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GALLSTONES DUE TO HEREDITARY SPHEROCYTOSIS WITH GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY*

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The manifestation of various hemolytic disorders occurring in children depends on the duration of the hemolytic process and its severity. Chronic hemolytic anemia can be differentiated from the acute form on a clinical basis. However, when acute and chronic hemolytic disorders are associated, such as glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and hereditary spherocytosis (HS), their coexistency may result in more severe disease[1].

In HS, intrinsic cellular defect can lead to cellular destruction in the presence of intact spleen. As erythrocytes age, they become more susceptible to osmotic lysis and destruction. With repeated passages through the spleen, they suffer a progressive loss of membrane plasticity. In addition to rapid blood destruction, temporary arrest of erythropoiesis can lead to aplastic crisis[1].

In G-6-PD deficiency, instability of glutathione causes hemolysis[2]. Hemolysis and anemia can be more severe as HS is coexistent with G-6-PD deficiency[3].

Case Report

A fourteen-year-old girl was admitted to the Çukurova University Hospital with complaints of jaundice, nausea, vomiting and right upper quadrant abdominal pain. The jaundice was first noticed when she was two days old but later disappeared. When the patient was eight-years-old, her family again noticed that she had temporary jaundice. These icteric episodes were repeated for a few month-long

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intervals up to date. The girl also complained of voiding dark urine during these icteric episodes. She was referred to the Çukurova University Hospital when her complaints became worse.

On admission the patient was icteric and her vital signs were normal. The liver extended three cm below the costal margin. The spleen was palpated about four cm. No other abnormalities were detected.

Laboratory examination revealed that the hemoglobin was 7.0 g/dl, RBCs count 2,100,000 / mm^3, reticulocyte count 6.0%, platelet count 215,000 / mm^3, WBCs count 8,800 / mm^3, with a distribution of 68% neutrophils, 24% lymyhocytes, 4% bands and 4% eosinophils. A moderate anisocytosis in RBCs with 44% of spherocytes was noted in the peripheral blood smear. Erythrocyte osmotic fragility increased from 0.45 to 0.70 g/dl. Erythrocyte G-6-PD activity was found to be moderately low[4] as 69.6 mU / 10^9 RBCs (48.9% activity of normal[5]). Heinz body formation was 70% of erythrocytes after incubation of RBCs with acetylphenylhydrazine. The hemoglobin pattern was A. Heat denaturation and direct Coombs tests were negative.

The blood chemistry was as follows: SGOT 43 IU, SGPT 10 IU, alkaline phosphatase 69 IU, serum total bilirubin 10.7 mg/dl with 10.1 indirect reacting fraction. Serum calcium was 11.0 mg/dl and phosphorus was 3.6 mg/dl. Serum total protein was 7.9 g/dl with 4.6 g/dl and 3.3 g/dl albumin and globulin respectively. Serum total lipids and cholesterol were 540 mg/dl and 140 mg/dl, respectively. The protein electrophoresis consisted of 58.48% albumin, 3.23% alpha-1 globulin, 6.96% alpha-2 globulin, 9.20% beta globulin, and 22.13% gamma globulin. The serum iron level was 92 mg/dl, and total serum iron-binding capacity was 375 mg/dl with 25% transferrin saturation. Urinalysis revealed that the linogen was (++) and the free hemoglobin in the urine was 90 mg/dl. Bone marrow aspiration showed normal cellularity with erythroid hyperplasia.

Erythrocyte survival time with ^{51}Cr demonstrated that it was as short as eight and a half days. Oral cholecystography revealed that the gallbladder was not visualized with radioopaque material, but there were several radioopaque gallstones. This finding was also confirmed by ultrasonography. The patient received two units of blood prior to operation.

Cholecystectomy and splenectomy were performed simultaneously and a liver wedge biopsy was taken for histopathologic study. The diameter of the common bile duct was normal and no exploration was carried out. Two accessory spleens measuring 1.5 x 1.5 cm in diameter within the splenic hilus were also removed.

The pathological report of the liver biopsy specimen confirmed that there were hemosiderin accumulation in the peripheral spaces of the parenchyma and

scattered mononuclear cell infiltration around the portal areas and in the sinusoids. The biopsy specimen of the spleen revealed an excessive hemosiderin deposition in the sinus macrophages. The gallbladder sections showed desquamation in the mucosal epithelial cells and submucosal edema and infiltration of mononuclear cells. Three large stones measuring about 1.5 cm in diameter and five more stones about 3-5 mm in diameter were removed from the gallbladder. The gallstones contained bilirubin, biliverdin, cholesterol, calcium and phosphates and had a dark brown appearance.

The patient's clinical and laboratory condition was uneventful in the post-operative period. No hemolysis was encountered and the percentage of spherocytes decreased steadily, from 50% to 20% within two weeks and then to 16% after one month. Her indirect reacting bilirubin level dropped from 12.1 mg/dl to 1.2 mg/dl within one week after the operation (Fig. 1). Her liver had decreased in size to two and half centimeters. She was discharged on the seventh post-operative day and was healthy at her post-operative control one month later.

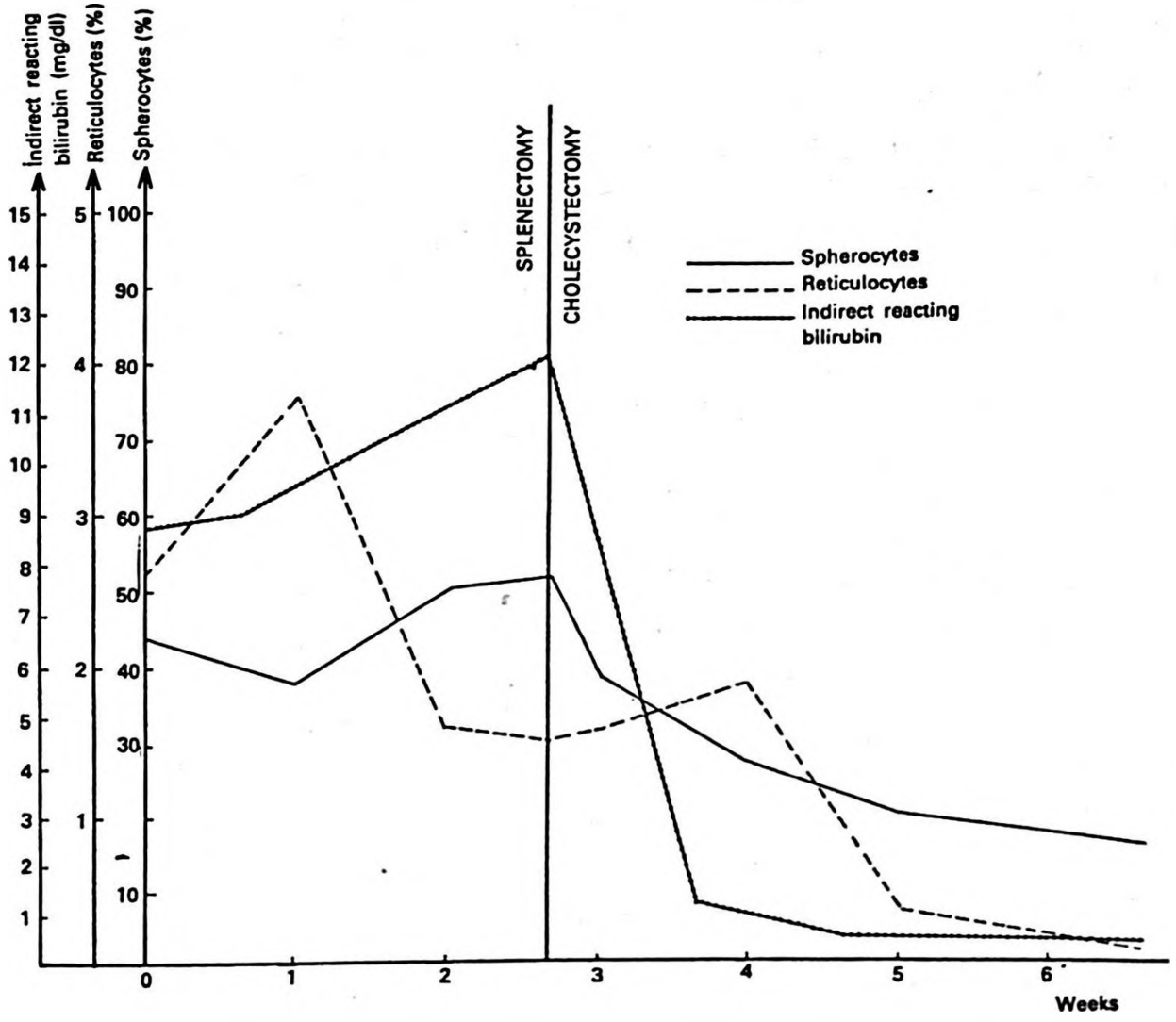

Fig. 1: Laboratory evaluation of the patient.

Discussion

Hereditary spherocytosis is a disease which is transmitted in an autosomal dominant manner while glucose-6-phosphate dehydrogenase deficiency is a sex-linked disorder. The coexistence of these two disorders is genetically independent from each other. While in HS, hemolysis is due to an intrinsic defect in red blood cells and an intact spleen, in G-6-PD deficiency[1] it is due to glutathione instability. The coexistence of HS and G-6-PD deficiency may aggrevate the hemolysis and clinical manifestations, such as in our patient and in the case of Rubins and Young[3].

Reports in the literature of HS associated with G-6-PD deficiency illustrate the coexistency of these two disorders[3,6], but there is no data on calculus formation and their composition in the gallbladder.

The incidence of cholelithiasis increases with the age of the patients[7]. It occurs most commonly in girls entering pubescence[8]. There is an increased incidence of gallstone formation in those races who are predisposed to congenital hemolytic anemia[9]. According to MacMillan et al[10] and Seiler[11], the most commonly associated condition with cholelithiasis is the hemolytic process in childhood.

The clinical symptoms and findings in childhood do not differ from those of adults[12-14]. Ulin et al[15] emphasized the absence of a history of dyspepsia or intolerance to fatty foods, which was so often present in adult cholecystic disease[12]. Prior to elective splenectomy for hemolytic disease, an examination of the gallbladder is indicated[10]. Before the introduction of ultrasonography, cholecystography was the best diagnostic test in the absence of jaundice and should be used more frequently with upper gastrointestinal series in children with epigastric complaints[14]. If the findings are abnormal, intravenous cholangiography should be performed[16,17].

In HS, splenectomy should be performed if the child has recurrent crises or severe anemia or cholelithiasis diagnosed at any age[18]. Early diagnosis will lead to splenectomy alone without a biliary operation. An early splenectomy will obviate the risk of crisis and cure anemia which is usually present[17]. Splenectomy consistently produces complete remission of the hematologic disorder[17,18]. Accessory spleens should be searched for and if there are any, they should be removed[19]. Failure to remove this residual splenic tissue is the main cause of the continuation of hemolytic disease following splenectomy[19]. When coexistent cholelithiasis is diagnosed preoperatively, or intraoperatively, simultaneous splenectomy and cholecystectomy are indicated[10,14,17,18]. Indications for exploration of the common bile duct are the same in children as in adults[14].

In our patient, a cholecystectomy and splenectomy were performed simultaneously. Two accessory spleens were also removed to avoid hemolytic relapses. As a result of her uneventful postoperative period, jaundice disappeared rapidly, and a fast improvement was noticed in her blood and clinical picture. This indicates that G-6-PD deficiency had not been the cause of the patient's chronic hemolytic anemia in the steady state.

Summary

A fourteen-year-old girl with hereditary spherocytosis and glucose-6-phosphate dehydrogenase deficiency is presented. She had pallor until eight years of age and experienced many icteric attacks until the day of admission. The intervals between the attacks became more frequent during the last year. Prior to her admission, abdominal pain developed and jaundice persisted because of gallstones. She was operated on and a gallbladder with stones and a spleen with two accessory spleens were removed. After the operation, the jaundice rapidly disappeared and improvement was observed in her blood and clinical picture.

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