ORIGINAL ARTICLE

Retrospective review of pediatric and adult autoimmune hepatitis in two quaternary care centres in British Columbia: Increased prevalence seen in British Columbia’s First Nations community

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BACKGROUND: It has been previously reported that British Columbia’s (BC) First Nations (Aboriginal) community has an increased risk of autoimmune diseases, including rheumatological conditions (rheumatoid arthritis, systemic lupus) and primary biliary cirrhosis. The researchers hypothesized that this community may also be at increased risk for autoimmune hepatitis (AIH).

METHODS: Independent, retrospective reviews of the databases of two separate tertiary/quaternary British Columbia university-affiliated health care institutions, the Adult Liver Transplant Program of the BC Transplant Society and the Division of Pediatric Gastroenterology, BC Children’s Hospital (Vancouver, BC), were performed. All patients referred with a diagnosis of probable or definite AIH who identified themselves as being of First Nations descent from 1988 to 2004 were reviewed. The liver transplant database records all adult patients in the province referred for transplant assessment. The pediatric database records records all children referred to the BC Children’s Hospital.

RESULTS: A total of 68 adult patients with a definite or probable diagnosis of AIH were referred to the liver transplant program. Twelve patients (17.6%) were Aboriginal, 11 of which were female. Similarly, a total of 30 children with probable or definite AIH were identified from the pediatric database. Six of these cases (20%) were identified in Aboriginal children.

CONCLUSIONS: The findings suggest an increased prevalence of AIH among BC’s First Nations community. A disproportionate First Nations representation was found on independent review of two databases. Further studies are needed to determine the true prevalence of AIH in this community, and to uncover the genetic predisposition and the environmental triggers explaining this phenomenon.

Key Words: Aboriginal; Adult; Autoimmune hepatitis; First Nations; Pediatric.

Une analyse rétrospective de l’hépatite auto-immune chez les enfants et les adultes dans deux centres de soins quaternaires de la Colombie-Britannique : Une plus forte prévalence au sein d’une communauté des Premières nations de la Colombie-Britannique

HISTORIQUE : Il a déjà été déclaré que la communauté des Premières nations (autochtones) de la Colombie-Britannique (CB) est plus vulnérable aux maladies auto-immunes, y compris les troubles rhumatologiques (polyarthrite rhumatoïde, lupus systémique) et la cirrhose hypertrophique de Hanot-Gilbert. Les chercheurs ont postulé que cette communauté serait peut-être également plus à risque d’hépatite auto-immune (HAI).

MÉTHODOLOGIE : On a procédé à des analyses rétrospectives indépendantes des bases de données de deux établissements de santé ter- tiaires et quaternaires affiliés à des universités de la CB, le programme de greffe du foie de la BC Transplant Society et l’unité de gastroentérologie pédiatrique du BC Children’s Hospital (Vancouver, CB). Tous les patients aiguillés pour subir une évaluation en vue d’une greffe ou identifiés comme autochtones ou de la première ascendance autochtone ont été répertoriés. La base de données pédiatrique contient le registre de tous les patients adultes de la province aiguillés pour subir une évaluation en vue d’une greffe. La base de données pédiatrique contient le registre de tous les enfants aiguillés vers le BC Children’s Hospital.

RÉSULTATS : Au total, 68 patients adultes présentant un diagnostic probable ou définitif d’HAI ont été aiguillés vers le programme de greffe du foie. Douze patients (17,6%) étaient autochtones, et 11 étaient des femmes. De même, on a repéré 30 enfants présentant un diagnostic probable ou définitif d’HAI dans la base de données pédiatriques. Six de ces cas (20 %) étaient des enfants autochtones.

CONCLUSIONS : Les observations laissent supposer une prévalence plus élevée d’HAI au sein de la communauté des Premières nations de la CB. On a constaté une représentation disproportionnée des Premières nations dans une analyse indépendante de deux bases de données. Il fau- dra mener d’autres études pour déterminer la véritable prévalence d’HAI au sein de cette communauté et établir la prédisposition génétique et les déclencheurs environnementaux qui expliquent ce phénomène.
There are currently 3,868,875 residents of British Columbia (BC), and of those, 170,025 people have identified themselves as Aboriginal or First Nations on the 2001 BC Census, representing 4.4% of BC's population (1). This community has a disproportionately high mortality rate from chronic liver diseases (2); however, it is difficult to ascertain the etiology of the liver disease, because National Vital Statistics has previously collected all deaths from chronic liver disease under the category 'alcohol-related' or under a separate category of 'digestive diseases' (3). It has been previously reported that this population has a higher incidence of rheumatological diseases (4-7). We subsequently reported that this population also suffers from liver disease, because National Vital Statistics has previously administered all aspects of solid organ transplantation in BC that administers all aspects of solid organ transplantation in BC, was retrospectively reviewed. This database includes all patients older than 19 years of age in BC referred for liver transplantation. The database includes both demographic information of referred patients and clinical information, including etiology of end-stage liver disease. A classification of AIH is based on clinical information provided by referring physicians and further investigations initiated by the BCTS. Clinical information supporting a database classification of AIH includes: negative viral hepatitis markers (specifically hepatitis B and C); the absence of any other possible etiology, including alcoholic liver disease; seropositivity for antinuclear antibodies and anti-smooth muscle antibodies; and liver biopsies consistent with a diagnosis of AIH, if available. Although the BCCTS database predates the International Autoimmune Hepatitis Score (12), the estimated score of patients classified with AIH was at least 10 ("probable AIH" [12]). All patients referred with a diagnosis of probable or definite AIH who identified themselves as First Nations or of Aboriginal descent from 1988 to 2004 were reviewed.

**Study associated with the BCTS**

The Adult Liver Transplant Referral Database of the BCTS, an agency of the Provincial Health Services Authority of BC that administers all aspects of solid organ transplantation in BC, was retrospectively reviewed. This database includes all patients older than 19 years of age in BC referred for liver transplantation. The database includes both demographic information of referred patients and clinical information, including etiology of end-stage liver disease. A classification of AIH is based on clinical information provided by referring physicians and further investigations initiated by the BCTS. Clinical information supporting a database classification of AIH includes: negative viral hepatitis markers (specifically hepatitis B and C); the absence of any other possible etiology, including alcoholic liver disease; seropositivity for antinuclear antibodies and anti-smooth muscle antibodies; and liver biopsies consistent with a diagnosis of AIH, if available. Although the BCCTS database predates the International Autoimmune Hepatitis Score (12), the estimated score of patients classified with AIH was at least 10 ("probable AIH" [12]). All patients referred with a diagnosis of probable or definite AIH who identified themselves as First Nations or of Aboriginal descent from 1988 to 2004 were reviewed.

**Study associated with the BCCH**

A retrospective review was performed of all children up to 19 years of age diagnosed with immune liver disease between 1992 and 2004 at the BCCH, a quaternary care referral centre for the province of BC. The diagnoses of immune liver disease were based on a detailed family history of all patients at the time of initial consultation, with supportive laboratory investigations and liver biopsy pathology. All liver biopsies were interpreted by a single pathologist to review the initial liver biopsies from each case. A detailed family history of all patients with immune liver disease was taken at the time of initial BCCH consultation.

**RESULTS**

**Adult Liver Transplant Referral Database review**

A total of 68 patients with a diagnosis of probable or definite AIH were referred to the BCTS for liver transplant assessment. The median age was 45 years. Forty-nine of the patients (72%) were female. Twelve of these patients (17.6%) identified themselves as First Nations and 11 of these 12 (92%) were female. Of the First Nations patients, four patients (33%) received a liver transplant, four (33%) died either during assessment or while wait-listed for a transplant, three (25%) were deemed unsuitable after transplant assessment and one (8%) refused transplantation. Of 170,025 First Nations people in BC, 101,710 were 20 years of age or older (of a total BC population of 3,868,875, or 4.4%), a statistically significant difference was found between the proportion of Aboriginal people referred for liver transplant assessment with a diagnosis of AIH and the proportion of First Nations people in the province (2001 Canada Census [12]) (P=0.0004). We note that the binomial distribution analysis was performed conservatively by comparing the proportion of First Nations patients referred with a diagnosis of AIH with all First Nations people in BC regardless of age group. The subset of First Nations people in BC older than 19 years of age (ie, 3.5% of BC’s adult population) achieved even greater statistical significance.

**Pediatric Immune Liver Disease Database review**

A total of 39 cases of immune liver disease were identified at the BCCH (Table 1). Thirty cases (76.9%) of probable or definite AIH were diagnosed. Of these, six definite cases of AIH (20%) occurred in First Nation’s children, and all cases were type 1. Four of the children (67%) were female and two (33%) were male; their average age at diagnosis was 10.3 years old. In the non-First Nations children, the average age at diagnosis was 10.9 years. Elevated biochemical values were similar between the two groups at presentation. Liver histology was also similar between these groups (Table 2). The non-AIH group (nine patients) included six cases of primary sclerosing cholangitis that were all associated with inflammatory bowel disease (IBD) and three patients with overlap syndromes (with two associated with IBD). All of these non-AIH cases were in...
AIH in Alaska Natives (ie, First Nations people) was more prevalent in First Nations children compared with non-First Nations children. Fifty per cent of the First Nations children were also found to have other autoimmune diseases. All of the First Nations children had a family history of autoimmune diseases, and this was significantly different from the non-First Nations group ($P=0.0017$).

**DISCUSSION**

AIH is a chronic hepatitis characterized by necroinflammation of the liver, as well as the presence of autoantibodies and hypergammaglobulinemia in the absence of any other causes (14). It has a female predominance, with a peak incidence between 10 to 30 years of age and then another peak after 40 years of age (11). The etiology of AIH is unknown; however, it is postulated that an environmental agent triggers a T cell-mediated response against liver antigens in a genetically susceptible individual (15). There are two major subtypes of AIH. Type 1 is associated with elevated antinuclear antibody, smooth muscle antibody, atypical perinuclear antineutrophil cytoplasmic antibody, and autoantibodies to soluble liver antigen and liver-pancreas antigen (15). Type 2 AIH is characterized by antibodies against liver-kidney microsome-1 and liver cytosol 1. Type 2 is rare, and tends to occur in younger people and almost exclusively in females (15,16). Immunosuppression with prednisone, azathioprine or 6-mercaptopurine is the mainstay of treatment (17).

Before the Autoimmune Hepatitis Group revised scoring system (12) there was no standardized method of diagnosing AIH. There are also few studies reporting the prevalence of AIH, and only two population-based studies have been published. An often quoted Norwegian study (18) demonstrated a point prevalence of 16.9 per 100,000 people, while in an Alaskan study (19), the prevalence of definite or probable AIH in Alaska Natives (ie, First Nations people) was more than double that at 42.9 per 100,000 people. The disease appears to be relatively uncommon in Asia, but one study reported that African Americans with AIH are more likely than Caucasians to present with advanced disease (20-24). Nevertheless, it appears to be present in diverse ethnic groups in both pediatric and adult populations.

We have previously reported that PBC appears to be common among the First Nations population of BC, has a strong First Nations familial association and appears to be geographically clustered along the Pacific coastal areas (8,9,25). Similar findings of an increased likelihood of PBC in First Nations people has been reported in Alaska (19), which is in close proximity to BC (ie, Southeast Alaska, also referred to as the Alaskan Panhandle). A demographic study of PBC in Ontario (26) did not reveal a higher than average incidence of PBC in their First Nations communities; however, it is not clear whether this difference is due to under-recognition of the condition in the First Nations people of Ontario or whether a different genetic ancestry may alter susceptibility compared with BC's First Nations community. Of interest, the Southeast Alaskan Indians, who likely share a common ancestry with the BC First Nations, have been reported to have a high rate of PBC and other autoimmune diseases, suggesting a genetic predisposition; however, it is not clear whether AIH has a similarly high rate in that same area. In BC, PBC has a strong familial component (9), consistent with our findings of a strong family history of autoimmune diseases in the pediatric component of our study. It is hypothesized that the increased burden of PBC carried by BC's First Nations community is due to a strong genetic predisposition to autoimmune diseases, combined with exposures to common environmental triggers (9). Our study found that significantly more First Nations children with AIH had a family history of autoimmune disease. Because the BCTS database did not capture family history data, we were unable to draw any similar inferences regarding First Nations adults. However, a recent report of a First Nations mother-daughter pair with PBC and AIH gives support to this hypothesis (27).

In our current study, a disproportionate prevalence of AIH was found among First Nations adults and children, even though two different populations were studied, ie, an adult liver transplant referral population and a pediatric quaternary care referral population. It is very interesting that the proportions of AIH in First Nations people were almost identical (17.6% and 20%) in these two databases. The BCCH is the only pediatric hepatology referral centre in BC, and therefore, our study likely reflects the true prevalence of AIH in BC's pediatric population. In the BCCH database, we found that First Nations and non-First Nations children had similar age, sex, and clinical and biochemical presentation distributions, as well as similar responses to therapy. Liver biopsy histologies were also very similar in both groups. All First Nations children had

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Non-First Nations (n=24)</th>
<th>First Nations (n=6)</th>
</tr>
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<tbody>
<tr>
<td>Prevalence (0 to 19 years of age)</td>
<td>2.4/100,000</td>
<td>9.9/100,000</td>
</tr>
<tr>
<td>Average age at diagnosis (years)</td>
<td>10.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Female-to-male ratio, n</td>
<td>13.8</td>
<td>4.2</td>
</tr>
<tr>
<td>Jaundice, n</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Elevated antinuclear antibody titre, n</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Presence of smooth muscle antibody, n</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>Other autoimmune disease*, n</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Result, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>Relapse</td>
<td>10</td>
<td>3</td>
</tr>
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</table>

*P=0.0017, two-sample test of proportion

**TABLE 2**

<table>
<thead>
<tr>
<th>Histological feature</th>
<th>Non-First Nations (n=16)</th>
<th>First Nations (n=6)</th>
</tr>
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<tbody>
<tr>
<td>Mean portal grade</td>
<td>3.12</td>
<td>3.50</td>
</tr>
<tr>
<td>Mean lobule grade</td>
<td>1.59</td>
<td>1.33</td>
</tr>
<tr>
<td>Stage (0-4)</td>
<td>2.71</td>
<td>2.33</td>
</tr>
<tr>
<td>Duct inflammation (%)</td>
<td>56.00</td>
<td>33.00</td>
</tr>
</tbody>
</table>

Liver biopsy scoring system, data from reference 30

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CONCLUSIONS

Our study suggests an increased prevalence of AIH among BC’s First Nations community; disproportionate First Nations representation was found on independent review of two databases. Special attention should be paid to this population to identify these patients so that early effective medical care can be provided. Future studies are required to determine the true prevalence of AIH in this community, as well as to uncover the genetic predisposition and the environmental triggers to explain this phenomenon.

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REFERENCES
