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ORIGINAL ARTICLE

Rapid human immunodeficiency virus disease progression is associated with human leukocyte antigen-B homozygocity and human leukocyte antigen-B51 in a cohort from Manitoba, Canada

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Abstract

Background: Human immunodeficiency virus type 1 (HIV-1) infection is associated with variable rates of disease progression, influenced by the quality of CD8 T-lymphocyte response, which is determined by human leukocyte antigen (HLA) I alleles. Some individuals progress slowly and maintain viral control, while at the opposite end of the spectrum some individuals endure a faster progression with rapid CD4 decline. We sought to determine the role of HLA-B allele frequency on rapid HIV disease progression. It was hypothesized that rapid progression is associated with the presence of high allele frequency of HLA-B35 and HLA-B homozygocity. *Methods:* This retrospective cohort study was conducted in the Manitoba HIV Program, Health Sciences Centre, a tertiary care facility in Winnipeg, Manitoba, Canada. We defined a set of new criteria to describe a subset of individuals with the most rapid HIV disease progression, and collected demographic, clinical, laboratory (CD4 count, viral load) and HLA data on a subset of 20 individuals meeting these criteria. *Results:* Among those individuals who display extreme rapid progression, an overrepresentation of Aboriginal ethnicities, high frequencies of HLA-B35 and significantly higher rates of HLA-B51, as well as a very high rate of homozygocity for HLA-B alleles, were observed. *Conclusions:* Individuals with the most rapid disease progression have higher rates of HLA-B homozygocity, HLA-B51 alleles and higher viral loads than those with normal progression rates. This group, at the extreme end of the spectrum of progression, should be targeted for early treatment.

Keywords: *CD4 decline, HIV disease progression, HLA homozygocity, HLA-B*

Introduction

Infection with human immunodeficiency virus type 1 (HIV-1) is associated with variable rates of decline in number of the CD4 T lymphocytes and hence disease progression. At one end of the spectrum are the elite controllers and viral controllers [1,2]. These relatively rare phenotypes are a focus of research with the hope that better understanding of the mechanisms that underlie viral control can be reproduced for the purpose of designing a vaccine that will be able to prevent infections or improve viral control. At the opposite pole of the spectrum, there is a poorly defined and perhaps a more heterogeneous group of individuals, whose HIV infection is characterized by rapid disease progression. Several viral, environmental and host factors have been associated with the rapid CD4 decline.

It is believed that $CD8^+$ T lymphocytes play a critical role in curtailing disease progression, a notion supported by multiple lines of evidence. These include the correlation of progression with the development of escape from $CD8^+$ T-cell responses during HIV infection, non-human primate models of simian immunodeficiency virus infection in which CD8 depletion leads to progression, and a plethora of reports linking several human leukocyte antigens (HLAs) with a slower disease progression [2–9]. Conversely, viral control and slow disease progression are associated with

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multiple effector functions of $CD8^+$ T cells found in long-term non-progressors [10]. HLA has attracted considerable attention given the role of $CD8^+$ T lymphocytes in HIV disease progression. Different HLA class I molecules select distinct epitopes derived from HIV proteins to stimulate cytotoxic T lymphocytes which, in turn, determine the quality of effector $CD8^+$ T-cell responses. The ability to mount a response that leads to effective viral control can be predicted based on structure of the HLA class I alleles and their peptide presentation [10,11]. The strongest and most consistent association of delayed disease progression with HLA class I allele is with HLA-B*5701 and HLA-B27, two alleles that have been reproducibly linked with slow HIV disease progression [12–16].

At the less favorable end of the spectrum are individuals who progress rapidly; however, the definitions are more variable. Multiple definitions are found in the literature for rapid progression, but most define rapid progression as more than two CD4 counts below 350 cells/mm^3 within 3 years of seroconversion, with no value above 350 cells/mm^3 in the absence of antiretroviral therapy (ART); or ART initiated within 3 years of seroconversion with at least one CD4 count of less than 350 cells/mm^3; or acquired immunodeficiency syndrome (AIDS)/AIDS-related death within 3 years of seroconversion and at least one sub-350 cells/mm^3 CD4 count [17]. Both host and viral factors have been correlated with rapid disease progression. In African adults infected with HIV, several studies documented faster progression among individuals infected with clade D compared to those harboring a clade A virus [18,19]. This faster disease progression may be the result of clade D viruses switching from R5 to X4 phenotype at higher $CD4^+$ cell count, as a consequence of altered chemokine receptor expression that is mediated by HIV accessory protein Nef, leading to higher levels of cytokines/chemokines [20–24].

HLA class I molecules select targets to be presented and stimulate cytotoxic T lymphocytes, and a number of major histocompatibility complex (MHC) class I HLA alleles have been linked to rapid HIV disease progression [5,22,24]. The effect on rate of progression could be attributed to responses that target epitopes that are dispensable, and therefore do not result in fitness cost for the virus [25,26]. Of these, HLA-B35 is probably the best characterized, with observations from distinct cohorts showing a hazard ratio of 2.2 for progression to a CD4 count of less than 200 cells/mm^3 among individuals with one copy of this allele and a hazard ratio of 9.0 for those homozygous for the allele [8,25–31].

The Canadian Prairie provinces, most notably Saskatchewan and to a lesser degree Manitoba, are experiencing a dramatic increase in the number of newly diagnosed HIV infections, and the fastest growing segment of those new infections is among women and those of First Nations descent. Aboriginal individuals represent roughly 10% of the general Manitoba population but accounted for approximately 50% of all new infections in Manitoba in 2011. Some individuals of First Nations ethnicities seem more likely to experience rapid CD4 decline, to present late to care, and to have opportunistic infections at the time of initial presentation (Ken Kasper, Manitoba HIV Program). We hypothesize that the most rapid progression is associated with the presence of high allele frequency of HLA-B35 and HLA-B homozygocity, both of which are more common among people of First Nations ethnicities. We report a cohort of individuals in Manitoba, Canada, with a subset of individuals experiencing rapid disease progression, beyond current definitions of rapid progression reported in the literature, and describe some of the features associated with this phenomenon.

Materials and methods

The research was approved by the research ethics board at the University of Manitoba, Canada.

Study setting and population

Screening for the HLA-B*5701 allele has decreased the risk of severe hypersensitivity to the nucleoside reverse-transcriptase inhibitor drug Abacavir. Since 2006 this test has become a standard of care; it is performed for every patient in care by the Manitoba HIV Program, and assists in selection of the appropriate antiretroviral regimen.

The Manitoba HIV Program has two principal sites for care delivery: an outpatient clinic at the Health Sciences Centre (HSC) Hospital and a community clinic in Winnipeg, Manitoba. Data from the HSC are presented here.

Definition

To collect a relatively narrow and unique population of rapid progressors, we used the following criteria: (1) documentation of a negative or indeterminate HIV serology followed by a positive test, and/or documentation of acute seroconversion illness; and (2) CD4 count decline to a number lower than 350 cells/mm^3 within 2 years of follow-up or ART initiation less than 2 years after seroconversion.

Data collection

Chart review was used to collect data regarding gender, ethnicity, prior HIV serology, first HIV positive

serology, recognized seroconversion illness, CD4 at presentation, CD4 rate of decline, HIV viral load and clade, presence of opportunistic infection, central nervous system symptoms, comorbidities and ART initiation.

Genomic DNA samples were sent to the Canadian Blood Services, where HLA typing was performed with LABType™ SSO by OneLambda (Canoga Park, CA, USA). If any antigen HLA-B57 was identified, further high-resolution MicroSSP™ by OneLambda was used to resolve for allele-level typing. HLA-B typing results were collected and allele frequencies were compared to historical controls from North American cohorts, as well as to the rates for the entire Manitoba HIV cohort.

Statistical analysis

Baseline immunological and clinical parameters were analyzed using the Mann–Whitney test for continuous variables. We compared the percentage of HLA-B35, B5701, homozygocity and B51 allele among the rapid progressors in Manitoba HIV cohort and the frequencies in North American Caucasian cohorts using Fisher's exact test, and performed a Bonferroni correction for multiple comparisons, with an alpha level for significance of 0.0125 (0.05/4 = 0.0125).

Results

A total patient population of 554 receiving care at the HSC site was reviewed to identify individuals meeting the inclusion criteria for the subset with fastest disease progression. The breakdown of self-reported ethnicities for the entire patient population was as follows: Caucasians comprised 42.8%, African descent 17.8%, and First Nations and Métis 33.8%. We identified 20 individuals (11 males and nine females) for whom data were available, who met the aforementioned inclusion criteria. The average age at the time of analysis was 32.25 years (range 20–48 years). All cases were diagnosed between 2005 and 2010. HIV clade B was the predominant viral clade, accounting for 18 patients, with the remaining two individuals harboring a clade C virus. Thirteen self-identified as First Nations or Métis and seven were Caucasian. The average CD4 nadir was 258 cells/mm^3. The viral loads ranged from 4360 to over 3 000 000, with an average of 736 578.3 copies/ml. Table I summarizes the 20 individuals included in this analysis. We compared the viral loads to normal progression controls from the Manitoba HIV Program and found a significantly higher viral load among the rapid progressors ($p = 0.04$ overall and $p = 0.0194$ for rapid progressors harboring HLA-B35). Three individuals had an initial presentation with aseptic meningitis and one had a peripheral neuropathy presenting early after diagnosis. At the

Table I. Summary of rapid progressors.

Patient no.	CD4 nadir	HIV clade	Year of diagnosis	Ethnicity	Viral load	HLA-B
1	281	C	2010	FN/M	4360	40/51
2	336	B	2008	FN/M	1 650 000	35/35
3	53	B	2008	FN/M	1 960 000	27/35
4	100	B	2009	CAU	16 600	27/62
5	167	B	2010	FN/M	2 630 000	7/51
6	175	B	2009	CAU	109 000	8/55
7	14	B	2010	FN/M	58 900	35/35
8	394	B	2010	CAU	71 400	35/35
9	302	C	2009	FN/M	76 300	39/51
10	11	B	2008	FN/M	590 000	35/35
11	91	B	2010	FN/M	390 000	51/51
12	129	B	2010	FN/M	45 500	35/51
13	989	B	2006	CAU	5250	51/51
14	114	B	2005	FN/M	>1 000 000	51/51
15	179	B	2009	FN/M	3 020 000	51/51
16	281	B	2010	CAU	24 700	18/38
17	76		2011	CAU		35/60
18	602	B		FN/M	1 930 000	62/64
19	567	B	2008	FN/M	48 400	51/51
20	314	B	2009	CAU	628 000	56/64
Median	177				249 500	

FN/M, First Nations/Métis; CAU, Caucasian.
Frequencies among rapid progressor (ERP) in Manitoba human immunodeficiency virus (HIV) cohort compared to reported rates in North American Caucasian cohorts. Viral load and clade are missing for patient 17. Average CD4 and viral load appear at the end of the respective columns.

time of presentation and within less than 2 years of seroconversion, two individuals had a documented opportunistic infection caused by *Pneumocystis jirovecii* pneumonia. One patient had hepatitis C coinfection with subsequent spontaneous clearance. The remaining 19 patients were hepatitis C antibody and RNA negative.

Fifteen of the 20 individuals had at least one of the alleles B35 or B51, and 12 out of 13 of First Nations or Métis descent had at least one of these two alleles. Nine individuals were homozygous for HLA-B (45%), four homozygous for HLA-B35 and five homozygous for HLA-B51 (25%). These rates are higher than those observed in North American cohorts and in those observed for the entire Manitoba HIV cohort, as shown in Table II. The frequency of HLA-B35 among the Manitoba population tested was 18.3% compared to a reported rate of 27.9% among the North American Caucasian population. The frequency of HLA-B35 alleles was 27.5% among individuals of self-reported Aboriginal ethnicity, similar to its rate among rapid progressors (Table II). The two most common subtypes were B*35:01:01G (82%) and B*35:03:01G (10.2%). The allele frequency of HLA-B51 was 20.1% among the entire patient population (HLA-B51:01:01G was the most common allele in our patient population), and it was significantly more common among individuals with rapid progression (45%; Fisher's exact test, $p = 0.022$, odds ratio 3.2, 95% confidence interval 1.22–8.34). The Manitoba rates are reported for the entire patient population in Table II. The overall rate for the entire patient population is followed by the rate for the subset of individuals with self-reported First Nations ethnicities (in parentheses). After adjustment for multiple comparisons, HLA homozygocity was associated with rapid progressors.

Strikingly, the rate of homozygocity was 6.8% for the Manitoba HIV population as a whole, 13.6% for individuals of self-reported Aboriginal ethnicity and 45% for individuals progressing rapidly (Table II).

Table II. Human leukocyte antigen (HLA)-B35 and B51 allele frequencies among the extreme subset of rapid progressors (RP) in the Manitoba human immunodeficiency virus (HIV) cohort compared to reported rates in North American Caucasian cohorts.

HLA allele	Allele frequency among RP (%) ($N = 20$)	Manitoba rates (First Nations rates) (%)
HLA-B35	30	18.3 (27.9)
HLA-B5701	0	4.3 (< 1)
HLA homozygocity	45[a]	6.8 (13.6)
HLA-B51	45[b]	20.1

Manitoba rates are reported in the right column; the overall rate for the entire patient population is followed by the rate for the subset of individuals with self-reported First Nations ethnicities (in parentheses).

[a]HLA-B homozygocity is significantly more common among rapid progressors (Fisher's exact test, $p < 0.0001$, odds ratio 11.6, 95% confidence interval 3.97–33.9).

[b]HLA-B51 is significantly more common among RP (Fisher's exact test, $p = 0.022$, odds ratio 3.2, 95% confidence interval 1.22–8.34).

Discussion

Late presentation to care is a common occurrence in Manitoba; however, the timing of seroconversion is not known for the majority of HIV-infected individuals. We identified a subset of individuals who demonstrated a precipitous decline in CD4 T cells, among the Manitoba HIV-positive patient population. These individuals were identified when data regarding the presumed time of seroconversion were available. We used a CD4 decline to below 350 cells/mm^3 within 2 years, which identified 20 individuals. (A more stringent criterion of progression to CD4 to below 350 cells/mm^3 within 1 year of diagnosis would be met by 14 of 20 individuals in the cohort. However, since this report represents retrospective data collection, in the remaining six individuals the absence of an accurate time of seroconversion precludes definitive assessment and hence we elected to use the definition above.)

This subset of individuals represents the fastest HIV disease progression, beyond previously defined rapid progression, and we therefore studied the associated HLA-B alleles in this group.

The group of individuals meeting the stringent criteria for rapid progression in our cohort has several characteristics: an overrepresentation of First Nations and Métis ethnicities, higher than expected frequencies of HLA-B35, a significantly higher frequency of HLA-B51 and a very high rate of homozygocity for HLA-B alleles. Taken together, these findings suggest that the HLA-B allele frequencies (a previously documented effect in the case of HLA-B35 and homozygocity) may contribute to rapid disease progression. Diminished ability of the CD8 T lymphocytes to achieve viral control may be speculated to be the consequence of the MHC distribution in this group, but remains to be determined in this cohort. In addition to the aforementioned features, as a group the rapid progressors reported herein have significantly higher viral loads, an observation that may translate to higher transmission capacity [32].

The rate of HIV disease progression is variable, ranging from slow progression represented by viral controllers and elite controllers to rapid progression at the polar opposite. Both ends of this range provide some important insights into the drivers of disease progression and CD4 T-cell decline. Rapid progression

is not as well defined as elite or viral control and may represent a more diverse patient population, manifesting the end result of multiple factors acting together, leading to earlier loss of viral control. Among these are environmental factors affecting mucosal integrity, bacterial colonization, target availability, viral factors influencing viral set point, viral clade, fitness, drug resistance and a myriad of comorbidities that decrease the ability to sustain viral control. To these aforementioned factors a growing list of host genetic determinants of the immune and inflammatory response could be added. The role of HLA-B35 in the rapid disease progression mechanisms to which this cohort is predisposed cannot be determined based on this retrospective analysis, and a combination of factors may account for the observation. An immunogenetic mechanism is strongly suspected to at least contribute to the rapid CD4 decline, based on a preponderance of HLA-B35 and HLA-B homozygocity, both of which have been linked to rapid HIV progression in multiple previous studies from geographically and ethnically diverse cohorts. In contrast, the role of HLA-B51 is not as simple to ascertain. Several observational studies have shown a protective effect while others have demonstrated a proclivity to rapid progression [15,33,34]. In our cohort this HLA allele is significantly more common among rapid progressors; however, understanding its contribution to disease progression will require a prospective study design controlling for the numerous potential confounders, a better resolution of the HLA typing and characterization of the CD8 T-cell responses.

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