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HIV dementia: 10 years on

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Subacute encephalitis was first associated with AIDS in 1983 and the first detailed clinical descriptions of AIDS dementia complex appeared in 1986. In the last decade, there have been major changes in our understanding of the timing, epidemiology, pathophysiology, and reversibility of this neurologic syndrome. Since being added as an AIDS-defining illness in 1987, the syndrome of progressive cognitive, behavioral, motor decline has been retitled '*HIV-associated dementia complex*' (or HIV dementia) and a new phrase has been coined for minor degrees of cognitive or motor dysfunction – '*HIV-associated cognitive motor disorder*'. Even now, the significance of this latter condition remains controversial and its relationship to more overt cognitive decline is uncertain.

Several prospective neurological and neuropsychological studies in different risk behavior groups have shown clearly that the onset of frank dementia or detectable cognitive decline is uncommon during the long phase of asymptomatic HIV infection. The findings from cross-sectional studies have been corroborated by longitudinal studies, both in the US and Europe. As yet, relatively few risk factors for the development of dementia have been identified, although in general dementia is more likely to occur in more advanced HIV infection and has been associated with lower hemoglobin concentrations and body mass index. The early promise of a protective effect of antiretrovirals noted in studies just after the introduction of zidovudine has not been noted in recent cohort studies. About 20% of people with AIDS will develop HIV dementia and the proportion is higher among children. The incidence rates of HIV dementia appear to have stabilized at approximately 7 to 10% per year in individuals with AIDS. Rates of progression with HIV dementia are variable, with some individuals surviving 2 or more years, particularly if high dose antiretroviral therapy can be tolerated. In general, however, response to antiretrovirals is short-lived or of little functional significance.

Our understanding of the pathophysiological mechanisms has advanced beyond characterizing HIV dementia simply as a chronic encephalitis. A state of macrophage hyperactivation is present within the CNS in AIDS and particularly in individuals with dementia. Levels of productive HIV replication may be relatively low and are often discordant with severity of neurologic dysfunction, suggesting that indirect mechanisms of neuronal damage, dysfunction, or loss are more important than viral 'burden'. Several groups of investigators have demonstrated 30 to 50% reduction in neuronal densities in AIDS, along with synaptic simplification and dendritic pruning. The exact relationship of these pathological changes to neurologic manifestations remains uncertain. Current hypotheses of neuronal dysfunction invoke mechanisms of neuronal death through excessive intracellular calcium triggered through glutamate activation or through other mechanisms involving the action of pro-inflammatory cytokines or HIV proteins. The advances in these pathophysiological mechanisms has led to several attempts to block the pathophysiological cascade therapeutically with cytokine blockers, calcium channel antagonists, and antioxidants. The results of these trials are still at a preliminary stage, but suggest that combination therapy with antiretrovirals and adjunctive neuroprotective therapies may be the future direction for HIV dementia treatment.