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Role of HLA class I alleles in Progressive Multifocal Leukoencephalopathy

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Abstract

Since HLA associations with various infectious diseases have recently been reported, we examined the role of HLA class-I alleles in the development of progressive multifocal leukoencephalopathy (PML) or its outcome in 152 patients, including 123 Caucasians and 29 African-Americans. Compared to an HIV+ control population, we observed decreased frequency of HLA-A3 (p=0.03) in the Caucasian PML group, while B18 (p=0.02), was more frequent. No such difference was found among African-American PML patients. We then sought to characterize differences in HLA between PML progressors, whose survival doesn't exceed one year, and survivors. Caucasian survivors were less likely to harbor A68 (p=0.01) while African-American survivors less frequently displayed Cw4 (p=0.01). However, none of these differences reached statistical significance after Bonferroni correction for multiple testing. Further investigations are needed to assess the role of genetics in the incidence of PML or its outcome. Physicians may exercise caution in the use of immunomodulatory medications in patients whose genetic background is associated with an increased risk of PML.

Keywords

progressive multifocal leukoencephalopathy; JC virus; HIV; HLA class I; immunomodulation

Introduction

The human major histocompatibility gene complex (MHC) is located on chromosome 6 and contains the Human Leukocyte Antigen (HLA) class I and II genes. HLA class I genes encode the highly variable HLA -A, -B and -C proteins, which are expressed on the surface of all nucleated cells. They bind viral peptides and present them on the surface of virus-infected cells. When CD8+ cells recognize these complexes, a cytotoxic response is initiated and infected cells are destroyed. Class II genes encode HLA-DR, -DQ and –DP, which are expressed on the surface of antigen presenting cells. They bind extracellular peptides and present them to CD4+ T lymphocytes. This in turn induces T-cell activation, clonal expansion, cytokine expression and antibody production by B cells.

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There is ample documentation for immunogenetic predisposition to certain diseases. Indeed, many autoimmune conditions have been associated with specific HLA loci, including type 1 diabetes, thyroiditis, celiac disease, multiple sclerosis and ankylosing spondylosis (Muller-Hilke and Mitchison, 2006). More recently, positive and negative HLA associations with infectious diseases have been reported (Hill *et al*, 1991; Hill *et al*, 1994; Ivic *et al*, 2007; McAulay *et al*, 2007; Thio *et al*, 2003; Thursz *et al*, 1995). Human immunodeficiency virus (HIV)-infected individuals who have HLA B27 and B57 alleles have a better prognosis, while those who are HLA B35-Px-positive have a worse outcome ((Gao *et al*, 2001), reviewed in (Carrington and O'Brien, 2003; Cooke and Hill, 2001)).These associations may be restricted to specific racial and gender groups. For example, HIV-1 infected Caucasian males who carry alleles of the HLA-B22 family have higher viral load and progress faster to AIDS (Dorak *et al*, 2003).

Progressive Multifocal Leukoencephalopathy (PML) is one of the deadliest opportunistic infections occurring in HIV-positive individuals. It is a demyelinating disease of the brain, caused by the polyomavirus JC (JCV). Up to 90% of the adult population has antibodies against JC virus and primary infection is asymptomatic. However, in AIDS patients, JCV can reactivate, and causes a lytic infection of oligodendrocytes, leading to multiple areas of demyelination in the CNS. Indeed, before the era of highly active anti-retroviral therapy (HAART), up to 5% of AIDS patients developed PML (Koralnik, 2006). The disease also occurs in patients with hematological malignancies, organ transplant recipients, and individuals with auto immune diseases treated with immunomodulatory medications. We examined a possible association between HLA class I alleles and the risk of PML development and outcome. We chose to focus on HLA class I alleles because JC virus is an intracellular organism. Viral peptides, which are degraded in the cell, are presented by HLA class I molecules to cytotoxic $CD8^+$ T lymphocytes (CTL). We previously showed that a strong JCV-specific CTL response is associated with longer patient survival (Du Pasquier *et al*, 2003; Du Pasquier *et al*, 2004; Koralnik *et al*, 2002). As previously suggested for Epstein-Barr virus (McAulay *et al*, 2007), we hypothesized that genetic variation in T cell responses may affect the JCV pathogenesis. We therefore sought to determine HLA associations with the likelihood of developing PML and its outcome. Since PML is a rare disease such genetic associations have never been studied. However, others have shown that a nephropathy caused by the JCV-related polyomavirus BK in renal transplant recipients, was associated with absence of an HLA C7 allele in either the donor or the recipient (Bohl *et al*, 2005).

Results

Results are shown in tables 1-3. Alleles displayed in tables 1-3 had a p-value of less than 0.2 in one of the ethnic groups between PML patients and controls, in the PML progressor versus survivor analysis, or were alleles of interest for polyomaviruses (Cw7 for BK virus and A2 for JC virus).

Table 1 shows the HLA class I allele frequency in all HIV^+ and HIV^- PML patients and HIV^+ controls and includes the frequently studied A2 allele and those showing trend differences with $p<0.02$. Since our PML group consisted of HIV+ and HIV− patients, we also compared only HIV+PML patients with the HIV+ control group (Table 2). HLA-A3 was less frequent in Caucasian PML patients than HIV+ patients (8.6% vs 13.6%, p-value 0.03, **OR 0.60).** However, HLA-A2 which is the most frequent allele in the Caucasian population and the most extensively studied in relation to JCV infection had a similar expression in the Caucasian and African-American PML groups and their control groups.

Among the B alleles, HLA-B18 was present in 8.2% Caucasian PML cases compared to 4.4% HIV+ controls (p-value 0.02, **OR 1.95**), which was confirmed in the HIV+ PML patients

subgroup (8.5%, p-value 0.03, **OR 2.02**,Table 2). No such differences of B alleles prevalence were found in the African-American PML patients compared to HIV+ controls, or among HLA C alleles in either populations.

We then sought to determine whether class I alleles were associated with PML outcome. Differences of allele frequencies between the PML progressors and survivors are displayed in Table 3. This table includes the frequently studied A2 allele and those showing trend differences with $p<0.02$. In the Caucasian patient population, HLA-A68 was less frequent in PML survivors than PML progressors among Caucasians (1.5% vs 8.6%, p-value 0.01, OR 0.16), while HLA-Cw4 was less frequent in the survivor group (9.7% vs 55.6%, p-value 0.01, OR 0.09) in African Americans.

Alleles known to have an association with faster or slower HIV progression (HLA-B22, B27, B35, B57) did not show any trends in any of our groups and are thus not displayed in the Tables 1-3.

Since we performed statistical analyses on multiple variables, we calculated the Bonferroni correction threshold for HLA-A, B or C alleles in all of the above analyses, which ranged from 0.0018 to 0.005: none of the trends observed reached statistical significance after correction for multiple testing.

Discussion

The PML patients reported in this study were mostly recruited from a North American population. Therefore, we used a North-American HIV-infected group as control, since there are no known HLA associations with HIV acquisition and thus this group can be considered as a general control population. Furthermore, most PML patients are HIV infected.

Even if no definitive conclusion can be drawn at this stage, the HLA analysis allowed us to observe possible differences between PML patients and HIV+ control subjects. First, HLA-A3 tended to be less frequent in Caucasian PML patients. It is possible that people who carry this allele are better able to prevent JC virus reactivation thus are less prone to the development of PML. However, once PML occurs, these patients do not appear to have a better outcome. It has already been reported that untreated A3 carriers are better able to clear hepatitis B and C virus, and are considered ‘cured’ (McKiernan *et al*, 2004; Thio *et al*, 2003). Conversely, A3 positive patients are more prone to auto-immune disease and this allele has recently been implicated in multiple sclerosis (MS) (Friese *et al*, 2008). One possible explanation is that A3 carriers have a more vigorous response against infections, but are also liable to self-recognition.

We observed differences in allele frequencies based on the race of PML patients. Whereas HLA-A33, B18, B50 tended to be more frequent in Caucasians, African-Americans displayed higher expression of B8 and B42 alleles. Similar racial trends had been demonstrated previously for these alleles in the context of other infectious diseases. For example, HLA-A33 was associated with enterovirus 71 infection in Taiwanese children (Chang *et al*, 2008). HLA-B8 was found more frequently in patients with chronic hepatitis B and C infection (McKiernan *et al*, 2004; Thio *et al*, 2003), while in Spanish hepatitis C patients, HLA-B18 was associated with hepatocellular carcinoma, a severe consequence of chronic infection (Lopez-Vazquez *et al*, 2004). Finally, a higher prevalence of B50 was already observed in children with hepatitis B persistence (Thursz *et al*, 1995). It might be that carriers of these alleles, in the context of specific genetic background, have less potent antiviral immune responses, including against JCV.

Interestingly, although JCV and BKV are closely related and share common CTL epitopes (Chen *et al*, 2006), the trend we observed for Cw7, which was more frequent in Caucasian

PML patients, is opposite than what is observed for BKV, where lack of the C7 allele predisposed to BK nephropathy (Bohl *et al*, 2005). The protective role of Cw7 had been underscored in hepatitis C- infected individuals, as Cw7+ patients displayed sustained virological response after treatment with α interferon (Ivic *et al*, 2007).

Finally, we also observed trends between allele frequencies and PML outcome. Among Caucasian PML patients A 68 tended to be more frequent in progressors. Among African-American progressors, HLA Cw4 seemed to be more frequent. Of note, the A68 molecule has a different structure than other A alleles, creating a less optimal binding between the infected cell and CD8, because of a valine residue at position 245 (Garrett *et al*, 1989; Salter *et al*, 1989). The reduced binding at the immunological synapse may translate in reduced cytotoxic activity of T lymphocytes. Interestingly, HLA-Cw4 has previously been associated with hepatitis C persistence (Thio *et al*, 2002) and with faster HIV progression in Caucasians, but not in African-Americans (Carrington *et al*, 1999).

There are several limitations to this study. First, PML is a rare disease, and the number of patients studied was relatively small. Since multiple analyses are performed to cover all A, B and C alleles, a much larger population would be needed to reach statistical significance after Bonferroni correction. The multiple comparison problem would have been even magnified if we had performed a four digit molecular typing of HLA alleles from PML patients, including all A, B and C sub-alleles, rather than the two digit serological typing performed in this study. Second, our PML patients are a heterogeneous population, comprised of a larger group of HIV + patients, and a smaller group of HIV-negative patients affected by a variety of predisposing conditions, including patients with hematological malignancies, organ transplant recipients and individuals with inflammatory or auto-immune diseases treated with immunomodulatory medications. Indeed, some of these conditions may have their own associations with class I alleles. We therefore carried-out two sets of analyses, with and without the HIV-negative PML patients (Table 1 and 2), and the results were similar. Finally, whether there are imunodominants epitopes restricted by HLA alleles that are less prevalent in PML patients compared to controls, or more prevalent among PML survivors compared to progressors, remains to be determined. This work, which is outside the scope of the present study, is currently in progress in our laboratory.

Over the past few years, the range of individuals at risk for PML has been increasing steadily. Indeed, this disease has now been reported in patients with multiple sclerosis, Crohn's disease and psoriasis treated with natalizumab or efalizumab (Genentech, 2009; Koralnik, 2006), leading to temporary or permanent withdrawal of these medications from the market. In addition, other medications, such as rituximab, may be associated with an increased risk of PML (Carson *et al*, 2009). There is no treatment for PML, and one year survival is only approximately 50% (Marzocchetti *et al*, 2009). Although the risk of developing PML in patients treated with these immunomodulatory medications remains small, our data represents a first step toward a better understanding of the individual risk of PML in these populations. Further genetic studies are needed to characterize markers associated with PML incidence or outcome. In the future, this will allow physicians to exercise caution in the use of immunomodulatory medications in patients with a genetic background associated with a greater risk of PML.

Materials and methods

Study subjects and alleles

PML diagnosis was made when one of the following criteria was present (Cinque *et al*, 2003): unior multifocal progressive neurological disease with typical MRI findings and positive brain biopsy (histology-confirmed PML) or with positive JCV DNA PCR in

cerebrospinal fluid (laboratory-confirmed PML) or clinical and radiological findings consistent with PML, but no demonstration of JCV in the CSF and no brain biopsy (possible PML).

152 patients fulfilled these diagnostic criteria. Since patients were enrolled after 1996, HIV+ patients received HAART. HIV− patients had a variety of underlying conditions including hematological or other type of malignancies, auto-immune diseases or were transplant recipients. In these patients, the management of PML always aimed to decrease chemical immunosuppression, when possible. These 152 patients were separated according to ethnicity into 123 Caucasian PML patients of which 81 were HIV+, and 29 African-American PML patients, of which 28 were HIV+. Each ethnic group was further subdivided in three groups: 1) survivors, who had survived for longer than one year after disease onset; 2) progressors, who died within one year of disease onset and 3) early PML patients, who were still alive, but had been followed for less than one year from disease onset. Using these criteria 71 survivors, 44 progressors, and 8 early PML patients were identified in the Caucasian patient population. Among the African-American patient population there were 20 survivors, 8 progressors, and 1 early PML patient.

We used HIV+ patients recruited by the MACS Cohort as controls. These patients were also separated in Caucasians and African-Americans. Among Caucasians, HLA-A data was available for 950 patients, HLA-B data was available for 938 patients, and HLA-C data was available for 946 patients. Among African-Americans, HLA-A data was available for 126 patients, HLA-B data was available for 127 patients, HLA-C data was available for 126 patients.

Alleles were counted in all the different groups mentioned above and comparisons were made between the PML group and HIV+ control group, HIV+ PML group and HIV+ control group, and the PML progressors and PML survivors. If patients were homozygous for any A, B or C allele, the specific allele was only counted once. If alleles could not be determined or testing gave dubious results, they were not taken into account for the total allele count. Subsequently, the allele frequency for each allele was calculated by dividing the number of alleles by the total number of alleles and multiplying by 100.

HLA typing

Typing of HLA class I A, B, C alleles was performed serologically for all PML patients at the blood bank laboratory of Beth Israel Deaconess Medical Center. HLA class I typing for all HIV+ control patients was performed following the PCR-SSOP (sequence-specific oligonucleotide probing) typing protocol recommended by the International Histocompatibility Working Group (http://www.ihwg.org/). The four digit classification was converted into two digit classification and the serological two digit classification was converted into two-digit immunological classification in accordance with the HLA Dictionary nomenclature (Schreuder *et al*, 2005).

Statistical analysis

We used the Fisher exact test to detect an association of any allele within each group, and Bonferroni correction for multiple testing. Odds ratios were calculated and reflect the likelihood of having a specific allele in the PML group versus the HIV+ control group, the HIV+PML group versus the HIV+ control group and the PML survivor group versus the PML progressor group.

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Table 1

HLA class I allele frequency in HIV+ and HIV− PML patients and controls.

	Caucasians					African-Americans				
HLA	**HIV+ controls (n=1762)**		**PML (n=233)**			**HIV+ controls (n=241)**		**PML (n=55)**		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
A2	445	25.3	59	25.3	1 (1.00)	46	19.1	12	21.8	0.71 (1.18)
A3	240	13.6	20	8.6	**0.03 (0.60)**	21	8.7	2	3.6	0.27 (0.40)
A31	55	3.1	3	1.3	*0.15 (0.40)*	9	3.7	1	1.8	0.69 (0.48)
A33	25	1.4	6	2.6	*0.17 (1.84)*	13	5.4	6	10.9	*0.14 (2.15)*
A68	68	3.9	10	4.3	0.72 (1.12)	24	10.0	6	10.9	0.81 (1.11)
	HIV+ controls (n=1798)		**PML (n=231)**			**HIV+ controls (n=247)**		**PML (n=51)**		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
B8	186	10.3	29	12.6	0.31 (1.24)	8	3.2	4	7.8	*0.13 (2.54)*
B18	79	4.4	19	8.2	**0.02 (1.95)**	6	2.4	2	3.9	0.63 (1.64)
B41	16	0.9	4	1.7	0.27 (1.96)	1	0.4	0	0.0	1 (0)
B42	2	0.1	0	0.0	1 (0)	14	5.7	6	11.8	*0.13 (2.22)*
B44	230	12.8	26	11.3	0.60 (0.86)	14	5.7	3	5.9	1 (1.04)
B50	18	1.0	5	2.2	*0.17 (2.19)*	1	0.4	1	2.0	0.31 (4.92)

	HIV+ controls (n=1758)		PML (n=174)			HIV+ controls (n=231)		PML (n=42)		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
Cw3	221	12.6	23	13.2	0.81 (1.06)	22	9.5	2	4.8	0.55 (0.48)
Cw4	204	11.6	18	10.3	0.71 (0.88)	39	16.9	8	19.1	0.82 (1.16)
Cw7	473	26.9	55	31.6	*0.18 (1.26)*	45	19.5	6	14.3	0.52 (0.69)
Cw12	130	7.4	13	7.5	1 (1.01)	5	2.2	0	0.0	1 (0)

Note: PML: HIV+ and HIV− PML patients, n: total number of all alleles, N: total number of specific allele, % allele frequency, calculated by dividing the total number of each allele by the total number of alleles and multiplying by 100, p-values are calculated with Fisher exact test, odds ratios reflect the likelihood of having a specific allele in the PML group versus the HIV+ control group.

Table 2

HLA class I allele frequency in HIV+ PML patients and controls.

	Caucasians					African-Americans				
HLA	**HIV+ controls (n=1762)**		**HIV+ PML (n=157)**			**HIV+ controls (n=241)**		**HIV+ PML (n=54)**		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
A2	445	25.3	39	24.8	1.0 (0.98)	46	19.1	11	20.4	0.85 (1.08)
A3	240	13.6	14	8.9	*0.11 (0.62)*	21	8.7	2	3.7	0.27 (0.40)
A31	55	3.1	2	1.3	0.32 (0.40)	9	3.7	1	1.9	0.70 (0.49)
A33	25	1.4	4	2.6	0.29 (1.82)	13	5.4	6	11.1	*0.13 (2.19)*
A68	68	3.9	4	2.6	0.52 (0.65)	24	10.0	6	11.1	0.80 (1.13)
	HIV+ controls (n=1798)		**HIV+ PML (n=153)**			**HIV+ controls (n=247)**		**HIV+ PML (n=51)**		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
B8	186	10.3	20	13.1	0.28 (1.30)	8	3.2	4	7.8	*0.13 (2.54)*
B18	79	4.4	13	8.5	**0.03 (2.02)**	6	2.4	2	3.9	0.63 (1.64)
B41	16	0.9	4	2.6	*0.07 (2.99)*	1	0.4	0	0.0	1 (0)
B42	2	0.1	0	0.0	1 (0)	14	5.7	6	11.8	*0.13 (2.22)*
B44	230	12.8	22	14.4	0.53 (1.14)	14	5.7	3	5.9	1 (1.04)
B50	18	1.0	4	2.6	*0.09 (2.66)*	1	0.4	1	2.0	0.31 (4.92)

	HIV+ controls (n=1758)		HIV+ PML (n=119)			HIV+ controls (n=231)		HIV+ PML (n=42)		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
Cw3	221	12.6	16	13.5	0.78 (1.08)	22	9.5	2	4.8	0.55 (0.48)
Cw4	204	11.6	14	11.8	0.88 (1.02)	39	16.9	8	19.1	0.82 (1.16)
Cw7	473	26.9	38	31.9	0.24 (1.27)	45	19.5	6	14.3	0.52 (0.69)
Cw12	130	7.4	8	6.7	1.0 (0.90)	5	2.2	0	0.0	1 (0)

Note: HIV+PML: HIV infected PML patients, n: total number of all alleles, N: total number of specific allele, %: allele frequency, calculated by dividing the total number of each allele by the total number of alleles and multiplying by 100, p-values are calculated with Fisher exact test, odds ratios reflect the likelihood of having a specific allele in the HIV+PML group versus the HIV+ control group.

Table 3

HLA class I allele frequency in PML progressors and survivors.

	Caucasians					African-Americans				
HLA	**PML P (n=81)**		**PML S (n=137)**			**PML P (n=14)**		**PML S (n=39)**		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
A2	23	28.4	33	24.1	0.52 (0.80)	3	21.4	9	23.1	1 (1.10)
A3	5	6.2	15	11.0	0.33 (1.87)	0	0.0	2	5.1	1 (NA)
A31	2	2.5	0	0.0	*0.14 (0)*	0	0.0	1	2.6	1 (NA)
A68	7	8.6	2	1.5	**0.01 (0.16)**	2	14.3	4	10.3	0.65 (0.69)
	PML P (n=83)		**PML S (n=133)**			**PML P (n=14)**		**PML S (n=36)**		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
B8	7	8.4	21	15.8	*0.15 (2.04)*	0	0.0	4	11.1	0.57 (NA)
B41	3	3.6	1	0.8	*0.16 (0.20)*	0	0.0	0	0.0	1 (NA)
B44	10	12.1	14	10.5	0.83 (0.86)	2	14.3	1	2.8	*0.19 (0.17)*
	PML P (n=59)		**PML S (n=99)**			**PML P (n=9)**		**PML S (n=31)**		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
Cw3	4	6.8	15	15.2	*0.14 (2.46)*	0	0.0	2	6.5	1 (NA)

	PML P (n=59)		PML S (n=99)			PML P (n=9)		PML S (n=31)		
	N	**%**	**N**	**%**	**P (OR)**	**N**	**%**	**N**	**%**	**P (OR)**
Cw4	8	13.6	9	9.1	0.43 (0.64)	5	55.6	3	9.7	**0.01 (0.09)**
Cw12	6	10.2	4	4.0	*0.18 (0.37)*	0	0.0	0	0.0	1 (NA)

Note: PML P: PML progressors, PML S: PML survivors, n: total number of all alleles, N: total number of specific allele, % allele frequency, calculated by dividing the total number of each allele by the total number of alleles and multiplying by 100, p-values are calculated with Fisher exact test, odds ratios reflect the likelihood of having a specific allele in the PML survivor group versus the PML progressor group.