Neonatal hepatitis associated with Australia antigen (Au-1)

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Kattamis, C., Demetrios, D., Karambula, K., Davri-Karamouzi, Y., and Matsaniotis, N. (1973). *Archives of Disease in Childhood*, 48, 133. **Neonatal hepatitis associated with Australia antigen (Au-1).** Two cases of neonatal hepatitis associated with Au-1 in infants aged 95 and 80 days are reported. The first infant died and Au-1 was detected in her parents, both of whom were asymptomatic carriers with normal liver function tests. Neonatal (giant cell) hepatitis in the second child might have been caused by an exchange transfusion on the 4th day of life. Clinical recovery was associated with the disappearance of antigen and a strong antibody response.

Australia antigen (Au-1) has been recently detected in young infants with no clinical or biochemical evidence of hepatitis (Schweitzer and Spears, 1970). In most cases it was probably transmitted orally from a symptomatic or an asymptomatic Au-1 positive mother (Schweitzer and Spears, 1970; Turner *et al.*, 1971; Lyons and Guze, 1971). Follow-up of a small number of Au-1 positive infants disclosed that some showed biochemical evidence of liver involvement with or without mild clinical symptoms.

In 1970 Gillepsie *et al.* described the first case of neonatal hepatitis in which Au-1 was detected in both infant and mother. We here describe two more cases of neonatal hepatitis associated with Au-1 antigen. The first was fatal and Au-1 was also detected in both parents; the second case was most probably related to an exchange transfusion performed on the 4th day of life because of hyperbilirubinaemia of unknown aetiology.

Methods

All serum specimens were tested for Au-antigen and antibody (Au-Ab) by two serological methods: the immunodiffusion procedure (Peters and Aschcavi, 1970) and cross-over electrophoresis (White *et al.*, 1971). The antibody used was obtained from pooled serum from patients with homozygous β -thalassaemia, who were frequently transfused.

Case reports

Case 1. A girl was born normally at term weighing 2,800 g. The mother was a 25-year-old gravida 1; the pregnancy had been uneventful. Neonatal bilirubinaemia was not noted. Since the age of 10 days she had been fed dried milk and was thriving. At the age of 95 days she passed bile-pigmented urine and clay-coloured stools. Two days later she was admitted to our department in good condition, but with mild jaundice which was visible mainly on the sclerae. The liver was palpable 4 cm below the right costal margin; the spleen was just palpable. The main laboratory findings on admission and during her stay in hospital are shown in the Table and the Fig.

FIG.—Bilirubin, SGOT, SGPT levels and presence of Au-1 and Au-antibody in 2 cases of neonatal hepatitis.

TABLE
Laboratory data in two cases of neonatal hepatitis

Laboratory data	Case 1					Case 2						
	16/8/71	23/8/71	30/8/71	Father	Mother	30/6/71	9/7/71	13/7/71	17/7/71	30/7/71	Father	Mother
Hb (g/100 ml)	11.0	11.3	8.6			7.8	10.0	10.5	10.9	11.2		
Bilirubin (mg/100 ml)												
Total	7.4	21.0	20.7	0.60	0.70	15.5	20.2	11.8	7.7	0.80		
Conjugated	4.3	7.1	11.7	—	—	8.7	10.9	7.8	5.3	—		
Urine bile pigment	+	++	+++	—	—	++++	+++	++	+	—		
SGOT (mU/ml)	>1000.0	26.0	36.0	15.0	18.0	>1000.0	100.0		100.0	36.0	10.0	10.0
SGPT (mU/ml)	>1000.0	60.0	28.0	3.0	8.0	680.0	100.0		46.0	30.0	7.0	6.0
Thymol	4.0	6.0		4.0	3.0	2.5			3.0	3.0	4.5	5.5
Turbidity units												
ZnSO ₄	4.5	4.0		3.0	7.0	1.5			3.0	3.0	4.5	7.0
Prothrombin time (%)	10.0					19.0	71.0		100.0			
Cholesterol (mg/100 ml)	270.0	260.0										
Alkaline phosphatase (King-Armstrong units)	35.0	44.0	38.0			40.0		44.5				
Wasserman and Kahn reactions	—	—	—			—	—	—	—	—	—	—
Cytomegalic inclusion	—	—	—			—	—	—	—	—	—	—
Australia antigen	+++	+++	—	+++	+++	+++	—	—	+++	+++	—	—
Australia antibody	—	—	—	—	—	—	—	—	—	—	—	—

The diagnosis of neonatal hepatitis was based on the clinical and biochemical findings (total bilirubin 7.4 mg/100 ml, conjugated 4.3 mg/100 ml; SGOT >1000 mU/ml, SGPT >1000 mU/ml).

Despite treatment with prednisone (2 mg/kg daily) and neomycin, her condition rapidly deteriorated. Jaundice increased progressively and on the 4th day she started vomiting. 5 days later she started to bleed from the skin and the intestine and became restless and tachypnoeic; she eventually went into hepatic coma and died 20 days after admission.

The child's serum was positive for Au-1. Au-1 was also detected in the serum of both parents, neither of whom had any clinical or laboratory evidence of liver disease. Two years earlier the father had had viral hepatitis (probably type B) but all liver function tests had returned to normal in a short time. The mother had never had any clinical sign of hepatitis and her liver function tests were normal (Table).

Case 2. An 80-day-old male infant was admitted to our department because of low grade fever, vomiting, bile-pigmented urine, light coloured stools, and mild jaundice of 3 days' duration. The infant had been delivered normally at the end of an uneventful gestation, and had fed since birth on dried milk. On the 4th day of life he developed severe hyperbilirubinaemia (bilirubin 25 mg/100 ml), and an exchange transfusion with 400 ml of whole blood had been performed at a hospital. From that hospital's records we were unable to identify the cause of the hyperbilirubinaemia, but we were able to exclude rhesus and ABO incompatibilities, and G6PD deficiency. The infant had been well until admission to our department, and his general condition was good, the only abnormal signs being moderate

jaundice, an enlarged liver 5 cm below the right costal margin, and a just palpable spleen.

Laboratory findings (Table) were suggestive of neonatal hepatitis; total bilirubin was 15.5 mg/100 ml with conjugated 8.7 mg/100 ml, SGOT >1000 mU/ml, and SGPT 680 mU/ml. The diagnosis was confirmed by liver biopsy which showed histological changes typical of neonatal hepatitis, with widespread infiltrations of inflammatory cells, mainly lymphocytes and histiocytes, between the hepatic cells; the latter showed granular degeneration and clarity of the cytoplasm. Some of these coalesced to form multinucleated giant cells.

Prednisone (2 mg/kg daily) was administered and the infant recovered fully in 30 days. He was in good general health when examined 6 months later. Unfortunately the parents refused biochemical investigation at this time.

Au-1 was detected in the serum of this patient on more than one occasion during the acute phase of hepatitis; it could not be detected on the 9th day in hospital, and on the 15th day he developed a strong antibody (Au-Ab) which was still detectable 15 days later (Fig.).

No history of hepatitis could be detected in either parents; both had normal liver function tests and were negative for Au-1.

The onset of hepatitis on the 80th day of life and the presence of Au-1 strongly suggested that the baby had been infected during the exchange transfusion since neither parent appeared to have been infected.

Discussion

Krugman and Giles (1970) have conclusively

shown that type B (serum) hepatitis can also be spread by personal contact by the oral-faecal route. Furthermore it is now widely accepted that the detection of Au-1 antigen late in the incubation period and during the acute phase of hepatitis easily distinguishes type B (serum) from type A (infectious) acute viral hepatitis.

In 1954 Stokes *et al.* suggested that viral hepatitis could be transmitted to the fetus through the placenta; however, recent studies here failed to confirm intrauterine transmission of Au-1 antigen (London, DiFiglia, and Rodgers, 1969; Lyons and Guze, 1971; Schweitzer and Spears, 1970; Smithwick and Go, 1970). Women affected with hepatitis associated with Au-1 during gestation gave birth to infants whose serum was negative for Au-1 at birth and during the first few days of life. Though the number of mothers and infants studied is very small, these findings do not justify the assumption that Au-1 is transmitted to the fetus through the placenta. Most of the infants born to women affected with Au-1 hepatitis during pregnancy acquired Au-1 later in life; usually they were clinically and biochemically normal, but occasionally biochemical evidence of liver involvement with or without mild clinical signs was obtained (Gillespie *et al.*, 1970; Turner *et al.*, 1971). On the basis of these data, Schweitzer and Spears (1970) suggested that Au-1 could be transmitted from a positive mother to her infant, either during delivery, by oral contamination with her blood or even her faeces, or post partum by the faecal-oral route during maternal care of the newborn. In nursing mothers Au-1 may be also transmitted via the milk.

In our first case Au-1 must have been transmitted from the asymptomatic positive mother at birth or shortly after; post partum transmission is more probable in view of the length of the incubation period of type B (serum) hepatitis and the age of onset of clinical hepatitis in this infant (95th day of life). The clinical and biochemical findings were diagnostic of severe liver involvement; the fatal outcome indicates that in exceptional cases prognosis may be poor in spite of appropriate treatment. To our knowledge this is the first case of fatal neonatal hepatitis associated with Au-1.

As already mentioned, most of the infants who were positive for Au-1 were clinically and biochemically normal. The same 'silent' carrier state for Au-1 is frequently detected in older children and adults, and is of paramount importance for the epidemiology of Au-1 associated hepatitis. The pathogenetic mechanisms contributing to the development of the 'silent' carrier state have been the subject of wide speculation but are still obscure.

The second case points to another very probable route of transmission of Au-1 to the newborn, namely exchange transfusion. The problem is serious in view of the number of exchange transfusions performed for neonatal jaundice. For many reasons, but mainly because of G6PD deficiency, the incidence of severe neonatal jaundice, for which exchange transfusion is necessary, is high in our country.

The danger of transmitting Au-1 by exchange transfusion is further aggravated by the high incidence of Au-1 carriers among the blood donors, which in Greece is about 3% (Hadziyannis *et al.*, 1971). Hence, with an annual rate of about 350 exchange transfusions in our department, 10 infants must be transfused yearly with Au-1 positive blood. In fact we must consider ourselves very fortunate to be able to say that our second case was the first documented case of neonatal (giant cell) hepatitis associated with Au-1 seen in our department. We suspect that we have failed to diagnose some others with mild clinical symptoms or only biochemical findings.

As our present knowledge is limited, a detailed investigation and close follow-up of all infants with Au-1 associated neonatal hepatitis and all Au-1 positive infants will provide useful information on the clinical, biochemical, and histological spectrum and prognosis of Au-1 associated neonatal hepatitis, and on the future of Au-1 positive asymptomatic infants.

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