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• *CLINICAL RESEARCH* •

Aspartate aminotransferase-immunoglobulin complexes in patients with chronic liver disease

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Abstract

AIM: To determine the complex of AST and immunoglobulin and to investigate its clinical significance in patients with liver disease.

METHODS: The complex of AST and immunoglobulin was determined by encounter immunoelectrophoresis and its clinical significance was investigated in 128 patients with liver disease.

RESULTS: AST was bound to immunoglobulin of anti-immunoglobulin A (IgA) class, but any binding to anti-immunoglobulin G and anti-immunoglobulin M classes was not observed. Although the incidence of AST–immunoglobulin complex was 41.8% in chronic hepatitis (CH), the incidences in liver cirrhosis and hepatocellular carcinoma were 62.2 and 90.0%, respectively. In alcoholic liver disease with high level of serum IgA, the incidence of the complex was 66.7%, which was higher than that in CH. The ratio of binding to lambda-chain of IgA was higher than that to kappa-chain of IgA. The serum level of IgA and the ratio of AST/alanine aminotransferase (ALT) were significantly higher in patients with AST–IgA complex than in those without complex.

CONCLUSION: These results suggest that AST–IgA complex in patients with progressive liver diseases and alcoholic liver injury can lead to elevation of the ratio of AST/ALT.

Key words: Alcoholic liver disease; Aspartate aminotransferase; AST/ALT; Chronic hepatitis; Chronic liver disease; Hepatocellular carcinoma; Immunoglobulin; Liver cirrhosis

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INTRODUCTION

Complexes between serum enzyme and serum immunoglobulin sometimes influence the serum concentration of enzymes. Alkaline phosphatase (Al-P)[1,2], amylase[3,4], creatinine phosphokinase[5] and lactate dehydrogenase (LDH)[6] occasionally make complexes with serum immunoglobulins. Because the serum activities of the enzymes are higher in patients with enzyme-immunoglobulin complexes, which are frequently observed in patients with autoimmune diseases, it is important to evaluate enzyme-immunoglobulin complexes in clinical practice. Some investigators[7-14] have reported that AST-immunoglobulin complexes are observed in several diseases, although the incidence is low. The ratio of AST to alanine aminotransferase (AST/ALT) increases with the progression of chronic liver diseases[15]. When the ratio of AST/ALT is over 1.0, progression of chronic hepatitis (CH) to liver cirrhosis (LC) is strongly suspected. In this study, we evaluated the AST-immunoglobulin complexes in patients with chronic liver disease and whether the increase of the ratio of AST/ALT in patients with progressive chronic liver disease was related to the formation of complexes between AST and immunoglobulin.

MATERIALS AND METHODS

Patients

A total of 128 patients with liver disease were treated at the out-patient clinic or admitted to Mie University Hospital between July 1992 and June 1993. Sixty-seven patients were diagnosed as CH, 45 as LC, 10 as hepatocellular carcinoma (HCC) and 6 as alcoholic liver injury without cirrhosis (Alc). Details of the patients including the positive ratio of hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (HCV) are summarized in Table 1.

Methods

Immunoglobulin complexed with AST was determined by counter-immunoelectrophoresis[8] on Titan III (Helena Ltd, Tokyo, Japan). Electrophoresis was performed in barbiturate buffer (pH 8.5) at a constant voltage of 300 V for 10 min, and then plates were washed with 0.9% sodium chloride to remove non-precipitated proteins. After the enzyme was stained at 37 ℃ for 60 min (Kokusai reagent, Tokyo, Japan),

Table 1 Clinical findings of 128 patients with liver disease

	Number of cases	Sex (M:F)	Mean of age (yr)	Positive rate of HBsAg, *n* (%)	Positive rate of anti-HCV, *n* (%)
Alcoholic liver injury	6	5:1	57±6	0	0
Chronic hepatitis	67	45:22	52±13	11 (16.4)	49 (73.1)
Liver cirrhosis	45	29:16	56±10	8 (17.8)	26 (57.8)
Hepatocellular carcinoma	10	9:1	66±7	3 (30.0)	5 (50.0)

Table 2 Comparison of clinical findings between the patients with and without AST-IgA complex in serum

	AST-IgA complex in serum		*P*
	(-)	(+)	
Number of cases	59	69	
Sex (M:F)	40:19	48:21	NS
Mean of age (yr)	52±13	58±12	<0.01
Number of patients with positive HBsAg	12	10	NS
Number of patients with positive anti-HCV	33	47	NS
Number of patients with liver cirrhosis	18	37	<0.02

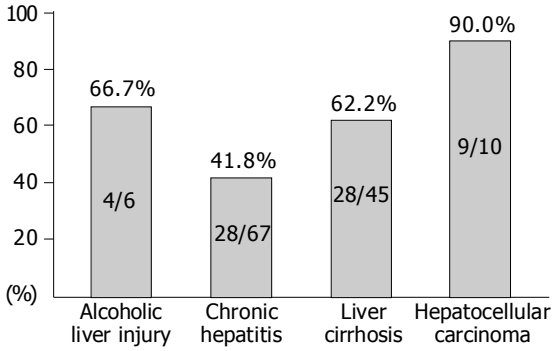

Figure 1 Incidence of AST–IgA complex in various liver diseases.

Table 3 Comparison of laboratory findings between the patients with and without AST–IgA complexes in serum (mean±SD)

	AST–IgA complex in serum		*P*
	(-)	(+)	
γ globulin (%)	21.0±5.8	24.5±6.5	<0.01
AST (IU/L)	55±25	115±50	<0.001
AST/ALT	1.16±0.56	1.37±0.61	<0.05
ChE (△pH)	0.79±0.25	0.61±0.27	<0.001
IgG (mg/dL)	1 980±568	2 211±532	NS
IgA (mg/dL)	299±150	397±195	<0.01
IgM (mg/dL)	178±114	195±101	NS

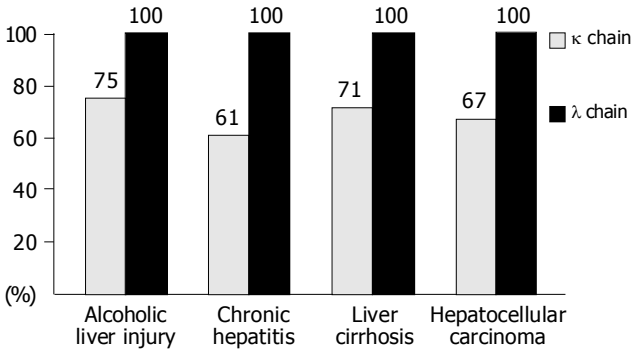

Figure 2 Investigation of light chains of AST-bound immunoglobulins in liver disease.

the plates were destained and fixed in 5% acetate. Anti-sera used to identify the immunoglobulin binding to AST were anti-immunoglobulin G (IgG), anti-immunoglobulin M (IgM), anti-immunoglobulin A (IgA), anti-Kappa chain and anti-lambda chain. The incidence of immunoglobulin-AST complexes and the types of immunoglobulin were discussed in various liver diseases. Furthermore, clinical findings and laboratory parameters were compared between patients with and without immunoglobulin-enzyme complexes. In this study, the data were expressed as mean±SD. Differences between mean values were tested for significance by Student's *t*-test and χ^2 test. $P<0.05$ was considered statistically significant.

Results

IgA was bound to AST. There were no complexes with IgG and IgM. Binding of IgA to AST was documented in 28 (41.8%) of 67 patients with CH, in 28 (62.2%) of 45 with LC, in 9 (90.0%) of 10 with HCC and 4 (66.7%) of 6 with Alc (Figure 1). When we investigated the type of immunoglobulin light chain that bound to AST, we found that AST-IgA complexes had binding to the kappa light chain in all patients. On the other hand, binding to the lambda light chain was documented in 61% of CH, 71% of LC, 67% of HCC and 75% of Alc (Figure 2). When the clinical findings were compared between the patients with and without AST-IgA complexes (Table 2), there were no significant differences in sex, positive rates of HBsAg and anti-HCV. The incidence of LC in patients with AST-IgA complexes was 53.6%, which was significantly higher than 30.5% in patients without complexes ($P<0.02$). Comparisons of biochemical parameters among 69 patients with AST-IgA complexes and 59 without are summarized in Table 3. Gammaglobulin, AST, ALT, gamma-glutamyl transpeptidase and IgA in the patients with complexes were significantly higher than in those without complexes.

DISCUSSION

ALT and AST serum values have been widely used as sensitive laboratory parameters in clinical practice to evaluate the degree of liver injury[16]. However, the serum values of these enzymes do not correctly reflect the degree of hepatic cell necrosis. Elevated serum AST and ALT may be observed when cells containing these enzymes are injured or the

permeability of cell membranes increases[16]. Although serum levels of both ALT and AST are elevated when liver cells are injured, the degree of elevation is not parallel to the degree of injury. The mechanism of the elevation is affected by many factors, such as etiology of the liver disease or severity of the liver cell necrosis. The ratio of AST to ALT is a useful parameter, which can predict the severity of liver disease[15]. On the other hand, some investigators[17] have suggested that the ratio of AST/ALT is not useful in differentiating liver diseases because elevated AST/ALT is observed in many liver diseases. However, elevated AST/ALT ratio is sometimes observed in patients who heavily consume alcohol[18]. When the ratio is over 2.0, alcoholic liver disease is strongly suspected. Furthermore, when the ratio is under 1.0, CH, chronic intrahepatic cholestasis or other liver diseases are suggested. Williams *et al*[17] reported that among patients who had chronic liver disease but no alcoholic aggravation, LC is suspected if the serum ratio of AST/ALT is over 1.0. The discrepancy in serum AST and ALT remains controversial. In general, the serum value of enzyme is regulated by factors such as degree of relapse from the organ containing large quantities of enzyme or degree of disappearance of enzyme from serum. The following mechanisms underlying the high AST/ALT values in patients with alcoholic liver disease have been speculated. (1) The injury to liver cell mitochondria in patients with alcoholic liver disease leads to dominant elevation of serum AST[19]; (2) The production of aminotransferase in hepatocytes is more disturbed in ALT than in AST[20]; (3) Patients are defined as having alcoholic liver disease based on pyridoxal 5' phosphatase deficiency, which is important in maintaining aminotransferase activity, especially that of ALT. Although these hypotheses can explain the mechanism of AST/ALT elevation in alcoholic liver disease, AST/ALT elevation cannot be elucidated in cirrhotic patients who do not consume alcohol. Williams *et al*[17] reported that in cirrhotic patients with elevated AST/ALT, there is impairment of AST excretion from kidney or the ability of AST intake in hepatic sinus is markedly disturbed. However, there are no reports to support their hypotheses. Enzymes, which in serum are sometimes complexed with serum immunoglobulin, might affect the elevation of serum enzyme activity. Binding of serum enzyme to serum immunoglobulin is well known in amylase, LDH, and Al-P[1-6]. Because AST is also complexed with immunoglobulins such as IgG and IgA[7-12], markedly high values of serum AST are sometimes observed whether liver disease exists or not.

In this study, we have confirmed that binding of AST to immunoglobulin in liver disease is frequently encountered. Binding of AST to IgA was more frequently observed in LC than that in CH. The purpose of this study was to investigate whether complex formation of AST with serum immunoglobulin was related to the elevation of serum AST in LC. Based on the reports that the incidence of ALT-immunoglobulin complexes was lower in liver disease, it is suggested that the elevation of AST/ALT in LC is closely related to the binding of AST to serum immunoglobulin, especially to IgA. High serum IgA levels correlative with the progression of chronic and alcoholic liver diseases support this speculation. However, in this study there was no significant difference in the incidence of complex formation of AST with IgA between LC and CH. This result cannot explain the mechanism of the elevated AST/ALT in LC. Finally, the activity of AST binding to IgA, the subclass of IgA and the degree of complex formation of ALT with immunoglobulin should be investigated.

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