

Clinical Implications of Concurrent HBsAg/HBsAb Positivity in Patients with Chronic Hepatitis B Infection

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ABSTRACT

AIM: Concurrent positivity for HBsAg and HBs antibody is an

unusual serological pattern in hepatitis B virus (HBV) infection. There is limited information on the clinical course of patients with this serological pattern. Here, we aimed to describe the clinical features of patients with chronic HBV infection presented with HBsAg+/HBsAb+ profile.

MATERIAL AND METHODS: This was a retrospective study on 309 patients with chronic HBV infection. The patients received either tenofovir, lamivudine, or no treatment based on the levels of liver enzymes. Serological profiles were recorded at the diagnosis and six months afterwards. Statistical analysis was performed in SPSS 19 software.

RESULTS: From 309 chronically HBsAg positive patients, 10(3.2%) showed concurrent positivity for HBsAg and HBsAb in their sera. There were no statistically significant association between this pattern with either gender, age, and HBeAg status. However, there was a close association between HBsAg+/HBsAb+ with seropositivity for anti-HBeAg ($p = 0.05$). There were also no significant associations between AST or ALT levels and HBsAg+/HBsAb+ neither at the diagnosis or six months afterwards.

CONCLUSION: It seems that patients with chronic HBV infection and persistent concurrent reactivity for HBsAg and HBsAb render comparable clinical course with those patients with single HBsAg positivity.

Key words: Hepatitis B virus; Escape mutant; Hepatitis B Surface Antigens

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INTRODUCTION

Hepatitis B virus (HBV) is one of the most dreadful infectious diseases worldwide. The incidence of dire complications such as

hepatocellular carcinoma (HCC), hepatic fibrosis, cirrhosis, and finally death is inevitable in untreated HBV infected patients. According to an estimation by the World Health Organization (WHO), there are currently 240 million individuals with chronic HBV infection^[1,2] from whom 780,000 are annually succumbed to the disease related complications^[3,4]. The high mortality and morbidity rates have urged the researchers and health providers to implement preventive measures to avoid heavy therapeutic costs.

Concurrent seropositivity for HbsAg and HBsAb (HBsAg+/HBsAb+) is an uncommon serological pattern in HBV infected individuals. HBsAg is one of the earliest detectable serological markers of HBV infection indicating acute infection. However, when HBsAg persists for more than six months, the chronic infection is warranted. Anti-HBs antibodies indicate successful immune reactivity against the infection and usually are identifiable as HBV infection is rectified^[5]. Despite this clinical and immunological asynchrony, these two serological markers may be identified simultaneously in some HBV infected individuals^[6].

Clinical and laboratory features of patients with chronic HBV infection and HBsAg+/HBsAb+ are not certain. This serological pattern has been suggested to be closely related to HBSAg escape mutants^[7]. In fact, the newly emerged concerns on the efficiency of HBV vaccination have been unleashed with the emergence of mutated HBV strains^[8]. Clinical impacts of HBsAg mutations varies from the failure of diagnostic assays to detect the mutated antigen (diagnosis escape), bypassing host derived antibodies (eradication escape), hiding from therapeutic immunoglobulins (treatment escape), as well as failing in promoting an immune response following vaccination (vaccine escape)^[9-11]. Some other possible mechanisms underlying concurrent HBsAg+/HBsAb+ have been factors associated with HBV different genotypes, and DNA viral replication rate^[7, 12-16]. However, the exact mechanisms and their clinical implications are yet to be divulged. In present study, we have clinical features of HBV infected patients with this distinct serological signature.

METHODS

Patients

This was a retrospective study performed in Zabol, a city in the north of Sistan and Baluchestan province in the south-east of Iran. The data was retrieved from clinical archives of 309 patients with chronic HBV infection diagnosed within 2004-2014 in Amir-Al-Momenin Hospital of Zabol.

Exclusion criteria included incomplete clinical records. Therapeutic protocols included administration of lamivudine or tenofovir disoproxil in patients with elevated hepatic enzymes at the time of diagnosis. Diagnosis of HBV infection was based on clinical and laboratory results. The patients underwent various procedures (i.e. liver biopsy, endoscopy, and ultrasonography) when indicated during the course of the disease. Serological results were recorded both at the diagnosis and the end of six month of diagnosis.

Statistical analysis

Statistical analysis was performed in SPSS 19 software. Kolmogorov-Smirnov test was applied for checking normality. Chi-square test was used for seeking any association between demographic and clinical variables with serological patterns. Wilcoxon rank test, paired-sample t-test, and Mann Whitney U test were applied for checking any significant difference in the means of hepatic enzymes in the two serological patterns.

RESULTS

From 309 patients who had positive HBsAg for at least six months from diagnosis, 10(3.2%) showed concurrent positivity of anti-HBs antibodies at six months from diagnosis. The mean age of the patients with HBsAg+/HBsAb+ was 34 ± 11.2 years old which was not significantly different from that (37.8 ± 14 years old) of HBsAg+/HBsAb- patients. Also, there were no significant distributional differences for gender, and HBeAg positivity regarding the two distinct serological groups. Nevertheless, a P value near the statistical significance threshold was obtained comparing the frequency of HBeAb positivity between HBsAg+/HBsAb+ (40%) and HBsAg+/HBsAb- (72.5%) groups ($p = 0.05$, table 1).

Neither at the diagnosis and nor at six months afterward, there were no significant differences in the means of hepatic enzymes between the HBsAg+/HBSAb+ and HBsAg+/HBsAb- groups (Table 2).

There were also no significant differences in the ratio of patients with abnormal AST or ALT between the studied serological patterns (Table 3).

Table 1 Characteristics of patients with chronic hepatitis B infection with concurrent positivity of HBsAg and HBsAb.

Parameters		HBsAg+/HBsAb- [N=299; n(%)]	HBsAg+/HBsAb+ [N=10; n(%)]	P
Sex	Male	156 (52.1)	8 (80)	0.21
	Female	143 (47.9)	2 (20)	
Age	< 40	185 (61.8)	7 (70)	0.46*
	> 40	114 (38.2)	3 (30)	
HbeAg	Positive	44 (14.7)	2 (20)	0.72*
	Negative	255(85.3)	8 (80)	
HbeAb	Positive	217 (72.5)	4 (40)	0.05
	Negative	82 (27.5)	6 (60)	

*: Fisher's exact test.

Table 2 Selected laboratory parameters in patients with chronic hepatitis B infection with concurrent positivity of HBsAg and HBsAb.

Parameters		HBsAg+/HBsAb- [N=299; n(%)]	HBsAg+/HBsAb+ [N=10; n(%)]	P
Aspartate amino transferase (IU/L)	1 st†	45.8 ± 54	36.4 ± 21.3	0.91***
	2 nd‡	40.3 ± 63.4	31.2 ± 20.9	0.96
	P	0.001*	0.23**	
Alanine aminotransferase (IU/L)	1 st	52 ± 63.9	49.3 ± 33.7	0.62
	2 nd	44.1 ± 68.9	38.3 ± 24.8	0.71
	P	0.001	0.14	
Hemoglobin (g/dL)	1 st	14.6 ± 12.1	14.7 ± 1.6	0.31
	2 nd	14.9 ± 16	13.2 ± 2.8	0.63
	P	0.27	0.04	
White blood cell count (*10 ³ /μL)	1 st	7.6 ± 6.5	6.2 ± 1.4	0.37
	2 nd	9.1 ± 23.5	5 ± 1.5	0.05
	P	0.65	0.07	
Platelet count (*10 ³ /μL)	1 st	216.1 ± 95.9	202.1 ± 45.5	0.69
	2 nd	214 ± 77	169.8 ± 80.5	0.16
	P	0.72	0.34	
Alkaline phosphatase (IU/L)	1 st	2451.8 ± 3662.6	207.1 ± 101	0.47
	2 nd	226.1 ± 110.2	244.6 ± 102.9	0.61
	P	0.56	0.79	

†: measurement at the diagnosis, ‡: measurement at six months after initial diagnosis, *: Wilcoxon signed-rank test, **: paired sample t-test, ***: Man-whitney U test.

DISCUSSION

In present study, we evaluated the clinical implications of an unusual serological phenomenon (i.e. concurrent HBsAg/HBsAb positivity) in patients with chronic HBV infection. Among 309 patients who retained HBsAg positivity after six months of diagnosis, 10(3.2%) were identified with HBsAb positivity. In previous studies, the incidence of this pattern has been reported as 2.9%-7%^(7,14,17-19).

A close association has been suggested between HBsAg/HBsAb concurrent positivity with HBsAg scape mutations^[14,20]. On one side, escape mutations can promote antigenicity of the viral peptides promoting specific immune responses. On the other hand, escape mutations can lead to failure of antigen recognition immune components to detect the antigenic determinants^[2]. HBsAg mutants have been described in association with hepatic graft failure, hepatic cancer, and progressed liver insufficiency. To what extent these clinical outcomes are related to immune modulatory effects of mutated antigens is unclear.

The underlying mechanisms of concurrent HBsAg and HBsAb positivity are not fully divulged. In some extent, this serological phenomenon can be explained by the presence of HBsAg scape mutations. However, the ratio of patients with established mutated HBsAg has been relatively higher than the HBV infected patients with HBsAg/HBsAb positivity^[21]. There have also been patients with concurrent HBsAg/HBsAb positivity and no mutated HBsAg further suggesting alternative mechanisms in this serological event^[7].

From other factors that may lead to concurrent HBsAg and HBsAb positivity have been age^[12,19], viral DNA load^[12,13], HBeAg status^[12,14], HBV genotype^[7,14-16], and hepatic enzymes levels^[19]. HBV infected patients older than 40^[12] or 50^[19] years old have shown higher incidence of concurrent HBsAg/HBsAb positivity^[12]. However, no such association was observed in present report with only 3 out of 10 patients > 40 years old revealed this serological profile. Nevertheless, age determinant can modulate immune responses, and immune functions are generally diminished with advanced age. Patients with positive HBsAg and HBsAb markers have also revealed higher positivity rate for HBeAg^[12,14,17,18]. In another study; however, no association was described between HBeAg positivity and concurrent reactivity of HBsAg and HBsAb^[22]. In present study, 2 out of 10 patients with concurrent positive HBsAg and HBsAb also demonstrated HBeAg positivity. This observation negated a strict interaction between these two serological responses. On the other hand, 4 out of 10 of our patients with double po for HBsAg/HBsAb also were reactive for HBeAb rendering an association near the statistically significant threshold ($p = 0.05$). The recent observation merits more evaluation in studies with higher statistical power to explore any significant link. Interaction between immune reactions against HBsAg and HBeAg follow a multiparameter event with poorly defined promoters. The specificity of antibodies against certain epitopes of "S" antigen may influence antibody detection in these circumferences^[22]. Furthermore, immune competency of patients with concurrent HBsAg/HBsAb positivity may be compromised with a report stating 69% of such patients have been immunosuppressed^[13]. Clinical implication of immune reactivity against HBsAg and HBeAg as antigens representative of acute and chronic infections should be more elucidated. Serological features of HBsAg escape mutants may further be modified by the genotypes of HBV^[7,14-16].

Higher AST and ALT levels have been reported in patients with double positivity of HBsAg/HBsAb in comparison with those with only HBsAg positivity^[19]. Nevertheless, we found no such difference in the levels of hepatic enzymes; AST and ALT, not at the diagnosis

Table 3 Hepatic enzymes levels in chronic hepatitis B patients with concurrent positivity for HBsAg and HBsAb.

Parameters	HBsAg+/HBsAb- [N=299; n (%)]	HBsAg+/HBsAb+ [N=299; n (%)]	P
Aspartate amino transferase (at diagnosis, IU/L)	<40	208	0.38*
	>40	91	
Aspartate amino transferase (after six months, IU/L)	<40	226	0.33*
	>40	73	
Alanine amino transferase (at diagnosis, IU/L)	<40	187	0.30*
	>40	111	
Alanine amino transferase (after six months, IU/L)	<40	201	0.37*
	>40	98	

*: Fisher's exact test.

and nor at six months after diagnosis. One major limitation of current study was the low number of patients with concurrent positivity of HBsAg and HBsAb. This limited the power of the study to identify statistically significant impacts of the serological pattern on the clinical course of chronic HBV infection.

In conclusion, it seems that patients with chronic HBV infection and persistent concurrent reactivity for HBsAg and anti-HBs render comparable clinical course with those patients without this pattern.

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