

## Effects of Endocrine on the Breakthrough of Immune-tolerant in Chronic Hepatitis B Virus Infected Children

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### ABSTRACT

The hepatitis B virus (HBV) infection in endemic areas usually starts since infancy and early childhood and persists lifelong chronic infected status. The clinical course and severity varies among different chronic infected subjects, especially between different genders. Majority of chronic HBV infected children present with immune-tolerant status initially with normal liver profile, hepatitis Be antigen (HBeAg)-positive and high HBV viral load. They will then experience the immune clearance phase with various degree of liver injury at various age, and majority during or beyond puberty, and then enter the inactive phase after HBeAg seroconversion.

The adrenarche and puberty onset modulate the start of immune clearance and the severity of liver inflammation in chronic HBV infected children. The sex steroid then acts differently on the host immune system, viral replication and even tumor suppressive genes. The difference between males and females are associated with different risk of HBeAg-negative hepatitis, liver cirrhosis, and even the occurrence of hepatocellular carcinoma in later life.

Early events in childhood during chronic HBV infection may serve as important predictors for the later outcomes in adulthood. Understanding the mechanisms triggering liver inflammation and their long-term impacts may enhance the development of better and earlier therapeutic strategies for patients with chronic HBV infection.

### KEYWORDS

Adrenarche; Hepatitis B Virus; Immune-Tolerant; Immune Clearance; Menarche; Puberty; Endocrine System.

### ABBREVIATIONS

Alanine aminotransferase, ALT; deoxyribonucleic acid, DNA; dehydroepiandrosterone sulphate, DHEAS; hepatitis B virus, HBV; hepatitis B surface antigen, HBsAg; hepatitis B e antigen, HBeAg; hepatitis B core antigen, HBcAg; hepatitis B X protein, HBx; hepatocellular carcinoma, HCC

### INTRODUCTION

Human hepatitis B virus (HBV) remains the leading cause of liver insufficiency, liver cirrhosis, and even hepatocellular carcinoma in the world [1]. HBV belong to hepadna virus, which is a small enveloped virus with partially double stranded circular deoxyribonucleic acid (DNA) that replicate by reverse transcription in human hepatocytes [2] The partial double stranded circular viral DNA is then converted to a covalently closed circular DNA (cccDNA) that serve as the transcriptional

template for pre-genomic ribonucleic acid (RNA) and messenger RNA (mRNA) for hepatitis B surface antigen (HBsAg), hepatitis B e antigen / core antigen (HBeAg / HBcAg), polymerase, and X protein (HBx) [3].

The clinical course of chronic HBV infection is diverse among individuals with different host genetic background, viral strains, and host-viral interactions. The HBV acquisition age is known to associate with the chronicity of viral infection [4-6]. In endemic areas, such as Taiwan, perinatal infection account for 90% of the cases of chronic HBV infection after the universal HBV vaccination program [7]. The natural course of chronic HBV infection was generally sub-divided into immune-tolerant, immune clearance/inflammatory, post HBeAg seroconversion inactive phases. Up to 10-25% of the infected subjects were expected to suffer from HBeAg-negative hepatitis reacti-

vation phase, and even develop liver cirrhosis or hepatocellular carcinoma (HCC) [8, 9]. Very minority of chronic HBV infected subjects may develop HBsAg seroconversion, and get rid off chronic infected status. The immune-tolerant phase is indicated by normal alanine aminotransferase (ALT) levels, high HBV viral load, and HBeAg-positivity. In majority of the patients during or after the adolescent stage, the flare of ALT and the HBeAg seroconversion to its antibody (Anti-HBe) indicate the immune clearance phase. HBeAg seroconversion generally indicates the decrement of active viral replication and hepatitis activity, while delayed HBeAg seroconversion with persistently high viremia after the 3rd decade of life indicates a higher risk of developing liver cirrhosis, and hepatocellular carcinoma (HCC) [10-14].

### AIM OF THE PAPER

The triggering host factors to terminate the immune-tolerant phase, shortening of the period of high viremia, modulating the course of immune-clearance are the key determinants to the life-long risk of liver injuries, liver cirrhosis and HCC. This article aimed to review the roles of human endocrine system on the breakthrough of immune-tolerant phase in chronic HBV infected children

### SUPPORTING EVIDENCE

#### Nature course of the breakthrough of immune-tolerant

From a long-term chronic HBV cohort study, the spontaneous HBeAg seroconversion rate was low before 10 years of age, and accelerated since the second decade of life [15]. The annual spontaneous HBeAg seroconversion rate was 1.70% (95% CI = 0.43%–2.97%) in the first decade of life, 3.78% (95% CI = 2.61%–4.94%) in the second decade of life, and 4.02% (95% CI = 1.61%–6.23%) in the third decade of life in genotype B and C chronic HBV infected patients [15]. The serum alanine transaminase (ALT) level elevated to above 30 IU/L, predict the occurrence of HBeAg seroconversion, indicating the breakthrough of immune tolerant. 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 in the study. These data indicated that the breakthrough of immune tolerance in chronic HBV infected children is around the peri-puberty period.

#### Effect of Puberty and androgen

In chronic HBV infected males, earlier puberty onset and increased steroid 5-alpha reductase type II (SRD5A2) enzyme activity are reported to associate with earlier HBeAg seroconversion [16]. Testosterone secretion in men increases beginning at the onset of puberty with the peak serum level occurring during their 20s, and then declines gradually after the 3rd decade of life with decreases of roughly 10% per decade thereafter.

In a chronic genotypes B and C HBV infected Taiwanese male cohort (mean enrollment age at  $6.8 \pm 1.6$  years and the mean follow-up duration of  $16.8 \pm 3.4$  years), earlier-onset puberty had higher serum testosterone levels than subjects with later-onset puberty in Taiwanese males at the age of 15 and 20 years [16]. In the survival analysis to assess the difference in spontaneous HBeAg seroconversion age, subjects with earlier-onset puberty had a younger spontaneous HBeAg seroconversion age than those with later-onset puberty (median age, 13.2 vs. 22.5 years, HR, 3.0; P, 0.005) [16]. The decrement in the HBV viral load from puberty to young adulthood was significantly higher in the subjects with earlier-onset puberty than those with later-onset puberty males (earlier vs. later-onset puberty:  $1.6 \pm 0.3$  vs.  $0.2 \pm 0.4$  log<sub>10</sub>copies/mL HBV viral load decrement from 15 to 20 years of age, P=0.01) [16].

#### Effect of Puberty and Menarche

From a chronically genotypes B and C HBV-infected Taiwanese young female cohort (mean enrollment was  $4.6 \pm 3.1$  years and the mean follow-up duration was  $24.0 \pm 3.8$  years), earlier menarche in females, also indicating earlier puberty-onset, is also associated with earlier HBeAg seroconversion in Taiwanese female subjects with chronic HBV infection [17].

The annual decrease in HBsAg titer from 15 to 20 years of age also was greater in the early menarche group compared with the late menarche group. The baseline HBV viral load was also borderline low in female subjects with earlier menarche as compared with others ( $6.10 \pm 2.29$  vs.  $7.02 \pm 1.89$  log<sub>10</sub> copies/mL; 95% CI = 5.06 - 7.15 vs. 6.60-7.44 log<sub>10</sub> copies/mL; P = 0.06). Earlier menarche onset was associated with higher spontaneous HBeAg seroconversion, HBsAg seroclearance, and HBsAg seroconversion rate before 15 years of age in females with chronic HBV infection [17].

#### Roles and Adrenarche and Dehydroepiandrosterone sulphate (DHEAS)

The clinical courses of infection with various pathogens differ greatly between males and females; the difference is thought to result from cross-talk between different sex steroids and immune effectors [18, 19]. The main sex steroids at puberty are testosterone and estradiol in male and female subjects, respectively. Animal studies showed the androgen pathway can increase HBV transcription, while the estrogen pathway may repress the efficacy of HBV genes transcription [20-22]. Hence, the association of puberty onset in both genders with the breakthrough of immune tolerance may not be answered by the sex steroids alone. 19,20 Other hormone factors other than sex steroids and common to both genders, acting during or even before the peri-puberty period, may contribute to the termination of immune tolerant phase [23].

DHEAS, an adrenarche marker, generally elevated 2 years before puberty is significantly associated with the age of HBeAg seroconversion in both genders [23]. The elevation of serum DHEAS is generally between 6-8 years of age in both genders, and peaks at the third decade of life [24, 25]. The pattern is quite similar to the immune breakthrough age in chronic HBV infected patients. The DHEAS, itself, is regarded as a potent immune modulator in human immune responses to various infectious pathogens [26-29]. Hence, the DHEAS may serve as a cross-talk window between human endocrine and immune systems. Higher serum DHEAS levels at mid-puberty was further showed to predict higher decay rate of HBV viral load and HBsAg titer from mid-puberty to young adulthood [23].

Although the immune factors play the key roles during the long-term host-viral interaction, inflammatory intensity, and immune escape HBV mutant strains selection [30-37]. The endocrine factors, particularly the DHEAS, change with the onset of adrenarche may be partially responsible for the breakthrough of immune tolerant, initiation of immune clearance in chronic HBV infection patients.

#### Effect of endocrine systems and early events on late clinical courses

HBeAg seroconverters in a pediatric cohort showed persist low HBV viral loads, normal ALT, and uneventful courses after HBeAg seroconversion [38]. However, HBeAg seroconversion beyond the 3rd to 4th decade of life in adults is associated with increased risk of increased HBV viral load, HBeAg-negative hepatitis flare, liver cirrhosis and even HCC [13, 14]. Hence, different endocrine trigger, immune mechanism and possible different HBV mutants selected during the immune clearance phase between young and old HBeAg seroconverters may result in different clinical courses and life-long outcomes.

From our cohort constitute 434 subjects [spontaneous HBeAg-seroconversion occurred in 359 subjects, and 75 subjects developed HBeAg-seroconversion after antiviral therapy followed for a median of 14.40 years (IRQ: 6.14–22.02 years) after HBeAg-seroconversion], gender was demonstrated to be a key determinant of the HBeAg-negative hepatitis risk after HBeAg seroconversion (Hazard ratio = 3.15; 95% CI = 1.06-9.32;  $P = 0.04$ ) [39]. The relative risk of HBV-related HCC and liver disease related death are consistently several fold (1.5-7.6 times) higher in males than females [40-42]. Our previous study also demonstrated the severity of liver inflammation is closely associated with the serum testosterone levels in chronic HBV infected males [16]. The different outcomes between chronic HBV infected males and females are closely related to the effect of sex steroids on HBV biosynthesis [20-22].

The HBeAg seroconversion age and the severity of liver dam-

age during the immune clearance phase are both important outcome determine factors during the natural course of chronic HBV infection. Extremely early HBeAg seroconversion before 3 years of age with severe liver damage was noted to increase the risk of childhood HCC [43,44]. While the HBeAg seroconversion during childhood without severe liver damage have been demonstrated to associate with a relatively uneventful course with low viremia profile, lower incidence of hepatitis reactivation after HBeAg seroconversion, and higher chance of spontaneous HBsAg seroconversion.<sup>38,39</sup> Recently, we demonstrated earlier breakthrough of immune-tolerance and earlier HBeAg seroconversion in children indicating lower risk of HBeAg negative hepatitis and higher chance of spontaneous HBsAg seroconversion in later life [39,45].

## DISCUSSION AND FUTURE PROSPECTS

The HBV infection in endemic area mostly occurred in infant, and resulted in chronic HBV infected status. The viral factors, host factors, and host-virus interactions performed as an orchestra, and acting together to modulate the natural course of chronic HBV infection. The early events of chronic HBV infection occurring during childhood, reflecting the complex interactions between the host and virus, are key earlier predictors of the life-long outcomes of chronic HBV infection. Realizing the relevant host and viral factors, and providing early and effective intervention may improve the long-term outcome of chronic HBV infected patients.

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