Incidence and Characteristics of Autoimmune Hepatitis

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BACKGROUND AND OBJECTIVES: Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease of unknown etiology, with limited population-based estimates of pediatric incidence. We reported the incidence of pediatric AIH in Canada and described its clinical characteristics.

METHODS: We conducted a retrospective cohort study of patients aged <18 years diagnosed with AIH between 2000–2009 at all pediatric centers in Canada.

RESULTS: A total of 159 children with AIH (60.3% female, 13.2% type 2 AIH) were identified. Annual incidence was 0.23 per 100,000 children. Median age at presentation for type 1 was 12 years (interquartile range: 11–14) versus 10 years for type 2 (interquartile range: 4.5–13) (P = .03). Fatigue (58%), jaundice (54%), and abdominal pain (49%) were the most common presenting symptoms. Serum albumin (33 vs 38 g/L; P = .03) and platelet count (187,000 vs 249,000; P < .001) were significantly lower and the international normalized ratio (1.4 vs 1.2; P < .001) was higher in cirrhotic versus noncirrhotic patients. Initial treatment included corticosteroids (80%), azathioprine (32%), and/or cyclosporine (13%). Response to treatment at 1 year was complete in 90%, and partial in 3% of patients had no response, and 3% responded and later relapsed. Nine patients underwent liver transplantation, and 4 patients died at a mean follow-up of 4 years.

CONCLUSIONS: AIH is uncommon in children and adolescents in Canada. Type 1 AIH was diagnosed 5.5 times more frequently than type 2 AIH. Most patients respond well to conventional therapy, diminishing the need for liver transplantation.

WHAT’IS KNOWN ON THIS SUBJECT: Pediatric autoimmune hepatitis is an uncommon condition; children and youth can present with a diverse and insidious clinical course and biochemical features. Response to treatment is generally good, and transplantation is rarely needed.

WHAT THIS STUDY ADDS: This population-based study adds knowledge regarding the incidence of pediatric autoimmune hepatitis in Canada, as well as a description of diagnostic and therapeutic approaches among centers. Long-term outcomes are also described.
Autoimmune hepatitis (AIH) is a progressive inflammatory liver disease of uncertain etiology. Its pathogenesis seems to be multifactorial, including genetic susceptibility, abnormal regulation of the immune response, and environmental triggers. Two subtypes have been recognized based on the presence of serum autoantibodies. Patients with type 1 AIH have anti-smooth muscle and/or antinuclear autoantibodies, whereas type 2 is characterized by the presence of anti-liver kidney microsomal and/or anti-liver cytosol type 1 (LC1) autoantibodies. 

Autoantibodies can be positive in other hepatic conditions such as viral hepatitis and Wilson’s disease, as well as sclerosing cholangitis; high titers favor the diagnosis of AIH. The presence of combined antibodies increases the accuracy of an AIH diagnosis.

Both types of AIH may be diagnosed in childhood, are more common in female subjects, and may be associated with an extrahepatic autoimmune disease such as arthritis, inflammatory bowel disease, thyroiditis, or diabetes. Risk factors for AIH include celiac disease, immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome. Drugs associated with AIH-like hepatotoxicity include diclofenac, methyldopa, hydralazine, nitrofurantoin, minocycline, and, more recently, statins and anti-tumor necrosis factor-α agents.

A recent study in pediatric patients reported an incidence of 0.4 case per 100 000 children. Another study from Poland reported an incidence of 3 to 4 per 100 000 children. Available adult data indicate an incidence varying from 0.67 to 2 cases per 100 000 people. Ethnic background has been reported as a key factor in clinical presentation and outcomes for patients with AIH, however, this finding is not universal. In the present national study, our primary aim was to determine the incidence of AIH in children and adolescents in Canada and to describe its clinical characteristics and natural history. In addition, we attempted to identify risk factors for poor outcomes.

METHODS

Under the auspices of the Canadian Pediatric Hepatology Research Group, we performed a multicenter retrospective review of all new cases of AIH diagnosed in children aged <18 years in Canada between January 1, 2000, and December 31, 2009, and who were followed up in an academic pediatric center. Representatives of each center were invited to participate. These representatives identified all eligible children by using health record departments as well as diagnosis support offices and personal databases. Patients were considered to have AIH when there was evidence of abnormal liver test results without any other identifiable liver disease. Although the presence of autoantibodies and/or elevation of immunoglobulin G supported the diagnosis, their absence was not an exclusion criterion. When possible, histologic abnormalities confirmed the diagnosis of AIH. Patients also had negative findings when undergoing imaging of the biliary tree. Response to treatment was reassuring of a diagnosis of AIH retrospectively. AIH scores at diagnosis were calculated according to the study group based on the revised diagnostic criteria.

Patients were excluded if they had evidence of any other liver disease. Investigations included viral serology (hepatitis B virus and hepatitis C virus), α-antitrypsin level, serum copper and ceruloplasmin, and metabolic evaluation were performed at each center if clinically indicated. Fatty liver was not a reason for exclusion; however, this factor was not captured in our database. Cases of autoimmune sclerosing cholangitis (defined by the presence of specific lesions of the intrahepatic or extrahepatic bile ducts [chronic inflammation, fibrosis, stenosis, and dilations] evident in histology or imaging and associated with features of AIH) and AIH secondary to minocycline use were excluded from the study. Patients with suspected drug liver injury were also excluded. Research ethics board approval was obtained at each center, and data were abstracted from the charts of the identified patients and entered into a standardized case report form.

Demographic data, symptoms, physical examination findings, biochemical results, diagnostic imaging, and liver biopsy reports were collected at the time of diagnosis. Autoantibodies were reported as positive or negative because the values and methods used in the different centers varied. Biochemical parameters were subsequently recorded at 3, 6, and 12 months after the initial diagnosis.

Initial therapy was recorded and included corticosteroids, azathioprine, and cyclosporine according to the preference by each center. Data on treatment over time at 3, 6, 12, and 18 months and at the last clinic visit were captured; however, indications for changes or introduction of new drugs (eg, ursodeoxycholic acid) were not available. Supplemental Table 5 describes definitions of response to therapy. Ultrasonographic findings of portal hypertension included any of the following: ascites, splenomegaly, reverse flow within the portal vein, portal vein dilation, and portosystemic collateral veins. Histologic findings were recorded at each center and included the presence of interface hepatitis, lymphoplasmacytic infiltrates, rosetting of hepatocytes, biliary changes, fibrosis, and cirrhosis.
AIH scores were calculated retrospectively by the study group based on the revised criteria \(^{21}\) when data were available. The scores assigned to the presence of autoantibodies depended on available titers; if the center reported a qualitative result as "positive," the score assigned was 1; if it was quantitative, the score was given according to the aforementioned recommendations.

Population estimates for children and youth aged \(<18\) years in each Canadian province and territory for each year from 2000 to 2009 were obtained from Statistics Canada.\(^ {23}\) These estimates were summed according to province/territory, as well as overall, to obtain the total number of person-years during the study period. The incidence of AIH was estimated by dividing the number of cases by the number of person-years. Exact Poisson 95% confidence intervals (CIs) for incidence rates were computed by using the EpiTools package in R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria).\(^ {24,25}\)

The remaining analyses were performed by using SPSS version 22 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).\(^ {26}\) Two separate analyses were performed to identify predictive factors for patient outcome. A series of univariate logistic regression analyses was performed to examine potential predictors of a favorable response to treatment at 12 months’ postdiagnosis. Two-sided \(P\) values \(<.05\) were considered statistically significant. A repeated measures analysis of variance was used to compare the difference in BMI \(z\) scores between participants who used corticosteroids and those who used cyclosporine. Favorable long-term outcome was defined as transplant-free survival. Time to transplant or death was computed, and loss to follow-up and transfer to adult care were treated as censoring events. Kaplan-Meier curves were used to display time to outcome in different groups. Log-rank tests were used for statistical comparison of survival times.

**RESULTS**

**Incidence**

A total of 200 children from the 13 participating centers were included. Forty-one patients were excluded due to the following: diagnosis of autoimmune sclerosing cholangitis \((n = 19)\); positive history of minocycline use \((n = 10)\) before the diagnosis of AIH; and diagnosis outside of the study period \((n = 12)\). The total population of children and youth aged \(\leq18\) years in Canada averaged 70 277 839. The incidence was thus \(\sim0.23\) per 100 000 children (95% CI: 0.19–0.26). There were statistically significant differences among provinces \((P = .01)\); when provinces were grouped (Atlantic, Central, West, and North), the incidence rates between regions did not vary significantly \((P = .10)\). Table 1 displays the incidence of AIH according to province, and Fig 1 shows the geographical distribution.

**Patient Characteristics**

Median age at presentation was 12 years (interquartile range: 11–14) in type 1 AIH versus 10 years (interquartile range: 4.5–13) in type 2 AIH \((P = .03)\); 60% were female, and there was no significant difference in gender between type 1 and 2. Mean time from onset of symptoms to diagnosis was 4.7 ± 7 months. Five patients presented with hematemesis, 4 of 5 had evidence of fibrosis, and 1 of 5 had cirrhosis according to liver biopsy results; only 1 had splenomegaly, and 2 had thrombocytopenia. One patient reported alcohol consumption >60 g/d. Less than 3% of patients were on other medications, including proton pump inhibitors, 5-aminosalicylic acid, and vitamin supplementation; no patients were taking nitrofurantoin. Patient characteristics at diagnosis are described in Table 2.

Patient history of previous or concomitant autoimmune diseases was positive in 32% (49 of 154) and included the following: ulcerative colitis, 12% \((n = 18)\); Crohn’s disease, 5% \((n = 8)\); rheumatoid arthritis, 4% \((n = 6)\); thyroid disease, 4% \((n = 6)\); and celiac disease, 2% \((n = 3)\). One patient had concomitant systemic lupus erythematosus. The timing of occurrence of such autoimmune diseases was not uniformly available. Family history of autoimmune disease in first-degree relatives was reported in 25% (38 of 154). Personal or family history of autoimmune diseases did not predict outcome.

**Biochemistry**

Liver biochemistry findings were elevated in all children at diagnosis (Table 2). Serum albumin levels were below normal limits in 43% (62 of 144). An increased international normalized ratio was reported in 45% (67 of 148), and immunoglobulin G levels were abnormal in 84% (125 of 148).

**Autoantibodies**

Data regarding autoantibodies at diagnosis, including antinuclear antibody, smooth muscle antibody, liver/kidney microsomal, and LC1 antibodies, are provided in Table 2.

**Imaging**

Abdominal sonography at diagnosis revealed hepatomegaly in 26% (37 of 141), splenomegaly in 50% (72 of 144), ascites in 9% (12 of 139), and signs of portal hypertension in 11% (15 of 135). Presence of portal vein thrombosis was not captured in the data set. Imaging of the biliary tree was undertaken in 59 children; 50 of these underwent magnetic resonance cholangiopancreatography (MRCP), and 4 of 50 underwent endoscopic retrograde cholangiopancreatography (ERCP) as well. ERCP alone was performed in 9 patients, and these
results were all normal. Indications for ERCP were not recorded. MRCP was performed in 58% (15 of 26) of patients with a concomitant diagnosis of IBD; 1 of these patients underwent ERCP as well. ERCP alone was performed in 2 patients with IBD. In 7 children, the initial MRCP revealed either mild dilation or prominence of bile ducts, including 3 with concomitant IBD, but no other signs consistent with sclerosing cholangitis. Initial liver biopsy results of these 7 children exhibited histologic evidence of biliary changes in 5 not consistent with sclerosing cholangitis. These children were considered to have AIH and were treated and followed as per usual local clinic routine. Of these, 6 had normalized liver function at 1 year, and 1 had normalized liver function at 18 months on immunosuppression. Follow-up imaging was not available for analysis. One child had a previously surgically repaired choledochal cyst and was diagnosed with AIH at 13 years of age. The MRCP showed no intrahepatic bile duct involvement, and the child was therefore included in the analysis.

**TABLE 1** Incidence of AIH According to Province

<table>
<thead>
<tr>
<th>Province</th>
<th>Person-Years (2000–2009), Age &lt;18 Years</th>
<th>Cases</th>
<th>Annual Incidence per 100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newfoundland and Labrador</td>
<td>1 036 840</td>
<td>6</td>
<td>0.58 (0.21–1.26)</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>310 115</td>
<td>0</td>
<td>0 (0–1.18)</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>1 922 478</td>
<td>10</td>
<td>0.52 (0.25–0.96)</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>1 531 376</td>
<td>0</td>
<td>0 (0–0.24)</td>
</tr>
<tr>
<td>Quebec</td>
<td>15 589 608</td>
<td>32</td>
<td>0.21 (0.14–0.28)</td>
</tr>
<tr>
<td>Ontario</td>
<td>27 761 503</td>
<td>54</td>
<td>0.19 (0.15–0.25)</td>
</tr>
<tr>
<td>Manitoba</td>
<td>2 846 356</td>
<td>4</td>
<td>0.14 (0.04–0.36)</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>2 461 172</td>
<td>8</td>
<td>0.33 (0.14–0.64)</td>
</tr>
<tr>
<td>Alberta</td>
<td>7 835 539</td>
<td>26</td>
<td>0.33 (0.22–0.49)</td>
</tr>
<tr>
<td>British Columbia</td>
<td>8 682 692</td>
<td>19</td>
<td>0.22 (0.13–0.34)</td>
</tr>
<tr>
<td>Yukon</td>
<td>74 457</td>
<td>0</td>
<td>0 (0–4.96)</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>124 468</td>
<td>0</td>
<td>0 (0–2.96)</td>
</tr>
<tr>
<td>Nunavut</td>
<td>121 255</td>
<td>0</td>
<td>0 (0–3.04)</td>
</tr>
<tr>
<td>Total</td>
<td>70 277 839</td>
<td>159</td>
<td>0.23 (0.19–0.26)</td>
</tr>
</tbody>
</table>

Incidence rates varied significantly between provinces (*P* = .01).

**Histology**

Initial liver biopsy reports (*n* = 152) noted interface hepatitis in 86% (127 of 147), lymphoplasmacytic infiltrates in 97% (148 of 152), and rosetting of hepatocytes in 18% (24 of 135). Biliary changes were noted in 39.8% (55 of 148), most commonly bile ductular proliferation in 65% (35 of 55); none had features of sclerosing cholangitis.

Cirrhosis at the time of diagnosis was reported in 30 (20.0%) of 150 patients; mean age was 12 ± 3.3 years, and 59% were female subjects. In this group, 67% were type 1 AIH (20 of 30), and 10% (3 of 30) were type 2; 13% were seronegative (4 of 30). Hepatomegaly was reported in 60% (18 of 30) of these cirrhotic cases, and 67% (20 of 30) had splenomegaly identified either on physical examination or according to ultrasound. Ascites was reported in 20% of the abdominal ultrasounds, and other signs of portal hypertension were found in 27% (8 of 30). Among children with no evidence of cirrhosis in the liver biopsy specimen (*n* = 120), 4% had signs of portal hypertension, 3% had ascites, and 40% had some degree of splenomegaly according to ultrasound. Serum albumin and platelet counts were significantly lower and the international normalized ratio was significantly higher in cirrhotic patients compared with noncirrhotic patients (Table 3).

**AIH Scoring**

Patients had a mean score of 15.9 ± 3.3 at diagnosis based on the international AIH scoring system; 56% (88 of 156) of the cases scored as definite AIH, and 44% (68 of 156) were probable AIH. The score could not be calculated in 3 patients (1.9%) due to missing data. Two of these patients responded well to therapy, and the other patient remained on low-dose prednisone with a partial response at the end of the study.
TABLE 2 Patient Characteristics at Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Type 1 (n = 109)</th>
<th>Type 2 (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>152</td>
<td>645 (191–1253)</td>
<td>583 (315–1296)</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>156</td>
<td>564 (220–1133)</td>
<td>622 (229–1429)</td>
</tr>
<tr>
<td>GGT, IU/L</td>
<td>146</td>
<td>108 (67–181)</td>
<td>80 (52–208)</td>
</tr>
<tr>
<td>Alkaline phosphatase, IU/L</td>
<td>148</td>
<td>330 (229–422)</td>
<td>341 (273–407)</td>
</tr>
<tr>
<td>Conjugated bilirubin, IU/L</td>
<td>127</td>
<td>14 (2–35)</td>
<td>16 (2–126)</td>
</tr>
<tr>
<td>Serum albumin, μmol/L</td>
<td>144</td>
<td>36 (32–40)</td>
<td>38 (29–40)</td>
</tr>
<tr>
<td>INR</td>
<td>148</td>
<td>1.2 (1.1–1.4)</td>
<td>1.2 (1.1–1.4)</td>
</tr>
<tr>
<td>IgG, g/L</td>
<td>148</td>
<td>30 (22–41)</td>
<td>18 (12–25)*</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>75</td>
<td>37 (20–65)</td>
<td>19 (6–43)</td>
</tr>
<tr>
<td>Platelets (range)</td>
<td>151</td>
<td>225 (151–317)</td>
<td>214 (152–300)</td>
</tr>
<tr>
<td>Positive autoantibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>144</td>
<td>81 (56)</td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>132</td>
<td>83 (63)</td>
<td></td>
</tr>
<tr>
<td>LKM</td>
<td>102</td>
<td>16 (10)</td>
<td></td>
</tr>
<tr>
<td>ANA + SMA</td>
<td>139</td>
<td>47 (34)</td>
<td></td>
</tr>
<tr>
<td>SMA + LKM</td>
<td>113</td>
<td>7 (6)</td>
<td></td>
</tr>
<tr>
<td>ANA + LKM</td>
<td>121</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>ANA + SMA + LKM</td>
<td>130</td>
<td>4 (3)</td>
<td></td>
</tr>
<tr>
<td>Seronegative for antibodies</td>
<td>156</td>
<td>9 (7)</td>
<td></td>
</tr>
<tr>
<td>LC1</td>
<td>22</td>
<td>3 (13)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Levels of antinuclear antibody: ANA, antinuclear antibody; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ESR, erythrocyte sedimentation rate; GGT, y-glutamyl transferase; IgG, immunoglobulin G; INR, international normalized ratio; IQR, interquartile range; LKM, liver kidney microsomal antibody; SMA, smooth muscle antibody.

**ANOVA:** Type 1 versus type 2, *P* < .01.

**Response to Therapy and Outcomes**

At 1 year after diagnosis of AIH, 90% of patients had complete response to therapy, 3.2% had a partial response, 3.8% did not respond, and 3.2% experienced a relapse. Nine (5.7%) patients underwent liver transplantation. Trends regarding aminotransferase levels over time are represented in Fig 3. Mean follow up was 4 ± 2 years. Of the 157 patients, 10 were lost to follow-up, 69 had been transferred to adult care, and 74 were still followed up in the respective centers; data were missing in 2 patients. Indications of liver transplantation included fulminant hepatic failure, "chronic" hepatic failure (patients with cirrhosis and no improvement of the liver failure despite appropriate treatment), and late liver failure in patients with

**Treatment**

Of the 159 participants, 147 had complete information on initial treatment. Initial treatment consisted of prednisone (unspecified route of administration) at a mean dose of 1.0 ± 0.5 mg/kg/d (range: 0.2–2 mg/kg/d) in 87% of children; 54% of patients received prednisone alone, and 33% received both prednisone and azathioprine (mean dose: 1.2 ± 0.6 mg/kg/d). Cyclosporine was used as initial therapy in a single center in 13% of the cases at a mean dose of 4 ± 0.8 mg/kg/d; 12% used cyclosporine alone, and 1% used both cyclosporine and prednisone. Cyclosporine trough levels were followed according to a previously described protocol. Levels of azathioprine metabolites were not consistently measured or recorded. No other drugs were used for induction of remission.

At 1 year after diagnosis, 61% of children were on low-dose prednisone (mean dose: 0.2 ± 0.2 mg/kg/d). Cyclosporine was used in 2.5% (mean dose: 4.9 ± 1.8 mg/kg/d) and mycophenolate mofetil in 5% at variable doses (500–750 mg twice a day). Those patients taking prednisone had a mean ± SD BMI of 1.1 ± 1.0, and those not on prednisone had a mean BMI of 0.84 ± 0.87 (*P* = .08). At the last clinic visit (mean time: 4 ± 2 years), 67.3% (99 of 147) patients were on azathioprine, 31.3% (46 of 147) were on low-dose prednisone, 8.2% (12 of 147) were on mycophenolate mofetil, 4% were on tacrolimus (6 of 147), 1.3% (2 of 147) were on cyclosporine, 16.3% (24 of 147) were on adjuvant therapy with ursodeoxycholic acid, and 7% (10 of 147) were receiving no treatment. Figure 2 illustrates patients’ medication use over time.
partial response to therapy. Characteristics of patients with poor outcomes are reported in Table 4.

Figure 4 shows the results of univariate logistic regression analysis, which failed to identify any significant associations between potential predictive factors and poor response to therapy at 12 months after diagnosis.

The BMI z score was significantly higher at 3 months after starting corticosteroid therapy compared with those patients receiving cyclosporine (1.16 [95% CI: 0.99–1.35] vs 0.64 [95% CI: 0.17–1.11]; P = .04); however, this difference was not maintained, and at 1 year there was no significant difference (prednisone 1.08 [95% CI: 0.85–1.25] vs cyclosporine 1.25 [95% CI: 0.67–1.83], P = .58) (Fig 5). Patient survival curve in the presence of cirrhosis is reported in Fig 6.

DISCUSSION

In this nationwide Canadian study of AIH in children, we identified an incidence of AIH of at least 0.23 per 100 000 children per year. Previous reports of pediatric prevalence are scarce and vary from 2.2 in non–First Nation (indigenous native Canadian) communities to 9.9 in First Nation communities per 100 000 children in British Columbia. A recent report by Deneau et al in Utah described an incidence of 0.4 case per 100 000 children and a prevalence of 3 per 100 000. The previously reported incidence in adults ranged from 0.1 to 1.9 per 100 000 per year (including some adolescents). There were significant differences in incidence among provinces in Canada, with the Atlantic provinces having the highest rates. Benchimol et al reported a higher incidence of IBD in eastern Canada. We speculate that unique environmental and/or genetic factors might play a role in the increased rates of immune-mediated disease in the region, but we did not capture data regarding ethnic background or other possible epidemiologic risk factors. Although AIH (mainly type 1) occurs in both genders, our study confirms the female predominance noted in most previous reports.

The number of patients in our cohort meeting the criteria for definite AIH proposed by the International Autoimmune Hepatitis Group was 56%, with 44% falling into the category of probable AIH. This finding differs from other studies in which application of the scoring system classified 82% as definite AIH pretreatment in the pediatric group. We recognize that human leukocyte antigen status was not tested in most of our study centers, and thus additional points could not be added.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cirrhosis No (n = 120)</th>
<th>Cirrhosis Yes (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>84 (70)</td>
<td>20 (67)</td>
<td>.19</td>
</tr>
<tr>
<td>Type II</td>
<td>14 (12)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Seronegative for AIH</td>
<td>5 (4)</td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (14)</td>
<td>3 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Biochemistry (median, IQR)

- AST, IU/L: 666 (191–1321) vs 553 (176–1278), P = .02
- ALT, IU/L: 614 (240–1259) vs 537 (186–870), P = .30
- GGT, IU/L: 102 (64–170) vs 94 (54–130), P = .26
- Alkaline phosphatase, IU/L: 305 (225–450) vs 371 (254–432), P = .49
- Conjugated bilirubin, IU/L: 14 (2–46) vs 18 (2–53), P = .83
- Serum albumin, µmol/L: 38 (32–40) vs 33 (30–39), P = .03
- INR: 1.2 (1.1–1.3) vs 1.4 (1.3–1.6), P < .01
- IgG, g/L: 26 (19–36) vs 27 (22–49), P = .19
- ESR, mm/h: 37 (18–65) vs 40 (20–80), P = .61
- Platelets: 249 (167–365) vs 188 (85–231), P < .01

Positive autoantibodies, n (%)

- ANA: 65 (54) vs 15 (50), P > .99
- SMA: 65 (54) vs 13 (43), P = .12
- LKM: 13 (11) vs 3 (10), P > .99
- LC1: 1 (50) vs 1 (50), P = .36
for this variable. In addition, some autoantibodies were reported as positive or negative only, without a titer. We therefore assigned the lowest points when a positive result was given, which could have resulted in a decrease of the total score and lower number of patients classified as having “definite AIH.” Nine percent of patients were seronegative; however, measurement of other autoantibodies (eg, LC1, perinuclear antineutrophil cytoplasmic antibodies, soluble liver antigen), which may have helped classify such patients, was not routinely performed. We could not calculate the AIH score posttreatment due to missing data.

The clinical presentation in our cohort was variable and perhaps reflected the prolonged time to diagnosis of ~5 months. However, many children with AIH have an insidious pattern of symptoms and signs and a fluctuating course of the disease that may also lead to a delay in diagnosis. Not surprisingly, fatigue was the most common complaint, followed by jaundice. Clinical evidence of chronic disease with the presence of portal hypertension was observed in approximately one-fifth of the patients, as indicated by the presence of splenomegaly and thrombocytopenia. This finding is higher than other reports in which splenomegaly was found in only 6% of children at onset of symptoms.22

Similar to other reports, one-third of the children in our cohort had a concomitant autoimmune disease.22,32 IBD was the predominant comorbidity in 17% of our patient population, which is similar to the report by Gregorio et al22 that

### TABLE 4 Characteristics of Patients Who Died or Required Liver Transplantation

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age at Diagnosis, y</th>
<th>Gender</th>
<th>AIH Type</th>
<th>Liver Histology</th>
<th>Initial Therapy</th>
<th>Time to Transplant/Death, mo</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>F</td>
<td>1</td>
<td>IH, LPI, bridging fibrosis</td>
<td>Corticosteroids</td>
<td>62</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>M</td>
<td>1</td>
<td>IH, LPI, fibrosis</td>
<td>Corticosteroids</td>
<td>12</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>M</td>
<td>1</td>
<td>IH, LPI, bile duct proliferation, minimal fibrosis</td>
<td>Corticosteroids</td>
<td>30</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>M</td>
<td>1</td>
<td>IH, LPI, cirrhosis</td>
<td>Cyclosporine</td>
<td>19</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>M</td>
<td>Uncertain (LKM not done)</td>
<td>IH, LPI, cirrhotic liver with submassive necrosis of 80% of parenchyma</td>
<td>Cyclosporine</td>
<td>1</td>
<td>D (died 4 d posttransplant)</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>F</td>
<td>2</td>
<td>IH, LPI, cirrhosis</td>
<td>Cyclosporine</td>
<td>8</td>
<td>A</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>M</td>
<td>1</td>
<td>Submassive necrosis</td>
<td>Cyclosporine</td>
<td>1</td>
<td>D (died 10 mo after first transplant due to acute liver failure)</td>
</tr>
<tr>
<td>8</td>
<td>13</td>
<td>M</td>
<td>1</td>
<td>IH, LPI, bile duct proliferation, periductal inflammation, fibrosis</td>
<td>Corticosteroids</td>
<td>60</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>M</td>
<td>1</td>
<td>IH, LPI, bile duct proliferation, mild fibrosis</td>
<td>Corticosteroids, azathioprine</td>
<td>17</td>
<td>A</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>M</td>
<td>1</td>
<td>IH, LPI, cirrhosis</td>
<td>Corticosteroids, azathioprine</td>
<td>–</td>
<td>D (died of lymphoma 8 y after diagnosis of AIH)</td>
</tr>
<tr>
<td>11</td>
<td>16</td>
<td>F</td>
<td>1</td>
<td>IH, LPI, moderate fibrosis</td>
<td>Corticosteroids, azathioprine</td>
<td>–</td>
<td>D (died of meningococcal meningitis 2 y after diagnosis of AIH)</td>
</tr>
</tbody>
</table>

A, alive; D, deceased; F, female; IH, interface hepatitis; LKM, liver kidney microsomal antibody; LPI, lymphoplasmacytic infiltrate; M, male; NA, not available.
described 18% of children having concomitant AIH/IBD. Other investigators\textsuperscript{1,32} have reported lower rates of \( \sim \)6% of AIH/IBD. These disparities could potentially be explained by the different ethnic background and perhaps by the overall higher incidence of IBD in Canada.\textsuperscript{33,34} Family history of a first-degree relative with autoimmune disease occurred in 25% of our cases; however, ethnic background was not recorded in our study. In British Columbia, Chung et al\textsuperscript{28} reported not only a higher prevalence of AIH among First Nations children but also a positive history of concomitant autoimmune disease in 50% of patients and a positive family history of autoimmune diseases in up to 100%.

Serum aminotransferase levels were universally elevated. Interestingly, a large number of children had abnormal \( \gamma \)-glutamyl transferase and/or elevated alkaline phosphatase levels at diagnosis although they did not fulfill criteria for diagnosis of autoimmune sclerosing cholangitis in their histology or imaging. Evidence of synthetic dysfunction by an increased international normalized ratio and hypoalbuminemia was seen in \( \sim \)40% to 45% of cases, which correlates with histologic findings of cirrhosis in the study group.

The type of AIH (1 or 2) has been described as a factor that influences clinical presentation, treatment decisions, and outcomes. In this cohort, children with type 2 AIH were significantly younger, but they did not have a higher incidence of poor outcomes such as the need for liver transplantation or death. In fact, the type of AIH did not predict response to therapy, as both groups had similar response rates.

We found that only approximately one-third of the patients underwent initial imaging of the biliary tree, which was not a standard practice during the study period. This pattern could potentially be currently different after the American Association for the Study of Liver Diseases guidelines were published in 2010 recommending that all children with the diagnosis of AIH undergo cholangiographic studies.

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**FIGURE 4**

Logistic regression analysis factors affecting response to therapy at 12 months. ANA, antinuclear antibody; LKM1, liver kidney microsomal antibody type 1; OR, odds ratio; SMA, smooth muscle antibody.

**FIGURE 5**

BMI z score (\( \pm SE \)) for cyclosporine versus prednisone. \(*P = .04.*\)
diagnosis. This practice will help differentiate from other autoimmune liver diseases such as primary or autoimmune sclerosing cholangitis. Initial liver histology revealed bile duct involvement in one-half of the liver biopsy specimens, including bile ductular proliferation and ductal/periductal inflammation, which is higher compared with other studies in which biliary changes were reported in 24% of adult cases and up to ~20% of pediatric cases. The negative impact of bile duct changes on the liver biopsy findings could have been a factor in the lower scores of patients in the study. The predominant histologic features, however, were interface hepatitis and lymphoplasmacytic infiltrates, as previously described. One could hypothesize that patients with bile duct involvement could evolve to an overlap syndrome if followed up long term, however, histologic evidence of biliary damage is a well-recognized feature of AIH. A small number of patients in our study did not have a liver biopsy performed, presumably due to coagulopathy; however, these patients had clinical and biochemical features of AIH, were treated as such, and exhibited good response. In a study in adults, Björnsson et al concluded that liver biopsies are not needed in most cases when patients have typical features of AIH. This conclusion could have some applicability in the pediatric population.

We calculated the AIH score retrospectively and found that approximately one-half of the patients met the criteria for definite AIH, contrary to the study by Miletì et al in which 94% were considered to have definite AIH. This discrepancy could be explained by the lack of reports of quantified autoantibodies providing a lower score in our cohort. For a similar reason, we could not assess the accuracy of the simplified score specifically developed for adults by Hennes et al in our pediatric patients. It is important that the AIH score be calculated because it is a tool for clinicians in the management of this condition.

Treatment of AIH typically consists of immunosuppressive drugs such as corticosteroids and azathioprine; in our series, however, 13% of cases were initially treated with cyclosporine at a single center. Importantly, steroid-induced weight gain had resolved by 1 year. An interesting study by Woynarowski et al reported significant weight gain with the use of prednisone compared with budesonide, with a similar response rate; however, in that study, the number of patients was too small to strongly recommend its use. Response to therapy at 1 year was similar in both groups (89.6% with corticosteroids vs 91.7% with cyclosporine; P = not significant). Other series have reported good outcomes and few adverse effects when short-term cyclosporine was used. At the time of their last clinic visit, two-thirds of the patients were off corticosteroids and were in remission, a rate comparable to the report by Dumortier et al in which 78% of patients at 5 years were completely off corticosteroids and in remission. Nonetheless, the use of steroids may still be necessary, particularly in those having associated extrahepatic autoimmune diseases such as IBD or rheumatoid arthritis.

Other therapeutic options such as mycophenolate mofetil and tacrolimus were not widely used and were limited to those children with poor response or poor tolerance to azathioprine. No patient received anti-CD20 therapy. It was not clear why some children received ursodeoxycholic acid at their last clinic visit. We speculate that in some cases, ursodeoxycholic acid was used as an adjuvant AIH treatment, based on reports of its immunosuppressive properties, or there may have been biochemical, histologic, or imaging changes prompting its use.

The retrospective nature of the present study is a limitation because the data were collected by each
individual center and abstracted from medical records. Some data were not available for analysis, such as timing of onset of other autoimmune comorbidities (eg, IBD, thyroid disease), or information on corticosteroid-related events apart from weight gain. Imaging and liver biopsy results were not reported systematically; in addition, biochemical assays and normal values varied from site to site.

A major strength of this study is that it is a population-based multicenter trial that likely captures data on the vast majority of patients aged ≤18 years with AIH, given that such patients are almost universally cared for at academic health centers in Canada, thus allowing for estimation of incidence of pediatric AIH. It is our experience that the majority of those diagnosed as teenagers living in remote geographical areas of Canada and with serious liver diseases are referred to specialized pediatric academic centers. Our data also revealed a wide variety of diagnostic and therapeutic approaches among centers; nevertheless, outcomes were favorable. Our findings suggest the need for instituting a more collaborative care approach model, with standardized protocols aimed at improving outcomes. Indeed, the establishment of disease registries, particularly for rare orphan pediatric conditions, is increasingly recognized as having a valuable role in assuring optimal pediatric health and high quality of care.46

CONCLUSIONS

AIH is an uncommon condition in the pediatric age range (~2 per 1 million children aged <18 years); clinical presentation is variable, although with excellent response to immunosuppressive therapy. Few patients will need liver transplantation, and the long-term survival rate is favorable. The findings would serve as a base for future prospective research aimed at characterizing these patients with better and improved outcomes.

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ABBREVIATIONS

AIH: autoimmune hepatitis
CI: confidence interval
ERCP: endoscopic retrograde cholangiopancreatography
IBD: inflammatory bowel disease
LC1: liver cytosol type 1
MRCP: magnetic resonance cholangiopancreatography

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