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Short communication

Hepatitis B virus infections in families in which the mothers are negative but the fathers are positive for HBsAg

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Abstract

We studied a total of 37 families, in which HBsAg was positive in either or both of father and mother, to assess intra-familial transmission of hepatitis B virus (HBV). The HBsAg positive rate for children with HBsAg-negative mothers was significantly lower than that with positive mothers (4 of 31, 12.9% versus 18 of 32, 56.3%, $p < 0.01$) of course. However, there were three families in which the infection source for children was thought to be fathers, not mothers, i.e., of eight children in these three families with HBsAg +/− father/mother pairs, 4 (50%) were positive for both HBsAg and HBV DNA of genotypes identical to those of their fathers, and another child was positive for HBcAb despite being negative for HBsAg. Interestingly, moreover, all the mothers in these three families were HBcAb-positive even though HBsAg-negative, suggesting that not only father-to-child but also inter-spouse HBV transmission might have occurred. With these findings we would suggest that all the family members with HBsAg-positive fathers should receive HBV vaccine, let alone for those with HBsAg-positive mothers.

Keywords: Hepatitis B virus; Intra-familial transmission; Vaccine

1. Introduction

The majority of chronic hepatitis B virus (HBV) infections occur during early childhood [1], and transmission of HBV from an HBsAg-positive mother to her infant during or just after birth results in the highest risk (70–90%) of persistent infection in countries of intermediate to high endemicity [1,2]. In Japan, all infants born to HBeAg-positive mothers have been receiving the HBV vaccine since 1985 [3]. As a result, the prevalence of chronic HBV infection at the age of 14–19 years has decreased to 0.44%, whereas chronic HBV infection at the age of 40–49 still affected as high a number as 1.46% in 1996 [4]. It is reported that the rate of HBV infection for children in families with HBsAg-negative mothers is very low [1,5,6]. However, intra-familial transmission of HBV, especially from fathers to children, was evidenced by sequence analyses of HBV [7,8].

The aim of the present study was to assess hepatitis B virus (HBV) infection from fathers to children in families with HBsAg-negative mothers.

2. Materials and methods

2.1. Patients

Enrolled, in this study, were 127 individuals in 37 families (15 fathers, ages 39–67; 37 mothers, ages 37–80; 75 children, ages 10–56, males/females = 38/37) who had visited Takegoshi Internal Medicine Clinic during the past 14 years. HBsAg status of the father/mother pairs in these fami-

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lies was +/− in 14 families (category 1), +/− in 22 (categories 2 and 3), and +/+ in 1 (category 4). In the father/mother +/− group, children of four families had been vaccinated (category 2) while those of the other 18 families unvaccinated (category 3).

2.2. Serology

All serum samples were tested for HBV and HCV serological markers using commercially available immunoassays, ARCHITECT® (Dinabot Co., Ltd.) and a Cobas R Core anti-HCV EIA kit (Roche Diagnostics GmbH, Mannheim, Germany), respectively. Informed consent was obtained from each individual, and the protocol of study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.3. HBV genotyping and sequencing

HBV genotypes were determined serologically by ELISA with monoclonal antibodies for type-specific epitopes in the preS2-region (Institute of Immunology, Co., Ltd.) [9].

A fragment of HBV DNA of nt positions from 1445 to 2157 was PCR-amplified by previously reported methods [10]. PCR products were then subjected to direct sequencing with use of ABI PRISM 377 DNA sequencer (Applied Biosystems, Foster City, CA). Nucleotide data analyses were done with GENETYX® 6.0 (Genetyx Co., Tokyo, Japan).

3. Results

3.1. Children in the families with HBsAg-positive mothers

As depicted synoptically in Fig. 1, the children in the families with HBsAg-positive mothers, if not protected by vaccine, were more prone to HBV infection as compared to those in the families with HBsAg-negative mothers: HBsAg positive rate was 59% (20/34) in the children of category 3 + 4, whereas it was only 13% (4/31) in those of category 1 ($p < 0.05$).

3.2. Children in the families where mothers were negative but fathers were positive for HBsAg

Among the 37 families studied, there were three families in which one or more children were HBsAg-positive although their mothers were HBsAg-negative. As shown in the lower part of Fig. 1, HBsAg tested positive in the father and two of his four children but not in his wife in the family A. Similarly, in the families B and C, the fathers and one of their respective children were positive but their wives were negative for HBsAg. Identical HBV genotypes were shared between father and child, respectively, i.e., genotype B in the family A while genotype C in the families B and C. Sequence analyses also supported the closeness of HBV strains within

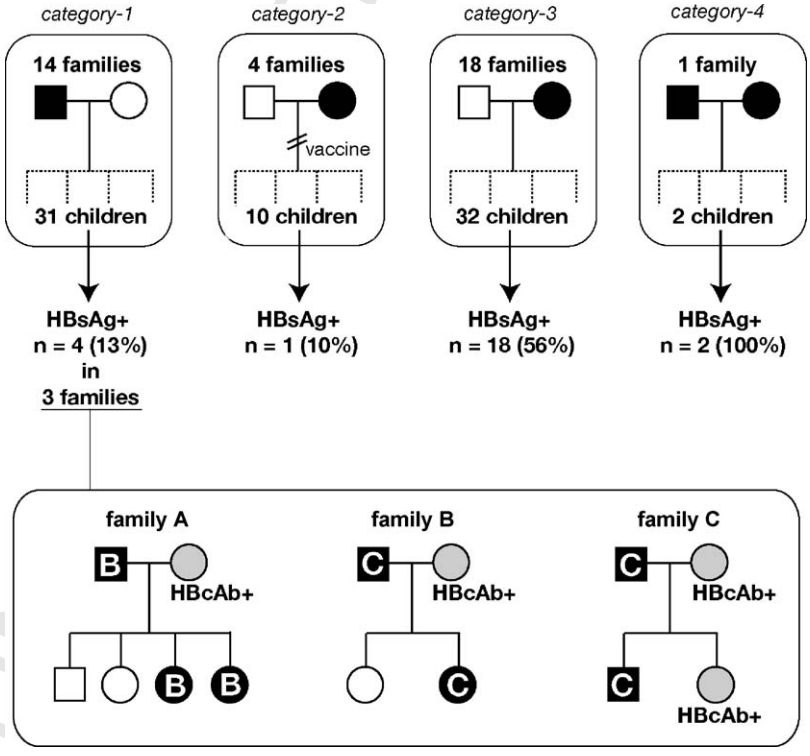

Fig. 1. Synopsis of the study results. Box and circle represent male and female, respectively. HBsAg-positive individuals were indicated by black-daubed boxes or circles, while those with HBcAb by gray ones. White characters on a black background of the boxes and circles indicate HBV genotypes.

each pair of father and child (data not shown here). Interestingly, all the mothers in these three families and a child in the family C were positive for antibodies against HBV core antigen (HBcAb) despite being negative for HBsAg, an evidence for cryptic HBV infection or past exposure to it at least.

4. Discussion

Franks et al. [5] reported that the father-to-child HBV transmission rate was 9.4%, and our present result (13% in view of HBsAg) almost corroborates this figure. However, it is noteworthy that these figures may still underestimate the actual risk of father-to-child transmission, because, as exemplified by the second child of the family C in Fig. 1, there might exist additional cases of infection, unnoticed by being negative for HBsAg although being positive for HBcAb.

The importance of HBsAg-positive father as a possible source of HBV infection within a family was also underscored by the finding that all the mothers in the families A–C were HBcAb-positive even though HBsAg-negative. Such inter-spouse HBV transmission could easily be understood because HBV is a sexually transmitted virus. Thus, it could be speculated that the apparent "father-to-child" HBV transmission in these families might indeed have been a "father-to-mother-to-child" transmission, because the contact between mother and child must have been much closer than that between father and child.

In conclusion, our present results strongly support the notion that all the family members with HBsAg-positive fathers should receive HBV vaccine, let alone for those with HBsAg-positive mothers.

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