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Fatal Intrahepatic Cholestasis*

Aytemiz Gürgey, M.D. / Şinasi Özsoylu, M.D.*** / Nurten Koçak, M.D.******

Fatal intrahepatic cholestasis is a rare disorder characterized by early appearing jaundice, foul smelling diarrhea, growth retardation, pruritus and hepatosplenomegaly. The jaundice is pronounced before the first year of age and occurs frequently with infections. The disease causes cirrhosis before fifteen years of age and results in death at an early life.[1, 2] Although there are some slight clinical differences, all cases have some common characteristics such as BSP, bilirubin and bile salt excretion defects.

In this article we would like to present two cases of fatal intrahepatic cholestasis which, to the best of our knowledge, are the first from Turkey.

Case Report

Case 1: (HCH/284702). This patient was first hospitalized at Hacettepe Childrens Hospital in 1971 when he was two years nine months old, thereafter five and six years of age with the complaints of pruritus and recurrent jaundice. The patient had a history of diarrhea recurring every 10-15 days since birth, each lasting 3 or 4 days. Jaundice first appeared when the baby was 4 months old and reoccurred more than ten times till his first admission to this hospital. During the jaundice period pruritus, darkening of urine, pailing of the stool were observed.

The patient was the fourth product of unrelated healthy parents. The three brothers were in good health but mother's brother and his daughter were splenectomized in Germany with the diagnosis of hemo-

* From Hacettepe University Faculty of Medicine, Department of Pediatrics and Hacettepe Childrens Medical Center, Ankara, Turkey.
** Associate in Pediatrics.
*** Professor of Pediatrics.
**** Associate Professor of Pediatrics.

lytic anemia. Physical examination revealed a slightly jaundiced malnourished boy (weight 12.7 kgm., height 88 cm.) with a marked hepatomegaly (8 cm. below right costal margin). With the exception of positive Babinsky sign other physical findings were not contributory.

Laboratory Examinations: Hemoglobin (13.26 gm/dl), white blood cell count (8600 mm3) and peripheral blood smear were normal. SGOT (65 KU), total lipids (1460 mg/dl), cholesterol (330 mg/dl) and alkaline phosphatese (39 BU) were elevated. Other laboratory findings including BUN, blood sugar, bilirubin, ceruloplasmin, calcium, phosphorus, alpha-l-antitrypsin, bone marrow aspiration, urine and blood aminoacids. EKG, sickling, osmotic fragility and autohemolysis were within normal limits. Occult blood and parasites were not shown in stool specimens. An EEG showed epileptiform activity and gallbladder could not be visualized with oral and intravenous cholecystography. A liver biopsy revealed active cirrhosis and cholestasis. The liver function tests and autohemolysis of the patient's mother and father were normal. The patient was admitted second time to this hospital at 5 years of age with the additional complaint of abdominal distention. Since his first discharge abdominal distention was observed which became more pronounced in the last 3 to 4 days and, very recently, edema of the feet were also noticed. Polydypsia was another complaint for a duration of one year.

Physical examination on this admission revealed that his height (95 cm.) and weight (16 kgm) were below 3 percentile and he had subicteric sclerae, ascites, hepatosplenomegaly (7 cm. below respective costal margins). Abdominal wall veins were distended and filled from downward to upwards. The esophagogram and IVP were normal. Laboratory examination showed anemia (Hb: 8.62 gm/dl), mild leukocytosis (WBC: 16.000 mm3); the peripheral blood smear was normal. The results of SGOT (140 KU), alkaline phosphatase (46.6 BU), prothrombin time (66 sec.), PTT (over 5 minutes), and serum albumin (2.9 gm/dl total protein 6.6 gm/dl) were abnormal. Serum protein electrophoresis showed albumin 18.9 %, $\alpha 1$ globulin 8 %, $\alpha 2$ globulin 24.8 %, β globulin 14.7 % and γ globulin 32.5 %. Hepatitis B surface antigen (HBs Ag) and alpha fetoproteins were negative. BUN, SGPT, CCF, total lipids, cholesterol, calcium, phosporus, ammonia sweat chloride were within normal limits. Occult blood in the stool was present. A laparotomy showed normal gallbladder and bile ducts and a liver biopsy interpreted as progressive cirrhosis.

The patient was admitted at 6 years of age with the complaint of gastrointestinal bleeding. On physical examination he was stuporous

and in respiratory distress. His skin and sclerae were icteric. Liver and spleen were 10 and 7 cm. below the respective costal margins. The patient died in four hours.

Case 2: (HCH: 641234) The second patient was a 13 year old girl who was admitted to Hacettepe Children's Hospital with the complaints of jaundice and pruritus. It was reported that she had her first jaundice attack about 9 months of age which was accompanied by pruritus and dark urine. In every occurrence of the jaundice, dark urine was also observed and none of the drugs helped her pruritus. For the last two years she had been icteric, accompanied by dark urine and acholuric stools.

The patient was the first offspring of nonconsanguinious healthy parents. Other two siblings were in good health. It was learned that the mother, mother's sister, and mother's father also had had jaundice.

Physical examination indicated marked growth retardation (weight 27 kgm, height 128 cm.) and she had scleral icterus. The liver and the spleen were palpable 3 to 4 cm. below respective costal margins. Bilateral palmar erythema and parakeratosis of the skin due to itching were present.

Laboratory Examinations: With the exception of mild leukopenia (4000 mm3) hematological findings (Hb: 12.6 gm/dl, platelets on smear) were within normal limits. SGOT (130 KU), SGPT (63 KU), total bilirubin (7.4 mg/dl), direct bilirubin (4 mg/dl) and thymol turbidity (6 U) values all were abnormal while alkaline phosphatase, CCF, serum proteins, prothrombin time, serum copper, ceruloplasmin, α1-antitrypsin and BUN were normal. In serum protein electrophoresis albumin was 40 %, α1 globulin 5.3, % α2 globulin 13.8 %, β globulin 18.1 % and γ globulin 22.8 %. The immunoelectrophoresis, chest X-ray, bone marrow and, with the exception of bilirubinuria, urinalysis were normal and HBs Ag was negative. Cholestasis and cirrhosis were detected by liver biopsy. The patient was discharged on oral phenobarbital (5 mg/kg). Since it did not help her pruritus, cholestyramine was started with marked improvement of her last symptom.

Discussion

Intrahepatic cholestasis is a large entity which could be separated into two categories.

Drugs, like estrogen, testosterone, infections and autoimmune conditions are the sources of acquired intrahepatic cholestasis, while biliary atresia, bile duct hypoplasia, benign recurrent intrahepatic

cholestasis and α1 antitrypsin deficiency are the congenital causes[3-8] of this entity. Besides these, some fatal cases with inherited hepatic excretion defects are reported fairly recently.[1, 2, 9-12]

In cases reported by Clayton et al, as Byler's disease, the diarrhea and gastrointestinal symptoms in infancy were followed by jaundice attacks, hepatosplenomegaly, growth retardation and cirrhosis before fifteen years of age. An increase in alkaline phosphatase activity and hypoprothrombinemia appear during the course of the disease. Elevated alkaline phosphatase values could be of hepatic origine or due to rickets which may accompany the disease.[1, 11, 13] Although the cholesterol values were generally normal or low, some cases with hypercholesterolemia and xanthoma were also reported.[11, 15] The cases which were described by Juberg et al were basically similar to Byler's disease but mental retardation of their patient was emphasized as an essential part of the entity.

Our cases could easily be differentiated from Dubin Johnson and Rotor syndrome by the result of liver functions tests and pruritus. Biopsy findings of our cases also excluded intrahepatic ductular hypoplasia and benign recurrent intrahepatic cholestasis. The possibility of biliary atresia was completely excluded by laparotomy findings.

Although mental retardation was not seen in either of our patients the presence of confusion and changes in EEG readings in the first case may indicate neurologic component. Besides this neurologic defect, if one considers the increase in the values of total lipids and cholesterol, the first case could be excepted as a variant of Byler's disease. Liver biopsy findings of our patients could easily be differentiated from those of the patients described by Aagenes et al with the excretion defect in bilirubin lipids and bile acids.[14]

Biliary abnormalities together with pancreas abnormalities have also been shown.[12] It was recently reported that the metabolic errors in Byler's disease is related to lithocholic acid metabolism.[12, 13] In fact, cirrhosis of the liver could be produced in mice by the oral administration of lithocholic acid.[15] The treatment in Byler's disease is symptomatic. Although phenobarbital gives good results in hepatic ductular hypoplasia,[16, 17] it has no effect in the case of fatal intrahepatic cholestasis. Cholestyramin may abolish some of the findings in Byler's disease[12] as in our first case.

Summary

Two cases of fatal intrahepatic cholestasis were presented, one of which was fatal.

The possibility of one of the patient having Byler's disease and the other, a variant of it was discussed.

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