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VENO-OCCLUSIVE DISEASE OF THE LIVER

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Veno-occlusive disease of the liver was first described in 1954 as a disease occurring in Jamaican children.[1] The characteristic pathologic features of the disease are obstruction of the smaller and medium-sized branches of the hepatic veins, centrolobular congestion, and, later, fibrosis of the nonportal type. Clinically, patients with the disease have ascites, hepatomegaly and, in long-standing cases, a cirrhosis which is indistinguishable from other types of cirrhosis.[2]

As veno-occlusive disease has not been previously reported from Turkey, the purpose of this article is to present two cases of veno-occlusive disease of the liver in patients seen at Hacettepe Children's Hospital, and to describe its rôle in the pathogenesis of childhood cirrhosis.

Case Reports

Case 1. A. U. (65 - 4963), a 25 month old female, was admitted to Hacettepe Children's Hospital with an abdominal enlargement of approximately one month's duration. The patient was the second child of the family. There was no history of complications either during pregnancy or delivery, or of familial disease. The child had eaten the same food as the rest of the family, including

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fruit juices. There was no record of intake of plant extracts. The patient's history revealed only mild upper respiratory infections.

Physical Examination : The patient weighed 8700 gm and was 82 cm tall. She was pale, but her general condition seemed fair. Auscultation and percussion revealed dulness of the right hemithorax. The enlarged abdomen measured 65 cm at the level of the umbilicus and there was evidence of collateral circulation. A firm, sharply defined liver could be felt 10 cm below the costal margin in the right mid-clavicular line. The spleen could not be palpated and there was no jaundice. Pitting edema was noted in the legs. Repeated abdominal taps yielded 600 to 700 cc of clear fluid. X-rays revealed no esophageal varices. A chest x-ray showed fluid in the right thoracic cavity and a tap produced 200 cc of clear fluid.

Laboratory Examination : Complete blood count showed hemoglobin, 8.40 gm per 100 ml; leukocytes, 8000 per cc. Total serum protein, 5 gm per 100 ml, with 3 gm albumin; NPN, 25 mg per 100 ml; SGOT, 268 units; phosphorus, 1.7 mg per 100 ml; C.C.F., 3 plus; thymol turbidity, 1.5 units. Total cholesterol was 115 mg per 100 ml with 50 mg free cholesterol. The diagnosis of veno-occlusive disease was made upon examination of a liver biopsy specimen. Despite supportive therapy, the patient died 23 days after admission to the hospital.

Postmortem examination findings were confined mainly to the liver and confirmed the biopsy diagnosis of veno-occlusive disease. The liver weighed 835 grams (normal for the patient's age is 400 grams). The cut surface of the liver had a mottled appearance with pale brown and dark red areas (Figure 1). Several vessels noted on examination of the cut surface were thick-walled and the luminae of some were completely obliterated. No thrombi or occlusive changes were noted in branches of the portal vein, the inferior vena cava, or in the hepatic veins. In addition to the liver findings, the postmortem examination revealed about 300 cc of clear fluid in the right pleural cavity, about 1000 cc of clear ascitic fluid, and peripheral edema. Second degree malnutrition was noted.[3]

Microscopic examination of the liver (Figures 2, 3 and 4) showed enlargement and fibrous thickening of the wall and occlusion of the luminae of the hepatic veins with centrolobular sinusoidal engorgement and necrosis of the hepatic parenchymal cells. There was no fibrosis, proliferation of bile ducts, or regeneration of liver nodules.

Case 2. N. D. (65 - 55987), a three year old female, was admitted to Hacettepe Children's Hospital with complaints of swelling of the abdomen, legs and face. She was apparently in good health until one month prior to admission when a sudden enlargement of the abdomen, and later swelling of the legs and face, were noted.

Physical Examination : The patient was the first child of a family with no history of familial disease. She had been breast-fed and later home-prepared foods were given. No history of ingestion of plant extracts was obtained. Her history was negative expect for measles. Her general condition was moderate; weight, 12 kg; height, 82 cm. Marked enlargement of the abdomen and ascites were noted. The liver could be palpated 8 cm below the right costal

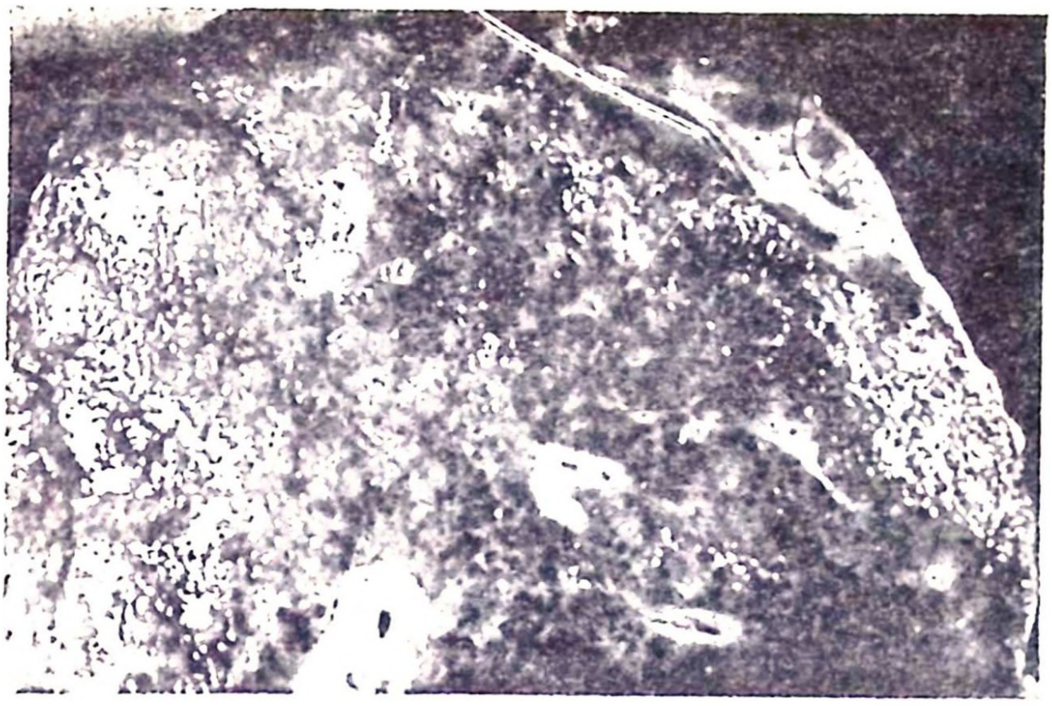

Figure 1. Cut surface of the liver showing mottled appearance with pale brown and dark red areas. The thickened walls of the medium and small hepatic veins are also visible.

margin, but the spleen was not palpable. There was evidence of collateral circulation and her extremities were edematous. Physical and x-ray examination revealed pleural fluid on the right side. No pathological conditions of the heart could be detected either on x-ray examination or on cardiac catheterization. During the course of her hospital stay she was sub-febrile. On the twenty-fifth hospital day she developed jaundice and on the twenty-eighth day she died.

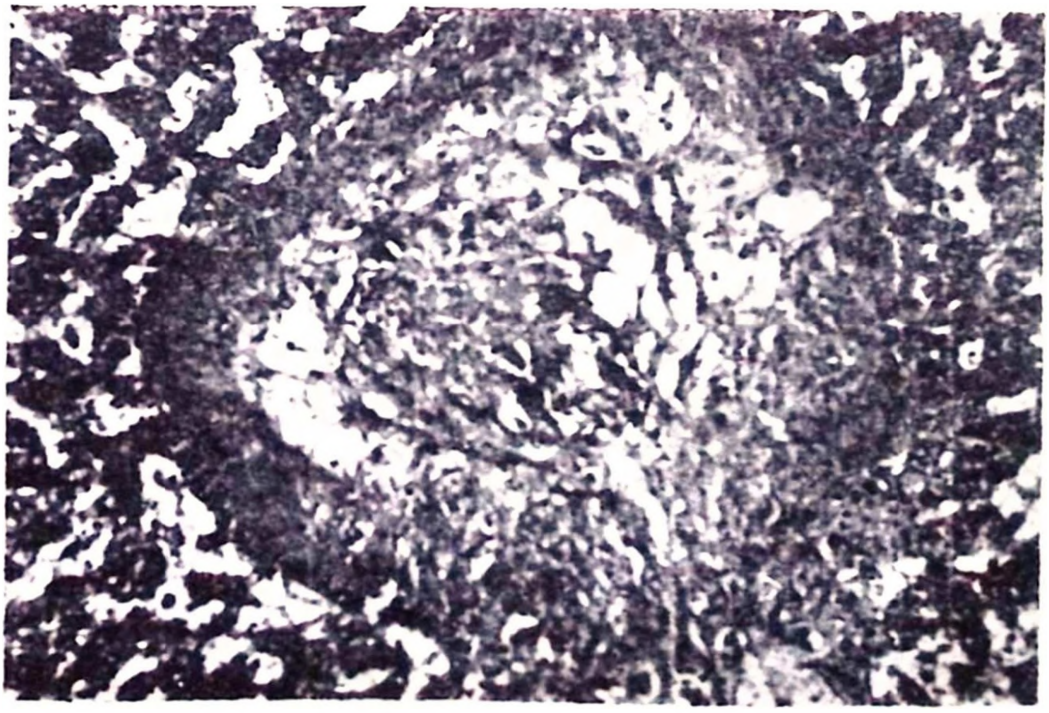

Figure 2. Hematoxylin and eosin stain. X100. Enlarged and occluded hepatic veins.

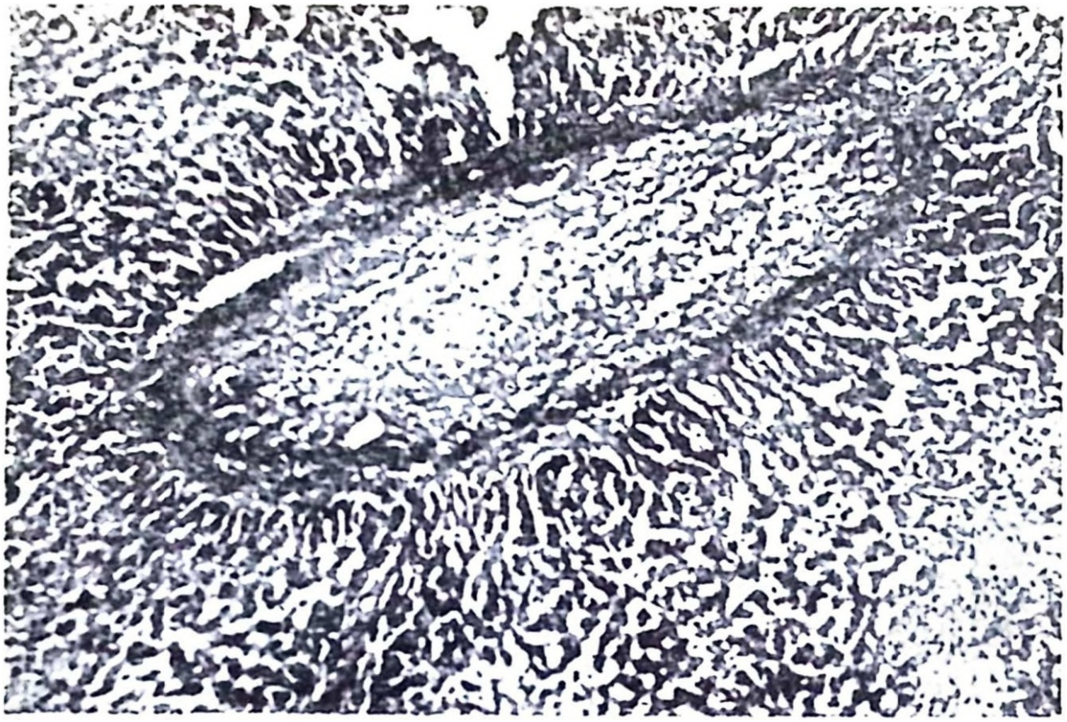

Figure 3. Hematoxylin and eosin stain. X40. Enlarged and occluded hepatic veins.

Laboratory Examination : Complete blood count: hemoglobin, 9.20 gm per 100 ml; leukocytes, 7200 per cc; NPN, 34 mg per 100 ml. Total serum protein, 7 gm per 100 ml with 4.2 gm albumin; SGOT at the time of admission, 24 units, one month later (one day prior to death) 220 units; C.C.F., 1 plus. Total serum cholesterol, 78 mg per 100 ml with 28 mg free cholesterol.

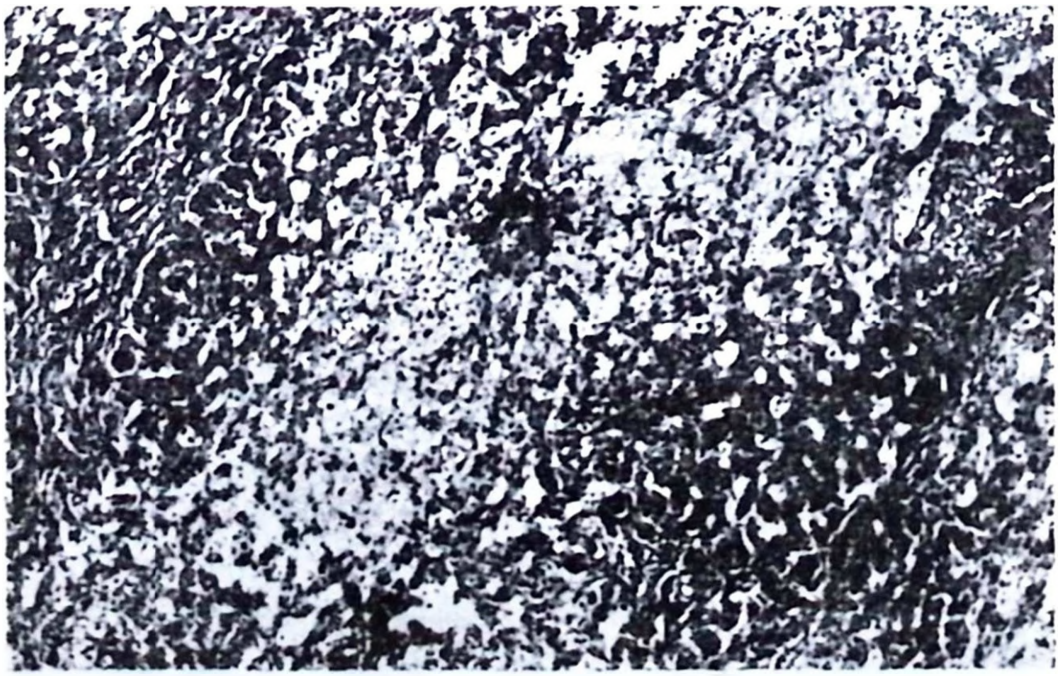

Figure 4. Hematoxylin and eosin stain. X40. Centrolobular sinusoidal dilatation with necrosis of parenchymal cells.

The main findings on postmortem examination were 1500 cc of clear ascitic fluid, hepatomegaly (560 gm; normal for the patient's age, 429 gm), splenomegaly (60 gm; normal for the patient's age, 41 gm). Gross liver findings were similar to those described in Case 1. As in that case, no thrombi were present in the inferior vena cava, the portal veins or in the large branches of the hepatic veins. No significant findings were noted in the arteries. Microscopic examination of the liver revealed a pattern similar to Case 1. In addition, there was mild fatty metamorphosis. All extrahepatic branches of the portal and hepatic veins were examined and no pathology was found. Aside from the liver findings, patchy bronchopneumonia and esophagitis with monilia were noted on the sections.

Discussion

Studies of the high incidence of cirrhosis in infants and children in Jamaica first led to the recognition of veno-occlusive disease of the liver.[1] Its characteristic morphology is now well established.[1, 2, 4, 5] Prior to these studies, the condition was erroneously called a serious hepatitis. Observations were made on the drinking of a plant infusion (known as bush tea) and on the poor nourishment of the affected children.[6]

Morphologically, obstruction occurs in the small and medium-sized branches of the hepatic vein. This is thought to be the result of intimal fibrous proliferation leading to centrolobular congestion and necrosis, and still later to fibrosis of the non-portal type. Clinically, the disease is primarily seen in children between the ages of two and five years,[2, 5] but it may occur at any age: adult cases have been reported.[4, 7] In contrast to Jamaican children, the peak age among South African children is earlier.[8] The disease develops suddenly with ascites, hepatomegaly and evidence of collateral circulation. Liver function tests may show hepatocellular injury. In a series of 99 cases,[2] 33 patients died either during the acute or chronic stage, 23 made complete clinical recoveries, and 26 were alive with cirrhosis. Of the 33 who died, the cause of death in 17 was bleeding from esophageal varices and in 12, hepatic decompensation.

Aside from Jamaica, the condition has been reported from South Africa, America, India, Germany, Egypt, Israel, and now from Turkey.[7–12] Although a case of Budd Chiari syndrome occurring in a child has been reported in the Turkish literature,[13] its pathology as described is quite different from that of veno-occlusive disease.

The pathogenesis of the disease is now believed to be limited to toxic effects on the hepatic veins. However, the etiology has by no means been established. Malnutrition does not appear to play a

major rôle in all the reported cases. The hepato-toxic action of the Senecio and Crotolaria alkaloids, retrorsine,[14] longilobine and monocrotoline [15] has been demonstrated in experimental animals. Veterinarians have noted a similar effect among animals eating these same plants, and experiments on cows with crotolaria fulva resulted in development of obliterating lesions in the hepatic veins.[16] In a study of Senecio plants found in Turkey, 39 varieties were classified.[17] However, there have been no reports so far of veno-occlusive disease occurring in animals in Turkey.

The disease among humans in Jamaica is thought to be caused by bush tea.[1, 2, 6, 8–10] Fibrosis of the central and hepatic veins may also occur after prolonged use of Urethane[R] in the treatment of multiple myeloma [18] or after irradiation and alkylating agents used in treating metastatic seminoma.[7] Some authors suspect that the toxic agent is contained in contaminated food.[8]

One hundred pathologically proven cases of cirrhosis were found in the files of the Hacettepe Children's Hospital for the years 1960 through 1966.[19] During this same period, only two cases of veno-occlusive disease (those reported here) were seen. In these two cases, cirrhosis was suggested clinically, but no pathological evidence was present. We know now that veno-occlusive disease does occur among Turkish children, but it probably does not represent a common health problem requiring preventive measures. In our cases, rapid development of the disease brought about fatal termination within a few months and before cirrhosis could develop.

In our cases there was no evidence of ingestion of plant infusions, administration of drugs containing pyrolizidine alkaloid, Urethane[R], alkylating agents or x-ray therapy, either before or during hospitalization. Viral hepatitis and significant malnutrition were not present. Thus, we could not specify any one etiological factor, but we are of the opinion that the condition may have been the result of various hepato-toxic agents acting on the hepatic venous channels. Further investigation of this subject is needed.

Summary

Presented here are the first two case reports of veno-occlusive disease occurring in Turkish children, along with a brief review of the pertinent literature. The condition was found to be rare among Turkish children whose clinical history suggests cirrhosis. No cirrhosis was found in these two patients, and, in the pathogenesis of 100 cases of cirrhosis treated at Hacettepe Children's Hospital, veno-occlusive disease had no significant rôle.

The clinical findings are similar to those of cirrhosis except that rapid enlargement of the liver and ascites may indicate veno-occlusive disease in younger children.

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