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## ORIGINAL ARTICLE

## Natural history of hepatitis B in perinatally infected carriers

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**Objectives:** To establish natural seroconversion rates and incidence of hepatic pathology in perinatally infected hepatitis B carriers.

**Methods:** Seventy three perinatally infected hepatitis B carriers identified through maternal screening were evaluated. Fifty three were born to parents from the Indian subcontinent, nine were Oriental, six were Afro-Caribbean, and five were white. Median follow up was 10.24 (range 2.02–20.16) years.

**Results:** Only three of the children followed up had cleared hepatitis B surface antigen during this period, and 30% of the children had seroconverted to anti-HBe. Seroconversions to anti-HBe were observed in Asian (18/50) and white (4/5) children, but not in Oriental or Afro-Caribbean children. More girls (40%) than boys (23%) had seroconverted, but the difference was not significant. All children were asymptomatic with normal physical examination, growth, and development. Almost half (48%) of the hepatitis B e antigen (HBeAg) positive children had normal hepatic transaminases and liver function. Thirty five liver biopsies were performed in children with active virus replication (HBeAg or hepatitis B virus DNA positive) who were being considered for antiviral treatment as part of a clinical trial and were scored using the Ishak method. Two thirds (62%) of the children had mild hepatitis, 60% had mild fibrosis, and 18% had moderate to severe fibrosis. There was a weak correlation between histological evidence of hepatitis and hepatic transaminase activity, implying that biochemical monitoring of hepatic disease activity may be ineffective.

**Conclusions:** These asymptomatic hepatitis B virus carrier children remain infectious in the medium to long term with notable liver pathology. They should receive antiviral treatment to reduce infectivity and to prevent further progression of liver disease. Hepatic transaminases alone are not a reliable marker of liver pathology, and liver histology is essential before consideration for antiviral treatment.

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Much is known about the natural history of hepatitis B virus (HBV) infection in adults and its implication for hepatic morbidity/mortality,<sup>1–5</sup> but the medium to long term outcome of HBV infection in perinatally infected children is unclear. Published observational studies of HBV infections in childhood have been carried out in countries with high endemicity, where the sources of infection have been a mixture of perinatal and horizontal transmission.<sup>6–9</sup> It is likely that the prognosis in perinatally infected children is different from those infected later or as adults.<sup>2, 10</sup> Further information is needed about the medium term outcome in those children who become asymptomatic carriers from perinatal infection, particularly in countries with a low endemicity of HBV infection.

The aim of this study was to establish the natural seroconversion rate and incidence of hepatic pathology in a cohort of children, born to known hepatitis B e antigen (HBeAg) positive carrier mothers,<sup>11–13</sup> who had been documented to be hepatitis B surface antigen (HBsAg) positive from early infancy, and to evaluate whether serum transaminases could be reliably used to screen for hepatocellular damage in HBV carriers.

## SUBJECTS AND METHODS

Data were available on 73 children, born to mothers who were both HBsAg and HBeAg positive, who had been identified as carriers in early infancy during previous studies. Fifty one of the children had been born before immunisation against hepatitis B became available. They were identified through studies on perinatal transmission of hepatitis B and family testing of siblings.<sup>11–13</sup> The remainder (22) were "vaccine failures" identified through follow up of vaccine intervention studies.<sup>14, 15</sup> Only nine of these 22 vaccine failure children had received what would now be considered

adequate post-exposure vaccination for babies of HBeAg positive mothers—that is, hepatitis B immunoglobulin at birth and vaccine within 48 hours of birth followed by further doses at 1, 2, and 6 or 12 months of age.<sup>15</sup> Four of the nine had received a complete course of four doses of vaccine according to the study protocol,<sup>15</sup> and five had received a complete course of four doses of vaccine plus hepatitis B immunoglobulin at birth. The remaining 13 children had had incomplete or wrongly scheduled courses.

Families were initially approached by letter, after the consent of their general practitioner had been sought. We then reviewed the family members either in the outpatient department of the Birmingham Children's Hospital or at their homes.

## Laboratory investigations

Laboratory estimates of urea and electrolytes, liver function indices, full blood count, clotting studies,  $\alpha$  fetoprotein, and HBV markers were obtained on two or more occasions over 12 months. Delta antibody was assayed once. Routine biochemical and haematological methods were used. Hepatitis B markers studied included HBsAg by enzyme immunoassay (Blood Products Laboratory, Elstree, Hertfordshire, UK), HBeAg and anti-HBe by radioimmunoassay (Abbott Laboratories, Chicago, Illinois, USA), and quantitative estimation of HBV DNA by solution hybridisation (Genostics; Abbott Laboratories, Chicago, Illinois, USA). Delta antibody was assayed using an enzyme immunoassay method (Noctech, Dublin, Ireland).

**Abbreviations:** ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus

A full medical examination, including nutritional parameters, was performed on all children at each clinic visit. Families were informed of the need for further investigation and/or indication for antiviral treatment depending on the results of the preliminary screening tests.

The indication for liver biopsy was HBV carriage with evidence of active viral replication, namely HBeAg positivity or measurable HBV DNA by solution hybridisation assay. Children were admitted to the Liver Unit of the Birmingham Children's Hospital for percutaneous liver biopsy and abdominal ultrasound. Patients over the age of 7 were discharged home eight hours after the procedure; younger children stayed overnight. None suffered any notable side effects from the procedure. Children found to have histological evidence of HBV infection were then invited to participate in a randomised, controlled trial of treatment with subcutaneous  $\alpha$  interferon.<sup>16</sup>

### Histopathological assessment

Blinded histological assessment was carried out on 36 percutaneous liver core biopsy specimens, representing the pretreatment arm of a separate study.<sup>16</sup> One of these specimens contained no liver tissue, bringing the total number to 35. The length of the specimen was recorded, and grading and staging were performed using the scoring methods of Ishak *et al.*<sup>17</sup> This scoring system is a modification of the Knodell histological activity index, examining and scoring various features of inflammation and architectural change in the liver biopsy, and is widely used in studies of chronic viral hepatitis. Before evaluation of the biopsy specimens, three pathologists (PJS, APD, and RAS) reached consensus on the grading and staging criteria. Because the degree of activity in many of the specimens was mild, particularly with regard to interface hepatitis, low thresholds were established for the lower grades to allow distinction between slight differences in these mildly inflamed livers. One observer (RAS) carried out scoring of the entire set of biopsy specimens. Uncertainties were resolved by review with the other observers (APD, PJS). About 10% of specimens from the study, randomly selected, were rescored by RAS to determine intraobserver variation.<sup>18</sup> These reassessments varied at most by one category in one component of the score, and after further review with APD a final consensus score was reached for each of the specimens. An additional note was made of the overall hepatitis activity as assessed subjectively, the amount of steatosis, presence and distribution of siderosis, and presence of ground glass hepatocytes (on the haematoxylin and eosin stained section, as well as HBsAg detecting stains—orcein and HBsAg immunostaining—where available).

### Statistical methods

The influence of sex, ethnicity, and age on pathology scores was compared in the different categories of pathology using  $\chi^2$  and Fisher's exact tests. Mann-Whitney or Kruskal-Wallis tests, as implemented in the SPSS statistical package, were used to compare the median activities of transaminases in different categories such as ethnic groups. The association of pathology scores with transaminase activity was considered using the Jonckheere-Terpstra test for comparing median transaminase activities in the ordered categories of hepatology score. Ordinal logistic regression was also used to explore whether there was multifactor association between pathology score and transaminase activity taking into account other factors such as sex, age, and ethnicity.

### RESULTS

Seventy three children were studied, 36 of whom were male. Fifty three were born to mothers from the Indian

subcontinent (Asian), six were Afro-Caribbean, nine were Chinese (Oriental), and five were white. Median follow up age was 10.24 (range 2.02–20.16) years.

All children were clinically well. Physical examination was normal; in particular, there was no hepatosplenomegaly. Abdominal ultrasound of the liver was normal in all children. All children were within the normal range for height, weight, and other nutritional parameters and attended normal schools. Routine laboratory indices were normal for renal function, haematology, and coagulation. Liver function tests indicated normal values for bilirubin, alkaline phosphatase, and albumin.

### HBV serology

Follow up was deemed to be equal to age at initial review, as all children had been documented carriers from infancy. No child was positive for delta antibody.

Three Asian children, two girls and one boy, had cleared HBsAg and had seroconverted to antiHBs. None of these children had been vaccinated; one was born before vaccine was available.

The presence of HBV DNA (75%) was similar to HBeAg carriage (66%) (table 1). More boys than girls were HBeAg positive (27/35 (77%) v 21/35 (60%)), and more girls than boys were anti-HBe positive (14/35 (40%) v 8/35 (23%);  $p = 0.2$ , Fisher's exact test; table 2). The latter was particularly true in the largest group, the Asian children: 11/28 (39%) v 7/22 (32%) ( $p = 0.77$ ). However, these differences were not significant. Overall HBeAg seroconversion in Asian HBV carriers was 18/50 (36%). Four of the five (80%) white children seroconverted to anti-HBe, but there was no seroconversion in any Chinese or Afro-Caribbean child. In this group of children, 30% had seroconverted to anti-HBe by 10 years of age.

It is difficult to establish the exact date of seroconversion in this study. However, the earliest age of the first anti-HBe results was 10.2 (4.0–19.7) years (median (range)) for girls and 9.96 (4.7–18.6) years for boys. The age of earliest seroconversion was 6.5 (5.8–8.0) years in white children and 11.8 (4.0–19.7) years for Asian children.

Results were analysed in terms of "high" (HBeAg positive) and "low" (anti-HBe positive) infectivity (table 2). All but one of the 48 HBeAg positive carriers was also HBV DNA positive, with a median concentration of 141 (2–616) pg/ml. The median HBV DNA concentration in the HBeAg positive children was higher than in those who were anti-HBe positive, the girls having a slightly higher median value. Only six of 22 (27%) anti-HBe HBV carriers had detectable HBV DNA, which was at a very low concentration, giving a median value of 0.0 (0.0–8.0) pg/ml. The age of the HBeAg positive girls was lower than that of the boys (8.46 (2.04–16.76) v 11.95 (2.65–20.16) years). There was no noteworthy difference in the clinical course between those children who had not been vaccinated (median age 12.94 years) and those

**Table 1** Hepatitis B markers and alanine transaminase activity in hepatitis B virus carrier children

Follow up (years)	10.24 (2.02–20.16)
Immune	3 (4.1)
HBeAg positive	48 (65.8)
Anti-HBe positive	22 (30)
ALT (U) (normal range 0–50 U/ml)	45 (13–167)
HBV DNA positive	55 (75)
HBV DNA (pg/ml)	81.6 (0–616)

Values are median (range) or number (%). HBeAg, hepatitis B e antigen; ALT, Alanine aminotransferase; HBV, hepatitis B virus.

**Table 2** Comparison of HBeAg positive and anti-HBe positive children

	HBeAg positive		Anti-HBe positive	
	Boys	Girls	Boys	Girls
Number	27	21	8	14
Age (years)	11.95 (2.65–20.16)	8.46 (2.04–16.76)	11.34 (5.09–18.44)	11.12 (4.23–19.55)
HBV DNA (pg/ml)	130 (2–527)	193 (33–616)	0 (0–8)	0 (0–4)
Median ALT (U) (normal 0–50 U)	46 (22–167)	49 (22–91)	57 (31–82)	29 (13–76)

Values are median (range).  
HBeAg, hepatitis B e antigen; ALT, Alanine aminotransferase; HBV, hepatitis B virus.

who had failed vaccination, except that the vaccine failures were younger (median age 6.14 years), because of the later development of vaccine programmes.

**Liver biochemistry**

Two thirds of the Oriental children and half of the Asian children who were HBeAg positive had normal alanine aminotransferase (ALT) activity. The anti-HBe girls had lower ALT activity than the HBeAg positive girls and boys whether HBeAg positive or anti-HBe positive (table 2).

There were no significant changes in the median aspartate aminotransferase (AST) and ALT activities over time for individual children, except for one child who had a threefold increase in AST and ALT and expression of HBV DNA over 300 pg/ml. On further follow up over two years, the patient seroconverted at the age of 10.6 years, becoming negative for HBV DNA with transaminase activity falling to within the normal range.

**Hepatic pathology**

Liver tissue was available in 35 children (table 3). In the subjective overall evaluation, one biopsy showed no evidence of hepatitis (Ishak grade and stage 0), 29% were minimally inflamed (Ishak grade (the sum of the necroinflammatory scores A–D 1–3), 63% showed mild hepatitis (Ishak grade 2–4), and 6% showed moderately severe activity (Ishak grade 5–6). This higher activity included both interface hepatitis and parenchymal (lobular, acinar) changes. Confluent necrosis was not seen in any of the biopsy specimens.

Similarly, the scores for staging (fibrosis and architectural distortion) were low; 20% of the specimens showed no evidence of fibrosis, 60% scored stage 1 or 2; 14% showed moderate fibrosis, scoring 3. Although no specimens showed fully developed changes of cirrhosis, two were scored 5 (“incomplete cirrhosis”) because of the formation of nodules (table 3).

Ground glass hepatocytes were not easily identified on the haematoxylin and eosin stain, only being clearly present in one specimen (3%). In most cases, orcein staining clearly showed cytoplasmic positivity, with abundant positive cells in 40% of specimens, and fewer cells staining in a further 37%. No orcein staining was seen in 23% of the specimens. HBsAg and HBeAg immunostaining was available for 11 specimens. Core antigen nuclear positivity was evident in all cases, although in one case only one nucleus stained positive,

and core antigen cytoplasmic staining was seen in two cases. Surface antigen staining was more variable. In three cases where no orcein staining was evident, HBsAg cytoplasmic staining was seen. Conversely, in three cases where orcein staining was seen, no HBsAg immunostaining was evident. Many of the biopsy specimens showed nuclear vacuolation, particularly in periportal hepatocytes. Mild hepatocellular siderosis (grade 1 in a 0–4 grading system) was present in two specimens only. In three (9%), focal mild hepatocyte macrovesicular and microvesicular steatosis was evident.

Ordinal logistic regression did not show any significant relation between degree of hepatic pathology (either individual components of the grade or stage) with age at biopsy, sex, ethnic origin, or vaccine status. There was a weak association between median AST activity and interface hepatitis grades (medians 49, 54, and 77 in grades 0, 1, and 2 respectively;  $p = 0.03$ , Jonckheere-Terpstra test), and also between ALT activity and lobular hepatitis and focal damage (medians 35, 45, and 81 in grades 0, 1, and 2;  $p = 0.05$ ). There was no noteworthy association between either ALT or AST and portal inflammation.

**DISCUSSION**

Seventy three children who were known to be perinatally infected from HBeAg positive mothers were studied over 10 years to evaluate seroconversion rates. These children were born before universal antenatal screening, and active immunisation of babies at risk of infection was a Department of Health recommendation. Most of the vaccine failures were due to failure to deliver a complete course of immunisation, and reflected the difficulty of access and communication with the families of babies at risk. In those who had received a full course of vaccine and hepatitis B immunoglobulin, failure to protect was associated with a high concentration of HBV DNA in the mother carrying a risk of in utero infection.<sup>19</sup> Much work has been done to improve vaccine uptake over the last decade, and perinatal transmission of hepatitis B is now a rare event.<sup>20, 21</sup> There were no clinical differences between the children who were vaccine failures and those who had become perinatally infected before vaccination was available.

**HBsAg clearance**

The HBsAg clearance in this group of children was low and is similar to that described in a cohort of Chinese children followed up for a similar period of time (0.6% per year).<sup>9</sup> This is lower than expected in those infected as adolescents and adults (1.8% per year),<sup>22</sup> as it is known that acquisition of infection by non-perinatal routes is associated with a higher HBsAg clearance.<sup>8</sup>

**HBeAg to anti-HBe seroconversion**

There was no difference in the number of boys and girls who became HBV carriers, but the anti-HBe seroconversion rate was higher in girls than boys, although this was not significant. Seroconversion was found to occur earlier in

**Table 3** Summary of Ishak grade and stage for liver biopsy specimens in 35 children with chronic hepatitis B

	Grade				Stage			
	0	1–2	3–4	5+	0	1–2	3–4	5–6
Number	1	8	24	2	7	21	5	2

girls than boys in a previous study of perinatally infected children,<sup>13</sup> but this was not confirmed in this larger and longer follow up study, in which the age at seroconversion in boys and girls was the same. Previous studies have shown that the clearance of HBeAg is higher in horizontally infected children (35%) and adults (5–18%) than in those infected perinatally, in whom clearance was less than 2% in children under 3 rising to 14% in those over 6 years.<sup>23–25</sup> This may explain the low seroconversion rate in this study. Other factors are associated with HBeAg seroconversion—for example, history of acute hepatitis B, higher ALT activity, being female.<sup>22 23 26 27</sup> To achieve a seroconversion, the level of virus replication must decrease, to slow down the production of HBeAg, and a sustained immune response is required to increase the concentration of anti-HBe and to further immune clearance of HBV infected liver cells. Sometimes during this process, variant viruses emerge with increased HBV DNA in the absence of HBeAg; such variants were not observed in this study.

Studies in the Far East show a very low rate of HBeAg clearance<sup>9 10 27 28</sup> in Oriental children, whereas European studies show more encouraging results.<sup>8 24</sup> It is interesting that we observed no seroconversion in any Oriental or Afro-Caribbean child and a high level of seroconversion in the few white children (four of the five). The earliest age at which seroconversion was observed was lower in the white children (median 6.5 years) than in the Asian children (11.8 years). However, owing to the small number of white children, no conclusions can be drawn. More intensive follow up of this group of children may reveal further seroconversions as they get older. The average age at seroconversion (10 years) makes it unlikely that seroconversion is associated with the onset of puberty. A large study on Chinese children did not observe a higher anti-HBe seroconversion rate in girls.<sup>27</sup> The number of Chinese girls in our group was small, but we have noted a strong trend for more female than male Asian patients to become anti-HBe positive.<sup>12 13</sup>

We have observed an HBeAg prevalence across all ethnic groups in Birmingham of 10–20% (unpublished observations) in adult female hepatitis B carriers detected through antenatal screening, suggesting that further anti-HBe seroconversion may occur in girls as they approach adulthood. There is no comparable study on healthy male HBV carriers to show if the differences in seroconversion that we have observed between boys and girls are maintained into adulthood.

### HBV DNA concentrations

More recent studies on the natural history of hepatitis B have included measurement of HBV DNA. Not all HBeAg positive carriers are found to be HBV DNA positive by relatively insensitive techniques such as the hybridisation assay used in this study. With more sensitive polymerase chain reaction techniques, all HBeAg positive carriers and many anti-HBe carriers can be shown to have HBV DNA.<sup>29</sup> The HBeAg positive children in our study had high concentrations of HBV DNA, only two of the 48 HBeAg positive children having a concentration less than 10 pg/ml (1 pg/ml is equivalent to 10<sup>6</sup> HBV DNA genome equivalents/ml). This has implications for their infectivity to siblings, other family members, and close social contacts who may be exposed to other body fluids<sup>30</sup> and who should now be protected by active immunisation with hepatitis B vaccine.<sup>31</sup>

### Histology

The children in this study were healthy with no obvious physical evidence of liver disease. Most biochemical indices of liver disease were within the normal range; in particular, transaminase activity was not significantly raised in any of the groups. Despite this, all of the children biopsied had

histological changes secondary to hepatitis B. Most of the biopsy specimens showed only mild inflammation, but 6% had a more active hepatitis. Furthermore, 60% showed a mild degree of fibrosis, with 18% showing moderate to severe fibrosis, suggesting a degree of progression, even in childhood. The weak correlation of interface and lobular hepatitis with transaminase activity implies that biochemical monitoring of hepatic disease may be ineffective, as has been shown with hepatitis C,<sup>32</sup> leading to an underestimate of liver pathology.

These data are similar to the results of a study in Mediterranean children,<sup>6</sup> which reported that 57% of children horizontally infected with hepatitis B had active hepatitis after 1–10 years of follow up, and some children had developed cirrhosis.<sup>7</sup> In contrast with our study, those children had more substantial biochemical evidence of liver disease, perhaps because they had been infected horizontally.

There may be important differences in the way carriers of different ethnic origins respond to infection with hepatitis B. As most of the children in this study were born to parents from the Indian subcontinent (53/73; 73%), this may explain why the results differ from those of perinatally infected patients from the Far East<sup>9 10 27</sup> or horizontally infected white children.<sup>8 24</sup>

In conclusion, within this group of perinatally infected children, HBeAg carriage was associated with high infectivity and substantial hepatic pathology, despite normal physical examination and minimally raised transaminase activity, suggesting that biochemical assessment alone underestimates the extent of liver pathology. We recommend that liver histology should be part of the assessment of these children who should be considered for antiviral treatment to prevent progression of disease.

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