Prognosis of chronic hepatitis B transmitted from HBsAg positive mothers

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SUMMARY Nine children born to HBsAg positive mothers, who became chronic HBsAg carriers with associated liver disease, were followed for five to 10 years. Five children with active hepatitis or active cirrhosis at presentation achieved complete remission within six years, while three HBeAg positive patients with minimal histological lesions remained unchanged.

A number of studies performed in the last decade have emphasised the role of perinatal transmission in the spread of hepatitis B virus (HBV) infection in endemic areas.[1] Indeed, children infected in the perinatal period by their mother positive for hepatitis B surface antigen (HBsAg) often become chronic HBsAg carriers with or without associated liver disease. Up to date, however, few studies have examined the long term outcome of HBV infection and disease acquired early in life.[2]

We report the natural history of chronic hepatitis B in nine children born to HBsAg positive mothers during a follow up of five to 10 years.

Patients and methods

The nine infants included in the study (five boys and four girls) were born to mothers known to be HBsAg positive at the time of delivery and had acquired HBV infection in the perinatal period.

The clinical and HBV state of the nine mothers at delivery is shown in the Figure. Three of them (cases 7, 8, and 9) had developed symptoms or signs of acute hepatitis B at the time of delivery or a few days later. Retrospective testing of serum samples revealed a transient hepatitis e antigen (HBeAg) positivity in all three cases, which subsequently resolved. Two mothers (cases 5 and 6) had biochemical features of liver damage associated with HBsAg positivity: retrospective testing revealed HBeAg positivity in both cases, while a liver biopsy examination performed a few months after delivery was consistent with chronic active hepatitis in both cases. The remaining four mothers (cases 1–4) were asymptomatic HBsAg carriers with normal transaminase activities. Testing for HBeAg and antibodies to HBeAg was not performed at delivery, but results obtained at the time when the children presented to us showed anti-HBe positivity in serum in all cases.

For different reasons none of the nine children received specific immunoglobulin at birth. HBV vaccine was not yet available when the children acquired the infection. During the perinatal period none of the other household contacts of these patients was found to be HBsAg positive.

Three infants (cases 1, 2, and 5 in the Figure) presented to us at 3 months of age with symptoms or signs (jaundice (1 case), anorexia, vomiting, and hepatomegaly) of liver disease. Peak alanine aminotransferase (ALT) activities, ranging between 350 (in the jaundiced patient) and 1600 IU/l (normal

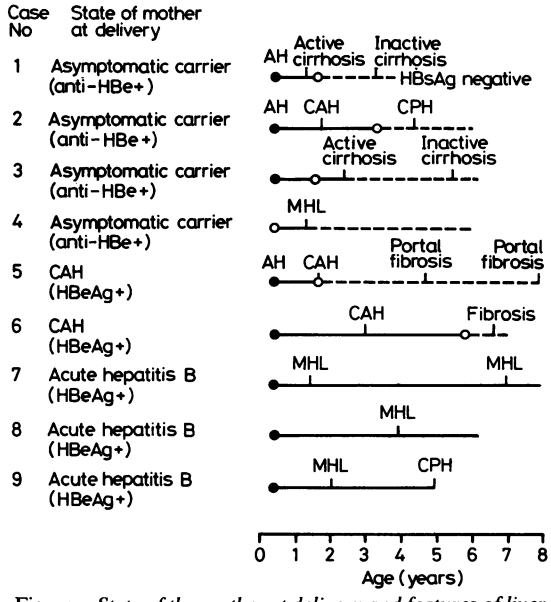

Figure *State of the mother at delivery and features of liver disease during follow up in nine children born to HBsAg positive mothers. ●=HBeAg positive; ○=anti-HBe positive; ——=abnormal alanine aminotransferase; – – –=normal alanine aminotransferase; AH=acute hepatitis; CAH=chronic active hepatitis; CPH=chronic persistent hepatitis; MHL=minimal histological lesions.*

values <50 IU/l) were consistent with acute hepatitis. In all three cases symptoms subsided spontaneously within eight weeks. The remaining six children were asymptomatic and were found to be HBsAg positive with abnormal transaminase activities (ALT range 60 to 150 IU/l) at the age of 3–4 months when routine tests were performed due to the HBsAg carrier state of their mother. Antibody to hepatitis delta antigen was negative in all cases. Six months after the onset of infection all nine children were still HBsAg positive and were therefore considered to be chronic HBsAg carriers. They have been followed up in the outpatient clinic and tested for ALT and HBV markers every four to six months. One or more liver biopsy examinations have been performed by the Menghini technique in each patient during observation.

Methods. HBsAg, HBeAg, and anti-HBe, as well as anti-delta antibody in serum, were detected by commercial radioimmunoassay techniques (Abbott Laboratories, Chicago, Illinois).

Results

All children were completely asymptomatic six months after the onset of infection and continued to be asymptomatic throughout the observation period of five to 10 years (mean (SD) 6·5 (1·0) years). Hepatomegaly was present in six cases and splenomegaly in two. None of the patients received treatment.

As shown in the Figure, three of four children born to asymptomatic anti-HBe positive mothers (cases 1, 2, and 3) were HBeAg positive and developed features of chronic active hepatitis, with associated cirrhosis in two cases. Seroconversion from HBeAg to anti-HBe with subsequent sustained normalisation of enzymes occurred in all three children within the third year of life. A liver biopsy taken one to three years after seroconversion showed disappearance of histological activity in all three cases. A boy with inactive cirrhosis cleared HBsAg from serum at the age of 3 years.

The fourth patient born to a anti-HBe positive mother (case 4), who was already anti-HBe positive at first testing, showed minimal histological lesions on biopsy examination (minimal lymphocellular infiltrate and mild fibrosis of the portal triad) and normalised ALT activities during the second year of life. Both children born to HBeAg positive mothers with chronic active hepatitis (cases 5 and 6) developed HBeAg positive chronic active hepatitis. They seroconverted to anti-HBe with subsequent remission of the disease at 18 months and 6 years of age, respectively. A liver biopsy taken after anti-HBe seroconversion was consistent with portal fibrosis in both cases.

Finally, all three children born to mothers with acute hepatitis at delivery (cases 7, 8, and 9) developed non-progressive liver disease. During the whole follow up they remained HBeAg positive with minor ALT fluctuations. During follow up none of the patients developed features of liver failure or clinical signs of portal hypertension.

Discussion

In this small series maternally transmitted HBV infection resulted in a chronic HBsAg carrier state associated with a variety of clinical and histological patterns, ranging from minimal liver lesions to cirrhosis. These patterns seemed to be related to the clinical and virological state of the mother at delivery. Indeed, all three children born to mothers with acute hepatitis B became asymptomatic HBeAg positive carriers with minor liver lesions, according to the observations of Schweitzer *et al*,[3] while children born to HBeAg positive mothers with chronic active hepatitis themselves developed an active liver disease. Two different patterns were observed instead in the offspring of asymptomatic anti-HBe positive mothers: a mild liver damage associated with anti-HBe positivity or a severe liver disease, sometimes presenting as acute hepatitis and progressing to early cirrhosis.

It has been hypothesised that maternally transmitted virus charge may influence the degree of specific immune response in the infected baby.[4] According to this hypothesis we could suggest that in our patients a heavy virus charge, capable of inducing immune tolerance, had been transmitted by mothers with acute hepatitis at delivery, while a lower charge, inducing an efficient, although inadequate, immune response to the infected hepatocytes, had been transmitted not only by anti-HBe positive mothers but also by HBeAg positive mothers with chronic active hepatitis.

The outcome of liver disease in our patients was closely related to the severity of liver lesions and to HBeAg/anti-HBe state at presentation, as also suggested by previous observations in children with chronic type B hepatitis.[5] In fact, remission of liver disease was observed not only in the child with minimal histological lesions associated with anti-HBe positivity but also in children with chronic active hepatitis or active cirrhosis after anti-HBe seroconversion. Conversely, all three children with minimal histological lesions and HBeAg positivity at presentation remained unchanged throughout the observation period, as also described by Tong *et al* in some of their cases.[2]

According to recent epidemiological observations[6] all our patients, who became chronic HBsAg carriers early in life, may develop hepatocellular carcinoma: continuing surveillance, however, will clarify whether the different histological and virological patterns observed in these children during the early phase of HBV infection may influence the final outcome of their liver disease.

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