Review

Diagnostic Criteria for Autoimmune Hepatitis : Historical Review and Present Problems

Mikio Zeniya and Hiroki Takahashi

Department of Gastroenterology and Hepatology, The Jikei University Hospital

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 al-

ways 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-

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-er, if AIH becomes severe because diagnosis has been de-layed, the response to corticosteroid therapy can be unsat-isfactory.   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 Jap-anese 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 respons-es to treatment are good[5].   Briefly, there are 2 susceptibil-ity 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 simi-lar 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 al-lowed international diagnostic criteria to be established.

Diagnostic Scoring Systems

Considering these findings, the International Autoim-mune Hepatitis Group (IAIHG) has prepared diagnostic cri-teria aimed at standardizing the diagnosis of AIH and has proposed a highly convenient scoring system for the diag-nosis of AIH[7].   Table 1 shows the brief history of the es-tablished criteria, with a focus on the criteria of the IAI-HG.   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 re-ceive 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 sys-tem.

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

The IAIHG has recently proposed simplified criteria to facilitate clinical application[14].   The simplified criteria sys-tem includes only 4 elements (i.e., seropositivity for anto-antibodies, elevated serum levels of IgG, histological fea-tures, 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 assess-ments of the simplified criteria system have not been per-formed, we can draw no conclusions about it.   The diag-nostic 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].   Ac-cording 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 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 Scoring system was firstly proposed involving descriptional criteria 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 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 be-

cause 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 his-tological 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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