Neonatal Hepatitis and Extrahepatic Biliary Atresia in the Same Sibship

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SUDA, J., NAKAJIMA, S., OKANIWA, M. and KAMOSHITA, S. Neonatal Hepatitis and Extrahepatic Biliary Atresia in the Same Sibship. Tohoku J. exp. Med., 1981, 133 (4), 445-450 — An instance of the rare occurrence of neonatal hepatitis and extrahepatic biliary atresia in the same sibship is reported. The older brother with neonatal hepatitis developed jaundice at the age of 4 days and had clay-colored stools from early infancy. Cholangiography by exploratory laparotomy at the age of 3 months showed a normal bile duct pattern. After laparotomy, jaundice rapidly disappeared, and stools became yellow. His liver function has been normal since age 6 months to the present (6 years old). The younger brother developed jaundice and clay-colored stools at the age of 1 month. The diagnosis of extrahepatic biliary atresia was made at laparotomy at the age of 4 1/2 months. Hepateojunostomy was performed with successful bile drainage, although he had frequent attacks of ascending cholangitis since operation. These cases support a recent hypothesis that neonatal hepatitis and extrahepatic biliary atresia may be produced by the same disease process.

CASE REPORT

Case 1. F.T. was born on May 30, 1974, the first child of healthy parents who are not consanguineous. His birth weight was 2950 g. During pregnancy, the

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mother had no jaundice nor itching, and has no history of hepatitis or blood transfusion. Delivery was uncomplicated, but the baby had a cephalohematoma at birth. Jaundice was noted at the age of 4 days.

At the age of 32 days, he was admitted to Jichi Medical School Hospital with the complaints of jaundice and clay-colored stools. On admission he was undernourished, weighing 3390 g, and showed moderately icteric sclerae and skin. Liver was palpable 4 cm below the right costal margin and spleen was 1 cm below the left costal margin. Abdominal cutaneous blood vessels were dilated.

Laboratory findings on admission were as follows: Blood type B, Rh (+), WBC 14,200/mm³ (metamyelocytes 1%, bands 3%, segments 27%, eosinophils 8%, monocytes 1%, lymphocytes 53%, atypical lymphocytes 7%), RBC 295 × 10⁴/mm³, Hb 10.1 g/100 ml, Ht 29.7%, reticulocytes 59%, platelets 6.2 × 10⁴/mm³, serum total bilirubin 8.9 mg/100 ml (direct bilirubin 6.6 mg/100 ml), s-GOT 268 U, s-GPT 170 U, α-fetoprotein 320 ng/ml. Serological tests for syphilis, HBsAg and HBsAb were negative. IgM was 36 mg/100 ml, herpes virus CF < ×8, toxoplasma CF < ×32. Urinalysis was within normal limits. No bile was obtained by duodenal tube, and ¹³¹I-rose bengal scintigraphy showed no significant bile excretion at 24 hr.

Exploratory laparotomy was performed at the age of 3 months. Cholangiography showed normal intra- and extra-hepatitic bile ducts. Needle biopsy of the liver showed intact lobular architecture with marked extramedullary hematopoiesis, mild distortion of hepatic cord pattern, a moderate number of multinucleated giant cells, and moderate invasion of portal areas by inflammatory cells. Bile stasis was prominent in liver cells, but not in bile ducts and there was no bile duct proliferation. Electron-microscopically, viral particles were not seen in the liver sections examined.

After exploratory laparotomy, the level of serum bilirubin rapidly decreased, and yellow stools were recognized by 4 days after operation.

At about the age of 6 months, liver function tests became normal, and he has been well for 5 1/2 years.

Case 2. F.A., brother of the Patient 1, was born on January 21, 1977, after full term gestation and uncomplicated delivery. Birth weight was 3250 g. His neonatal period was unremarkable, but from the age of 1 month, clay-colored stools and jaundice were noted by his mother. He was brought to Jichi Medical School Hospital at the age of 3 months.

On admission he was well nourished, weighing 5890 g. Jaundice was moderate. Liver was palpable 2 cm below the right costal margin, and spleen was not palpable. Laboratory findings on admission were as follows: Blood type B, Rh(+) WBC 11,400/mm³ (bands 1%, segments 15%, eosinophils 2%, monocytes 5%, lymphocytes 75%), RBC 419 × 10⁴/mm³, Hb 12.3 g/100 ml, Ht 36.2%, reticulocytes 21%, platelets 47.6 × 10⁴/mm³, serum total bilirubin 9.9 mg/100 ml (direct bilirubin 7.0 mg/100 ml), s-GOT 154 U, s-GPT 907 U, α1-antitrypsin 360 mg/100 ml, IgM 64 mg/100 ml. Serological tests for syphilis, HBsAg, and HBsAb
were negative. Cytomegalovirus CF < ×4, rubella virus CF < 16, herpes virus CF < ×4, coxsackie virus CF < ×4, toxoplasma CF < ×32. Urinalysis was within normal limits. Total serum bile acid was 59.9 µg/ml, and cholic acid/chenodeoxycholic acid ratio was 0.16. Neither lithocholic acid nor 3β hydroxy-5-cholenoic acid was recognized.

After admission there was no improvement in the clay-colored stools or jaundice. Needle liver biopsy showed a distorted pattern of liver cell cords due to numbers of multinucleated giant cells with marked invasion of inflammatory cells in portal areas, and moderate extramedullary hematopoiesis. Bile stasis was mild in liver cells, but was moderate in bile ductules. There was no bile duct proliferation, but there was an increased amount of fibrous tissue in portal areas (Fig. 1). 131I-rose bengal scintigraphy showed no bile excretion at 24 hr.

The diagnosis of neonatal hepatitis was proposed, but his jaundice did not regress with time, and his liver became firmer, so that laparotomy was performed at age 4 1/2 months. Macroscopically, the liver was deep green and firm, the gallbladder was atrophic, and the extrahepatic bile ducts were fibrous and had no apparent lumens. Hepatojejunostomy with Roux-en-Y anastomosis was performed. Histological examination showed microscopic residual ducts buried in dense connective tissue, without inflammatory cells, at the porta hepatis. The liver showed marked alteration of lobular pattern, with marked fibrosis, not only in portal areas, but also replacing parenchymal elements within lobules. Bile ductular proliferation was marked, and bile plugs were numerous in interlobular bile ducts and bile canaliculi (Fig. 2). Immunofluorescent studies with non-specific staining (Yoshizawa et al. 1977) to HBsAg were negative in the liver.

Fig. 1. Liver section of Case 2. Needle biopsy at the age of 3 months shows many multinucleated giant cells, moderate bile stasis, but no bile duct proliferation.
sections examined, and virus cultures of the liver biopsy gave no proliferation in monkey kidney, rabbit kidney (RK 13), or human embryo lung cell strains. Electron microscopic study of neither the needle biopsy of the liver nor the biopsy obtained at laparotomy did show viral particles.

Two days after the hepatojejunostomy, yellow stools were recognized. The level of serum bilirubin fell gradually from 19.9 mg/100 ml to 1.7 mg/100 ml over 90 postoperative days. Three weeks after operation, total bile acid level in intestinal secretion obtained from the jejunal fistula was within normal limits. Chenodeoxycholic acid was initially dominant in the bile but gradually cholic acid became dominant. Since operation, he has frequently had ascending cholangitis which has responded on each occasion to appropriate antibiotics.

Family studies. Both parents are in good health, and their liver function tests are normal. The mother's blood type is O, Rh(+)\. HBsAg and HBsAb, and serological tests for syphilis are negative in both parents.

**DISCUSSION**

In the siblings described here, one brother suffered from neonatal hepatitis, and the other was shown to have biliary atresia. The occurrence of both entities in the same sibship seems, although rare, to shed a light on the causal relationship of these two diseases.

In the literature, there are a few well documented families in which neonatal hepatitis and extrahepatic biliary atresia have occurred in the same sibship. Scott et al. (1954) reported siblings, the firstborn of which had extrahepatic biliary
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Neonatal hepatitis and the fourth and the fifth neonatal hepatitis. Two other siblings and their mother showed transient abnormalities of liver function. Alagille (1972) reported a family of which the second child had neonatal hepatitis, the third extrahepatic biliary atresia, and the first and fourth intrahepatic biliary atresia. One of the patients in the report of neonatal hepatitis in siblings by Peterman (1957) suggests extrahepatic biliary atresia. It is conceivable that other similar cases may have been overlooked. Such observations seem to support the hypothesis of a common insult proposed by Landing (1974).

The younger brother in this report seemed to be more consistent with neonatal hepatitis at the beginning, because of the delayed onset of jaundice, the high α-fetoprotein level, and the prominent inflammatory changes in the earlier liver biopsy. However, later laparotomy at the age of 4 1/2 months revealed the fibrous extrahepatic bile duct without lumens, necessitating hepato-jejunostomy. Such a case strongly supports that the disease process in the same patient changes from that of neonatal hepatitis to that of biliary atresia (Hays et al. 1967; Montogomery and Ruebner 1976).

As to the etiology in the present patients, the possibility of transplacental infection by serum hepatitis virus could be excluded by negative serological examination and immunofluorescent study as well as electron microscopic observations on the liver biopsies. Infections of conventional viruses including rubella, herpes simplex, coxsackie, cytomegalovirus, adenovirus and reovirus were excluded by normal CF titers and negative cultures. Already known genetic causes of neonatal hepatitis such as galactosemia and α₁-antitrypsin deficiency were excluded by clinical symptoms and the course of both patients.

Although not permitting distinction of infections from genetic or toxic causes of “infantile obstructive cholangiopathy”, the family described in this report, with neonatal hepatitis in one brother, and apparent neonatal hepatitis with progression to extrahepatic biliary atresia in the other, provides data supporting the hypothesis that neonatal hepatitis and biliary atresia can result from the same cause (Landing 1974). Further accumulation of such cases is needed to make necessary information available.

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References


