Factors Affecting the Natural Decay of Hepatitis B Surface Antigen in Children with Chronic Hepatitis B Virus Infection during Long-Term Follow-Up

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Objective To investigate the factors predicting spontaneous clearance of hepatitis B surface antigen (HBsAg) in a long-term, prospectively followed cohort from childhood into adult life.

Study design Children with chronic hepatitis B virus (HBV) infection without treatment were followed longitudinally every 6 months. At each visit, liver profiles and HBV markers were assessed. Hepatitis B vaccination history and the maternal HBV markers also were studied.

Results A total of 349 children (205 male) were followed for 20.6 ± 4.4 years with initial ages of 8.4 ± 3.9 years; 42 (12.0%) cleared HBsAg spontaneously. The HBsAg titers decayed with age, with an average annual clearance rate of 0.58%. Children had a lower annual HBsAg decay rate if their mothers are HBsAg carriers ($P < .001$). Hepatitis B e antigen-seroconversion is a favorable predictor for spontaneous HBsAg clearance ($P = .04$). Those with HBsAg titer ≤1000 IU/mL at enrollment during childhood have a higher rate of HBsAg clearance (hazard ratio = 5.23; $P < .001$). Using HBsAg titer ≤1000 IU/mL to predict HBsAg clearance, the sensitivity is 38.1%, specificity is 90.6%, positive predictive value is 35.6%, and negative predictive value is 91.4%.

Conclusions During long-term follow-up, spontaneous HBsAg clearance is most likely to occur in a patient born to a non-HBsAg-carrier mother, is a hepatitis B e antigen-seroconverter, and had an initial HBsAg level ≤1000 IU/mL. *(J Pediatr 2014;165:767-72)*.

During the natural course of chronic hepatitis B virus (HBV) infection, patients with high serum levels of viral DNA and hepatitis B e antigen (HBeAg) may gradually and spontaneously clear HBeAg and develop antibody to HBeAg.[1,2] HBeAg seroconversion also may be facilitated by antiviral treatment. However, after HBeAg seroconversion, most patients remain hepatitis B surface antigen (HBsAg)-positive with various levels of HBV DNA titers, ranging from high to undetectable levels for a long period of time.[3] HBeAg seroconversion is no longer the ultimate goal for the management of patients with chronic hepatitis B. HBsAg clearance is considered to be a more favorable outcome if there is no preexisting cirrhosis or viral superinfection.[4-6] Hepatic decompensation is rare after HBsAg seroclearance.[6] According to the previous reports, the prognosis after HBsAg seroclearance is generally good compared with those persistently HBsAg seropositive.

Undetectable HBsAg in the serum is often due to diminished viral replication and is associated with a good prognosis, including histologic and biochemical improvement.[7] Serum HBsAg quantification has been evaluated as a marker of covalently closed circular HBV DNA.[8] In contrast to HBeAg loss, clearance of HBsAg rarely occurs in patients with chronic hepatitis B. The annual rate of HBsAg clearance in adults was reported to be 0.5%∼0.8%.[4,9] In highly endemic areas, the prevalence of HBsAg carriers in the general population ranges from 2%-20%, and infection occurs mainly during infancy and early childhood.[10] Children are asymptomatic and in an immune tolerance state with normal alanine aminotransferase (ALT) levels and high viral loads. There is limited information regarding the long-term longitudinal changes in HBsAg titers leading to HBsAg clearance starting from childhood. Bortolotti et al[11] reported a longitudinal study of 99 Caucasian children with parenterally acquired chronic hepatitis B. At follow-up, 15 of the 89 patients who were initially HBeAg-positive and 2 of 8 who were initially HBeAg-negative had cleared HBsAg. Children with chronic HBV infection in endemic regions, such as Asia, are infected through mother-to-infant transmission.[12,13] Using the recently available quantitative method for the determination of serum HBsAg titers sequentially, this study aimed to investigate the longitudinal natural decay rates in HBsAg titers, annual spontaneous HBsAg clearance, and responsible factors.

ALT	Alanine aminotransferase
HBV	Hepatitis B virus
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen

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Methods

Children who had been HBsAg-positive for more than 6 months were defined as having chronic HBV infection. From January 1977 to May 2011, children with chronic hepatitis B, followed for more than 5 years, were enrolled in this study with parental consent. They were followed prospectively every 6 months or at shorter intervals. At each visit, patients received physical examination and assessment of liver function profiles and HBV markers. Information regarding HBV vaccination history and maternal HBV status also were collected.

In order to study the natural history of chronic HBV infection, patients who received antiviral or immunosuppressive therapy, or those with HIV infection, were excluded from this study (n = 38). The criterion for initiation of antiviral treatment include positive HBsAg >6 months and ALT elevation ≥2-fold the upper limit of normal level for ≥3 months. The institution review board of the National Taiwan University Hospital approved the study protocol.

HBsAg seroclearance is defined as disappearance of HBsAg from serum sample for at least 2 measurements 6 months apart or longer duration, without reappearance of HBsAg in the last 2 determinations. We analyzed the annual decay trend of HBsAg titers, HBsAg annual seroclearance rates, and possible factors affecting spontaneous HBsAg clearance, including sex, HBV genotype, peak ALT levels, HBV vaccination history, HBeAg seroconversion, and maternal HBsAg and HBeAg status. The HBV vaccination program in Taiwan began in July 1984 for infants of HBsAg carrier mothers and universal HBV vaccination for all infants in July 1986. Hepatitis B immunoglobulin was given within 24 hours after birth for all infants of mothers seropositive for both HBeAg and HBsAg. The administration of 3 or more doses of HBV vaccine was considered completion of HBV vaccination.

Aminotransferase, HBV Markers, HBV Genotypes, and Hepatitis C Antibody

Serum HBV markers, including HBsAg, antibody to HBsAg, antibody to hepatitis B core antigen, HBeAg, antibody to HBeAg, and hepatitis C antibody were assayed by immunoassay using commercial kits (Abbot Laboratories, North Chicago, Illinois). The ALT levels were determined by autoanalyzer (7450; Hitachi, Tokyo, Japan). The HBV genotypes were analyzed by polymerase chain reaction with type-specific primers as described previously.[14]

Statistical Analyses

Association between the baseline characteristics and the subsequent status of HBsAg clearance were examined by χ^2 test, Student t test, or their corresponding nonparametric methods. The probabilities of HBsAg clearance, stratified by maternal HBsAg status and by initial HBsAg titers, were estimated by Kaplan-Meier survival analysis where log-rank tests were used for comparing the significance of difference between groups. Including all observations of HBsAg titers during the follow-up period into analysis, changes of HBsAg titers by age for whole population or for specific subgroups were characterized. Life table analysis was used to illustrate the HBsAg clearance of each 5-year age group.

Statistical analyses were performed using Small STATA 12.0 (StataCorp, College Station, Texas) and MedCalc 12 (MedCalc Software bvba, Mariakerke, Belgium). The significance level is set at P value of <.05.

Results

A total of 349 children with HBV infection (205 male and 144 female) were enrolled into our study; their ages at enrollment was 8.4 ± 3.9 years (birth to 16 years). They were followed for 20.6 ± 4.4 years (**Table I**). During follow-up, 259 of the 331 patients who were HBeAg-positive achieved HBeAg seroclearance, and 37 of them cleared HBsAg. Five of the 18 patients who were initially HBeAg-negative became HBsAg-negative during follow-up (**Figure 1**). Of the 349 patients, 42 (12.0%) cleared their serum HBsAg spontaneously; 23 of the 42 had achieved HBsAg seroconversion with the presence of antibody to HBsAg. The mean annual spontaneous HBsAg clearance rate was 0.58% (male 0.70%, female 0.41%). The age at HBsAg clearance ranged from 4.1-33.0 years with a mean age of 17.7 ± 7.8 years. Life table analysis further displayed the cumulated HBsAg clearance rate in the time interval of 5 years (**Table II**; available at www.jpeds.com).

Genotype B was the prevailing genotype, accounting for 75.4% of our study population, followed by genotype C (20%), and mixed genotypes B and C (4.6%). We collected HBV vaccination records during infancy for 310 patients; 55 (17.7%) patients received ≥3 doses of HBV vaccination,

Table I. Demographic data of the case cohort (total N = 349 patients)

	No. (%) of the patients
Sex	
Male	205 (58.7%)
Female	144 (41.3%)
Initial age	8.4 ± 3.9 years old
Follow-up duration	20.6 ± 4.4 years
Initial HBeAg	
Positive	331 (94.8%)
Negative	18 (5.2%)
HBsAg titer at enrollment (IU/mL)	
≥10 000	234 (67.0%)
1000-9999	71 (20.3%)
100-999	23 (6.7%)
<100	21 (6.0%)
Maternal HBsAg status	(n = 297)
HBsAg (+)	211 (71.0%)
HBsAg (−)	86 (29.0%)
Maternal HBeAg status	(n = 210)
HBeAg (+)	105 (50.0%)
HBeAg (−)	105 (50.0%)
Peak ALT (U/L)	
≥1000	6 (1.7%)
100-999	170 (48.7%)
40-99	99 (28.4%)
<40	74 (21.2%)