Anticardiolipin and Antibeta$_2$glycoproteinI Antibodies in Patients with Hepatitis B and C Infections

Zahra Habibagahi *, Mohammad Ali Nazarinia, Elham Aflaki, Akbar Rajaee

Department of Internal Medicine, Rheumatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background: The clinical significance of antiphospholipid antibodies in patients with chronic hepatitis C virus (HCV) and some other viral infections is controversial. **Objective:** To study the prevalence of anticardiolipin antibody (ACLA) and antibeta$_2$glycoproteinI antibody (antibeta$_2$GPI antibody) in HCV and hepatitis B virus (HBV) infected patients and its association with liver clinical parameters. **Methods:** Serum levels of ACLA, antibeta2GPI antibody as well as platelet count, ALT (alanine transaminase), PT (prothrombine time), disease duration and liver histologic findings of 38 patients with HBV and 15 patients with HCV infections were compared with those of 58 healthy controls. **Results**: Serum titres of ACLA in HCV and HBV patients (13.4 ±7.1 GPL units/ml), and in each of the HCV (15.18±9.91 GPL units/ml) and HBV (12.7 ± 5.7 GPL units/ml) patients were significantly higher than that of the control group (3.4±2.3GPL units/ml). However, there was no significant difference in serum levels of antibeta$_2$GPI antibody from patients with HCV and HBV (3.3 ± 1.3 GPL units/ml) or HCV alone (2.79 ± 1.01 GPL units/ml) or HBV alone (3.4±1.3GPL units/ml) and that of the control group (3.3±1.1GPL units/ml). **Conclusion**: The findings suggest that the presence of ACLA has no pathologic significance in patients with HBV and HCV infections.

Keywords: Anticardiolipin antibody, Antibeta$_2$GPI antibody, Hepatitis B, Hepatitis C, Antiphospholipid syndrome

*Corresponding author: Dr. Zahra Habibagahi, Rheumatology Research Center, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. Fax: (+) 98 711 6261089, e-mail: zagahi@sums.ac.ir

INTRODUCTION

Anticardiolipin antibody (ACLA) is associated with a variety of clinical scenarios, such as infectious diseases, alcoholic intoxications and liver cirrhosis (1). The antibody is also found in antiphospholipid syndrome (APS), an autoimmune disease that occurs as a primary disorder or secondary to connective tissue diseases like systemic lupus erythematosus, rheumatoid arthritis and scleroderma. The increased level of the antibody may be associated with repeated venous or arterial thrombosis, recurrent pregnancy losses and positive tests for lupus anticoagulants (2).

It has been proposed that in order for ACLA to bind its ligands in patients with APS, the presence of beta$_2$GPI is required (3, 4). Some authors believe that the requirement for beta$_2$GPI clearly distinguishes the ACLA that occurs in autoimmune diseases from that found in infectious disorders (4-7). It is believed that in the absence of beta$_2$GPI, ACLA has no thrombogenic specificity in infectious diseases (8-10). On the other hand, some studies revealed thrombogenic diathesis in patients with Epstein Barr Virus (EBV), Cytomegalovirus (CMV), hepatitis C virus (HCV), adenovirus or parvovirus infections in the absence of clear association with beta $_2$GPI (11-14).

Considering such varied results, this study was conducted to examine the presence of ACLA and antibeta$_2$GPI antibodies in patients with hepatitis B and C, and to investigate the clinical significance of these antibodies in such patients relative to healthy controls. It was also intended to determine if the occurrence of indicators of liver damage severity including ALT, PT, platelet counts as well as histologic findings were associated with the production of the autoantibodies.

SUBJECTS AND METHODS

The study is a retrospective analysis of medical records of 38 patients with HBV and 15 patients with HCV from southern Iran, referring to hepatology clinic, Namazi Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. All patients with chronic HBV infection were HBS antigen positive and HCV antibody negative, and all those with HCV infection (HCV RNA positive) were HBS antigen negative. Patients with diabetes mellitus, cirrhosis, Wilson disease, hepatocellular carcinoma and α_1-antitrypsin deficiency were excluded. All patients were HIV negative. For each patient, medication history for the last six months as well as prior histories of arteriovenous thrombotic events such as myocardial infarction, ischemic stroke, pulmonary emboli, venous thrombosis, recurrent fetal losses, and neuropsychiateric disorders including convulsion, migraine, and chorea, was recorded. Moreover, serum levels of ALT, PT as well as platelet counts, and liver histologic evaluations, done by needle biopsy, were documented.

A control group, 58 (45 males and 13 females) healthy blood donors were also included. The control group was matched in terms of age and sex with the patient group. In addition to the collection of data from medical records, ACLA of IgG isotype and IgG antibeta$_2$GPI antibody were determined prospectively for all participants using quantitative enzyme linked immunosorbent assay (Genesis diagnostic, UK). The characteristics of patients and controls studied are shown in Table 1.

Statistical analysis was performed using SPSS software. Serum levels of the antibodies (mean± SD) were compared using Mann-Whitney U-test. The association between the oc-

currence of antibody and those of platelet counts, ALT, PT and liver histology were examined using Chi-Square test. A p value of < 0.05 was considered statistically significant.

Table 1. Characteristics of the patients and controls

	Patients (n=53)	Controls (n=58)
Male/Female	40/13	45/13
Mean age ± SD	35.4 ± 8.4	35 ± 8.4

SD, Standard Deviation.

RESULTS

Serum level of ACLA from patients with chronic infective hepatitis was significantly ($p <0.001$) higher than that of control group. However, there was no statistically significant difference between the serum levels of antibeta$_2$GPI antibody in patients and controls (Table2).

Table 2. Serum levels of anticardiolipin antibody and antibeta$_2$glycoproteinI antibody in patients and controls

	Patients	Controls
ACLA (GPL/ml) Mean ± SD	13.39 ± 7.05	3.4 ± 2.33
AntiB_2GPI (GPL/ml) Mean ± SD	3.27 ± 1.25	3.25 ± 1.09

ACLA, anticardiolipin antibody; Antiβ_2GPI, antibeta$_2$glycoproteinI antibody; SD, standard deviation; GPL, anticardiolipin immunoglobulin G levels

Serum level of ACLA in patients with HBV was significantly ($p <0.001$) higher than that of healthy controls. However the serum level of antibeta$_2$GPI antibody in these patients was not significantly different from that of healthy controls. Moreover, there was no significant association in serum level of ACLA or antibeta$_2$GPI antibody and platelet counts, ALT, PT, disease duration, vascular thrombosis or liver histology in patients with HBV infection (Table 3).

Serum level of ACLA in patients with HCV infection was significantly ($p<0.001$) higher than that of the healthy controls. However, the serum level of antibeta$_2$GPI antibody was not significantly different in HCV patients and the controls ($p >0.05$). Moreover, the serum levels of the antibodies were not affected by age, sex, disease duration, ALT, PT or pathologic changes of liver and vascular thrombosis (Table 3).

Table 3. Laboratory characteristics of patients with hepatitis B and C infection

		ACLA				Antiβ_2GPI	
		HBV 12.73±5.66GPL/ml		HCV 15.18±9.91GPL/ml		HBV 3.42±1.31GPL/ml	
		Negative 12/31.6%	Positive 26/68.4%	Negative 6/40%	Positive 9/60%	Negative 35/92.1%	Positive 3/7.9%
Sex	M	12	18	4	6	28	2
	F	o	8	2	3	7	1
Age	≤30	3	9	2	1	10	2
	>30	9	17	4	8	25	1
ALT	<40	6	8	3	6	12	2
	≥40	6	18	3	3	23	1
Duration	<24M	2	11	2	4	12	1
	≥24M	10	15	4	5	23	2
PT	≤12	0	20	3	4	18	2
	13-15	10	3	1	2	12	1
	>15	2	3	2	3	5	0

ACLA, anticardiolipin antibody; AntiB_2GPI, antibeta$_2$glycoporotein I antibody; ALT, alanine transaminase; PT, prothrombine time.

DISCUSSION

The present study showed that the patients with chronic HBV and HCV infection had significantly higher serum levels of ACLA compared to healthy controls, but the differences in the levels of antibeta$_2$GPI did not reach statistical significance. Moreover, there was no association between the serum levels of ACLA or antibeta$_2$GPI antibody and age, sex, platelet counts, ALT, PT, or duration, stage and grading of the diseases. None of the patients had any clinical symptoms or signs of venous or arterial thrombosis.

The increased levels of ACLA in HBV and HCV patients in the present study are similar to a number of previous reports (15, 16). High levels of the antibody are important in the classification criteria of APS. The elevated levels of the antibody may cause recurrent venous or arterial thrombosis by binding to negatively charged phospholipids of the cell membrane. The clinical significance of arterial and venous thrombosis, as a result of elevated ACLA in viral infections, is not settled. While some studies, including the present one, suggest the absence of thrombosis, some others indicate the occurrence of thrombosis in viral infections (11-13). The presence of ACLA in viral or other infections may be induced by disturbances in the regulation of cellular and humoral immunity, which are the consequence of infectious diseases (1). In patients with chronic viral hepatitis, induction of neoantigens may provoke antibody formation by disrupting liver cell membrane (17). Moreover, the stimulation of apoptosis by the viruses may lead to redistribution of plasma membrane phospholipids and their over expression on the apoptotic cell membrane surfaces resulting in ACLA formation (16).

The present study also showed that serum levels of antibeta$_2$GPI antibody did not increase in patients with viral hepatitis. Such a finding is in agreement with previous reports examining the levels of the antibody in various viral infections. Viral infections are believed to induce a lower antibeta2GPI than APS or other autoimmune diseases (18, 19). Beta$_2$GPI is a single chain glycoprotein with 326 amino acid residues arranged in five consecutive homologous domains called Sushi domains. It is suggested that ACLA and antibeta$_2$GPI antibodies recognize neoepitopes on Sushi-4 domain induced after binding of antibeta$_2$GPI antibody to the lipid surface (20). No arterial or venous thrombosis was observed in the present study. The reason for such a finding might be related to low levels of antibeta$_2$GPI antibody. However the reported

thrombosis in some studies might have been due to a homology between viral particles and phospholipid binding region of beta$_2$GPI antibody resulting in antibeta$_2$GPI antibody formation (21).

The findings of this study also indicate that the age, sex, platelet count, or stage and grading of the liver pathology are not affected by the serum levels of ACLA. Such findings are similar to those of Zachou and colleagues (16). Therefore, it might be concluded that the presence of ACLA in hepatitis patients is only a non-specific epiphenomenon of liver disease, and can not be considered as a key factor in the pathogenesis or prognosis of viral hepatitis infections.

In conclusion, some patients with viral hepatitis infections may produce ACLA as an epiphenomenon of the infectious diseases. Such patients may not show clinical signs of venous or arterial thrombosis in the absence of antibeta$_2$GPI antibody. Therefore antibeta$_2$GPI antibody can be considered a determinant factor in the production of thrombogenic diathesis in hepatitis B and C associated ACLA.

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