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Predictive Effect of Serial Serum Alanine Aminotransferase Levels on Spontaneous HBeAg Seroconversion in Chronic Genotype B and C HBV–Infected Children

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Abstract

Objective—The present study aimed to investigate the association between serial serum alanine aminotransferase (ALT) and spontaneous hepatitis B e antigen (HBeAg) seroconversion age in chronic hepatitis B virus (HBV)–infected children.

Patients and Methods—One hundred four HBeAg-positive chronic genotype B or C HBV–infected patients were included in this long-term prospective cohort study (mean initial age 7.20 years). Serial serum ALT levels and HBV serology markers were measured every 6 to 12 months. The 104 subjects made a total of 2525 visits during the study period, and the majority (93.6%) of visits were within a 1-year interval apart from previous visits. Cox proportional hazards model with time-dependent covariates was used in the survival analysis of HBeAg in these subjects.

Results—During the chronic course of HBV infection, the median remaining times to spontaneous HBeAg seroconversion were 8.35, 5.14, 4.25, 3.95, and 2.80 years after the ALT levels crossed 20, 30, 40, 60, and 150 IU/L, respectively. The incidence rate of spontaneous HBeAg seroconversion within 6 months when a subject entered the phase of ALT between 60 and 150 IU/L was 5.57 times that of the phase with ALT <60 IU/L. The incidence rate of HBeAg seroconversion once ALT levels were above 150 IU/L was 9.87 times that of the phase of ALT <60 IU/L.

Conclusions—The ALT levels above 30 IU/L served as a cutoff of the inflammatory phase in chronic genotype B and C HBV–infected patients. Serial ALT levels in chronic HBV–infected subjects offer a predicted effect on the occurrence of spontaneous HBeAg seroconversion.

Keywords

alanine aminotransferase; hepatitis B e antigen; hepatitis B virus; liver immunology

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Chronic hepatitis B virus (HBV) infection is a major health problem (1,2). Hepatitis B virus e antigen (HBeAg) seroconversion is an important goal of antiviral treatment (3). Spontaneous HBeAg seroconversion in children is associated with a relatively uneventful course and fewer events of HBeAg-negative hepatitis (4). Persistent HBeAg positivity beyond the third to fourth decades of life in chronic HBV–infected subjects is associated with a higher risk of HBV-related liver cirrhosis and hepatocellular carcinoma (5,6).

Various host and viral factors associated with the spontaneous HBeAg seroconversion process have been mentioned (7–10). Some of these host factors such as earlier puberty onset in boys and the high interleukin-12 production genotype are associated with higher peak ALT levels before HBeAg seroconversion and predict earlier onset of spontaneous HBeAg seroconversion (9,10). The flare of serum ALT levels in subjects with chronic HBV infection indicates the breakdown of immune tolerance and entry into the immune clearance/inflammatory phase. Some finish the seroconversion after a dramatic flare of serum ALT levels and others with only mild elevation before the seroconversion. A lower serum ALT level cutoff in subjects with chronic liver disease may enhance the detection sensitivity and specificity of immune clearance/inflammatory phase occurrence (11).

The present study investigated the cutoff of inflammatory phase and the longitudinal profiling of serial serum ALT levels based on a long-term prospective cohort design study from childhood to adulthood in determining the significant cutoff thresholds to predict spontaneous HBeAg seroconversion by a sophisticated statistical procedure.

PATIENTS AND METHODS

Study Subjects

One hundred four (56 boys and 48 girls) chronic HBV–infected subjects from 49 unrelated families with positive HBeAg studied between 1984 and 1998 until January 2009 at the National Taiwan University Hospital were included in this long-term prospective cohort study at the Department of Pediatrics. Ninety-six subjects (92.3%) were infected by genotype B HBV, 7 subjects (6.7%) by genotype C, and 1 subject (1.0%) by mixed genotype B and C HBV. Each child was examined at 6 to 12 monthly intervals or more frequently if abnormal liver profiles were identified. Physical examinations and phlebotomy were performed at each visit. None of the subjects received antiviral agents or immune therapy before HBeAg seroconversion. The study was approved by the institutional review board of the hospital, and all of the subjects or their parents gave written consent to enter the study for long-term prospective follow-up. Serum ALT levels and HBV serology tests were measured at each medical visit to determine whether spontaneous HBeAg seroconversion had occurred.

The 104 subjects made a total of 2525 visits during the study period, and the majority of the visit intervals were less than 1 year (n = 2363, 93.6%). We collected age-specific longitudinal ALT data.

HBV Serologic Tests

Serum samples were obtained from the 104 chronic HBV–infected children at each visit for HBV markers and liver function profile examinations. HBV markers including HBsAg and its antibody (anti-HBs), HBeAg and its antibody (anti-HBe), and hepatitis B core antibody (anti-HBc) were assessed by radioimmunoassay (Abbott Laboratories, North Chicago, IL). HBeAg seroconversion was defined as spontaneous clearance of serum HBeAg, with the appearance of anti-HBe antibodies lasting for more than 6 months.

Statistical Analysis and Models

Patients were recruited at different ages before HBeAg seroconversion, and this resulted in left truncation of the data in the survival analysis (12). Those recruited into the study were further subjected to right censorship either because they were lost to follow-up or if spontaneous HBeAg seroconversion had not taken place by the end of the study. The midpoint of the time interval from the final medical visit with HBeAg(+) and anti-HBe(−) to the first visit with HBeAg(−) and anti-HBe(+) was used as the age at HBeAg seroconversion for a subject. Finally, a shared frailty variable was used to reflect the potential dependency among ages at the HBeAg seroconversion of the subjects within the same family (12). The upper limit of normal (UNL) of ALT levels was adjusted to enhance the sensitivity of clinical diagnosis (13); however, the exact cutoff of inflammatory phase from the immune tolerance to inflammatory phase is unclear in the pediatric population.

We adopted the Cox proportional hazards model with time-dependent covariates and adjusted for the sampling plan of left truncation and right censoring with a shared gamma-frailty term among family members. The change rate of a longitudinal ALT levels as a covariate in the statistical model (14,15). The statistical model and fitted ALT-related covariates are detailed in the online-only appendix (http://links.lww.com/MPG/A57). Statistical software R was used for the statistical analysis in the present study.

RESULTS

General Characteristics

The general characteristics of the study samples are summarized in Table 1. The median entry age was 7.2 years, the median follow-up period was 23.7 years in the study population, and 79.8% of study population finished the spontaneous HBeAg seroconversion during the long-term follow-up. One hundred and four subjects came from 49 families, out of which 4 families had 1 child, 35 had 2 children, and 10 families had 3 children. Thirty-six (73.5%) mothers from these 49 families had chronic HBV infection. Seventy-eight (75%) subjects of the 104 HBeAg-positive chronic HBV–infected patients were born to HBV seropositive mothers, and were regarded as having mother-to-infant transmission of HBV, whereas another 26 (25%) subjects were suspected of acquiring HBV from a horizontal route. On average, there were 25.3 ALT measurements from each individual before being detected as seroconverted or at the end of the follow-up. Majority (93.6%) of the adjacent ALT measurements were taken at an interval of less than 12 months. Nobody of these study populations have spontaneous HBsAg clearance during the study period. During the follow-up course, there was no significant difference in the peak ALT levels before HBeAg seroconversion between boys and girls in the study population (mean ± SD, 240.46 ± 495.82 vs 164.50 ± 218.69; 95% confidence interval [CI] 96.49–384.43 vs 107.00–222.00 IU/L; P = 0.33 by Student t test with unequal variance). The annual spontaneous HBeAg seroconversion rate was 1.70% ± 1.78% (95% CI 0.43%–2.97%) in the first decade of life, 3.78% ± 1.63% (95% CI 2.61%–4.94%) in the second decade of life, and 4.02% ± 2.29% (95% CI 1.61%–6.23%) in the third decade of life of the study population. The annual spontaneous HBeAg seroconversion rate in the first decade of life is significantly lower than that in the second and third decade of life (P = 0.03 by ANOVA test).

Determining the Critical ALT Thresholds Predicting Spontaneous HBeAg Seroconversion

The estimated 25th, 50th, and 75th percentiles of these remaining times since the first crossing of the given threshold to spontaneous HBeAg seroconversion are listed in Table 2. The median remaining time to spontaneous HBeAg seroconversion was 8.35 years with the ALT level above 20 IU/L, which is significantly longer than that with ALT levels above 30 IU/L (5.14 years), 40 IU/L (4.25 years), 60 IU/L (3.95 years), and 80 IU/L (3.42 years)

(Table 2). Hence, the ALT cutoff above 30 IU/L served as a cutoff of the immune inflammatory phase with 50% of subjects developing spontaneous HBeAg seroconversion within 5.14 years. Hence, we regarded ALT 30 IU/L as the new UNL and 40 IU/L as the old UNL in the present study.

The 2× and 5× of ALT UNL associated with different antiviral treatment response during the chronic course of HBV infection. Thus, we also compared 2 pairs of ALT thresholds, (60 and 150 IU/L) and (80 and 200 IU/L) for 2× and 5× new and old UNL of the ALT levels. Kaplan-Meier estimators for the condition survival function of remaining time to HBeAg seroconversion after the first crossing of a given threshold value are displayed in Supplementary Figure 1 (http://links.lww.com/MPG/A59). No significant differences between these 2 pairs of thresholds were identified.

The percentiles were comparable between 60 and 80 IU/L (2× new and old UNL) and between 150 and 200 IU/L (5× new and old UNL) in Table 2. The median remaining times to spontaneous HBeAg seroconversion were 3.95, 3.42, 2.80, and 2.80 years after the serum ALT levels crossed 60 (2× new UNL), 80 (2× old UNL), 150 (5× new UNL), and 200 IU/L (5× old UNL), respectively.

Hence, in the following survival analysis (60 and 150) IU/L (2× and 5× new UNL) threshold was used to define 3 different phases: ALT <60 IU/L (2× new UNL), 60 (2× new UNL) < ALT <150 IU/L (5× new UNL), and ALT >150 IU/L (5× new UNL), during a course of detecting the spontaneous HBeAg seroconversion.

Different ALT Phases and Spontaneous HBeAg Seroconversion

Several 3-phase models that relate the incidence rate of HBeAg seroconversion to the ALT levels of a subject 6 months earlier were considered. The 6-month lag and the use of 6-month-earlier change rate ([current ALT − 6-month-earlier ALT]/0.5 year) are intended for prediction purpose; details and rationales of the models may be found in the online-only appendix (http://links.lww.com/MPG/A57) and Supplementary Table 1 (http://links.lww.com/MPG/A58). There is no significant association between the siblings from the same family in the ALT pattern before spontaneous HBeAg seroconversion. When remaining in the phase of ALT < 60 IU/L, a subject's incidence rate of spontaneous HBeAg seroconversion had an average of a 1.16 times ($P = 0.014$) increase for 1 U decrease of the square root of the 6-month-earlier change rate. This effect may well explain the spontaneous HBeAg seroconversion in the phase of ALT <60 IU/L. The incidence rate of spontaneous HBeAg seroconversion increased to 5.57 times ($P < 0.001$) when a subject entered the phase of ALT between 60 and 150 IU/L as compared with that of the phase with ALT <60 IU/L. As entering the phase of ALT between 60 and 150 IU/L, the incidence rate of spontaneous HBeAg seroconversion had a further 1.05 times ($P = 0.05$) increase for 1-U decrease of the square root of the 6-month-earlier ALT change rate. The incidence rate of HBeAg seroconversion, once ALT levels surged above 150 IU/L, was 9.87 times ($P < 0.001$) that in the phase of ALT <60 IU/L, but the effect of 6-month-earlier change rate is no longer significant in this phase. The abrupt increase of the incidence rate further demonstrates the large predictive effect of HBeAg seroconversion with elevation of ALT levels. Subgroup analysis in 78 subjects regarded as having mother-to-infant transmission of HBV yielded similar results to the whole population (data not shown).

DISCUSSION

HBeAg seroconversion to its antibody is a critical event during the chronic course of HBV infection, (16) and the delay in this process is associated with prolonged liver injury and various HBV-related complications (5,6). Elevation of serum ALT levels in chronic HBV–

infected subjects indicates the breakthrough of immune tolerance, the entrance into the inflammatory stage, and the emergence of HBV mutant strains under the host and viral interactions (17). After the HBeAg seroconversion, some chronic HBV–infected patients may have persistent low viremia status with few HBV precore mutations, but others may have high rates of HBV precore gene mutation with fluctuating high viremia (17).

The longitudinal serial ALT profiles before the spontaneous HBeAg seroconversion vary greatly between different individuals. Some may be persistent HBeAg positive and anti-HBe negative even after repeated events of ALT elevation during the chronic course of HBV infection. Others may develop spontaneous HBeAg seroconversion immediately after the ALT surge. The exact cutoff value of ALT levels, which may help clinicians to predict the occurrence of spontaneous HBeAg seroconversion in chronic HBV–infected children, has not been clear. Study patients entered the cohort at the median age of 7.2 years and developed spontaneous HBeAg seroconversion at the median age of 15.5 years, and immediately after puberty served as good subjects to analyze the cutoff of the inflammatory phase in chronic HBV–infected children and the observation of cutoffs in predicting the occurrence of spontaneous HBeAg seroconversion.

On-treatment serum ALT levels above 2× UNL and even 5× UNL have been noted to be associated with better antiviral agent treatment responses (18–20); however, the previous ALT thresholds have been noted to be too high in detecting children with chronic hepatitis, and there is a significant difference in the remaining time to spontaneous HBeAg seroconversion between the ALT 20 and 30 IU/L threshold in the present study. Chronic HBV–infected children may enter their inflammatory phase and develop spontaneous HBeAg seroconversion shortly after the onset of puberty (10,11,21,22). The predicted effect of spontaneous HBeAg seroconversion based on adult data with cutoff values of 80 and 200 IU/L is not clear in children and early puberty. Hence, the present study offers a cutoff of the inflammatory phase in chronic HBV–infected children as 30 IU/L in Taiwan. At the same time, we also defined the ALT cutoff thresholds in predicting the occurrence of spontaneous HBeAg seroconversion based on a prospective long-term cohort study with time-dependent serial ALT levels and HBV markers in chronic HBV–infected subjects studied from early childhood to young adulthood. This is the first time in our relevant studies that the longitudinal data of serum ALT were incorporated into the fitting of the Cox model to predict the occurrence of spontaneous HBeAg seroconversion.

Kaplan-Meier analysis showed no difference ($P > 0.05$) between the cutoff between 60 vs 80 IU/L and 150 vs 200 IU/L in predicting spontaneous HBeAg seroconversion after crossing these thresholds. The median remaining times to spontaneous HBeAg seroconversion were also similar between the cutoff of 60 and 80 IU/L (3.95 vs 3.42 years) and 150 and 200 IU/L (2.80 vs 2.80 years). Hence, lowering the cutoff of 2- and 5-fold UNL from (80 and 200 IU/L) to (60 and 150 IU/L) may enhance the sensitivity of predicting subsequent HBeAg seroconversion in chronic HBV–infected patients, especially in children and early puberty. The decline in serum ALT levels in subjects at the phase of ALT <60 IU/L and between 60 and 150 IU/L were noted to predict the occurrence of spontaneous HBeAg seroconversion. The drop in serum ALT levels may reflect the shift from cytolytic to noncytolytic inhibition of HBV (21). The change in ALT cutoff from (80 and 200 IU/L) to (60 and 150 IU/L) needs further study to clarify the treatment response to antiviral agents in children.

In this long-term prospective cohort, 93.6% of appointed visits were less than 1 year and 60.1% of visits were less than 6 months. The dataset gave us an opportunity to closely monitor the serial trend of serum ALT levels and spontaneous HBeAg seroconversion occurrence in these chronic HBV–infected children. The actual HBeAg seroconversion age was only known to be somewhere between the 2 consecutive appointments. This problem

may not be serious because the time intervals between the 2 visits were usually short, so we took, for simplicity, the midpoint of the time interval within which HBeAg seroconversion took place as the event time for a patient.

Chronic HBV–infected patients should be studied from birth to the occurrence of spontaneous HBeAg seroconversion in an ideal condition. These patients entered the study at different ages, rendering left-truncated data and a biased sample that tended to include patients with longer HBeAg seroconversion times. Hence, the bias generated by such a sampling plan has been corrected in our analysis. Some patients having persistent HBeAg until the final visit were subjected to right censoring. Managing the data as both left truncated and right censored, which is frequently overlooked in medical studies, we used proper statistical methods as a remedy in the data analysis (8,12,23).

Because the major HBV genotypes in Taiwan are B and C, only subjects infected with genotypes B and C were included in the present study. Thus, our data may apply only to genotype B and C chronic HBV–infected patients. The study population is relatively small; we did not further analyze the difference in the ALT cutoff predicting spontaneous HBeAg seroconversion between boys and girls in present study.

The HBeAg seroconversion and HBsAg clearance rate reported by Bortolotti et al (24) are 97.8% and 16.5%, respectively, in 91 HBeAg-positive chronic genotype D and A HBV–infected white children during a mean of 19.7 years follow-up period. The HBeAg seroconversion and HBsAg seroclearance rates in our population are much lower (79.8% and 0%, respectively) during the median of 23.7 years follow-up period. The difference may associate with different HBV genotype (genotypes D and A are the dominant strains in Europe, and genotypes B and C are the major strains in Taiwan), transmission route (mother-to-infant transmission 10% in the Italian group and 75% in our population), normal or elevated ALT levels at enrollment, and host genetic background (24,25).

In conclusion, serum ALT level 30 IU/L in chronic genotype B and C HBV–infected subjects from childhood to young adulthood served as a cutoff of the immune active or the inflammatory phase before HBeAg seroconversion. The ALT thresholds, 60 (2× new UNL) and 150 (5× new UNL) IU/L, are reliable in predicting the occurrence of spontaneous HBeAg seroconversion in genotype B and C chronic HBV–infected patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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TABLE 1

General characteristics of the study subjects

Characteristic	All subjects (N = 104)
HBeAg seroconversion during follow-up (%)	83/104 (79.8)
Male sex (%)	56 (53.8)
Follow-up period, median (range), y	23.7 (14.5–33.3)
Age at entry, median (range), y	7.2 (0.6–15.0)
HBeAg seroconversion age, median (range), y (n = 83)	15.5 (1.0–33.3)
No. longitudinal measurements (mean ± SD), times	25.3 ± 17.8
Intermittent time interval (mean ± SD), y	0.5 ± 0.5
Intermittent time interval, y (total 2525 visits) (%)	
<0.5	1517 (60.1)
0.5–1	846 (33.5)
>1	162 (6.4)
HBV genotype (%)	
B	96 (92.3)
C	7 (6.7)
Mixed genotype B and C	1 (1.0)

HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; SD = standard deviation. The 104 chronic HBV–infected patients were recruited from 49 unrelated families and delivered by 49 mothers.

TABLE 2

Percentiles of remaining time (in years) to seroconversion under various ALT threshold

ALT threshold, IU/L	20	30	40	60	80	150	200
Effective sample size, n	96	89	82	67	63	44	32
25%*	4.56	2.77	2.29	1.77	1.78	1.19	1.17
50%†	8.35	5.14	4.25	3.95	3.42	2.80	2.80
75%‡	13.88	11.75	7.93	5.25	5.19	4.35	4.11

ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen.

*Years taken for 25% of subjects with ALT above the threshold to finish spontaneous HBeAg seroconversion.

†Years taken for 50% of subjects with ALT above the threshold to finish spontaneous HBeAg seroconversion.

‡Years taken for 75% of subjects with ALT above the threshold to finish spontaneous HBeAg seroconversion.