Infection with hepatitis B virus in infancy

A longitudinal study of 8 cases

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SUMMARY Eight infants who developed HB_sAg aged between 1 and 5 months were identified in the greater Copenhagen area during the period 1970-76. 7 had acquired the infection from their mothers and one had received a HB_sAg-positive blood infusion. 3 infants had a transient infection lasting 2 to 8 months while the remaining cases developed persistent antigenaemia with evidence of minor liver dysfunction during a follow-up of one to 6 years. HB_eAg was persistently present in 4 of 5 infants, indicating infectivity in these patients. Prematurity or administration of specific immunoglobulin at delivery apparently did not affect the course of infection.

Infection with hepatitis B virus is a rare cause of the hepatitis syndrome in infancy (Mowat *et al.*, 1976; Danks *et al.*, 1977). However vertical transmission from an infectious mother to her newborn infant has been recognised as an important mechanism for the maintenance and dissemination of hepatitis B in many areas (Mazzur and Blumberg, 1974; Okada *et al.*, 1975; Stevens *et al.*, 1975), and this type of infection may account for most asymptomatic HB_sAg carriers found in adults (Sevens *et al.*, 1975).

In the few series of neonatal infection reported, considerable differences have been observed regarding the infants' mothers, the clinical features of the infection, and the incidence of persistent infection in the children (Dupuy *et al.*, 1975; Schweitzer, 1975; Stevens *et al.*, 1975). In order to delineate the course of this infection in infants, a prospective study of all recognised cases of hepatitis B in children aged less than one year between 1970 and 1976 in the greater Copenhagen area (population 1.5 million) is presented.

Materials and methods

All obstetric and paediatric departments, and the department of infectious diseases, in the greater Copenhagen area reported any case in which infection with hepatitis B virus was suspected in a pregnant woman or in an infant. By surveying discharge summaries in 1976 we confirmed that no further cases had occurred.

The diagnosis of hepatitis B infection was based

on the detection of HB_sAg in the blood at age one to 6 months. No case of congenital hepatitis B—i.e. a persistent positive HB_sAg reaction from the day of birth—was identified.

Serological evaluation of the children was made in hospitals; children persistently positive for HB_sAg were investigated further by regular clinical examination and measurement of the levels of prothrombin, alkaline phosphatases, bilirubin, albumin, immunoglobulin G, A, and M, and (by radioimmunoassay) HB_sAg and anti-HB_s (Skinhøj *et al.*, 1976). HB_eAg and anti-HB_e were estimated by agar-gel diffusion (Skinhøj *et al.*, 1976).

Results

The survey resulted in identification of 8 cases of hepatitis B infection (Table).

Origin of infection. The mothers of 7 infants were known to be HB_sAg-positive at delivery or less than 2 weeks before. 4 of these mothers had uncomplicated acute hepatitis with transient antigenaemia, while 2 were persistent carriers of HB_sAg. One had chronic persistent hepatitis, the other had had a renal transplant and received prednisone and azathioprine; she had two children 3 years apart and both were included in the study.

Case 7 was born to a healthy woman, and the infant required exchange transfusions for neonatal hyperbilirubinaemia. At age 2 months the infant was also given a blood transfusion, for anaemia, from a donor subsequently found to be a healthy carrier of Hb_sAg.

Table Eight cases of hepatitis B infection

Case	Sex	Birth-weight (kg)	Mode of delivery	Source of infection	Immunoprophylaxis
1	F	1.9	Spontaneous	Mother AHB	None
2	M	2.8	Caesarean section	Mother RT	None
3	M	3.0	Caesarean section	CHB HB _e Ag+	2 ml HBIG
4	F	2.4	Spontaneous	Mother AHB	None
5	M	2.6	Spontaneous	Mother AHB	None
6	F	3.6	Spontaneous	Mother CPHB	2 ml HBIG
	F	2.3*	Spontaneous	Blood donor healthy	None
8	F	2.3	Caesarean section	HB _e Ag carrier Mother AHB	1.5 ml HBIG

*Weight at infection.

AHB = acute hepatitis B;

RT = renal transplant, receiving prednisone and azathioprine;

CHB = chronic hepatitis B; CPHB = chronic persistent hepatitis B;

HBIG = hepatitis B immunoglobulin.

The 4 infants born to mothers with acute hepatitis were all born 4 to 6 weeks before term, but their neonatal course was unremarkable.

Course of infection. The infants showed no physical disorder, although one (Case 8) was slightly jaundiced for 2 weeks.

Laboratory data are summarised in the Figure. All

infants became antigenaemic within 6 months, but specific hepatitis B immunoglobulin (Skinhøj and Balstrup, 1975) given to 3 infants tended to prolong the incubation period to 12–15 weeks, compared with 6–10 weeks for the untreated infants. In 3 infants (Cases 6, 7, 8) a more than 2-fold increase of s-ALAT was found within one month after development of HB_eAg: 2 subsequently eliminated this antigen.

The course of infection in an infant was apparently not influenced by the state of the mother—e.g. HB_eAg carrier or transiently infected at delivery (Table)—nor by the infant's birthweight or mode of delivery.

Follow-up studies. The 5 children still HB_eAg-positive at 12 months remained so throughout the period of study. 3 cases had persistently raised s-ALAT values, but other liver function tests remained normal in all infants.

HB_eAg was present in all 5 infants and remained so in 4. In the transiently infected children, a normal anti-HB_s response was observed after elimination of HB_eAg.

Discussion

In accordance with previous observations in Caucasians (Papaevangelou *et al.*, 1974; Schweitzer,

Numbers above lines give s-ALAT titres (normal upper limit 40 U/l).

Numbers below lines show results of HB_eAg tests, + = positive, 0 = negative, e = HB_eAg.

HBIG = hepatitis B immunoglobulin, BT = blood transfusion.

Figure Course of hepatitis B infection in 8 infants.

1975; Skinhøj *et al.*, 1976) our group of children acquired the infection from their mothers who in several cases had acute hepatitis, but 3 of the mothers were immunosuppressed because of a renal graft or had chronic persistent hepatitis. This is known to carry a high risk of infectivity and should be separated from the healthy carrier state.

HB_e antigen is usually present in infectious cases. Its presence in the serum in pregnancy is associated with an increased incidence of infection in infants (Okada *et al.*, 1976; Skinhøj *et al.*, 1976; Beasley *et al.*, 1977; Gerety and Schweitzer, 1977).

In contrast with some previous reports (Wright *et al.*, 1970; McCarthy 1973; Dupuy *et al.*, 1975, 1977), our study indicates that some infected children may be expected to eliminate the agent before the age of one year with no major complications.

Our results suggest that s-ALAT may perhaps be a prognostic marker. 2 of the 3 children with abnormal values terminated the infection, while 4 out of 5 without measurable inflammatory reaction became chronic carriers of HB_sAg. Similar findings in adults (Barker and Murray, 1971) suggest that liver damage is related to the immune response rather than to viral replication (Edgington and Chirari, 1975).

With regard to prevention of the infection, neither preterm caesarean section nor withholding breast feeding has been effective (Beasley *et al.*, 1975). Hepatitis B immunoglobulin (Kohler *et al.*, 1974; Schweitzer, 1976) was given to 3 of our patients but all subsequently became infected, and the course was similar to that of the other cases, except that the incubation period tended to be longer.

Similar disappointing results have been obtained in another study (Cossard and Cohen, 1976). Pharmacological immunostimulation with levamisole or similar substance might provide a measure for terminating the prolonged infection. Otherwise, children still positive for HB_sAg at one year are likely to become carriers, and although these children apparently develop normally, the long-term prognosis is unknown, while the persistence of HB_eAg indicates that these individuals will be vectors of hepatitis B virus for many years.

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