

Liver disease in the indigenous populations of the Arctic, sub-Arctic, and Pacific Northwest: An approach to investigations in Alaska and British Columbia

Special attention should be paid to viral hepatitis, autoimmune hepatitis, and primary biliary cirrhosis when considering the chronic liver diseases that commonly affect Aboriginal people.

ABSTRACT: The global health of Aboriginal people in Alaska and British Columbia is suboptimal when compared with the rest of the North American population. In particular, Native and First Nations people carry a disproportionate mortality burden from chronic liver diseases. Although chronic liver disease mortality may be attributed in part to documented higher rates of alcohol consumption in these populations, it is also important to consider the contribution of other common liver conditions, such as viral hepatitis and autoimmune liver diseases. Timely diagnosis and treatment for these conditions will only happen when health care providers, especially those involved in Native health, have a better general understanding of Alaska and BC Aboriginals, their health care services, and the liver diseases commonly seen in these populations.

The global health of Aboriginal people is suboptimal when compared with the health of the general North American population, and many disease processes, some with a genetic component, appear to be more prevalent. The 1991 to 1999 BC Vital Statistics Report states that deaths from chronic liver disease were five times more common in First Nations women than non-First Nations women.¹ Similarly, the death rates from chronic liver disease among American Indian (AI) and Alaska Native (AN) people were more than twice those of other racial groups.² Furthermore, a retrospective study of BC Transplant Society data found that indications for liver transplantation in Aboriginal people differed significantly from those of the overall liver transplant cohort. From 1989 to 1998, BC First Nations people were significantly more likely to undergo liver transplantation for liver diseases such as autoimmune hepatitis and primary biliary cirrhosis.³

The First Nations of BC and the AI/AN populations carry a dispropor-

tionate mortality burden from chronic liver diseases. Although chronic liver disease due to alcohol abuse is common, Aboriginal people also have high rates of viral hepatitis and autoimmune liver disease. More timely diagnosis and treatment for these conditions will only be possible once health care providers, especially those involved in Native health, give special

Dr Ko is a second-year internal medicine resident at the University of British Columbia. Dr Chung is a gastroenterology fellow at UBC. Dr McMahon is the scientific program and clinical director of the Liver Disease and Hepatitis Program at the Alaska Native Tribal Health Consortium. He is also a guest researcher at the Arctic Investigations Program. Dr Hurlburt is an internist who works with Dr McMahon at the Liver Disease and Hepatitis Program. Dr Arbour is the clinical geneticist and assistant professor in the Department of Medical Genetics at UBC. Dr Yoshida is an associate professor of medicine and head of the Division of Gastroenterology at UBC. He is also the medical director of the Liver Transplant Program for the BC Transplant Society.

consideration to all the liver diseases commonly seen in these populations.

Alaska and BC Aboriginals and their health care system

The Alaska Native population consists of three main ethnic groups: Eskimo (55%), Aleut (24%), and Indian (21%).⁴ The Indian population is further subdivided into Southeast (Tlingit, Haida, and Tsimshian) and Athabascan (Interior) groups,⁵ while the Eskimo population is further subdivided into Yupik and Inupiat groups.

Alaska Native people receive health care as an entitlement in an integrated health care system.^{6,7} Primary care for residents of rural areas is provided by the village community health aides. Residents are referred to regional or "hub" medical centres for more specialized care, and to the Alaska Native Medical Center (ANMC) for tertiary care as needed. Specialists from ANMC regularly travel to regional field clinics to provide outpatient services.^{4,7}

In British Columbia, the Aboriginal population consists of 40 First Nations groups. Aboriginal people make up about 4% of the total BC population, and about half live in urban centres. There are no significant Inuit (Eskimo) or Aleut populations in BC, but there are people from the coast Salish, Wakashan, Haida, and Tlingit language families, as in southeast Alaska. The provincial Medical Services Plan covers health care costs for all BC residents, including patients of First Nations ancestry. In addition, the government of Canada covers outpatient medication costs (noninsured benefits) of First Nations patients who have registered status. Those who do not have status may be eligible for BC Pharmacare drug coverage, as are all residents of BC.

Liver diseases in BC First Nations, American Indians, and Alaska Natives

Based on the limited number of population-based studies, viral hepatitis, autoimmune hepatitis, and primary biliary cirrhosis are the most common liver diseases in the Aboriginal communities of both BC and Alaska. The actual prevalence of these liver diseases might be underestimated in these studies, since 10% to 20% of Alaska Native people seek medical care outside the integrated statewide health care delivery system.⁶ Furthermore, about 60% of the cases reported in these studies were either asymptomatic or mildly symptomatic, suggesting that more cases might not be recognized.

Types of viral hepatitis seen in these populations include hepatitis A, B, and C. Along with viral hepatitis, autoimmune hepatitis is also common. This progressive inflammation of the liver has been identified by a number of different names, including autoimmune chronic active hepatitis, idiopathic chronic active hepatitis, and lupoid hepatitis. The cause of this condition is unknown. Although primary biliary cirrhosis is a rare, autoimmune liver disorder, its prevalence in these populations is disproportionately high. It is characterized by progressive destruction of intrahepatic bile ducts, resulting in portal inflammation, scarring, cirrhosis, and, eventually, liver failure.

Viral hepatitis

Although published data specifically about BC are lacking, we do know that viral hepatitis is common in the Canadian Inuit and First Nations populations.⁸ The prevalence of hepatitis A antibody (HAV-A6) positivity in these populations is high (ranging from 75% to 95%) and is approximately three times that of non-Aboriginal Canadians.⁸ The prevalence of hepatis

is B virus (HBV) infections in the Canadian Inuit population is about 5% (20 times that of non-Aboriginal Canadians), and the risk of exposure to HBV is 25% (5 times higher).⁸ In the First Nations population, the prevalence of HBV infections ranges from 0.3% to 3%, and the risk of exposure is 10% to 22%, which are similar to the rates in non-Aboriginals. Hepatitis C virus (HCV) infections are more common among Canadian Inuit and First Nations populations (1% to 18%) than among non-Aboriginal populations (0.5% to 2%).⁸

Similarly, high rates of viral hepatitis have been found in the American Indian and Alaska Native populations. Before a vaccination program was implemented, the hepatitis A incidence rates among these populations were 6 to 17 times higher than for other ethnic groups. By 2003, the incidence among Native Americans declined by 98.8% and was not significantly different from that of any other ethnic group. Hepatitis A cases among Native Americans accounted for 1.1% of all cases reported in 2003, compared with 8.5% of cases reported previously.⁹ According to the NHANES III survey, the age-adjusted seroprevalence of HBV infection in the US was 4.9% (95% CI, 4.3%–5.6%), which is low compared with other areas of the world. However, the prevalence of hepatitis B surface antigen (HBsAg) positivity among Alaska Native people was 6.4%, on average, with prevalence rates varying from 0% to 20% in different villages.¹⁰ In a large population-based cohort study,⁴ the minimum prevalence of HCV in the AN population was found to be 0.82%, with the highest prevalence, 2.63%, found in those aged 40 to 59 years. In accordance with other reports from North America and Europe,¹¹⁻¹⁷ the major risk factor for HCV among Alaskan Natives was IV drug use

(60%), followed by a history of blood transfusion before 1992 (14%).⁴ Compared with the rest of the US population, a lower prevalence of HCV genotype 1a (42% vs 56.7%) and a higher prevalence of genotype 2a (7.8% vs 3.5%) and genotype 3a (14.3% vs

25.1–49.7),⁶ which was more than twice as high as the prevalence of 16.9 per 100 000 found in the Norwegian study.²³ When the cases were examined in terms of Alaska Native ethnicity, the prevalence of definite or probable AIH was 63 per 100 000 for

Nations patients referred for AIH was 17%, suggesting that AIH is also not uncommon among BC's Aboriginal population. Health care providers should be aware of this, since liver transplantation can be avoided if AIH is diagnosed early. In fact, more than 90% of patients will achieve long-term remission on corticosteroids with or without azathioprine.²⁵

Sixty percent of patients diagnosed with AIH were either asymptomatic at presentation or had mild fatigue as their only symptom, making early diagnosis difficult.

7.4%) was reported among AN patients.⁴ Persons infected with HCV genotypes 2 and 3 tend to have a higher success rate with antiviral treatment than those infected with genotype 1,¹⁸ implying that a higher proportion of Alaska Natives have a greater likelihood of responding to antiviral therapy.

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is chronic hepatitis characterized by necroinflammation of the liver, a positive antinuclear antibody (ANA) test or smooth muscle antibody (SMA) test, hypergammaglobulinemia, and the absence of other causes.¹⁹ In the US, autoimmune hepatitis afflicts 100 000 to 200 000 persons²⁰ and accounts for 5.9% of transplants.^{21,22} There is very limited information on the prevalence of autoimmune hepatitis and only two population-based studies can be found: one done in Alaska and the other in Norway. In the Alaskan study, the prevalence of definite or probable autoimmune hepatitis in Alaska Natives was 42.9 per 100 000 (95% CI,

Eskimos, 85.5 per 100 000 for Southeast Indians, 25.6 per 100 000 for Athabascans, and 59.7 per 100 000 for Aleuts.⁶ Forty percent of patients diagnosed with AIH presented acutely with icterus, jaundice, and/or marked elevated aminotransferase levels, suggesting that AIH should be considered in the differential diagnosis of acute hepatitis in Alaska Native patients. However, 60% were either asymptomatic at presentation or had mild fatigue as their only symptom, making early diagnosis difficult.

Although the prevalence of autoimmune hepatitis among the Canadian First Nations is not known, AIH was the second most common cause for liver transplantation among BC First Nations people from 1989 to 1998,³ and 27% of Aboriginal liver transplant recipients were treated because of autoimmune hepatitis. More recently, both the liver transplant candidate referral database of the BC Transplant Society²³ and the AIH database of BC Children's Hospital²⁴ have been reviewed. In both the adult and pediatric databases, the proportion of First

Primary biliary cirrhosis

Primary biliary cirrhosis (PBC) is a cholestatic liver disease characterized by immune-mediated damage to intrahepatic bile ducts, leading to portal inflammation, scarring, cirrhosis, and, eventually, liver failure.^{26,27} Although it has been estimated to have a prevalence of between 2 and 5 cases per 100 000 worldwide,²⁶ PBC is not rare among Native peoples of the Pacific coast. The prevalence of PBC among Alaska Native people was 16 per 100 000 (95% CI, 9.1–25.9), which was similar to the prevalence found in Norway.⁶ When examined in terms of ethnicity, the data indicate that Southeast Indians had the highest prevalence (57.2 per 100 000), followed by Eskimos (18 per 100 000), Aleuts (9.9 per 100 000), and Athabaskan Indians (8.5 per 100 000).⁶

Although PBC is considered to be rare in the general Canadian population, it is the leading indication for liver transplant in the BC First Nations population.³ In fact, 53% of First Nations liver transplant recipients had PBC.³ Despite the fact that First Nations peoples account for only about 4% of the BC population,²⁸ 25% of patients referred for liver transplant assessment with a diagnosis of PBC from 1989 to 1999 were of First Nations descent.³ Furthermore, a recent expanded analysis of the BC transplantation database indicates that 34 (26.5%) of 128 patients referred for liver transplantation for PBC were of

First Nations descent.²⁹ Thus, based on population sizes, a First Nations person is eight times more likely to be referred for liver transplant because of PBC than a non-Aboriginal person. In addition, the average age for referral for liver transplant in First Nations patients on the BC transplant list is lower than for non-Aboriginal patients: 45.9 (range 32 to 59) years of age compared with 54.3 (range 29 to 72) years of age.³⁰

It is still unclear why there is such a high prevalence of PBC among the First Nations. Genetic factors together with environmental factors such as the presence of predisposing viruses and lifestyle have been proposed. Whatever the reason for the high prevalence, early diagnosis is important because the progression of PBC can be slowed down and even arrested in some cases with treatment with ursodeoxycholic acid.³¹

Approach to suspected liver diseases in Aboriginal populations

A detailed history and thorough physical exam are essential when liver disease is suspected in patients from any ethnic background. When obtaining the patient history, the physician should focus on previous liver disease or gastrointestinal hemorrhage, decompensated liver disease (e.g., abdominal distention suggesting ascites, peripheral edema of the legs, episodes of confusion, difficulty speaking that may suggest hepatic encephalopathy), family history of liver disease or liver cancer, and family history of autoimmune disorders. Patients should be asked about extrahepatic manifestations of viral hepatitis or cholestatic liver disease (e.g., arthritis, skin rash, pruritus, dry mouth, and eyes suggestive of sicca syndrome). They should also be asked about risk factors for viral hepatitis (e.g., IV drug use, blood

Table. Laboratory investigations for liver diseases common in Aboriginal people of Alaska and British Columbia.

Tests for chronic viral hepatitis

- HBsAg (hepatitis B surface antigen)
- Anti-HCV (hepatitis C antibody)

Tests for autoimmune liver disease

- ANA (antinuclear antibody)
- SMA (smooth muscle antibody)
- AMA (antimitochondrial antibody)
- Serum IgG
- Serum IgM

Tests for fatty liver

- Fasting serum glucose
- Fasting serum cholesterol
- Fasting serum triglyceride
- Ultrasound of the liver

Tests for treatable metabolic liver diseases*

- Serum ferritin for hereditary hemochromatosis
- Serum ceruloplasmin for Wilson disease (only in persons <45 years)
- Serum alpha-1 antitrypsin concentration or alpha-1 antitrypsin phenotype for alpha-1 antitrypsin deficiency

*All liver disease patients should be screened for these diseases, although there is no evidence that Aboriginal people are at increased risk.

transfusion, body piercing, tattooing, multiple sexual partners), medication use (including over-the-counter medications and herbal preparations), alcohol intake, and personal and family history of liver diseases/autoimmune diseases (e.g., rheumatoid arthritis, lupus). In general, there is an increased prevalence of rheumatoid arthritis and connective tissue disease in AI/AN populations, while the rate of spondyloarthropathies is higher among Eskimos.³² The rheumatoid arthritis seen in AI populations, specifically the Tlingit, Yakima, Pima, and Chippewa Indians,³³ is generally severe, with an early age of onset and frequent extra-articular manifestations.

In addition, the growing epidemic of obesity and diabetes in North America is associated with nonalcoholic fatty liver disease (NAFLD), and patients should be asked about a personal history or family history of both diabetes and hyperlipidemia. Once pertinent details are obtained, the physician can proceed to a global general exam-

ination, which should include determining the patient's body mass index (BMI) and completing a focused physical exam of the abdomen, looking for any abnormal distention, hepatomegaly, or splenomegaly. The physician can also look for the stigmata of liver disease, which include scleral icterus, jaundice, palmar erythema, Dupuytren contracture, asterixis, spider angioma, gynecomastia, bruises, and muscle wasting. During the first visit, appropriate blood work can be ordered, including tests for alanine aminotransaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), markers of liver function such as total bilirubin and serum albumin, and a coagulation screen such as INR. Specific blood tests to rule out viral hepatitis, autoimmune liver diseases, and metabolic liver diseases may then be considered (see **Table**).

Ancillary tests may be appropriate, depending on the results of initial investigations. If serologic markers for hepatitis C (anti-HCV) are found, then nucleotide assay tests should be performed, including HCV RNA and HCV genotype.³⁴ In the case of hepatitis B, if HBsAg is positive, testing for additional serologic markers such as HBe antigen, anti-HBe, and HBV DNA should be ordered, since baseline testing will help to classify the phase of hepatitis B and determine if treatment will be needed.³⁵ In addition, family members, household contacts, and sexual contacts of patients found to be HBsAg-positive should be screened for HBV seromarkers and receive hepatitis B vaccination if they are found to be seronegative. Diagnostic imaging, including abdominal ultrasound and CT scans, may be necessary.

Patients with suspected or known cirrhosis secondary to chronic hepatitis B or C are at risk of hepatocellular carcinoma (HCC). Men older than 40 with hepatitis B and patients with a family history of HCC are also at risk. These persons should be screened with ultrasound and alpha-fetoprotein (AFP) testing every 6 months. Confirmatory biphasic CT scan may be necessary if the screening suggests HCC, or if AFP is above 100 µg/L.

If the investigations suggest a diagnosis of autoimmune liver disease, timely referral to a gastroenterologist and early treatment can slow the progression of the condition.

Prevention of liver diseases

Among the different types of liver diseases discussed here, viral hepatitis, specifically hepatitis A and B, is preventable by immunization. BC is one of the first North American jurisdictions to introduce a school-based, preadolescent hepatitis B immunization program. The vaccination pro-

gram was introduced in 1992 to provide universal immunization for all grade 6 students (children age 11 years). It was then enhanced by the introduction of a universal infant hepatitis B immunization program in January 2001. Between 1993 and 2001, the overall rate of reported acute hepatitis B declined from 7 per 100 000 to just over 2 per 100 000, while the rate for 12- to 21-year-olds declined from 1.7 per 100 000 to 0 per 100 000,³⁶ indicating that the immunization program is an effective strategy to prevent hepatitis B infection.

Conclusion

The BC First Nations, American Indian, and Alaska Native populations carry a disproportionate mortality burden from chronic liver diseases. Although chronic liver disease mortality among Aboriginal people may be attributed in part to documented higher rates of alcohol consumption, it is important to consider other causes of liver disease that are not alcohol-related, such as autoimmune liver diseases and viral hepatitis. With timely diagnosis and treatment, much can be done to mitigate the effects of these conditions.

Competing interests

Dr Yoshida has received honoraria for CME lectures sponsored by Hoffman-La Roche Canada, Schering Canada, Providence Health Care, Provincial Health Services Association (PHSA), the University of British Columbia Department of CME, the Canadian Association of Gastroenterology (CAG), and the Canadian Association for the Study of the Liver (CASL). He has received unrestricted research grants from Hoffman-La Roche Canada, Fujisawa Canada, Schering Canada, Pfizer Canada, Janssen Ortho Canada, and GlaxoSmithKline Canada. He has been a participant and received honoraria for attending Advisory Board meetings of Hoffman-La Roche Canada and

Novartis Canada. He has been a consultant and received honoraria from BC Pharmacare.

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