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Abnormal Liver Function in Patients with Sjögren's Syndrome

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We measured the liver function tests of 145 patients with Sjögren's syndrome (SjS) (75 patients with primary SjS, 70 patients with secondary SjS), and characterized the SjS patients with abnormal liver function tests from several points of view : 1, the incidence of them in the primary SjS comparing with that in secondary SjS. 2, the staining pattern of anti-nuclear antibodies, and 3, the existence of anti-hepatitis C virus (HCV) antibody, hepatitis B surface (HBs) antigen, and antibody against human T-lymphotropic virus type I (HTLV-I). Abnormal liver function tests were detected in 38 out of 145 patients (26.2%) with SjS. Fifteen of the 38 patients (20.0%) had primary SjS while the remaining patients (32.9%) had secondary SjS. Histopathological examination identified primary biliary cirrhosis (PBC) in 2 patients, autoimmune hepatitis in 4 patients, and autoimmune cholangitis in a single patient with SjS. No significant difference in the presence of antinuclear antibody (ANA) was found between SjS patients with and without abnormal liver function tests. However, the incidence of discrete speckled pattern was significantly higher in SjS patients with abnormal liver function than in the patients with normal liver function. Two sera showing cytoplasmic pattern of ANA were also positive for anti-mitochondrial M2 antibody, allowing the diagnosis of PBC. All 11 sera exhibiting discrete speckled pattern contained significant amounts of anti-centromere antibody. Abnormal liver function tests were detected in 8 of 11 sera with these antibodies, 2 patients with PBC, 2 patients with autoimmune hepatitis, one patient with autoimmune cholangitis, one patient with chronic hepatitis B and 2 other patients with unconfirmed diagnosis. The percentages of anti-HCV antibody-positive, HBs-Ag-positive and anti-HTLV-I antibody-positive in sera of patients were higher than those of blood donors from the same geographical area. However, no significant difference was seen of these percentages in sera between the patients with and without abnormal liver function. Taken together, present study indicated that SjS patients with anti-centromere antibody may have some susceptibility for acquiring autoimmune liver disease.

Key words : Sjögren's syndrome, primary biliary cirrhosis, autoimmune hepatitis, autoimmune cholangitis, anti-centromere antibody

Introduction

Sjögren's syndrome (SjS), which is considered an autoimmune disease, is characterized by chronic lymphocytic infiltration of salivary and lachrymal glands and the occasional presence of serum autoantibodies[1,2]. SjS may exist as a primary disorder or as a secondary condition associated with a variety of diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or progressive systemic sclerosis (PSS). In some SjS patients, involvement of the extraglandular organs may occur, including the skin, kidney, liver, lung, gastrointestinal tract and nervous system. Clinical or biochemical evidence of liver disease is found in 5 to 10% of patients with primary SjS[3,4]. The elevation of liver enzymes is usually mild and of little clinical significance. However, when higher levels are noted, a further investigation is warranted.

Although several etiological mechanisms have been proposed, the pathogenesis of SjS remains unknown. Viral infections, such as infections with Epstein-Barr virus[5], human immunodeficiency virus[6], human T lymphotropic virus type I (HTLV-I)[7-9] or hepatitis virus C[10-13] have been suggested as possible etiologic factors. In the present study, we examined liver function tests, autoantibodies and anti-viral antibodies in the sera of SjS patients, and determined the relationship between liver function tests and these autoantibodies and/or virus infection.

Materials and Methods

Patients.

The test group included 75 patients with primary SjS [4 males and 71 females, age ; 51.5±13.0 years (mean±SD)] and 70 patients with secondary SjS [8 males and 62 females, age ; 53.3±12.1 years]. These patients attended the outpatient clinic of Nagasaki University School of Medicine. All patients fulfilled the criteria for diagnosis of SjS set out by the European Community[14]. Patients with secondary SjS composed of 33 patients with rheumatoid arthritis (RA) diagnosed according to the criteria of the

American Rheumatism Association (ARA)[15], 16 patients with systemic lupus erythematosus (SLE) diagnosed according to the criteria of ARA[16], 11 patients with mixed connective tissue disease (MCTD) diagnosed according to the guidelines outlined by Bennet RM[17], 5 patients with progressive systemic sclerosis (PSS) diagnosed according to the criteria of ARA[18], 4 patients with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactylia, telangiectasia) syndrome, 2 patients with polymyositis (PM) diagnosed according to the classification criteria by Bohan A et al[19], one patient with polyarteritis nodosa (PAN) diagnosed based on clinical features and histological examination and one patient with Behçet's disease diagnosed according to the criteria of International Study Group for Behçet's disease[20]. The control subjects for the percentage of positive antibodies and antigen for the viruses consisted of 71,748 normal subjects who donated blood at the Red Cross Blood Center in Nagasaki. Informed consent was obtained from all the patients examined, and the study was conducted in accordance with human experimentation guidelines of the authors' institution.

Clinical laboratory tests.

Tests for liver function were performed in all patients. The following test kits were used in all assays ; AST (GOT HQ auto "Nissui", Nissui Pharmaceuticals, Tokyo, Japan), ALT (GPT HQ auto "Nissui", Nissui Pharmaceuticals), γ-GTP (Auto A "Mizuho" γ-GTP, Mizuho Medy, Saga, Japan), and alkaline phosphatase (Iatrotech ALP rate, Iatron laboratory, Tokyo, Japan). Anti-nuclear antibodies (ANA) were detected with an indirect immunofluorescence procedure using HEp-2 cells (Fluoro Hep Ana test, Medical & Biological Laboratories (MBL), Nagoya, Japan). Antibodies to SS-A (Ro), SS-B (La) antigens and mitochondrial M2 were determined by the enzyme-linked immunosorbent assay (ELISA ; Mesacup SS-A/Ro test, Mesacup SS-B/La test, and Mitochondria M2 test, MBL). Antibodies to HTLV-I were measured by ELISA (Eitest-ATL test, Eisai, Japan), the particle agglutination assay (Serodia-ATL kit, Fuji Rebio, Japan). The positive sera for antibodies to HTLV-1 were confirmed by western blot analysis using a commercial immunoblotting kit (Problot, HTLV-I, Fuji Rebio, Japan). Antibodies to Hepatitis C virus (HCV) were measured by second generation ELISA (Imucheck HCV Ab, International reagents, Kobe, Japan) and Hepatitis B surface (HBs) antigen and antibodies to HBs antigen were detected by radioimmunoassay (RIA ; AUSRIA II-125 and Ausab, Dinabot, Tokyo, Japan). Antibodies to mitochondria and smooth muscle were detected by immunofluorescence assay (IFA ; using rat kidney and stomach, FITC conjugated anti-human immunogloblin, MBL) and liver kidney-microsomal antibody by IFA (using rat kidney, liver, stomach, heart, and striated muscle, as well as mouse stomach, Specialty Laboratories, CA).

Groups of patients.

Patients were tentatively divided into two groups. The first group consisted of patients with abnormal liver function tests, defined as AST (GOT) >40 IU/l, ALT (GPT) >40 IU/l, and γ-GTP >50 IU/l or alkaline phosphatase (Al-P) >270 IU/l, detected at least twice throughout the course of the disease (mean duration ; 4.2 ± 2.3 years). The second group consisted of patients with normal liver function tests. Abnormal liver function defined to be caused by drugs such as non-steroid anti-inflammatory drugs (NSAIDs), slow acting anti-rheumatic drugs, immunosuppressants including methotrexate, or other drugs as well as to be caused by the active complicated diseases of SLE, MCTD, PM and PAN were excluded from the assessment in the present study. Seven of 15 patients whose liver function tests are AST >80 IU/l, ALT >80 IU/l, and γ-GTP >100 IU/l or ALP >540 IU/l were histologically confirmed by liver biopsy under laparoscopy.

Data analysis

Statistical analyses were performed using χ^2 test between the groups. A p level of <0.05 was considered statistically significant.

Results

Prevalence of abnormal liver function test in patients with primary and secondary Sjögren's syndrome.

Abnormalities of liver function tests were found in 38 out of 145 (26.2%) patients with SjS. Of these, 15 had primary SjS while the remaining were patients with secondary SjS (Table 1). The incidence of abnormal liver enzymes was higher in secondary SjS than that in primary SjS, but the difference was not statistically significant ($p = 0.078$). The percentages of abnormal AST, ALT, γ-GTP and Al-P were similar in primary SjS patients (9.3-10.7%), and in secondary SjS patients (12.9-18.6%). SjS patients who had AST >80 IU/l, ALT >80 IU/l, γ-GTP >100 IU/l orALP >540 IU/l were found in 15 out of 145 patients (10.3%) (Table 2). In these 15 patients, incidence of patients with primary SjS was lower than the patients with secondary SjS, but the difference was not statistically significant ($p = 0.13$).

Table 1. Incidence of abnormal liver function tests in patients with primary and secondary Sjögren's syndrome

Subject	AST>40 IU/l	ALT>40 IU/l	γ-GTP>50 IU/l	Al-P>270 IU/l	Total
primary SjS (75 patients)	7 (9.3%)	8 (10.7%)	8 (10.7%)	8 (10.7%)	15 (20.0%)
secondary SjS (70 patients)	12 (17.1%)	9 (12.9%)	11 (15.7%)	13 (18.6%)	23 (32.9%)
Total (145 patients)	19 (13.1%)	17 (11.7%)	19 (13.1%)	21 (14.5%)	38 (26.2%)

Table 2. Incidence of abnormal liver function tests (more than twice of upper limit of normal range) in patients with primary and secondary Sjögren's syndrome

Subject	AST>80 IU/l	ALT>80 IU/l	γ-GTP>100 IU/l	ALP>540 IU/l	Total
primary SjS (75 patients)	3 (4.0%)	1 (1.3%)	3 (4.0%)	4 (5.3%)	5 (6.7%)
secondary SjS (70 patients)	4 (5.7%)	2 (2.9%)	7 (10.0%)	4 (5.7%)	10 (14.3%)
Total (145 patients)	7 (4.8%)	3 (2.1%)	10 (6.9%)	8 (5.5%)	15 (10.3%)

Table 3. Clinical characteristics of seven patients with Sjögren's syndrome with abnormal liver function confirmed by histological examination

Cases	age	sex	Complication	ANA pattern	AMA	ASMA	Diagnosis based on histological examination
1 (T. K)	51	F	−	speckled	−	−	autoimmune hepatitis (type 1)
2 (F. S)	65	F	−	speckled	−	−	autoimmune hepatitis (type 1)
3 (M. K)	51	F	−	discrete speckled	−	−	autoimmune hepatitis (type 1)
4 (K. H)	39	F	SLE	discrete speckled	+	−	PBC
5 (S. Y)	51	F	CREST	(−)	+	−	PBC
6 (Y. K)	60	F	MCTD	speckled	−	−	autoimmune hepatitis (type 1)
7 (H. Y)	58	F	CREST	discrete speckled	−	−	autoimmune cholangitis

ANA : anti-nuclear antibody, AMA : anti-mitochondrial antibody, ASMA : anti-smooth muscle antibody, PBC : primary biliary cirrhosis, CREST : calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactylia, telangiectasia, SLE : systemic lupus erythematosus, MCTD : mixed connective tissue disease.

Histopathological examination of the liver.

Seven of 15 patients who had AST>80 IU/l, ALT>80 IU/l, γ-GTP>100 IU/l or ALP>540 IU/l gave their informed consent to be performed liver biopsy under laparoscopy. The patients consisted of 3 patients with primary SjS and 4 patients with secondary SjS. Six of the seven patients showed ANA positive in their sera. Neither HBs-antigen nor anti-HCV antibody was detected in these patients. As shown in Table 3, three primary SjS patients were diagnosed as having autoimmune hepatitis (type 1), none of the sera showed anti-smooth muscle antibody (AMSA) nor anti-mitochondrial antibody (AMA), and the staining pattern of the serum ANA was speckled in 2 patients and discrete speckled in one. Two out of the four secondary SjS patients showed discrete speckled pattern of the serum ANA, and two of them exhibited AMA in their sera were diagnosed as having PBC, and one patient was diagnosed as having autoimmune cholangitis, and one patient autoimmune hepatitis (type 1).

Relationship between ANA and liver function.

Thirty-one out of 38 sera (81.6%) from SjS patients with abnormal liver enzymes produced positive nuclear fluorescence and 2 sera (5.2%) positive cytoplasmic fluorescence (Table 4). Of the 31 ANA-positive sera with abnormal liver function tests, one (3.2%) showed a diffuse pattern, 22 (71.0%) showed a speckled pattern, and 8 (25.8%) showed a discrete speckled pattern, no patient showed a nucleolar pattern. Seventy-seven out of 107 sera (72.0%) from SjS patients with normal liver function

Table 4. Pattern of anti-nuclear antibodies and abnormal liver function in patients with Sjögren's syndrome

pattern of anti-nuclear antibodies	Sjögren's syndrome	
	normal liver function	abnormal liver function
diffuse	19	1*
speckled	51	22
discrete speckled	3	8**
nucleolar	4	0
total	77/107	31/38

*$p<0.02$ against the patients with normal liver function, **$p<0.001$ against the patients with normal liver function

Table 5. Relation between the presence of anti-centromere antibody and liver function tests found in patients with Sjögren's syndrome

cases	complications	titer of discrete speckled pattern	ACA (ELISA)	AMA M2-Ab	HBsAg	anti-HCV Ab	abnormal liver function tests	diagnosis of the liver disease
1 N. T.	−	320×	237	<10	−	−	−	normal
2 H. N.	−	2560×	203	<10	−	−	−	normal
3 T. T.	CREST	640×	273	<10	−	−	−	normal
4 H. T.	−	640×	222	<10	−	−	+	not determined
5 U. R.	−	640×	257	<10	−	−	+	not determined
6 K. H.	SLE	2560×	267	99	−	−	+	autoimmune hepatitis
7 M. K.	−	160×	139	<10	−	−	+	PBC
8 K. I.	RA	160×	180	<10	+	−	+	chronic hepatitis B
9 S. Y.	CREST	2560×	284	200	−	−	+	PBC
10 H. Y.	CREST	2560×	237	<10	−	−	+	autoimmune cholangitis
11 M. H.	CREST	640×	69	<10	−	−	+	autoimmune hepatitis

ACA : anti-nuclear antibody, AMA : anti-mitochondrial antibody

Table 6. Prevalence of antibodies to HCV and HTLV-1, and HBs-antigen in patients with Sjögren's syndrome

	anti-HCV positive patients		patients positive for HBs antigen		anti-HTLV-1 positive patients	
Age	B. D.[a]	SjS	B. D.	SjS	B. D	SjS
	positive/total(%)	positive/total(%)	positive/total(%)	positive/total(%)	positive/total(%)	positive/total(%)
~19	6/3395 (0.18)	0/0 (−)	71/8031 (0.88)	0/0 (−)	8/2147 (0.37)	0/0 (−)
20~29	21/3685 (0.54)	0/2 (0)	25/2003 (1.25)	0/2 (0)	13/1588 (0.82)	1/4 (25.0) *
30~39	22/1960 (1.12)	0/8 (0)	14/739 (1.89)	0/7 (0)	17/873 (1.94)	2/10 (20) *
40~49	21/1642 (1.28)	0/8 (0)	7/728 (0.96)	1/10 (10.0) *	29/944 (3.07)	5/14 (35.7) *
50~64	44/1240 (3.55) *	4/43 (9.3)	10/392 (2.55) *	3/30 (10.0)	38/926 (4.10) *	9/37 (24.3)
65~	−	1/13 (7.7)	−	0/12 (0)	−	5/20 (25.0)
total	114/12102 (0.94)	5/74 (6.8)	127/11893 (1.07)	4/61 (6.6)	105/6478 (1.62)	22/85 (26.2)

a B. D.: Blood Donors in Nagasaki city *$P<0.001$

tests were positive for ANA. Of these, 19 sera (24.7%) showed a diffuse pattern, 51 sera (66.2%) a speckled pattern, 3 sera (3.9%) a discrete speckled pattern , and 4 sera (5.2%) a nucleolar pattern. The prevalence of ANA in SjS patients with abnormal liver function tests was similar to that in patients with normal liver function tests ($p = 0.24$). However, discrete speckled pattern was seen more frequently in abnormal liver function tests group compared with those of normal liver function tests ($p<0.001$). In contrast, diffuse pattern was seen less commonly in SjS patients with abnormal liver function tests than those with normal liver function tests ($p<0.02$).

All 11 sera exhibiting discrete speckled pattern contained significant amounts of anti-centromere antibody (ACA) measured by ELISA method. Table 5 shows the clinical features of SjS patients carrying these antibodies. Abnormal liver function tests were detected in 8 of 11 sera (72.7%) with ACA. Three of the eight patients were primary SjS, and the five patients were secondary SjS complicated with SLE, RA and CREST syndrome. PBC was found in 2 patients, autoimmune hepatitis in 2 patients and autoimmune cholangitis in a patient. Case 8, who was positive for HBs-Ag, was diagnosed as chronic hepatitis B. The etiology of abnormal liver function test in 2 other patients was not determined.

Prevalence of antibodies to HCV, HTLV-I and HBs-antigen.

The incidences of anti-HCV antibody-positive sera, HBs-Ag-positive sera and anti-HTLV-I antibody-positive sera in SjS patients were 6.8% (5 out of 74 patients), 6.6% (4 out of 61 patients) and 26.2% (22 out of 85 patients), respectively (Table 6). The rates for the same antibodies and the antigen in the control group were 0.9%, 1.1% and 1.6%, respectively. The incidence of positive anti-HCV antibody in the age of 50 to 64 in Sjögren's syndome was significantly higher than that of the blood donors ($P<0.001$). In the age of 40 to 49, and 50 to 64, the insidence of positive HBs antigen in Sjögren's syndome was siginficantly higher ($P<0.001$). And in the age of 20 to 29, 30 to 39, 40 to 49, and 50 to 54, the incidence of positive HTLV-1 antibody was significantly higher than that of the blood donors ($P<0.001$, Table 6). To examine the relationship between liver function and 2 antibodies or antigen, we investigated their prevalence in SjS patients with abnormal liver function tests. The percentage of positive sera from these patients were 6.3% (2 out of 32 patients) for anti-HCV antibody, 7.1% (2 out of 28 patients) for HBs-antigen, and 27.3% (9 out of 33 patients) for anti-HTLV-I antibody (data not shown). There was no significant difference in the incidence of these antibodies and antigen between patients with and without abnormal liver function tests.

Discussion

Our results demonstrated the presence of abnormal liver function tests in 38 out of 145 patients with SjS (26.2%). The incidence of abnormal liver functions in our population samples was higher than that reported in previous studies[3,4]. As far as we investigated the patients using abdominal ultrasound, none of the SjS patients who showed abnormal liver function tests were diagnosed as having fatty liver or alcoholic liver disease. However, it is possible that the abnormal liver function tests in some of the patients may be caused by fatty liver change.

Liver biopsy was performed in seven patients. Four patients in this group were identified to have autoimmune chronic hepatitis (type 1) according to the classification of autoimmune hepatitis[21]. Three other patients showed histological features consistent with PBC, including marked cellular infiltration of the portal areas and damage of the bile duct. Mild forms of interlobular inflammation and piecemeal necrosis were observed in these specimens. One of these patients (case 7 in Table 3) did not have serum anti-mitochondrial antibodies but have ACA, and responded well to treatment with prednisolone.

A subgroup of patients with autoimmune chronic active hepatitis has been recently identified as autoimmune cholangitis. This form of hepatitis is characterized by positive serum ANA but negative anti-mitochondrial antibodies, although serum biochemical values in these patients indicate the presence of cholestasis, and liver biopsy shows features of inflammatory bile duct damage[22-24]. These patients respond well to prednisolone[22]. Also in common with PBC, patients with autoimmune cholangitis are at risk of acquiring other autoimmune disorders. It has also been reported that primary autoimmune cholangitis is complicated with polyarthralgia, sicca syndrome, Raynaud's phenomenon and hypothyroidism[23,24]. In the present study, one patient with autoimmune cholangitis was complicated with Sjögren's and CREST syndromes, and high titers of ACA were present in the serum.

The frequency of serum ANA in SjS patients detected in the present study using immunofluorescent techniques was comparable with that reported in previous studies[1,2]. The observed pattern of ANA was diverse and included speckled, diffuse, discrete speckled, nucleolar and cytoplasmic staining. Increased incidence of discrete speckled staining was found in the present study in the sera of SjS patients, particularly in sera of patients with abnormal liver function tests. In addition, the presence of ACA was verified in sera with discrete speckled pattern, using the enzyme-linked immunosorbent assay (ELISA). Thus, all 11 sera contained significant amounts of these antibodies. ACA has been identified in the sera of patients with the CREST variant of scleroderma[25,26]. Patients with CREST positive for ACA are considered as a subset of patients

who do not usually progress to diffuse scleroderma or manifest major organ involvement[27-32]. Recent reports, however, indicate that patients with SLE, diffuse scleroderma, idiopathic Raynaud's phenomenon, drug-induced SLE[32] and primary SjS[33] have positive titers for ACA. Our laboratory tests identified 2 SjS patients with ACA who had SLE or RA, respectively. A high incidence of Raynaud's phenomenon and limited features of CREST syndrome were identified, together with positive ACA, as described previously[27-32].

ACA detected by indirect immunofluorescence on HEp-2 cells are found in 10%[34] or 24%[35] of patients with PBC. In the present study, the following diagnosis was made in 8 ACA positive patients with abnormal liver function tests ; PBC (2 patients), autoimmune hepatitis (2 patients), autoimmune cholangitis (one patient), and HBs-Ag positive chronic hepatitis B (one patient). A definite diagnosis could not be made in other 2 patients. In serum ACA positive SjS patients, the number of patients with abnormal liver function tests was significantly increased compared with that in serum ACA negative SjS patients ($p<0.001$), even when the patients with HBs-antigen positive chronic hepatitis were excluded from the statistical analysis. This indicated that SjS patients with serum ACA positive have susceptibility to be complicated with abnormal liver function tests. In contrast, serum diffuse pattern ANA positive patients were at lower risk to show abnormal liver function tests. Relationship of the presence of ACA with liver function test abnormalities may result from the complicating disorder such as CREST syndrome. However, even when the patients with CREST syndrome were excluded from ACA positive group, the number of patients with abnormal liver function tests were increased (5 patients) than that of patients with normal function (2 patients).

We also investigated the relationship between abnormal liver function tests and virus infections, including hepatitis B virus, hepatitis C virus and HTLV-I. The incidence of these infections were higher than those of blood donors, consistent with those of previous studies demonstrating the presence of a significantly high HTLV-I seroprevalence rate among patients with primary SjS compared with blood donors[8,9]. Extra-hepatic immunological abnormalities have been shown to occur frequently in patients with chronic hepatitis C virus infection[10-13]. These include the presence of cryoglobulin, rheumatoid factor and various autoantibodies. Salivary gland lesions, characterized by lymphocytic capillaritis, are observed in about half of the patients and sometimes associated with lymphocytic sialoadenitis resembling to that of the SjS[13]. The seroprevalence rate of anti-HCV antibody in SjS patients was higher than that in blood donors, whereas there was no significant difference in the incidence of abnormal liver function tests between SjS patients seropositive for HCV and those seronegative for the same antibody. From the above results, it is unlikely that HCV infection contributed to the high frequency of abnormal liver function tests found in SjS patients. Whether infection with HCV or HBV could be associated with the pathogenesis of SjS remains to be determined.

In summary, we have identified a high prevalence of autoimmune liver diseases in patients with SjS. The liver disease were diverse, and composed of autoimmune hepatitis, autoimmune cholangitis and PBC. It is suggested that ACA in SjS patients may be involved in the pathogenesis of autoimmune liver diseases.

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