Original Article

Comparison of Autoimmune Hepatitis in Elderly and Nonelderly Patients

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Abstract: AIM: To compare the clinical features of autoimmune hepatitis (AIH) in elderly and nonelderly patients at our hospital.

METHODS: We investigated 58 consecutive patients diagnosed with AIH based on results of liver biopsies and admitted to our hospital between January 2007 and December 2016. Twenty-eight elderly (≥65 years) and 30 nonelderly (＜65 years) patients were included. Clinical features, laboratory data, histological stage, response to prednisolone (PSL) therapy (the cumulative rates of normalization of serum ALT levels within 2 months, period until normalization, the cumulative rates of achieving PSL maintenance dose of ≤5 mg/day within 12 months, or frequency to reactivation during treatment), development of hepatocellular carcinoma (HCC), and prognosis were evaluated.

RESULTS: Elderly patients had statistically lower serum albumin levels ($p = 0.013$). The proportions of advanced fibrosis (stage 3 or 4) tended to be higher in the elderly patients. The response to PSL therapy were almost similar or slightly better in the elderly patients. HCC development was only observed in the elderly patients. Four patients died by liver failure, and 1 patients died by infectious disease.

CONCLUSION: Certain characteristics of elderly patients are more likely to have a high risk for advanced asymptomatic liver fibrosis and developing HCC.

Key Words: autoimmune hepatitis, elderly patients, advanced liver fibrosis, hepatocellular carcinoma.

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Introduction

Autoimmune hepatitis (AIH) is a progressive liver disease of unknown etiology. It generally manifests in middle-aged women, resulting in increased aspartate and alanine aminotransferase (AST and ALT), autoantibody, and immunoglobulin G (IgG) levels[1)2)]. Histological characteristics include interface hepatitis, plasma-cell infiltration, and lobular hepatitis. Clinical presentations of this disease are variable, ranging from abnormal liver enzyme levels seen in asymptomatic patients to acute, severe manifestations, such as fulminant hepatitis or advanced decompensated cirrhosis[3-7)]. Moreover, although AIH is known to commonly occur in middle-aged women, recent epidemiological studies suggest that it might be more predominant in older women[8)9)]. In this study, we investigated the clinical characteristics of AIH in 28 elderly (≥65 years) and 30 nonelderly (< 65 years) patients at our hospital. We focused mainly on the clinical presentation of elderly AIH patients in this comparative study.

Materials and Methods

Patients

We investigated 58 consecutive patients, with a median age of 64.5 years (range, 24-87 years) at diagnosis, admitted to the Japanese Red Cross Kyoto Daiichi Hospital between January 2007 and December 2016. Study protocols were approved by the ethics committee of the Japanese Red Cross Kyoto Daiichi Hospital and conformed to the tenets of the Declaration of Helsinki. Patients enrolled in this study were diagnosed and treated by board-certified hepatologists. Patients with coinfection with chronic hepatitis B, chronic hepatitis C, human immunodeficiency virus, primary biliary cirrhosis, hemochromatosis, or Wilson's disease were excluded from the study. Patients with excessive alcohol intake (≧ 60g/day) or the use of known hepatotoxic drugs were also excluded. All patients enrolled in this study underwent liver biopsy. Patients with definitive diagnoses of concomitant PBC and AIH[10)], based on the liver biopsy, were excluded. A definite diagnosis of AIH was based on the liver biopsy and clinical course of disease.

Clinical, laboratory, and histological assessments

The laboratory assessment included assessments of the levels of serum ALT, alkaline phosphatase (ALP), total bilirubin (T-Bil), albumin (Alb), IgG, antinuclear antibody (ANA) levels, and platelet count.

Fibrosis was staged as follows: F1, fibrous portal expansion; F2, bridging fibrosis; F3, bridging fibrosis with architectural distortion; and F4, cirrhosis[11)]. Advanced fibrosis was classified as stage-3 or stage-4 disease (bridging fibrosis with architectural distortion or cirrhosis). All patients were graded according to the revised scoring system proposed by the International Autoimmune Hepatitis Group[12)]. In principle, we evaluated pre-treatment scores using scoring system and definite AIH (> 15) cases or probable AIH (10-15) cases were diagnosed as AIH. As criteria for the type of clinical onset, patients with acute-onset liver dysfunction (ALT levels > 10 times the upper limit of normal or T-Bil levels > 3 times the upper limit of normal) without a history of prior liver disease were diagnosed as acute-onset AIH. The remaining patients were diagnosed as non-acute-onset AIH. Reactivation was defined as serum ALT levels elevations above normal and a requirement for prednisolone (PSL) or ursodeoxycholic acid (UDCA) treatment.

Treatment

In this study, the standard initial treatment was PSL monotherapy (15-40 mg/day). In patients with histologically low-grade inflammatory activity, the initial treatment was low-dose PSL (≤10 mg/day) or UDCA (600 mg/day). Patients who refused treatment with PSL were treated with UDCA. PSL was continued until

normalization of serum ALT levels and was tapered to maintain remission. PSL titration was carefully done by decreasing the dose by 5 mg every week or every 2 weeks until a dose of 5 mg/day was achieved. A further reduction to 2.5 mg/day or drug-free treatment has been considered for maintaining stable ALT levels in AIH patients. The maintenance regimen was then continued until disease resolution, treatment failure, or drug intolerance.

Statistical analysis

Statistical analysis was performed using the SPSS statistical program (release 22, SPSS Inc., Chicago, IL). Continuous variables were expressed as medians and interquartile ranges. Categorical variables were expressed as numbers and percentages. The Mann-Whitney U-test was used to evaluate differences in the continuous variables. Dichotomous variables were compared using the χ^2 test. p values of < 0.05 were considered statistically significant.

Results

Clinical features of patients

The median observation period was 41.5 months. Twenty eight patients (48.3%) were ≥65 years of age at the time of diagnosis (Table 1). The median age at diagnosis was 64.5 (range, 24-87) years. The peak incidence of AIH occurred between 60 and 69 years of age. The clinical profiles of all 58 patients, divided into elderly (≥65 years) and nonelderly (< 65 years) patient groups, are shown in Table 2. There were no differences in ALT, ALP, or ANA levels between the elderly and nonelderly patients. Serum Alb levels were significantly lower in the elderly patients than in the nonelderly patients. Serum T-Bil levels tended to be higher, and platelet counts tended to be lower in the elderly patients, respectively. Serum IgG levels tended to be higher in the nonelderly patients. Histological examination showed that elderly patients had a higher frequency of advanced fibrosis (stage F3 or F4) than nonelderly patients.

Clinical course

The clinical courses of disease in the elderly and nonelderly patients are shown in Table 3. For the initial medical treatment, 39 of the 58 patients (67.2%) were treated with PSL (≥15 mg/day), whereas 19 patients were treated with UDCA (300-600 mg/day) or a combination of low-dose PSL (< 15 mg/day) and UDCA. ALT levels were normalized spontaneously in two patients within a relatively short period.

Table 1 Baseline patient characteristics

Number of patients	$n = 58$	
Age (years)	64.5	(55.0–69.3)
Gender (male/female)	11/47	
Observation period (months)	41.5	(19.5-68.3)
Laboratory data		
ALT (IU/L)	215	(93–634)
ALP (IU/L)	443	(320–666)
T-Bil (mg/dL)	1.3	(0.7–5.3)
Albumin (g/dL)	3.7	(3.3–4.0)
Platelet count ($\times 10^4/mm^3$)	18.0	(12.7–22.7)
IgG (mg/dL)	2320	(1700–3010)

Data are presented as numbers or medians with interquartile ranges in parentheses.
ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-Bil, total bilirubin; IgG, immunoglobulin G

Table 2 Clinical profiles of elderly (≥65 years) and nonelderly (< 65 years) patients

Number of patients	Elderly $n = 28$		Nonelderly $n = 30$		p value
Gender (male/female)	4/24		7/23		0.38
Observation period (months)	33	(14–58)	50	(29–89)	0.199
Concurrent autoimmune disease	2		4		
Onset (acute/non-acute)	12/16		10/20		0.455
Laboratory data					
ALT (IU/L)	242	(77-799)	191	(110–463)	0.823
ALP (IU/L)	423	(339-566)	433	(300–714)	0.943
T-Bil (mg/dL)	1.5	(0.8–6.6)	0.9	(0.6–3.9)	0.193
Albumin (g/dL)	3.5	(3.2–3.8)	4.0	(3.4–4.1)	0.013
Platelet count ($\times 10^4$/mm^3)	16.1	(12.2–22.0)	18.5	(13.9–25.9)	0.137
IgG (mg/dL)	2040	(1600–2740)	2420	(1705–3270)	0.155
ANA titers	160	(80–320)	160	(80–345)	0.843
IAHG score	16.0	(15–17)	16.0	(13–17)	0.576
Fibrosis grade(F1,F2,F3,F4)	6/7/13/2		11/10/6/3		
Advanced fibrosis patients	15		9		0.069

Data are presented as numbers or medians with interquartile ranges in parentheses.ALT, alanine aminotransferase; ALP, alkaline phosphatase; T-Bil, total bilirubin; IgG, immunoglobulin G; ANA antinuclear antibody; IAHG score, International Autoimmune Hepatitis Group score. Concurrent autoimmune disease: One elderly patient had thyroid disease and one elderly patient had systemic lupus erythematosus. Two nonelderly patients had thyroid disease, one nonelderly patient had idiopathic thrombocytopenic purpura, and one nonelderly patient had ulcerative colitis.
p values were calculated using the χ^2 or Mann-Whitney U test for continuous variables.

Table3 Clinical courses of elderly (≥65 years) and nonelderly (< 65 years) patients

Number of patients	Elderly $n = 28$		Nonelderly $n = 30$		P value
PSL treatment	18		21		
Observation over 12 months	17#		21		
Normalized ALT within 2 months	15	(88.2%)	16	(76.2%)	0.302
Period until normalization (months)	0.7	(0.5–1.4)	1.0	(0.6–2.0)	0.090
Achieving under ≤5mg/day within 12 months	15	(88.2%)	18	(85.7%)	0.604
Reactivation	7	(41.2%)	12	(57.1%)	0.328
Malignancy					
HCC	2		0		
Cause of death					
Fulminant hepatitis	1				
Liver failure	2*		1		
Infection	1		0		

#: One elderly patient developed fulminant hepatitis and subsequently died within 2 months of starting the treatment.
*: Two elderly patients had comorbid HCC.
Data are presented as numbers with percentage in parentheses or medians with interquartile ranges in parentheses.
PSL, prednisolone; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma
P values were calculated using the χ^2 or Mann-Whitney U test for continuous variables.

Unfortunately, one elderly patient developed fulminant hepatitis and subsequently died within 2 months of starting the treatment. Except this patient, 17 elderly patients and 21 nonelderly patients were observed for > 12 months of PSL treatment. The cumulative incidence of normalization of serum ALT levels within 2 months after PSL introduction were similar in the elderly and nonelderly patients (88.2% vs. 76.2%, respectively; P = 0.302). Although period until normalization were shorter in elderly patients, the difference between the two groups was not statistically significant (p =0.09). The cumulative incidence of achieving a maintenance dose of PSL under ≤5 mg/day within 12 months and reactivation rates were also similar between the elderly and nonelderly patients, respectively.

Five patients died in observation period. HCC occurred in two elderly female patients (86 years, F3 stage; 69 years, F3 stage), and they died. One elderly female patient died of fulminant hepatitis. One elderly female patient died of infection. One nonelderly female patient died of liver failure. (Table 3).

Discussion

In the present study, we evaluated and compared the clinical features of elderly and nonelderly AIH patients. AIH in the elderly is more common than previously thought. The proportions of advanced fibrosis (stage F3 or F4) tended to be higher in the elderly patients than in the nonelderly patients. Liver related deaths were more frequently occurred only in elderly patients.

The first point to be discussed is that the age of peak incidence. Although AIH is commonly known to present in middle-aged women, some recent epidemiological studies showed that age at diagnosis of AIH is more common in elderly women[8]. Limited population-based epidemiological studies confirmed that AIH are predominantly made diagnoses in older women, peaking during the sixth decade of life[8)13.15)]. It is unclear why AIH incidence is higher among the elderly. One possible explanation for increasing elderly AIH is that the clinical criteria for AIH have been more clearly established, and more atypical cases might now be diagnosed as AIH[12)16)]. The other explanation is that differences in human leukocyte antigen DR (HLA-DR) status may affect the age distribution of patients with AIH. Among Japanese patients with AIH, 72% were positive for HLA-DR4, and studies have suggested that HLA-DR4 is more frequent in elderly patients[8)9)]. However, 30%-40% of Caucasian patients are positive for HLA-DR3, which is associated with a younger age of AIH onset[17)18)]. The advances of epidemiological databases might offer more accurate age of onset in the future.

The second point to be discussed is that the histological examination of elderly AIH patients. According to the histological examination, stage F3 or F4 disease were more common in the elderly patients than in the nonelderly patients at diagnosis (15 patients in elderly group; 53.6% vs. 9 patients in nonelderly group; 30.0%), respectively, which is consistent with data from a previous report[9]. The higher advanced fibrosis stage in elderly patients may be help to explain that some elderly patients may be asymptomatic for many years and diagnosed AIH at an old age. Histological examination is considered important to distinguish acute-onset AIH from the acute exacerbation of chronic AIH, and therefore more accurately predict the prognosis[20].

The clinical presentation of AIH onset is variable. One elderly patient presented with fulminant hepatitis, and 21 patients had acute-onset AIH in the present study. Meanwhile, other cases presented with vague clinical symptoms. As laboratory results, no significant differences were observed between the two groups with regard to serum ALT, ALP, ANA, IAHG score at onset. Elderly patients had significantly lower serum Alb levels, which have been shown to further decline with age[19]. Serum T-Bil levels were higher, and platelet

count was lower in the elderly patients, respectively. These laboratory data might reflect a decreased physiological liver function associated with aging or high frequency of advanced liver fibrosis in the elderly patients.

As the treatment response of AIH, the cumulative rates of normalization of serum ALT levels within 2 months of initial treatment, period until normalization, and frequency of reactivation during treatment were almost the same or slightly better in the elderly patients. Two patients refuse to be treated with PSL, and one patient was not treated by medical issue, respectively in each group. We advise that initial treatment should include PSL if not contraindicated, even in elderly patients. Except for one elderly patient who developed fulminant hepatitis, patients were treated with PSL or UDCA; fortunately, non-standard pharmacological treatments[21] were not used for treatment.

Although the observation period was limited, two patients developed HCC and one patient died of infection in the elderly group. The increased HCC development in elderly patients may result from the high frequency of advanced fibrosis. Because of improvements in the prediction of the prognosis and increases in the number of elderly patients with AIH, complications from malignancies and monitoring for side effects of PSL may become important considerations. Screening for malignancies is thus particularly important in elderly patients.

One limitation of this study was that HLA-DR was not evaluated because a commercial database was unavailable. HLA status likely affects clinical manifestation, behavior, and treatment outcomes[22]. Another limitation of the present study was the relatively small number of patients assessed. A study including more patients could clearly reveal if elderly patients show a statistically higher risk of progression of liver fibrosis. Further studies are necessary to evaluate the characteristics of elderly patients with AIH.

In conclusion, AIH in the elderly is more common than previously thought. Elderly patients experienced a higher frequency of progressive liver fibrosis and HCC development, both of which are of considerable clinical importance.

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Conflict-of-interest statement

The authors have no conflicts of interest to declare.

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〈和文抄録〉

高齢者と非高齢の自己免疫性肝炎の比較

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目的：高齢者と非高齢者の自己免疫性肝炎の臨床的特徴を比較する．

方法：2007年1月から2016年12月の生検で診断された58例の連続する自己免疫性肝炎について検討した．28例の65歳以上の高齢者と30名の非高齢者で，臨床データ（ALT，ALP，Alb，IgG，ANA抗体価，血小板），線維化，プレドニゾロン（PSL）の治療反応性（2か月以内にALTが正常化した割合，正常化までの期間，12か月までにPSLを5mg/日以下の維持量まで減量できた割合，再燃），肝癌と予後について検討した．

高齢者は統計的にAlbが低値であった（P=0.013）．進行した線維化症例（Stage3または4）の割合が高齢者のほうが高かった．PSL治療の反応性は同様か，高齢者でややよい傾向であった．高齢者のみ肝癌を認めた．死亡原因は肝不全（高齢者3名，うち2名は肝癌合併と，非高齢者1名）と感染症であった．

結語：高齢者の特徴として無症候に進行した肝線維化と肝癌の危険性がある可能性が高い．

キーワード：自己免疫性肝炎，高齢者，線維化進行，肝癌．