The mystery of primary biliary cirrhosis in British Columbia’s First Nations people

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ABSTRACT

Objectives. Primary biliary cirrhosis (PBC) is a rare chronic, progressive liver disorder leading to transplantation or death, with a known autoimmune basis. Although it has been estimated to have a prevalence of between 2-5 cases per 100,000 worldwide, it is not rare in British Columbia’s (BC) First Nations (FN) peoples, where it is the leading indication for liver transplant in that population. A study of indications for liver transplant from 1989 to 1998 demonstrated that although just 3.9% of the population of BC is of FN descent, 25% of those requiring transplantation for PBC were of FN descent. From this, it can be calculated that PBC is about 8 times more common than in the non-native population.

Methods. We studied the prevalence of PCB on Vancouver Island, where about 50% of the cases on the transplant Society List are reported. Results and discussion. As with many autoimmune diseases, PBC affects women predominantly. Genetic predisposition and environmental factors are thought to contribute to the development of PBC. A strong genetic component is postulated in the BC population where 6 affected individuals are all related through common great grandparents. Nonetheless, both genetic and environmental components are being explored in this unique population.

Key words: Primary biliary cirrhosis, First Nations, American Indians, genetics

INTRODUCTION

Primary biliary cirrhosis (PBC) is a rare chronic, progressive liver disorder with a known autoimmune basis. Progressive destruction of intrahepatic bile ducts leads to portal inflammation, progressive scarring and liver cirrhosis. The median length of survival is 7–16 years, depending on whether the condition is recognized asymptptomatically or symptomatically (1). Treatment modalities such as ursodeoxycholic acid have been found to reduce the likelihood of liver transplantation when used in a timely manner (2,3). Not unusual for genetically complex traits, familial cases are reported to account for 1-5% of those affected, and these are generally limited to recurrences of 2 to 3 cases per kindred, most often mother-daughter pairs (4-7). Although considered a model complex disease with a genetic basis, previous attempts to delineate the genetic basis of PBC have been largely unsuccessful, primarily because the disease is relatively rare, and large affected kindreds are exceedingly rare (8,7). There have been associations made with some HLA alleles; as well, weak associations with tumour necrosis factor (TNF-α), CTLA-4, Vitamin D receptor polymorphisms and specific mannose-binding lectin (MBL) genotypes have been described however (9-12). One apolipoprotein E allele has been associated with less responsiveness to ursodeoxycholic acid (UCDA) therapy (13) and may explain, at least in some, an increased vulnerability to rapid progression of the disease.

The condition is observed world-wide, with British and Swedish statistics demonstrating amongst the highest occurrence, with incidence 4-20/million and prevalence of 10-150/million.
There has been previous suggestion that the condition is largely associated with European ancestry. In Canada, the prevalence in Ontario is amongst the lowest, with an incidence of 3/million and prevalence of 22/million (1/50,000) (14).

As with many autoimmune diseases, PBC affects predominantly women, with male to female ratios averaging about 1:10 (15,16). It is associated with other autoimmune disorders including scleroderma, rheumatoid arthritis, Sjogren syndrome, polymyositis, vasculitis, as well as hypothyroidism (1). Although several immunological markers have been documented to be associated with PBC, antimitochondrial antibodies (AMA) are most specific and are present in 95% of those with the disorder (17). Other associated circulating antibodies include antinuclear antibodies (ANA), antithyroid antibodies, lymphocytotoxic antibodies, anti-acetylcholine receptor antibodies, antihistone antibodies and anti-centromere antibodies (1). Although HLA class I antigens do not seem to play a role in the development of PBC, HLA class II antigens may do so in some populations. Those that have been shown to confer risk include in particular HLA DQB1, DRB1 and DPB1. This has been further delineated with the use of sequence specific oligonucleotides showing that DRB1*0803, 0801, and DPB1*0501 have significantly higher frequencies in some populations affected with PBC (18).

In addition to genetic factors, infectious agents have also been implicated in the induction of the immune response causing PBC (19). Of interest is the suggestion that Hepatitis C Virus (HCV) may induce both Type 2 diabetes and autoimmune liver disease (20). This is of particular importance in BC’s FN peoples, in whom Type 2 diabetes (21) and HCV infection (22) are common. As well, there is now interest in the human beta retrovirus, which has been isolated from biliary tissue of those affected with PBC (23). Thus, given the presence of one or more genetic factors predisposing to PBC, with the environmental exposure of key viruses these people may be at a particularly high risk for the condition.

The BC Vital Statistics report (1991-1998) (24) suggests that deaths from chronic liver disease are five times more common in FN women than non-FN women (on Vancouver Island). The problem with this is that all deaths from chronic liver disease are tabulated as “alcoholic related deaths” for public health purposes. In the case of First Nations women, these statistics may be misleading, which may influence diagnostic practices, preventing timely treatment.

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METHODS
The British Columbia (BC) Transplantation Society database was reviewed for cases of PBC. Demographic differences between those of First Nations descent and not of First Nations descent were compared. 1) Comparative frequencies for referrals, place of residence and sex were compared. 2) In addition, cases with First Nations descent were ascertained, family history was taken, for recurrent cases and other autoimmune disease. Medical records were reviewed for natural history of the condition, and laboratory results including the presence of immunogenetic markers. DNA is being collected for family studies. This paper will discuss the results of the database analysis only.

RESULTS
In British Columbia the First Nations peoples account for about 4% (171,000) of the population of 3.9 million. However, when reviewing indications for liver transplant, in BC over a 10-year period of time, 25% of those transplanted for PBC were of First Nations descent. PBC is the leading
indication for liver transplantation in the First Nations people of British Columbia (25). Furthermore, 34 of a total of 128 cases referred for liver transplantation for PBC in BC were of First Nations descent (1 in 3). Thus, based on population size of respective populations, FN people were referred 8 times more frequently for PBC than non-FN people.

Place of residence: Vancouver Island is a large island off the west coast of British Columbia inhabited by about 17% of the province’s population, including 18% of the province’s First Nations population. A disproportionate number of first Nations people with PBC (45% of cases) live on Vancouver Island. Of the non-first nations population, about 20% of cases are found on Vancouver Island.

Male to female ratio: The BC transplant society data demonstrates that for non-FN people the male:female ratio is 1:7. However, among the FN population, only 1 out of 34 cases was male.

CONCLUSION
PBC is the leading indication for liver transplant in British Columbia First Nations people, where based on population sizes, it is 8 times more likely for a person of First Nations descent to be referred for liver transplant for PBC than for one not of first nations descent. There is a preponderance of cases on Vancouver Island that may reflect a strong genetic and/or environmental component.

The male:female ratio is markedly lower in the BC Transplantation data than in published data. The reason for this is unclear and may suggest that men of First Nations descent in BC are not affected with PBC as frequently as in other populations, or more likely, they might be diagnosed or referred for transplantation less frequently.

We propose that one or more genetic factors, coupled with key environmental factors, are responsible for the excessively high rate of PBC in the First Nations Peoples of BC. The currently recognized high rate of PBC in the known familial and sporadic cases will likely allow one or more genes to be identified predisposing to this condition, and perhaps other autoimmune disease. By using well-established molecular techniques of genetic linkage and genomic searching, common genetic markers within this population will be sought. As important, environmental factors which may contribute to the onset and alter the course of the disease, such as the presence of predisposing viruses, lifestyle and treatment modalities (traditional and western) will be analysed.

The health of BC native women is being affected disproportionately by PBC. Research into the etiology and natural history of the condition will serve to inform those involved in native health care and the communities affected, allowing for more timely diagnosis and treatment, which may mitigate the debilitating effects of the condition and afford prevention.

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