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Type 1 autoimmune hepatitis: patterns of clinical presentation and differential diagnosis of the 'acute' type

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Summary

Background: Autoimmune hepatitis (AIH) has three different presentations: chronic, acute and asymptomatic.
Aim: To evaluate AIH presentation in Italian patients and investigate criteria that differentiate between acute-type AIH and acute viral hepatitis.
Design: Prospective observational study.
Methods: Eighty-six consecutive patients with type 1 AIH and 41 with acute viral hepatitis (controls) were studied. 'Acute' AIH was defined as recent-onset (<30 days) symptoms (jaundice and/or fatigue and/or fever) with marked alterations in serum liver tests; the 'asymptomatic' pattern as the occasional detection of liver abnormalities, and the 'chronic' pattern as the presence of signs and/or symptoms of long-lasting liver disease.
Results: Of 86 AIH patients, 59 (68%) presented with the chronic pattern, 22 (26%) with the acute pattern, and 5 (6%) were asymptomatic. 'Acute' patients had higher AST, ALT and bilirubin serum levels ($p < 0.0001$). No differences were detected with respect to age and serum levels of alkaline phosphatase, γ-GT, albumin or γ-globulin. All three groups had similar prevalences of moderate/severe (vs. mild) histological findings and liver cirrhosis. When compared with controls with acute viral hepatitis, 'acute' AIH patients 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, $p < 0.0001$).
Discussion: Although in Italy type 1 AIH patients usually present with a chronic pattern, some 25% have an acute presentation resembling that of viral hepatitis. 'Acute' AIH and viral hepatitis can be reliably differentiated by simple parameters such as gender, gamma-globulin serum levels and AST/ALT ratio.

Introduction

Autoimmune hepatitis (AIH) is a chronic progressive inflammatory liver disorder of unknown aetiology that is presumed to be due to aberrant autoreactivity, with a fluctuating course, potentially progressing to hepatic failure.[1,2]

A panel of international experts (the International Autoimmune Hepatitis Group, IAHG) recently set up a cumulative score system for the diagnosis of AIH.[3] According to this system, AIH can be diagnosed when other main causes of liver disease are ruled out and when typical immunological (serum autoantibodies), histological (interface hepatitis), clinical (associated autoimmune disorders) and biochemical (hypergammaglobulinaemia, high IgG)

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features are present. Therapeutic criteria should also be considered, as AIH is characterized by a marked responsiveness to immunosuppression.

A heterogeneous presentation of the disease has been described:[4–6] most patients present with signs and symptoms of established chronic liver disease, up to decompensated cirrhosis; some show a picture of acute, rarely fulminant, hepatitis with jaundice and marked elevation of transaminases serum levels; and some are completely asymptomatic and seek medical advice only because of liver laboratory abnormalities.

Most of the data about AIH presentation come from studies conducted in the UK, North America, and Japan.[6–9] Similar reports are lacking from Italy and the Mediterranean area. We retrospectively evaluated the presentation of the disease in a well-characterized series of Italian patients suffering from probable or definite type 1 AIH. In particular, we focused on the acute type of presentation of AIH and the clinical problems in differentiating it from acute viral hepatitis.

Methods

AIH patients

We enrolled 86 consecutive Italian patients with AIH referred to our Institute. The present study focused mainly on type 1 AIH; the vast majority of cases (79–92%) were therefore positive for anti-nuclear (ANA) and/or smooth muscle antibodies (SMA). Seven patients (8%), however, were auto-antibody-negative,[2,10,11] a condition sometimes referred to as type 4 AIH. Subjects with type 2 AIH, marked by antibodies to liver-kidney microsomes (LKM_1), were not included. According to the IAHG criteria,[3] 52 (60%) patients reached the score for 'definite' AIH and 34 (40%) that for 'probable' AIH, at the time of assessment. Eleven were males (13%) and 75 females (87%). Each case was evaluated at presentation, before any therapy.

Three distinct pattern of presentation could be identified. The 'acute' pattern was defined by the presence of recent onset (<30 days) symptoms (jaundice and/or fatigue and/or drowsiness and/or fever) in conjunction with marked alterations in serum liver tests. Most of these patients had been originally admitted to an 'infectious disease' ward with the diagnostic suspicion of acute viral hepatitis. Virological markers, however, were consistently negative.

The 'asymptomatic' form of presentation was characterized by the absence of any clinical symptoms and the occasional detection of liver abnormalities within a panel of laboratory investigations performed for some other reason.

The 'chronic' pattern was displayed by the remainder of the patients: clinical and biochemical features compatible with a chronic liver disorder. Symptoms had been persisting for at least 10 months and were usually minor and unspecific, such as fatigue, anorexia and arthralgias. In a minority of cases, evidence of an established cirrhosis was present.

In each patient we considered common clinical, biochemical, histological and genetic parameters (Table 1): age and gender; serum levels of transaminases (AST and ALT), bilirubin, alkaline phosphatase (ALP), gamma-GT, albumin, gamma-globulin and single-class immunoglobulin (IgG, IgA, IgM); positivity for serum ANA and SMA (tested by indirect immunofluorescence (IFL) on rat liver and kidney sections at 1:40 dilution); histological and/or clinical (ascites and/or esophageal varices) evidence of liver cirrhosis and, where available, histological activity on liver biopsy (graded as 'mild', 'moderate' or 'severe') and presence of the HLA alleles DR3 and DR4.

All patients gave informed consent.

Controls

A total of 41 consecutive patients with acute hepatitis of viral aetiology formed the control group. They included 20 (49%) with hepatitis A virus, 18 (44%) with hepatitis B virus (all positive for IgM anti-HBC and >1.0 mUI/ml) and 3 (7%) with hepatitis-C-virus-related acute hepatitis. In all these patients, only a first-line biochemical screening was done; they did not undergo IFL for serum autoantibodies, or liver biopsy.

Statistics

The comparison of categorical variables was performed using χ^2 and Fisher's exact test when applicable. The Kruskal-Wallis test was used for the comparison of continuous data. Nominal variables were correlated by contingency tables. A p value < 0.05 was considered significant. Statistical analysis was performed using GraphPad InStat version 3.0a for Macintosh (GraphPad Software), and StatView 5.0.1 for Macintosh, (SAS Institute Inc).

Results

Of the 86 AIH patients, 22 (26%) had an acute presentation. Five (6%) were completely symptom-free at diagnosis, showing only occasional

Table 1 Presentation of autoimmune hepatitis (AIH) by pattern: acute, chronic and asymptomatic

	'Acute' AIH ($n=22$)	'Chronic' AIH ($n=59$)	'Asymptomatic' AIH ($n=5$)	p
Age (years)	39.5±20.2	44.2±19.5	48.4 ± 16.7	NS
Females	18 (82%)	52 (88%)	3 (60%)	NS
AST (×UNV)	29.11 ± 16.08	9.09 ± 11.46	2.80 ± 2.77	<0.001 acute vs. chronic, <0.001 acute vs. asymptomatic**
ALT (×UNV)	25.33 ± 13.41	9.36 ± 9.81	2.99 ± 1.20	<0.001 acute vs. chronic, <0.001 acute vs. asymptomatic**
Bilirubin (mg/dl)	7.89 ± 6.16	3.61 ± 5.93	0.72 ± 0.35	<0.001 acute vs. chronic, <0.001 acute vs. asymptomatic**
Alkaline phosphatase (×UNV)	1.59 ± 0.79	1.41 ± 0.95	1.17 ± 0.58	NS
γ-GT (×UNV)	3.66 ± 3.18	2.89 ± 2.93	2.61 ± 3.11	NS
Albumin (g/dl)	3.37 ± 0.65	3.63 ± 0.60	3.92 ± 0.55	NS
γ-Globulin (g/l)	26.9 ± 10.8	27.4 ± 9.6	25.4 ± 7.9	NS
IgG (×UNV)	1.64 ± 0.59	1.75 ± 0.77	1.59 ± 0.62	NS
IgA (×UNV)	0.81 ± 0.41	0.84 ± 0.51	1.08 ± 0.44	NS
IgM (×UNV)	0.81 ± 0.55	1.17 ± 0.71	0.94 ± 0.87	NS
Autoantibodies (IFL, 1:40)	ANA and SMA 14 (64%), isolated ANA 2 (9%), isolated SMA 4 (18%), negative 2 (9%)	ANA and SMA 30 (51%), isolated ANA 6 (10%), isolated SMA 18 (31%), negative 5 (8%)	ANA and SMA 2 (40%), isolated SMA 3 (60%)	NS
Moderate–severe histological findings	10/14 (71%)	27/45 (60%)	3/5 (60%)	NS
Cirrhosis*	5 (23%)	22 (37%)	1 (20%)	NS
HLA DR3	6/16 (37.5%)	13/37 (35%)	1/2 (50%)	NS
HLA DR4	2/16 (12.5%)	7/37 (19%)	1/2 (50%)	NS

Data are means ± SD, or numbers (%). * Histology and/or ascites and/or esophageal varices. ** Kruskal-Wallis test. UNV, upper normal value; AST, aspartate transaminase; ALT, alanine transaminase; γ-GT, γ-glutamyl transpeptidase; ANA, antinuclear; SMA, smooth muscle; NS, not significant.

laboratory abnormalities. Most (59, 69%) presented with a chronic form of liver disease, sometimes with marked biochemical activity and jaundice, but always without acute symptoms.

We compared the three patterns of presentation (acute, asymptomatic and chronic) with respect to the parameters considered (Table 1). Patients with an acute presentation had significantly higher transaminases and bilirubin serum levels ($p<0.001$). There were no other significant differences between the groups. Mean age of presentation was lower in the acute (39.5 years) than in the chronic and asymptomatic patients (44.2 and 48.4 years, respectively), but the difference was not statistically significant. γ-Globulin serum levels were similarly raised above the normal range in all three groups, mainly due to an increase in IgG. By contrast, the IgA and IgM classes were mostly within their normal ranges in all three groups. The proportion of patients with histology graded 'moderate' or 'severe' (vs. 'mild') was comparable in acute (71%), chronic and asymptomatic cases (both 60%). The prevalence of liver cirrhosis, assessed by histological and/or clinical data, was also similar among the three groups (23, 37 and 20%, respectively).

The 22 AIH patients with an acute presentation were compared with the 41 controls with acute viral hepatitis (Table 2). Mean γ-globulin serum levels were significantly higher in the AIH patients (26.9 g/l) than in controls (13.4 g/l, $p<0.0001$). This difference again resulted from a significant increase in serum IgG (1.64× upper normal value

Table 2 Autoimmune hepatitis (AIH) with an acute pattern of presentation: comparison with acute viral hepatitis

	Acute AIH ($n=22$)	Acute viral hepatitis ($n=41$)	p
Age (years)	39.5 ± 20.2	33 ± 13.1	NS
Females	18 (82%)	10 (24%)	<0.0001*
AST (×UNV)	29.11 ± 16.8	25.9 ± 19.9	NS
ALT (×UNV)	25.33 ± 13.41	40.6 ± 28.3	<0.05**
AST/ALT ratio	1.20 ± 0.55	0.61 ± 0.2	<0.0001**
Bilirubin (mg/dl)	7.89 ± 6.16	10.1 ± 5.8	NS
ALP (×UNV)	1.59 ± 0.79	1.85 ± 0.89	NS
γ-GT (×UNV)	3.66 ± 3.18	5.1 ± 3.8	NS
γ-Globulin (g/l)	26.9 ± 10.8	13.4 ± 4	<0.0001**
IgG (×UNV)	1.64 ± 0.59	0.76 ± 0.2	<0.0001**
IgA (×UNV)	0.81 ± 0.41	0.63 ± 0.1	<0.05**
IgM (×UNV)	0.81 ± 0.55	0.94 ± 0.5	NS

Data are means ± SD, or numbers (%). * Fisher's exact test. ** Unpaired *t* test. UNV, upper normal value; AST, aspartate transaminase; ALT, alanine transaminase; γ-GT, γ-glutamyl transpeptidase; NS, not significant.

in AIH vs. 0.76× in controls, $p<0.0001$). Mean IgA and IgM serum levels were within normal ranges in both groups. IgA was higher in acute AIH vs. controls (0.81× vs. 0.63× upper normal limit); IgM was lower (0.81× vs. 0.94× upper normal limit). The IgA difference was just significant ($p<0.05$); the IgM difference was not.

Gender distribution was significantly different between the two groups: acute AIH patients were mainly women (18/22, 82%) and controls with viral hepatitis, mainly men (31/41, 76%) ($p<0.001$).

Mean serum ALT elevation was greater in controls (40.6× upper normal value) than in acute AIH patients (25.33× upper normal value; $p<0.05$) whereas mean AST elevation was comparable in both groups (25.9× and 29.11×, respectively). Consequently, the AST/ALT ratio was higher in acute AIH (1.20) than in acute viral hepatitis (0.61) ($p<0.0001$).

Figures 1 and 2 summarize the ROC curve for the most significant parameters in the differential diagnosis between acute AIH vs. viral hepatitis, i.e. γ-globulin and AST/ALT ratio. The optimal cut-off for γ-globulin levels is 19.1 g/l (sensitivity 76.5%, specificity 93.5%), while the optimal cut-off for AST/ALT ratio is 0.7 (sensitivity 84.2%, specificity 77.4%).

Other parameters, including age, bilirubin and cholestatic enzymes, were similar in the two groups.

Discussion

The aim of our study was to evaluate the clinical onset of type 1 AIH in a well-characterized series of Italian patients. Our data confirm previous observations about the identification of three main patterns of presentation: acute, chronic, and asymptomatic. Their relative frequencies are similar in all geographical areas so far considered.[6,12] Also, in Italy, most AIH patients (69%) present with a picture of symptomatic established chronic liver disease. In 25% of cases, however, AIH presents with an acute pattern that clinically resembles viral hepatitis. These patients are usually first referred to an 'infectious' ward, and as this study was conducted in a department involved mainly in hepatology and internal medicine, their actual number may have been underestimated for this reason.

Acute AIH is commonly regarded as a paediatric condition. This is well recognized in the clinical setting of type 2 AIH,[1,5,11,13–6] which represents a typical childhood disease. The present study, however, shows that an acute presentation of type 1 AIH is frequently observed in adults too. Our acute patients tended to be younger than the other AIH cases, but the age difference did not reach statistical significance. None of these adult patients exhibited a fulminant evolution, which, according to literature data, is much more frequent in children.[5,10,11,16–18]

Only a few AIH patients (6% in our data) are asymptomatic at the time of diagnosis. This represents a clear-cut difference between AIH and HCV-related hepatitis, which is much more frequently diagnosed in the absence of any symptoms, and following the occasional finding of biochemical abnormalities.[19–21] Because of its clinically silent presentation, the prevalence of asymptomatic AIH is likely to be underestimated.[22]

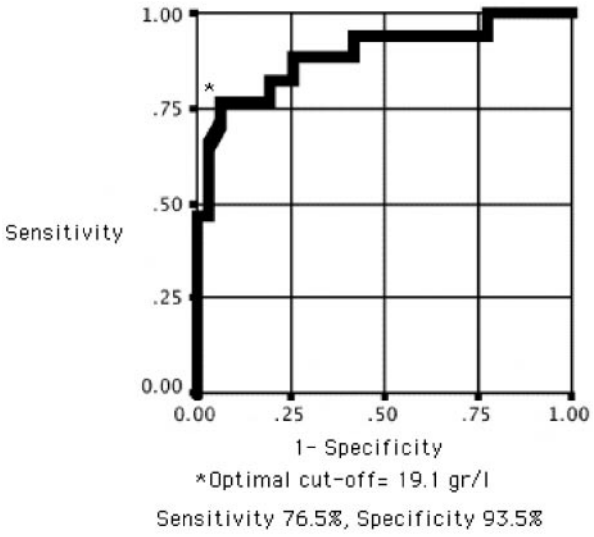

Figure 1. γ-Globulin ROC curve for the diagnosis of 'acute' autoimmune hepatitis vs. acute viral hepatitis (AVH). Area under the ROC curve = 0.891; standard error = 0.056; 95%CI = 0.767 − 0.962.

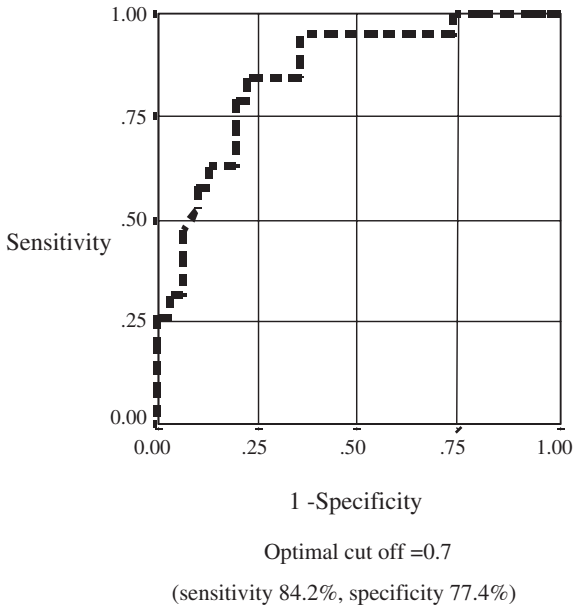

Figure 2. AST/ALT ratio ROC curve for the diagnosis of 'acute' autoimmune hepatitis vs. acute viral hepatitis (AVH). Area under the ROC curve = 0.853; standard error = 0.060; 95%CI = 0.724 − 0.937.

Regarding common clinical and biochemical parameters, all three presentations of AIH share some features: (i) serum levels of γ-globulin are consistently raised; (ii) histological activity, reflecting a chronic process such as interface hepatitis, is similar in terms of both frequency and grading (moderate–severe in 60–70%); and (iii) the prevalence of liver cirrhosis is comparable (20–40%). Each of these elements is thus an intrinsic feature of type 1 AIH, with a key diagnostic role, independent of the mode of presentation.

Thus, despite its variability in clinical presentation, AIH should be regarded as a basically homogenous condition characterized by immunological hyperreactivity, histological chronicity and tendency to progression. This holds true even when the opposite poles in the clinical spectrum of AIH (i.e. symptom-free and acute presentation) are considered.

In line with the above considerations, acute AIH does not represent a 'true' acute disease of recent onset, but rather an acute-like flare of an ongoing chronic disorder which has been so far clinically silent. AIH presenting with an acute pattern might better be referred to as 'acute' AIH, the quotation marks reminding us that the disease is not actually an acute one. The factor(s) accounting for the flare are not yet fully elucidated, and it cannot be ruled out that a proportion of our 'acute' patients might be affected by a chronic aggressive hepatitis, rapidly progressing to cirrhosis.

According to our data, two clear-cut biochemical differences were detected between autoimmune and viral acute hepatitis: (i) higher γ-globulin serum levels in the former, due to a selective increase of the IgG class; (ii) lower AST/ALT ratio in the latter, resulting from a disproportionately higher increase in ALT than in AST serum levels. Hypergammaglobulinemia is due to the already mentioned immunological hyperreactivity typical of AIH. Its close association with acute AIH has not been fully emphasized in the previous literature: high serum γ-globulin levels have been commonly reported in chronic AIH cases, but not in acute ones.[23] The AST/ALT ratio has not previously been evaluated in AIH. An increased AST/ALT ratio (normal value <1) has been claimed to be a marker of more severe disease in chronic hepatitis C.[24–27] A similar prognostic relevance has been reported also in acute viral hepatitis.[28,29] In the light of these observations, it can be speculated that the higher AST/ALT ratio detected in 'acute' AIH might reflect the more aggressive clinical course of this disease, compared to viral hepatitis.

In our series of unselected consecutive acute cases, the distribution of patients' gender was also significantly different between AIH patients and controls, as women were largely prevalent in the former and men in the latter.

Acute-type AIH and acute viral hepatitis can thus be confidently discriminated by means of three simple, quick and easy parameters: gender, γ-globulin serum levels and pattern of elevation of transaminases. In this setting, other diagnostic

elements included in the IAHG score are less feasible. Liver biopsy is frequently prevented by clotting defects. Response to steroids requires adequate follow-up, and these drugs can be contraindicated in acute viral hepatitis. Serum autoantibodies are not always available in primary or secondary referral centres and are seldom included in the biochemical screening of acute hepatitis. Our data suggest that, in clinical practice, the differential diagnosis between autoimmune and viral acute hepatitis may well rely on the evaluation of the above-mentioned triad, which should not be overlooked. IFL for the detection of serum autoantibodies can be left as a second line confirmatory test. If not contraindicated, liver biopsy should finally be done, but only in patients with clear-cut 'acute' AIH.

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