Hepatitis B : long-term outcome and benefits from mass vaccination in children

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Abstract

Hepatitis B viruses can cause chronic liver diseases in both children and adults. In hyperendemic areas, although most related complications occur during adulthood, nearly half of the primary infection in chronic hepatitis B virus carriers occurs in perinatal period through maternal transmission and the other half are from horizontal transmission mainly through intrafamilial spread or injection using unsteriled needles.

Children with chronic hepatitis B virus infection are mostly asymptomatic. They are generally active and growing well with very rare exceptions. Even with acute exacerbation of liver function and active inflammation, jaundice or growth failure is uncommon. Mild histologic abnormalities in the liver begins early in life and may progress to severe liver impairment in later life. Severe liver damage, with bridging hepatic necrosis or fibrosis, or cirrhosis of the liver may occur, but is rare during childhood.

Universal immunization program of hepatitis B virus has been proved to be effective in reducing hepatitis B carrier rate for more than 10 folds, and the incidence of hepatocellular carcinoma in children has also been reduced significantly. (Acta gastroenterol. belg., **1998**, 61, **210-213**).

Key words : hepatitis, hepatitis B, children, vaccine, liver cancer.

Introduction

Chronic hepatitis B virus (HBV) infection can cause hepatitis, liver cirrhosis, and even liver cancer in both children and adults. About one billion people in the world have been infected by HBV, and 200 million of them became chronic hepatitis B surface antigen (HBsAg) carriers. In hyperendemic areas where most of the complications of chronic HBV infection develop in adulthood, primary HBV infection occurs mainly during infancy or early childhood (1). Chronic HBV infection can occur in children of any age, as early as perinatal period. Since carcinogenesis takes years or decades, hepatocellular carcinoma related to HBV infection in children will occur much earlier than those infected in adulthood. Understanding of the long-term natural course and prevention of HBV infection in children are very important.

Epidemiology of HBV infection in chidlren

HBV infection is prevalent in Asia, Africa, southern Europe and Latin America, where the HBsAg seropositive rate ranged from 2 to 20%. In those hyperendemic areas, HBV infections occurs mainly during infancy and early childhood. In Taiwan, the HBsAg carrier rate is approximately 10 to 20%. Before the implementation of universal HBV vaccination program, the HBsAg seropositive rate was 5% in infants, and increased to 10% at 2 years of age and remaining at the same rate thereafter. However, the infection rate reflected by anti-HBc seropositivity, reaches 50% by the age of 15 years. This suggests that most chronic HBsAg carriers are infected before 2 years of age in this population (1). In rural Senegal, by the age of 2 years, 25% of children are infected, while at age 15, the infection rate rises to 80% (2).

Perinatal transmission from HBsAg carrier mothers to their infants is a very important route of transmission leading to chronicity. It accounts for the transmission route of 40-50% of HBsAg carriers in hyperendemic areas in Asia. Around 90% of the infants of the HBeAg seropositive carrier mothers became HBsAg carriers (3), irrespective of a high or low HBsAg carrier rate in the population.

Age is an important factor determining the outcome of infection (4,5). The two most important routes of horizontal transmission are highly infectious family members, such as elder siblings, and improperly sterile syringes (6). Other sources of infection include institutionized children and multiple or large amount of blood transfusions, etc.

Long-term outcome of chronic HBV infection

Children with chronic hepatitis B virus infection are mostly asymptomatic. They are generally active and growing well with very rare exceptions. Even with acute exacerbation of liver function and active inflarnmation, jaundice or growth failure is very rare. General malaise is usually subjective in those whose school load is heavy.

1. *Serial Changes of Hepatitis B e Antigen/antibody and Liver Enzymes*

Hepatitis B e antigen (HBeAg) is an important marker reflecting active viral replication and infectivity (7). Its clearance is therefore used as a marker for the success of antiviral therapy. Although it is generally considered beneficial to clear serum HBeAg as early as possible, we have observed a poor outcome in a small group

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of HBsAg carrier children who were seroconverted in early childhood during longterm follow-up (8). The significance of HBe seroconversion in children thus needs careful evaluation.

Children with chronic hepatitis B virus infection are HBeAg seropositive at the initial stage of infection. During this stage, the child is immune tolerant to HBV, and the virus is highly replicative. Serum HBV DNA levels are usually high. The child is highly infectious, thus is an important source of horizontal infection in the family and community. Aminotransferase levels fluctuate within the high upper normal limit or mildly elevated with mean levels higher than that in non-carrier healthy children (9). Peak ALT level > 100 IU/L in this phase is extremely unusual. The status of hepatitis B e antigenemia can persist for years after primary infection.

For yet unclear reasons, serum HBeAg was gradually cleared and the viral replication is reduced while the child is growing. This process of HBeAg clearance is usually preceded by an elevation of aminotransferases. The peak level of aminotransferase elevation can be very mild and transient. An ALT level > 600 IU/L is uncommon, and < 1000 IU/L is exceptional. This process of HBe seroconversion takes place insidiously in most individuals for a period of 2 to 7 years. After the detection of an elevation of aminotransferases, around 40% of children will clear HBeAg within one year. Children with high aminotransferase levels of > 100 IU/ml and low HBV DNA levels of < 1000 pg/L often seroconvert during the subsequent 1 to 3 years (9).

Exceptionally, HBeAg/anti-HBe seroconversion may occur as early as in infancy with a unclear or brief period of HBeAg seropositive phase. However, in most occasions the rate of HBeAg clearance is very slow before three years of age, particularly during infancy. This might be due to the immune tolerance to HBcAg and HBeAg in infected children. Immune tolerance due to transplacental e antigen has been demonstrated by the absence of T-cell response to hepatitis B core antigen (HBcAg) in infants and children of hepatitis B e antigen positive HBsAg carrier mothers, while the T-lymphocytes from acute hepatitis infants of hepatitis B e negative HBsAg carrier mothers response very well to HBcAg (10).

Age is an important determinant factor of the rate of HBeAg seroconversion (11). Before 3 years of age, the spontaneous HBeAg clearance rate is very low (< 2% per year). The HBe seroconversion rate is increased gradually to around 5% per year after 3 years of age. The age of HBe seroconversion varies in different individuals. It ranged from infancy to more than 40 years of age. But the most common period is from 15 to 30 years of age. Before 15 years of age, the majority (85% in Taiwan) of HBsAg carrier children are HBeAg seropositive. While age increases, HBeAg are cleared gradually and anti-HBe developed.

Another factor affecting the HBe seroconversion rate in children is maternal HBsAg (11). Those with HBsAg carrier mothers have a lower rate of HBeAg clearance rate than those whose mothers were not HBsAg carriers. Maternal carrier state reflects perinatal transmission or early infection, which will lead to a longer duration of immune tolerance to HBV.

After HBeAg clearance, aminotransferase levels gradually return to within normal limits, and anti-HBe develops spontaneously. By conventional dot blot hybridization method, HBV DNA is usually low or undetectable in this phase. In our series, HBV DNA was detectable in only 1% of the anti-HBe sera. However, using polymerase chain reaction (PCR), HBV DNA persists for long-term in the serum of children with chronic hepatitis B after HBe seroconversion. Bortolotti *et al.* studied 39 children after HBe seroconversion (12). They found 87% of children had detectable HBV DNA by PCR within 5 years of follow-up, in 58% of cases 10 years after seroconversion. ALT levels were persistently normal in 92%, while 8% had slightly elevated ALT.

Acute excerbation with reactivation of HBV replication and re-elevation of aminotransferases is unusual in children (8,13). Permanent liver damage has occurred, and integration of the genome of HBV has emerged insidiously and gradually despite of the clearance of HBeAg. Development of liver cirrhosis or hepatocellular carcinoma is occasionally observed, but is rare dunng childhood (14). They are mostly (around 80%) anti-HBe seropositive (15).

2. *Hepatitis B Surface Antigen/Antibody Seroconversion*

In our long-term follow-up of carrier children, the annual HBsAg clearance rate was very low (only 0.56%) (16). It occurs only after clearance of HBeAg. After loss of HBsAg, its antibody (anti-HBs) remains low or undetectable in the majority (0 to < 100 mIU/mL). The underlying mechanism of poor anti-HBs response in HBsAg carriers who lost HBsAg are multifactorial, including specific failure of antigen presentation or T-cell activation, or the lack of T helper (Th_2) cell-like response to HBsAg (17). Hepatitis B immunization are not beneficial to them. In our long-term follow-up study, one of the 420 HBsAg carrier children cleared HBsAg, but hepatocellular carcinoma developed later at the age of 11 years.

3. *Histopathologic Findings*

Liver histology in HBeAg positive HBsAg carrier children generally reveals very mild inflammation and fibrosis (18). During the process of HBV and HBeAg clearance, the abnormal changes include various lobular activities, portal inflammation and fibrosis, with or without piecemeal necrosis. The inflammation is usually milder than that observed in adults. Bridging hepatitis

necrosis may occur, but is uncommon. Within 6 months of HBe seroconversion, the inflammation is less active, and beyond 6 months, becomes inactive with mild to minimal inflammation and fibrosis in most children.

We have studied the liver histology in 42 long-term followed, asymptomatic HBsAg children at 1 to 9 years of age, who were perinatally infected by their HBeAg-positive, HBsAg carrier mothers. The histologic findings included chronic active hepatitis (n = 1) ; chronic persistent hepatitis (n = 8) ; chronic nonspecific hepatitis (n = 30) ; and normal (n = 2). The histologic abnormalities in the liver begins early in life and may progress to severe liver impairment in later life.

Mass immunization for HBV and its benefits

Immunoprophylaxis of HBV can be divided into passive and active immunization. Before the era of HBV vaccination, passive immunization with three doses of hepatitis B immunoglobulin starting from within 24 hours after birth was useful in preventing perinatal HBV infection in high-risk infants (of HBeAg positive HBsAg carrier mothers) with an efficacy of around 75% (19). Active immunization with 3 or 4 doses of hepatitis B vaccine has proved to be immunogenic in more than 90% of neonates of non-carrier mothers or HBeAg-negative carrier mothers (20), and with around 75% efficacy in infants of high risk mothers. With combination of passive and active immunization, i.e. one dose of hepatitis B immunoglobulin within 24 hours after birth and three or four doses of hepatitis B vaccine, the efficacy can be inceased to 85-95% in high-risk infants (21).

The first univeral hepatitis B vaccination program in the world was launched in Taiwan since July 1984 (22). During the first two year of this program, only neonates of the HBsAg positive mothers were included. It extended to all the neonates since the third year of the program. It then further extended to preschool, and then school children, and later all the adults gradually. The coverage rate of hepatitis B vaccine for neonates is around 84-94%. The HBsAg carrier rate decreased significantly from around 10% before to < 1% after the vaccination program in children of < 10 years old. The infection rate was decreased in all the children, even in those above 10 years of age who were not vaccinated during infancy (anti-HBc seropositivity declined from 38% to 16%). This vaccination program has indeed reduced both the perinatal and horizontal transmission of HBV (23). The decrease of horizontal infection was contributed by both the decline of the infection source and the vaccination of the older children.

After the universal vaccination program of hepatitis B virus in Taiwan, we have successfully demonstrated the decline of the incidence of hepatocellular carcinoma in children. The average annual incidence of hepatocellular carcinoma in children of 6 to 14 years declined from 0.70 per 100,000 children between 1981 and 1986, to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994 (24). Further studies are needed, and are expected to see the further decline of the incidence of hepatocellular carcinoma in adults.

Conclusions

Universal immunization for HBV should be integrated into the Expanded Program of Immunization (EPI) in children. It is particularly urgent in areas where HBV infection and hepatocellular carcinoma are hyperendemic. The World Health Organization has recommended that universal hepatitis B immunization should be introduced in all countries at the end of 1997. Up to 1997, a total of 85 countries have followed this recommendation. With the integration of the hepatitis B vaccination program into EPI in most countries of the world, chronic HBV infection and its complications will be further reduced in the next century.

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