Vertical transmission of hepatitis B surface antigen in carrier mothers in two west London hospitals

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SUMMARY 126 children of 102 hepatitis B surface antigen (HBsAg) carrier mothers were delivered at Hammersmith Hospital and Queen Charlotte's Maternity Hospital, between 1971 and mid-1978. Blood tests on 110 of these children showed that 8 out of the 18 with Chinese mothers, but only 6 out of the 92 other children, have become HBsAg positive. The presence of maternal hepatitis B e antigen (HBeAg) is also significantly correlated with transmission of HBsAg to the children. The management of children whose mothers are carriers is discussed.

Since the discovery of hepatitis B antigen (Australia antigen) in 1965 leading to the identification of the causative agent of hepatitis B (Blumberg et al., 1965; Prince, 1968; Krugman and Giles, 1970), awareness of its position as a major source of both acute and chronic disease has been growing (Ohbayashi et al., 1972; Kattamis et al., 1974; Dupuy et al., 1975; Welsh et al., 1976). Sensitive and rapid tests for the detection of the whole virus (HBV) and its components, the surface antigen (HBsAg) and core antigen (HBeAg) are now available, and these have contributed to our knowledge about the prevalence and modes of transmission of HBV. Besides these antigenic particles and their corresponding antibodies (anti-HBs and anti-HBc), other markers have been found in association with HBV, notably hepatitis B 'e' antigen (HBeAg) and anti-HBe (Magnusi et al., 1975).

It is known that the prevalence of HBV varies geographically, and is estimated to be 0·1% in northern Europe and North America, but up to 20% in Taiwan (Shih et al., 1971; Gerety et al., 1974; Helske, 1976; Chen and Sung, 1977). Modes of spread of the virus include direct or accidental inoculation of infected blood or blood products through transfusion, intravenous drug abuse, tattooing, acupuncture, dental work, shared razors, laboratory accidents, and perhaps insect vectors (Metselaar et al., 1973; Patterson et al., 1974), sexual contact (Heathcote et al., 1974b), and 'vertical' transmission from mother to baby (Turner et al., 1971; Merrill et al., 1972; Papaevangelou et al., 1974; Anderson et al., 1975; Stevens et al., 1975), probably through ingestion or passage of blood through broken skin or mucous membranes during delivery. Most body fluids, including saliva (Bancroft et al., 1977), sweat (Telatar et al., 1974), semen (Heathcote et al., 1974a), pleural fluid (DeFlora and Forci, 1977), breast milk (Krugman, 1975), and blood may contain the virus. Horizontal spread in ways other than through blood seems likely but has not been well defined (Szmuness et al., 1975).

As the virus is able to persist in man for long periods (after acute hepatitis or without detectable illness), producing so-called 'carriers', defined as those in whom HBsAg is present for more than 6 months (World Health Organisation, 1977), it would appear that a large reservoir may preclude its eventual eradication.

Through screening and the gradual elimination of HBsAg-positive carriers from panels of blood donors, once an important source of hepatitis, vertical transmission may rapidly become the principal means of viral spread, especially in countries with a large number of carriers. One report (Derso et al.,
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1978) indicated that certain ethnic groups, particularly the Chinese, may be genetically prone to such transmission, and the increased risk does not appear to be related to the birthplace of the mother but to her ethnic origin. We report here a study based on all the infants delivered of HBsAg-positive carrier mothers at two hospitals in west London, the Hammersmith Hospital and Queen Charlotte's Maternity Hospital. This study appears to confirm earlier work. Some of the mothers from the Hammersmith Hospital were the subject of a previous report (Waterson et al., 1977).

Methods and subjects

Since July 1971 at Hammersmith Hospital, and since January 1972 at Queen Charlotte's Maternity Hospital, all antenatal patients have been screened for the presence of HBsAg. From those dates up to August 1978, a total of 102 HBsAg-positive carriers have been detected who subsequently delivered 126 live infants. There were no stillbirths. The total number of deliveries during those periods in the two hospitals was 33 467, giving a prevalence of 0.4 per 1000 deliveries. Ten abortions, 6 acute cases of hepatitis, and 6 cancelled bookings of carrier mothers have been excluded, as we were only interested in liveborn infants of carriers.

Cord blood samples were sent in the early years of the study for HBsAg screening by gel diffusion or immunoelectrophoresis, and after 1974, by direct passive agglutination (Hepatest, Wellcome). In a few cases that were positive, a sample of the baby's blood was also tested. 60 cases in which the cord blood was negative were also sent for radioimmunoassay (RIA) testing (at the Public Health Laboratory Services, Colindale, London).

Between February 1972 and May 1974, 8 randomly selected infants whose cord bloods were negative were given 1 ml (100 mg) of hepatitis B immune globulin (HBIG) at birth, and one was given 2.5 ml at birth. A further 10 infants were given 1 ml of HBIG at birth with a single repeat of this dose between 2 and 8 months, if blood was still negative for HBsAg. This trial was stopped in 1974.

Breast feeding was allowed freely, as we agree with other workers (Beasley et al., 1975) that transmission of virus through breast milk and/or ingestion of blood from excoriated nipples is negligible compared with the infant's exposure to contaminated maternal blood at delivery and subsequent close contact at home.

Mothers were asked to bring their children to the clinic at intervals up to age 2 years for testing of HBsAg, both of their infants and themselves. The infant's liver function tests were also requested if sufficient blood had been obtained.

In August 1977, an effort was made to recall all the children for physical and developmental examinations and repeat blood specimens. Liver function tests were obtained if possible, and in about half of the cases, if blood was negative for HBsAg by Hepatest, a sample was sent for further RIA testing (PHLS, Colindale).

93 of the 102 mothers were also tested for the presence of HBeAg and anti-HBe by agar gel diffusion (by M. Supran, PHLS).

Results

Mothers. The birthplaces and ethnic origins of the 102 carrier mothers and the numbers of children are given in Table 1. No mother had clinical signs of hepatitis at any time during pregnancy or follow-up. Of 58 mothers who had liver function studies done, 5 had abnormal results at least once, and of these, one was positive for HBeAg, one positive for anti-HBe, and 3 were not tested for either.

It is of interest to note that 21 of the 102 mothers had worked in hospitals before the discovery of their HBsAg carrier state. Several were nurses who had had contact with jaundiced patients or those undergoing haemodialysis.

### Table 1

<table>
<thead>
<tr>
<th>No. of mothers (n = 102)</th>
<th>Ethnic origin</th>
<th>Places of birth</th>
<th>No. of children delivered (n = 126)</th>
<th>No. followed up (n = 110)</th>
<th>No. HBsAg+ after 1st week (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>N. European</td>
<td>France, Poland, Uganda, UK</td>
<td>17</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>S. European</td>
<td>Cyprus, Greece, Italy, Yugoslavia</td>
<td>17</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>N. African</td>
<td>Egypt, Morocco</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>41</td>
<td>W. African</td>
<td>Aruba, Ghana, Gambia, Grenada, Guyana, Jamaica, Nevis, Nigeria, St Kitts, Sierra Leone, Trinidad, UK, USA</td>
<td>51</td>
<td>44</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>E. African</td>
<td>Uganda</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>E. and S.E. Asian</td>
<td>Brunei, Hong Kong, Japan, Malaysia, Mauritius, Philippines, Singapore</td>
<td>23</td>
<td>20*</td>
<td>8†</td>
</tr>
<tr>
<td>5</td>
<td>S. Asian</td>
<td>Bangladesh, Guyana, India, Pakistan, Trinidad</td>
<td>6</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>S.W. Asian</td>
<td>Iran, Iraq</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

*18 had Chinese mothers, all had Chinese mothers.
The HBeAg status of the 93 mothers tested for this is given in Table 2. Chinese mothers are much more likely than non-Chinese mothers to be HBeAg positive (P<0.001). Eight of the 10 HBeAg-positive mothers produced 9 of the 14 HBeAg-positive children. Of the remaining 2 HBeAg-positive mothers, one was Japanese and had 3 children, all HBeAg negative. We were unable to follow up the child of the other mother.

Children. Of the 126 children 53 (43%) were girls. We were able to see 110 after the first week of life. The mean age of follow-up was 24.8 months (range 2 months to 5 years 9 months). Three of the remaining 16 had died (one due to congenital heart disease at age one week, and 2 due to cot deaths at ages 3 and 16 months), and 12 could not be located or had parents who refused to allow blood to be taken. From one child, in Malaysia, a blood sample could not be obtained in spite of several attempts.

The results of cord blood testing are given in Table 3.

14 (13%) of the 110 children were later HBSAg-positive, 4 by RIA testing only. Details are given in Table 4. Five of the 14 were girls. All the children were growing and developing normally, and no hepatomegaly was found. Alanine transaminase (ALT) results were normal in the 9 positive children who were tested. Two of the 14 positive children had received 1 ml of HBIG at birth only; the rest received none. Table 4 shows that 8 of the 13 mothers were positive for HBeAg, and in fact 7 of these 8 were Chinese. In 2 of these Chinese families, both with HBeAg-positive mothers, we were able to test siblings; in one, the sibling was found to be positive, while in the other, she was negative. Six of the 13 fathers were tested and all were HBsAg negative.

As noted in Table 4, one of the children (Case 1) was negative when tested at ages 3, 6, and 12 months, but at ages 15 and 24 months she was RIA positive. This may indicate some form of horizontal transmission. Her father was negative for HBsAg.

There was no significant difference in the incidence of breast feeding between the groups of positive and negative children.

Discussion

Our results reflect the mixed ethnic origins of the population in London and seem to confirm the findings of others regarding a racial tendency to vertical transmission of the HBV, as detected by the presence of HBsAg. There have been interesting theories regarding the genetics of such transmission (Hug, 1976; Blumberg, 1977).

Some recent work has dealt with the sex distribution of carriers, as more men than women are carriers (Goodman et al., 1971; Curtis et al., 1973), and it also seems that where one parent is a positive HBsAg carrier, there is an increased secondary sex ratio (number of males per 100 females) (Drew et al., 1978). Our 102 mothers have produced, to our knowledge, a total of 223 children, 125 (56%) boys and 98 (44%) girls. The numbers are too small for valid analysis, however, and complete data are not available.

Our cord blood results, as those of others (Aziz et al., 1973), would appear to show the unreliability of such specimens in predicting the future HBsAg status of the child. Contamination with maternal blood may account for most if not all positive cord bloods; in several cases in which cord blood was positive, a blood sample from the infant was checked and found to be negative. In fact, at Hammersmith Hospital cord blood testing is no longer done.

Table 3 Positive cord bloods

<table>
<thead>
<tr>
<th>Cord blood</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive on initial screen</td>
<td>Positive by RIA only</td>
</tr>
<tr>
<td>9</td>
<td>10*</td>
</tr>
</tbody>
</table>

*One child positive by RIA only at birth was positive by Hepatet at 2 months, but negative by both RIA and Hepatet at 6 months.
instead a specimen is taken from the child some time during its first week of life. **In utero** transmission has been reported but is thought to be rare (Schweitzer and Spears, 1970), and usually comes not from carrier mothers but from overt cases of hepatitis during the last trimester of pregnancy or early in the postpartum period (Schweitzer et al., 1972, 1973).

The HBeAg positive state of the mother increased the transmission of HBV to the child, as has been shown by others (Beasley et al., 1977; Chaudhuri et al., 1977; Gerety and Schweitzer, 1977; Murata et al., 1977). Anti-HBe was not necessarily protective, as can be seen from Table 2, although this has been suggested (Okada et al., 1976). There are those who now say that HBeAg may not be a marker of HBV but an indication of liver damage (Fay et al., 1977; Tiku et al., 1977; Vyys et al., 1977); we did not have adequate maternal liver function studies to be able to corroborate this.

The infants, therefore, who were at greatest risk from vertical transmission of HBV in our study were those whose mothers were Chinese and/or HBeAg positive. This raises the question of passive protection such as that recommended by the World Health Organisation (1977) for a single acute exposure— one might argue that during parturition this is the type the child receives. The two positive children who received only a single dose of HBIG at birth might have benefited from larger, repeated doses (Dosik and Jhaveri, 1978; Iwarson and Norkrans, 1978). It is concluded that an adequate trial of HBIG prophylaxis is not feasible in London or elsewhere in the UK, where there are so few carrier mothers.

Concerning the continued surveillance of the children with HBsAg-positive mothers, we would agree with those (Melnick et al., 1976; Woolf and Williams, 1976; Barker et al., 1978) who feel blood should be tested at birth, 6 months, and 12 months, and if the child remains negative, he could be discharged (although we did have one conversion after this age). In the case of children found to be positive, yearly examinations and liver function tests for life ought to be considered. This would not necessarily be adequate in diagnosing chronic active hepatitis or hepatocellular carcinoma, but at least one's index of suspicion would be high. It would seem that very long-term follow-up studies will be needed before questions such as the necessity for frequent liver biopsies can be answered adequately. Management of the carrier has been discussed at length (Cossart, 1977).

Mothers, too, ought to be referred for follow-up in medical clinics once their obstetric need has ended (Babb, 1976). We found that few of the women were seen regularly except for antenatal care. We tended to be reassuring about good future health, despite the mounting evidence of possible liver disease later, as almost all our mothers were very upset at the idea of being 'infectious' and a few felt constrained in handling their new babies.

Mothers were warned about the need for care in handling their own blood from any source, as well as the need to inform their dentists and anyone who might later seek blood samples (general practitioners were officially informed). When a child was found to be positive we gave similar advice, but have found that perhaps the child's positive status should not be mentioned at school, as he may then be regarded with suspicion. One 6-month-old child in our study was rejected by a nursery as a result of this information, probably due to fear and ignorance by the nursery staff. There have been studies in schools indicating that cross-infection in groups of schoolchildren does not occur (Follett et al., 1978).

Micromethods are being developed for HBV screening using finger prick blood samples on filter paper (Farzadegan et al., 1978). Perhaps with the perfection of such methods, very large population studies may become feasible.

We thank Mr A. Holley and Mr T. Ross of the Virology Departments of Hammersmith Hospital and Queen Charlotte's Maternity Hospital for their help, as well as the children, their families, and the many housestaff who made the study possible.

References


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Nathalie Masse

Nathalie Masse Research Fellowship. This is intended to help young workers engaged in research on problems in social and preventive paediatrics. It was granted for the first time in 1978 and will subsequently be granted in every even-numbered year. The next fellowship will be awarded in 1980, for which applications are invited by 31 December 1979.

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All grant and prize winners will be chosen without regard to nationality by an international jury.

Details and application forms for the fellowship and prize are obtainable from the Memorial Committee, International Children’s Centre, Château de Longchamp, Bois de Boulogne, 75016 Paris.
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