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RAPID COMMUNICATION

Serum soluble interleukin-2 receptor levels in patients with chronic hepatitis B virus infection and its relation with anti-HBc

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Abstract

AIM: To investigate the relationship between serum soluble interleukin-2 receptor (sIL-2R) level and anti-HBc in patients with chronic hepatitis B virus (HBV) infection.

METHODS: Sera from 100 patients with chronic HBV infection and 30 healthy controls were included in this study. The patients were divided into group A [HBsAg (+), HBeAg (+) and anti-HBc (+), $n = 50$] and group B [HBsAg (+), HBeAg (+) and anti-HBc (−), $n = 50$]. sIL-2R levels were determined using ELISA. HBV DNA and alanine aminotransferase (ALT) were also detected.

RESULTS: Serum sIL-2R levels were significantly higher in patients with chronic HBV infection than in healthy controls. Moreover, serum sIL-2R levels were significantly higher in patients with HBsAg (+), HBeAg (+) and anti-HBc (+) ($976.56 \pm 213.51 \times 10^3$ U/L) than in patients with HBsAg (+), HBeAg (+) and anti-HBc (−) ($393.41 \pm 189.54 \times 10^3$ U/L, $P < 0.01$). A significant relationship was found between serum sIL-2R and ALT levels ($P < 0.01$) in patients with chronic HBV infection, but there was no correlation between sIL-2R and HBV DNA levels. The anti-HBc status was significantly related to the age of patients ($P < 0.01$).

CONCLUSION: The high sIL-2R level is related to positive anti-HBc in chronic hepatitis B patients. Positive anti-HBc may be related to T-lymphocyte activation and negative anti-HBc may imply immune tolerance in these patients.

Key words: Chronic hepatitis B; Hepatitis B virus; Anti-HBc; Soluble interleukin-2 receptor; Immune tolerance

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INTRODUCTION

About 350 million persons are chronically infected with hepatitis B virus (HBV) in the world[1]. Carriers of HBV are at an increased risk of developing cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC)[2]. China has the greatest burden of hepatitis B and liver cancer in the world. A third of all chronic HBV carriers live in China. Each year, about half a million Chinese die of liver cancer or liver failure due to hepatitis B. However, HBV has no cytopathic effect on hepatocytes. Some liver damages caused by HBV are attributed to immune clearance of virus-infected cells and associated immune reactions. While antibody response in patients with HBV infection plays a critical role in viral clearance through the formation of complexes with viral particles and their removal from the circulation[3], specific cellular immune response plays a main role in hepatic necrosis due to HBV infection and in the persistence of viral infection[4].

IL-2R system plays an important role in the activation and proliferation of lymphocytes[5]. IL-2R is expressed on the cell membrane of lymphocytes and contains at least three different chains. Serum sIL-2R is predominantly released from activated T lymphocytes and can serve as an index of activation of T lymphocytes[6]. Serum sIL-2R levels are significantly higher in patients with chronic HBV infection than in healthy controls[7]. The serum sIL-2R level one year after interferon administration may be a useful marker of interferon's therapeutic effectiveness[8].

In the present study, we determined the serum levels of sIL-2R in chronic hepatitis B patients with positive or negative anti-HBc to analyze the elevated patterns of sIL-2R in patients with different anti-HBc status.

MATERIALS AND METHODS

Patients

Serum samples were obtained from 100 Chinese patients

Table 1 Levels of sIL-2R, ALT, and HBV DNA in sera of patients with chronic HBV infection (mean ± SD)

Group	Number	sIL-2R ($\times 10^3$ U/L)	ALT (IU/L)	HBV DNA (copies/mL, lgC)
A	50	967.56±213.51[b]	79±21.2[d]	7.954±1.754
B	50	393.41±189.54[a]	24±12.3	7.875±1.011
Control	30	243.59±121.34	13±6.5	0

[b]$P<0.01$ *vs* group B and control group; [a]$P<0.05$ *vs* control group; [d]$P<0.01$ *vs* group B and control.

positive for HBsAg and HBeAg. All the patients were followed up from 2001 to 2004. The patients were divided into two groups. Group A consisted of 50 patients positive for HBsAg, HBeAg, and anti-HBc (age range, 3-71 years; mean age, 37 years). Group B consisted of 50 patients positive for HBsAg and HBeAg but negative for anti-HBc (age range, 12-33 years; mean age, 22.5 years). Another 30 healthy persons negative for all HBV markers served as the control group.

Blood sampling

Venous blood samples were taken to detect sIL-2R, alanine aminotransferase (ALT), HBV DNA and HBV markers (HBsAg, HBeAg, and anti-HBc). All serum samples were separated and stored at -20 °C until testing.

Determination of sIL-2R

Serum sIL-2R levels were determined by sandwich ELISA using commercially available sIL-2R assay kits (Department of Immunology, Dr Bethune Medical University, Changchun, China). An anti-sIL2R monoclonal antibody was adsorbed onto the substrate of polystyrene microtiter wells. The sIL-2R present in the samples or in the standard solutions was bound to the antibody-coated wells. The unbound sample components were removed by washing thrice. A peroxidase-linked anti-sIL-2R monoclonal antibody against another epitope on the sIL-2R molecule was then added to complete the sandwich. After being washed, the unbound materials were removed and a substrate solution was added into the wells. A stopping solution was added to stop the reaction and then light absorbance at 492 nm was measured. A standard curve was prepared from four IL-2R standards. The values were expressed as unit (U) per L.

Assay of HBV markers and HBV DNA

HBsAg, HBeAg, and anti-HBc were detected using commercially available EIA or ELISA kits (Reagents Development Center, Shanghai Hospital for Infectious Diseases, Shanghai, China). HBV DNA levels were tested using real-time PCR on ABI 7000 real-time detection system (Applied Biosystems, Foster City, CA, USA).

Measurement of ALT

ALT was tested on a CX4 chemistry analyzer (Beckman Coulter, Fullerton, CA, USA) using commercially available kits.

Table 2 Age difference between anti-HBc (+) and anti-HBc (–) patients with chronic HBV infection

Group	Number	Median (yr)	Rank sum
A	50	37[b]	66.88
B	50	22.5	40.12

[b]$P<0.0001$ *vs* group B.

Statistical analysis

The significance of difference between the two groups was determined with Student's *t* test and Wilcoxon's rank-sum test. $P<0.05$ was considered significant.

RESULTS

Serum sIL-2R levels were significantly higher in patients with chronic HBV infection than in healthy controls. Moreover, serum sIL-2R levels were significantly higher in patients with HBsAg (+), HBeAg (+) and anti-HBc (+) (group A, $976.56 \pm 213.51 \times 10^3$ U/L) than in patients with HBsAg (+), HBeAg (+) and anti-HBc (–) (group B, $393.41 \pm 189.54 \times 10^3$ U/L, $P< 0.01$). ALT levels were significantly higher in group A ($79 \pm 21.2 \times 10^3$ U/L) than in group B ($24 \pm 12.3 \times 10^3$ U/L, $P<0.01$). Serum sIL-2R levels were significantly related to ALT levels. There was no significant difference in HBV DNA levels between the two groups (Table 1). Anti-HBc status was related to the age of the patients. Positive anti-HBc was detected in older patients ($P< 0.01$, Table 2).

DISCUSSION

HBV infection is a major health problem. About 350 million persons are chronically infected with HBV in the world. HBV itself is non-cytopathic and it is widely accepted that the mechanism of hepatocellular injury is the host anti-viral immune response[9]. A human leukocyte antigen (HLA) class I-restricted cytotoxic T-lymphocyte (CTL) response to one or more HBV-encoded antigens on the hepatocyte membrane is a major mechanism of hepatocellular injury and clearance of infected cells[10]. Serum sIL-2R is predominantly released from activated T lymphocytes[11]. It was reported that serum sIL-2R levels reflect cellular IL-2 receptor expression[6]. Hence, levels of serum sIL-2R are useful in monitoring T-lymphocyte activity and serial measurement aids in assessing the progression of the disease[12].

High levels of serum sIL-2R have been observed in patients with chronic HBV infection[7,8,12-14] and hepatitis C virus (HCV) infection[15]. Serum sIL-2R levels indicate the degree of liver damage in patients with chronic HBV infection[8]. Our results showed that serum sIL-2R levels were significantly higher in patients with chronic HBV infection than in healthy controls. The serum sIL-2R levels were significantly related to the serum ALT levels, but did not correlate with serum HBV DNA levels in patients with chronic HBV infection. These results are consistent with previous findings of Sawayama *et al*[8].

Anti-HBc is detected in virtually all patients exposed

to HBV[16] and typically persists for life[17]. However, many patients with chronic HBV infection are negative for anti-HBc in China probably due to the fact that Chinese people acquire the infection at birth or during the early postnatal period[18,19]. These patients may have an immune tolerance to the virus for several decades of life[20,21]. We found that serum sIL-2R levels were significantly higher in patients with HBsAg (+), HBeAg (+) and anti-HBc (+) than in patients with HBsAg (+), HBeAg (+) and anti-HBc (–). Furthermore, patients with anti-HBc (+) were older than those with anti-HBc (–). Transfer of hepatitis B core antigen-reactive T cells is associated with the resolution of chronic HBV infection[22]. Based on these results, it seems that patients with chronic HBV infection who are negative for anti-HBc may be in a status of immune tolerance to the virus. Serum sIL-2R levels and anti-HBc may be useful indicators of immune status in patients with chronic HBV infection. Serum sIL-2R levels reflect the activation of T lymphocytes[5]. Hence, positive anti-HBc may be related to the activation of T lymphocytes.

Though interferon alpha to some extent hastens the loss of HBeAg in Chinese patients, the treatment is generally less effective than in white patients. This is probably due to the fact that the majority of Chinese people have a long period of immune tolerance to the virus[23]. Several studies have revealed that serum sIL-2R levels can serve as an index of the activation of T lymphocytes[5,6]. The serum sIL-2R level one year after interferon administration may be a useful marker of its therapeutic effectiveness[8]. Our results showed that elevated serum sIL-2R and positive anti-HBc were related to the high levels of serum ALT in patients with chronic HBV infection. Low serum ALT levels are associated with the poor response to interferon alpha treatment in patients with chronic HBV infection[23]. Hence, we can deduce that elevated serum sIL-2R levels, positive anti-HBc and high ALT concentrations may serve as indicators for interferon alpha treatment in Chinese patients with chronic HBV infection. However, further exploration is needed.

In conclusion, serum sIL-2R levels are related to anti-HBc and serum ALT concentrations, but not related to HBV DNA levels in patients with chronic HBV infection. Positive anti-HBc may be related to T-lymphocyte activation and negative anti-HBc may imply immune tolerance in these patients.

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