**Table 4** Shared epitopes in AIH [19, 20]

| Allotype | Allele | 26 | 67–72 | 74 |
|---|---|---|---|---|
| HLA-DR3 | DRB1*0301 (White) | Y | LLEQKR | R |
| HLA-DR4 | DRB1*0401 (Europe, North America) | F | LLEQKR | A |
| | DRB1*0405 (Japan, China, Argentina) | F | LLEQRR | A |
| | DRB1*0404 (Mexico) | F | LLEQRR | A |
| HLA-DR13 | DRB1*1304 (Brazil) | F | ILEDER | A |
| | Most Pts followed by Hep A infection | | | |

additional disease susceptibility and onset mechanism of AIH are currently being conducted based on a genome-wide association study, and the results are awaited.

## Differences in clinical manifestations

It has become known that differences in disease susceptibility affect clinical manifestations, especially response to treatment.

As shown in Table 5, response to treatment is poorer in AIH patients positive for HLA-DR3 compared with those positive for HLA-DR4, and the recurrence rate after treatment is also higher in the former patients. This is also reflected in the slight differences in standard therapy shown by regional treatment policies, guidelines, etc. In UK and the USA, where a lot of HLA-DR3-positive patients exist, the administered dose of adrenocorticosteroids is large in the early phase of treatment, and concurrent use of azathioprine is a standard practice. In Japan, where health insurance issues exist, single-drug therapy with an adrenocorticosteroid is mainly performed at the beginning, and the initial dose is as low as 30–40 mg/day according to the nationwide survey conducted in 2010 [9]. Even in UK and the USA, which have AIH patients positive for both HLA-DR3 and -DR4, we think that these differences should be considered for treatment policies if determination of disease-susceptibility genes becomes routinely available in the future. However, attention should be paid to individual differences in response to treatment among HLA-DR4 carriers, the disease-susceptibility gene found in AIH patients in UK, the USA, and Japan. This difference may be attributable to alleles DRB1*0401 and DRB1*0405. Moreover, genes associated with AIH onset other than HLA, such as cytotoxic T lymphocyte-associated antigen-4 and tumor necrosis factor-α 2, besides their single nucleotide polymorphisms (SNPs), have been reported. However, it has also been found that SNPs vary in UK, the USA, and Japan (data not shown).

Despite the differences in response to treatment, no marked difference has been observed in laboratory findings at onset. Although we have not found any report on histological findings in studies focused on disease-susceptibility genes, the findings presented by IAIHG have been used worldwide without any problem. Given that no inconsistency has been pointed out in Japan either, there may be no histological differences.

**Table 5** Clinical differences among HLA-DR allotype

| | DR3+[a] | DR4+[a] | Japanese DR4+[b] |
|---|---|---|---|
| No. of Pts | 41 | 44 | 66 |
| Age (Ave ± SD) | 38 ± 3 | 51 ± 2 | 49 ± 13 |
| M:F | 1:22 | 1:7.8 | 1:12 |
| ALT (U/L) | 428 ± 52 | 568 ± 68 | 326 ± 402 |
| IgG (g/dl) | 2.7 ± 0.2 | 3.3 ± 0.2 | 2.5 ± 1.0 |
| ANA (%) | 65.8 | 79.5 | 90.9 |
| AMA (%) | 75.6 | 90.9 | 53.7 |
| Therapy response (%) | | | |
| Good | 13.2 | 12.5 | 83.3 |
| Fair | 63.2 | 85.0 | 10.4 |
| Re-bout | 50.0 | 72.5 | 6.3 |
| None | 31.6 | 10.0 | 0 |

[a] Czaja et al. (1993) Gastroenterology 105:1502

[b] Data from Jikei University in the same year (not published)

**Table 6** Concurrent immunologic disorder in AIH [13]

| | Europe | | | Asia |
|---|---|---|---|---|
| | England | France | Austria | Japan |
| AIH type 1 | Thyroid 9% | PSC 5% | Sicca | Thyroid 9.2% |
| | RA 2% | UC 4% | Thyroid | SJS 7.2% |
| | NIDDM 6% | Crohn 5% | | RA 2.8% |
| | IDDM 1% | SJS 5% | | |
| | IBD 1% | RA 5% | | PBC 1.9% |
| | | Scleroderma 1% | | |
| AIH type 2 | | Vitiligo 7% | | Thyroid |
| | | IDDM 3% | | |
| | | Graves 2% | | |

In Japan nationwide study (2010) 27.4% pts (284/1,037) showed other autoimmune disorder, and frequency in female is significantly high (<0.0001)

On the contrary, differences have been noted when other autoimmune diseases are present as it is often observed with autoimmune diseases in several countries (Table 6) [13]. However, because the frequencies of complicated autoimmune diseases vary among countries, at present it is difficult to clarify the relationship between this difference in response to treatment and the pathology.

## AIH in the Asian Pacific countries

Though the nationwide survey of AIH was not reported from the Asian Pacific countries except Japan, several studies of hospital-based survey of AIH were reported from several Asian Pacific countries (Table 7).

Gupta et al. [21] reported 39 cases of AIH diagnosed at their hospital in India from 1992 to 1999. That was the first report of the survey of AIH from India and Asian Pacific countries except Japan. They revealed that percentage of AIH in the whole liver disease was 2.9%. Eighty percent of them were Type 1 AIH and there was no LKM-1 positive patient. Average age at onset was 31 years and male:female ratio was 1:3. Unfortunately, 76% of the patients had liver cirrhosis at the time of diagnosis. Another three studies were reported from India [22–24]. Those reports disclosed that AIH patients in India were younger (average age at onset was below 50 years in all studies) compared with other Asian Pacific countries. The interesting point observed in the reports from India was higher frequency of AIH in the autoimmune liver diseases. The percentage of AIH in whole autoimmune liver diseases including PBC and PSC was around 80%. Three out of four studies presented same tendency.

The study from Singapore [25], which analyzed 24 cases of AIH who were diagnosed within 6 years, clarified that all of them were Type 1 AIH, average age at onset was 57 years and male:female ratio was 1:11. Though 42% of them had liver cirrhosis at the time of diagnosis, the response to corticosteroid therapy was good and 89% of treated patients became remission. However, 61% of the patients showed relapse after discontinuing of therapy. The survival rate at 5 years was 71%.

Two studies were reported from Taiwan [26, 27]. The previous study, which analyzed 22 cases of AIH who were diagnosed from 1990 to 2000, showed that average age at onset was 64 years and male:female ratio was 1:2.1. Twenty-three percent of the patients had liver cirrhosis at the presentation. Though most of the patients received low dose of corticosteroid (average initial dose was 20 mg/day), the remission rate was good at 87.5%. However, 50% of the patients showed relapse after discontinuing the therapy. The latter study analyzed 48 cases diagnosed from 2000 to 2004. All of them were Type 1 AIH. The average age at onset and male:female ratio was almost same compared with previous study. The survival rate at 5 years was 85%. It is of particular interest that the number of AIH cases reported by latter study increased twice compared with previous study though the survey period was shorter in latter study. As we mentioned above, the number of AIH cases increased compared with previous survey in Japan and same tendency was observed also in Taiwan. There is a possibility that the number of AIH cases increase in the Asian Pacific countries in near feature.

The report from Korea also presented the same clinical manifestation as reported from other Asian Pacific countries [28]. The study, which analyzed 86 cases of AIH who were diagnosed from 1994 to 2008, revealed that they are all Type 1 AIH, average age at onset was 51 years, and male:female ratio was 1:5.1. Most of them responded to corticosteroid therapy well and 83.7% of them became remission. The relapse rate was 54.1%. The survival rate at 5 years was 91.2%.

Though there was no comment about the ethnicity of the patient, the report from Australia also presented the same clinical manifestation as other Asian countries presented [29]. The analysis of 42 cases made clear that they are all

**Table 7** Clinical manifestation of AIH in Asian Pacific countries [24–30]

| Country | Reported year | Number of cases | Survey duration | Type 1 AIH (%) | Age at onset | M/F | LC at presentation (%) | Remission rate | Relapse rate | 5 year survival | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| India | 2001 | 39 | 1992–1999 | 80 | 31 | 1/3 | 76.0 | | | 75.0 | [18] |
| Singapore | 2001 | 24 | 1990–1996 | 100 | 57 | 1/11 | 42.0 | 89.0 | 61.0 | 71.0 | [22] |
| Taiwan | 2002 | 22 | 1990–2001 | | 64 | 1/2.1 | 23.0 | 87.5 | 50.0 | | [23] |
| India | 2003 | 50 | 1995–2001 | 98 | 48 | 1/6 | 20.0 | | | | [19] |
| India | 2005 | 38 | 1999–2002 | 92 | 36 | 1/4 | 34.2 | | | | [20] |
| Taiwan | 2006 | 48 | 2000–2004 | 100 | 58 | 1/3.4 | 35.0 | | | 85.0 | [24] |
| India | 2007 | 79 | 1997–2003 | 79 | 44 | 1/2.3 | | 71.0 | | | [21] |
| Korea | 2010 | 86 | 1994–2008 | 100 | 51 | 1/5.1 | 13.0 | 83.7 | 54.1 | 91.2 | [25] |
| Australia | 2010 | 42 | | 100 | 53 | 1/3 | 24.0 | 67.0 | | | [26] |

type 1 AIH, average age at onset was 53 years and male:female ratio was 1:3. The remission rate was 67%.

All of these reports revealed that AIH of Asian Pacific countries share the similar clinical manifestation which is different from those of UK and the USA. The frequency of Type 2 AIH and younger patients were quite low and most of the patients showed a good response to corticosteroid therapy with mild dosage.

## HLA that is Susceptible for AIH in the Asian Pacific Countries

As we mentioned above, HLA that is susceptible for AIH is different compared with UK, USA, and Japan. It is of interest to know whether such difference is also observed when compared with UK, USA, and other Asian Pacific countries. However, only a limited number of the studies for HLA responsible for AIH are reported from Asian Pacific countries up to now (Table 8).

The study from Turkey which analyzed 17 AIH patients revealed that 29.4% of patients had HLA-DR3 and 58.8% of patients had HLA-DR4 in Turkey [30]. However, those frequencies were not significantly increased in patients compared with control. Though there was no significant different, HLA-DR3-positive patients showed higher serum bilirubin and IgG compared with HLA-DR4-positive patients. Eighty percent of HLA-DR3 positive patients presented with cirrhosis and all of HLA-DR4-positive patients showed the mild clinical course. These clinical profiles are similar to those of Western countries and Japan as we mentioned above. The differences were found in age and response to therapy. HLA-DR3-positive patients were older compared with HLA-DR4-positive patients and no difference of the response to therapy was observed between HLA-DR3- and HLA-DR4-positive patients in Turkey.

The study from Taiwan which analyzed 22 AIH patients made clear that HLA-DQ5 was found in 50% of patients and that was the only HLA phenotype which was proved to be statistically significant in comparison with control. This is the unique phenotype which was not recognized as susceptible gene for AIH in Western countries and Japan. Though there was no significant increase in frequency in patients compared with control, HLA -CW7 (50%), HLA-A11 (55%), and HLA-DR4 (36%) were more frequent in patients. Interestingly, a lack of association with phenotypes HLA-A1, -B8, and -DR3, which are prevalent in Western countries, was noted in Taiwan as well [27].

The study from Korea which analyzed 62 AIH patients tried to identify the specific HLA alleles that are susceptible to AIH by using sequence-based typing [31]. At first, they revealed that only HLA-DQ4 was significantly linked with AIH. Both HLA-DR3 and -DR4 had not any association with AIH though their frequencies were relatively higher in patients when compared with control. The frequency of HLA-DQ3 was relatively reduced in patients when compared with control. High-resolution analysis of class II HLA revealed significantly increased frequency of DRB1*0405, which was also significantly increased in Japan, and DQB1*0401 allele in patients compared with controls. DRB1*0301, which is the most frequently observed allele in Western AIH patients, was not correlated to AIH and another most frequently observed allele DRB1*0401 was absent in both patients and control. The six amino acid motif represented by the single letter code LLEQRR or LLEQKR at positions 67–72 of the DR$\beta$polypeptide, which were identified in Western countries, South American countries and Japan, was not sufficient to show an increased risk for AIH. Interestingly, the QRRAA motif at positions 70–74 was significantly increased in Korean patients.

These results clearly show that HLA that is susceptible for AIH is different compared with UK, USA, and Asian Pacific countries. Each Asian Pacific country has its own susceptible gene for AIH and HLA-DR4 was not a common susceptible gene among Asian Pacific countries though its frequency was relatively higher in AIH in several countries. Since the number of the patients enrolled in the studies was not enough, further study should be projected by increasing the number of the patients to identify susceptible HLA for AIH, which might be common in Asian Pacific countries.

**Table 8** HLA that is susceptible for AIH in Asian Pacific countries

| | Turkey [27] | | | Taiwan [24] | | | Korea 28 | | |
|---|---|---|---|---|---|---|---|---|---|
| | AIH | Control | *p* | AIH | Control | *p* | AIH | Control | *p* |
| *n* | 17 | 110 | | 22 | 81 | | 62 | 154 | |
| DR3 | 29% | 36% | ns | | | | 9% | 5% | ns |
| DR4 | 59% | 44% | ns | 36% | 22% | ns | 48% | 34% | ns |
| DQ3 | | | | | | | 46% | 66% | ns |
| DQ4 | | | | 14% | 11% | ns | 44% | 20% | 0.002 |
| DQ5 | | | | 50% | 25% | 0.034 | | | |

Data and problems of the recent nationwide survey done in Japan

The nationwide survey conducted in Japan in 2010 showed an increase in the age of patients at the time of AIH diagnosis. This disease is generally asymptomatic. When hepatic disorder is detected by chance through a blood test, AIH is diagnosed by excluding the known factors of the disorder and the presence of elevated autoantibodies titers, including ANA and serum immunoglobulin G. In Japan, where blood tests are frequently conducted for the health-care of elderly women, asymptomatic AIH may be detected in this way in the future. While older age is a factor to consider because of osteoporosis caused by adrenocorticosteroids, cosmetic issues also become problems for maintaining good treatment compliance because many elderly patients and young patients are women. Although the use of budesonide, a second-generation steroid causing fewer adverse reactions, is one of the solutions, it has not been listed in the Japanese pharmacopeia yet. Moreover, no clear evidence of the efficacy of steroids has been obtained.

One of the changes revealed by this survey is the decrease in serum ANA titer. IAIHG sets indirect fluorescent antibody technique using fresh-frozen sections of rodent liver, kidney, and stomach as the mainstay procedure to determine ANA [32]. The guidelines recently developed by the American Association for the Study of Liver Diseases (AASLD) [33] also recommend this technique. However, the number of institutions where ANA is determined at the laboratory level is extremely limited. The fact is that most institutions outsource ANA tests to commercial laboratories. In addition, they never use fresh-frozen sections. Instead, indirect fluorescent antibody technique is mostly performed using a kit of HEp-2 cells. The ANA test using HEp-2 cells is more sensitive than using fresh-frozen sections. In the survey done in Japan, most of the tests were conducted with HEp-2 cells. Consequently, AIH may have been diagnosed in patients with low titers. Yet, in our recent study with serum from the same AIH patients, there was no significant difference between antibody titers determined by using HEp-2 cells and fresh-frozen sections [34]. Thus, a decrease in ANA titer with aging may be a recent trend. This is a factor that complicates the diagnosis of AIH; thus, establishment of a more specific diagnostic method is an issue to be resolved. Meanwhile, it should be noted that enzyme-linked immune absorbent assay with solid-phase antigens that are widely used for autoimmune diseases including systemic LE has markedly poor sensitivity for ANA in case of AIH [23]. This finding suggests that there may be antigenic determinants in AIH different from those found in common autoimmune diseases. In regard to the methods to determine ANA, further investigations including standardization are important. If ANA were negative, liver–kidney microsomal antibodies would be of diagnostic value; however, these antibodies are rare in Japan especially in positive cases [13].

## Summary

We have reviewed the differences in AIH between cases in UK and the USA, and those in Asian Pacific countries, especially in Japan. We have also mentioned diagnostic problems that should be solved in the future. It should be noted that the number of patients diagnosed with AIH is increasing in Japan where the frequency has been considered low and also the number of male patients is increasing. In the future, AIH will be more important as a component of chronic hepatitis and studies on the pathology of AIH will provide us with extremely important findings suggesting the mechanism of immunological liver cell damage. As Czaja [35] has pointed out, further clinical development from conventional diagnosis by exclusion to that by inclusion as immunological hepatic disorder is widely expected.

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***Review Article***

# Acute presentation of autoimmune hepatitis: Does it exist? A published work review

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Autoimmune hepatitis (AIH), initially called chronic aggressive hepatitis, is conceptually classified as a primary chronic disease; periportal fibrous expansion and periportal infiltration of mononuclear cells, including plasma cells, have also been considered to be histologically important diagnostic signs of AIH. However, several manuscripts which reported the acute presentation of AIH have been published recently and the reported cases of acute presentation in these manuscripts contained two different clinical entities. One is acute exacerbation of chronic AIH (acute exacerbation form) and the other is genuine acute AIH without chronic histological changes (acute form). It is clinically important to distinguish the acute form from the acute exacerbation form. The reports of the acute form revealed that the existence of centrilobular necrosis without chronic changes was the most important histological finding related to the acute form. Because the elevation of serum levels of immunoglobulin G and antinuclear antibody are not observed in some acute presentation AIH patients, the physician may not consider AIH when they encounter such patients. Therefore, it is very important to bear in mind a possibility of acute presentation AIH when the physician encounters patients with hepatic dysfunction of unknown cause because it became clear that delay of the diagnosis and start of therapy lead to the poor prognosis of AIH. In this review, we outline the current state of acute presentation of AIH including the genuine acute form based on the published clinical studies and case reports.

**Key words:** acute exacerbation form of chronic autoimmune hepatitis, acute form of autoimmune hepatitis, acute presentation of autoimmune hepatitis, autoimmune hepatitis, centrilobular necrosis

## DOES ACUTE PRESENTATION OF AUTOIMMUNE HEPATITIS (AIH) EXIST?

SINCE LEFKOWITCH *ET AL.* first reported a case of "acute" AIH in 1986,[1] 20 case reports and nine clinical studies of acute presentation of AIH have been published (Table 1). Those reports and studies revealed that the cases with acute presentation of AIH showed the presence of recent onset (<30 days) without previous history of liver diseases, remarkable clinical symptoms (e.g. jaundice, fatigue, fever, nausea, general malaise), marked alternation in serum liver tests (serum level of alanine aminotransferase was higher than fivefold the upper normal limit and bilirubin level was >2 mg/dL) and most importantly, virus infection, drug-induced hepatitis and other causes were ruled out.

Ferrari *et al.* conducted a prospective study of 86 patients with AIH whose clinical onset was similar to that of acute viral hepatitis; they reported that out of 86 AIH patients, 59 (68%) presented with the chronic pattern, 22 (26%) with the acute pattern, and five (6%) were asymptomatic.[4] Krawitt *et al.* reported that 26% of all cases of AIH were of acute onset.[11] In a Japanese nationwide survey study, 5.6% of patients with AIH were found to have a feature of acute hepatitis upon histological examination.[12] The most recent Japanese nationwide survey study of AIH which was performed in 2009 revealed that the percentage of acute hepatitis had increased to 10.9%. These reports suggested the existence of genuine acute AIH which has no chronic histological changes.

The problem we have to solve first is the confusion of the terms which were used in these manuscripts. As Ferrari *et al.* reported,[4] acute presentation of AIH seems to contain two different types of clinical entities. One is

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**Table 1** Comparison of laboratory data between acute presentation of AIH and chronic AIH

| Year | Country | Acute (*n*) | Total (*n*) | Biochemical data† | ANA† | IgG† | Pathological findings | Ref |
|---|---|---|---|---|---|---|---|---|
| 1994 | USA | 12 | | | | | Severe lobular hepatitis | 2 |
| 2003 | Japan | 9 | 38 | Higher ALT | | lower | CN (76%) | 3 |
| 2004 | Italy | 22 | 86 | Higher ALT, TB | | | CN (87%) | 4 |
| 2006 | Austria | 47 | 114 | Higher ALT, TB | | | | 5 |
| 2006 | Italy | 27 | 73 | Higher ALT, TB, γ-GTP lower PT | | | | 6 |
| 2007 | Japan | 23 | 77 | | lower | | CN (100%) Plasma cell infiltration (100%) | 7 |
| 2008 | Japan | 9 | | Higher ALT, TB, γ-GTP | | lower | | 8 |
| 2008 | Japan | 7 | | Higher ALT, TB | lower | lower | CN (100%) Plasma cell infiltration (100%) | 9 |
| 2010 | Japan | 53 | 176 | Higher ALT, TB | lower | | CN (53%) | 10 |

†Compared with chronic AIH.
AIH, autoimmune hepatitis; ALT, alanine aminotransferase; CN, centrilobular necrosis; IgG, immunoglobulin G; PT, protrombin time; TB, total bilirubin; γ-GTP, γ-glutamyltransferase.

acute exacerbation of chronic AIH and the other is genuine acute AIH which has no chronic histological changes. However, acute presentation of AIH was called by several different terms such as acute onset, acute form and acute type. Acute exacerbation of chronic AIH and genuine acute AIH were called by several different terms as well. In this review, we define the acute onset of AIH as "acute presentation", acute exacerbation of chronic AIH as "acute exacerbation form" and genuine acute AIH as "acute form".

## CLINICAL PROFILE OF ACUTE PRESENTATION OF AIH

FERRARI *ET AL.* REPORTED that patients of acute presentation of AIH had higher serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin ($P < 0.0001$).[4] With respect to age and serum levels of alkaline phosphatase, γ-glutamyl transpeptidase (γ-GTP), albumin or γ-globulin, there were no differences between acute presentation of AIH and so-called chronic hepatitis-like AIH. Furthermore, the prevalence of moderate or severe (vs mild) histological findings and liver cirrhosis was similar among the acute, chronic and asymptomatic patterns of AIH. When compared with controls with acute viral hepatitis, the patients of acute presentation of AIH were more often female (82% vs 24%, $P < 0.0001$) and had higher serum γ-globulin levels (26.9 vs 13.4 g/L, $P < 0.0001$) and AST/ALT ratio (1.20 vs 0.61, $P < 0.0001$).

Anther previous report has stated that there are no differences in sex, age of disease onset, type of human leukocyte antigen (HLA) or immunoserological indices between cases with acute presentation of AIH and cases with the chronic form of AIH (Table 2).[13] Although clinical indices characteristic for the acute presentation of AIH remain unclear, Floreani *et al.* reported that the incidence of acute presentation of AIH is high among the elderly; however, because most of their patients responded well to the treatment and few were severe, these patients are highly likely to have had acute exacerbation of the disease.[6] On the contrary, Miyake *et al.* reported that patients of acute presentation of AIH with histological acute hepatitis were younger than those with histological chronic hepatitis though there was no age difference between acute presentation of AIH and chronic AIH.[10]

Blood chemistry tests reported in many studies have shown that acute presentation of AIH, as well as acute virus hepatitis, is associated with higher serum levels of ALT, AST and total bilirubin as compared with chronic AIH (Table 3). However, patients with acute presentation of AIH had a tendency to not present with an elevated immunoglobulin (Ig)G level that was characteristic of the usual AIH.[8,9]

In addition, some patients of acute presentation of AIH were associated with negativity of autoantibody including antinuclear antibody that was also characteristic of the usual AIH.[9,10] This phenomenon makes the diagnosis of acute presentation of AIH difficult because the presence of autoantibody and elevated serum IgG

**Table 2** Comparison of clinical features between acute presentation of AIH and chronic AIH

| | | Acute presentation | Chronic | *P* | Ref |
|---|---|---|---|---|---|
| Age | | 39.5 ± 20.2 | 44.2 ± 19.5 | NS | 4 |
| | | 56.0 ± 20.0 | 45.5 ± 15.0 | <0.05 | 6 |
| | | 54 (16–76) | 56 (18–79) | NS | 10 |
| Male : female (%) | | 18:82 | 12:88 | NS | 4 |
| | | 11:89 | 15:85 | NS | 6 |
| | | 13:87 | 13:87 | NS | 10 |
| HLA | DR3 | 37.5% | 35.0% | NS | 4 |
| | DR4 | 12.5% | 19.0% | NS | 4 |
| | | 69.0% | 70.0% | NS | 7 |
| | | 66.0% | 71.0% | NS | 10 |
| Histological findings (CN) | | 53% | 20% | <0.0001 | 10 |

AIH, autoimmune hepatitis; CN, centrilobular necrosis; HLA, human leukocyte antigen.

levels are defined as useful factors for the diagnosis of AIH according to the criteria proposed by the International Autoimmune Hepatitis Group (IAIHG)[14] and the recently introduced simplified criteria.[15] Therefore, these scoring systems are also unlikely to be helpful in the diagnosis of acute presentation of AIH.

On the contrary, it is a fact that many of the reported cases of acute presentation of AIH are regarded as the acute exacerbation form of chronic AIH. Okano *et al.* reviewed 29 Japanese patients with acute presentation of AIH, and they reported that many of these patients had acute exacerbation of chronic AIH and few patients showed the histological characteristics of acute presentation such as pericentral necrosis and sublobular necrosis.[3] Burgart *et al.* also investigated liver biopsy specimens within 6 months after the onset in 26 patients diagnosed with acute presentation of AIH, and they reported that 25 of the 26 cases showed the characteristics of chronic active hepatitis, such as periportal inflammatory cell infiltration, and interface hepatitis.[16] These reports indicated that even if the patient's condition presents with clinical features of acute presentation, it is histologically diagnosed as chronic hepatitis, actually supporting the theory that acute presentation of AIH is a potentially acute exacerbation form of chronic AIH.

However, as we summarize the case reports later, there are actually a certain number of AIH cases in

**Table 3** Comparison of laboratory data between acute presentation of AIH and chronic AIH

| | Acute presentation | Chronic | *P* | Ref |
|---|---|---|---|---|
| ALT (IU/l) | 25.3 × UNV | 9.4 × UNV | <0.001 | 4 |
| | 901.0 ± 579.7 | 368.5 ± 405.4 | <0.001 | 6 |
| | 864.1 ± 881.9 | 189.0 ± 207.6 | <0.001 | 7 |
| | 939 (109–2161) | 120 (23–1027) | <0.0001 | 10 |
| Bilirubin (mg/dL) | 7.9 ± 6.2 | 3.6 ± 5.9 | <0.001 | 4 |
| | 5.4 ± 6.0 | 1.4 ± 0.9 | <0.001 | 6 |
| | 9.5 ± 6.8 | 3.0 ± 4.5 | <0.01 | 7 |
| | 5.0 (0.6–29.2) | 0.8 (0.3–5.0) | <0.0001 | 10 |
| ANA (>1:40) | 73% | 61% | NS | 4 |
| | 96% | 90% | NS | 7 |
| | 89% | 98% | NS | 10 |
| IgG (mg/dL) | 1.64 × UNV | 1.75 × UNV | NS | 4 |
| | 2386.8 ± 685.8 | 2298.7 ± 1077.1 | NS | 6 |
| | 2023.1 ± 208.0 | 2827.2 ± 1039.6 | NS | 7 |
| | 2430 (724–4528) | 2568 (1085–4562) | NS | 10 |

AIH, autoimmune hepatitis; ALT, alanine aminotransferase; ANA, antinuclear antibodies; IgG, immunoglobulin G; UNV, upper normal value.

which there are no histological characteristics of chronic hepatitis or any clinical laboratory findings indicative of hypergammaglobulinemia or positive serum autoantibodies. Those patients may have the genuine acute form of AIH. The serious clinical problem is, as we mentioned above, the lack of characteristic findings of AIH that makes it difficult to diagnose the disease. A delay in the diagnosis leads to a delay in the initiation of treatment intervention, thereby precluding the prognosis of the patient. Therefore, the diagnosis of acute presentation of AIH needs to be further investigated because of its "difficult diagnosis".

## REVIEW OF THE REPORTED CASES OF ACUTE PRESENTATION OF AIH

THE CASE OF acute presentation of AIH has frequently been reported so far. Lefkowitch *et al.* first reported two AIH cases presenting histologically acute hepatitis.[1] Abe *et al.* and Hofer *et al.* reported cases of the clinically acute form of AIH not associated with typical characteristics of AIH, such as so-called periportal inflammation.[5,7] According to their reports, histological characteristics of the acute form of AIH were centrilobular necrosis (CN), none or mild inflammatory infiltration in the portal area and no portal fibrosis, and the serum γ-globulin or IgG concentrations in cases of the acute form of AIH were clinically often lower than those in cases of chronic AIH.

In 1997, Pratt *et al.* reported a case with AIH which responded well to corticosteroid therapy and had an autoimmune disorder. The pathological examination revealed that this case had CN, which is different from histological characteristics of typical AIH.[17] They ruled out drug-induced hepatic dysfunction that can cause CN and circulatory impairment in their patient, and proposed that the case of their patient should be regarded as a new histological feature of AIH. Similar reports were thereafter published by Singh *et al.* and Misdraji *et al.*; these reports revealed that some of the cases of AIH show CN as the major sign, but no evidence of histologically typical feature, namely, periportal cell infiltration, irrespective of nationality.[18,19] These reports revealed that cases of acute presentation of AIH with the characteristic pathological findings which contrast to chronic AIH existed truly.

The cases which we clinicians should pay attention to distinguishing from acute presentation of AIH were also reported. Patients with de novo AIH,[20] which has recently been attracting attention, present with so-called histological characteristics of the typical AIH, whereas patients with atorvastatin-induced AIH,[21] which has been reported as one of the drug-induced forms of AIH, mainly present with portal inflammation, which is different from those with acute presentation of AIH. Therefore, it is possible to differentiate acute presentation of AIH from these two types of AIH. There were some cases in which an initial diagnosis was acute presentation of AIH but the subsequent definitive diagnosis was hepatitis E virus infection.[22] These cases are reportedly associated with high serum IgG levels and high incidence of positive autoantibodies. On the other hand, some reports revealed that virus infection, such as hepatitis A[23] or Epstein–Barr virus,[24] leads the occurrence of the acute presentation of AIH. These findings suggested that it is important to definitively rule out infections with viruses known to induce hepatic dysfunction and think about the acute presentation of AIH when liver damage continues after the infection of such a virus is over.

## CN WITHOUT PORTAL INFLAMMATION: THE MOST IMPORTANT HISTOLOGICAL LIVER FINDING WHICH RELATES TO ACUTE FORM OF AIH

AS WE MENTIONED above, the acute presentation of AIH is most characterized by histological findings. Hofer *et al.* reported that CN, which is rare in patients with the usual AIH, can be characteristic of the acute presentation of AIH, although in rare cases.[5] The incidence of plasma cell infiltrations in both the periportal region and the central veins is reportedly higher in patients with the acute presentation of AIH than in patients with acute virus hepatitis. It is also said that biliary damage occurs at a high incidence in patients with the acute presentation of AIH.[8] Nikias *et al.* reported that lobular hepatitis is an important histological feature in AIH with an acute presentation.[2] Singh *et al.* suggested that the pattern of predominant centrizonal injury might be an early presentation of AIH according to sequential liver biopsy findings.[18] Furthermore, Abe *et al.* reported that the acute presentation of AIH can be histologically characterized by the presence of CN, none or mild inflammatory infiltration in the portal area, and no portal fibrosis.[7] Fujiwara *et al.* have recently analyzed liver biopsy specimens in 18 cases of acute presentation of AIH and revealed that the evidence of CN is the most useful for the diagnosis of acute presentation of AIH.[8,25] These reports revealed that CN was observed at high frequency (53–100%) in cases of acute presentation of AIH. Alhough we have to keep in mind that CN is also observed in other liver disease such

**Table 4** Histological findings of acute presentation of AIH

| CN (+)/PI (−) | CN (+)/PI (+) | CN (−)/PI (+) | Ref |
|---|---|---|---|
| 4% | 69% | 27% | [16] |
| 19% | 34% | 47% | [10] |
| 39% | 61% | 0% | [8] |
| Acute form | Acute exacerbation form | | |

AIH, autoimmune hepatitis; CN, centrilobular necrosis; PI, portal inflammation.

as acute viral hepatitis or drug-induced hepatic injury, CN seems to have a significant role for the diagnosis of the acute presentation of AIH.

On the other hand, Burgart *et al.* reported that only 4% of cases of acute presentation of AIH showed lobular hepatitis without portal inflammation, concluding that most patients with acute presentation of AIH had histological evidence of chronic hepatitis.[16] However, Miyake *et al.* reported that 19% of cases of acute presentation of AIH showed CN without portal inflammation, 34% showed both CN and portal inflammation and 47% showed portal inflammation without CN.[10] In addition, Fujiwara *et al.* reported that 39% of cases of acute presentation of AIH showed CN without portal inflammation and 61% showed both CN and portal inflammation (Table 4).[8] These findings indicated that it is possible to distinguish the acute form of AIH from the acute exacerbation form of AIH by checking the existence of both CN and portal inflammation. If only CN is observed without portal inflammation, the case may be the acute form of AIH but not the acute exacerbation form of AIH. Thus, CN without portal inflammation is considered to be the histological characteristic in the early stage of the acute form of AIH.

Taken together, there are difficult-to-diagnose cases of AIH with no histological findings characteristic of so-called typical AIH or no characteristic clinical laboratory findings, and many of these cases are considered to be associated with the presence of CN. That is, acute AIH associated with only CN can exist as a new disease entity because CN has not been listed in the conventional diagnostic guidelines or in the scoring system, and thus it becomes necessary to identify CN by liver biopsy as a diagnostic index. CN may become a new histological index for the diagnosis of acute presentation of AIH. In the future, an international collaboration study is necessary to confirm the utility of this important index by accumulating the number of patients.

However, necrosis around the central veins is also observed in patients with drug-induced hepatic injury (DILI). The only way to differentiate the acute presentation of AIH from DILI is to perform a detailed interview and take the patient's medication history. Recent studies have shown the involvement of so-called nonmedical products, such as health foods and food additives, in the occurrence of hepatic injury; therefore, it is extremely difficult to rule out these factors. Certain drugs are well-known to induce AIH. Thus, it is a great challenge to establish the way of differential diagnosis of DILI, acute hepatitis-like AIH and AIH originating from DILI.

## CASES PRESENTING WITH FULMINANT HEPATITIS AND ACUTE HEPATIC FAILURE

FULMINANT HEPATIC FAILURE is one of the most clinically important presenting forms of acute presentation of AIH. Since Motoo *et al.*[26] and Harzog *et al.*[27] first reported a case of severe subfulminant hepatic failure of acute presentation of AIH, nine case reports and nine clinical studies of such cases have been reported.

A recent nationwide study of Japan revealed that AIH should be regarded as an important factor for acute hepatic failure, particularly late-onset hepatic failure.[28] Among the cases of pediatric fulminant hepatitis reported in Turkey, 2.9% have been shown to progress from AIH.[13] Therefore, awareness of the acute presentation of AIH and its diagnosis are important even when the physician encounters a case of fulminant hepatic failure.

Yasui *et al.* reported that 25% of severe and fulminant acute presentation of AIH patients showed normal IgG levels and 29% of the patients showed negative or low titers of antinuclear antibody. However, most of those patients had CN which was frequently observed in acute presentation of AIH.[29] Very recently, the clinical and histological criteria of "autoimmune acute liver failure" was proposed and it revealed that its histological features are predominate in the centrilobular zone.[30] These reports indicated the importance of earlier liver biopsy to get the evidence of CN. In order to prepare the guidelines for therapeutic measures, the guidelines for diagnosis of acute presentation of AIH characterized by the presence of CN should be established.

Recently, Tufano *et al.* reported on female patients with fulminant AIH due to the 23q13 deletion syndrome, including a disruption of the *ProSAP2* gene known as the *Shank3* gene.[31] In their report, a typical AIH associated with periportal inflammation was diagnosed based on histological findings which were

different from those of acute presentation of AIH, but further studies are necessary to determine whether such histological findings are the risk factor for progressing to the serious disease.

## THERAPEUTIC MEASURES

SOME REPORTS HAVE stated that both patients with acute presentation of AIH and patients with the usual AIH respond well to corticosteroid (CS) therapy.[2,7] Other reports have described that acute presentation of AIH is more refractory to CS therapy than the usual AIH.[32] A poor response to CS therapy is generally inferred to be due to a delay in the start of therapy, particularly due to a delay in diagnosis. That report indicated that a low titer of antinuclear antibody and an elevated serum bilirubin level are associated with a poor response to CS therapy; however, most of these cases are rather attributed to a delay in the start of therapy due to a delay in diagnosis.[32] Reports accumulated to date have shown that patients with acute presentation of AIH associated with CN respond well to CS therapy. However, it remains unclear how acute presentation of AIH responds to CS therapy; one possible explanation for this is a delay in the start of treatment intervention due to difficult diagnosis.

Kaymakoglu *et al.* and Potthoff *et al.* reported that, even if no immunological abnormalities were observed in patients with serious hepatic dysfunction of unknown cause, CS therapy should be taken into consideration because it is effective in such patients.[33,34] Ichai *et al.* have shown CS therapy to be useful for the treatment of fulminant or acute presentation of AIH and suggested CS to be the drug of first choice for acute presentation of AIH as well as for the typical AIH.[35]

In case progressive hyperbilirubinemia continues during CS therapy, urgent liver transplantation should be considered. The Model for End-Stage Liver Disease (MELD) score has been reported to be useful in identifying patients who are likely to fail CS therapy and require liver transplantation. When MELD scores are over 12 points, treatment failure with CS therapy is strongly expected and preparedness for liver transplantation is needed.[36] The treatment period of CS therapy before the decision for or against liver transplantation is made should be no longer than 2 weeks.[37]

## CONCLUSION

ALTHOUGH AIH WAS formerly regarded as a type of chronic hepatitis, recent studies have revealed that not a few cases of AIH showed acute presentation and a certain percent of such cases are of the genuine acute form of AIH not associated with any histological characteristics of chronic hepatitis but develop as acute hepatitis.

It is clinically important to note that patients with acute presentation of AIH including the acute form do not always show the increase of the serum IgG level or positivity of autoantibody including antinuclear antibody that are typical features of the usual AIH. Therefore, existing diagnostic guidelines, scoring system or simplified criteria cannot be useful for the diagnosis of the acute presentation of AIH. This would greatly lead to a difficulty to diagnose. However, we clinicians should think about acute presentation of AIH when we encounter such patients because a delay in treatment intervention leads to poor prognosis and treatment resistance in AIH.

The difference of the immunological pathogenesis between the acute form of AIH and chronic AIH have not yet been made clear. As we mentioned in the review of case reports, some instances of the acute form of AIH could be induced by drugs or viral infection. These findings indicated that acute liver damage which induces the release of a great deal of liver antigens may be needed to develop the acute form of AIH in addition to the breakdown of the immunological tolerance which activates the autoreactive T cell that is commonly observed in chronic autoimmune diseases. There is a possibility that such an immunological context may be different between the acute form of AIH and chronic AIH.

In conclusion, when a physician encounters a patient with acute hepatitis or fulminant hepatic failure of unknown cause, he/she should bear in mind the possibility of acute presentation of AIH including the acute form of AIH and perform early liver biopsy and take appropriate therapeutic measures.

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Review

# Diagnostic Criteria for Autoimmune Hepatitis : Historical Review and Present Problems

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*ABSTRACT*

Autoimmune hepatitis (AIH) is a chronic hepatitis of unexplained etiology. Because no specific clinical marker has been identified, ruling out other liver diseases of known etiology is important when diagnosing AIH. The International Autoimmune Hepatitis Group (IAIHG) has prepared diagnostic criteria aimed at standardizing diagnosis. The IAIHG scoring system has been used extensively for diagnosing AIH. However, because this scoring system covers a variety of elements, using it at the bedside can be difficult. Recently, the IAIHG proposed simplified criteria system composed of only 4 elements which reportedly has excellent diagnostic capabilities. Problems have also been identified in assays for serum autoantibodies. Although the IAIHG recommends the indirect immunofluorescent method with frozen sections of rodent liver, kidney, and stomach to check for autoantibodies involved in AIH, this method is now used at only a few institutions, and a enzyme-linked immunosorbent assay and a method with established cell lines are more widely used. In any event, the method for autoantibody detection must be standardized and quantified. Liver biopsy is important for diagnosis ; however, histological findings are not always specific. In this review we describe the history of the diagnosis of AIH and related problems. (Jikeikai Med J 2011 ; 58 : 89-93)

Key words : autoimmune hepatitis, diagnostic criteria, autoantibody

## INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic hepatitis of unexplained etiology. It has been strongly suggested that autoimmune mechanisms are intimately involved in the onset and progression of AIH[1] Clinically, AIH has been characterized by elevated serum levels of gamma-globulin or immunoglobulin (Ig)G ; the presence of autoantibodies, e.g., antinuclear antibodies (ANAs) and anti-smooth muscle antibodies ; histological signs of highly active chronic hepatitis ; and an abundance of plasma cells among infiltrating cells. However, these signs and findings are not always specific to AIH but are also seen in cases of viral hepatitis and drug-induced liver injury. To date, no clinical marker specific to AIH has been identified. For this reason, ruling out other liver diseases of known etiology is important in the diagnosis of AIH, as well as checking for the above-mentioned clinical manifestations. Furthermore, because cases of AIH can be atypical, e.g., complicated by or overlapping with other autoimmune diseases or autoimmune liver diseases[2], the diagnosis of AIH becomes more difficult. Because a delay in the diagnosis of AIH can lead to a delay in the start of treatment and a poor prognosis, prompt diagnosis is essential. Patients with AIH, particu-

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larly Japanese patients with AIH, usually respond well to corticosteroid therapy, and a definite diagnosis of AIH can be made in suspected cases by evaluating the responses to corticosteroid therapy, i.e., therapeutic diagnosis. However, if AIH becomes severe because diagnosis has been delayed, the response to corticosteroid therapy can be unsatisfactory. Therefore, the early, definite diagnosis of AIH is important.

## GENETIC FACTORS RELATED TO DIAGNOSIS

Some persons have increased genetic susceptibility to AIH. Genes reported to confer increased susceptibility to AIH include human leucocytes antigen (HLA)-DR4 for Japanese people[3] and HLA-DR3 for people in Europe and the United States[4]. Because HLA-DR3 is seldom found in Japanese people, the clinical features of AIH in Japan differ from those in Western countries. Subsequent studies have demonstrated that in HLA-DR3-free patients with AIH in Western countries HLA-DR4 serves as a second disease susceptibility gene and that the clinical features of AIH in HLA-DR4-positive patients in Western countries are similar to those of AIH in Japanese patients in that the prevalence among middle-aged women is high and responses to treatment are good[5]. Briefly, there are 2 susceptibility genes for AIH, and the clinical features of AIH differ slightly depending on the gene. Interestingly, subsequent studies have revealed that the peptide-binding site is similar for both HLA-DR3 and HLA-DR4[6]. Despite these findings, the target antigen for AIH has not been identified, and the etiology of AIH remains unclear. Nevertheless, the major clinical findings of AIH are similar in patients with HLA-DR3 and patients with HLA-DR4 and have allowed international diagnostic criteria to be established.

## DIAGNOSTIC SCORING SYSTEMS

Considering these findings, the International Autoimmune Hepatitis Group (IAIHG) has prepared diagnostic criteria aimed at standardizing the diagnosis of AIH and has proposed a highly convenient scoring system for the diagnosis of AIH[7]. Table 1 shows the brief history of the established criteria, with a focus on the criteria of the IAIHG. The scoring system, proposed in 1998, was aimed at eliminating, as far as possible, factors known to be involved in the onset of hepatopathy. This diagnostic system has enabled the pathophysiological assessment of AIH to be standardized, thereby establishing a firm basis for research on AIH. This scoring system has been extensively used as a means of diagnosing AIH[8]. If this scoring system were applied, most patients with AIH in Japan would receive diagnoses of suspected or definite AIH[9]. When the ratings based on this diagnostic system were reviewed in North America[10], Europe[11], and Japan[12] the sensitivity was 97% to 100% and the overall rate of accurate diagnosis was 89.8%. We may thus say that, by and large, a consensus has been reached regarding the validity of this scoring system.

However, because this scoring system aimed at standardizing the diagnosis of AIH covers a variety of elements, it can be difficult to use at the bedside. In addition, the diagnosis of AIH with this scoring system can be delayed owing to several problems, such as cases diagnosed as AIH despite low scores and the large number of criteria, including items for which data collection is difficult[13].

The IAIHG has recently proposed simplified criteria to facilitate clinical application[14]. The simplified criteria system includes only 4 elements (i.e., seropositivity for anto-antibodies, elevated serum levels of IgG, histological features, and ruling out viral infection responsible for liver damage) and has been reported to have excellent diagnostic capabilities, with a specificity of greater than 99% and a sensitivity of 81%. Because adequate follow-up assessments of the simplified criteria system have not been performed, we can draw no conclusions about it. The diagnostic capability of the simplified criteria system is reportedly low in atypical cases of AIH[15] and is insufficient in cases of acute-onset AIH[16]. However, the simplified criteria system appears to be useful for rapidly identifying typical cases of AIH and starting treatment on the basis on this rapid diagnosis. Katsushima et al. have reviewed 59 cases of AIH in Japanese patients using this new criteria system and found it simple to use and highly useful[17]. According to their report, the percentage of definite cases with the new scoring system was 74.6% and markedly higher than with the original revised scoring system (37.6%). We may, therefore, say that this set of criteria enables an early start to treatment and is of high clinical value for bedside use.

On the basis of the diagnostic criteria reported to date,

Table 1. Brief history of classification of autoimmune hepatitis by International autoimmune hepatitis Study Group (IAIHG)

| Year | IAIHG activities | Publications |
|---|---|---|
| 1967 | A classification of chronic hepatitis and advocated the term of autoimmune hepatitis | Mackay IR,Whittingham S. Postgrad Med 1987 ; 41 : 72-83. |
| 1992 | The first meeting at IASL Brighton<br>First IAIHG group chair : I. R. McFarlane 1992-2006 followed by D Vergani (2006-) | JohnsonPJ, McFarlane IG, and IAIHG members. Hepatology 1993 ; 18 : 998-1005. |
| 1994 | IASL Meeting Cancun : Classification of chronic hepatitis | Desmet V, Gerber B, Hoofnagle J, et al. Hepatology 1994 ; 19 : 1513-20. |
| 1998 | AASLD : IAIHG Report : Review of criteria for diagnosis of autoimmunehepatitis<br>Scoring system was firstly proposed involving descriptional criteria<br>Many papers have been published for evaluating this score system | Alvarez F, Berg PA, Bianchi L, et al. J Hepatol 1999 ; 31 : 929-38. |
| 2004 | IAIH serology<br>In this paper, rodent frosen tissue should be uused for detecting ANA | Vergani D, Alvarez F, Bianchi FB, et al. J Hepatpl 2004 ; 41 : 677-83. |
| 2005 | AASLD : Simplified scoring system | Abstract only |
| 2008 | Simplified Criteria | Hennes EM, Zeniya M, Czaja AJ, et al. Hepatology 2008 ; 18 : 169-76. |
| 2009 | Pediatric autoimmune hepatitis | Mieli-Vergani G, Heller S, Jara P, et al. J Pediatr Gastroenterol Nutr 2009 ; 49 : 158-64. |

liver biopsy is indispensable. Histological features of AIH include interface hepatitis with plasma cell infiltration, hepatocyte rosette formation, and emperiporesis. However, none of these features are specific for AIH, and making a definitive diagnosis of AIH is difficult on the basis of liver biopsy findings alone. However, liver biopsy is useful for ruling out other diseases for the differential diagnosis of AIH. Another problem with the simplified criteria system is confusion about how to incorporate these characteristic pathological features into the diagnosis. The criteria fail to describe in detail about when the presence of pathologically typical features may be affirmed (e.g., when all findings presented are typical or when at least 2 of the presented findings are typical). According to our empirical rules, the finding of interface hepatitis accompanied by at least one of the typical pathological features of AIH (hepatocyte rosette formation, plasma cell infiltration, and emperiporesis) will justify affirmation of the presence of pathologically typical features, and all findings need not be typical. However, the validity of this empirical approach is not assured because the criteria do not clearly specify how pathological findings should be selected. Further review of this point for verification is essential. Because a fundamental step in the diagnosis of AIH is to rule out other diseases similar to AIH (diagnosis by exclusion), liver biopsy is useful. However, difficulties can be encountered when attempting to perform liver biopsy in a timely fashion. This difficulty of timely liver biopsy is a significant problem with current diagnostic criteria. We often encounter cases in which treatment is started when a diagnosis of AIH is suspected but not yet proven with biopsy ; the diagnosis of AIH is then established by the marked response to treatment with corticosteroids. Further attempts with a similar approach are important for achieving the goal of establishing a simpler and more rapid means of diagnosing AIH.

## The Problems of ANA Assays

Problems have been noted regarding assays for serum autoantibodies, a striking feature of AIH. Although the

IAIHG recommends the indirect immunofluorescence method with frozen sections of rodent liver, kidney, and stomach to check for autoantibodies involved in AIH[18], this method is now used only at a limited number of institutions ; a larger number of institutions have adopted enzyme-linked immunosorbent assay (ELISA) or a method using established cell lines. The method recommended by the IAIHG can also reliably detect type 2 AIH and should, ideally, be adopted by all institutions. However, we believe this method is unlikely to easily gain widespread acceptance.

We have shown that the sensitivity for ANA in patients with AIH is lower with the ANA-ELISA kit widely used in Japan than with the indirect fluorescent antibody method with frozen rodent sections (data not shown). This lower specificity can probably be attributed to the antigen set contained in the common ANA-ELISA kit being designed for the diagnosis of systemic lupus erythematosus rather than of AIH. Using ELISA for screening for AIH is, therefore, inappropriate. Although a kit for the indirect fluorescent antibody method using the HEp-2 cell line has also been widely used, it has several problems, such as a lack of consistency in the HEp-2 cell cycle among different measurement sessions and a high false-positive rate due to excessively high sensitivity. An ELISA kit incorporating a solid layer, composed of HEp-2 cell nucleus components, and an additional ELISA antibody is also available, but its validity has not been sufficiently verified by assessing the consistency of results with the original rodent frozen sections. For the time being, it seems rational to use ELISA and cultured HEp-2 cells to assay ANAs only as a means of confirming the results from the original method and for following the clinical course of patients.

In practice, the American Association for the Study of Liver Diseases Guidelines on AIH, published in 2010[18], also adopted an indirect fluorescent antibody technique with rodent frozen tissue as the basic procedure for detecting ANAs. In any event, the method for autoantibody detection should be standardized and quantified.

## DIAGNOSIS OF THE ACUTE ONSET, OVERLAP, IgG-4-RELATED FORM OF AIH

AIH is a chronic disease, but cases of acute onset are sometimes seen[19]. Clinical manifestations, including histological findings, specific for AIH are lacking in cases of acute onset.

The pathophysiologic features of IgG-4-related AIH[20] and of the overlap of AIH with primary sclerosing cholangitis have been reported as new disease entities associated with AIH[21]. Particularly difficult are diagnosing AIH in children and distinguishing AIH from primary sclerosing cholangitis[22]. AIH accompanied by bile duct disease and the overlap of AIH with primary biliary cirrhosis have also been described as cases of AIH with clinical problems related to treatment[23]. Such cases are difficult to diagnosis with current diagnostic criteria, which focus on cases with typical manifestations. An important unresolved issue is how to make a rapid and precise diagnosis in these atypical cases. To solve this problem, we created a 7-variable formula based on 3 laboratory tests and 4 histological features to distinguish AIH from primary biliary cirrhosis and overlap syndrome[24].

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今月のテーマ●自己免疫性肝炎診療のポイント

# 自己免疫性肝炎の診断におけるスコアリングシステムの位置付け

高橋宏樹　銭谷幹男[1)]

**要旨**：自己免疫性肝炎（AIH）の診断には，国際自己免疫性肝炎グループが作成した検討項目が13項目のスコアリングシステム（従来型），4項目の簡易型スコアリングシステムが汎用されている．従来型は診断感受性，簡易型は診断特異性に秀でている．簡易型は利便性が高いが，IgG値，抗核抗体価が低い症例，急性・劇症発症例，小児例などの診断は十分でなく，従来型の併用を適宜行い対応する必要がある．スコアリングシステムはあくまで診断の補助手段であることを忘れず，点数にこだわりすぎずに個々の症例の病態を十分に吟味して診断することが肝要で，診断に難渋する症例は組織所見の評価も含めて早期に専門施設にコンサルトすることが望ましい．

**索引用語**：自己免疫性肝炎，診断，スコアリングシステム

## はじめに

自己免疫性肝炎（autoimmune hepatitis；AIH）の診断は，過去においては肝炎ウイルス，アルコール，薬剤などの関与がない原因不明の肝疾患を対象に行われてきた．現在でもそれらの除外が重要であることはかわりないが，世界各国のAIHに興味を持つ臨床研究者からなる国際自己免疫性肝炎グループ（International Autoimmune Hepatitis Group；IAIHG）が1993年にスコアリングシステムを作成し[1)]，1999年にその改訂版が発表された[2)]．わが国のAIH診断指針（厚生省「難治性の肝炎」調査研究班，1996年）（Table 1）でも，この国際診断基準を参考に診断すると記されている．

このシステムは13項目の検討項目について点数を付け，その合計点数によりAIHの診断を行うものであるが，項目数が多く煩雑で臨床的利便性が高いとはいえない．また元来はAIHの病態や薬物治療の研究対象となり得る症例を抽出するために作成されたもので，日常診療における診断を念頭においたものではないことの留意が必要である．

そこでIAIHGでは臨床的利便性の改善を目指したスコアリングシステム開発が試みられ，2008年に検討項目を4項目にしぼった簡易型スコアリングシステムが提示された[3)]．

AIHの診断にはこの2種類のスコアリングシステム（従来型，簡易型）が存在するので，2つの使い分け，いかなる症例でどちらのシステムを参考にすべきかについて，臨床現場では少なからず戸惑いや混迷があると思われる．

早期の適切な診断と治療開始がAIHの予後を規定する重要な因子であることから，AIHの診断においてスコアリングシステムをどのように活用すべきか理解することは非常に重要である．こうした観点から本稿では，AIHの診断におけるスコアリングシステムの位置付けについて解説する．

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The significance of scoring systems in the diagnosis of autoimmune hepatitis

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**Table 1.** 自己免疫性肝炎診断指針

＜概念＞
中年以降の女性に好発し，慢性に経過する肝炎であり，肝細胞障害の成立に自己免疫機序が想定される（*1）．診断にあたっては肝炎ウイルス（*2），アルコール，薬物による肝障害，および他の自己免疫疾患にもとづく肝障害を除外する．免疫抑制剤，特にコルチコステロイドが著効を奏す（*3）．

＜主要所見＞
1. 血中自己抗体（特に抗核抗体，抗平滑筋抗体など）が陽性
2. 血清γ-グロブリン値またはIgG値の上昇（2g/dL以上）
3. 持続性または反復性の血清トランスアミナーゼ値の異常
4. 肝炎ウイルスマーカーは原則として陰性（*2）
5. 組織学的には肝細胞壊死所見およびpiecemeal necrosisを伴う慢性肝炎あるいは肝硬変であり，しばしば著明な形質細胞浸潤を認める．特に急性肝炎像を呈する．

*1：本邦ではHLA-DR4陽性症例が多い．
*2：本邦ではC型肝炎ウイルス血症を伴う自己免疫性肝炎がある．
*3：C型肝炎ウイルス感染が明らかな症例では，インターフェロン治療が奏効する例もある．

＜診断＞
上記の主要所見1.から4.より自己免疫性肝炎が疑われた場合，組織学的検査を行い，自己免疫性肝炎の国際診断基準を参考に診断する．

厚生省「難治性の肝炎」調査研究班，1996より一部抜粋．

## I 従来型スコアリングシステム

1989年にC型肝炎ウイルス（hepatitis C virus；HCV）が同定され，それまでは除外診断により診断されてきたAIHが独立した疾患として存在することが明らかとなるとともに，AIHの新たな診断基準の作成が望まれるようになった．

そこで1992年にAIHの臨床と病態に興味を持つ世界各国の臨床医，病理医がIAIHGを組織し，1993年に初めてAIHの診断スコアリングシステムが作成された[1]．このシステムは日本を含む世界各国で多数の臨床症例により評価され，その結果に基づいて1996年に原発性胆汁性肝硬変（primary biliary cirrhosis；PBC）や原発性硬化性胆管炎（primary sclerosing cholangitis；PSC）との鑑別をより鋭敏にすることを目的とした改訂が加えられ，汎用されている[2]．

Table 2に示すように，このシステムでは病理組織像，副腎皮質ステロイド治療への反応性を含む13項目について点数を付け，合計点が治療前に15点，治療後に17点を上回る場合は確診，10点，12点以上の場合は疑診となる．

AIHに特徴的な臨床像に合致する，女性，ALPよりALTの上昇が顕著，γグロブリンまたはIgGが高い，自己抗体価（抗核抗体：antinuclear antibody（ANA），抗平滑筋抗体：anti-smooth muscle antibody（ASMA），抗LKM-1抗体：anti-liver-kidney microsomal antibody）が高い，病理組織像でinterface hepatitisやリンパ球・形質細胞浸潤を認めるといった所見はプラス点となる．また肝炎ウイルスマーカー，薬物服用，過度のアルコール摂取がない場合はプラス点となるが，ある場合は逆にマイナス点となる．さらに副腎皮質ステロイド治療により寛解導入され，その後に再発した場合もプラス点となる．またAIHとPBC・PSCとの鑑別を念頭において作成されたため，ALTに比しALPの上昇が著明な場合，抗ミトコンドリア抗体（anti-mitochondrial antibody；AMA）陽性，胆管病変を認める場合はマイナス点が付く．

このシステムでは上記項目のいくつかについて詳細な説明が付記されている[2]．患者本人のみならず一親等の血縁者が自己免疫性疾患既往歴を有する場合はプラス1点，他の自己抗体やHLA-DR3，DR4が陽性の際に1点プラスされるのは

**Table 2.** 従来型スコアリングシステム

| | | | | | |
|---|---|---|---|---|---|
| 性別 | 女性 | +2 | HLA | DR3 または DR4 | +1 |
| ALP/ALT 比 | >3 | −2 | 他の自己免疫疾患の合併あり | | +2 |
| | <1.5 | +2 | | | |
| | | | 他の自己抗体 (SLA 抗体，LC1 抗体，pANCA) | | +2 |
| グロブリン または IgG 値 (正常上限比) | >2.0 | +3 | | | |
| | 1.5 ～ 2.0 | +2 | | | |
| | 1.0 ～ 1.5 | +1 | 組織所見 | Interface hepatitis | +3 |
| | <1.0 | 0 | | 形質細胞浸潤 | +1 |
| | | | | ロゼット形成 | +1 |
| ANA，ASMA，LKM-1 抗体 | >1：80 | +3 | | 上記所見なし | −5 |
| | 1：80 | +2 | | 胆管病変 | −3 |
| | 1：40 | +1 | | 他の所見 | −3 |
| | <1：40 | 0 | | | |
| | | | 治療反応性 | 著効 | +2 |
| AMA | 陽性 | −4 | | 再発 | +3 |
| ウイルスマーカー | 陽性 | −3 | | | |
| | 陰性 | +3 | | | |
| 薬剤 | あり | −4 | | | |
| | なし | +1 | | | |
| アルコール | <25g/day | +2 | 確診：>15 点 | | |
| | >60g/day | −2 | 疑診：10 ～ 15 点 | | |

文献 2) Dig Dis Sci. 41：305-14, 1996 より和訳.

ANA・ASMA・抗 LKM-1 抗体陰性症例に限る，といった見落とし，または勘違いしがちな事項が記されているので，それら付記も熟読してスコアリングすることが望まれる.

この従来型スコアリングシステムは，AIH の基礎的，臨床的研究で検討するに値する AIH 症例の囲い込みのための基準として作成されたが，発表以来日常診療における診断に広く汎用され，診断感受性は 97～100% と極めて高いことが検証され，いわゆる診断基準として扱われているのが現状である．わが国の症例でもその診断有用性が確認されている[3].

しかし IAIHG は，本システムは上述したように研究目的のために作成されたもので，臨床現場での診断に用いることはできるものの，過度にスコアに固執すべきではないと注意を喚起している[2].

## II 簡易型スコアリングシステム

従来型スコアリングシステムが作成されてから約 10 年が経過した 2008 年，IAIHG は新たな簡易型スコアリングシステムを作成した[4]．このシステムが作成されるに至った背景には，従来型システムは検討項目が多く複雑なため，日常臨床での利便性に欠けるという批判があった.

そこで日本を含めた世界 10 カ国より 359 例の AIH 症例のデータを収集して統計学的な解析を行い，診断に寄与する独立因子として明らかになった自己抗体価が高い，γグロブリン，IgG が高い，肝炎ウイルスマーカー陰性，特徴的な病理組織像を有する，の 4 項目のみで検討する非常にシンプルなスコアリングシステムを作成した.

Table 3 に示すようにこのシステムではマイナス点は付かず，6 点で疑診，7 点以上で確診となる．6 点での診断感受性は 88%，特異性は 97%，