Transmission of hepatitis type B from healthy HBsAg-positive mothers

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Summary

Seventeen mothers, all apparently healthy carriers of hepatitis-B surface antigen (HBsAg) during pregnancy, and their children were studied for four to five years to determine the transmission rate of hepatitis-B virus infection. All the mothers had antibody against hepatitis-B core antigen in addition to HBsAg. One of them, a renal transplant recipient, was persistently positive for hepatitis-B-associated e antigen (HBeAg), while the remaining 16, who were detected during screening of healthy pregnant women, were positive for anti-HBe. Evidence of infection was found in the child and husband of the woman positive for HBeAg, while none of the 29 children and five husbands of the anti-HBe-positive women became infected.

Introduction

In several populations over 90% of people with circulating hepatitis-B surface antigen (HBsAg) appear to be healthy long-term carriers. Their role in the maintenance and transmission of hepatitis-B virus (HBV) is not fully understood.¹ Some of these carriers may be non-infectious by blood donation^{2,3} and personal contact.^{4,5} Similarly, in contrast to women with acute hepatitis, mothers who are healthy carriers of HBsAg do not usually transmit hepatitis to their babies.⁶⁻¹⁰ To confirm these observations a series of families in which the mothers were carriers of HBsAg was followed up for four to five years.¹¹

Tests for HBV transmission included radioimmunoassay for HBsAg and its antibody and, in addition, tests for the newer HBV-associated antigens hepatitis-B core antigen (HBcAg) and hepatitis-B-associated e antigen (HBeAg).

Materials and methods

During an eight-month period in 1970 all the pregnant women in Denmark were investigated for HBsAg by counter-immuno-electrophoresis (CIE). Of the 82 women found to be positive for HBsAg 81 appeared to be healthy carriers.¹¹ The cord blood of 51 babies born to these mothers failed to show transplacental passage of the antigen, and no case of infection was found on follow up of 36 of the children for up to five months.¹¹ Sixteen of the children selected geographically still showed no evidence of transmission one year after birth. These 16 families are considered here. They include the 16 index mothers and children, 13 additional siblings aged 18 months to 8 years, and five husbands who agreed to be investigated.

One further family included in the study comprised a mother with a renal graft since 1970, her child aged 3 years, and her husband. The mother had been an asymptomatic carrier of HBsAg since an outbreak of hepatitis in her dialysis unit in 1968; she had never had biochemical evidence of liver damage.

In January 1975 all the patients were examined for clinical signs of liver disease and the case histories were carefully checked for symptoms of hepatitis. Biochemical liver function tests performed by routine methods included determination of alanine aminotransferase, bilirubin, albumin, and prothrombin-proconvertin and IgG, IgM, and IgA levels. HBsAg was detected by a double-antibody radioimmunoassay using ¹²⁵I-labelled HBsAg, rabbit anti-HBsAg, and swine anti-rabbit IgG.¹² The detection limit of this assay was 10-15 µg HBsAg/l serum. Anti-HBs was detected by means of radioimmuno-precipitation,¹³ which dilution experiments indicated was 5000 times more sensitive than CIE. HBeAg and its antibody were detected by double diffusion in agar gel,^{14,15} reference sera containing HBeAg or antibody being kindly provided by Dr J O Nielsen, of Copenhagen. Determination of anti-HBc was done on coded specimens by CIE, as described.¹⁶

Results

The results of the follow-up study are summarised in the table. All the women had remained HBsAg carriers throughout the four to five years of observation, and none had developed clinical or biochemical signs of liver damage. At follow-up all had circulating antibodies to HBcAg. HBeAg was found only in the renal transplant recipient, while all 16 healthy HBsAg carriers had antibodies to the e determinant. Examination of stored sera obtained during pregnancy showed an identical HBe antigen-antibody status.

Serological characteristics of members of families studied

	Mothers			
	No studied:	1 (Renal transplant recipient)	16 (Healthy carriers of HBsAg)	
HBsAg-positive ..		1	16	
Anti-HBc-positive ..		1	16	
HBeAg-positive ..		1	0	
Anti-HBe-positive ..		0	16	
	Children		Husbands	
	1	1	29	5
HBsAg-positive ..	1	0	0	0
Anti-HBs-positive ..	0	1	0	0
Anti-HBc-positive ..	1	NS	3*	0*
HBeAg-positive ..	1	NS	0	0
Anti-HBe-positive ..	0	NS	0	0

*Sera from two children and two husbands were not available for test.
NS = Not studied.

The children of the 16 healthy HBsAg carriers had developed normally without evidence of liver disease. At follow-up all gave normal liver function test results and had remained negative for HBsAg and anti-HBs. Anti-HBc was found in three children from different families. Their case histories and biochemical status did not differ from those of the remaining children. None of the fathers studied showed evidence of infection.

In contrast to the other children, the child born to the HBeAg-positive mother was positive for HBsAg, HBeAg, and anti-HBc and had a slightly raised alanine aminotransferase value. He had been studied regularly since birth and had been positive for HBsAg since 3 months of age. HBeAg and anti-HBc were also found in two stored samples obtained at 6 months and 1½ years of age. The father had no clinical evidence of infection or history of jaundice. He was, however, positive for anti-HBs, and his alanine aminotransferase level was

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twice the upper limit of normal. A second child in this family was born in April 1975. He became positive for HBsAg in October despite prophylactic hyperimmune γ -globulin at birth.

Discussion

The impression of a strong association between the presence of HBsAg and actual infectivity of the blood gained from early blood transfusion studies³ was modified by failures to detect evidence of infection after exposure to such blood.²⁻⁶ After the recognition of the Dane particle¹⁷ as the likely virus it was observed that this particle is present in only some HBsAg-positive blood and, notably, is found only rarely in apparently healthy carriers of HBsAg.¹⁸⁻¹⁹ These findings indicated a need for a serological marker for the presence of Dane particles in HBsAg-positive blood. Serological testing for the Dane-particle-associated core antigen-antibody system²⁰ has been technically difficult, and only recently have assays of the antibody by radioimmunoassay, complement fixation, or CIE become possible.²¹

The presence of anti-HBc has been thought to be a marker of viral replication and thus of infectivity.²¹ This antibody, however, might be present for a long time after infection²² and could therefore indicate past as well as present infection. The more recently described e antigen-antibody system is not yet characterised in detail but the antigen appears to be of low molecular weight and is not particle-bound.²³ Although the origin and composition of HBeAg is unknown, its presence in sera rich in Dane particles led to the assumption that it might be a viral product and a marker of infectivity.¹⁴⁻²³

Our study confirmed that the healthy HBsAg carriers, although all positive for anti-HBc, did not infect their children during the four to five years. Nor was there evidence of infection in the 13 older and younger children or in the husbands studied.

The positive anti-HBc reaction in three of the children could not be correlated with any other findings. None of the two sisters and one father from the three families had any sign of infection, and the mothers and children did not differ from those in the

remaining families in any other serological test. In contrast, several tests confirmed transmission of hepatitis to the children and husband of the HBeAg-positive mother. This mother differed clinically from the remaining mothers by having a renal graft and being on immunosuppressive treatment. Biochemical tests of liver damage gave negative results, however, as they did for the other women studied, and serologically only the presence of HBeAg suggested her infectivity.

These preliminary studies on the importance of HBeAg tests are at present being extended to areas with a higher mother-infant transmission rate.

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Jejunal mucosal abnormalities in patients with recurrent aphthous ulceration

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Summary

Jejunal biopsies in 33 patients with troublesome recurrent aphthous ulceration seen over one year showed eight with flat mucosa compatible with coeliac disease. All remitted completely on a gluten-free diet, both clinically and haematologically, and the aphthous ulceration did not recur. Gluten sensitivity is aetiologic-

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ally important in patients with recurrent aphthous ulceration and flat mucosa, and patients with recurrent ulceration should undergo jejunal biopsy.

Introduction

The aetiology of aphthous stomatitis is not clear and is probably diverse.¹ The association between oral ulceration, diarrhoea, and weight loss has been noted for 300 years,² and the incidence of recurrent aphthous ulceration is high in idiopathic steatorrhoea³ and coeliac disease.⁴ It seemed relevant, therefore, to study the jejunal mucosa of unselected patients presenting with recurrent aphthous stomatitis.

Patients and methods

The patients studied came from two sources. All patients referred by their general practitioners to the nutritional and intestinal unit (eight patients) or to one of us (MKB) at the Dental Hospital, Birmingham (25 patients), over one year with recurrent aphthous ulceration⁵⁻⁶ were studied. To be included patients had to have had recur-