Progressive Multifocal Leukoencephalopathy Development Is Associated With Mutations in JC Virus Capsid Protein VP1 That Change the Receptor Specificity of the Virus

To the Editor—Gorelik et al \[1\] recently published an interesting study regarding intrapatient acquired JC virus (JCV) VP1 mutation within patients with progressive multifocal leukoencephalopathy (PML), which favors brain invasion of JCV through impairment of sialic-acid-dependent binding in the periphery. It is proposed that host cell entry by JCV occurs in a sialic-acid-independent manner in the central nervous system (CNS). Of particular note, this study demonstrates the ability of wild-type JCV virion-like particles (VLPs) to bind to primary cultures of human B and T lymphocytes in vitro \[1\], suggesting that these may be critical cells responsible for spread of JCV from the periphery to the CNS.

Here, we report latent in vivo JCV infection of peripheral blood mononuclear cells (PBMCs) in patients without PML. Our study establishes systemic JCV latency in PBMCs, using previously published methods for detection of early and late gene DNA of JCV by polymerase chain reaction \[2\] through the analysis of circulating PBMCs (n = 70).

Our study demonstrated the presence of JCV Large T (LT) antigen DNA in 50 (93%) of 54 immunocompromised patients (including 8 of 8 patients with human immunodeficiency virus [HIV] infection/AIDS, 31 of 35 transplant recipients, and 11 of 11 autoimmune patients). The high prevalence of viral DNA suggests that JCV persists in the PBMCs of healthy individuals following initial infection, in accord with the results of other studies \[3–4\]. We also detected JCV LT DNA in 16 (100%) of 16 immunocompetent control individuals. JCV VP1 DNA was detected in 19 (34%) of 56 immunocompromised patients (including 6 of 8 patients with HIV infection/AIDS, 11 of 35 transplant recipients, and 2 of 11 autoimmune patients). JCV VP1 DNA was not detected in any of the immunocompetent control individuals, which makes immunocompromised patients significantly more likely to be JCV VP1 DNA positive than immunocompetent control individuals (P = .007).

Patients who were JCV VP1 DNA positive had lower total lymphocyte counts (reported as range +/- standard error of the mean) than those who were JCV VP1 DNA negative (0.79 ± 0.12 × 10^9 cells/L vs 1.46 ± 0.11 × 10^9 cells/L, respectively; P < .001). Patients with HIV infection/AIDS were more likely to be JCV VP1 DNA positive than any other immunocompromised patient group (P = .01). The 6 patients with HIV infection/AIDS who were JCV VP1 positive had lower CD4 cell counts (reported as median [lower limit–upper limit]) than those of patients who were JCV VP1 DNA negative (74 [20–193] cells/μL vs 470 [428–576] cells/μL, respectively; P = .008).
In our study, we were more likely to detect JCV VP1 DNA in patients with HIV infection/AIDS than in all other immunocompromised patient groups. Infection of mononuclear cells with HIV has been shown to upregulate cytokine expression [5], which may promote JCV DNA replication at the transcriptional level. Likewise, Tat regulatory protein has been demonstrated to drive JCV reactivation [6]. This may explain the high incidence of JCV VP1 DNA in patients with HIV infection/AIDS and the dose-dependent link between JCV VP1 DNA and CD4 cell counts.

Low detection levels of JCV VP1 DNA are consistent across most studies [2, 7–8]. In our study, the ability to detect JCV VP1 DNA appears to be dependent on immune status. This supports the concept that there is immunomodulation of viral latency. In line with the findings reported in the recent study of Gorelik et al 1, this may lead to more frequent mutation of the VP1 region, resulting in viral substrains that favor brain invasion by JCV.

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References

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