Autoimmune Hepatitis: Recent Advances in the Pathogenesis and New Diagnostic Guidelines in Japan

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Abstract

Autoimmune hepatitis (AIH) is thought to be associated with various genetic and immunological abnormalities. Concerning the pathogenesis of AIH, increasing attention has been paid to genome-wide association studies, toll-like receptors and Treg/Th17 balance. For Japanese patients with AIH, novel diagnostic guidelines have been proposed in view of the differential clinical features between Japanese and Caucasian patients. However, the diagnosis of some patients in acute hepatitis phase is not easy. Histologically, centrilobular necrosis without portal inflammation is particularly characteristic in the acute hepatitis phase. Some patients become resistant to steroid therapy and have a very poor prognosis once they progress to acute hepatic failure. Therefore, additional revision of the current diagnostic criteria, including severity grading, will be needed in the future.

Key words: acute presentation, centrilobular necrosis, severity grading, hepatitis C virus, autoantibodies

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Introduction

The liver is a unique organ capable of inducing immune tolerance, although it can also be affected by autoimmunity (1). Autoimmune hepatitis (AIH) is a typical autoimmune-mediated liver disease caused by an immune disorder in the liver (2, 3). A nationwide survey in Japan showed a male/female ratio of 1:6 and a mean age at diagnosis of 60 years (4), indicating increasing trends in the proportion of male patients and age compared to that observed in previous surveys (5, 6). Although there are no specific signs or symptoms of AIH, various patterns of symptom onset have been reported, ranging from asymptomatic cases to patients with acute hepatitis-like symptoms, such as loss of appetite, malaise and jaundice. Some patients present with these symptoms at an advanced stage, along with cirrhosis and associated symptoms, such as encephalopathy and hemorrhage of esophageal varices (7, 8). AIH may be accompanied by other autoimmune disorders, such as chronic thyroiditis, Sjögren's syndrome and rheumatoid arthritis (7). In Japan, several new initiatives are being implemented, including a nationwide survey and revision of the diagnosis and treat-

ment guidelines (4, 9-11). This article outlines the recent research progress regarding the pathogenesis of AIH from an international point of view and discusses the current diagnostic guidelines in Japan.

Pathophysiology

AIH is characterized by an increased serum IgG level and the emergence of autoantibodies, such as antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) (12). Histological findings of interface hepatitis, such as marked infiltration of lymphocytes and plasma cells, are observed in typical cases (3, 8). AIH develops and progresses based on immune tolerance against autologous hepatocytes and the subsequent immune response; the etiology of AIH is thought to be associated with various genetic and immunological abnormalities (13-15).

1) Genetic factors

Suggested genetic factors include HLA and various genetic polymorphisms. In particular, HLA-DR4 is known to be a disease-susceptibility gene in Japanese AIH patients and is distinct from HLA-DR3 in Caucasian pa-

tients (16-18). Studies of its relationship to disease progression and response to treatment have shown that the HLA haplotype is associated with the patient's prognosis (19). With regard to non-HLA molecules, polymorphisms of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), Fas and vitamin D receptor have been shown to be involved in the pathogenesis of AIH (20-23). A recent genome-wide association study (GWAS) of 649 adults in the Netherlands with type I AIH identified Src homology 2 adaptor protein 3 (SH2B3) and caspase recruitment domain family member 10 (CARD10) as novel disease susceptibility genes of AIH (24). In Japan, a nationwide GWAS is currently underway and its results are being awaited with great interest.

2) Innate immunity

Concerning innate immunity, viral infection and drugs have been identified to be the most common environmental factors associated with the onset of AIH. Type I AIH has been reported to be associated with infection with hepatitis A, hepatitis B and Epstein-Barr (EB) viruses, whereas type II AIH is associated with infection with hepatitis C virus, cytomegalovirus and herpes virus (25-27). The onset of AIH has also been demonstrated after various drug therapies, such as treatment with antibiotics and statins (28, 29). These infectious microbes and drug metabolites are involved in immune activation and disrupted immune tolerance to self-antigens, which have been suggested to be related to the impaired functions of immune cells and various toll-like receptors (TLRs) expressed on hepatocytes (30-32). Another suggested mechanism is the role of damage-associated molecular patterns (DAMPs) released from damaged cells in activating immune cells by acting on TLRs as an autoantigen (33).

3) Acquired immunity

The acquired immunity-related pathogenesis of AIH is primarily driven by activated autoreactive T cells (34-36). These T cells are normally suppressed by regulatory T cells (T_{reg}); however, once this mechanism is disrupted, immune tolerance disturbances and the onset of autoimmune disease subsequently follow. Based on the reduction in peripheral T_{reg} cells and TGF- β production in the setting of AIH, quantitative and qualitative defects of T_{reg} were originally suggested to be involved in the pathogenesis of AIH, until recent evidence contradicted this hypothesis (37-39). Therefore, further investigations on this issue are needed. Furthermore, although CD8-positive cytotoxic T lymphocytes (CTL), which infiltrate into the liver, were traditionally considered to play a central role in hepatocellular disturbances as effector cells, recent studies have paid more attention to Th17 cells (35). Increases in the IL-17 level in peripheral blood and the number of intrahepatic Th17 cells have also been reported in AIH patients (40, 41). In the presence of TGF- β , the production of IL-6 results in Th17 induction, while its absence results in T_{reg} induction. This T_{reg} /Th17 balance is drawing increasing attention (42). It has also been

demonstrated that the blockade of IL-17 in AIH results in T_{reg} induction (43).

4) Animal models

Animal models involving the spontaneous development of AIH are thought to be valuable in elucidating the pathophysiology of the disease. Kido et al. developed a unique model using mice deficient in inhibitory co-stimulatory molecule PD-1, in which thymectomy results in the reduction of Foxp3-positive T_{reg} cells and the subsequent development of human AIH-like hepatitis characterized by ANA production (44). In the spleen, CD4-positive T cells activated in the absence of regulatory mechanisms differentiate into T follicular helper (T_{FH}) cells, which activate B cells to promote IgG production and induce ANA production (45). These T_{FH} cells also migrate from the spleen to the liver in response to chemokines via the "CCR6-CCL20 chemokine receptor system" and play a role in AIH induction (45). In the model of fulminant AIH, IL-18-producing dendritic cells and the "CXCR3-CXCL9 system" have been shown to be involved in the development of AIH (46). The effectiveness of splenectomy as a curative therapy has been suggested in this model of AIH (47, 48). Further analyses are needed to determine how accurately the model reproduces human AIH.

Diagnosis

1) Diagnostic criteria

In Japan, the diagnosis of AIH is made based on the Japanese diagnostic guidelines (Table 1) (9) and the revised international diagnostic criteria proposed by the International Autoimmune Hepatitis Group (IAIHG) (49). The Japanese diagnostic guidelines were developed in 2013 based on the results of a nationwide survey conducted in 2009 and recent research findings (4, 9). Major changes include the change in the definition of an increased IgG level from 2,000 mg/dL to 1.1 times the upper limit of normal and the inclusion of the response to treatment as a criterion for diagnosis. According to the guidelines, AIH may be diagnosed in patients in whom a liver biopsy cannot be performed due to an advanced age, hepatic failure or other reasons, although the liver histology should be assessed as often as possible given the importance of histological findings in diagnosing the condition.

The international diagnostic criteria proposed by the IAIHG include the revised international diagnostic criteria (1999) and simplified international diagnostic criteria (2008) (49, 50). It is important to understand the characteristics of both sets of criteria. The revised version is superior in terms of sensitivity and the ability to detect atypical cases with few typical findings, such as a positive autoantibody test and increased IgG level, whereas the simplified version has better specificity and is useful for differentiating true AIH from AIH-like conditions and determining the appropriateness of steroid therapy (9, 51). Taken together, the re-

Table 1. Diagnostic Guide in Japan (2013).

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- 1 Exclusion of other, known, specific causes of liver injury.
 - 2 Presence of serum ANA or ASMA.
 - 3 High serum immunoglobulin G levels (>1.1 times the upper limit of normal).
 - 4 Histological features such as interface hepatitis and/or plasma cell infiltration into the portal area.
 - 5 Excellent response to corticosteroid treatment.
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A typical case of AIH: should fulfil criterion 1 and at least three of the remaining criteria.

An atypical case of AIH: should fulfil criterion 1 and one or two of the remaining criteria.

Adapted from Onji M, et al. Hepatol Res 2014;44:368-370

Table 2. Two Types of Autoimmune Hepatitis Presentation.

1 **Acute exacerbation phase** in which patients show clinical features of acute hepatitis with histological evidence of chronic hepatitis, such as the presence of fibrosis and moderate to severe inflammatory cell infiltration in the portal tracts.

2 **Acute hepatitis phase** in which patients exhibit histological features of acute hepatitis, such as centrilobular necrosis, without or with minimal periportal hepatitis. These patients sometimes show lower serum levels of IgG, and/or the absence or low titers of serum autoantibodies. Some patients may exhibit histological features of transition to chronicity.

Adapted from Onji M, et al. Hepatol Res 2011;41:497

vised version is effective for diagnosing the condition, whereas the simplified version is helpful in daily clinical practice and should be carefully applied when diagnosing atypical cases.

2) Acute presentation

Some patients with AIH exhibit a clinical course and liver function test patterns of acute/severe hepatitis or acute liver failure (fulminant hepatitis and late-onset liver failure). A nationwide survey also identified a substantial proportion of histologically confirmed acute hepatitis cases (95/871, 10.9%) (4). Acute presentation is histologically characterized by portal fibrosis and moderate to severe inflammatory cell infiltration and consists of the acute exacerbation phase and acute hepatitis phase, which are characterized by acute exacerbation of chronic liver disease and findings indicative of acute hepatitis, respectively (Table 2) (52). Some patients in the acute hepatitis phase show lower serum levels of IgG and negative autoantibody test results, which make confirming the diagnosis difficult (9, 53). The possibility of AIH should always be considered when treating patients with acute hepatitis of an unknown cause.

Diagnosing the acute hepatitis phase of AIH is not easy, although centrilobular necrosis (CN) is frequently observed on liver histology in patients with an acute presentation (54-57). CN itself is a nonspecific finding observed in cases of drug-induced hepatic injury, heart failure, acute viral hepatitis or ischemia and not a histopathological finding

of AIH. According to a review by Takahashi et al., CN is found at a frequency of 53-100% in cases of acute hepatitis of AIH, and CN without portal inflammation is particularly characteristic in the acute hepatitis phase of AIH (53). In addition, in some cases of AIH with an acute presentation, heterogeneous low-density areas are observed on plain CT scans and can be used to differentiate the disease from acute hepatic failure of other causes (57, 58).

Since delayed diagnosis and treatment in severe cases is associated with a poor prognosis, the severity grading (Table 3) proposed by the subgroup of the Intractable Hepato-Biliary Disease Study Group in Japan should be followed when making the diagnosis in order to provide prompt treatment. Patients diagnosed with a moderate status on the severity grading may also be referred to a specialist if severe jaundice or a prothrombin time of less than 60% of normal is noted (9). In order to estimate the utility of the severity grade, further prospective studies are needed.

3) Hepatitis C virus (HCV)-positive AIH

Positivity for HCV complicates the ability to differentiate between chronic hepatitis C complicated by AIH and that associated with autoimmune phenomena. Cases involving combined AIH and HCV infection may be identified as uncertain, as such cases are not definitively diagnosed according to the revised diagnostic criteria by the IAIHG. These criteria are not intended to diagnose AIH complicated by chronic hepatitis C.

Table 3. Severity Grading.

Clinical signs
1 Hepatic encephalopathy
2 Reduction or disappearance of hepatic dullness
Clinical laboratory tests
1 AST/ALT of more than 200 U/L
2 Bilirubin of more than 5 mg/dL
3 Prothrombin time of less than 60%
Imaging tests
1 Hepatic atrophy
2 Heterogeneous liver parenchyma pattern

Severe: should fulfill at least one of these three findings:

- 1) Clinical signs: 1 or 2
- 2) Clinical laboratory tests: both 1 and 3, or both 2 and 3
- 3) Imaging tests: 1 or 2

Moderate: should fulfil these findings:

- Clinical laboratory tests: one of the criteria (1, 2 or 3) or both 1 and 2, without clinical signs (neither 1 nor 2), and imaging tests (neither 1 nor 2)

Mild: none of the above criteria are observed.

Adapted from Onji M, et al. *Hepatol Res* 2014;44:368-370

Chrétien et al. found that 32% and 15% of 186 patients with chronic hepatitis C were positive for ANA and ASMA, respectively, with 8% positive for both autoantibodies and 13% exhibiting a titer of 1:320 or higher. The authors concluded that differentiation based only on the autoantibody status is not feasible (59). The lack of findings differentiating between AIH with concurrent HCV infection and typical AIH has also been reported in Japan (60). Chronic hepatitis C with positive anti-liver/kidney microsomal-1 (LKM-1) antibodies, as observed in type II AIH cases, may be attributed to molecular mimicry and not the co-existence of AIH (61).

Histology provides important information for differentiating between the two conditions. Czaja et al. proposed that type C chronic hepatitis complicated by AIH may be divided into autoimmune-predominant and viral-predominant types, which are characterized by moderate to severe interface hepatitis with plasma cell infiltration and severe steatosis, biliary damage and extensive lymphocyte accumulation in the portal region, respectively (62). However, Badiani et al. reported that severe interface hepatitis is also observed in approximately 5% of patients with chronic hepatitis C (63). Therefore, the diagnosis of HCV-positive AIH should be made based on comprehensive data, including the results of diagnostic scoring systems, the autoantibody status and liver histology findings.

4) Autoantibodies

Various autoantibodies have been detected in patients with AIH. In particular, ANA, ASMA and anti-soluble liver antigen/liver pancreas (anti-SLA/LP) antibodies are conventionally known. Recently, Zhang et al. reported the findings of a

meta-analysis regarding the diagnostic value of these autoantibodies in the diagnosis of AIH (64). The authors showed that ANA provides moderate sensitivity and specificity, whereas ASMA yields moderate sensitivity and high specificity. On the other hand, anti-SLA/LP exhibits low sensitivity and high specificity. In addition, it has been reported that a high titer of ASMA correlates with the disease activity (65).

The utility of several autoantibodies, including anti-programmed cell death-1 (anti-PD-1) antibodies and anti-phosphoenolpyruvate carboxykinase 2 (PCK-2), has been reported in Japan (66-68). Serum anti-PD-1 antibodies show high specificity for AIH and have been reported to be useful for differentiating AIH from drug-induced liver injury (69). In addition, anti-HLA class II antibodies are frequently detected in patients with AIH, and the presence of the antibody for self HLA class II alleles was recently confirmed for the first time, suggested to be associated with the acceleration of liver injury (70).

However, antibodies with high sensitivity specific for AIH have not yet been discovered, and future studies are therefore warranted.

Conclusion

After reviewing current trends concerning AIH in Japan, we determined that further efforts are needed to address several unresolved issues. Based on the understanding of differences in the clinical features of AIH between Japanese and Caucasian patients, these issues include the management of an acute presentation and pediatric AIH and identifying patients who do not require treatment.

The authors state that they have no Conflict of Interest (COI).

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