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Diagnostic and Prognostic Significance of Plasma JCV-DNA in HIV-related Progressive Multifocal Leukoencephalopathy (PML)

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Background

Progressive multifocal leukoencephalopathy (PML), caused by polyomavirus JC (JCV), remains a severe opportunistic disease in HIV-infected patients. Detection of JCV-DNA in plasma and peripheral leukocytes has been reported in immunocompromised subjects, with or without PML, but it was neither regarded as a sensitive and specific diagnostic marker of PML. Moreover, it is not known whether it can be considered as a marker of more aggressive PML course. The aim of this study was to assess the diagnostic and prognostic significance of JCV-DNA levels in plasma at PML onset on clinical outcome.

Methodology

This is a cross-sectional, retrospective, multicentre study of 79 patients with HIV-related PML and 49 HIV positive controls whose plasma samples were collected within 90 days from onset of symptoms and available for virological analysis. Patients were enrolled in Italy between 1993 and 2012. PML diagnosis was confirmed by JCV-DNA detection in CSF in 68 cases, at autopsy in 2 cases, or based on typical clinical and radiological features in 9 cases. Associations between categorical measures were assessed by the Fisher's exact test. The Mann Whitney test was used to compare continuous variables. Correlations between continuous variables were assessed by the Spearman correlation. The effect of a number of factors on time from onset of symptoms to the end of follow-up due to progressive disease or death was assessed by Kaplan-Meier and Cox proportional-hazard models.

Table1. PML patients characteristics at the time of sampling

	All	On cART[a] (N=41)	Off cART (=38)	p[b]
Male gender (n, %)	63 (80%)	30 (73%)	33 (87%)	ns
Age (median years; IQR)	38 (34-43.5)	39 (34-43)	38 (34-47)	ns
Malignancies (n, %) [c]	6 (8%)	3 (7%)	3 (8%)	ns
OI (n, %) [d]	31 (40%)	16 (39%)	13 (34%)	ns
CD4+ (median cells/μL; IQR)	80 (38-220)	99 (51-261)	59 (16-193)	ns
Plasma HIV-RNA (median log_{10} c/mL; IQR)	3.87 (1.69-4.98)	3.37 (1.70-4.98)	4.25 (3.64-5.11) (N=17)	ns
Anti JCV-VP1 IgG titre (median unit; IQR)	1.27 (0.87-1.99) (n=66)	1.73 (0.85-2.15) (n=33)	1.24 (0.88-1.94) (n=33)	ns
Site(s) of PML lesions at MRI (nr. of pts)				
Brain	58/74 (78%)	29/40 (72%)	29/34 (85%)	ns
Cerebellum	26/74 (35%)	17/40 (42%)	9/34 (26%)	ns
Brain-stem	26/74 (35%)	13/40 (32%)	13/34 (38%)	ns
Gadolinium enhancement at MRI	15/74 (20%)	11/40 (27%)	4/34 (12%)	ns
IRIS [e]	7/78 (9%)	7/40 (18%)	0/38 (0%)	ns
IV high doses steroids [f]	6/75 (8%)	5/41 (12%)	1/34 (3%)	ns

a. Eighteen patients started cART after sampling
b. Comparison between patients reciving cART at the time of sampling and patients not receiving cART.
c. Non-Hodgkin Lymphoma (n=3), Hodgkin Lymphoma (n=1), ovarian carcinoma (n=1), Kaposi Sarcoma (n=1)
d. OI: opportunistic infections, including neurotoxoplasmosis, criptococcosis, esophageal candidiasis, disseminated CMV infection or mycobacteriosis, Pneumocystis jirovecii pneumonia
e. Five patients developed IRIS after sampling
f. Six patients received high dose steroids after sampling

Results

Sixteen/79 patients (20.3%) were female and 63 (79.7%) male, median (IQR) age was 38 years (34-43.5), CD4+ were 80 (38-220) cells/μL, plasma HIV-RNA was 3.87 (1.69-4.98) log10 copies/mL at the time of PML and 59/79 (74%) were exposed to combined antiretroviral treatment (cART). Fifteen patients showed contrast enhancement at magnetic resonance imaging, 12 experienced immune reconstitution inflammatory syndrome (IRIS), and 10 received high-dose steroids. (Table1). JCV-DNA was detected in plasma of 4/49 (0.1%) control subjects and of 29/79 (36%) PML patients. The sensitivity and specificity of the presence of JCV-DNA in plasma was 36.7% and 91.8%, respectively. (Figure 1)

Figure 1. JCV-DNA in body fluids

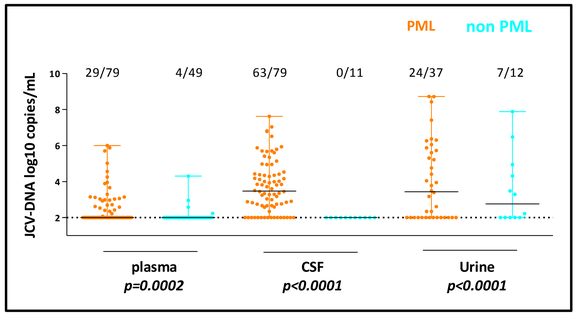
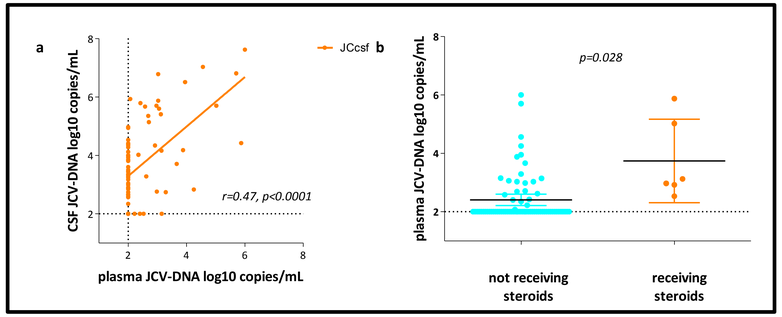
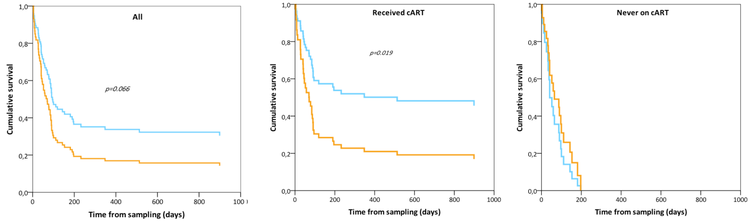


Figure 2. Correlations between plasma and CSF JCV-DNA (a) or use of high dose steroids (b)



The only independent factors associated with JCV-DNA detection in plasma were JCV-DNA in CSF and high dose steroids prior to sampling. Moreover, there was a positive correlation between plasma and CSF JCV-DNA (Figure2a) and plasma JCV-DNA levels were higher in patients that received high dose steroids prior to sampling.(Figure 2b).

Figure 3. PML survival according to JCV DNA detection in plasma



The occurrence of IRIS was associated with more favourable clinical outcome. cART therapy was associated with an 8-fold reduction in the hazard of progression or death among patients without JCV-DNA in the plasma (p=0.003) but only a 3-fold reduction among patients with JCV-DNA in plasma (p=0.005) and patients with JCV-DNA in CSF (p=0.012).

Table 2. Predictive value of JCV-DNA detection in plasma and in CSF

	Plasma		CSF	
	HR for PML progression	*p*	HR for PML progression	*p*
Not on cART – undetectable JCV-DNA	-	-	-	-
Not on cART – detectable JCV-DNA	0.52	*0.196*	1.40	*0.506*
On cART – undetectable JCV- DNA	0.13	*0.003*	0.13	*0.003*
On cART – detectable JCV- DNA	0.35	*0.0051*	0.294	*0.012*

Conclusions:

Clinical significance of detection of JCV-DNA in plasma:
- **In PML diagnosis:** low sensitivity, high specificity
- **To monitor PML outcome:** higher plasma level associated with higher risk of progression also on cART