

# Autoimmune liver disease and the Canadian First Nations Aboriginal Communities of British Columbia's Pacific Northwest

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## Abstract

Primary biliary cirrhosis (PBC) is a well-known but uncommon chronic liver disease that is presumed to be of autoimmune etiology. Recently, investigations in British Columbia (BC), a province of Canada situated along the Pacific North-West of North America, have suggested that PBC is not a rare disease amongst BC's Aboriginal (i.e. First Nations) communities. Geographically, BC is adjacent to South East Alaska, an American state that has also reported an increased prevalence of PBC amongst its Aboriginal communities. In this article, the medical evidence supporting a hypothesis of increased risk of PBC amongst BC's First Nations communities is reviewed. Evidence suggesting that autoimmune hepatitis is also more likely amongst BC's First Nations communities is also presented.

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**Key words:** Primary biliary cirrhosis; Aboriginal; First Nations; British Columbia

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## INTRODUCTION

Primary biliary cirrhosis (PBC), autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) constitute a triad of liver diseases that are widely accepted to be of autoimmune etiology with differing targets of immunologic

attack. In PBC, it is the microscopic intra-hepatic bile duct that is the immunologic target, whereas in PSC, both intra- and extra-hepatic bile ducts are involved and in AIH, the antigenic target is located on the hepatocyte. Aside from the fact that all three diseases will result in end-stage cirrhosis, resulting in morbidity and premature mortality unless rescued by an increasingly scarce liver transplant, there are similarities between all these three liver diseases. Overlap syndrome, in which a patient may have features of both PBC and AIH<sup>[1]</sup> or PSC and AIH<sup>[2]</sup>, is well recognized to occur and is often seen by clinicians. Occasionally, patients have been reported to have overlap with PBC and PSC as well as all three<sup>[3]</sup>. Furthermore, it is well recognized that patients with PBC and AIH can have many associated extra-hepatic autoimmune disease, especially rheumatologic conditions<sup>[4,5]</sup>. PSC, although classically occurring in the context of ulcerative colitis, is also reported to be associated with an increased likelihood of co-existent extra-intestinal, extra-hepatic autoimmune diseases compared to those with ulcerative colitis alone<sup>[6]</sup>. Recently, we have reported evidence that suggests that the Aboriginal population of British Columbia (BC), Canada (i.e. part of Canada's First Nations) has a significant burden of PBC<sup>[7-9]</sup> and possibly AIH<sup>[10,11]</sup>. It is commonly accepted by the gastroenterology community of BC that inflammatory bowel disease is extremely rare amongst its First Nations peoples, a fact that most likely explains the rarity of PSC in the First Nations population.

The finding of an increased rate of PBC and AIH in BC's First Nations community has clinical, epidemiologic, anthropologic as well as socio-political implications. First Nations of Canada, also referred to as American Indians or Native Americans in the United States, are the original inhabitants of the continent and pre-date, by millennia, the subsequent European colonizers. In Canada, the First Nations peoples constitute about 4% of the population. In British Columbia, with a total population of close to 4 million people, about 170 000 are First Nations in demographic background. Often plagued by socioeconomic injustice, it is well recognized in recent years that the global health of Canada's First Nations communities is disproportionately worse than the rest of Canadian society. Chronic health problems, including diabetes mellitus, obesity, coronary artery disease, etc, are over-represented in our First Nations communities<sup>[12,13]</sup>. Excessive alcohol consumption remains a problem amongst some within the First Nations communities<sup>[14]</sup>, however, the stereotypic generalization that all chronic liver diseases amongst First Nations are a result of alcoholic liver disease more likely

reflects societal bias or arises from clinical encounters in poor urban inner city areas. Within our own studies<sup>[7-9]</sup>, we found that some PBC patients were initially misdiagnosed as suffering from alcoholic liver disease. The potential for accidental perpetuation of this stereotype remains in BC, since according to National Vital Statistics, all deaths from chronic liver disease are collected under the category of "alcohol-related" under a separate category of "Digestive Diseases"<sup>[15]</sup>, the distinction between the two being unclear.

## PRIMARY BILIARY CIRRHOSIS AND THE FIRST NATIONS COMMUNITIES OF BRITISH COLUMBIA

Prior to the work formally studying the question of PBC amongst BC's First Nation Community, there had been indirect evidence suggesting that autoimmune liver disease was relatively common in this community. The British Columbia Vital Statistics Report<sup>[15]</sup> from 1991-1999 reported that deaths from chronic liver disease amongst First Nations women were five times higher than that in non-Aboriginal women, an interesting finding since both PBC and AIH are overwhelmingly afflictions amongst women. Furthermore, a study of the racial demographics of solid organ transplantation in British Columbia noted that organ recipients of First Nations background were significantly more likely to receive a liver allograft than any other transplanted organ (i.e. kidney, heart, lung)<sup>[16]</sup>. Lastly, anecdotal reports amongst BC's gastroenterologists<sup>[17]</sup> suggested that PBC was common amongst the province's First Nations community. The first direct evidence that PBC may be more common amongst BC's First Nations community came from the referral database of the BC Transplant Society's Liver Transplant Program<sup>[7]</sup>. It was discovered that of all patients referred for liver transplant assessment with a diagnosis of PBC, regardless of whether transplantation occurred or not, 25% were First Nation in demographic background. This was statistically significant compared to the 3.8% demographic proportion of First Nations Aboriginals within BC's population as a whole. Not surprisingly, over half of all liver transplant recipients, who were First Nations in background, had a pre-transplant diagnosis of PBC<sup>[7]</sup>. A subsequent review of the BC Transplant Society referral database, performed a few years later, again confirmed that the trend of PBC referrals amongst the First Nations population was disproportionate to the expected<sup>[8]</sup>, with a population odds ratio calculated at 8.3 with a 95% confidence interval between 5.6-12.21. The discovery, independent of the BC Transplant Society database, of an extended First Nations family with seven PBC cases in three sibships, related via common great grandparents led to a formal medical genetics population-based study of PBC in this community. This study<sup>[9]</sup> found a family history of PBC in 33% of PBC First Nations patients. A segregation analysis, which included five multiplex families, calculated the recurrence risk for PBC for all first-degree relatives, for first-degree relatives over the age of 21 years and for females over the age of 21 years as 4%, 4% and 10%, respectively. A calculation of the risk ratio ( $\lambda$ ), an estimate of genetic effect in complex traits based on the frequency in families, compared to the population prevalence, yielded a  $\lambda$  for siblings of 1500, if

one used a PBC population prevalence of 22 per million as previously reported in Ontario, Canada<sup>[18]</sup>, and 100 if one used a PBC population prevalence of 289 per million as reported in the state of Alaska<sup>[19]</sup> which is geographically adjacent to BC. Considering that most autoimmune diseases have a  $\lambda$  between 8 and 20<sup>[18]</sup>, a strong genetic predisposition of PBC amongst BC's First Nations population is implied.

We note that no other Canadian province has reported the finding of an increased prevalence of PBC in its First Nations community. In fact, the most well-known Canadian epidemiological study of PBC, based in the province of Ontario<sup>[19]</sup>, did not report a significant association of PBC amongst First Nations. This leads to the question of whether an association of PBC in BC truly exists or whether the association is a spurious false positive one. Of importance, the First Nations communities of Canada do not constitute one homogeneous entity. From an anthropologic perspective, geographic distribution of the First Nations peoples of North America follows different temporal waves of migration from Asia. Culturally and linguistically, similarities exist within geographically linked communities and disparities exist when comparing geographically removed First Nations communities. It may not be surprising that BC's First Nations community differ in medical disease predisposition compared to Ontario's communities. Our studies have suggested that the distribution of PBC amongst BC's First Nations communities is not geographically uniform throughout the province and the predilection appears strongest amongst the communities along the Pacific Coastal areas as opposed to the non-coastal interior of BC<sup>[8,9]</sup>. We note that the American Indians of Southeast Alaska have also been reported to have an increased prevalence of PBC<sup>[20]</sup>. Southeast Alaska (i.e. the Alaskan Panhandle) is geographically adjacent to the Pacific Coast of BC where most of our First Nations patients with PBC are located. Moreover, there are cultural and anthropologic similarities between these Alaskan and BC coastal communities that appear to share a predisposition to PBC. Furthermore, it is interesting that the First Nations communities of BC's Pacific Northwest and Southeast Alaska have both been long recognized to suffer a disproportionate burden of rheumatologic diseases<sup>[21-23]</sup> including lupus and arthritis. In general, similar rheumatologic diseases are well-known to be associated with PBC<sup>[4]</sup>, suggesting that the independent reports of PBC and rheumatologic diseases within geographically proximate First Nations communities may not be spurious.

## AUTOIMMUNE HEPATITIS AND THE FIRST NATIONS COMMUNITIES OF BRITISH COLUMBIA

Studies on AIH in BC's First Nations communities are still preliminary, however, there is a suggestion that this population may also be at risk for AIH. Two separate and independent database reviews have yielded similar proportions of First Nations patients amongst the BC AIH population. The first database review was of the BC Transplant Society's liver transplant candidate referrals<sup>[10]</sup> and the second was of the BC Children's Hospital AIH

Database<sup>[11]</sup>. Despite the fact that both database reviews looked at separate populations of AIH patients (i.e. adult *versus* pediatric), the proportion of First Nations with AIH was strikingly similar, approximately 17% in both. Since AIH is, in most cases, readily treated with corticosteroids and other immunosuppressive medications, unlike the situation of PBC where definitive cirrhosis-preventing treatment is not available, reviewing transplant centre and quaternary centre databases may be more prone to selection and referral bias. The discovery of classic PBC and classic AIH in a First Nations mother-daughter pair<sup>[24]</sup>, although anecdotal, dramatically suggests that these autoimmune diseases are both related and associated with BC's First Nations community.

## CONCLUSION

In closing, the story of PBC in BC's First Nations community underlines several important points. The first is that North American's First Nations people may have a genetic predisposition to autoimmune disease. Non-genetic factors, including recent changes in nutritional/dietary habits, environmental change/contamination, infectious agents, *etc.*, may also be co-factors that interact with a genetic predisposition to produce phenotypic disease. For researchers, the reasons for disease association remain to be determined and should be the subject of further epidemiologic, basic science and clinical research. In order to accomplish this, however, researchers must be sensitive to the needs and concerns of the First Nations community. If the community is to be expected to participate, then it is a reasonable expectation that the community will, in the long-term, derive some benefit from its participation. For clinicians, a high index of suspicion is required when encountering members of an at-risk population group as is the case of chronic liver disease and BC's First Nations community. Secondly, the First Nations communities across North America are not homogeneous from a cultural anthropologic perspective and the same may also be true with regards to disease predisposition. Lastly, the dynamic interaction between medical culture and medical research can not be down-played. Currently in BC, when encountering a First Nations patient with chronic liver disease, screening for PBC and AIH is considered mandatory and alcoholic liver disease is a diagnosis of exclusion. The same may not have been true in the past.

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