

# Evaluation of patients with autoimmune hepatitis in a specialized outpatient clinic in Southern Brazil

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**ABSTRACT – Background** – Autoimmune hepatitis (AIH) is a chronic liver disease, characterized by necroinflammation and autoimmune etiology. Studies evaluating the characteristics of patients with AIH are scarce in Brazil. **Objective** – Our objective was to evaluate the profile of patients with AIH in a specialized center in Southern Brazil and to verify factors related to treatment response. **Methods** – this was a retrospective cohort study, which analyzed demographic, epidemiological, clinical, laboratory, and histologic data. Patients with AIH diagnosed according to the criteria of the International Autoimmune Hepatitis Group (IAIHG) were included. In liver biopsies, the degree of fibrosis, histological activity, presence of hepatocyte rosettes, plasma cell infiltrates, and confluent necrosis were evaluated. In the statistical analysis, the significance level was 5%. **Results** – Forty adults patients diagnosed with AIH were included. The evaluated population predominantly consisted of women (75.0%) and the average age at diagnosis was 44.2 years. The association with extrahepatic autoimmune diseases occurred in 20.0% of cases. Clinically, 35.0% of patients presented with acute onset hepatitis, 37.5% with cirrhosis, and 27.5% with other forms of presentation. The most common clinical manifestation was jaundice (47.5%). Thirty-five patients were treated, and of these, 97.1% used prednisone combined with azathioprine. The average treatment time was 2.7 years. Response to treatment was complete or partial in 30 (85.7%) and absent in 5 (14.3%) patients. There was no statistically significant difference when evaluating response to treatment in relation to forms of presentation, histological findings, and the presence of autoantibodies. Regarding fibrosis, regression was observed in 18.75% of the cases. **Conclusion** – Most patients with AIH were young at presentation and of female sex. The association with extrahepatic autoimmune diseases and cirrhosis at presentation was seen in a considerable proportion of patients. Treatment was effective, but there were no clinical, histological or serological parameters capable of predicting treatment response.

**HEADINGS** – Autoimmune hepatitis. Treatment outcome. Demographic data. Immunosuppressive agents.

## INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic liver disease, characterized by necroinflammation and autoimmune etiology. Its triggering agents are still not completely well-established<sup>(1)</sup>. It affects children and adults of all age groups, and is characterized by the presence of circulating autoantibodies, hypergammaglobulinemia, and histologic findings such as interface hepatitis, lymphocytic or lymphoplasmacytic inflammation, and hepatocyte rosetting. However, these characteristics are not always present, which hinders an accurate diagnosis<sup>(2)</sup>.

AIH is considered a relatively rare disease. Its prevalence ranges from 16 to 18 cases/100,000 inhabitants in Europe and has been increasing in both sexes<sup>(3)</sup>. Incidence in Europe and North America ranges from 0.1 to 1.9 cases per year/100,000 inhabitants<sup>(4,5)</sup>. Women are affected more often than men, in a ratio of 3.6:1, and the disease can affect all ethnic groups<sup>(6-9)</sup>.

In up to 50% of cases, presentation can be insidious, with nonspecific symptoms, such as lethargy and fatigue, and findings in the physical examination may suggest cirrhosis<sup>(1,10,11)</sup>.

A study conducted in Argentina evaluated 84 adult patients with AIH and demonstrated that the disease had a different pattern

compared to that usually seen in the pediatric population, since adults were more likely to present with extrahepatic manifestations and autoimmune markers (antinuclear antibody)<sup>(12,13)</sup>. On the other hand, when comparing patients from a Southeastern Brazilian center with a North American population, it was observed that Brazilian patients had earlier disease onset, lower frequency of concurrent autoimmune diseases, higher serum levels of aspartate aminotransferase and gammaglobulin, higher frequency of smooth muscle antibodies and lower frequency of antinuclear antibodies than the patients from the United States cohort<sup>(14)</sup>. Given the genetic diversity of patients with AIH in Latin America<sup>(12-17)</sup>, we believe it was also important to study a population in the South of Brazil, especially considering that population in this region is mainly of European ethnicity<sup>(18)</sup>.

The objective of the present study was to evaluate the profile of patients diagnosed with AIH in a reference center in Southern Brazil and to verify factors associated to treatment response.

## METHODS

For this retrospective cohort study, we have reviewed the medical records of all adult patients with AIH. The diagnosis of

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AIH was based on histological abnormalities (interface hepatitis), characteristic clinical and laboratory findings (elevated aminotransferase levels and increased serum immunoglobulin G concentration) and the presence of one or more characteristic autoantibodies<sup>(19)</sup>, and classified under the criteria of the International Autoimmune Hepatitis Group (IAIHG)<sup>(2)</sup> and followed between 2005 and 2017 in the outpatient clinic of Gastroenterology and Hepatology of *Irmandade Santa Casa de Misericórdia de Porto Alegre*, one of the largest tertiary hospitals in Southern Brazil.

Patients with significant intake of alcoholic beverages (more than 40 g/day for men and 20 g/day for women), infected with hepatitis B or C virus, using hepatotoxic medications that could mimic AIH clinical pattern, who were chronically using corticosteroids for reasons other than AIH or who had overlap syndromes with primary biliary cholangitis and/or primary sclerosing cholangitis were excluded from the study. Moreover, those who had incomplete medical records, not containing at least the information necessary to calculate the diagnostic score revised according to the IAIHG<sup>(2)</sup>, were also excluded.

Gender, age at diagnosis, ethnicity, personal history of autoimmune diseases (evaluated by anamnesis and laboratory tests), forms of presentation of the disease (asymptomatic, acute onset, compensated or decompensated cirrhosis), clinical manifestations in the presentation of AIH (ascites, jaundice, upper gastrointestinal bleeding, or hepatic encephalopathy), and the presence of hepatocellular carcinoma were evaluated. The ethnicity was self-declared. If there were any disagreement between the self-informed ethnicity and the assessment made by the attending physician, another colleague was called upon. Regarding the management of AIH, all medications used (prednisone, azathioprine, or others) and treatment lengths (in years) were recorded, as well as the indication for liver transplantation. Response to treatment was analyzed according to the IAIHG criteria (complete response, partial response, or absence of response)<sup>(2,20)</sup>.

The following laboratory tests were evaluated: aspartate (AST) and alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), prothrombin time (PT), total (TB) and direct bilirubin (DB), albumin, gamma-globulin, platelets, antinuclear antibodies (ANAs), smooth muscle antibodies (SMA), and liver kidney microsome type 1 antibody (anti-LKM1). Autoantibodies were determined by indirect immunofluorescence, and considered when titration was over 1:40.

We considered for the analyses tests performed at the moment of disease presentation and 2 years following presentation (with the purpose of evaluating treatment response). When patients were followed for less than 2 years, the latest tests available in medical records were used.

The initial liver biopsy and, when available, a liver biopsy performed for treatment control were evaluated. Liver biopsies performed for treatment control followed the guidelines of the American Association for the Study of Liver Disease (AASLD)<sup>(19)</sup> and the European Association for the Study of the Liver (EASL)<sup>(21)</sup>, which recommend a control liver biopsy only for patients with clinical and biochemical response to treatment.

The degree of hepatic fibrosis and the histological activity were evaluated according to the METAVIR score<sup>(22)</sup>. The presence of hepatocyte rosettes, type of infiltrate (predominance of plasma cells), and bridging or confluent necrosis were also evaluated. All liver biopsies were analyzed by the same expert on liver pathology.

Categorical variables were described as proportions while con-

tinuous variables were described as means and standard deviations. For the univariate analysis, categorical variables were compared using the Chi-square test or Fischer's exact test. To compare the form of presentation of the disease in relation to hepatic histology we used the non-parametric Kruskal-Wallis test. Analyses were performed in the SPSS software version 24, and we adopted a significance level of 5%.

The research project was submitted and approved by the local Ethics Committee.

## RESULTS

The medical records of 58 patients with AIH diagnosis were evaluated. Eighteen patients were excluded: 9 (15.52%) of them due to insufficient data in medical records or irregular follow-up; 2 (3.45%) due to infection with hepatitis C virus; and 7 (12.07%) due to presenting overlap syndrome with primary biliary cholangitis or primary sclerosing cholangitis. Finally, 40 patients were included in the study, 27 (67.5%) of whom had a definite diagnosis of AIH prior to treatment. The remaining 13 (32.5%) included patients had a probable diagnosis of AIH prior to treatment, but received a definite diagnosis of AIH according to their treatment response. The average age at diagnosis of the disease was  $44.2 \pm 18.1$  years. Thirty-two patients were women (75.0%). Regarding ethnicity, 25 (62.5%) patients were Caucasian (TABLE 1).

TABLE 1. Demographic and clinical characteristics of patients with autoimmune hepatitis (n=40).

Characteristics	N=40
Age (years); m $\pm$ SD	44.2 $\pm$ 18.1
Women; n (%)	32 (75.0)
Caucasian; n (%)	25 (62.5)
Forms of presentation; n (%)	
Acute onset	14 (35.0)
Compensated cirrhosis	10 (25.0)
Decompensated cirrhosis	05 (12.5)
Asymptomatic	11 (27.5)
Clinical manifestation; n (%)	
Jaundice	19 (47.5)
Ascites	05 (12.5)
Asymptomatic	16 (40)
Associated autoimmune diseases; n (%)	08 (20.0)
Rheumatoid arthritis	02 (5.0)
Celiac disease	01 (2.5)
Systemic lupus erythematosus	02 (5.0)
Psoriasis	02 (5.0)
Thyroiditis	01 (2.5)

M: mean; SD: standard deviation.

Concerning forms of presentation of the disease, 14 (35.0%) patients initially presented with acute onset; 10 (25.0%) with compensated cirrhosis; and 5 (12.5%) with decompensated cirrhosis. The most frequent clinical manifestations at presentation were jaundice (19 patients, 47.5%) and ascites (5 patients, 12.5%). Sixteen (40.0%) patients were completely asymptomatic. Eleven (27.5%) patients were asymptomatic and did not present findings suggestive of chronic liver disease. In such cases, diagnosis was triggered by elevated liver tests. Association of AIH and extrahepatic autoimmune diseases occurred in 8 (20.0%) patients, all of them women (TABLE 1).

At presentation, 34 (85.0%) patients had AST, and 32 (80.0%) patients had ALT above the upper limit of normal (ULN), while 31 (77.5%) had gamma-globulin above 1.5 g/dL. Data on laboratory tests can be seen in TABLE 2.

TABLE 2. Biochemical changes at presentation (n=40).

Laboratory test	Mean ± SD	Minimum value	Maximum value
AST (U/L)	448.8 ± 581.0	23	2269
ALT (U/L)	461.2 ± 602.9	20	2407
Alkaline phosphatase (U/L)	197.2 ± 161.0	37	942
GGT (U/L)	295.7 ± 292.0	18	1135
Prothrombin activity (%)	75.0 ± 19.1	22	100
Total bilirubin (mg/dL)	4.8 ± 6.9	0.3	35
Albumin (g/dL)	3.6 ± 0.6	2.4	4.6
Gamma-globulins (g/dL)	2.5 ± 1.2	0.8	6.1
Platelets (/mm <sup>3</sup> )	178,361 ± 88,483	27,000	431,000

SD: standard deviation; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase.

In relation to the autoantibodies, 17 (42.5%) patients had both ANA and SMA, 8 (20%) had isolated ANA, 7 (17.5%) had isolated SMA, 2 (5.0%) presented with positive anti-LKM1 (one isolated and one in association with ANA), and 6 (15%) did not present with any of these autoantibodies. Regarding titration, 26 (65.0%) patients presented with positive ANAs in titers higher than 1:40 and 24 (60.0%) presented with positive SMA in titers higher than 1:40.

As for the histological evaluation, 37 (92.5%) patients were submitted to liver biopsy at presentation, and 16 (40.0%) patients were also submitted to control liver biopsy in order to verify treatment-induced remission. It is noteworthy that, in the initial biopsy, 29 (78.4%) patients presented with moderate (A2) or intense (A3) histological activity, 14 (37.8%) had advanced fibrosis (F3) and 13 (35.1%) had cirrhosis (F4). Hepatocyte rosettes were observed in 14 (37.80%) patients, plasma cell infiltrates in 25 patients (67.6%), and bridging necrosis or confluent necrosis in 11 (29.7%). On the other hand, in the control liver biopsy, there were 6 (37.5% cases) patients without histological activity, and only 1 (6.25%) patient presented with intense activity (A3). Regarding fibrosis in the control biopsy, 6 (37.5%) patients presented with advanced fibrosis (F3) and 5 (31.2%) had cirrhosis (F4). Hepatocyte rosettes, plasma cell infiltrates, and confluent necrosis were less frequently observed in control liver biopsies (5.0%, 7.5%, and 2.5% respectively). Among the 16 patients who were submitted to control liver biopsy, histologic activity remained unchanged in 6 (37.5%), increased in 1 (6.2%), and improved in 9 (56.3%) patients. As for fibrosis, it remained unchanged in 10 (62.5%), improved in 3 (18.75%), and progressed in 3 (18.75%) patients.

Among patients who presented with acute onset (n=14), 9 (64.3%) had stage 3 or 4 fibrosis.

Concerning treatment, 34 (85.0%) patients used prednisone combined with azathioprine; 1 (2.5%) patient used prednisone alone; and 5 (12.5%) patients did not undergo any treatment. Among the 35 treated patients, 22 (62.8%) were treated for over 2 years; 9 (25.7%), for 1 to 2 years; and 4 (11.4%), for less than 1 year at the time of data collection (average 2.7±0.7 years). Response to

treatment was complete or partial in 30 (85.7%) and absent in 5 (14.3%) patients. There was no statistically significant difference regarding type of response to treatment (complete, partial, or absent) irrespective of the presence of autoantibodies (ANAs and SMA), gamma-globulin levels, forms of presentation of disease, and histological findings. TABLE 3 shows type of response to treatment according to the presence of autoantibodies and gamma-globulin levels.

TABLE 3. Response to treatment versus presence of autoantibodies and pretreatment gamma-globulin level (n=35).

	Complete or partial (n=30) n (%)	Absence of response (n=5) n (%)	P value*
ANAs+ (n=25)	22 (73.3)	3 (60.0)	0.610
SMA+ (n=21)	19 (63.3)	2 (40.0)	0.369
Anti-LKM1 (n=02)	2 (100.0)	–	–
GGlob >1.5 (n=29)	24 (80.0)	5 (100.0)	0.561

ANAs: antinuclear autoantibodies; SMA: smooth muscle antibodies; GGlob: gamma-globulin. \*Fisher's exact test.

In the follow-up period, 4 (10.0%) patients were listed for liver transplantation, and there were no deaths. None of the patients developed hepatocellular carcinoma during follow-up.

## DISCUSSION

AIH is a relatively rare disease, and studies assessing the profile of adult patients in Brazil are scarce<sup>(14,17,23,24)</sup>. This is the first study which evaluates such patients in a referral center in the South of Brazil.

Our study was composed of a homogeneous population, because both the diagnostic definition and the evaluation of response to treatment were based on IAIHG criteria<sup>(2)</sup>.

AIH can emerge at any age and in all ethnic groups<sup>(25,26,27)</sup>. In most studies, it was reported in a bimodal age pattern at presentation, with a peak during childhood/adolescence, and another in middle age between the fourth and sixth decades of life<sup>(3,19,25-27)</sup>. According to studies conducted in Europe, the average age at the onset of the disease ranged from 47.7 to 50 years<sup>(28-30)</sup>. In most North American studies, the average age ranged between 45 and 47 years<sup>(31-33)</sup>, and, in Latin America, the average age is around 40 years<sup>(12)</sup>. These data are consistent with those observed in the present study. Moreover, in this study, women were more affected than men, in a 4:1 ratio, corroborating what is described in literature (3.6:1 ratio)<sup>(6,7)</sup>.

Extrahepatic autoimmune manifestations are observed in 22% to 50% of adult patients<sup>(17,19,34-37)</sup>. In Brazil, where the disease preferentially affects children, the frequency is much lower than that, being around 14% to 18%<sup>(17)</sup>. In the present study, 20% of the patients had association with extrahepatic autoimmune diseases, and all were women. These data are very close to what has been shown in other countries and also in Brazil<sup>(14,17,19,34-37)</sup>.

The initial manifestation of AIH ranges from asymptomatic forms, occurring in 10% to 20% of cases, to very symptomatic ones. The most frequent symptoms at presentation are fatigue and jaundice, affecting 30% to 40% of cases<sup>(1,10,11)</sup>. In our study, the most frequent symptom at presentation was jaundice (47.5%) and many patients were asymptomatic (40%).

European and North American studies<sup>(25-27,33,38-40)</sup> have shown

that cirrhosis is present in variable frequency at presentation of the disease, ranging between 26% and 42%. Many studies demonstrate that the diagnosis of cirrhosis at presentation is associated with lower overall survival<sup>(25,26,41,42)</sup>. Nevertheless, this association was not evaluated by other studies<sup>(12,14,15)</sup>.

One third of patients present with an insidious onset and gradual progression of the disease, without any apparent symptoms at diagnosis. In such cases, diagnosis is usually made during the investigation of increased aminotransferases<sup>(3,25,27,41)</sup>. Approximately 25% to 34% of patients present with an acute onset of AIH, phenotypically similar to acute onset in other casuistries<sup>(27,43)</sup>. In our study, 35.0% of patients presented with acute onset hepatitis, which is similar to what is described in literature. In addition, it is noteworthy that, among patients who presented with a clinical pattern of acute onset at diagnosis, 64.3% already had stage 3 or 4 fibrosis.

In relation to autoantibodies, ANAs occur in about 60–70% of patients with AIH, and SMA, in 60–87% of cases. Anti-LKM1 is rare in the United States of America, occurring in about 4% of adult patients; in Europe, its positivity can reach up to 20%, and, in Latin America, a Mexican study did not observe positivity of anti-LKM1<sup>(1,14,15,44,45)</sup>. In our study, ANAs were present in 65% of cases; SMA, in 60%; and anti-LKM1, in 5%.

The development of hepatocellular carcinoma in patients with AIH is rare<sup>(3,46-48)</sup>, significantly less common than with most of other causes of liver cirrhosis. Among the 40 patients evaluated in our study, there were no cases of hepatocellular carcinoma.

In relation to treatment, 85% of the patients used a combination of prednisone with azathioprine, which is the initial therapy choice for the AIH. In addition, 85.7% of cases showed complete or partial response to treatment, in accordance with other studies<sup>(10,19,39,46,49)</sup>. There were no differences regarding response to treatment when comparing cirrhotic patients with non-cirrhotic ones, which is in agreement with other studies<sup>(25,26)</sup>.

There are few studies that evaluated autoantibodies as markers of inflammatory activity in AIH, and although they have demonstrated an association with inflammatory activity<sup>(24,50)</sup>, it has been suggested that autoantibodies should not be used for monitoring the response to treatment<sup>(50)</sup>. Our results corroborate this recommendation.

Our study has potential limitations, especially related to its retrospective design, to the small number of patients included and to the fact that it was performed in a single center. Nevertheless, as our results are in agreement with what is described in literature, we believe that they probably are representative of the profile of patients with AIH in Southern Brazil.

## CONCLUSION

Most patients with AIH in Southern Brazil are young at presentation, women and Caucasian. The association with extrahepatic autoimmune diseases and cirrhosis at presentation occurs in a considerable proportion of patients. Treatment is effective, although there are no clinical, histological, or serological parameters with which it is possible to predict the response to therapy.

## Authors' contribution

All authors contributed to this paper with conception, drafting, revision, and approval of the final version of the manuscript.

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**RESUMO – Contexto** – A hepatite autoimune (HAI) é uma doença hepática crônica, de caráter necroinflamatório e etiologia autoimune. Os estudos que avaliam as características de pacientes com HAI são escassos no Brasil. **Objetivo** – Nosso objetivo foi avaliar o perfil dos pacientes com HAI atendidos em um centro de referência do sul do Brasil e verificar fatores relacionados à resposta ao tratamento. **Métodos** – Este foi um estudo de coorte retrospectivo, que analisou dados demográficos, epidemiológicos e clínicos. Nas biópsias hepáticas, foram avaliados o grau de fibrose, a atividade histológica, a presença de rosetas, de infiltrado plasmocitário e de necrose confluenta. Na análise estatística, o nível de significância foi de 5%. **Resultados** – Foram incluídos 40 pacientes adultos com diagnóstico de HAI. Houve predomínio do sexo feminino (75,0%), e a média de idade no diagnóstico foi de 44,2 anos. A associação com doenças autoimunes extra-hepáticas ocorreu em 20,0% dos casos. Clinicamente, 35,0% dos pacientes se apresentaram sob forma de hepatite aguda, 37,5% com cirrose e 27,5% com outras formas de apresentação. A manifestação clínica mais comum na apresentação foi a icterícia (47,5%). Trinta e cinco pacientes foram tratados, sendo que destes, 97,1% utilizaram prednisona associada com azatioprina. A média do tempo de tratamento foi 2,7 anos. A resposta ao tratamento foi completa ou parcial em 30 (85,7%) e ausente em 5 (14,3%) pacientes. Não houve diferença estatisticamente significativa quando avaliada a resposta ao tratamento em relação à forma de apresentação, aos achados histológicos e à presença de autoanticorpos. Em relação à fibrose, foi observada regressão em 18,75% dos casos. **Conclusão** – A maioria dos pacientes era jovem no momento do diagnóstico e do sexo feminino. A associação com doenças autoimunes extra-hepáticas e com cirrose na apresentação foi vista em uma parcela considerável dos casos. O tratamento foi eficaz, mas não houve parâmetros clínicos, histológicos ou sorológicos capazes de prever a resposta ao tratamento.

**DESCRIPTORIOS** – Hepatite autoimune. Resultado do tratamento. Dados demográficos. Imunossuppressores.

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