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Is HIV Brain Disease Preventable?

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There are 2 major issues in the field of neuro-HIV. Is HIV present in the brain in most if not all patients? This is important to facilitate eradication strategies given the difficulties of delivering therapies across the blood-brain barrier. Second, what is the mechanism of brain damage when HIV is suppressed by antiretroviral drugs (the therapeutic paradox)? This too is significant as the field is divided as to possibilities: residual brain damage occurring before adequate antiretroviral drugs—the so-called legacy effect, ongoing HIV replication at levels below what are currently detectable, the effect of comorbidities such as vascular disease, or antiretroviral toxicity.

In this issue of *Neurology® Neuroimmunology and Neuroinflammation*, Sari et al.[1] used advanced brain imaging (a PET/MRI scanner with a second-generation TSPO ligand that identifies glial/macrophage activation) in 14 aviremic patients (HIV RNA <50 copies/mL; CD4 count 708 ± 260 cells/μL) on combination antiretroviral therapy (cART), 6 elite controllers (ECs) (HIV RNA <50 copies/mL; CD4 count 692 ± 188 cells/μL), and 16 healthy controls (HCs) focusing on the thalamus, putamen, amygdala, hippocampus, parietal operculum cortex, superior temporal white matter, and brainstem. Neuropsychologic assessment was performed though limited. ECs and HCs were not different in the degree of binding and therefore glial activation, whereas cART patients had significantly more binding implying neuroinflammation.

There are some limitations to the study. It is predicated on brain inflammation as a signal for ongoing infection in the context of HIV disease. There is possibly an alternate cause, namely cART neurotoxicity. The number of patients was small, neuropsychologic testing was not comprehensive, CSF was not assessed for HIV, and the frontal white matter was not studied, although it is known to be a site of HIV replication and inflammation.

Nonetheless, the study findings are important and advance the field. Why are ECs no different from HCs? ECs likely suppress brain infection given that replication was suppressed in the blood. Why are ECs different from cART-treated patients who show increased inflammation despite viral suppression? This suggests that ECs may prevent seeding of the brain by HIV and that ultra-early cART (around seroconversion) may mirror this. Why are cART-treated patients still showing neuroinflammation? cART may not fully control HIV brain replication, or it may cause neuroinflammation without there being any HIV replication—cART-related neurotoxicity the evidence for which is both in vitro and observational in vivo studies[2,3] but counterbalanced by long-term pediatric studies into adulthood generally showing cognitive improvement and stability.[4] It is well known that cART at least in some cases has limited ability to effectively suppress brain infection likely because of difficulties in brain entry, intrinsic brain cell efficacy (microglia, astrocytes, and pericytes as opposed to T cells), and lack of effect on early transcription.[5-8]

How do these findings address the 2 main questions in the neuro-HIV field? Eradication from the brain may not be necessary if cART is commenced at the earliest time, namely seroconversion. Second, brain disease may be prevented by such ultra-early treatment. However, existing data do not support these suggestions,[9,10] possibly because cART was commenced early but not ultra-early, a very difficult practical issue. In addition, existing cART only partially

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treats brain disease—better drugs possibly of a new class such as transcription inhibitors should be considered. Further studies are needed.

The findings of Sari et al. have relevance beyond neuro-HIV. Very early intervention possibly in the presymptomatic disease phase is pertinent to many neurologic diseases but perhaps especially in Alzheimer and possibly in multiple sclerosis. Nonetheless, this has to be counterbalanced by consideration of the potential for long-term neurotoxicity of therapies that have to be administered for years. Finally, the significance of brain inflammation in relation to particular diseases needs cautious interpretation, not necessarily reflecting the pathophysiologic process under investigation.

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