

ORIGINAL ARTICLE

Non-alcoholic fatty liver disease in patients with autoimmune hepatitis

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Key words

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Introduction

Unhealthy lifestyle behaviors such as irregular eating habits (including overnutrition) and low physical activity can trigger non-alcoholic fatty liver disease (NAFLD).^{1–3} Therefore, NAFLD can develop in anyone, and its incidence has dramatically increased all over the world in parallel with the increasing incidence of metabolic syndrome.^{1–3} The presence of hepatic steatosis is characteristic of NAFLD. Non-alcoholic steatohepatitis (NASH) is histologically characterized by inflammation together with hepatocyte ballooning, in addition to the presence of hepatic steatosis.^{4,5} NASH is diagnosed

Abstract

Background and Aim: The incidence of non-alcoholic fatty liver disease (NAFLD) is increasing all over the world. NAFLD develops in patients with liver disease, including patients with autoimmune hepatitis (AIH). NAFLD and AIH have some similar laboratory and histological findings. The aim of this study was to elucidate the characteristics of AIH patients with NAFLD.

Methods: We re-evaluated the nationwide survey performed in Japan in 2015 of AIH patients diagnosed between 2009 and 2013.

Results: A total of 1151 subjects (144 men and 1007 women) were enrolled in the present study. The overall prevalence of NAFLD was 17.0%. Compared to AIH without NAFLD, AIH patients with NAFLD had the following characteristics: (i) low female-to-male ratio, (ii) older age, (iii) mild elevation in hepatobiliary enzymes, (iv) histologically progressive fibrosis and mild plasma cell infiltration or mild lobular hepatitis, (v) lower prevalence of prednisolone administration and higher prevalence of ursodeoxycholic acid administration, (vi) higher levels of hepatic enzymes and immunoglobulin G after treatment, and (vii) similar prevalence of autoimmune and malignant complications.

Conclusion: AIH patients with NAFLD have many features that are different from AIH patients without NAFLD. Understanding these differences is essential for the proper diagnosis and treatment of AIH patients with NAFLD.

based on histological findings because of a lack of specific diagnostic markers.

Autoimmune hepatitis (AIH) is immune-mediated hepatic disease, the cause of which has not been established. Although prednisolone (PSL) is the first-line therapy for AIH,^{6–8} it causes side effects such as insulin resistance or dyslipidemia and can induce the development of fatty liver.⁶ Therefore, physicians should pay careful attention to the treatment of AIH patients with NAFLD. Distinguishing between AIH patients with NAFLD and patients with NASH is sometimes difficult because some patients with NASH test positive for antinuclear antibody (ANA).^{9–12} Evaluation of liver histology is useful for the differential

diagnosis, but advanced fibrosis or interface hepatitis sometimes makes diagnosis difficult.¹⁰

A recent study was the first to report the natural history of patients with AIH and coincident NAFLD.¹³ The study demonstrated that patients with AIH and coincident NAFLD were more likely to present with cirrhosis and were more likely to develop adverse clinical outcome with decreased survival. However, the study was conducted in a small number of patients in a single center, and the differences in patient backgrounds, except metabolic factors, between AIH patients with and without NAFLD remain unclear. Recently, we reported a nationwide survey of patients with AIH in Japan. Of 1391 patients, 249 (17.9%) showed fatty change in liver histology.¹⁴ The present study aimed to elucidate the clinical features of AIH patients with NAFLD by using the results of this nationwide survey of AIH in Japan.

Methods

Participants. The nationwide survey has previously been reported in detail.¹⁴ Questionnaires were sent to 437 hospitals and clinics throughout Japan. Completed questionnaires describing 1682 AIH patients were collected from 105 hospitals and clinics. Of the returned questionnaires, the following candidates were excluded from the study: 236 patients in whom fatty change could not be evaluated histologically, 137 patients with insufficient data on alcohol intake status and hepatitis virus, 77 subjects reporting alcohol intake greater than 20 g/day in women and 30 g/day in men, 64 subjects who were hepatitis C antibody positive, and 17 subjects who were hepatitis B surface antigen positive. The diagnosis of NAFLD was based on the Japanese guidelines for NAFLD.¹⁵ The evidence of hepatic steatosis was detected by liver histology in the absence of other causes of

chronic liver disease (e.g. hepatitis C antibody negative, hepatitis B surface antigen negative, or alcoholic consumption >20 g/day in women and >30 g/day in men). After these exclusions, the data of 1151 subjects (144 men and 1007 women) were used for the analyses.

Questionnaire. The questionnaire was composed of topics based on the previous survey, as follows: age at diagnosis, sex, past and family history, alcohol and medication history, laboratory findings at diagnosis and the time of investigation after treatment, liver histological findings at diagnosis, presence of other autoimmune or malignant diseases, treatment, and outcome.¹⁴ Basic histological findings were graded as follows: interface hepatitis, portal inflammation, plasma cell infiltration, and lobular necrosis or inflammation (0: none, 1: mild, 2: moderate to severe); fibrosis (0: none, 1: mild, 2: moderate, 3: severe, 4: cirrhosis); bile duct injury; hepatocyte rosette formation; centrilobular necrosis; emperipolesis; and fatty change (0: none, 1: present).

Statistical analysis. Results are presented as medians (interquartile range) for continuous variables and percentage values for categorical variables. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS, Inc., Chicago, IL, USA). If there were missing values, statistical analysis was performed using available data. The two groups were compared using the chi-square test and Fisher's exact test for categorical variables and the Mann-Whitney *U*-test for continuous variables. Values of *P* < 0.05 were considered indicative of significant differences.

Results

Characteristics of AIH patients with and without NAFLD. Fatty change was present in 196 (17.0%) of the 1151 study patients. The frequency of female patients was significantly lower in AIH patients with NAFLD compared to patients without NAFLD (Table 1). AIH patients with NAFLD were significantly older than patients without NAFLD. The levels of total bilirubin and hepatobiliary enzymes, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ -glutamyl transferase (γ -GTP), were significantly higher in AIH patients without NAFLD than in patients with NAFLD. There were no significant differences in levels of immunoglobulin G (IgG); ANA titer; and in the positivity rate for ANA, anti-smooth muscle antibody, human leukocyte antigen (HLA)-DR4, and HLA-DR2.

Liver histological findings. Although there was no difference in histological diagnosis between AIH patients without NAFLD and patients with NAFLD, the prevalence of acute hepatitis tended to be more frequent in AIH patients without NAFLD than in AIH patients with NAFLD (without NAFLD 13.2% vs with NAFLD 7.8%; *P* = 0.052) (Table 2). Regarding the basic histological characteristics of AIH, plasma cell infiltration and lobular necrosis/inflammation had progressed to a greater degree in patients without NAFLD. Conversely, fibrosis had progressed to a greater degree in patients with NAFLD.

Table 1 Laboratory characteristics at diagnosis in AIH patients with and without NAFLD

| Variables | Without NAFLD (<i>n</i> = 955) | With NAFLD (<i>n</i> = 196) | <i>P</i> -value |
|-------------------------|---------------------------------|------------------------------|-----------------|
| Female sex | 88.4% (845) | 82.7% (162) | 0.033 |
| Age (years) | 61 (51–69) | 64 (55–70) | 0.004 |
| AST (U/L) | 239 (97–556) | 112 (57–253) | <0.001 |
| ALT (U/L) | 285 (109–643) | 126 (59–279) | <0.001 |
| ALP (U/L) | 439 (321–611) | 351 (275–486) | <0.001 |
| γ -GTP (U/L) | 161 (87–271) | 124 (74–244) | 0.016 |
| Total bilirubin (mg/dL) | 1.2 (0.8–3.1) | 0.9 (0.7–1.6) | <0.001 |
| IgG (mg/dL) | 2178 (1764–2794) | 2108 (1755–2782) | 0.348 |
| ANA positivity | 89.0% (850/955) | 91.8 (178/194) | 0.313 |
| ANA (median) | 160 (80–640) | 160 (80–640) | 0.794 |
| ASMA positivity | 43.2% (144/333) | 33.9% (19/56) | 0.246 |
| HLA-DR4 positivity | 66.4% (142/214) | 64.0% (16/25) | 0.990 |
| HLA-DR2 positivity | 10.8% (22/204) | 4.3% (1/23) | 0.509 |

Data are expressed as the median with interquartile range in parentheses for continuous variables and as the percentage with the number in parentheses for categorical variables.

γ -GTP, γ -glutamyl transferase; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; HLA, human leukocyte antigen; IgG, immunoglobulin G; NAFLD, non-alcoholic fatty liver disease.

Treatment. Of the 1138 patients whose data were available, 943 (82.9%) patients were treated with PSL. PSL was used at a higher rate in the patients without NAFLD than in the AIH patients with NAFLD (Table 3). The usage rate of PSL alone was also higher in patients without NAFLD. There were no significant differences in initial dosage, maintenance dosage, or duration of PSL between the groups. Moreover, the efficacy and discontinuation of PSL or relapse rate during administration were similar in the two groups. The usage rate of ursodeoxycholic acid was significantly higher in patients with NAFLD regardless of whether it was used in combination with PSL. In AIH patients with NAFLD, the levels of total bilirubin, AST, ALT, γ -GTP, and IgG were significantly higher in patients with PSL administration than in those without PSL administration (Table S1, Supporting information). In addition, there were no significant differences in histological liver findings between the groups.

Laboratory findings after treatment. After treatment, the levels of AST, ALT, ALP, total bilirubin, and IgG were significantly higher in the AIH patients with NAFLD than in the patients without NAFLD (Table 4). To confirm that the differences in these laboratory values were the results of differences in treatment, we compared only the patients who were treated with PSL (Table 5). The significant differences in the levels of ALP,

Table 2 Comparison of liver histological findings between AIH patients with and without NAFLD

| Variable | Without NAFLD | With NAFLD | P-value |
|--|-------------------|-----------------|---------|
| Histological diagnosis | | | |
| Acute hepatitis | 13.2% (124/942) | 7.8% (15/192) | 0.052 |
| Chronic hepatitis | 79.3% (124/942) | 83.3% (160/192) | 0.240 |
| Liver cirrhosis | 6.1% (58/942) | 7.8% (15/192) | 0.490 |
| Basic histology | | | |
| Interface hepatitis 0/1/2 (n) | 42/212/657 | 6/41/139 | 0.426 |
| Portal inflammation 0/1/2 (n) | 22/211/670 | 6/45/130 | 0.480 |
| Plasma cell infiltration 0/1/2 (n) | 92/306/455 | 27/75/78 | 0.010 |
| Fibrosis 0/1/2/3/4 (n) | 97/299/266/136/59 | 11/57/56/42/13 | 0.010 |
| Bile duct injury frequency (n) | 27.7% (229/825) | 25.8% (42/163) | 0.671 |
| Hepatocyte rosette formation frequency (n) | 39.1% (285/728) | 45.8% (65/142) | 0.168 |
| Lobular necrosis/ inflammation 0/1/2 (n) | 76/311/492 | 15/80/80 | 0.024 |
| Centrilobular necrosis frequency (n) | 34.8% (218/627) | 30.6% (33/108) | 0.456 |
| Emperipolesis frequency (n) | 13.9% (53/382) | 9.0 (6/67) | 0.366 |

Values are given as the number of patients or as the percentage with the number in parentheses.

AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease.

Table 3 Comparison of treatments between AIH patients with and without NAFLD

| Treatment | Without NAFLD | With NAFLD | P-value |
|---------------------------------|-----------------|-----------------|---------|
| PSL | 84.5% (796/942) | 75.0% (147/196) | 0.002 |
| Initial dosage (mg/day) | 30 (30–40) | 30 (30–40) | 0.688 |
| Maintenance dosage (mg/day) | 5.0 (5.0–7.3) | 5.0 (4.8–7.1) | 0.934 |
| Maintenance duration (month) | 15 (6–33) | 17 (6–37) | 0.730 |
| PSL alone | 31.2% (243/778) | 22.4% (32/143) | 0.043 |
| PSL + ursodeoxycholic acid | 52.1% (415/796) | 75.5% (111/147) | <0.001 |
| Steroid pulse | 12.6% (92/730) | 10.6% (15/141) | 0.471 |
| Efficacy of PSL | 98.0% (700/714) | 98.5% (135/137) | 0.958 |
| Relapse during PSL | 26.8% (186/693) | 21.2% (28/132) | 0.217 |
| Discontinuation | 12.5% (92/735) | 10.2% (14/137) | 0.540 |
| Ursodeoxycholic acid alone | 12.6% (119/942) | 21.4% (42/196) | 0.002 |
| Azathioprine | 10.6% (101/955) | 7.1% (14/196) | 0.184 |

Data are expressed as the median with interquartile range in parentheses for continuous variables and as the percentage with the number in parentheses for categorical variables.

AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease; PSL, prednisolone.

total bilirubin and IgG between AIH patients without and with NAFLD were lost for the patients who received PSL.

Complications. Autoimmune diseases were present in 289 (25.4%) of 1140 patients with AIH whose data were available (Table 6). There was no significant difference in the prevalence of autoimmune diseases between AIH patients without and with NAFLD (without NAFLD 26.0% vs with NAFLD 22.2%; $P = 0.287$). With respect to malignancy, hepatocellular carcinoma (HCC) was the most frequent malignancy in both groups (without NAFLD 1.1% vs with NAFLD 1.5%; $P = 0.846$). There was no significant difference in the prevalence of malignancy between the two groups.

Discussion

The present study has shown various characteristics of AIH patients with NAFLD. This is the largest report to date on laboratory values, liver histology, treatment, and complications in AIH patients with NAFLD, especially laboratory findings before and after treatment.

Although a previous study reported no differences in sex or age,¹³ the present study found a low female-to-male ratio and older age in AIH patients with NAFLD compared to patients without NAFLD. The reason can be explained by a significant threefold difference in the mean prevalence of NAFLD between males (41.0%) and females (17.7%) in a large Japanese multicenter study.¹⁶ Diagnosis at older age in AIH patients with NAFLD can be explained by several factors. First, the diagnosis of AIH is difficult in female patients with NAFLD because some patients with NAFLD test ANA-positive, and those female patients often satisfy the diagnostic criteria for AIH.⁹ Moreover, the distributions of both AIH and NAFLD in females have a single peak in patients

Table 4 Comparison of laboratory findings after treatment between AIH patients with and without NAFLD

| Variables | Without NAFLD (n = 955) | With NAFLD (n = 196) | P-value |
|-------------------------|-------------------------|----------------------|---------|
| AST (U/L) | 21 (17–27) | 23 (19–38) | 0.001 |
| ALT (U/L) | 16 (11–23) | 20 (13–32) | <0.001 |
| ALP (U/L) | 212 (164–278) | 228 (170–323) | 0.027 |
| γ-GTP (U/L) | 22 (15–40) | 23 (15–45) | 0.198 |
| Total bilirubin (mg/dL) | 0.6 (0.5–0.8) | 0.7 (0.5–0.9) | 0.026 |
| IgG (mg/dL) | 1300 (1075–1580) | 1390 (1133–1703) | 0.037 |

Data are expressed as the median with interquartile range.

γ-GTP, γ-glutamyl transferase; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G; NAFLD, non-alcoholic fatty liver disease.

in their 60s.^{14,15} Therefore, the diagnosis of AIH may be delayed because physicians treat AIH patients with NAFLD as having only NAFLD or NASH. Second, NAFLD can develop after AIH onset through lifestyle or hormonal changes. Interestingly, ANA-positive patients with NAFLD/NASH are older and female-dominant.^{11,16} These factors may support the above observations of low female-to-male ratio and older age in AIH patients with NAFLD compared to patients without NAFLD.

Hepatic steatosis exerts an influence as a “cofactor” on a liver affected by other disease.¹⁸ AIH patients with NASH are more likely to develop adverse clinical outcomes and poor survival compared with AIH-only patients.¹³ In the present study, the levels of hepatobiliary enzymes were lower in AIH patients with NAFLD compared to the patients without NAFLD. It is unknown whether this observation reflects the nature of AIH with NAFLD or only the phase at diagnosis. However, these laboratory findings are consistent with liver histological findings, such as advanced fibrosis and less lobular inflammation in AIH patients with NAFLD.

Both laboratory and histological findings affect treatment decisions. In the treatment of AIH with NAFLD, it is important to be clear on what has to be treated, and a liver biopsy is helpful for making this distinction.⁸ The lower frequency of PSL administration in AIH patients with NAFLD can reflect laboratory and histological findings in addition to avoiding the worsening of NAFLD or administration in those of older age. However, the laboratory findings in AIH patients without NAFLD improve to

Table 5 Comparison of laboratory findings after prednisolone treatment between AIH patients with and without NAFLD

| Variables | Without NAFLD (n = 796) | With NAFLD (n = 147) | P-value |
|-------------------------|-------------------------|----------------------|---------|
| AST (U/L) | 21 (17–27) | 22 (18–38) | 0.023 |
| ALT (U/L) | 16 (11–23) | 19 (13–34) | <0.001 |
| ALP (U/L) | 204 (160–266) | 214 (162–287) | 0.260 |
| γ-GTP (U/L) | 22 (15–39) | 23 (16–46) | 0.137 |
| Total bilirubin (mg/dL) | 0.6 (0.5–0.9) | 0.7 (0.5–0.9) | 0.113 |
| IgG (mg/dL) | 1250 (1045–1505) | 1333 (1081–1577) | 0.050 |

Data are expressed as the median with interquartile range.

γ-GTP, γ-glutamyl transferase; AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IgG, immunoglobulin G; NAFLD, non-alcoholic fatty liver disease.

Table 6 Comparison of complications between AIH patients with and without NAFLD

| Complications | Without NAFLD | With NAFLD | P-value |
|-------------------------------------|-----------------|----------------|---------|
| Autoimmune disorder | 26.0% (246/946) | 22.2% (43/194) | 0.287 |
| Chronic thyroiditis | 7.9% (75/946) | 7.7% (15/194) | 0.957 |
| Sjögren's syndrome | 7.0% (66/946) | 4.6% (9/194) | 0.300 |
| Primary biliary cirrhosis | 3.9% (37/946) | 2.1% (4/194) | 0.294 |
| Rheumatoid arthritis | 3.5% (33/946) | 1.5% (3/194) | 0.237 |
| Systemic lupus erythematosus | 2.4% (23/946) | 4.6% (9/194) | 0.145 |
| Graves' disease | 1.4% (13/946) | 0% (0/194) | 0.204 |
| Raynaud's phenomenon | 0.7% (7/946) | 0.5% (1/194) | 0.896 |
| Systemic sclerosis | 0.5% (5/946) | 1.0% (2/194) | 0.756 |
| Idiopathic thrombocytopenic purpura | 0.5% (5/946) | 0.5% (1/194) | 0.606 |
| Others | 2.5% (24/946) | 2.6% (5/194) | 0.913 |
| Malignancy | 5.8% (54/938) | 6.2% (12/194) | 0.903 |
| Hepatocellular carcinoma | 1.1% (10/938) | 1.5% (3/194) | 0.846 |
| Breast cancer | 1.0% (9/938) | 0.5% (1/194) | 0.853 |
| Gastric cancer | 1.0% (9/938) | 0.5% (1/194) | 0.853 |
| Colon cancer | 0.6% (6/938) | 0.5% (1/194) | 0.766 |
| Uterine or ovarian cancer | 0.4% (4/938) | 0.5% (1/194) | 0.669 |
| Lung cancer | 0.4% (4/938) | 0.5% (1/194) | 0.669 |
| Others | 1.7% (16/938) | 1.5% (3/194) | 0.886 |

Values are given as the number of patients or as the percentage with the number in parentheses.

AIH, autoimmune hepatitis; NAFLD, non-alcoholic fatty liver disease.

a greater extent than the laboratory findings of patients with NAFLD after treatment despite higher elevation before treatment. This result indicates that appropriate PSL administration is essential to control the activity of AIH. Attention must be given to AIH patients with NAFLD such that their NAFLD does not worsen through PSL administration. This is because, in the present study, the hepatic enzymes were still significantly higher in AIH patients with NAFLD after PSL administration. Therefore, immunosuppressive therapy with drugs such as azathioprine may be useful for AIH patients with NAFLD, and its efficacy has been confirmed in other countries as azathioprine is not covered by the National Health Insurance system in Japan.

Patients with AIH sometimes develop other autoimmune diseases or malignancy. The present study found no differences in prevalence and types of malignancy between AIH patients with or without NAFLD. Liver fibrosis, which is a risk factor for HCC in AIH patients,¹⁹ was at an advanced stage in AIH patients with NAFLD in the present study; therefore, periodic screening for HCC may be more essential in AIH patients with NAFLD.

The strengths of the present study were the large sample size of subjects and the evaluation of various features of AIH patients with NAFLD. A limitation of the current study was that it was based on the analysis of a questionnaire; thus, there was no information on body mass index. Moreover, NAFLD cannot be classified as simple steatosis and NASH. In a previous study, AIH patients with simple steatosis had features similar to AIH patients without NAFLD.⁸ Therefore, identification of the presence of NASH is important to elucidate the precise influence of NAFLD on AIH. However, diagnosis of NASH in AIH patients

is difficult because NASH and AIH sometimes have common histological features as well as common laboratory findings.¹⁰ In the future, discovery of specific markers for AIH or NASH may solve this problem.

In conclusion, AIH patients with NAFLD have features that are different from AIH patients without NAFLD. These differences affect the decision for PSL administration and the activity of AIH after treatment. AIH patients with NAFLD require appropriate treatment from the standpoint of controlling both AIH and NAFLD.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 Comparison of autoimmune hepatitis patients with non-alcoholic fatty liver disease with and without prednisolone administration.