EDITORIAL

Lipids and cognition make good bedfellows for neuroAIDS

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During a recent discussion of HIV-1-associated neurocognitive deficits (HAND), a colleague whispered across the 2 empty seats of a large auditorium to ask a simple but profound question, "So what causes HIV cognitive impairment?" Over 20 years ago, the answer might have been, "It's the virus, stupid." Now, there isn't a pat answer.

As a result of highly efficacious combination antiretroviral therapy (cART), HIV-associated dementia is no longer a death sentence for an HIV-infected person.[1] The nosologic umbrella we call HAND is caused by a spectrum of pathogenic processes linked to the virus and disruption of normal synaptic communication.[2,3] Cognitive dysfunction may also be associated with drugs of abuse, peripheral metabolic disorders, concurrent illnesses including opportunistic infections, inadequate nutrition, liver failure, antiretroviral drug toxicities, immune dysregulation, depression, and other psychiatric maladies.[4] The search for specific biomarkers to gauge the severity of HAND and its response to treatment is confounded by these factors, but also by our evolving understanding of viral neuropathogenesis in the CNS, an immunologically protected "sanctuary" or "reservoir" site of residual infection. The virus thus remains a critical determinant in our pursuit of disease eradication.[5]

The study in the current issue of *Neurology*® by Bandaru et al.[6] appears to have found at least one answer. In the study, lipidomic techniques (i.e., the quantitative study of biochemical pathways and networks of cellular lipids in biological systems) were used to evaluate CSF from infected people who were either cognitively normal or had neurologic deficits ranging from mild cognitive impairment to moderate dementia, and seronegative, cognitively normal people followed at 7 clinical research centers. HIV-seronegative controls could be differentiated from infected people by reductions in a single ceramide species and increases in multiple forms of cholesterol. Importantly, cART influenced the changes in cholesterol metabolism. No cross-sectional differences in lipid metabolites were seen according to cognitive status. There were also no correlations between CSF levels of sphingolipid metabolite (SM) (i.e., lipids containing open carbon chains with the amino alcohol sphingosine), ceramide (*N*-acyl precursor of sphingosine), or sterols and CD4 cell count, CD4 nadir, and plasma or CSF viral loads. Higher baseline levels of triglycerides were associated with a greater probability of cognitive improvement in follow-up visits within a year. However, a single SM and reduced levels of esterified cholesterols were indicators of cognitive decline. The observations have parallels to lipid profiles associated with lipid storage disorders, raising the question of whether dietary and pharmacologic interventions could restore brain lipid balance in HIV-infected individuals.

The data presented are exciting because they raise the possibility of biomarkers that may provide us with surrogates for assessing the complex and sometimes contrary or fluctuating cognitive changes that occur in patients with HAND. Even more important, these biomarkers might allow us to assess efficacy of new CNS-oriented therapeutic approaches directed at neuroinflammation and normal synaptic function, the substrate of HAND. However, many of the comorbidities that exist with HIV-1 brain infection can affect cognitive decline and are likely to contribute to changes in lipidomic profiles. These comorbid etiologies must be carefully sorted out. Each of these factors alone or in tandem could alter lipid metabolism. How this occurs in the setting of advanced HIV infection and stable cART remains unclear.

First, it's the macrophage.[7] Secretory products from the immune response and HIV-infected mononuclear phagocytes (MP; microglia and bloodborne perivascular macrophages) could be important culprits.[8] Indeed, HIV-infected MP, rather than CD4+ lymphocytes, are responsible for the spread and persistence of HIV infection within the CNS and certainly mediate neuronal injury and death in CNS disease.[9,10] Second, we cannot ignore persistent immune activation that occurs through the trafficking of CD14+/CD16+ macrophages. Perivascular macrophages have a high rate of trafficking between peripheral blood and brain and contribute to the evolution of viral population compartments.[11] Third, the CNS viral "sanctuary" has effects on viral kinetics but also allows immune-mediated effects on lipid metabolism. This includes the inflammatory factors and viral proteins secreted as

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a consequence of immune activation.[12] Fourth, differences in cART CNS penetration could reflect changes in "micro"-foci of HIV-1 infection in patients in whom parenchymal microglia harbor more long-lived reservoirs[13] that could be responsible not only for altered lipid metabolic rates but subsequent neuronal injury. The authors advance a very provocative hypothesis, and their findings are strikingly similar to lysosomal storage diseases that result from inborn errors of lipid metabolism in the pediatric population; all are characterized by inexorably progressive loss of CNS function. This may provide considerable impetus to explore the basis for white matter changes in HAND where viral loads are well-controlled by cART. It does not, however, address the fact that HAND does not follow the unipolar progression to death that is the outcome of these inborn errors of metabolism.

This study gives us a framework for lipidomic biomarker signatures associated with HAND and provides fresh insights into the progression of HAND and the consequences of cART. But it also raises more questions as we face the continuance of a disease that is far more complex than that solely due to the viral infection within the CNS, which brings us back to where we started: drugs of abuse, concurrent illnesses (CNS and peripheral), and altered metabolism may all have regional CNS heterogeneity that can influence HAND clinical phenotypes. We must continue to focus on what happens to the entire CNS and peripheral ecosystem as people treated with cART continue to live and age with HIV-1. The challenges that lie ahead rest in embracing the complexities of interpreting biomarkers in chronic diseases, not simply for diagnostic and prognostic purposes, but utilizing the insights they provide for the pathophysiology and efforts to find clinically useful therapies to eradicate the virus along with the residual and unavoidable damage to the CNS.

AUTHOR CONTRIBUTIONS

Harris Gelbard: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Howard Gendelman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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DISCLOSURE

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