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Neonatal Hepatitis

(Etiology and Prognosis)*

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Neonatal hepatitis was first described and related to viral cause by Stokes et al in 1951.[1] The characteristic histology of the liver in this entity was described by Craig and Landing in 1952.[2,3]

The differential diagnosis between neonatal hepatitis and biliary atresia in the evaluation of prolonged obstructive jaundice in infancy still remains a difficult clinical problem. These two entities may be distinguished by clinical findings, cholangiography, radioactive Rose Bengal and liver function tests but especially by liver biopsy. However, the coexistence of atresia and hepatitis has been reported.[4]

In the neonatal period, viral hepatitis, namely hepatitis B, hepatitis A, cytomegalovirus, herpes simplex, rubella, coxsackie B, and adenoviruses are frequently seen. Toxoplasmosis, syphilis and other bacterial infections such as those of E. coli, streptococci, staphylococci[5,6] and urinary tract infections[7] may also be considered as causes of hepatitis in early infancy. Metabolic diseases and familial predispositions are also indicated as causes of neonatal jaundice.[8,9] Besides these, there remains a group of which the etiology is unknown and, in those cases, familial neonatal giant cell hepatitis should be considered.

The aim of this presentation is to summarize our findings in the neonatal hepatitis cases.

Materials and Methods

Fourty-five cases of neonatal hepatitis seen at Hacettepe Children's Hospital between 1968 and 1976 were evaluated. Pertinent physical

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findings and laboratory investigations, namely bilirubin, transaminases, cholesterol, lipid, alkaline phosphatase, prothrombin time, PTT, dye test, sweat chloride, HBs Ag, α1-antitripsin, VDRL, cytomegalic inclusions, blood and urine aminoacids were determined and needle biopsies were performed in all cases. In 3 cases viral isolations, and in 15 α-fetoprotein were also carried out.

Findings

Twenty-eight of the 45 patients were boys and 17 girls, their ages ranging from 1 to 4 months. Five of there are alive, 20 died and 20 did not attend follow up. The following clinical findings were observed in these cases.

Jaundice was seen in all cases beginning with the first week of life. With the exception of two cases, 1 with α1-antitripsin deficiency and the other with B virus hepatitis, hepatosplenomegaly was found in all. Acholic stool was observed in only nine of them.

Histologic findings of neonatal hepatitis were found in all cases (Figure 1,2). Ten patients showed cholestasis, 9 of them showed diffuse giant cell transformation and 7 patients showed cirrhosis.

The etiology could be determined in 8 of these patients; hepatitis B in 2, cytomegalovirus in 1, syphilis in 1, toxoplasmosis in 1, galactosemia in 1, Niemann-Pick disease in 1, α1-antitrypsin deficiency in 1. The patients with hepatitis B (Case 1) and α1 antitrypsin deficiency (Case 2) are still healthy. These eight cases are described in detail below:

Case 1: E.S. (290067) This two month-old girl had jaundice since 3 days of age. These rest of the physical findings were not contributory. Bilirubin (total 13 mg/dl, conjugated, 9 mg/dl) and transaminases (SGOT 1400 KU, SGPT 730 KU) were found elevated. HBs Ag was shown in her serum and in the mother's. Liver biopsy showed neonatal giant cell hepatitis. The patient is now 6 years old and does not have any complaints; her HBs Ag is negative.

Case 2: F.K. (374948) was a fourty-five day old boy who had been icteric since 2 days of age. Liver and spleen were 5 cm and 1 cm palpable, respectively. Bilirubin was markedly elevated (total 12.4 mg/dl, conjugated 11.8 mg/dl) and transaminases were mildly high (SGOT 130 KU, SGPT 60 KU). HBs Ag was found in his serum but not in his mother's. The liver biopsy was compatible with cholestatic hepatitis and he died at 3 months of age.

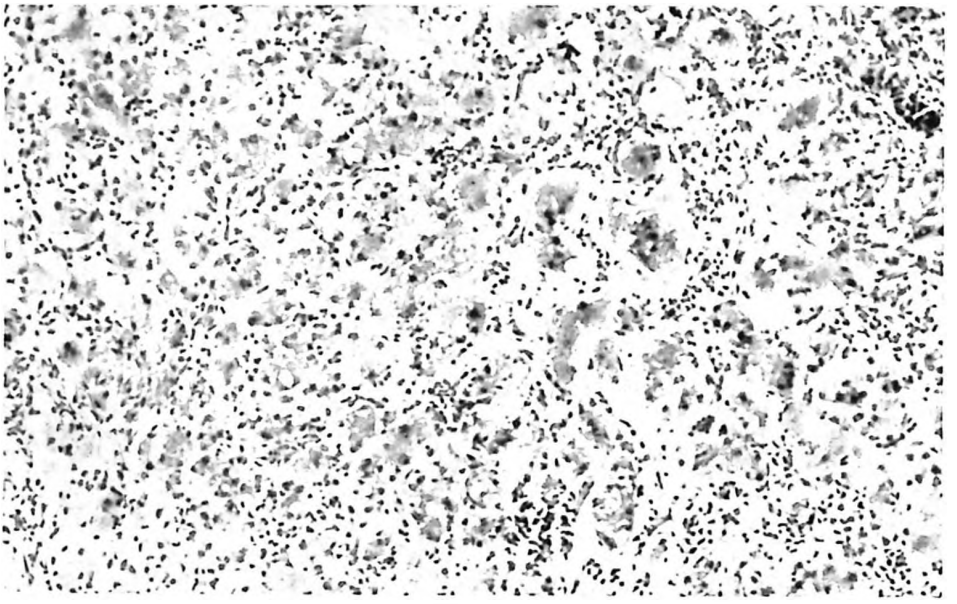

Figure 1
Hepatic architecture is distorted; there are inflammatory and diffuse multinucleated giant cells. HEx10x10x0.3.

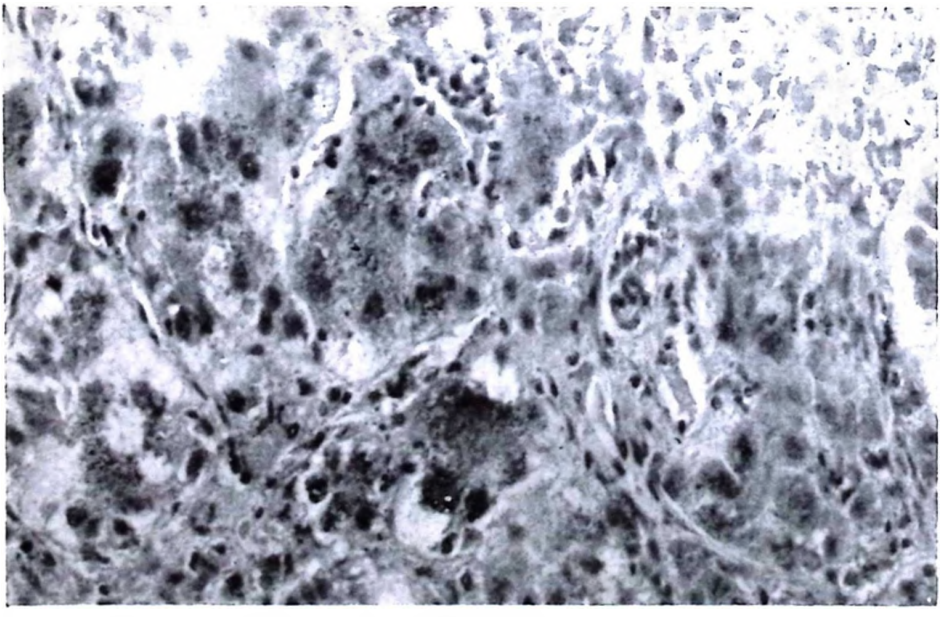

Figure 2
Higher magnification of multinucleated giant liver cells shows intracellular cholestasis. HEx100x10x0.3.

Case 3: K.C. (385187) was a 56 day old boy who had been icteric since 3 days of age. With the exception of a 2 cm palpable liver, other clinical findings were not contributory. Bilirubin (total 5.8 mg/dl, conjugated 4 mg/dl) and transaminases (SGOT 125 KU, SGPT 120 KU) were elevated. α1 antitrypsin level was found markedly decreased (0.35 mg/dl), and in the heterozygote level in his mother, father, brother, grandfather, paternal aunt and uncle. This case has been previously reported.[10] A biopsy showed portal fibrosis, bile duct proliferation, moderate fatty metamorphosis, abundant hemosiderin pigment and some PAS positive material adjacent to the portal space (Figure 3,4). He is now 4 years old and does not have any complaints.

Case 4: (566877) A 2 month old boy who had been icteric since birth. The liver and spleen were palpable 7 cm and 2 cm below the respective costal margins. Bilirubin (total 13.4 mg/dl; conjugated 10.4 mg/dl) and transaminases (SGOT 170 KU, SGPT 110 KU) were elevated. VDRL was reactive with his and his parents serums. Trepanoma pallida was also shown in his cerebrospinal fluid. Osteochondritic changes were present in the femur and radius. Marked hepatitis was found in the liver biopsy. In spite of vigorous penicillin treatment he died within a week with and intercurrent infection.

Case 5: (69/79074) A 2 month old boy who had been icteric since the second day of life. The liver and spleen were 7 cm palpable. Bilirubin (total 14.1 mg/dl; conjugated 6.8 mg/dl) and transaminases (SGOT 640 KU, SGPT 110 KU) were elevated. Toxoplasma Gondii was seen in the liver biopsy and he died soon after discharge from the hospital (Figure 3).

Case 6: N.C. (708047) was an 18 day old boy who had icterus since the 4th day of life. The liver and spleen were 4 cm and 1 cm palpable, respectively. Galactose was seen in the urine chromatography. Bilirubin (total 16.5 mg/dl; conjugated 10.6 mg/dl) and transaminases (SGOT 140 KU, SGPT 58 KU) were elevated. The liver biopsy showed hepatitis and glandular or tubular transformation with mild cholestasis (Figure 5). He died in 10 days with severe diarrhea and dehydration.

Case 7: A.S. (586045) was a 15 day old boy who had icterus and hematemesis, melena, since 2 days of age. The liver and spleen were 5 cm and 7 cm palpable, respectively. Bilirubin (total 8 mg/dl, conjugated 5.4 mg/dl) and transaminases (SGOT 225 KU, SGPT 95 KU) were elevated. The liver biopsy showed neonatal hepatitis. He died at 2 months

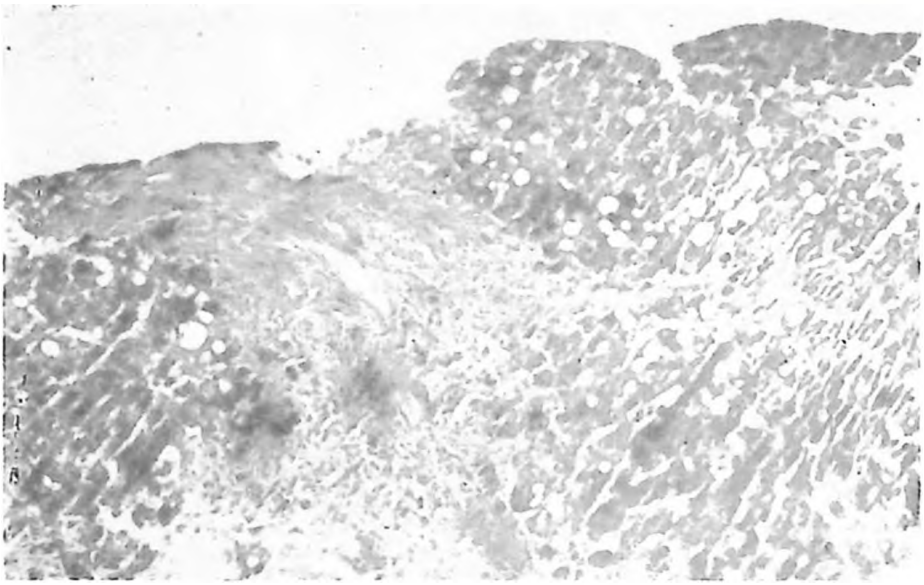

Figure 3

Moderate degree of fatty metamorphosis, fibrosis of portal space with bile duct proliferation. HEx10x10x0.3.

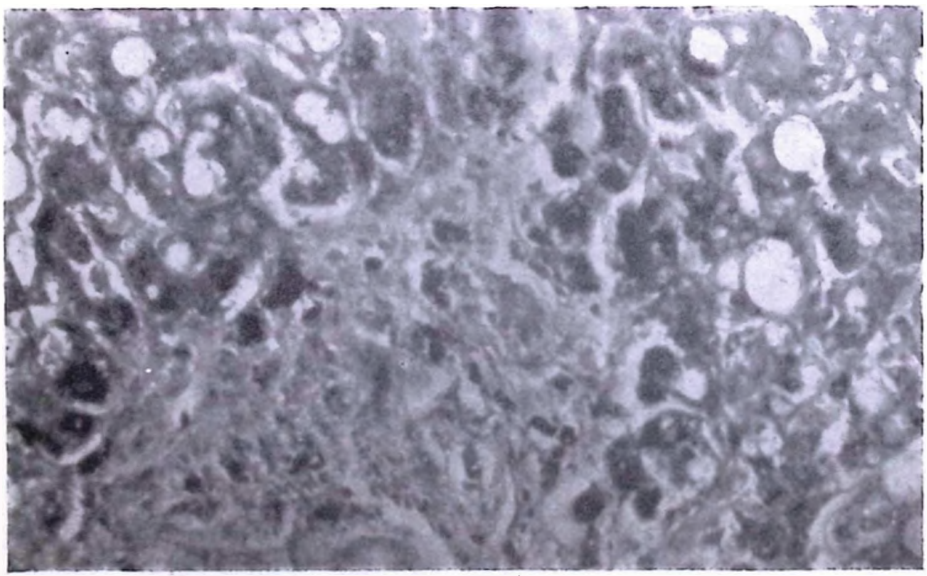

Figure 4

Higher magnification of periportal space PAS (+) and PAS (—) globules are seen. (PAS (—) globules were iron positive). PASx100x10x0.3.

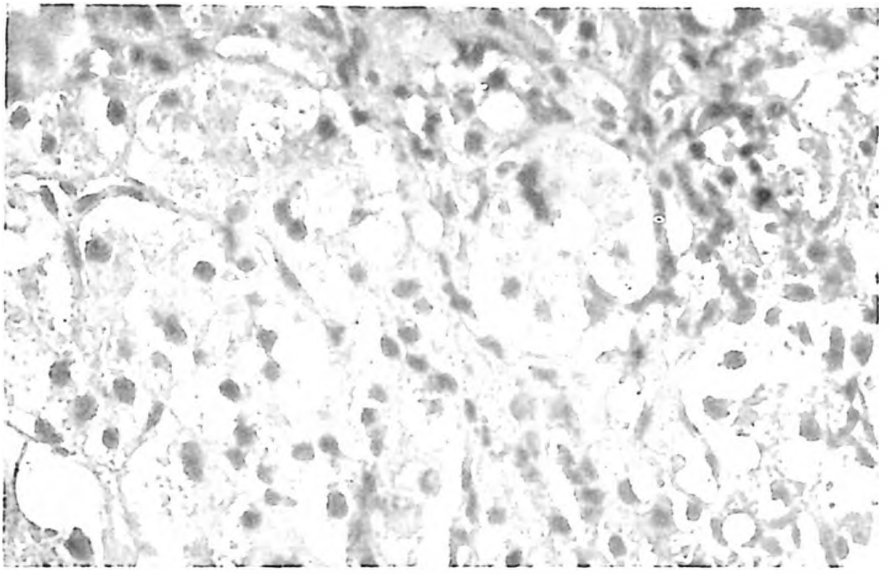

Figure 5
Swollen hepatocytes with fine granular and tubulus like arrangements. HEx100x10x0.3.

of age. Postmortem examination revealed Niemann-Pick disease. His parents were first cousins and one of his sisters had died in another hospital with the diagnosis of Niemann-Pick disease.

Case 8: (657540) was a 2 day old girl who had icterus soon after birth and petechia all over her body. The liver and spleen were 2 cm and 1 cm palpable, respectively. Bilirubin (total 18 mg/dl, conjugated 17.2 mg/dl) and transaminases (SGOT 135 KU, SGPT 12 KU) were elevated. The liver biopsy showed hepatitis and extramedullary hematopoesis. No typical cytomegaly was seen; however there were a few inclusion-like structures in a few cells. Cytomegalovirus was isolated from the liver, urine, blood and feces. She died at 4 months of age.

Discussion

Early and positive differentiation of neonatal hepatitis from biliary atresia is essential for the avoidance of unnecessary laparotomy. Since the conclusions of Thaler and Gellis[1] have not been refuted, it is considered that unnecessary laparotomy in patients with neonatal hepatitis would increase the incidence of cirrhosis. Our impression is that it would also increase the incidence of operative deaths.

For the differentiation on these two main entities several laboratory and clinical findings have been indicated, unfortunately indirect met-

hods for the differential diagnosis such as the ratio of serum bile salts,[12] red cell hemolysis[13], serum alpha fetoprotein concentration[14], serum leucine amino peptidase[15], 5'nucleotidase activity[16], which have been claimed to be the discriminatory values, have not been confirmed in practice.[17] Lipoprotein X decreased following cholestramine in intrahepatic cholestosis but increases in bile duct obstruction.[18] Rose Bengal fecal excretion, cholangiography and percutaneous liver biopsy are the most important investigations for the differential diagnosis of these entities and in this study biopsy findings correlated well with the clinical findings. Conjugated hyperbilirubinemia in infants is not a benign condition therefore less likely possibilities such as hereditary recurrent intrahepatic cholestasis[19], familial intrahepatic cholestasis with mental retardation[20], and Byler's disease[21, 22] should be remembered.

For that reason in all our cases, sweat chloride, α1 antitrypsin, HBs Ag, cytomegalic inclusions, galactosemia and tyrosinosis were investigated and in addition, VDRL and dye tests were carried out in all the patients and mothers.

Viral infections probably are the most frequent cause of neonatal hepatitis. Porter et al[23] have shown evidence of viral infection in 6 out of 15 cases in their prospective studies. Two of our cases had hepatitis B infection, shown by the presence of HBs Ag. Hepatitis B virus infection may be acquired from blood, feces, or saliva of the mother. It may also be transmitted transplacentally or through breast milk.[24, 25] The infected infant may develop hepatitis[26] or may become a chronic carrier of HBs Ag.[27] HBs Ag was present in only one mother but as our method was gel diffusion, which is not very sensitive, this result can not be considered conclusive. Cytomegalovirus was the cause of neonatal hepatitis in one of our cases. Hepatosplenomegaly, jaundice, purpura, extramedullary hematopoesis and multinucleated giant cells were present in this case. This common neonatal infection is usually acquired transplacentally from an asymptomatic mother.[6] However infection may occur by exchange or intrauterine blood transfusion which was not considered in our case.

Congenital syphilis is not a rare fetal infection and may lead to cirrhosis.[5] In our case the diagnosis was verified by serologic and X-ray studies. The parent's syphilitic infection was also shown.

Toxoplasma diagnosis was accepted in a baby by the presence of toxoplasma gondii in his liver biopsy material, who had the clinical findings of the disease in spite of the fact that his mother's dye test was not found elevated. α1 antitrypsin deficiency is usually associated with

cholestatic jaundice in the newborn period which may lead to childhood cirrhosis. Histochemical characteristics of the globules seen in the liver biopsies have been well documented in literature,[28, 29] but we could perform only limited special staining in our case because of insufficient material. However, the diagnosis of α1 antitrypsin deficiency was established by serological means. Morphologic evidence may become prominent as the patients get older. In galactosemia, hepatic changes in the first few weeks of life, are diffuse hepatocellular fatty infiltration and later there are giant cells and pseudoglandular structures which lead to nodular cirrhosis.[30] Among our 11 cases of Niemann-Pick disease in which liver biopsies were obtained, this was the first case that presented with the findings of neonatal hepatitis. Therefore we accept that it is an unusual clinical form of the disease.

Although herpes simplex, adeno virus and coxsackie virus infections are reported as a cause of neonatal hepatitis, they were not considered in the rest of our cases because necrosis or inclusions were absent, which would indicate these virus infections. Clinical findings were also not compatible with the above viral diseases.

After the investigation of all of the etiological factors there remains a group in which the etiology is unknown.[31] Some of these are often familial, and hepatic histology shown multinucleated giant cell transformation with a poor diagnosis.[3] Except for metabolic disease no family history was detected in our series.

In this study etiologic diagnosis could be ascertained in only eight of the cases; the rest of the cases should be considered as idiopathic neonatal hepatitis. The stated mortality rate is about 1/3 of the patients.[32] More than 40 percent of our cases died. This is probably related to the prolonged courses of the disease due to late referral. About 1/3 or 10-20 % of the patients usually develop macronodular or postnecrotic cirrhosis.[5, 11, 32] In our series cirrhosis was present in about 15-16 % of the cases. Treatment of neonatal hepatitis is purely symptomatic. Steroids may be tried but have not given impressive results as in our cases.

Recently, rickets as a complication of neonatal hepatitis has been reported.[33, 34] This complication was also found in two of our cases in whom appropriate treatment was given.

In conclusion we would like to point out that neonatal hepatitis with giant cell transformation either diffuse or focal, may be caused by many different factors, some of which are still unknown. Therefore if is necessary to investigate the whole range of possibilities so that some of the patients could be given more specific treatment.

Summary

The etiology and prognosis of 45 neonatal hepatitis cases are presented. Clinical, laboratory and histopathological findings of this disease are discussed and related literature is reviewed.

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