Clinical Features of Japanese Elderly Patients with Type 1 Autoimmune Hepatitis

Yasuhiro Miyake, Yoshiaki Iwasaki, Akinobu Takaki, Haruhiko Kobashi,
Kohsaku Sakaguchi and Yasushi Shiratori

Abstract

Objective In Caucasian type 1 autoimmune hepatitis patients with a main susceptibility of human leukocyte antigen DR3 and DR4, elderly patients have a higher frequency of concurrent autoimmune disease and cirrhosis at presentation. However, in Japanese patients, the disease is dominantly associated with DR4, and their clinical features may be different from those of previous reports. In this study, we assessed the clinical features of Japanese elderly patients with type 1 autoimmune hepatitis.

Methods We investigated 160 consecutive patients with type 1 autoimmune hepatitis, consisting of 34 elderly patients (≥ 65 years) and 126 younger patients (< 65 years).

Results There were no differences in form of clinical onset, frequencies of concurrent autoimmune disease, positive proportions of anti-nuclear antibody and/or anti-smooth muscle antibody, and human leukocyte antigen DR status between the two groups. However, the elderly patients had lower serum levels of albumin ($p=0.0049$), and higher frequencies of cirrhosis (F4) and pre-cirrhosis (F3) ($p=0.014$) compared with the younger patients. In contrast, in elderly patients, the cumulative incidental rate of the normalization of serum alanine aminotransferase levels within 6 months after the introduction of initial treatment was higher in those treated with prednisolone ≥ 20 mg/day than those treated only with ursodeoxycholic acid ($p=0.001$).

Conclusion We speculate that more years may pass between the occurrence of the disease and the presentation in Japanese elderly patients than in younger patients, and we considered that, even in elderly patients, those with advanced fibrosis should be treated with prednisolone in order to prevent progress of the disease into liver failure.

Key words: age, human leukocyte antigen, cirrhosis

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Introduction

Autoimmune hepatitis is an unresolving inflammation of the liver of unknown cause with the presence of interface hepatitis and portal plasma cell infiltration on histological examination, hypergamma-globulinemia, and autoantibodies (1).

Autoimmune hepatitis has been considered to be a disease of females with a peak incidence between ages 16 and 30 years (2). Recent reports from the patients with a main susceptibility of human leukocyte antigen DR3 and DR4, however, reveal that peak occurrences are between ages 10 and

30 years and between 40 and 50 years, and elderly patients have higher frequencies of human leukocyte antigen DR4, concurrent autoimmune disease, and cirrhosis at presentation (3-6).

In Japanese patients with autoimmune hepatitis, the disease is associated with human leukocyte antigen DR4, and the frequency of human leukocyte antigen DR3 is near zero (7). Human leukocyte antigen DR status has been reported to affect the clinical features of patients with autoimmune hepatitis (1). Thus, the clinical features of Japanese elderly patients may differ from those of previous reports (3-6). Here, we evaluated the clinical features of Japanese elderly patients (≥ 65 years) with type 1 autoimmune hepatitis com-

pared to those of Japanese younger patients (<65 years).

Patients and Methods

Study design

We investigated 160 consecutive patients, with a median age of 55 years (16-79 years) at presentation, admitted to the Okayama University Hospital and 12 affiliated hospitals between November 1988 and December 2005. All patients, who were seronegative for hepatitis B surface antigen, anti-hepatitis C virus antibody, hepatitis C virus-RNA (as determined via polymerase chain reaction after reverse transcription), and anti-mitochondrial antibody, underwent liver biopsy and were graded according to the revised scoring system proposed by the International Autoimmune Hepatitis Group (8). Only pretreatment scores were analyzed. A definite diagnosis of autoimmune hepatitis based on these criteria required a pretreatment score exceeding 15, while a probable diagnosis required a score between 10 and 15.

Criteria for the form of clinical onset

Patients with acute-onset liver dysfunction (serum alanine aminotransferase levels higher than 10-fold the upper normal limit) and without a history of any prior liver disease were diagnosed as acute-onset autoimmune hepatitis. The remaining patients with abnormalities of liver function test on medical checkup or in the past history, or with increased serum alanine aminotransferase levels under 10 fold the upper normal limit were diagnosed as classical-onset autoimmune hepatitis.

Histological evaluation

Liver biopsy was performed with a Vim-Silverman needle (14-G) under laparoscopy or with a 17-G needle under ultrasonography guidance, before or just after commencing the initial treatment. Liver biopsy specimens were evaluated by two pathologists and diagnosed as acute or chronic hepatitis. The diagnosis of acute hepatitis was made on the presence of histologically predominant centrilobular necrosis with minimal lymphocytic and plasma cell infiltration into portal tracts, in the absence of interface hepatitis or portal fibrosis. Liver biopsy specimens diagnosed as chronic hepatitis underwent histological staging based on the classification of Desmet et al (9).

Treatment

In this study, the standard initial treatment was prednisolone monotherapy (30-40 mg/day) or a combination of prednisolone (20-40 mg/day) and azathioprine (50-100 mg/day). In patients with histological low-grade inflammatory activity, the initial treatment was low-dose prednisolone (20 mg/day). Elderly patients with histological low-grade inflammatory activity and comorbidities such as osteoporosis and diabetes were treated with ursodeoxycholic acid (300-600 mg/day) or a combination of lower doses of prednisolone (<20

mg/day) and ursodeoxycholic acid. An initial treatment was defined as any therapy that was started within 3 months after the diagnosis of autoimmune hepatitis. It was continued until the normalization of serum alanine aminotransferase levels.

Statistical analysis

Statistical analysis was performed using the SPSS statistical program (release 11.0.1 J, SPSS, Inc., Chicago, IL).

Continuous variables were expressed as medians and ranges. The Mann-Whitney *U* test was used to evaluate differences in the continuous variables. Dichotomous variables were compared by the χ^2 -test. Cumulative incidental rates were estimated using the log-rank test. *p* values <0.05 were considered significant.

Results

A peak incidence was between ages 50 and 60 years in both male and female patients. At presentation, 34 (21%) were identified at ≥ 65 years. Clinical, biochemical, and histological features are summarized in Table 1. There were similar in the proportions of male patients and patients with definite diagnosis according to the revised scoring system proposed by the International Autoimmune Hepatitis Group (8), and form of clinical onset between elderly and younger patients. Of 34 elderly patients, 6 (18%) had a concurrent autoimmune disease (2 patients each had autoimmune thyroiditis, and ulcerative colitis, one patient each Graves' disease, and Sjögren's syndrome), and 32 of 126 younger patients (25%) had a concurrent autoimmune disease (14 patients had autoimmune thyroiditis, 2 patients each had Sjögren's syndrome, Graves' disease, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, rheumatoid arthritis, autoimmune hemolytic anemia, and progressive systemic sclerosis, one patient each had ulcerative colitis, autoimmune thyroiditis and autoimmune hemolytic anemia, autoimmune thyroiditis and Sjögren's syndrome, and systemic lupus erythematosus and Sjögren's syndrome).

Regarding biochemical data, elderly patients had lower serum levels of albumin compared with younger patients [3.5 g/dL (2.4-4.5 g/dL) vs. 3.9 g/dL (2.1-5.1 g/dL); *p*=0.0049]. However, there were no differences in serum levels of total bilirubin, transaminase, and immunoglobulin G.

A serum titer of 1:40 or higher was considered positive for anti-nuclear antibody or anti-smooth muscle antibody. At the time of diagnosis, 135 patients (84%) were positive for anti-nuclear antibody. Of 118 patients screened for anti-smooth muscle antibody, 75 (64%) were positive, and 152 patients (95%) were positive for anti-nuclear antibody and/or anti-smooth muscle antibody. Of 34 elderly patients, 33 were positive for anti-nuclear antibody and/or anti-smooth muscle antibody. There were no differences in positive proportions of anti-nuclear antibody and/or anti-smooth muscle antibody between elderly and younger patients (97% vs. 94%; *p*=0.53).

Table 1. Clinical Features of Elderly Patients Compared with Younger Patients

	Elderly (≥ 65 years)	Younger (< 65 years)	p Value
Patients, n	34	126	
Gender, male/female (% male)	6/28 (18)	14/112 (11)	0.31
Criteria of the International Autoimmune Hepatitis Group:			
Definite/probable (% definite)	28/6 (82)	99/27 (79)	0.63
Form of clinical onset, acute-onset/classical-onset (% acute-onset)			
	10/24 (29)	36/90 (29)	0.92
Concurrent autoimmune disease, n (%)			
	6 (18)	32 (25)	0.39
Laboratory data:			
Albumin (g/dL) ^a	3.5 (2.4-4.5)	3.9 (2.1-5.1)	0.0049
Total bilirubin (mg/dL) ^a	1.2 (0.5-22.6)	1.0 (0.3-29.2)	0.34
AST (IU/L) ^a	150 (35-1704)	170 (28-2330)	0.60
ALT (IU/L) ^a	180 (25-1283)	211 (23-2161)	0.45
ALP ratio to ULN ^a	1.22 (0.53-2.70)	1.08 (0.20-3.81)	0.17
IgG (mg/dL) ^a	2676 (1085-6016)	2544 (1170-6562)	0.47
ANA or ASMA $> 1:80$, n (%)	26 (76)	91 (72)	0.62
Fibrosis staging, n (%):			
Acute hepatitis	1 (3)	8 (6)	
Chronic hepatitis:			
F1	6 (18)	40 (32)	
F2	9 (26)	40 (32)	
F3	12 (35)	28 (22)	
F4	6 (18)	10 (8)	
F3 + F4	18 (53)	38 (30)	0.014

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ULN, upper limit of normal; IgG, immunoglobulin G; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody.

^a median (range).

Of 79 patients screened for class II human leukocyte antigen by LABTypeSSO Typing Tests (VERITAS, Tokyo, Japan), 55 patients (70%) had DR4, and 23 (29%) had DR2. Thirteen patients (16%) had both DR2 and DR4. None had DR3. Of 17 elderly patients, DR4 and DR2 were positive in 13 (76%) and 6 (35%), respectively, and 5 had both DR2 and DR4. Frequencies of DR4 and DR2 were similar between elderly and younger patients. On the other hand, of 14 patients without neither DR2 nor DR4, 6 had DR9, and 4 had DR8. Of 3 elderly patients without neither DR2 nor DR4, one had DR9, and none had DR8. In patients without neither DR2 nor DR4, frequencies of DR9 and DR8 were similar between elderly and younger patients.

Histologically, the proportion of cirrhosis (F4) and pre-cirrhosis (F3) was higher in elderly patients (53% vs. 30%; $p=0.014$).

As an initial medical treatment, 105 of 160 patients (65%) were treated with prednisolone (≥ 20 mg/day), 19 (12%) with low-dose prednisolone (20 mg/day), and 36 (23%) with ursodeoxycholic acid (300-600 mg/day) or a combination of lower doses of prednisolone (<20 mg/day) and ursodeoxycholic acid. Of 124 patients treated with prednisolone ≥ 20 mg/day, 9 (7%) were transferred to other hospitals without follow-up. Of the remaining 115 patients, 22 (19%) were elderly. A cumulative incidental rate of the normalization of serum alanine aminotransferase levels within 6 months after the introduction of corticosteroid treatment was similar in elderly and younger patients (95% vs. 89%; $p=0.41$). On the other hand, 25 of remaining 36 patients were treated with only ursodeoxycholic acid. Of 25 patients, one was transferred to another hospital without follow-up. Of 24 patients, 8 were elderly. A cumulative incidental rate of the normalization of serum alanine aminotransferase levels within 6 months after the introduction of ursodeoxycholic acid was similar in elderly and younger patients (50% vs. 63%; $p=0.41$). Thus, in elderly and younger patients, the cumulative incidental rate of the normalization of serum alanine aminotransferase levels within 6 months after the introduction of initial treatment was higher in those treated with prednisolone ≥ 20 mg/day than those treated with only ursodeoxycholic acid ($p=0.001$).

Discussion

In this study, elderly patients had lower serum levels of albumin and a higher frequency of cirrhosis and pre-cirrhosis at presentation than younger patients. Concerning clinical features of Japanese elderly patients, these are consistent with the report by Miyake et al (10). In Caucasian patients, human leukocyte antigen DR status is reported to affect progression of fibrosis (11). However, in Japanese patients, the disease is dominantly associated with human leukocyte antigen DR4 (7). Granito et al (4) reported that Caucasian elderly patients were more asymptomatic than younger patients. We speculate that, in Japanese patients, elderly patients may be more asymptomatic than younger

patients, and that more years may pass between the occurrence of the disease and the presentation in elderly patients than younger patients.

In type 1 autoimmune hepatitis, ursodeoxycholic acid is reported to improve serum transaminase levels in the short term (12, 13). Recently, Miyake et al (10) reported that 4 elderly patients were successfully managed by ursodeoxycholic acid alone, and they explained that ursodeoxycholic acid may be an effective drug for management of elderly patients. In this study, 14 patients achieved the normalization of serum alanine aminotransferase levels within 6 months after the introduction of ursodeoxycholic acid alone, and 4 of these were elderly patients. However, the cumulative incidental rate of the normalization of serum alanine aminotransferase levels within 6 months after the introduction of initial treatment was significantly higher in those treated with prednisolone ≥ 20 mg/day than those treated only with ursodeoxycholic acid. Thus, we consider that, even in elderly patients, those with advanced fibrosis should be treated with prednisolone in order to prevent progress of the disease to liver failure.

In the report by Miyake et al (10), 5 of 13 patients aged 70-89 years (38%) and 2 of 27 patients aged 41-60 years (7%) had concurrence of autoimmune thyroiditis, and frequencies of concurrence of autoimmune thyroiditis were higher in the older patients. However, in this study, 1 of 16 patients aged ≥ 70 years (6%) and 14 of 78 patients aged 41-60 patients (18%) had concurrence of autoimmune thyroiditis. Patients with human leukocyte antigen DR4 have a higher frequency of concurrent autoimmune disease, especially autoimmune thyroiditis (14). Honda et al (15) reported that the frequency of DRw53, which is in positive linkage disequilibria with DR4, was significantly elevated in Japanese patients with autoimmune thyroiditis compared with healthy controls. In the report by Miyake et al (10) and in this study, frequencies of human leukocyte antigen DR4 were similar between the two groups. In Japanese patients, the relation between autoimmune hepatitis and autoimmune thyroiditis has yet to be fully analyzed. Further studies are required in larger numbers of patients with type 1 autoimmune hepatitis.

In this study, a peak incidence of autoimmune hepatitis was between ages 50 and 60 years. The proportion of patients between ages 10 and 30 years was smaller in the present study than in the previous reports from Caucasian patients with a main susceptibility of human leukocyte antigen DR3 and DR4 (3-6). These findings are consistent with the report by the Japanese National Study Group of Autoimmune Hepatitis Group (7). The Japanese National Study Group of Autoimmune Hepatitis Group (7) reported that 72% of Japanese patients were positive for human leukocyte antigen DR4, that there were no human leukocyte antigen DR3-positive patients, and that only 14% of the patients with autoimmune hepatitis were between ages 10 and 30 years. On the other hand, approximately 30-40% of patients in the previous reports from Caucasian patients were posi-

tive for human leukocyte antigen DR3. Human leukocyte antigen DR3 is associated with a younger age of onset (1, 2). We speculate that the difference in human leukocyte antigen DR status may affect the age distribution of patients with autoimmune hepatitis.

In conclusion, elderly patients had lower serum levels of albumin and a higher frequency of cirrhosis and pre-cirrhosis at presentation than younger patients. Also more years seem to pass between the occurrence of the disease and the presentation in elderly patients than in younger patients. However, the frequencies of concurrent autoimmune disease, age distribution, and response to corticosteroid treatment were similar between the two groups, and these fea-

tures may be due to human leukocyte antigen DR status. Furthermore, the cumulative incidental rate of the normalization of serum alanine aminotransferase levels within 6 months after the introduction of initial treatment was significantly higher in those treated with prednisolone ≥ 20 mg/day than those treated only with ursodeoxycholic acid. Thus, we consider that, even in elderly patients, those with advanced fibrosis should be treated with prednisolone in order to prevent development of the disease into liver failure. Importantly, here the number of elderly patients was small, and further studies are necessary in larger numbers of elderly patients.

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