

# The early neurologic signs and symptoms of HIV infection

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Since the earliest days of the HIV pandemic, the acute and subacute phases of infection have been characterized by some extent of CNS involvement,<sup>1</sup> most prominently aseptic meningitis.<sup>2</sup> These early reports were hampered by the variable availability of tests for the presence of antibodies to HIV (ELISA in 1985, Western blot in 1987) and the lack of quantitative assays for viral RNA until the early 2000s.

The development of effective combination antiretroviral therapy (cART) is one of the great success stories in modern medicine. In addition to reducing the incidence and prevalence of AIDS and extending life expectancy for individuals with HIV disease to near normal,<sup>3</sup> the incidence of neurologic manifestations of HIV disease has decreased<sup>4</sup> as well. HIV-associated dementia is almost unknown, and HIV encephalitis (e.g., multinucleated giant cells and white matter pallor at autopsy) has all but disappeared in effectively treated individuals.

Nevertheless, there remains a persistent, often low-grade pattern of cognitive impairment and neurologic manifestations in HIV disease. For reasons that are not altogether clear, some infected individuals may also have viral escape that results in substantial viral replication in the CNS in the context of low or undetectable viral load and normal or near normal CD4 cell counts in the periphery.<sup>5</sup>

In this context, it is important to remember that there are CNS manifestations of HIV disease that can be detected within a short period of time following infection. In the report by Hellmuth et al.<sup>6</sup> in this issue of *Neurology*<sup>®</sup>, we find a careful analysis of a group of 139 individuals from Thailand who were approximately 16 days postinfection (range 3–56 days). Neurologic, neuropsychological, virologic, and brain imaging data were acquired from this unique study sample. The investigators found neurologic abnormalities in 53% in the 12 weeks following acute infection. Age, sex, use of illicit drugs, duration of infection, and infection stage were not associated with the presence of the neurologic findings. The cognitive complaints were nonspecific, and included increased effort to complete tasks (8%), problems with concentration (24%), and difficulties with

memory (16%). The patients reported symptoms of gait disturbance (9%) and 17% were found to have neuropathy on examination. Nearly half of the neurologic abnormalities were detected at the first visit, prior to the initiation of cART, and 90% of these signs/symptoms were absent or milder 4 weeks following treatment initiation. Brain imaging data were mainly normal, with the exception of a few cases of white matter abnormalities.

This study reminds us that even now the acute manifestations of HIV disease include signs and symptoms of CNS involvement. However, with the exception of a higher plasma viral load, the individuals with at least one neurologic sign or symptom did not differ from the unaffected patients with regard to other characteristics of their HIV disease.

This raises several paradoxes; perhaps the most important is the extent to which these changes are the direct result of HIV infection, an indirect consequence of HIV infection mediated through another mechanism (e.g., reactive inflammation), a nonspecific response to systemic infection, or some combination of these. The individuals who complained of cognitive dysfunction also had lower mean performance on the neuropsychological tests at baseline and 12 and 24 weeks following diagnosis. However, their performance still fell within normal limits. The extent to which this lower performance among the individuals with subjective complaints persists over time may provide some insight into the mechanism responsible for asymptomatic cognitive impairment in HIV disease.<sup>7</sup>

The individuals with neurologic findings had higher plasma viral load than those without, although there were no differences among these subgroups in the markers of macrophage activation. These patterns of association suggest the possibility that while the presence of the virus is an important factor, there may be other mediating associations that explain the presence of CNS abnormalities. The mediated response may be nonspecific, and less related to HIV as to viral infection itself. For example, upper respiratory tract infections can result in alterations in cognition within hours of infection, and prior to the onset of symptoms of cold or flu.<sup>8</sup> Although the

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precise mechanism underlying this infection-based malaise is unknown, it appears in part due to alterations in attentional processes, which result in decreased cognitive functions.<sup>9</sup> Smith<sup>9(p749)</sup> summarizes this research as “a malaise that includes mood changes and impairments of aspects of mental performance. These illnesses also make the person more sensitive to the negative effects of other factors (e.g., prolonged work, alcohol, and stress).” There is some suggestion that the underlying cause may be related to cytokines, but this is less clear.

If a similar association between viral replication—even on a low level—and cognition exists in HIV disease, then this may explain some of the waxing and waning of symptomatology, and the persistence of complaints even in the context of relatively well-controlled systemic infection. At the very least, it suggests the possibility of interactions between HIV disease and other stressors that affect cognition and neuropsychological test performance. To the extent that viral infections may directly or indirectly affect specific neurotransmitters, this may explain why brain imaging data sensitive to synaptic function reveal HIV-related abnormalities.<sup>10,11</sup>

Medical comorbidities are increasingly important in understanding the neurologic complications of chronic HIV disease. However, careful analysis of neurologic symptomatology and associated biomarkers in acute disease may provide important information about both direct and indirect effects of HIV on the brain, and these associations may extend to other infectious agents.

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### DISCLOSURE

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