analysis of erythrocyte membranes is recommended if initial screening tests are not definitive.[6]

Treatment of HS involves managing the anemia and the complications of chronic hemolysis. Blood transfusions may be needed for severe anemia. Splenectomy is indicated for those with several hemolysis and may improve anemia. If needed, splenectomy should ideally be done after age six to help decrease the risk of infectious complications. Cholecystectomy may be needed for gallstones.

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