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CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

Comparability of Probable and Definite Autoimmune Hepatitis by International Diagnostic Scoring Criteria

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BACKGROUND & AIMS: The diagnostic scoring systems for autoimmune hepatitis categorize some patients as having probable disease; this designation can affect treatment strategies and recruitment to clinical studies. A retrospective study was performed to determine the bases for the classification of probable autoimmune hepatitis and its clinical importance. **METHODS:** The study included 185 adult patients who had been assessed at presentation for findings common to both international diagnostic scoring systems. **RESULTS:** Seventeen patients (9%) were graded as probable autoimmune hepatitis by the revised original scoring system, and 28 patients (15%) were similarly designated by the simplified scoring system. These patients were distinguished from those designated as definite autoimmune hepatitis by male sex, concurrent immune diseases, lower serum γ-globulin and immunoglobulin G levels, and lower titers of autoantibody. Patients with definite or probable designations by either scoring system responded similarly to conventional corticosteroid regimens during comparable intervals of treatment. Full, partial, or nonresponses and treatment dependence were evident in all diagnostic categories with similar frequencies. Twenty-seven patients designated as probable autoimmune hepatitis by one system were designated as definite autoimmune hepatitis by the other system. **CONCLUSIONS: The designation of probable autoimmune hepatitis by the international scoring systems is based on differences in clinical manifestations and does not reflect differences in the validity of the diagnosis or its treatment response. Large multicenter prospective studies are necessary to establish these observations.**

Keywords: Clinical Phenotypes; Treatment Responses; Diagnostic Classifications; Scoring Systems.

The diagnosis of autoimmune hepatitis has been codified by an international panel,[1] and diagnostic scoring systems are available to quantify the strength of the diagnosis before[1,2] and after corticosteroid therapy.[1] The revised original scoring system is a comprehensive template that grades multiple clinical, laboratory, and histological features,[1] and the simplified scoring system assesses 4 features deemed important by multivariate analyses.[2] These systems have not been validated by prospective studies, and the simplified scoring system does not assess treatment response.[3] Nevertheless, they have each been incorporated into diagnostic algorithms.[4,5]

Both the revised original and simplified diagnostic scoring systems render diagnoses of either definite or probable autoimmune hepatitis.[1,2] The nature and outcomes of patients with a probable diagnosis by one or both scoring systems are unknown, and it is unclear if they can be included in clinical studies containing patients with scores indicative of definite disease. Furthermore, it is uncertain that patients with a probable diagnosis by one system are similar to those classified as probable by the other system. Patients with a probable diagnosis of autoimmune hepatitis may have nonclassical features that warrant their designation as a separate syndrome.[6,7] Such patients may not have the same outcomes as patients with definite autoimmune hepatitis, and they should be studied and treated separately. Alternatively, patients with probable autoimmune hepatitis may have bona fide autoimmune hepatitis but with less pronounced immune manifestations.[8]

The revised original and simplified diagnostic scoring systems each grade the serum level of IgG and the degree of autoantibody production, and these factors can vary spontaneously during the course of the disease or reflect host-related differences in the intensity of immune expression.[9–11] The difference between definite and probable autoimmune hepatitis might simply reflect these spontaneous variations or host-related differences rather than the nature of the disease. Such patients might well

Abbreviations used in this paper: AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; IIF, indirect immunofluorescence; SMA, smooth muscle antibodies.

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be included in clinical studies of treatment outcomes and treated with vigor and confidence in clinical practice. The designation of probable autoimmune hepatitis might wrongly impugn the legitimacy of an otherwise appropriate diagnosis. The elimination of an imprecise designation that might adversely impact on recruitment to clinical trials and patient care would improve each scoring system.

The goals of this retrospective study are to define the clinical phenotype of probable autoimmune hepatitis as defined by each scoring system, assess the distinctions between patients with definite and probable diagnoses by the same scoring system, and evaluate the responses of patients with each designation to conventional corticosteroid therapy. In this fashion, the nature and treatment outcomes of probable autoimmune hepatitis will be determined for each scoring system, and the need for revision of the scoring systems assessed.

Materials and Methods

Study Population

One hundred and eighty-five patients satisfied the codified clinical criteria for the diagnosis of autoimmune hepatitis at presentation,[1] and they comprised the study population. Study patients had been selected from 310 patients because they were adults (aged 18 years or older) and each had been assessed at presentation for histological features and other findings common to the revised original and simplified diagnostic scoring systems.[1,2] The accession interval was between 1967 and 2005, and 99 patients (54%) were assessed after 1990.

Of the 125 patients excluded from the analysis, 7 were younger than 18 years; 6 did not undergo histological assessments at presentation; 18 did not have determinations of serum IgG levels at presentation; and 77 underwent serological assessments by enzyme immunoassay rather than indirect immunofluorescence (IIF). Seventeen patients had multiple exclusion factors, including determinations of autoantibodies by enzyme immunoassay and absence of serum IgG assessments (10 patients), age younger than 18 years and serological determinations by enzyme immunoassay (4 patients), and lack of histological examination at presentation and no serological assessments by IIF (3 patients).

One hundred and forty-seven patients in the study population (79%) were women, and the mean age of the study group was 48 ± 1 year (range, 18−82 years; median age, 49 years). Thirty-six patients (19%) had smooth muscle antibodies (SMA) only; 51 patients (28%) had antinuclear antibodies (ANA) only; and 93 patients (50%) had both SMA and ANA at presentation. Five of 168 patients who were tested (3%) had antibodies to liver kidney microsome type 1 (anti-LKM1). Three patients with anti-LKM1 had only this marker; one patient had anti-LKM1 and SMA; and one other patient had anti-LKM1 and ANA. The study had been approved by the Institutional Review Board of the Mayo Clinic.

Clinical, Laboratory, and Scoring Assessments

Clinical examinations had been performed in accordance with a previously published protocol by one physician (AJC).[12] Concurrent extrahepatic disorders of an immune nature had been systematically sought in all patients.[12] Conventional laboratory tests of liver inflammation and function had been performed at each evaluation, and serum IgG concentrations had been assessed by immunonephelometry.[13] Smooth muscle antibodies had been determined by IIF on tissue sections of murine stomach and kidney in all patients; ANA had been assessed by IIF on HEp-2 cells in all patients; and anti-LKM1 had been evaluated by IIF on combined mouse kidney/stomach sections and confirmed by IIF of mouse liver sections in 168 patients (91%).[14] Antimitochondrial antibodies (AMA) had been determined in all patients by IIF of murine kidney and stomach tissue in 183 patients (99%) and by a previously reported enzyme immunoassay in 2 patients.[15] Hepatitis B surface antigen and antibodies to hepatitis C virus had been assessed in all patients by second-generation enzyme immunoassays. Stored frozen (−70°C) serum samples obtained at accession were tested for ANA, SMA, anti-LKM1, and hepatitis C virus in those patients who had accessed before the availability of the current assays. Diagnoses of definite autoimmune hepatitis, probable autoimmune hepatitis, or nondiagnostic chronic hepatitis were rendered pretreatment by applying the revised original diagnostic scoring system (Table 1) and the simplified diagnostic scoring system (Table 2).[1,2]

Histological Assessments

Liver tissue examinations had been performed at accession in all patients, and the liver specimens had been examined by members of the liver pathology working group at the Mayo Clinic. The pathological diagnoses were rendered in accordance with pre-established criteria.[16] Previous validation studies have indicated that the reproducibility of the histological interpretations by this method is 94%.[17] All tissue specimens had been judged to be typical or compatible with the diagnosis of autoimmune hepatitis.

Treatment Regimens

One hundred and fifty-eight patients (85%) had been treated with either prednisone in combination with azathioprine (96 patients) or a higher dose of prednisone alone (62 patients) in accordance with a previously published protocol.[18] Prednisone (30 mg daily) in conjunction with azathioprine (50 mg daily) or prednisone (60 mg daily) constituted the induction phase of treatment. Medication doses were then decreased according to a standardized protocol until maintenance doses of medi-