Lessons learned from liver transplantation with the Canadian First Nations

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Evaluation of liver transplantation outcomes may provide unique insight into the pathobiology of idiopathic liver diseases. For example, it is often suggested that individual disorders, including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC), are triggered by unknown environmental agents in genetically susceptible individuals. Each of these disorders recur in a minority of liver transplant recipients (1,2), implying that the initial trigger may persist in the host. Conversely, most patients do not develop recurrent autoimmune liver disease; therefore, if an infectious process is believed to trigger recurrent disease, some allografts may provide protection as a result of inherent innate immune responses to specific microbial infections. At this juncture, we are only just beginning to unravel the genetic factors that predispose to or protect against the development of specific autoimmune liver disorders (3).

It is, therefore, instructive that different populations appear to be at risk for autoimmune liver disease. In the current issue of *The Canadian Journal of Gastroenterology*, Zhang et al (4) (pages 307-310) from the University of Manitoba (Winnipeg, Manitoba) report that 45% of Canadian First Nations (FN) liver-transplant recipients had a diagnosis of autoimmune liver disease, compared with 28% of non-FN patients (4); 30% of FN had AIH, a percentage six-fold higher than non-FN recipients. In contrast, no FN patients were transplanted for PSC, and the proportion of patients with PBC was comparable between groups. Notably, FN patients were younger and more often female compared with their non-FN counterparts. These data suggest that AIH is more common and has a poorer prognosis in FN populations. Indeed, investigations in the nontransplant populations of Manitoba and British Columbia suggest that AIH is more prevalent and rapidly progressive in FN individuals (5,6). Similarly, a higher likelihood of acute and icteric presentation of AIH has been reported in Alaskan native patients compared with other Alaskan Americans (7). Although confounding factors must be considered when interpreting these data (eg, differential access to health care and the possibility that therapeutic intervention may obviate transplantation), the disproportionate prevalence of AIH in FN liver transplant recipients is noteworthy.

Studies from the liver transplant program in British Columbia provide a slightly different twist on this issue. Similar to Manitoba, AIH is four times more common in FN liver transplant recipients than in non-FN patients, and is the second most common indication for transplantation in the FN population (6). However, PBC is the most common indication for transplantation in the coastal FN, with a strikingly high prevalence (8-10). While the proportion of FN compared with non-FN patients undergoing transplantation in British Columbia and Manitoba are similar, it is notable that 10% of all PBC transplant recipients are FN in origin in Manitoba compared with 25% in British Columbia (8). Similar to experiences with AIH, FN patients with PBC tend to be referred for transplantation at a younger age, and the accumulated data suggest a more rapid disease course compared with non-FN patients (8-10).

Several studies suggest a robust genetic predisposition for PBC among the FN population of British Columbia. In one study, extended

families with a PBC prevalence of up to 33% have been described, predominantly in the coastal FN communities derived from the Salishan coastal cultural group (10). Indeed, the prevalence of PBC in the coastal FN is an order of magnitude higher on Vancouver Island (10). Importantly, a high prevalence of PBC has also been documented in Aboriginal Alaskans, who share the Salish ancestry (7). In contrast, the Manitoban FN with a predisposition to AIH are derived from Ojibwa-Cree, a separate cultural group (4). Because inflammatory bowel disease is relatively rare in FN populations, it is not surprising to see a lack of PSC in the FN populations who undergo liver transplantation in both provinces (4,7).

What lessons can we learn from these FN transplant data? The first lesson confirms what we already know based on overlap syndromes of AIH and PBC – specifically, that the distinction between these conditions can be blurry. They may be found as a single entity in the same patient or in different family members, as illustrated by the diagnosis of PBC in the mother and classical AIH in her daughter from an FN family (11). Collectively, these data suggest that FN have a genetic (and/or environmental) predisposition to autoimmune liver disease. Indeed, several autoimmune disorders are more common in FN including juvenile rheumatoid arthritis (12), rheumatoid arthritis, systemic lupus erythematosus (13), multiple sclerosis (14) and vasculitides, such as polyarteritis nodosa (15). Although genome-wide association studies that address the complexity of the genetic predisposition to autoimmune liver diseases in FN communities are lacking, the data suggest that specific FN populations have different innate immune responses to microbial infections. Indeed, elegant studies from the University of Manitoba have documented differential interleukin-10 responses to hepatitis C virus infection that modulate the outcome of disease (16).

The second lesson to be learned is that there remains an oversimplified conception that most cases of end-stage liver disease in FN patients are the consequence of heavy alcohol consumption. While alcohol abuse constitutes a health problem in general and among some FN communities (17), it is noteworthy that many patients referred with presumed alcoholic cirrhosis actually have an autoimmune liver disorder when appropriately evaluated. Because multiple studies across Canada have documented a high prevalence of autoimmune liver disease in FN populations (5,6,10,18), all clinicians should be aware of this susceptibility to ensure adequate screening and correct diagnosis. Only these measures will lead to appropriate medical management including referral for transplantation in patients with end-stage liver disease. Reassuringly, the study by Zhang et al (4) confirms that transplantation outcomes are similar between FN and non-FN patients; therefore, ethnicity should not play a role when considering a patient's liver transplant candidacy.

Finally, additional studies are required to understand the predominance of autoimmune liver diseases in FN populations. Although we have derived excellent genome-wide association data in PBC from a multi-centre Canadian study (3), corresponding data in FN populations are lacking. Such studies will enhance our understanding of the genetic and environmental factors that predispose to autoimmune liver disease in general, and in these often heterogeneous FN communities.

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REFERENCES

1. Montano-Loza AJ, Mason AL, Ma M, Bastiampillai RJ, Bain VG, Tandon P. Risk factors for recurrence of autoimmune hepatitis after liver transplantation. *Liver Transpl* 2009;15:1254-61.
2. Montano-Loza AJ, Wasilenko S, Bintner J, Mason AL. Cyclosporine A protects against primary biliary cirrhosis recurrence after liver transplantation. *Am J Transplant* 2010;10:852-8.
3. Hirschfield GM, Liu X, Xu C, et al. Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants. *N Engl J Med* 2009;360:2544-55.
4. Zhang M, Uhanova J, Minuk GY. Liver transplant outcomes in a Canadian First Nations population. *Can J Gastroenterol* 2011;25:307-10.
5. Minuk GY, Liu S, Kaita K, et al. Autoimmune hepatitis in a North American Aboriginal/First Nations population. *Can J Gastroenterol* 2008;22:829-34.
6. Chung H, Ho JK, Leung B, et al. Autoimmune hepatitis referrals to the British Columbia Transplant Society: A disproportionate representation from BC's First Nation's Community. *Can J Gastroenterol* 2005;19:177 (Abst).
7. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska Natives. *Am J Gastroenterol* 2002;97:2402-7.
8. Yoshida EM, Riley M, Arbour LT. Autoimmune liver disease and the Canadian First Nations Aboriginal Communities of British Columbia's Pacific Northwest. *World J Gastroenterol* 2006;12:3625-27.
9. Yoshida EM, Caron NR, Buczkowski AK, et al. Indications for liver transplantation in British Columbia's Aboriginal population: A 10-year retrospective analysis. *Can J Gastroenterol* 2000;14:775-9.
10. Arbour L, Rupps R, Field L, et al. Characteristics of primary biliary cirrhosis in British Columbia's First Nations population. *Can J Gastroenterol* 2005;19:305-10.
11. Riley M, Ho JK, Schreiber R, Yoshida E. PBC and AIH in a First Nations mother-daughter pair. *Can J Gastroenterol* 2005;19:191 (Abst).
12. Oen K, Schroeder M, Jacobson K, et al. Juvenile rheumatoid arthritis in a Canadian First Nations (aboriginal) population: Onset subtypes and HLA associations. *J Rheumatol* 1998;25:783-90.
13. Boyer GS, Templin DW, Lanier AP. Rheumatic diseases in Alaskan Indians of the southeast coast: High prevalence of rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol* 1991;18:1477-84.
14. Warren S, Svenson LW, Warren KG, Metz LM, Patten SB, Schopflocher DP. Incidence of multiple sclerosis among First Nations people in Alberta, Canada. *Neuroepidemiology* 2007;28:21-7.
15. McMahon BJ, Heyward WL, Templin DW, Clement D, Lanier AP. Hepatitis B-associated polyarteritis nodosa in Alaskan Eskimos: Clinical and epidemiologic features and long-term follow-up. *Hepatology* 1989;9:97-101.
16. Aborsangaya KB, Dembinski I, Khatkar S, Alphonse MP, Nickerson P, Rempel JD. Impact of aboriginal ethnicity on HCV core-induced IL-10 synthesis: Interaction with IL-10 gene polymorphisms. *Hepatology* 2007;45:623-30.
17. Rothe JP. Towards a better understanding of First Nations communities and drinking and driving. *Int J Circumpolar Health* 2005;64:336-45.
18. Chung HV, Riley M, Ho JK, et al. 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. *Can J Gastroenterol* 2007;21:565-8.