

# Investigation on Hepatitis B Virus infection in a four-generation family in China

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## Abstract

China has had a high prevalence of hepatitis B virus infection (HBV) infection since the 20th century. Vertical mother-to-child transmission always leads to family aggregation of HBV infection. This study investigated the HBV infection status of a four-generation family by telephone consultation and review of outpatient and hospitalization medical records. The first generation consisted of 1 female relative born in 1906 who died of ascites due to cirrhosis at 60 years of age. The second generation consisted of 4 people born between the 1920s and 1930s. All of them had an HBV infection. One male relative died from ascites due to cirrhosis at 43 years of age. One female relative, aged 90 years, was an HBV carrier. Her liver function had been normal for a long time. Another female relative, aged 86 years. She had hepatic failure at age 40 years. One female relative died from liver cancer at age 66 years. The third generation consisted of 13 people. Six people had HBV infection, of whom 5 were male and one was female. One male relative died from liver cancer at age 48 years. Another male relative was diagnosed as having cirrhosis at 45 years old. The fourth generation consisted of 21 people, none of whom had an HBV infection. They were born between the 1960s and 1980s. Conclusions: This four-generation family has an obvious family aggregation of HBV infection. The infection rate was higher and the infection severity was greater in males than in females. The spread of HBV infection in this family was reduced in every succeeding generation.

**Keywords:** HBV infection; China; Four-generation family; Family aggregation; Mother-to-child transmission

## Background

China has a high incidence of hepatitis B virus (HBV) infection [1], which peaked in the 20th century. A survey conducted by the Chinese Centers for Disease Control and Prevention in 1992 showed that the HBsAg positivity rate in China had reached 9.65%, indicating that approximately 100 million people in China were infected with the HBV [2]. HBV infection is mainly transmitted through blood, and mother-to-child vertical transmission is the main reason for the high incidence of HBV infection in China [3]. Since 1992, China has included HBV vaccine in its planned inoculation, requiring all newborns to receive HBV vaccine free of charge to block mother-to-child vertical transmission, so mother-to-child transmission has been reduced significantly, and the HBV infection rate has

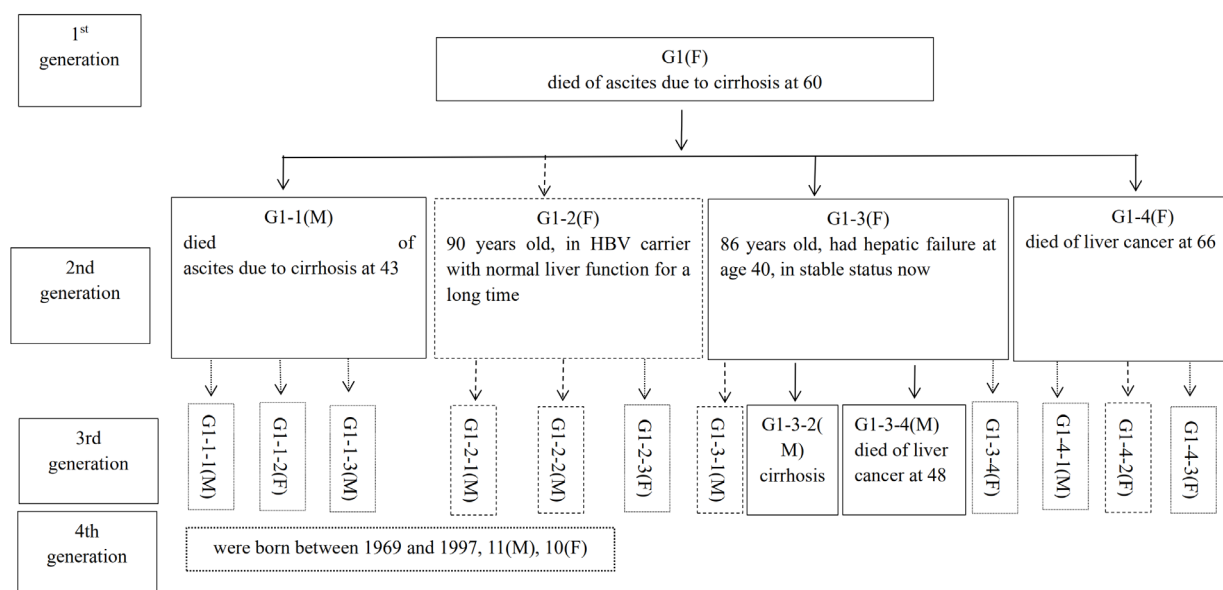
decreased significantly [4]. Owing to mother-to-child vertical transmission, HBV infection often presents the phenomenon of family aggregation. This article investigates the situation of HBV infection in a large family with four generations, which is a miniature model of the general situation of HBV infection in China in the 20th century.

## Investigation methods

A family with a high incidence of HBV infection was selected to investigate four generations of the family. Detailed information on the deceased family members was inquired by telephone calls. Those alive were inquired personally by telephone calls, and test results of the five markers of HBV were provided. For some patients in the family who were hospitalized, their medical records were reviewed. Among them, those in the first and second

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**Figure** HBV Infection Status of a Four-generation Family

Tips:  patient  HBV carrier  healthy individual M: male F: female

generations who died young and could not be tested for HBV markers at that time were presumed to have HBV infection mainly on the basis of the manifestation of ascites due to cirrhosis and the infection status of their relatives. Other people were confirmed to be infected with HBV through the five markers of HBV.

### Investigation findings

Among the 39 family members, 2 died and 37 were still alive, and 19 were male and 20 were female. Eleven people were infected with HBV, accounting for 28.2% of the total number of family members, including 8 males and 3 females. In this family, the proportion of infected males was 42.1%, while the proportion of infected females was 15%.

### First generation

One female family member (coded as G1 for ease of expression) born in 1906 died of ascites due to cirrhosis in 1966, with a life span of 60 years. As no etiological examination result for HBV was available in 1966, her diagnosis was based on her family situation.

### Second generation

Four family members (born in between the 1920s and 1930s), 1 male and 3 females, were infected with HBV, with an infection rate of 100%. They are numbered as G1-1 (male), G1-2 (female),

G1-3 (female), and G1-4 (female) according to the descending sequence of age. Their outcomes were as follows:

G1-1 (male), born in 1926, died of ascites due to cirrhosis in 1969, with a life span of 43 years.

G1-2 (female), born in 1928, aged 90 years in the year of this study, was a carrier of HBV who had normal long-term liver function and good health.

G1-3 (female), born in 1932, aged 86 years old in the year of this study, had chronic HBV. Liver failure occurred at the age of 40 years. After treatment, the condition was improved and stabilized for a long time. At present, the patient is healthy with normal liver function for a long time and negative virus quantitation.

G1-4 (female), born in 1934, had chronic HBV infection and was found to have liver cancer in 1995 and died of liver cancer in 2000, with a life span of 66 years.

### Third generation

Of the 13 family members in this generation (born between the 1940s and 1950s), 7 were male and 6 were female. Six of them were infected with HBV infection, including 5 males and 1 female, accounting for approximately 46.2%.

G1-1 (male) had 3 children, 2 males and 1 female, all of whom were HBsAg negative. They are coded as G1-1-1 (male), G1-1-2 (female), and G1-1-3 (male) according to age.

G1-2 (female) had 3 children, 2 males and 1 female. Both male children were HBsAg positive, carried HBV for a long time, had normal liver function, and were > 60 years. The female child was HBsAg negative. They are numbered as G1-2-1 (male), G1-2-2 (male), and G1-2-3 (female).

G1-3 (female) had 4 children, 3 males and 1 female. The 3 males were HBsAg positive, and the daughter was HBsAg negative. One of the male children died of liver cancer at the age of 48 years. Another male child was found to have liver cirrhosis and had upper gastrointestinal hemorrhage at the age of 45 years. Splenectomy was performed. When upper gastrointestinal hemorrhage occurred, he tested negative for the antigen HBVDNA, so no antiviral treatment was given. No upper gastrointestinal hemorrhage occurred after the splenectomy. Currently, he is not taking any drugs. His liver function has been normal according to long-term monitoring, with HBVDNA (-). His condition is stable without recurrence of the upper gastrointestinal hemorrhage. Another male child had been carrying HBV for a long time, and his liver function remained normal.

G1-4 (female) had 3 children, 1 male and 2 females. One of the females carried HBV. The other two children were HBsAg negative.

#### Fourth generation

This generation consisted of 21 people, including 11 males and 10 females. None of them had HBV infection. The fourth-generation family members were born between 1969 and 1997.

#### Discussion

##### **This large family, which included four generations, shows a clear family aggregation phenomenon of HBV infection**

It reflects the typical characteristic of vertical mother-to-child transmission and no phenomenon of father-to-child transmission in the whole family. Of the 39 people in the whole family, 11 were found to be infected with HBV, which was transmitted from generation to generation by the female patient with HBV infection in the first generation. Ten people from the second to the fourth generations were infected with the virus, of whom 4 in the second generation were infected, with an infection rate of 100%. The third generation included 13 people, of whom 6 (6/13) were infected with HBV, with an infection rate of nearly 50%. None of the family members in the fourth generation was infected with

HBV. All the family members with the infection contracted the virus through mother-to-child transmission. Although all the children had been in close contact with their fathers since childhood and the overall health condition in rural China in the 20th century was poor, no male patient had transmitted the virus to the next generation. This suggests the low probability of transmission from father to child, which is basically consistent with the current literature [5].

##### **The proportion of males with the infection in the family was significantly higher than that of the females, and the disease conditions of the male patients were significantly worse than those of the female patients**

Although the male-to-female ratio in this four-generation family was close to 1:1 (19:20), the number of males with HBV infection was significantly higher than that of females.

Among the family members in the four generations, 6 males and 5 females were infected. Two of the 6 males with the infection died, one of liver cirrhosis at the age of 43 years and one of liver cancer at the age of 48 years. One patient developed decompensated cirrhosis complicated by upper gastrointestinal hemorrhage at the age of 45 years. The other 3 males are still alive and in good health. The outcomes of the 5 females with HBV infection were as follows: The infected female in the first generation died at the age of 60 years. In the second generation, the infected female died of liver cancer at the age of 66 years, while the others are still alive and in good health, and both > 80 years old. The disease situation in this family shows that the males with the infection had significantly more severe disease conditions and significantly shorter life spans than the females with the infection, which is consistent with the current conventional understanding [6]. The reason may be that males have more opportunities of infection due to more frequent social interactions and that their alcohol consumption is higher than that of females. Some people also believe that males have more opportunities to engage in manual labor than females, with longer time and higher intensity, while their social welfare benefits such as rest and medical care are poorer than those of females. Studies have also reported on sex-related differences in the rival response of patients with chronic HBV to interferon antiviral and nucleoside analog antiviral drugs such as entecavir, which may be related to sex-related differences in the body's immune response. In particular, sex hormones play an important role in

regulating the body's immunity. Androgens inhibit cellular and humoral immunity, estrogen enhances humoral immunity, and progesterone enhances conversion of cellular immunity to humoral immunity. Research in this respect is relatively lacking in China and the rest of the world, and further large-scale in-depth research is needed [7, 8].

### **The transmission of HBV in this family decreased in each succeeding generation.**

According to the overall situation of this family, as the mother had HBV infection, all four children in the second generation also had the infection. However, only a proportion of the children born to the female patients in the second generation were infected with HBV. None of those in the fourth generation was infected. The family members in the third generation were all born before the 1980s. At that time, no HBV vaccine was available, so they were not inoculated. The reason for the decrease in the mother-to-child transmission of HBV cannot be attributed to the prevention of mother-to-child transmission (PMTCT). The main reason may be the improvement of hygienic conditions during delivery. The family members in the second generation were born between the 1920s and 1930s. At that time, the sanitary conditions were very poor, and rural females in China delivered their babies at home, without the concept of disinfection during delivery and with more blood loss during labor, causing more serious blood contamination to newborns, which may be the main reason why all the children were infected. Over time, reproductive health conditions for females have gradually improved. The children in the fourth generation were born between 1969 and 1997, mostly in health centers. The delivery conditions were improved as compared with those in the previous generation. The chances of children being infected were relatively reduced. Some children without vaccination against HBV have not been infected. In addition, HBV vaccination in children born after the 1990s is another important factor that has reduced transmission. Research has shown no direct relationship between the mother-to-child transmission of HBV and the delivery mode chosen by the pregnant women [9]. Not all children will be infected even if born naturally.

This four-generation family with 39 members reflects the general situation of the mother-to-child transmission of HBV in China in the 20th century. The transmission status of this family demonstrates that the improvement of female reproductive conditions and HBV vaccination have

significantly controlled the family aggregation of HBV. Since 1992, China's health system has attached great importance to the transmission of HBV, strengthened the management of blood donors, and actively carried out the prevention of mother-to-child transmission, thereby achieving effective control of HBV transmission in China. The 2006 China CDC survey showed that the infection rate of HBV among Chinese aged 1–59 years had decreased to 7.18% [10]. In 2014, the China Centers for Disease Control and Prevention conducted an HBV seroepidemiological survey among Chinese aged 1–29 years, which showed that the detection rates of HBsAg were 0.32%, 0.94%, and 4.38% for ages 1–4, 5–14, and 15–29 years, respectively [4]. These data suggest that China will completely get rid of chronic HBV in the 21st century. In May 2016, at the 69th World Health Assembly, governments unanimously voted to adopt the first global strategy for viral hepatitis and set a plan of global elimination of viral hepatitis by 2030 [11]. China's health system is working out detailed measures to make positive efforts to achieve this goal. Among these measures, strict management of blood donors, universal free HBV vaccination, prevention of mother-to-child transmission, and active treatment of existing patients with HBV infection by nucleoside analogues are important measures to achieve this goal [12, 13]. As the country with the largest number of patients with HBV infection, China will make an important contribution to achieving this global goal [14, 15].

S.F.X. contributed to the conception and design of the article, drafted the manuscript. L.X.L. and L.M.L. contributed to the data collection and reference supplement of the manuscript. All authors read and approved the final manuscript.

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**Competing interests:** The authors declare that they have no conflict of interest.