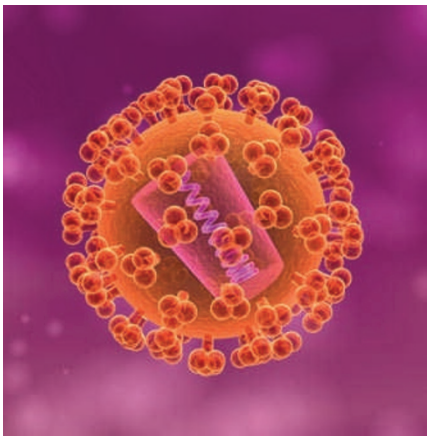
DEMENTIA

Biomarker profiles in HIV-associated cognitive disorders and Alzheimer disease

The pathophysiology of cognitive dysfunction in individuals with HIV, although seemingly exacerbated by age, is poorly understood. Limited evidence suggests that the mechanisms that underlie HIV-associated cognitive disorders resemble aspects of the molecular pathology of Alzheimer disease (AD). A new study, published in *Neurology*, now reports that patients with HIV-associated cognitive disorders and individuals with AD exhibit similar cerebrospinal fluid (CSF) amyloid-β (Aβ) biomarker profiles but different levels of CSF tau markers. "Thus, only the biology of the amyloid system mimics AD in HIV patients with a cognitive disorder," explains lead author David Clifford, at Washington University in St Louis, MO, USA.

In the developed world, the incidence of HIV-associated dementia has dramatically fallen with the increasing use of HIV antiviral therapies—in particular, highly active antiretroviral therapy. Cognitive dysfunction, however, is still a common feature of HIV infections, even in patients with well-controlled viral loads. Indeed, the prevalence of mild forms of HIV-associated cognitive disorders has been reported to be rising, as the HIV-positive population ages. "We wondered if something about living with a chronic infectious disease in the CNS might trigger the early onset of other more common conditions such as AD," explains Clifford.

To gain insights into the possible links between AD and cognitive dysfunction in HIV, the researchers measured AD CSF biomarkers in patients with one or other of these conditions and in appropriate controls. In total, CSF samples were analyzed from 49 patients with HIV-associated cognitive disorders, 21 individuals with HIV but no cognitive impairment, 68 patients with mild dementia of the Alzheimer type (DAT), and 50 cognitively normal HIV-negative controls.



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As expected, Clifford *et al.* found that patients with DAT had markedly lower CSF levels of the 42 amino acid form of Aβ ($A\beta_{1-42}$)—the main constituent of neuritic plaques—than cognitively normal HIV-negative controls. The presence of cognitive dysfunction was associated with a similar phenomenon in patients with HIV. Individuals with HIV-associated cognitive disorders had comparable CSF $A\beta_{1-42}$ levels to patients with DAT, whereas cognitively normal HIV-positive individuals did not exhibit a reduction in the level of this biomarker. The levels of CSF $A\beta_{1-40}$ remained unaltered across all groups in this investigation. This finding was consistent with results from other studies, which have shown that CSF $A\beta_{1-40}$ does not decrease in patients with AD.

The CSF levels of total tau (t-tau) and Thr181-phosphorylated tau ($p\text{-}tau_{181}$)—biomarkers of neurofibrillary tangles—were, as expected, substantially increased in patients with DAT compared with cognitively normal HIV-negative controls. By contrast, patients with HIV, irrespective of the presence of cognitive impairment, exhibited slight decreases in the CSF levels of t-tau and $p\text{-}tau_{181}$.

The researchers attempted to identify possible associations between the biomarker findings and measures of HIV biology, but no such correlations could be found.

Several studies have now investigated the potential biological links between AD and the cognitive impairment that occurs in HIV. Neuropathological studies have revealed that patients with HIV-associated cognitive disorders exhibit AD-like Aβ brain pathology, including diffuse and neuritic plaques. Several CSF biomarker studies have also been conducted, although the results of these investigations have been somewhat inconsistent. For example, one study found that HIV patients with advanced cognitive impairment, while exhibiting low CSF $A\beta_{1-42}$, had high CSF levels of both tau biomarkers, as in AD. In contrast to the investigation by Clifford and colleagues, this study failed to report the CSF levels of $A\beta_{1-40}$ levels, leaving the biomarker profiles unvalidated. Furthermore, the t-tau and $p\text{-}tau_{181}$ results reported by Clifford *et al.* are in line with two other studies, which have shown that these biomarkers remain at normal levels in HIV-associated cognitive disorders.

As the HIV-positive population ages, the accurate determination of the cause of cognitive dysfunction in this setting might become increasingly challenging. "The results from our study indicate that we have a system for differentiating our old patients with HIV who get dementia from those individuals who may be developing AD," claims Clifford. "This might be therapeutically helpful."

The researchers aim to learn more about Aβ biology in the context of HIV, partly through PET studies with Pittsburgh compound B, a technique that enables amyloid in the brain to be visualized *in vivo*.

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Original article Clifford, D. B. *et al.* CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease. *Neurology* **73**, 1982–1987 (2009)