Incidence and Clinical Features of Autoimmune Hepatitis in the Province of Santa Fe (Argentina)

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ABSTRACT

Objectives: The aim of the study is to investigate the incidence and clinical features of autoimmune hepatitis (AIH) in children from the province of Santa Fe, Argentina, for 10 years.

Methods: From the records of all of the pediatric hepatologists in the province of Santa Fe, Argentina, we reviewed the clinical charts of patients <18 years who were diagnosed with AIH (simplified score >6 points) and followed between January 2003 and December 2013. Population data were extracted from the 2010 national census. Values were expressed as percentages and median ± interquartile range. Mann-Whitney U test was used for comparison between the groups.

Results: Sixty-seven patients fulfilled inclusion criteria, from which 11 (16%) were later reclassified as having “autoimmune sclerosing cholangitis” according to biochemical, histological, and radiological findings. A final sample of 56 patients (39 F) with AIH was analyzed, giving an annual incidence of 0.56/100,000. Median age at presentation was 8 (5.7–11) years, and the median follow-up was 4 (2–7) years. Type 1 AIH was diagnosed in 89%. An acute presentation was observed in 53%, while 13 (23%) showed cirrhosis on initial biopsy. Prednisone (87%) and azathioprine (60%) were the most common drugs prescribed. At the end of follow-up, 53/56 (95%) were alive, including 4 patients (7%) who underwent liver transplantation.

Conclusions: AIH has an estimated incidence of 0.56/100,000 per year in children from the province of Santa Fe (Argentina). Overall survival rate was 95%. A subgroup of patients diagnosed as AIH develops predominant biliary disease and should be better classified as autoimmune sclerosing cholangitis.

Key Words: autoimmune hepatitis, autoimmune sclerosing cholangitis, children, incidence

What Is Known
• Autoimmune hepatitis is a progressive, immunologic-based liver disease with good response if properly diagnosed and treated.
• Population-based studies are scarce, especially from developing countries.

What Is New
• Our study estimates the incidence of autoimmune hepatitis in a population-based cohort of children of age 0 to 18 years living in a province of Argentina.
• Clinical characteristics and responses to different treatments are described.
• Some children with biliary tree disease can be distinguished from autoimmune hepatitis based on gammaglutamyl transpeptidase values despite fulfilling criteria for autoimmune hepatitis.
Primary sclerosing cholangitis was ruled out on clinical (increase gamma-glutamyl transpeptidase/ALT ratio), histologic (periductal fibrosis and/or neoductular proliferation) and imaging studies (periductal fibrosis and/or dilatations/strictures of the biliary tree). “Autoimmune sclerosing cholangitis” (ASC) was diagnosed in children initially fulfilling diagnostic criteria for AIH, but eventually developing the characteristic features of primary sclerosing cholangitis during follow-up. Magnetic resonance imaging (MRI) cholangiography was performed when values of GGT continued to rise or did not normalize despite immunosuppressive treatment, especially if values of aminotransferases decreased as expected. These patients were excluded for epidemiologic analysis.

Data were extracted from the patient’s records, and ad-hoc formularies were filled. For the purposes of the study we focused on demographics, clinical findings, biochemistry, and histology both at diagnosis and during follow-up (liver biopsies were only repeated if needed).

Values were expressed as percentages and median ± interquartile range. Mann-Whitney U test was used for comparison between groups. A P < 0.05 was considered significant. Ethical approval was obtained from the Institutional Board of each participating center.

RESULTS

Initial diagnosis of AIH was made on 67 patients, from whom 11 (16%) were later reclassified as ASC. Therefore, a final sample of 56 patients (39 girls) with AIH was analyzed, giving an annual incidence of 0.56/100,000 (total calculated 0–18 years old population of 10,017,106 people during the 10-year study period). In our cohort, only 1 patient (a girl with a sister experiencing AIH) showed a score of 6 points (“definite AIH”), and 55/56 scored 7 or more points, (“definite AIH”). Female to male ratio was 2.3/1, median age at presentation was 8 (5.7–11) years, and the median follow-up was 4 (2–7) years. Age distribution of AIH patients at diagnosis is depicted in Figure 1. No differences were found between AIH and ASC patients.

Type 1 AIH was diagnosed in 89%, and the remaining 11% were type 2. In 13/56 (23%) of children, another immune mediated disease was found: ulcerative colitis in 3 patients; insulin-dependent diabetes, celiac disease, and psoriasis in 2 patients each; systemic erythematous lupus, hemolytic anemia, thyroiditis, and glomerulonephritis in one patient each. An acute (icteric) form of presentation was observed in 53% of the cases, from whom 3 (5%) developed severe acute liver failure, while 13 (23%) had cirrhosis on the first biopsy.

Prednisone (87%) and azathioprine (60%) were the most common prescribed medications. Mycophenolate-mofetil (7%), cyclosporine (5%), tacrolimus (3.5%), and rituximab (3.5%) were used in non-responder patients or when severe side effects such as uncontrolled diabetes, rising intraocular pressure, severe osteopenia, or bone marrow suppression were present. At the end of the first year 68% of patients showed normal values of aminotransferases (complete response), and 53/56 (95%), were alive at the end of the follow-up period. Three patients died, 2 from sepsis and 1 from uncontrolled variceal bleeding. Liver transplantation was performed in 4 patients (7%), 2 with acute liver failure without previous history of liver disease, 1 with pulmonary hypertension (mean pulmonary artery pressure [mPAP] of 36 mm Hg, with a pulmonary vascular resistance [PVR] of 573 dyn/sec/cm-5 which reverted after liver replacement), and the remaining with acute encephalopathy after transjugular intrahepatic portosystemic shunt placement for refractory bleeding and ascites. The 4 transplanted patients were alive and well at the end of the study period.

When comparing children with AIH versus ASC, we observed significantly higher values of GGT at presentation in ASC patients as a whole, but some overlap was also seen: AIH 71 IU/L (37–140 IU/L); ASC 481 IU/L (107–864 IU/L); (P = 0.007) (Table 1). No patient with normal serum value of GGT at baseline was seen in the ASC group. Patients diagnosed with ASC were initiated on ursodeoxycolic acid at a dose of 10 to 20 mg/kg per day.

DISCUSSION

Population-based data on AIH in pediatric patients are scarce. In the present study, we estimate an incidence of 0.56/100,000 is recently reported in Canadian children. Of note, some eastern provinces in this last study show incidences of 0.58 and 0.52/100,000, similar to estimates in the series from Deneau et al.

![FIGURE 1. Age distribution of autoimmune hepatitis (AIH) versus autoimmune sclerosing cholangitis (ASC) patients.](image-url)

*AIH mean 8 years (5.7–11 IQR), ASC mean 9 years (6.5–11.5 IQR) (p = 0.26, Mann-Whitney “U” test). No patient with ASC was less than 5 years.*
and our own (4,5). Reliability of these types of studies depends on the correct categorization of cases and the assumption that practically all patients from the population studied are included.

We are confident about the validity of our study population because the 3 participating centers are the only pediatric gastroenterology-hepatology divisions in our province, covering an area of 1 million people aged less than 18 years. In addition, results from our cohort are representative and similar to other published pediatric series with respect to clinical and laboratory findings and response to treatment (3–6).

Diagnosis of AIH is based on established criteria, but some overlap with ASC patients, especially in children, is unavoidable (1–3,7). Two recent consensus statements, from the American Association for the Study of Liver Disease and the European Society of Pediatric Gastroenterology Hepatology and Nutrition, recommend performance of a cholangiographic study as part of the evaluation of every pediatric patient to rule-out biliary disease (8,9).

In our series, cholangiographic studies were indicated only in cases of a suboptimal response to treatment or either clinical or biochemical evidence of cholestasis. Therefore, some ASC patients were likely misclassified as AIH. Although this topic will continue to be controversial, we think that in the present study the incidence of that “misclassification” is low, owing to our high scores at diagnosis of AIH and a low level of threshold to do an MRI cholangiography in suspected patients. We found that 16% of patients initially diagnosed as AIH were later reclassified as ASC, in accordance with other published reports (3,10,11). This group, as a whole, showed GGT levels significantly higher than AIH patients at presentation, similar to previous reports (12).

Type 1 AIH was diagnosed in the majority of our children (nearly 90%), while other immune mediated diseases were also observed in a significant proportion (almost 1 in 4), a finding very similar to the study from Canada (5). Ulcerative colitis was the main comitant associated disease, found in 6% of AIH patients, although this rate could be higher with more widespread use of colonoscopy (2). Other coexistent immune-related diseases in our patients were celiac disease, psoriasis, systemic lupus, hemolytic anemia, thyroiditis and glomerulonephritis. Clustering of immune mediated diseases is a well-known characteristic of this group of disorders, raising the need to look for liver disease in those scenarios, and vice-versa (12).

Clinical presentation of AIH shows a very diverse spectrum, from acute hepatic failure to asymptomatic patients detected only on biochemical tests. Half of our patients presented with an acute form characterized by jaundice and elevated aminotransferases. Two of them developed liver failure and underwent liver transplantation, highlighting the potential seriousness of this condition, which could be otherwise controlled with appropriate immunosuppression, even in the most severe situations (13). Conversely, we also observed a chronic, silent form characterized by a systemic, more insidious course with asthenia and hepatomegaly in the remaining children, and 23% showed cirrhosis on the first biopsy. It should be kept in mind that cirrhosis could be underestimated based on needle samples (14). Nevertheless, it is clear that it is already present from the outset in a significant proportion of the patients and should always be sought to accurately plan follow-up.

For more than 40 years, corticosteroids and azathioprine have constituted the backbone of treatment (15,16). Recently, however, new drugs have been introduced as alternatives, mainly adopted from the transplantation field, to improve outcomes and minimize side effects (2,17,18). In our cohort, more than two-thirds of patients received the standard treatment with corticosteroids and azathioprine, but mycophenolate mofetil, calcineurin inhibitors, and even rituximab was eventually used, especially in refractory cases, as previously published by our group (19). The 1-year rate of remission of 68% is somewhat lower than expected but could reflect suboptimal adherence from the patients (20). Nevertheless, at the end of follow-up, 95% of the patients were alive, including the 4 transplanted children.

In summary, AIH has an estimated annual incidence of 0.56/100,000 among children 0 to 18 years old living in the province of Santa Fe, Argentina. Current therapies are effective in halting the progression of the disease, with 5-year survival above 90%. GGT levels can help to identify a subgroup with predominant biliary disease, “Autoimmune Sclerosing Cholangitis,” that should be approached in a different way compared with AIH.

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REFERENCES


