

Letter to the Editor

Search for human herpesvirus 6 DNA in cerebrospinal fluid from AIDS patients with progressive multifocal leukoencephalopathy

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Recent studies have demonstrated a high frequency of cells containing human herpesvirus 6 (HHV6) genome in progressive multifocal leukoencephalopathy (PML) lesions, as well as coinfection of oligodendrocytes by JC virus (JCV) and HHV6, suggesting a role of HHV6 as a cofactor in the pathogenesis of PML (Blumberg *et al*, 2000; Mock *et al*, 1999). To explore the possibility that genome of HHV6 might be detected in cerebrospinal fluid (CSF) from acquired immunodeficiency syndrome (AIDS) patients with PML, we reviewed all cases of human immunodeficiency virus (HIV)-infected patients with a diagnosis of PML in whom a multiplex polymerase chain reaction (PCR) assay for herpesviruses was performed in CSF during the diagnostic work-up. This multiplex PCR assay for herpesviruses, described elsewhere (Quereda *et al*, 2000; Tenorio *et al*, 1993), may detect in a single run herpes simplex virus, cytomegalovirus, varicella-zoster virus, Epstein-Barr virus, and HHV6.

Forty-one CSF specimens from 40 AIDS patients with a diagnosis of PML (Table 1) were tested for herpesviral DNA. Neuroimaging studies demonstrated in all the patients the characteristic nonenhancing demyelinating lesions without mass effect. JCV DNA was detected in CSF in 17 out of 22 patients studied by means of a multiplex PCR for polyomaviruses (Fedele *et al*, 1999). CSF was obtained a mean of 31 days after the onset of neurological symptoms, and a median of 62 days before death in 30 fatal cases. In none of the 41 CSF specimens was the HHV6 DNA detected by the multiplex PCR.

Our results indicate that the association of active HHV6 infection with PML lesions cannot be confirmed by PCR study of CSF in AIDS PML patients, and suggest that a significant infection of the central nervous system by HHV6 does not occur in the majority of these patients. The lack of detectable HHV6 in CSF from AIDS-associated PML in this study can be explained in several ways. First, we cannot exclude that the HHV6 DNA burden in CSF that could be associated with PML might simply fall below the detection limit of the PCR technique. However, the detection limit for HHV6 DNA of the technique used, estimated to be 50 to 100 molecules per 50 μ l (Casas *et al*, 1997), allowed the detection of HHV6 DNA in CSF from 1% of HIV-infected patients (Quereda *et al*, 2000), a proportion only slightly inferior to that found in other studies, using even more sensitive PCR assays (Bossolasco *et al*, 1999; Broccolo *et al*, 2000; Cinque *et al*, 1996; Portolani *et al*, 1997). In a previous study, HHV6 was not detected by PCR in CSF of 39 patients with pathologically confirmed PML (Cinque *et al*, 1996), although the sensitivity of the test was not reported. Given the high frequency of HHV6 DNA-positive cells and the presence of active HHV6 infection reported in PML lesions (Blumberg *et al*, 2000; Mock *et al*, 1999), detectable amounts of viral DNA in CSF might have been expected. More sensitive PCR assays may detect HHV6 DNA in CSF in up to 30% of HIV-infected patients with neurological problems, but also in a similar proportion of controls (Liedtke *et al*, 1995), suggesting that passenger HHV6-positive blood lymphocytes may be detected in CSF if a very sensitive assay is used (Bossolasco *et al*, 1999). Another possible explanation for the inability to detect HHV6 in CSF from AIDS patients with PML is that reactivation of HHV6 within PML lesions might be a terminal event in these patients and, therefore, demonstrable only at autopsy and not in diagnostic CSF specimens, obtained at the beginning of the clinical course.

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Table 1 Diagnostic category and survival of 40 AIDS patients with PML who had PCR for herpesviruses performed in CSF

Diagnosis	Diagnostic criteria	Number of patients	Survival mean days (range)
Definite	Pathologically proven	1	93
Probable	Neuroimaging findings Positive PCR for JC virus	16	371 (37–1298)
Possible	Neuroimaging findings	23	545 (1–2785)

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