Indications for liver transplantation in British Columbia's Aboriginal population: A 10-year retrospective analysis

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OBJECTIVES: To study the indications for liver transplantation among British Columbia's First Nation population.

MATERIALS AND METHODS: A retrospective analysis of the British Columbia Transplant Society's database of Aboriginal and non-Aboriginal liver transplant recipients from 1989 to 1998 was undertaken. For primary biliary cirrhosis (PBC), the transplant assessment database (patients with and without transplants) was analyzed using a binomial distribution and compared with published census data regarding British Columbia's proportion of Aboriginal people.

RESULTS: Between 1989 and 1998, 203 transplantations were performed in 189 recipients. Fifteen recipients were Aboriginal (n=15; 7.9%). Among all recipients, the four most frequent indications for liver transplantation were hepatitis C virus (HCV) infection (n=57; 30.2%), PBC (n=34; 18.0%), alcohol (n=22; 11.6%) and autoimmune hepatitis (n=14; 7.4%). Indications for liver transplantation among Aboriginal people were PBC (n=8; 53.3%; P<0.001 compared with non-Aboriginal people), autoimmune hepatitis (n=4; 26.67%; P=0.017), acute failure (n=2; 13.3%) and HCV (n=1). Among all patients referred for liver transplantation with PBC (n=43), 29 (67.44%) were white and 11 (25.6%) were Aboriginal. A significant difference was found between the proportion of Aboriginal people referred for liver transplantation and the proportion of Aboriginal people in British Columbia (139,655 of 3,698,755 [3.8%]; 1996 Census, Statistics Canada) (P<0.001).

CONCLUSIONS: Aboriginal people in British Columbia are more likely to be referred for liver transplantation with a diagnosis of PBC but are less likely to receive a liver transplant because of HCV or alcohol than are non-Aboriginal people.

Key Words: *Aboriginal people; Autoimmune hepatitis; British Columbia; Liver; Liver transplantation; Primary biliary cirrhosis*

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Indications de la greffe du foie dans la population aborigène de la Colombie-Britannique : Analyse rétrospective de dix ans

OBJECTIF : Étudier les indications de la greffe du foie parmi les populations des Premières nations en Colombie-Britannique.

MATÉRIEL ET MÉTHODES : Analyse rétrospective de la base de données de la Société de transplantation de la Colombie-Britannique pour les receveurs de greffes du foie aborigènes et non-aborigènes entre 1989 et 1998. Dans les cas de cirrhose biliaire primaire, la base de données des transplantations (patients ayant ou non subi des greffes) a été utilisée selon une distribution binominale et comparée avec les données de recensement publiées sur la proportion de personnes d'origine aborigène de la Colombie-Britannique.

RÉSULTATS : Entre 1989 et 1998, 203 greffes ont été effectuées chez 189 receveurs. Quinze receveurs étaient d'origine aborigène (n = 15; 7,9 %). Parmi tous les receveurs, les quatre indications les plus fréquentes de la greffe étaient l'hépatite C (n = 57; 30,2 %), la cirrhose biliaire primaire (n = 34; 18,0 %), l'alcool (n = 22; 11,6 %) et l'hépatite autoimmune (n = 14; 7,4 %). Les indications de la greffe parmi les personnes d'origine aborigène ont été la cirrhose biliaire primaire (n = 8; 53,3 %; $p < 0,001$, comparativement aux personnes non aborigènes), l'hépatite autoimmune (n = 4, 26,67 %; $p = 0,017$), l'insuffisance aiguë (n = 2; 13,3 %) et l'hépatite C (n = 1). Parmi tous les patients adressés pour une greffe et souffrant de cirrhose biliaire primaire (n = 43), 29 (67,44 %) étaient de race blanche, 11 étaient aborigènes (25,6 %). Une différence significative a été notée entre la proportion de personnes Aborigènes adressées pour greffe du foie et la proportion d'aborigènes de la Colombie-Britannique (139 655 sur 3 698 755 [3,8 %]; recensement de 1996, Statistique Canada), ($p< 0,001$).

CONCLUSION : Les Aborigènes de la Colombie-Britannique sont plus susceptibles d'être adressés pour une greffe du foie avec un diagnostic de cirrhose biliaire primaire, mais sont moins susceptibles de recevoir une greffe du foie en raison d'un problème d'hépatite C ou d'alcoolisme comparativement aux personnes non aborigènes.

It is well recognized that the health and general well-being of North America's Aboriginal people are suboptimal compared with those of the North American population as a whole. Epidemiological studies (1,2) from both the western and eastern regions of the United States have reported excess mortality among Aboriginal people secondary to infectious diseases, diabetes mellitus and cirrhosis, as well as traumatic injuries and alcohol use. Low birth weight and infant mortality, traditional indicators of a community's global well-being, are also significantly worse among Aboriginal people than among North Americans as a whole (2). Although some of the health problems encountered by North America's Aboriginal people are symptomatic of lower socioeconomic class, which itself is a risk factor for increased mortality (3), it has been suggested that specific disease processes with a possible genetic predisposition may also be more prevalent among Aboriginal groups. Rheumatoid arthritis has been well-studied among the various Aboriginal bands and tribes (4-6), and more recently, two independent studies have reported an increased prevalence of gestational diabetes mellitus among northern Canadian Cree Aboriginal people of Ontario and Quebec (7,8).

In a recent study investigating the racial composition of organ donors and recipients in British Columbia (9), it was noted that First Nation Aboriginal people in British Columbia were significantly more likely to receive a liver transplant than any other organ transplant. Although the cause of the liver diseases of the Aboriginal transplant recipients was not examined, it was noted that the transplantation centre has strict pretransplant selection criteria with regards to alcohol and substance abuse (10). This led to speculation that British Columbia's Aboriginal people with end-stage liver disease may be at an increased risk for nonalcoholic liver disease. In the present study, we retrospectively analyzed the indications for transplantation among British Columbia's Aboriginal population and compared them with those of the non-Aboriginal population for the 10-year period from 1989 to 1998, inclusive.

MATERIALS AND METHODS

The liver transplant database of the British Columbia Transplant Society, a provincial organization that administrates all aspects of solid organ transplantation in British Columbia, was examined retrospectively for the years 1989 to 1998, inclusive. The primary diagnoses of all liver transplant recipients of Aboriginal origin (as indicated by the patient's racial categorization in the most recent Canada Census) who received their transplants in British Columbia were compared with those of the liver transplant recipient cohort as a whole. After the initial analysis of transplant recipients was completed, the database was further examined, and the racial composition of all patients referred with a diagnosis of primary biliary cirrhosis (PBC), including both those who received transplants and those who did not receive transplants, was analyzed. The diagnostic classification of PBC by the database is defined as antimitochondrial antibody (AMA) seropositivity in association with elevated serum alkaline phosphatase and gamma glutamyltransferase concentrations.

In the initial analysis of transplant recipients, statistical analysis was performed with the χ^2 test and, if the requirements for the χ^2 test were not fulfilled, the Fisher's exact test was used. Statistical analysis was performed using the SPSS 8.5 computer software program (SPSS, USA). In the analysis of patients referred with a diagnosis of PBC, statistical analysis was performed to compare the binomial distribution of the PBC cohort with the published data from the 1996 Canada Census (11). The data were analyzed using the Splus computer software program (Statistical Software, USA). In all cases, the alpha level of significance for a two-tailed test was 0.05.

RESULTS

In the 10-year period from 1989 to 1998, inclusive, 203 liver transplantations were performed on 189 recipients. The primary diagnoses of the entire liver transplant recipient cohort are shown in Table 1. The three most common reasons for

TABLE 1
Distribution of liver transplant recipients in British Columbia from 1989 to 1998 by primary pretransplantation diagnosis

Primary diagnosis	Number of recipients (%)
Hepatitis C	57 (30.16)
Primary biliary cirrhosis	34 (17.99)*
Alcoholic cirrhosis	22 (11.64)
Autoimmune hepatitis	14 (7.41)†
Primary sclerosing cholangitis	12 (6.35)
Crytogenic cirrhosis	10 (5.29)
Hepatitis B	9 (4.76)
Acute liver failure	9 (4.76)
Alpha-1 antitrypsin deficiency	5 (2.65)
Miscellaneous	5 (2.65)
Wilson's disease	3 (1.59)
Malignancy	3 (1.59)‡
Not classified	2 (1.06)
Total	189 (100)

**Includes one patient (non-Aboriginal) with autoimmune cholangitis (ie, seronegative antimitochondrial antibody); †Includes one patient (Aboriginal) with autoimmune cholangitis and autoimmune hepatitis overlap syndrome; ‡One patient with hepatoma, two patients with nonhepatocellular cancers*

liver transplantation in British Columbia were hepatitis C virus (HCV) infection (30.16%), PBC (17.99%) and alcoholic liver disease (ALD) (11.64%). During this period, 15 (7.94%) of the 189 allograft recipients were of Aboriginal origin. All of the Aboriginal recipients were residents of British Columbia and were members or descendants of First Nation Aboriginal bands (ie, tribes) indigenous to British Columbia. Examination of the primary diagnoses of the Aboriginal recipients (Table 2) revealed that 53% (n=8) received liver transplants because of PBC, and 27% (n=4) received allografts because of autoimmune hepatitis. Autoimmune cholangitis (seronegative AMA)/autoimmune hepatitis overlap syndrome was diagnosed clinically in one Aboriginal transplant recipient but was coded in the database as 'autoimmune hepatitis'. The other three Aboriginal liver transplant recipients underwent transplantation because of acute liver failure (n=2) and chronic HCV (n=1). Compared with the total number of liver transplant recipients, the number of Aboriginal people who received liver transplants because of PBC (P<0.001) and autoimmune hepatitis (P=0.017) was significantly greater than expected.

After the initial analysis of liver transplant recipients was completed, the racial distribution of all patients referred for liver transplant assessment with a diagnosis of PBC was examined (Table 3). This database included both liver transplant recipients and those who did not receive liver transplants because they were still undergoing assessment, were considered too early for transplantation, had died before transplantation or were considered unsuitable for transplantation. During the 10-year period from 1989 to 1998, inclusive, 43 patients with a primary diagnosis of PBC were referred for liver transplant assessment. The largest racial group was white (n=29; 67.44%), but Aboriginal people were the next largest group and constituted over 25% (n=11) of all PBC referrals. When the proportion of Aboriginal people in the PBC referral cohort was compared with the proportion of British Columbia's Aboriginal population (139,655 of a total population of 3,689,755 [3.8%]) (11), a statistically significant difference was found (P<0.0001). In comparison, of all patients referred and assessed for liver transplantation (n=587), 8.5% were Aboriginal.

TABLE 2
Distribution of Aboriginal liver transplant recipients by primary pretransplantation diagnosis

Primary diagnosis	Number of recipients (%)
Primary biliary cirrhosis	8 (53.33)*
Autoimmune hepatitis†	4 (26.67)‡
Acute liver failure	2 (13.33)
Hepatitis C	1 (6.67)
Total	15 (100)

**P<0.001 compared with all liver transplant recipients; †Includes one patient with autoimmune cholangitis and autoimmune hepatitis overlap syndrome; ‡P=0.017 compared with all liver transplant recipients*

TABLE 3
Racial distribution of all patients referred for liver transplantation from 1989 to 1999, inclusive, with a diagnosis of primary biliary cirrhosis

Race	Number of patients (%)
White	29 (67.44)
Aboriginal	11 (25.58)*
Asian Indian†	2 (4.65)
Chinese	1 (2.33)
Total	43 (100)

**P<0.0001 compared with the proportion of Aboriginal people in British Columbia's population; †Includes one patient with autoimmune cholangitis (seronegative antimitochondrial antibody)*

DISCUSSION

Our study, which examined the indications for liver transplantation among British Columbia's First Nation Aboriginal people, is, to our knowledge, the first formal review of North America's Aboriginal people and liver transplantation. The findings of this study, however, can be generalized beyond the narrow confines of transplantation. When one considers that liver transplantation is an accepted form of therapy for end-stage liver disease, then a cohort of liver transplant recipients or patients referred for transplant assessment is a sample (albeit a selected sample) drawn from the larger population of all patients with end-stage disease. In British Columbia, our centre is in a unique position because it is the only referral centre for the entire province

and, under the Canada Health Act, lack of health care insurance is not an issue for patients; therefore, socioeconomic status should not be an issue with regard to referral for transplant assessment. The interesting finding from our study was that the indications for liver transplantation in Aboriginal people differed significantly from those of the overall liver transplant cohort. Whereas HCV and ALD were the indications for 30% and 12% of liver transplantation overall, among Aboriginal people, only one recipient underwent transplantation because of HCV, and none received a transplant because of ALD. Instead, 80% of Aboriginal liver transplant recipients in British Columbia underwent liver transplantation because of autoimmune liver disease: 53% underwent transplantation because of PBC and 27% underwent transplantation because of autoimmune hepatitis (AIH). Compared with the non-Aboriginal cohort of transplant recipients, these proportions, especially PBC, were significantly greater than expected.

Despite the finding that autoimmune liver diseases were the most likely indications for transplantation among Aboriginal people in British Columbia, these results may be secondary to either a referral or selection bias. The results of our second analysis – that 25% of all patients referred for liver transplant assessment with a diagnosis of PBC over 10 years were Aboriginal – is less likely to be the result of referral or selection bias. This proportion of Aboriginal people with PBC is significantly greater than the proportion of Aboriginal people in British Columbia's general population (less than 4%). In fact, our findings in this regard may be an under-representation because Aboriginal people with end-stage PBC may not be referred by primary care physicians for liver transplant assessment because of comorbid conditions, including alcohol or substance abuse, misdiagnosis (eg, alcoholic cirrhosis for PBC) or suboptimal social circumstances (eg, lost to follow-up).

Our study is the first to suggest that a specific population of First Nation Aboriginal people may have an increased risk of autoimmune liver diseases – especially PBC. Cholestatic liver disease has previously been reported among Cree and Ojibwa-Cree children of Northern Quebec (12,13). Our patients, however, were all well-investigated adults suffering from well-defined autoimmune liver diseases. Although a previous Canadian study from Ontario (14) did not find any racial predisposition for PBC, gastroenterologists in British Columbia have long speculated that First Nation Aboriginal people in this province may have an increased prevalence of PBC (15,16). This theory has been further supported by the identification of a large kindred with PBC among the Nuu-Chah-Nulth Nation of Vancouver Island (H Henderson, unpublished data), which has previously been found to have a high prevalence of rheumatological diseases (17). The lack of similar findings reported elsewhere in Canada and the United States leads us to speculate either that PBC and autoimmune hepatitis are under-reported in the Aboriginal population or that the First Nation population of the Pacific northwest has a unique genetic or environmental predisposition. We suspect that, although there is a tendency to view North America's First Nation Aboriginal people as a homogenous group, there is significant heterogeneity historically, culturally and geographically. This heterogeneity likely also exists with regard to disease predisposition. We find it interesting that investigators in Alaska, which is geographically close to British Columbia and shares a northern border with British Columbia along the Alaskan Panhandle, as well as historical and cultural ties among the region's coastal indigenous people, have also reported an increased prevalence of AIH and PBC among that state's mixed Aboriginal population (Aleut, Eskimo, Indian) (18).

Our study is limited by its retrospective design and the fact that it is a review of the provincial transplant agency's database. The findings of this study, as with all retrospective database/chart review studies, cannot be considered definitively conclusive. The findings are, however, hypothesis-generating and can be used as a starting point for further studies. In this situation, prospective, population-based genetic and phenotypic studies of British Columbia's First Nation people, with respect to autoimmune liver diseases, would be both of academic interest and potentially beneficial to members of this community. A study of such a nature is currently in the initial stage.

CONCLUSIONS

In British Columbia, First Nation Aboriginal people are significantly more likely to undergo liver transplantation for autoimmune liver diseases, specifically, AIH and PBC. It also appears that the proportion of Aboriginal people in British Columbia with PBC who are referred for transplant assessment is significantly greater than the proportion of Aboriginal people in the general population. This study supports the hypothesis that British Columbia's Aboriginal population has an increased risk of PBC and possibly AIH; however, definitive epidemiological studies are required.

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