The Journal of Infectious Diseases
EDITORIAL COMMENTARY

Could We Harness Human Immunodeficiency Virus Antibodies to Monitor the Brain?

David B. Clifford

Melba and Forest Seay Professor of Clinical Neuropharmacology in Neurology, Washington University in St. Louis, Missouri

(See the Major Article by Burbelo et al, on pages 1024–32.)

Keywords. HIV associated neurocognitive disorder; HAND; HIV antibodies; CSF; HIV cure.

In the quest to control and ultimately eliminate human immunodeficiency virus (HIV) from patients, the brain presents unique and critical challenges. It is well accepted that the brain represents a potential body "compartment" for HIV that is likely colonized in the early days of the infection, and it ultimately may support a degree of independent evolution of the virus not precisely mirrored in systemic blood samples. The blood-brain barrier (BBB) that makes the compartment a reality consists, at a minimum, of a unique endothelial barrier of brain vessels with tight junctions, a basement membrane, and an astrocytic barrier, making distribution of both pathogens and therapies significantly different in brain compared with most other organs. The brain is also too precious and well protected to be sampled repeatedly for research purposes. However, cerebrospinal fluid (CSF) that literally floats the brain has proved to be a meaningful, albeit imperfect, window to the brain environment that can be safely sampled. In this issue of *the Journal of Infectious Diseases*, Burbelo et al [1] have performed an important analysis on CSF from a series of patients and described important insights gleaned from the analysis of anti-HIV antibodies. The results have implications for optimal therapeutics, enhancing our understanding of persisting HIV-associated cognitive impairment, and efforts to cure HIV infection.

Given the challenges for direct sampling of brain tissues, biomarkers reflecting any infection in the brain are of particular value. Perhaps because the fundamental pathophysiology driving disability in HIV/acquired immune deficiency syndrome primarily reflects cellular immune damage, attention to humoral responses has typically been superficial at best. Burbelo et al [1] more carefully consider the potential use of the humoral immune response as a sensitive and semiquantitative monitor for the status of viral expression. Measured antibodies in CSF seem likely to primarily reflect the environment in brain or CSF, but, as done in this investigation, parallel investigation of peripheral antibodies is required for interpretation. Furthermore, the status of the BBB should be monitored because pathologic breakdown of the BBB would degrade the fidelity of the CSF measurements. The modest changes in CSF albumin and other proteins attest to the gross preservation of BBB in the settings studied here. Passive entrance of antibodies through the BBB is modest, and so it appears that much of the humoral response in the CSF is generated within the brain compartment, thus reflecting the status of antigens in the brain.

This study includes a description of antibodies in "typical HIV patients" whose disease is discovered after years of chronic infection, after which they are started on HIV therapy. Antibody response to HIV antigens is strong in peripheral blood and in CSF before starting therapy, and only modestly reduced through pharmacologic control of the infection, even after >10 years of excellent control. Although virus is "undetectable" in blood and CSF by clinical assays, it is hypothesized that there is enough ongoing viral expression to maintain robust humoral immunity. This article also provides a fascinating contrast with the "Berlin patient" whose functional HIV cure has resulted in parallel loss of specific HIV antibody responses in brain and in the peripheral blood [2]. Presumably, this is the result of loss of ongoing antigen stimulation that markedly differs from patients in whom virus is simply suppressed by effective antiretroviral therapy (ART).

It is notable that the dynamics of building up robust ongoing antigen presentation in the periphery occurs faster than the CSF after acute infection. The dynamics of developing antibodies is tracked during the first months of infection in a small number of cases

Received 12 December 2017; editorial decision 12 December 2017; accepted 18 December 2017 ; published online February 1, 2018.

Correspondence: D. B. Clifford, MD, Melba and Forest Seay Professor of Clinical Neuropharmacology in Neurology, Washington University in St. Louis, Box 8111, Neurology, 660 South Euclid, St. Louis, MO 63110 (cliffordb@wustl.edu).

The Journal of Infectious Diseases® 2018;217:1017–9

DOI: 10.1093/infdis/jix663

reported here, and it clearly shows the buildup of CSF antibodies trailing that in the periphery. When treatment is started in this early timeframe, it appears that there is a much greater impact on persisting HIV antibodies in the CSF, suggesting that the cellular pool of antigen in the central nervous system is also substantially restricted in the brain relative to the rest of the body through acute therapy. A fascinating pair of patients reported in this article happened to start prevention therapy just after they were infected, thus initiating therapy at the earliest possible moment. Their acute diagnosis, when already on therapy shortly afterward, reinforced with full ART, resulted in impressive normalization of antibody responses in the brain. Sadly, even this unrealistically early treatment appears not to have been curative, because a later treatment interruption proved that pathogenic virus emerged in the absence of ART. However, the impressive ability of early ART to minimize abnormal HIV antibodies, presumably due to minimizing persistent HIV antigen presentation, still does not achieve functional cure.

This report also helps to frame thought about therapy for HIV-associated neurocognitive disorder (HAND). If, as many experts suspect, the HAND that plagues many HIV patients is driven by persistent immune responses to residual viral antigen, these results give hope that patients who are diagnosed early and treated immediately might be substantially spared from cognitive complications of HIV infection. However, it would be premature to conclude that better control of virus in the brain compartment through early therapy will be protective, because other concerns, including potential ART neurotoxicity, the impact of other coinfections, or other morbidities, as well as vascular mechanisms threatening the brain integrity, remain plausible mechanisms individually or, more likely, work together to contribute to HAND.

The careful studies reported on anti-HIV antibodies certainly add weight to the current trends to recommend HIV therapy as early as possible after infection. It is sobering in the light of present evidence that some leaders in the field for many years recommended against starting HIV therapy until the immune system had crumbled to the point that opportunistic infections were common. Of course, the thinking in the early years of the epidemic was driven by the availability of only a small number of antivirals that were both less potent and more toxic than our current drugs. Costly investments in making patients feel worse while driving development of viral resistance made it reasonable to delay treatment. However, the gratifying development of a substantial number of highly effective drugs with different mechanisms, and very modest apparent toxicity, has transformed the landscape. The observations from this report, demonstrating that the brain compartment, in particular, may benefit from early therapy, should motivate all clinicians to try very hard to diagnose acute HIV infection and offer early therapy.

This study should also motivate very careful evaluation of the cognitive impact of early therapy. A critical task for the neurologic community is to dissect the key factors contributing to the ongoing observation of HAND in our clinics. Real-world estimates of approximately half of HIV patients in care demonstrating some degree of measurable cognitive impairment is an unreasonable burden that should be reversed as soon as possible [3]. Careful studies of HIV cohorts that have received early therapy may help evaluate the potential contributions of early therapy, compared with the typical patients who are only diagnosed after long periods of infection. Several groups have assembled research cohorts of acutely infected patients, and the longer term cognitive outcomes achieved in this population will help factor in the degree to which early therapy might protect patients from HAND. If there is an effect, it will also need to be determined how early the therapy has to be to accomplish protection of the brain compartment. Sadly, given the challenge of identifying acute HIV infection, it appears overly optimistic to assume that the HAND problem will be reversed by guidelines that merely call for therapy at the time of diagnosis.

CONCLUSIONS

The lofty goal of finding a practical functional cure for HIV is an ambitious but worthy scientific target currently being pursued. The brain compartment will be an essential part of working out a cure strategy. Therapies are harder to implement in the brain, and the potential cellular sites of viral infection are expanded by evidence suggesting primarily monocyte/macrophage cells in the central compartment, with the added concern about a reservoir in glial cells of the brain. It will be reasonable to consider the evidence from the important study by Burbelo et al [1] that specific anti-HIV antibodies may be a biomarker of the status of HIV in this hard-to-study region of the body. Given the evidence that the 1 individual with a functional cure demonstrates essentially normalized antibody status in CSF means that this should be considered as a potential (relatively) convenient marker of the status of HIV in the brain. A marked decline in CSF-specific HIV antibodies might be a reassuring marker of progress toward a cure.

Notes

Financial support. This work was funded by grants from the National Institute of Neurological Disorders and Stroke (NS077384), National Institute of Allergy and Infectious Diseases (5UM1A1069439), National Institute

of Mental Health (MH1073458, UL1 TR000448), and **National Institute on Aging** (U01AG042791, 1RO1AG053267).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Burbelo PD, Price RW, Lagberg L, et al. Anti-HIV antibodies in the cerebrospinal fluid (CSF): evidence of early treatment impact on CNS reservoir? J Infect Dis **2018**; 217:1024–32.
2. Hütter G, Nowak D, Mossner M, et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med **2009**; 360:692–8.
3. Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology **2010**; 75:2087–96.