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BRIEF ARTICLE

Role of international criteria in the diagnosis of autoimmune hepatitis

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Abstract

AIM: To study the clinical and laboratory characteristics of autoimmune hepatitis (AIH), and compare them with International Autoimmune Hepatitis Group (IAHG) criteria.

METHODS: Sixty consecutive patients with AIH attended the University Clinic at Tabriz University of Medical Sciences, Iran for a 12 mo period and were assessed in a case series study. Serological and biochemical evaluations were carried out in all patients. Autoantibodies, such as antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver-kidney microsomal antibody (ALKM-1) type 1, and perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) were evaluated in these patients. A liver biopsy was performed after diagnosis of the disease. Patients were evaluated in terms of their signs and symptoms, and laboratory results and the degree to which they corresponded with the diagnostic criteria of IAHG. In this study, both a comprehensive diagnostic scoring system and a simplified diagnostic scoring system were employed for AIH.

RESULTS: Sixty patients, 20 male, 40 female, mean age 39.45 ± 17.50 years, participated in the study. Treatment began immediately after enrolment into the study. The percent distribution of the study population into definite and probable did not change after the treatment. The most common symptoms in descending order were fatigue (100%), icter (66.7%), abdominal discomfort (33.3%), abdominal distension (28.3%), dark urine (23.3%), edema (23.3%), hematemesis (20.0%), pruritus (20.0%), melena (11.7%) and pale stool (10.0%). At the physical examination, splenomegaly, ascites, hepatomegaly, epigastric tenderness and an abdominal mass were found in 50.0%, 16.7%, 13.3%, 5.0% and 3.3% of patients, respectively. Hypergammaglobulinemia was detected in 95.0% of cases. ALKM-1, P-ANCA, ANA and ASMA were positive in 71.4%, 66.7%, 42.4% and 19.4% of cases, respectively. Portal hypertensive gastropathy (45.0%), esophageal varices (41.7%) and cirrhosis (40.0%) were the most prevalent complications of AIH, and there was no evidence of primary sclerosing cholangitis, ulcerative colitis and overlap syndrome in these patients. According to IAHG criteria, 80.0% of cases had a definite diagnosis, 15.0% had a probable diagnosis and 5.0% had no AIH. The percent distribution of the study population into definite, probable and no AIH did not change after using the simplified diagnostic scoring system for AIH.

CONCLUSION: This research showed that the majority of cases in our study were appropriately diagnosed according to the IAHG criteria and simplified scoring system. Thus, these criteria are very useful.

Key words: Autoimmune hepatitis; International criteria; Diagnosis; Clinical; Paraclinical

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INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammation of the liver, the cause of which is unknown. It is characterized by the presence of interface hepatitis on histological examination, hypergammaglobulinemia, and autoantibodies[1]. Autoimmune hepatitis occurs predominantly in women and affects all ages[2]. Autoimmune hepatitis afflicts 100000 to 200000 persons in the United States[3], and accounts for 2.6% of transplant recipients in Europe[4] and 5.9% in the United States[5]. Among Northern European Caucasians, the mean annual incidence of AIH is 1.9 per 100000 population, and its point prevalence is 16.9 per 100000 population[6]. Three types of AIH have been proposed based on immunoserologic markers[7]. The International Autoimmune Hepatitis Group (IAHG) devised and subsequently revised scoring systems to aid in the diagnosis of AIH[8,9]. The revised 1999 criteria evaluated up to 12 patient variables to derive a score which identified individuals as "not AIH", "probable AIH" or "definite AIH"[8]. Despite a high degree of sensitivity and specificity, these criteria have proven cumbersome in day-to-day clinical practice. Subsequently, the IAHG published simplified diagnostic criteria, evaluating just four parameters[10]. This study was designed to determine a standard and reliable method for early diagnosis and close follow-up by using the IAHG simplified diagnostic criteria and comparing clinical and laboratory characteristics in Iranian AIH patients.

MATERIALS AND METHODS

All patients who had been diagnosed with autoimmune hepatitis and had been referred to the outpatient clinic of Tabriz University of Medical Sciences from 2010 to 2011 were evaluated for clinical and laboratory parameters and compared with the diagnostic criteria of IAHG. Patient evaluation started by recording their medical history, and performing a physical examination and complete blood count. Serological and biochemical evaluation included aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, serum γ-globulin, serum albumin, total and direct bilirubin, erythrocyte sedimentation rate, prothrombin time, serum creatinine, triglyceride, total cholesterol and fasting blood sugar. The researchers also evaluated the autoantibodies such as antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-liver-kidney microsomal antibody (ALKM-1) type 1 and perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) by indirect immunofluorescence. A titer of $\geqslant$ 1:40 was considered to be positive. Chronic viral hepatitis, Wilson's disease and hemochromatosis were also assessed using hepatitis B core antibody, hepatitis B surface antibody, hepatitis C antibody, serum ceruloplasmin, urine copper, serum iron and total iron-binding capacity. Hepatitis B surface antigen was detected by enzyme-linked immunosorbent assay (Stat Fax Awareness Technology Inc., Palm City, FL, United States) and hepatitis C virus (HCV) antibody was analyzed using a third generation enzyme linked immunosorbent assay test (Ortho-Clinical Diagnostics, Amersham, United Kingdom).

A percutaneous liver biopsy was taken from all patients for histology after diagnosis of the disease. Specimens were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin, Masson's trichrome, and reticulin. All specimens were evaluated by a single pathologist. Liver biopsies were adequate if there were at least 6 portal tracts per high-power field. A modified Hepatitis Activity Index was used to score specimens, in which necroinflammation was graded from 0 to 18 and fibrosis from 0 to 6[11].

An abdominal ultrasound examination was performed in all patients, and liver size and echogenicity, splenomegaly, gallstones and ascites were assessed. The exclusion criteria were having viral (hepatitis B and C), metabolic (Wilson's disease, hemochromatosis), or drug-induced liver disease or overlap syndrome. Continuous variables are expressed as mean ± SD. Statistical analysis was carried out using SPSS, version 16.0 (SPSS Inc., Chicago, IL, United States). The study protocol was approved by the Ethics Committee of the Liver and Gastrointestinal Diseases Research Center of Tabriz University of Medical Sciences, and informed consent was procured from all patients before enrolment in the study.

RESULTS

Sixty patients with AIH were evaluated, of whom 40 (66.7%) were female. The mean age was 39.45 ± 17.50 years (range, 19-75 years). Twelve patients had a familial history of liver disease (20.0%) and 8 patients had a familial history of AIH (13.3%). Four patients (6.7%) were diagnosed with other simultaneous autoimmune diseases. None of the patients had a history of hepatotoxic drug use. Patient characteristics are described in Table 1.

The most common symptoms in descending order were fatigue (100%), icterus (66.7%), abdominal discomfort (33.3%), abdominal distension (28.3%), dark urine (23.3%), edema (23.3%), hematemesis (20.0%), pruritus (20.0%), melena (11.7%) and pale stools (10.0%). At the time of physical examination, splenomegaly, ascites, hepatomegaly, epigastric tenderness and abdominal mass were found in 50.0%, 16.7%, 13.3%, 5.0% and 3.3% of the patients, respectively. Portal hypertensive gastropathy (45.0%), esophageal varices (41.7%) and hepatic cirrhosis (40.0%) were the most common complications in the patients.

The proportion of patients seropositive for ALKM1, P-ANCA, ANA and ASMA patients was 71.4%, 66.7%,

Table 1 Characteristics of patients with autoimmune hepatitis

Parameter	*n* (%)
Female	40 (66.7)
Male	20 (33.3)
Single	22 (36.7)
Married	38 (63.3)
Educated	46 (76.7)
Uneducated	14 (23.3)
Alcohol intake	3 (5)
Smoking	11 (18.3)
History of blood transfusion	17 (28.3)
History of hospitalization	48 (80)

Table 2 Serological, biochemical and histologic findings in patients with autoimmune hepatitis

Parameter	Result	Range
AST, IU/L	127.8 ± 108.6	17-812
ALT, IU/L	146.0 ± 98.4	14-916
Total bilirubin, mg/dL	2.7 ± 2.2	0.5-8.6
Direct bilirubin, mg/dL	1.3 ± 1.2	0.05-4.3
Alkaline phosphatase, IU/L	499.9 ± 386.2	71-997
White blood cell, No./mm^3	6052.4 ± 2461.5	800-13500
Hemoglobin, g/dL	12.1 ± 3.0	7-17
ESR	40.0 ± 28.7	3-95
Platelet count (× 1000), No./mm^3	139.2 ± 91.4	36.4-464
Prothrombin time	15.8 ± 3.3	12.5-31
Creatinine, mg/dL	0.8 ± 0.3	0.5-2.1
FBS, mg/dL	106.9 ± 48.6	68-302
Triglyceride, mg/dL	163.2 ± 109.5	50-506
Total cholesterol, mg/dL	208.1 ± 106.3	47-472
Albumin, g/dL	3.8 ± 0.7	2.1-5.1
Grade	5.5 ± 2.7	
Stage	3.2 ± 1.5	

All values are mean ± SD. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar.

42.4% and 19.4% respectively. Simultaneous seropositivity for ASMA/ANA occurred in 6.7%, ANA/P-ANCA in 6.7%, ANA/ALKM1 in 5.0%, and ALKM1/ASMA and/or ANA in 3.3%. Hepatitis C virus antibody was assessed in all patients, and all were negative. There was no evidence of primary sclerosing cholangitis, ulcerative colitis or overlap syndrome in these patients.

Liver biopsy and histological assays were performed in all the patients, and all had interface hepatitis. Forty-five cases of pathology reports were descriptive and the rest showed autoimmune hepatitis. The researchers found portal fibrotic expansion (stage 1-2) in 15 patients (33.3%), bridging fibrosis (stage 3-4) in 17 patients (37.8%) and cirrhosis (stage 5-6) in 13 patients (28.8%).

Blood proteins (electrophoresis analysis) were assessed in patients whose mean level of α1 protein was 3.0 ± 1.6 g/dL (0-7.1 g/dL). The mean level of α2 protein was 10.0 ± 3.2 g/dL (0.3-16.6 g/dL). The mean level of β protein was 11.4 ± 4.4 g/dL (0.5-17.0 g/dL). The mean level of γ protein was 25.8 ± 11.4 g/dL (3.7-44.1 g/dL). Hypoalbuminemia was found in 20 (33.3%) patients. Further serological and biochemical data are shown in Table 2.

Table 3 Autoimmune hepatitis diagnosis using simplified score and revised International Autoimmune Hepatitis Group criteria

AIH score	Probable AIH	Definite AIH	No AIH
Revised IAHG			
Pre-treatment	17.7 ± 1.7	12.8 ± 1.4	7.7 ± 1.5
Post-treatment	19.7 ± 1.4	14.8 ± 1.4	9.7 ± 1.5
Simplified	7.5 ± 0.5	5.6 ± 0.5	3.3 ± 0.6

Data are mean scores ± SD. AIH: Autoimmune hepatitis; IAHG: International Autoimmune Hepatitis Group.

Liver and bile duct ultrasonic imaging was performed in all patients and increased echogenicity in liver was found in 36 (60.0%). Splenomegaly was found in 32 patients (53.3%). Increased liver size (hepatomegaly) was found in 12 patients (20.0%), decreased liver size in 20 (33.3%) and normal liver size in 28 (46.7%). A gallstone was found in 11 patients (18.3%) a dilated bile duct in 9 (15.0%), and ascites in 13 (21.7%).

There was a good outcome during the 1-year follow-up in 58 patients (96.7%), one patient (1.7%) had no response to treatment and one patient with complications died while the research was being conducted. The 1-year mortality rate was 1.7%.

According to the revised IAHG criteria, 80.0% of cases had a definite diagnosis of AIH, 15.0% of cases had a probable diagnosis and 5.0% of cases had no AIH. Using the simplified diagnostic scoring system for AIH, the percent distribution of the study population into definite, probable and no AIH did not change. The mean scores and standard deviations for both the revised IAHG and simplified scoring criteria are presented in Table 3.

DISCUSSION

The researchers surveyed 60 patients with AIH. The most common symptoms were fatigue, icterus, abdominal discomfort, abdominal distension, dark urine, edema, hematemesis, pruritus, melena and pale stools. At the physical examination, splenomegaly, ascites, hepatomegaly, epigastric tenderness and abdominal mass were discerned in 50.0%, 16.7%, 13.3%, 5.0% and 3.3% of the patients, respectively.

Koay *et al*[12] had performed a similar study in Taiwan, and the most common clinical findings of AIH were fatigue, icterus and loss of appetite. Another study conducted by Choudhuri *et al*[13] in India reported icterus (55.2%), edema (44.7%), fatigue (44.7%), encephalopathy (23.6%), pruritus (23.6%), abdominal pain (23.6%), fever (21.0%), arthritis (18.4%), hepatomegaly (44.7%), splenomegaly (34.2%) and ascites (34.2%) in their clinical findings. In a study by Gupta *et al*[14] in India (2001), the most common manifestations were fatigue, icterus and loss of appetite.

Variable findings can be seen in the studies reported above. Nevertheless, there is a similarity between the

general findings of the present study and those studies. The characteristic laboratory findings in the patients in the present study were an increase in bilirubin and abnormalities in liver enzyme levels. The pathologic found interface hepatitis in all patients, and 71.4%, 66.7%, 42.4% and 19.4% seropositivity for ALKM1, P-ANCA, ANA and ASMA, respectively.

Koay *et al*[12] reported abnormalities in liver tests and increased bilirubin. Patients were 98.0% positive for ANA. Zhao *et al*[15] in China reported interface hepatitis in all their AIH cases. In a study by Choudhuri *et al*[13], reported positivity for ANA in 39.4%, ASMA in 63.1% and P-ANCA in 2.6%. Johnson *et al*[9] reported ANA or ASMA in 70.0%-80.0% and ALKM1 in 3.0%-4.0%. In a study by Nezu *et al*[16] in Japan, 34.0% of patients were positive for ANA. In another study in Japan by Omagari *et al*[17], 34.0% of patients were positive for ANA. In another study by Terjung *et al*[18] in 175 patients, 81.0% were positive for P-ANCA. Pavić *et al*[19] in Serbia had reported ANA seropositivity in 15.0%-60.0%, ASMA in 34.0%-60.0% and ALKM1 in 0-6.0%. In a study by Adams *et al*[20] in the United States, 20.0% of patients were positive for ANA and 3.0% for ASMA.

In summary, the range of antibody positivity in the above-mentioned studies were: ANA 15.0%-98.0%, ASMA 3.0%-80.0%, ALKM1 0%-6.0% and P-ANCA 2.6%-81.0%. The ranges in the present study are mostly in the reported ranges. Although technical differences in measurement of antibodies in different centers can produce some variability in the results, these wide differences may be a sign of racial differences in patients with AIH. This issue requires more controlled studies. Also, the present study had a small sample of patients and larger studies are required in future to examine the applicability of antibody measurements.

In the present study, 95.0% of patients were diagnosed using the diagnostic criteria of the IAHG. Several studies which had been conducted around the world that insisted on using these criteria, including Heurgué *et al*[21] in Italy, Koay *et al*[12] in Taiwan (China), Lee *et al*[22] in Southern Korea, Michalska *et al*[23] in Poland, Primo *et al*[24] in Spain, Zhao *et al*[15] in China, McFarlane *et al*[25] in England and Yatsuji *et al*[26] in Japan.

In conclusion, this research showed that the majority of cases in the present study were diagnosed according to the criteria of IAHG and the simplified scoring system. There were some deficiencies in the assessment of autoantibodies; therefore, recommendations are made for controlled studies to diagnose the probable causes of these deficiencies. The results of this study conform with reports in the literature. Further studies should be carried out in similar centers.

COMMENTS

Background

Autoimmune hepatitis (AIH) is an unresolving inflammation of liver, the cause of which is unknown. It is characterized by the presence of interface hepatitis on histological examination, hypergammaglobulinemia, and autoantibodies.

Research frontiers

Despite a high degree of sensitivity and specificity, the diagnostic criteria have proven cumbersome in day-to-day clinical practice. Subsequently, the International Autoimmune Hepatitis Group (IAHG) have published simplified diagnostic criteria, evaluating just four parameters.

Innovations and breakthroughs

This study was designed to determine a standard and reliable method for early diagnosis and close follow-up by using IAHG criteria and simplified diagnostic criteria and comparing clinical and laboratory characteristics in Iranian patients.

Applications

This research showed that the majority of cases in the present study were diagnosed according to the criteria of IAHG and simplified scoring system. There were some deficiencies in autoantibodies assessment; therefore, recommendations are made for controlled studies to diagnose the probable causes of these deficiencies.

Peer review

The authors collected data for one of the largest AIH cohort in the Middle East and compared laboratory and histologic findings with the international AIH Score. Using the score they found a definite AIH in 80% of their patients and a probable AIH in 15%. So the authors showed that the score is useful and can be used in patients of the Middle East without limitations. Altogether the achievement of the study is to collect such a cohort in a single center. The study was well performed.

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