The Turkish Journal of Pediatrics
Volume 22 / Nos. 1-2 / Jan.-April 1980 / pp. 39 – 43

Hemolytic Anemia as a Presenting Manifestation of Wilson's Disease*

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Since it has rarely been demonstrated that a severe acute hemolytic anemia can be a first manifestation of Wilson's disease[1,2] we would like to present such a patient among the 62 cases who had this diagnosis at Hacettepe Children's Hospital during last twelve years. Because of this it should be emphasized that Wilson's disease must be considered in the differential diagnosis of acute Coombs negative hemolytic anemias.

Report of A Case

S. B. (Hacettepe Children's Hospital, protokol 1035577) was an eight year old girl who became sick 1 1/2 month prior to her admission to this hospital with epistaxis, icterus, pallor, loss of weight and dark urine and stool. Later, night blindness were among her complaints.

Physical examination revelaled pallor mild jaundice, enlarged spleen and liver (11 and 2 cm below respected costal margins) and spider nevi on shoulders. The neurological examination was normal and no Kayser-Fleischer rings were visible. She was the third product of a non-consanguines marriages and there was no history of liver and central nervous system disease in the family.

Her hemoglobin (4.6 gr/dl) and hematocrit (19 %) values indicated severe anemia with mild leukopenia (4300 / µl) and thrombocytopenia (124.000 / µl). Marked poikilocytosis, polychromasia, anisocytosis with

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mild basophilic stippling, hypochromia and normoblastemia (1-2 %) were detected on peripheral smear. Hemoglobin electrophoresis and fetal hemoglobin determinations (0.9 %) were normal. Bone marrow examination revealed marked erythroid hyperplasia, and Coombs test, cold agglutinins, HB_s Ag and anti HB_s were found negative. Serum iron (160 µg/dl) and iron binding capacity (358 µg/dl) findings were explained by hypersplenism. Prothrombin time (20 sec N: 12 sec) and PTT (132 sec, N: < 120 sec) were found slightly prolonged and hyperbilirubinemia (total 5.4 mg/dl; conjugated 1.2 mg/dl) hypoalbuminemia (2.2 gr/dl) hypovitaminosis A (10.5 µg/ml; N: 30-65 µg/ml, E (0.18 µg/ml), D (3.65 µg/ml) with normal cholesterol (140 µg/dl) total lipid (665 mg/dl), alkaline phosphatase (5.9 Bodansky), alanine, (28 u) and aspartate (50 u) transaminases and G-6PD (by screening) were documented. Urinary findings (including sugar, protein, calciuria and amino aciduria) were normal. Hypoceruloplasminemia (1.09-4.07 mg/dl) hypercupriuria (232 µg/24 hours; controls < 100 µg/24 hours) were detected. Splenic pulp pressure was found (410 mm/H_2O) elevated but occult blood was not shown on several stool examinations.

Although pigmentation was found around the cornea, slit-lamp examination at this time did not revealed Kayser-Fleisher rings. Liver biopsy confirmed the diagnosis of Wilson's disease but tissue copper content could not be determined.

Several transfusions were required over the course of the 2 weeks following admission, when the signs of hemolysis abated. Evaluation of the available family members revealed all were hypoceruloplasminemic (Figure 1).

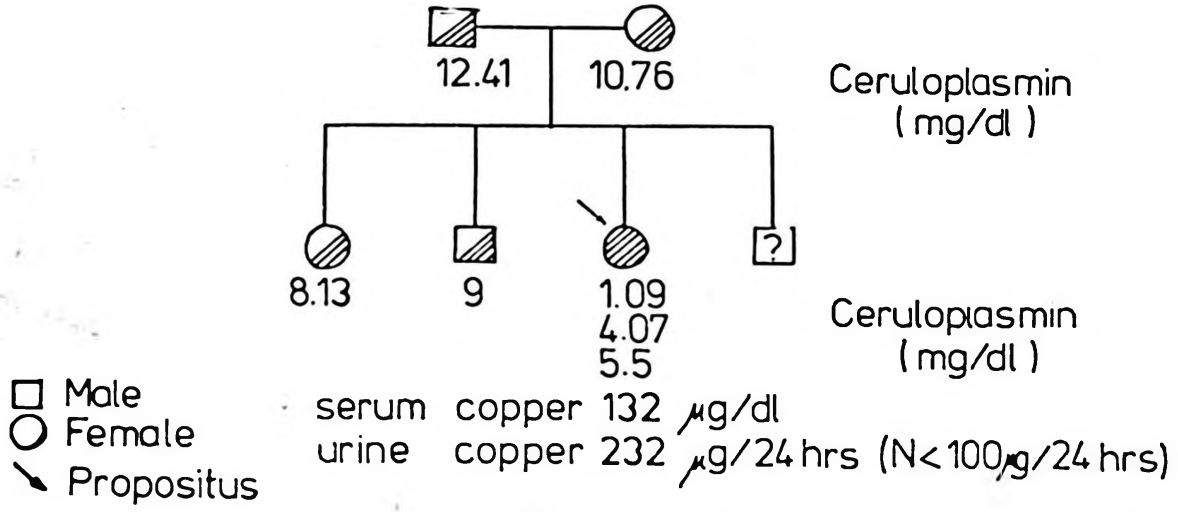

Figure 1
Family tree of the patient

Since penicillamine and triethylene tetramine dihydrochloride (T.E.T.A.)[3] were not available, oral zinc (3 x 150 mg/day before meals)[4] was started. Unfortunately she did not return for follow up and the other members of family could not be treated.

Discussion

Wilson's disease in childhood usually manifests itself with liver involvement. Less than one third of our patients in this hospital were seen originally with the complaints related to neurologic dysfunction and she is the only case who was admitted with the diagnosis of hemolytic anemia. Since no cause was found for her short durated hemolytic anemia the conclusion was that it was related to her liver disease which was diagnosed as Wilson's disease.

The diagnosis of Wilson's disease was dependent upon hypoceruloplasminemia, postnecrotic cirrhosis of the liver and hypercupriuria. Although hypoceruloplasminemia with elevated cupriuria are strongly suggestive evidence of the disease, they do not differentiate each case of chronic active hepatitis from Wilson's disease.[5] But liver biopsy findings were more compatible with the diagnosis. Kayser-Fleischer ring a characteristic but not pathognomonic[6] sign is seen more often in the neurologic stage of the disease.[7] Less than a decade ago it was suggested that "absolute" diagnosis of Wilson's disease should in all cases be made by determination of the hepatic copper concentration (> 50 µg/gr wet weight).[8] At that time we commented that it should also be found elevated in primary liver cirrhosis.[9] Today Indian childhood cirrhosis,[10, 11] chronic copper intoxication, tyrozinosis,[12] chronic active hepatitis[5] in addition to familial hepatic copper storage disease[13] and above conditions should also be considered when such findings are obtained. Although pathognomonic sign and symptom are non-existent for Wilson's disease as many probable findings should be obtained to establish the diagnosis as in our case.

Hemolytic anemia is included in the manifestations of acute copper intoxication in addition to jaundice and oliguria.[4] But the pathogenesis of hemolytic anemia in Wilson's disease has been related to massive hypercupremia following abrupt severe hepatic necrosis, similar to enjootic jaundice of sheep. Although hypercupremia of our case did not reach the animal experiment levels, as in other reported cases with hemolytic anemia with this disease, it seems probable to us that in the presence of hypovitaminosis E and hypersideremia, cooper might be more toxic as in this case.

Other investigators have claimed that abnormalities in the functions of hexose monophosphate shunt may account for the hemolysis by reducing the ability of erythrocytes to withstand oxidative stress by the decreased level of reduced glutathione. The rarity of acute hemolysis in Wilson's disease may suggest that there should be an additional condition to increase serum copper effect on red blood cell membrane, such as hypovitaminosis E and/or red cell glycolytic or membrane enzyme defects.

Anemia of this patient was not solely explained by the history of epistaxis or G-I bleeding related to portal hypertension since the iron deficiency was not shown and occult blood was not present in the stool. Although most of the hemolytic findings might be explained by hypersplenism, the red cell morphology was more suggestive of marked hemolytic anemia. Therefore the causes of it were looked for on the admission, and it was found to be related to liver disease which had most of criteria of Wilson's disease.

Summary

An eigth year old girl with hepatosplenomegaly, spider nevi, hypoceruloplasminemia, hypercupriuria, portal hypertension due to post necrotic cirrhosis and decreased level of lipid soluble vitamins had marked hemolytic anemia. Hypoceruloplasminemia was also detected in both parents. The diagnosis of Wilson's disease was made with the above findings and her short durated hemolytic anemia was considered to be related to her disease. It was suggested that her hypercupremia was more destructive on her erythrocytes in the presence of vitamin E deficiency.

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