Clinical Characteristics and Prognosis in Children and Adolescents With Autoimmune Hepatitis and Overlap Syndrome

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ABSTRACT

Objectives: This is a cohort study of 134 children and adolescents with a known diagnosis of autoimmune hepatitis (AIH). During follow-up, some of them developed autoimmune sclerosing cholangitis (ASC). This study describes the characteristics of the patients upon diagnosis, and their response to treatment and any complications, and compares the patients who developed ASC during follow-up (ASC group) with those who did not (AIH group).

Methods: A total of 73.1% of the patients were girls with a median age upon diagnosis of 10.41 (7.41–12.53) years.

Results: Of 134 patients, 28 (20.9%) developed cholestatic manifestations, with features of ASC. A few differences were observed between the AIH and ASC groups when they were analyzed by χ^2 test, such as the smaller predominance of girls in ASC group ($P = 0.04$), and more common asymptomatic presentation in the ASC group ($P = 0.01$). Cirrhosis was observed in 68% of biopsies, with no significant difference between groups ($P = 0.43$). Of 16 deaths, 15 were in the AIH group and 1 in the ASC group ($P = 0.22$). Of 11 transplants, 10 were in the AIH group and one in the ASC group ($P = 0.53$). The presence of cirrhosis at baseline was associated with a smaller survival probability ($P = 0.015$). The survival rate by Kaplan-Meier method was 94% at 5 years and 80% at 10 years, and was similar in both the groups ($P = 0.08$).

Conclusions: No statistically significant difference was observed between the groups in relation to prognosis and response to treatment.

Key Words: autoimmune hepatitis, characteristics, children, overlap syndrome, prognostic

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What Is Known

- Autoimmune hepatitis is a rare autoimmune liver disease. It is known that autoimmune hepatitis has different clinical presentations and responses to treatment.

What Is New

- The present study describes the characteristics of children with autoimmune hepatitis, and their response to treatment and any complications, and compares the patients who developed autoimmune sclerosing cholangitis during follow-up with those who did not.
- The groups were similar in clinical presentation, laboratory findings, prognosis, and response to treatment, except that relapses were more frequent among those who developed autoimmune sclerosing cholangitis and normal gamma glutamyl transferase levels were not found in patients with ASC.
- Relapses did not alter survival probability but cirrhosis did.

Autoimmune hepatitis (AIH) is a chronic inflammatory disease, but is rare in childhood and adolescence (1); it is related to the loss of immunological tolerance to one's own liver (2–6). AIH has variable clinical manifestations (7–11). The peak incidence is in the second and third decades of life (4). It is associated with female sex, hypergammaglobulinemia, the presence of autoantibodies, and other autoimmune conditions in the patient and their families (11,12). The diagnosis is based on a scoring system (12–14) and exclusion of other chronic liver diseases. Primary sclerosing cholangitis (PSC), by contrast, is a progressive hepatobiliary disease of unknown etiology characterized by inflammation and stenosis of the intra- and extrahepatic biliary ducts (15,16). Diagnosis relies on evidence of abnormalities of the intra- or extrahepatic ducts, such as stenosis or dilatation on cholangiography (15).

Overlap between the manifestations of cholestasis and the classic manifestations of AIH, similar to PSC or primary biliary cirrhosis (PBC), has been described (2,11,16–19). Gregorio et al (18) proposed the term autoimmune sclerosing cholangitis (ASC) for children with radiographic features suggestive of sclerosing cholangitis and with a biopsy revealing interface hepatitis, associated with the presence of high levels of antibodies and

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immunoglobulin G in the serum (8,18,20). The response to treatment and prognosis of these patients is still uncertain, necessitating further studies to determine more appropriate management of this group.

Therefore, the present study aims to compare patients who developed ASC with those who did not, in an attempt to identify differences between the 2 groups, as well as their responses to treatment.

METHODS

This was a cohort study of 134 children and adolescents up to 18 years of age, with a known diagnosis of AIH, treated in the Hepatology Division of the Pediatric Gastroenterology Department at the Clinical Hospital of the Federal University of Minas Gerais (UFMG) from January 1986 to March 2014. The UFMG Ethics Committee approved this study.

The diagnosis of AIH was established according to the criteria set forth by the International Group for the Study of AIH and a simplified scoring system (12–14), and included patients with definite or probable diagnosis. A protocol was conducted in all patients to rule out other chronic liver diseases (21). Upon diagnosis or during follow-up, those patients who presented increased levels of gamma glutamyl transferase (GGT) and/or poor response to immunosuppressive treatment were referred for magnetic resonance imaging (MRI) of the biliary tract. The diagnosis of ASC was established when the MRI showed the presence of abnormalities in the biliary tract, such as stenosis and/or dilatation of the intra- and/or extrahepatic ducts. Two different trained hepatologists reviewed the biliary tract images.

Colonoscopy and antineutrophil cytoplasmic antibodies search was performed only in those who showed changes in MRI.

Clinical, Laboratory, and Histopathological Evaluation

The study evaluated the clinical presentation and the findings of laboratory tests. Clinical presentations were classified into prolonged acute form, similar to the clinical picture of acute viral hepatitis; chronic form, identified by the presence of ascites, hepatomegaly, intermittent jaundice, and splenomegaly; severe liver failure, with appearance similar to fulminant hepatic failure; and silent, characterized by the absence of complaints or obvious physical symptoms, but with the presence of abnormal laboratory test results. The severity rating of liver disease in patients with cirrhosis was conducted by means of the Child-Pugh score (22).

The following laboratory tests were conducted: complete blood count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), GGT, serum bilirubin, and serum proteins; quantitative and qualitative autoantibody levels, such as antinuclear antibody (ANA), antismooth muscle antibody (ASMA), and antimicrosomal antibody liver and kidney type 1 (anti LKM1), were detected by indirect immunofluorescence. Liver tissue was obtained by ultrasound-guided percutaneous puncture or by blind percutaneous biopsy. The fragments were fixed in 10% formaldehyde-saline and processed according to routine histological techniques, until paraffin embedding. The paraffin blocks were cut by a microtome and 4 slides obtained from each block contained serial histological sections 5- to 7-μm thick; these were prepared with hematoxylin-eosin, reticular, and Gomori or Massons trichrome stains. The histopathological evaluation of the liver was performed by trained pathologists and reviewed at the Pathology Department of the UFMG Clinical Hospital.

Evaluation Criteria for the Treatment and Suspension of Immunosuppression

The treatment consisted of a combination of prednisone ($1–2\ mg \cdot kg^{-1} \cdot day^{-1}$, up to $60\ mg \cdot day^{-1}$) and azathioprine ($1.5\ mg \cdot kg^{-1} \cdot day^{-1}$, up to $100\ mg \cdot day^{-1}$). Prednisone dose was reduced slowly to maintain the patient in clinical and laboratory remission. Azathioprine was maintained at the same dose from the beginning of treatment. In the event of leukopenia (<1500) and/or thrombocytopenia (<50,000), the introduction of azathioprine was delayed until the improvement of these parameters; otherwise only prednisone was maintained. A dose of 15 to 20 $mg \cdot kg^{-1} \cdot day^{-1}$ of ursodeoxycholic acid was added to the treatment for those who developed ASC. The treatment response was evaluated according to the criteria of the International Group for the Study of AIH, published in 1999 (12).

The suspension of pharmacological treatment was possible if a complete response to treatment had been achieved, characterized by clinical and laboratory remission (aminotransferases, autoantibodies, and gamma globulin within reference ranges), negative autoantibodies (ANA, ASMA, anti-LKM1) for at least 24 months, and no inflammatory activity on liver histopathology. The reactivation criteria were as follows: presence of any clinical manifestations suggestive of the disease, elevated aminotransferase levels, increased gamma globulin fractions, or the reappearance of autoantibodies. Any change in at least 1 of these parameters led to resumption of the original pharmacotherapy.

Liver transplantation was indicated for patients with cirrhosis and Model for End-Stage Liver Disease score >12, Child-Pugh grade B8 or greater, or no response to treatment.

Statistical Analysis

Data were analyzed using the Epi Info 7.1.3.3 program (Atlanta, GA). In order to compare continuous variables, this study applied analysis of variance testing for parametric data or the Mann-Whitney/Wilcoxon and Kruskal-Wallis tests when analysis of variance was not recommended. The comparison of the distribution of categorical variables was analyzed by the 2-tailed Fisher exact test or χ^2 test with Yates correction. The result was considered statistically significant for $P < 0.05$. Continuous variables without normal distribution were expressed as medians and interquartile ranges (IR 25%–75%). Continuous variables with normal distribution were expressed as mean and standard deviation. Survival analysis was performed using the Kaplan-Meier method correlating classical AIH and ASC clinical presentations and patients with and without cirrhosis at diagnosis. The log-rank and Wilcoxon tests were used and considered significant when $P < 0.05$.

RESULTS

At baseline, a total of 134 patients had only the diagnosis of AIH. Ninety-eight (73.1%) were girls; the median age at diagnosis was 10.41 years (Table 1). Acute (37.3%) and chronic forms (38.8%) were equally common. Twenty-eight (20.9%) patients developed cholestatic manifestations during follow-up (ASC group). The median time between initial diagnosis of AIH and the characterization of ASC was 5 months, ranging from 2 to 21 months. The comparison between the AIH and ASC groups during follow-up is shown in Table 1.

Laboratory abnormalities, found in all of the 134 patients at baseline, are described in Table 2. When comparing AIH group and ASC group, no statistically significant difference was observed.

Regarding the GGT level in the early follow-up period, no difference was observed between the AIH and the ASC groups

TABLE 1. The baseline clinical characteristics of patients with a known diagnosis of autoimmune hepatitis and the comparison between those who developed autoimmune sclerosing cholangitis during the follow-up (ASC group) and those who did not (AIH group)

	Total (134)	AIH group (106)	ASC group (28)	*P*
Score diagnosis: AIH definitive	73	57	16	
AIH likely	61	49	12	0.83
Female sex*	98 (73.1%)	82 (77.3%)	16 (57.1%)	0.04
Age at diagnosis,† y	10.41 (7.4–12.5)	10.5 (7.3–12.8)	10.7 (8.4–11.5)	0.76
Clinical presentation				
Prolonged acute hepatitis*	50 (37.3%)	42 (39.6%)	8 (28.6%)	0.38
Chronic form*	52 (38.8%)	38 (35.8%)	14 (50%)	0.19
Liver failure*	20 (14.9%)	18 (17%)	2 (7.1%)	0.24
Silent*	11 (8.2%)	5 (4.7%)	6 (21.4%)	0.01
Other*	1 (0.74%)	1 (0.94%)	0	1
Other autoimmune manifestations				
Hemolytic anemia*	3 (2.2%)	3 (2.8%)	0	0.49
Thyroiditis*	4 (2.9%)	4 (3.7%)	0	0.38
Vitiligo*	3 (2.2%)	1 (0.9%)	2 (7.1%)	0.11
Arthritis and/or arthralgia*	10 (7.5%)	8 (7.54%)	2 (7.1%)	0.65
Acneiform lesions*	4 (2.9%)	3 (2.8%)	1 (3.5%)	0.61
Autoimmune disease in relatives*	49 (36.6%)	39 (36.8%)	10 (35.7%)	0.57
Liver disease in relatives*	14 (10.4%)	11 (10.4%)	3 (10.7%)	0.76

AIH = autoimmune hepatitis; ASC = autoimmune sclerosing cholangitis.

AIH group: patients who did not develop ASC during follow-up; ASC group: patients who developed ASC during follow-up.

Less frequent autoimmune manifestations: psoriasis (1 patient), uveitis (1 patient), idiopathic thrombocytopenic purpura (1 patient), systemic lupus erythematosus (1 patient), celiac disease (1 patient), and inflammatory bowel disease (1 patient).

* Number (frequency, %).

† Median (interquartile range 25%–75%).

TABLE 2. Comparison between autoimmune hepatitis group and autoimmune sclerosing cholangitis group concerning the laboratory parameters at baseline, the histological changes at the first biopsy and the Child-Pugh score among those patients that received the diagnosis of liver cirrhosis

	Total (134)	AIH (106)	ASC (28)	*P*
DB, mg/dL*	1.8 (0.6–3.5)	1.85 (0.59–3.5)	1.65 (0.6–4.7)	0.89
TB, mg/dL*	3.3 (1.34–5.9)	3.55 (1.32–5.7)	2.7 (1.4–7)	0.85
ALT increase (UNL)*	6.31 (2.53–13.12)	6.31 (2.45–13.41)	6.1 (3.24–12.8)	0.39
AST increase (UNL)*	9 (4–17)	8.7 (4–17)	10.06 (4.46–18)	0.60
AP increase (UNL)*	1.22 (0.69–2.06)	1.05 (0.56–2.29)	1.43 (1.11–1.71)	0.70
Ratio AP/AST*	0.16 (0.045–0.34)	0.16 (0.04–0.32)	0.16 (0.06–0.44)	0.53
Albumin, g/dL*	3.57 (3.11–3.92)	3.57 (3.1–3.9)	3.57 (3.17–3.94)	0.79
GGT increase (UNL)*	3.28 (2–5)	3 (1.8–4.33)	4.5 (2.3–6.23)	0.07
IgG increase (UNL)*	1.67 (0.75–2.5)	1.67 (0.8–2.46)	1.6 (0–2.63)	0.55
ANA: n (%)	77 (57.7%)	59 (55.7%)	18 (64.3%)	0.54
ASMA: n (%)	91 (69.7%)	71 (67%)	20 (71.4%)	0.82
Anti-LKM1: n (%)	5 (3.7%)	5 (4.7%)	0 (0%)	0.58
ANA title*	1: 320 (160–640)	1: 320 (80–640)	1: 320 (320–640)	0.85
ASMA title*	1: 320 (80–640)	1: 320 (80–640)	1: 640 (80–640)	0.98
Anti-LKM1 title*	1: 640 (160–640)	1: 640 (160–640)	0	0.11
Biopsy performed*	103	81	22	
Cirrhosis†	71 (68%)	54 (67%)	17 (77%)	0.43
Hepatitis interface†	56 (54%)	50 (62%)	6 (27%)	0.008
Rosettes†	27 (26%)	25 (31%)	2 (9%)	0.05
Child-Pugh A‡	27%	24%	35%	0.80
Child-Pugh B‡	56%	55%	59%	1.00
Child-Pugh C‡	18%	22%	6%	0.27

AIH = autoimmune hepatitis; ALT = alanine aminotransferase; ANA = antinuclear antibody; Anti-LKM1 = anti-liver and kidney microsomal antibody type 1; AP = alkaline phosphatase; ASMA = antismooth muscle antibody; ASC = autoimmune sclerosing cholangitis; AST = aspartate aminotransferase; Child-Pugh A = mild hepatic insufficiency; Child-Pugh B = moderate hepatic insufficiency; Child-Pugh C = severe hepatic insufficiency; DB = direct bilirubin; IgG = immunoglobulin G; TB = total bilirubin; UNL = upper normal limit.

* Median (interquartile range 25%–75%).

† Number (frequency, %).

‡ Percentage.

TABLE 3. The comparison of the treatment response between those patients who developed autoimmune sclerosing cholangitis during the follow-up (ASC group) and those who did not (AIH group)

Evolution	AIH group (106)	ASC group (28)	*P*
Treatment type			
Prednisone + azathioprine*	67 (63.2%)	9 (32.1%)	0.006
Prednisone*	5 (4.7%)	4 (14.3%)	0.09
Prednisone at first and latter azatioprine was added*	33 (31.1%)	15 (53.6%)	0.04
Not started*	1 (0.9%)	0 (0%)	0.47
Response to treatment			
Complete response*	75 (70.8%)	21 (75%)	0.81
No response*	8 (5.97%)	5 (17,85%)	0.1
Normalization of AMT (aminotransferases)*	82 (77.35%)	22 (78%)	0.9
Time (mo) of treatment by AMT normalization†	6 (3–12)	11.5 (5–19)	0.39
Time (mo) of treatment to remission†	13.5 (6.5–23)	23 (10–27.5)	0.18
Time (mo) of remission in maintenance dose†	84 (36–156)	36 (24–60)	0.03
Patients with a relapse during treatment*	41 (38.67%)	16 (57.1%)	0.04

AIH = autoimmune hepatitis; AMT = aminotransferases; ASC = autoimmune sclerosing cholangitis
AIH group, patients with AIH who did not develop ASC; ASC group, patients with AIH who develop ASC.
* Number (frequency, %).
† Median (interquartile range 25%–75%).

($P = 0.07$). Those patients whose GGT level increased during follow-up period, however, had the diagnosis of overlap syndrome more often than those whose GGT level remained normal ($P = 0.018$). It was also observed that none of the patients whose GGT values were normal or rose up to 1.5 times the upper normal limit at baseline developed ASC ($P < 0.017$).

Thirty-six patients presented increased levels of gamma glutamyl transferase (GGT) and/or poor response to immunosuppressive treatment and were referred for magnetic resonance imaging (MRI) of the biliary tract. Twenty-five showed stenosis and/or dilatation of the intrahepatic ducts and 3 patients had both, extra- and intrahepatic changes.

Regarding histological findings, biopsy was performed just once at baseline in most patients (Table 2). The clinical condition of some patients would not permit biopsy, which was delayed until their condition improved. Patients with AIH had a higher frequency of interface hepatitis than the overlap syndrome group ($P = 0.008$). Regarding the presence of rosettes, the difference only showed a trend ($P = 0.05$). No difference was identified between the groups ($P = 0.43$) when comparing the presence of cirrhosis or the Child-Pugh score.

The most common treatment was the combination of prednisone and azathioprine (63.2%), followed by the use of prednisone at baseline with azathioprine added later (31.1%). Cyclosporine and mycophenolate were prescribed for 1 patient by the transplantation team. This patient responded well to treatment, transplantation was not needed, and the treatment was later changed. Relapses were frequent and occurred most often in the ASC group in which 51.7% of those who had responded to treatment had at least 1 versus 38.67 % in AIH group ($P = 0.04$). The number of relapses per patient was 1 (0–2); this median was also 1 (0–1) in the AIH group, and 1 (1–3) among those with ASC ($P = 0.018$). The total of relapses were 1 to 9 among patients with AIH and 1 to 7 in ASC group; however, 21% of the patients with ASC had 3 or more relapses against 7.5% in AIH group ($P = 0{,}032$). Among patients with relapse, only 6 died. The probability of death was similar between patients who did or did not present with relapse during treatment ($P = 0.45$). Treatment was discontinued in 15 (11.2%) patients with AIH; however, reactivation occurred in 4 (26.7%). The comparison between the clinical course and response to treatment between AIH and ASC groups is shown in Table 3.

Of 16 deaths (11.9%), 15 (14%) were in the AIH group and 1 (3.5%) in the ASC group ($P = 0.32$). The causes of death were end-stage liver failure (9/16), septic shock (3/16), digestive hemorrhage (1/16), intracranial bleeding (1/16), motorcycle accident (1/16), and chirurgical complications during liver transplantation (1/16). The end-stage liver failure was linked to not taking the medicines (5/9), digestive bleeding (2/9), and treatment failure (2/9). Of 11 patients (8.2%) who underwent liver transplant, 10 (9.4%) were in the AIH group and 1 (3.5%) in the overlap syndrome group ($P = 0.28$). One death and no relapse occurred in patients submitted to liver transplant. The median follow-up was 6.08 (2.75–10.5) years in the total group of patients, 7.08 (2.67–11.67) years in the AIH group, and 4.08 (2.75–7.16) years in the ASC group ($P = 0.06$). Nine patients (6.7%) of the total presented treatment complications, but no difference was observed between patients in the AIH and ASC groups ($P = 0.23$). The observed complications were thrombocytopenia (2 patients), pancreatitis (2), diabetes mellitus (1), leukopenia (1), and pancytopenia (1).

Survival analysis was performed using the Kaplan-Meier method, comparing patients from AIH and ASC groups, and no significant difference was identified (log-rank: $P = 0.4$), Wilcoxon test: $P = 0.37$). In a comparison of AIH and ASC groups, the 5-year survival rate was 93% and 89%, and the 10-year survival rate was 79% and 89%, respectively.

The probability of survival among patients with and without cirrhosis at baseline revealed a significant difference (log-rank: $P = 0.0159$, Wilcoxon test: $P = 0.0194$). Pearson correlation coefficient was 0.97. In patients with cirrhosis, the 5-year survival rate was 88%, and the 10-year survival rate was 76%. In patients without cirrhosis, the survival rate was 100% at both 5 and 10 years. Some of the patients (31/23%) had no record of having biopsies. Among these, the 5-year survival rate was similar to those without cirrhosis, but the 10-year survival rate was lower (Fig. 1); the rates in this group were 100% and 87%, respectively.

With regard to clinical presentation, the following 5- and 10-year survival rates were found. Among those with the acute form, the 5- and 10-year survival rates were 100% and 83%, respectively. Among those with the chronic form, they were 84% and 82%. Among those with the acute/fulminant form, they were 83% and 72%. For those with the silent form the 5- and 10-year survival rates were both 89% (log-rank: $P = 0.5$, Wilcoxon test: $P = 0.27$).

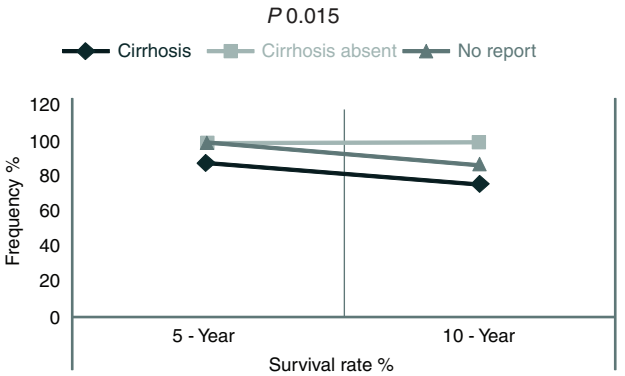

FIGURE 1. Probability of survival among the patients according to the presence or absence of cirrhosis at baseline. Kaplan-Meier method: (log-rank: $P = 0.015$, Wilcoxon test: $P = 0.019$).

DISCUSSION

AIH is defined by clinical, laboratory, and histological criteria that have been specifically revised to exclude cholestatic manifestations (19). The estimated frequency of the cholestatic phenotype is 14% to 20%, and is 2% to 11% in adults with the AIH/PSC overlap syndrome (19). This study aimed to determine the possible differences between patients with AIH who did and did not develop overlap syndrome. The reasons for the coexistence of these phenotypes in AIH are still uncertain. They could be part of the same disease with different clinical manifestations of a transitional stage in the evolution of PSC, or they may be 2 coexisting but different autoimmune diseases (18). The ASC happens mostly in patients with AIH or patients with inflammatory bowel disease or both (15). In this cohort, patients showed predominantly AIH phenotype. That could be an explanation by the low number of patient with inflammatory bowel disease.

There is also uncertainty concerning the course and the prognosis of these groups. The presence of signs of cholestasis, such as an increased level of AP and/or GGT, presence of aggressive involvement of the biliary tract seen on histological exam, or changes found on cholangiography are associated with a worse response to conventional therapy with corticosteroids (19).

The clinical presentations most often found in this cohort differed somewhat from those reported by other authors who observed a higher frequency of acute forms (3,23–27). In this cohort, the acute and chronic forms appeared equally common. When the data of the 2 groups were analyzed separately, it was, however, found that the acute form was more frequent in the AIH group, whereas in the ASC group, the chronic form was more common. The silent form was observed more frequently among the ASC group than among those of the AIH group. Concerning sex, a less-pronounced frequency in girls was observed in the ASC group, which has also been observed by other authors (15,18).

Laboratory findings at baseline were similar in both groups in this study. Gregorio et al (2001) studied 28 children and adolescents with AIH and 27 with ASC and reported higher values of total bilirubin, AST, and international normalized ratio in the AIH group, as well as higher values of the AP/AST ratio, and a higher proportion of positive antineutrophil cytoplasmic antibody in the ASC group. The authors found no differences in GGT levels or positive results for other autoantibodies or immunoglobulins (18). Rojas et al (27) in 2014, in a study involving 34 children and adolescents, in which 23 had AIH and 11 had ASC, found a few differences, such as a higher level of AST and positive ANA rates in the AIH group, and a higher level of GGT in the ASC group. In the present study, the level of GGT at baseline was similar in the 2 groups, but during the follow-up period, an increase suggested overlap syndrome.

Regarding histology at baseline, not all patients had biopsy performed, mostly due to critical clinical status and coagulopathy; however, they showed clinical and laboratory signs suggestive of AIH. In all who had a biopsy (103/134), histopathology was suggestive of AIH, but there were no biliary changes or lesions. As this was a long-term cohort study, some of these critical patients had the diagnosis of AIH established before 2008, according to the criteria set forth in 1993 or 1999 (12–14). Interface hepatitis was more prevalent in the AIH group. Presence of cirrhosis was observed in more than half of the biopsies, which was similar in both groups. Gregorio et al (18) in 2001 found interface hepatitis to be the main biopsy feature in both groups; however, changes in the histology of the bile ducts could also be observed in the overlap group, which was not observed in the present study. Gregorio et al (18) found a 15% prevalence of cirrhosis in patients with overlap syndrome, compared with 23% in patients with AIH. In this article, another biopsy was not performed by the time the changes on cholangiography were observed, because it was believed that those changes were sufficient for a diagnosis of ASC. This could be a reason why there was no biliary component or biliary cirrhosis in the ASC group. Another possibility was that established cirrhosis may have hindered histological evaluation.

In this study, the diagnosis of overlap syndrome was established by magnetic resonance cholangiography, which was recommended in those with GGT changes during follow-up, those whose response to treatment was considered unsatisfactory, or those who had no response to treatment. Of 134 patients studied, 28 (20.9%) developed cholestatic manifestations. In this study, the median time between initial diagnosis of AIH and the characterization of overlap syndrome was 5 months, ranging from 2 to 21 months.

Proper treatment improves the prognosis and reduces the formation of fibrosis and progression to cirrhosis in patients with AIH (9,21). The expected frequency of remission with treatment is around 80% (6,28). In this study, most patients (78.3%) improved with treatment, but relapses were frequent. The presence of relapses did not change the survival rate.

Although some authors report that adults with overlap syndrome are less responsive to treatment (20), no difference was observed in response to treatment or in prognosis among AIH or ASC groups in the present study. The frequency of complete response to treatment was similar among AIH and ASC groups. The percentage of patients who experienced relapse was higher in the ASC group, but this did not change the survival rate. Liver transplantation was performed in 8.2% of patients, similar to that in the report of Mieli-Vergani and Vergani (24) that identified the need for transplantation in 8.5% of patients after 8 to 14 years of treatment.

In the present study, the observed survival rate ranged from 78% to 100%. The presence of overlap or the presentation form did not influence the survival rate, but the presence of cirrhosis at baseline did. Gregorio et al (2001) reported a good prognosis for patients with overlap syndrome, with a survival rate reaching 100% after 7 years of follow-up, and 4 of 27 patients requiring transplantation at between 2 and 11 years of treatment.

The question of whether AIH and overlap syndrome are different diseases or different clinical manifestations of the same disease remains. This study series showed that the 2 groups had similar presentations regarding clinical, laboratory, and histopathological changes. The overlap syndrome, however, revealed a less-pronounced predominancy in girls, whereas the silent form appeared more often. Moreover, an increase in GGT levels during follow-up was also more significant in the ASC group. On the other hand, normal GGT levels at baseline were not found among patients with ASC. There was no statistically significant difference between

the groups regarding the prognosis and response to treatment. Relapses did occur, but, however, did not affect the survival rate and the need for liver transplantation. On the other hand, the presence of cirrhosis was linked to a decrease in the probability of survival, regardless of the group and clinical presentation.

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