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Association between ethnicity and human leukocyte antigen (HLA) alleles on late presentation to care and high rates of opportunistic infections in patients with HIV

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Within Manitoba, Aboriginal people make up 15% of the province's population, but accounted for 53% of new human immunodeficiency virus (HIV) diagnoses in 2011. For over a decade, research has linked the human leukocyte antigen (HLA) class I alleles as having both protective and harmful effects in HIV disease progression. The abundance of HLA alleles that predispose to rapid disease progression, together with the rarity of protective HLA allele types, may be a contributing factor to a more rapid disease progression amongst individuals of Aboriginal ethnicity. We completed an epidemiological study on all HIV patients new to care in the Manitoba HIV Program in 2010, looking at markers of disease severity, such as CD4 cell count, rates of opportunistic infections (OI), and HLA type. In this cohort, the Aboriginal population was overrepresented, and presented with significantly more advanced HIV infection (lower CD4 counts, higher rates of OI), compared to patients from a Caucasian background. Our data supports previously identified associations between HLA type and disease progression, and demonstrates a difference in distribution of HLA type by ethnicity.

Key words: Aboriginal, disease progression, ethnicity, HLA B27, HLA B35, HLA B51, HLA B5701, human immunodeficiency virus, human leukocyte antigen, opportunistic infection.

INTRODUCTION

The human immunodeficiency virus (HIV) is a clinically important disease, contributing to tremendous morbidity and mortality. The prevalence of HIV infection in Canada is on the rise (Public Health Agency of Canada, 2008). In 2008, an estimated total of 65,000 people in Canada were living with HIV infection, which represents an increase of about 14% from the 2005 estimate of 57,000 cases (Public Health Agency of Canada, 2008).

A trend of higher proportion of HIV diagnosis among indigenous peoples was identified in the recent International

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Policy Dialogue on HIV/AIDS and Indigenous Peoples (International Affairs Directorate, 2010). Within Canada, Aboriginal people make up 4% of the Canadian population, but 8% of the Canadian population living with HIV, and this proportion is likely even higher with the increase in new HIV cases in the Prairies over the last 5 years (Public Health Agency of Canada, 2008). This over-representation is even more striking within Manitoba, as Aboriginal people make up 15% of the province's population, but 43% of new HIV diagnoses in 2009, and 53% of new HIV diagnoses in 2011 (Statistics Canada, 2006; Manitoba HIV Program, 2011). The province with the highest rates is Saskatchewan, with 172 new diagnoses in 2010, representing a rate of 16.1/100,000, almost double the average Canadian rate of 8.2/100,000 (Public Health Agency of Canada, 2010; Saskatchewan Ministry of Health, 2010). While the factors influencing these trends are undoubtedly complex and multi-factorial, they may not be entirely attributable to social and structural factors.

For over a decade, research has linked the human leukocyte antigen (HLA) class I alleles as having both protective (HLA B27, B51, B5701) and harmful (HLA B35) effects in HIV disease progression (Brumme et al., 2007; Carrington and O'Brien, 2003; International HIV Controllers Study, 2010; Kaslow et al., 1996; Pelak et al., 2010, Smeraldi et al., 1986). The enrichment of HLA alleles predisposing to rapid disease progression, together with the rarity of the protective HLA alleles among individuals of Aboriginal descent may be a contributing factor to a more rapid disease progression, as evidenced by the degree of immune suppression seen at presentation among the persons in care within the HIV clinics in Manitoba.

We completed an epidemiological study of all patients with HIV new to care in the Manitoba HIV Program in 2010. Factors analyzed included basic epidemiologic data such as age, gender, ethnic background, and major risk factors in acquiring HIV. We also looked at markers of disease severity, such as CD4 cell count on presentation, and opportunistic infections (OI). Finally, as HLA typing has been routinely performed in Canada since 2006 (in order to predict Abacavir hypersensitivity), each patient's HLA type was recorded. The aim of this study was to look for the presence of significant associations between markers of disease severity at presentation to care in the Manitoba HIV Program and HLA type.

METHODOLOGY

Medical chart reviews were completed at the Nine Circles Community Health Centre, a community-based HIV clinic and a hospital-based HIV clinic at the Health Sciences Centre in Winnipeg, Manitoba. These clinics are the two sites of the Manitoba HIV Program, which provides specialized care for over 1100 people living with HIV in Manitoba or about 90% of people with HIV in care in the province. Data from both centers were pooled for all analyses. Ethics approval was obtained from Health Research Ethics Board at the University of Manitoba.

Charts reviewed were of all 102 patients in the Manitoba HIV Program presenting new to HIV care in 2010. A set list of epidemiological categories were identified and defined prior to the onset of the chart review and used for data extraction. These included year of birth, gender, HIV transmission risk including emigrating from an area known to have a high prevalence of HIV infection (such as Africa, Eastern Europe, and Asia), ethnic background (this was self-reported), CD4 count, CD4 percentage (percentage of total lymphocytes that are CD4 cells); HLA type, presence (and if applicable, type) of OI. Patients self-reporting as Aboriginal ethnicity included people of First Nations, Métis, and Inuit descent. Two people were lost to follow-up prior to completing their initial assessment, and therefore limited epidemiologic data was available for them.

Analyses were carried out in Stata v10.0 (College Station, Texas) and Microsoft Excel. We described our population with means and medians for continuous variables and percentages for categorical variables. We compared groups using Mann-Whitney tests for continuous variables and Fisher exact tests for categorical variables.

RESULTS

Sociodemographic

The majority of the patients in our cohort were male (75%). The most common risk factor identified in acquiring HIV was heterosexual contact (63%), followed by men who have sex with men (MSM) (22%), originating from an HIV endemic area (20%), and intravenous drug use (16%) (Table 1).

Patients of Aboriginal ethnicity made up 37.6% of our patient cohort. The average age of Aboriginal patients was 34.4 for females and 39.2 for males, compared to the average age of 35.1 for non-Aboriginal females and 39.7 for non-Aboriginal males.

Clinical characteristics

The majority of patients (53%) presented with a CD4 count of less than 350 cells per microliter (µl) (Table 1). Over 1/3 of the patients had a presenting CD4 count less than 200 cells/µl, and of this group, 54% were Aboriginal (Table 2).

The majority of Aboriginal cases presented with a CD4 count <200 cells/µl, while the majority of people from Caucasian, African, and other ethnic backgrounds presented with CD4 counts >350 cells/µl (Table 2). The median CD4 count at presentation amongst Aboriginal patients (201 cells/µl, p=0.010, Mann-Whitney) and African patients (311 cells/µl, p=0.039, Mann-Whitney) was significantly lower than that of Caucasian patients (421 cells/µl) (Table 2). Aboriginal patients also presented with a lower median CD4 cell count percentage (17%) compared to non-Aboriginal patients (21%) (p=0.029, Mann-Whitney) (Table 2).

Opportunistic infections were diagnosed at presentation in 30% of our cohort, most commonly esophageal/

Table 1. Socio-demographic and clinical characteristics of patients presenting with a new diagnosis of HIV in Manitoba in 2010. Several people presented with more than one opportunistic infection (OI) at presentation.

Characteristic	N (%)
Age (n=102)	
10-17	1
18-24	14
25-29	14
30-39	28
40-49	28
50+	17
Mean (IQR)	38.4 (29.0 – 46.8)
Gender (n=102)	
Male	76
Female	26
Risk factors for acquisition of HIV (n=101)	
Heterosexual	64
Endemic	22
IVDU	16
MSM	20
CD4 count (cells/ul, n=101)	
<200	35
200-350	19
>350	47
Median (IQR)	319 (145 – 485)
Median CD4 % (IQR)	19.0 (13.5 – 27.0)
OI (n=30)	
Candidiasis	14 (47)
Pneumocystis jirovecii pneumonia	9 (30)
Herpes simplex	4 (13)
Tuberculosis	4 (13)
Cryptococcal meningitis	1 (3)
Burkett's lymphoma	1 (3)
Other	3 (10)
HLA type (n=100)	
HLA B27	2
HLA B35	14
HLA B51	25
HLA B5701	4

oropharyngeal candidiasis (47%) and *Pneumocystis jirovecii pneumonia* (PJP) (30%) (Table 1). In the 30 patients presenting with opportunistic infections, 14 were Aboriginal, while 10 were Caucasian (Table 2). Individuals who were Aboriginal were significantly more likely to present with an OI (P=0.0027, Fisher Exact test, OR 4.4, 95% CI 1.7-11.9) (Table 2).

Of the 54 patients who presented to care with CD4 counts less than 350 cells/µl, 31% were either heterozygous or homozygous for the HLA B51 allele (Table 3). This allele was only present in 17% of those people presenting with CD4 counts over 350 cells/µl (Table 3). HLA B35 and HLA B27 were equally distributed between patients presenting with CD4 counts greater than and less

Table 2. Comparison of selected socio-demographic, clinical characteristics, and human leukocyte antigen (HLA) type with self-reported ethnicity, in people presenting to care with a new diagnosis of HIV in Manitoba in 2010.

Characteristic	Ethnicity [N (%)]				p-value
	Aboriginal (n=38)	African (n=22)	Caucasian (n=36)	Other (n=5)	
Age at presentation (n=101)					
10-17	0	1 (5)	0	0	-
18-24	6 (16)	3 (14)	5 (14)	0	-
25-29	6 (16)	3 (14)	4 (11)	1 (20)	-
30-39	11 (29)	7 (32)	9 (25)	1 (20)	-
40-49	9 (24)	6 (27)	10 (28)	2 (40)	-
50+	6 (16)	2 (9)	8 (22)	1 (20)	-
Mean	37.7	36.0	39.9	42.8	-
CD 4 count (cells/ul, n=101)					
<200 (n=35)	19 (50)	9 (41)	6 (17)	1 (20)	-
200-350 (n=19)	7 (18)	2 (9)	9 (25)	1 (20)	-
>350 (n=47)	12 (32)	11 (50)	21 (58)	3 (60)	-
Median	201* (p=0.010, Mann-Whitney)	311* (p=0.039, Mann-Whitney)	420	369	-
Median CD4 %	17.0**	17.5	23.0	21.0	(p=0.029, Mann-Whitney)
Presence of any OI (n = 30)	14 (37)**	4 (18)	10 (28)	2 (40)	(p=0.0027, Fisher Exact)
HLA type					-
HLA B27 (n=2)	1 (3)	0	1 (3)	0	-
HLA B35 (n=15)	8 (21)	1 (5)	5 (14)	0	-
HLA B51 (n=25)	17 (45)	3 (14)	5 (14)	0	(p=0.005, Fisher's exact)
HLA B5701 (n=4)	0	0	4 (11)	0	(p=0.071, Fisher's exact)
Homozygous HLA of any type (n=15)	9 (24)	3 (14)	3 (8)	0	-

*Compared to the Caucasian cohort. **Compared to non-Aboriginal cohort.

than 350 cells/µl (Table 3). All patients with HLA B5701 presented with CD4 counts >350 cell/µl Interestingly, 19% of patients with a CD4 count <350 cells/µl were homozygous for their HLA alleles, compared to only 11% of those presenting with CD4 counts >350 cells/µl (Table 3).

HLA type

HLA type varied amongst ethnic groups. Of 15 patients with a homozygous HLA type, 60% were Aboriginal; one quarter of the Aboriginal cohort had homozygous HLA alleles (Table 2). Nearly one quarter of the Aboriginal cohort possessed an allele for HLA B35, compared to only 14% of Caucasian patients (Table 2). Almost half of Aboriginal patients had an allele for HLA B51, while only 14% of the Caucasian cohort did (Table 2). Amongst patients with at least one allele for

Table 3. Comparison of the CD4 count (cells/ul) and presence of opportunistic infection (OI) in people presenting to care with a new diagnosis of HIV arranged by human leukocyte antigen (HLA) type.

HLA type	CD4 count N (%)		OI N (%)	
	< or =350, n=54	>350, n=46	Present, n=30	Absent, n=70
HLA B35	7 (13)	7 (15)	5 (17)	9 (13)
HLA B27	1 (2)	1 (2)	1 (3)	1 (1)
HLA B51	17 (31)	8 (17)	8 (27)	18 (26)
HLA B5701	0	4 (9)	0	4 (6)
Homozygous HLA of any type	10 (19)	5 (11)	4 (13)	11 (16)

either HLA B35 or HLA B51, 63% were Aboriginal (Table 2). HLA B27 was uncommon, with only one Aboriginal and one Caucasian person possessing it (Table 2). Alleles for HLA B5701 were only found in Caucasian patients (Table 2).

In persons presenting with an OI, 17% had an allele for HLA B35, which was only found in 13% of those without an OI at presentation (Table 3). HLA B51 was fairly evenly divided, present in 27% of people with an OI at presentation to care and 26% of those without an OI (Table 3). However, of those people presenting with an OI, it was the most prevalent HLA type (Table 3). Only 1 individual with an OI had the HLA B27 allele (Table 3). Notably, no patients carrying the HLAB5701 presented with an OI (Table 3).

DISCUSSION

Our 2010 cohort demonstrated an association between HLA type and the severity of HIV disease at presentation to care, as represented by CD4 count and rates of opportunistic infection. It also emphasized several unique socio-demographic characteristics amongst the Manitoba HIV population, as compared to the HIV population in the rest of Canada.

Our cohort had a higher incidence of acquiring HIV through a heterosexual mode of transmission (63%) compared to the rest of Canada (36%) (Public Health Agency of Canada, 2008). While MSM is the most common mode of transmission in developed countries, it was reported in only 22% of the cases in our cohort (International Affairs Directorate, 2010). Similar to the 2009 Manitoba data, Aboriginal individuals were overrepresented among patients new to care in 2010, making up 37% of new patients with a diagnosis of HIV, but only 15% of the province's population.

Not only is the Aboriginal population numerically overrepresented, but they are also presenting with a significantly higher burden of HIV infection compared to patients from a Caucasian background, as measured by CD4 count and CD4 cell percentages. Individuals of an Aboriginal background were more likely to present late in the course of their infection, with half of new diagnoses of HIV presenting with CD4 counts less than 200, an AIDS defining criteria. These late presentations will not only negatively affect health outcomes of the individual, but also result in high disease transmission rates and are associated with higher costs to the health-care system (Krentz and Gill, 2012). A recent retrospective cost-analysis out of Calgary demonstrated that mean monthly healthcare costs for patients with HIV were inversely proportional to their CD4 count (Krentz and Gill, 2008).

Rates of OI at presentation in the 2010 cohort were quite high, with 1/3 of new patients in 2010 presenting with an OI. The majority of these infections were candidiasis or PJP. Perhaps reflecting their significantly lower CD4 count at presentation, there were significantly more Aboriginal patients who presented with an opportunistic infection (47%) compared to patients from a Caucasian background (33%).

Our data show high rates of HLA alleles previously shown to be associated with fast CD4 T cell count decline, while at the same time a paucity of the protective HLA B5701 allele, as 17% of patients presenting with an OI had an allele for HLA B35 and none had HLA B5701. Interestingly, 27% of patients presenting with an OI had an allele for HLA B51, which has previously been shown to have protective effects on HIV disease progression in a Chinese cohort (Zhang et al., 2011). In addition, 31% of patients presenting to care with CD4 counts less than 350 cells/µl had at least one allele for HLAB51. Research in Japan has suggested that some HLA alleles that have been shown to have protective effects on HIV progression in Caucasians, particularly, HLA B51 may lose their protective effect in other ethnic populations over time (Koga et al., 2010). This could explain the high incidence of the HLA B51 allele in patients presenting with advanced HIV disease, in particular, the high incidence of this allele in the Aboriginal population of our cohort (45%).

Indeed, our data did demonstrate a difference in distribution of HLA type by ethnicity. The majority of patients with HLA B35 were Aboriginal, while the protective HLA B5701 type was found only in Caucasian patients. In addition to HLA type, homozygosity of HLA type has been shown to contribute to rapid progression of HIV (Brumme et al., 2007; Carrington et al., 1999). In our cohort,

the majority of patients with a homozygous HLA type were Aboriginal (60%).

STRENGTHS AND LIMITATIONS

Our study had a number of strengths, including the population-based nature of the dataset; the Manitoba HIV program is the single point of HIV care in Manitoba, and thus theoretically all HIV positive individuals will receive their care through the program. Other strengths include the availability of HLA type, as well as additional clinical features of the case at presentation. There were a number of limitations to the study, including data being cross-sectional, and therefore it is impossible to determine causality in some of our analyses, such as the effect of HLA alleles on disease progression. The retrospective nature of these data may introduce some confounders and prospective confirmation of these associations is required. In addition, factors influencing disease progression in HIV are multiple, and include a diverse array of viral and host characteristics, as well as socioeconomic issues. Risk factors such as socio-economic disadvantage, culture and language diversity; and dispersion and remote location of communities are difficult to measure, but are also important contributors to the increased vulnerability of the Aboriginal population to HIV (International Affairs Directorate, 2010).

Nonetheless, the data from our cohort reflects an unequal distribution of HLA types and homozygosity amongst ethnic groups as well as in those patients presenting with advanced HIV infection. Our observations indicate that new strategies in healthcare may need to be developed to expand testing and linkage to care among this population to allow for earlier identification and to prevent advanced disease and its complications, particularly amongst the Aboriginal population.

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