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厚生労働科学研究費補助金
肝炎等克服緊急対策研究事業

**B型及びC型肝炎の疫学及び
検診を含む肝炎対策に関する研究**

(課題番号 H16 - 肝炎 - 一般 - 016)
(3年計画の3年目)

平成18年度 研究成果

主任研究者 吉澤 浩司

平成19 (2007) 年 3月

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以下、Ⅰ. Ⅱ. は、平成18年度 総括研究報告書・分担研究報告書 **【別冊】**
に集録した。

Ⅰ. 総括研究報告

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III. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

【書籍】

著書名	論文タイトル名	書籍全体の編集者名	書籍名	出版者名	出版地	出版年	ページ
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IV. 研究成果の刊行物

【書 籍】

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Perinatal Hepatitis B Virus Infection in Japan

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Introduction

In areas where infection by hepatitis B virus (HBV) is prevalent and persistent, perinatal transmission from HBV-infected mothers is an essential route for establishing a persistent carrier state.

These babies carrying HBV can transmit it via a secondary horizontal route to infants of the same generation, who frequently acquire persistent HBV infections. Approximately 30% of the infants exposed to HBV when under 3 years of age become HBV carriers. Together, they serve as a reservoir of HBV throughout their lives in the community, and may therefore cause, or contribute to, a continuous spread of the infection.

Perinatal HBV infections resulting in the persistent carrier state occur in approximately 90% of babies born to mothers who are positive for hepatitis B surface antigen (HBsAg) as well as hepatitis B e antigen (HBeAg) in the serum (Okada et al., 1976; Stevens et al., 1979). Persistent infections rarely occur in babies born to mothers who carry HBsAg, but are negative for HBeAg or are positive for the antibody to HBeAg (anti-HBe). Only around 10–15% of babies contract transient HBV infections (Shiraki et al., 1980).

In countries where the prevalence of HBsAg is less than 0.2–1.0% in children, the perinatal HBV transmission is the major route where the HBV carrier state is established. In these countries, a selective vaccination program, i.e., combined passive–active immunoprophylaxis of babies born to mothers with HBsAg and HBeAg by anti-HBs hyper-immune globulin (HBIG) and hepatitis B vaccine (HB vaccine), is a rational approach to the control of HBV infection.

In contrast, in countries where the prevalence of HBsAg exceeds 8%, perinatal transmission accounts for only 10–20% of infants who are persistently infected with HBV (Yao, 1996; Lee, 1997). Since horizontal transmission to children younger than 5 years old is the major route by which the HBV carrier state becomes established in these hyperendemic countries, universal vaccination of babies is recommended.

It is important to realize that universal vaccination prevents mainly horizontal HBV transmission, but not perinatal HBV infection. In addition, the fact that universal vaccination has the potential for inducing HBV mutants remains a serious problem of this particular approach (Zanetti *et al.*, 1988; Brunetto *et al.*, 1999).

In two model areas in Japan, Shizuoka and Iwate prefectures, the immunoprophylaxis of babies born to HBV carrier mothers with HBeAg, by means of combined hepatitis B HBIG and HB vaccine, was started as a clinical trial in the early 1980s and became a national project in 1986. This chapter presents an account of the experience gained in the prevention of perinatal HBV transmission from the 1980s into the 1990s in Shizuoka and Iwate prefectures.

Carrier rates of hepatitis B virus in Japan

To understand the sero-epidemiological background of HBV infection in Japan, the age-specific HBV carrier rates were estimated on a national basis (Tanaka *et al.*, 2004). To avoid selection bias, only the data of first-time blood donors aged 16–64 years in the Japanese Red Cross Blood Center were collected and analyzed.

During the 6 years from January 1995 to December 2000, 3,485,648 individuals visited their local Japanese Red Cross Blood Centers for the first time to donate blood. The proportion of HBsAg-positive subjects, determined by reversed-passive hemagglutination (R-PHA) reagents made in-house by the Japanese Red Cross Blood Center, was calculated. To ascertain the influence of age on the proportion of HBsAg-positives, the ages of all first-time blood donors were adjusted, taking the year 2000 as the current year. The sex- and age-specific HBsAg-positive rates are shown in Table 1. Overall, HBsAg was detected in 22,018 (0.63%) of 3,485,648 blood donors. The prevalence of HBsAg was significantly higher in men (0.73%) than in women (0.53%, $p < 0.001$), and increased in both with time until the age of 60 years. The HBsAg-positive rates were lowest in the age group under 20: 0.26 and 0.20% in men and women, respectively.

These data suggest that the improvement of sanitary conditions in Japan has helped to decrease the horizontal transmission of HBV and the HBV carrier state in the age groups born before the prevention of perinatal HBV transmission was started in the 1980s.

Prevention of perinatal transmission of hepatitis B virus in Japan

The prevention of perinatal HBV infections has been followed up in two model areas of Japan, namely, Shizuoka and Iwate prefectures.

Table 1

Age-specific HBsAg positive rates in first-time male and female blood donors in Japanese Red Cross Blood Center from 1995 to 2000

Age groups in 2000 (year of birth)	Total number of first-time donors	HBsAg positives (%)	Men		Women	
			Number	HBsAg positives (%)	Number	HBsAg positives (%)
16–19 (1981–1984)	582,415	1327 (0.23)	273,842	709 (0.26)	308,573	618 (0.20)
20–29 (1971–1980)	1,929,147	10,054 (0.52)	1,004,986	5955 (0.59)	924,161	4099 (0.44)
30–39 (1961–1970)	472,447	3988 (0.84)	277,627	2828 (1.02)	194,820	1160 (0.60)
40–49 (1951–1960)	247,020	2950 (1.19)	120,576	1796 (1.49)	126,444	1154 (0.91)
50–59 (1941–1950)	198,477	2984 (1.50)	80,336	1388 (1.73)	118,141	1596 (1.35)
60–69 (1931–1940)	56,142	715 (1.27)	22,782	314 (1.38)	33,360	401 (1.20)
Total	3,485,648	22,018 (0.63)	1,780,149	12,990 (0.73)	1,705,499	9028 (0.53)

In Shizuoka prefecture, immunoprophylaxis of perinatal HBV infection was initiated in 1980 as a clinical trial and became a national project in April 1986 (Noto et al., 2003). In a similar way in Iwate prefecture, following the clinical trial that began in 1981, prophylaxis of perinatal HBV infection in all babies was started in 1986 (Koyama et al., 2003).

The same protocol was used in both prefectures, and was executed as follows: babies born to HBV carrier mothers who were HBeAg reactive (high-risk babies) received HBIG at birth (within a maximum of 48 h after delivery) and the second injection was given 2 months thereafter. The babies were inoculated with HB vaccine 2, 3 and 5 months after birth and were followed until the baby reached 12 months of age (arrows, Fig. 1). In cases in which the antibody titer fell to less than 22–23 PHA, inoculation was repeated as necessary at months 9 and 12 (arrows in parentheses).

Immunoprophylaxis of perinatal HBV transmission in Shizuoka prefecture and its effectiveness in decreasing the transmission of the HBV carrier state

Shizuoka prefecture is located near the center of the main island of Japan, at the foot of Mt. Fuji, and has 3.6 million residents. In this prefecture, the first clinical trial was started in 1980 (Tanaka et al., 2004).