Primary HIV infection alters brain neurochemistry, but does antiretroviral treatment help?

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Neurology® 2014;83:1588–1589

Primary HIV infection (PHI) in the brain is increasingly hypothesized as being key for determining the future risk of HIV-associated neurocognitive disorders (HAND) through early brain damage. However, in vivo neuroimaging studies during this period of HIV infection are lacking. Knowledge of early HIV dynamics in the CNS has been explored through the CSF,[1] but this does not inform on brain regional neuropathologic mechanisms. Proton magnetic resonance spectroscopy (^{1}H-MRS) provides in vivo information on neurochemistry with both accuracy and reliability, and the pattern of neurochemical abnormalities in HAND is well-established.[2] Cross-sectional studies[3–5] during PHI using ^{1}H-MRS have been conducted principally to investigate the association between cerebral metabolites and biomarkers in the plasma and CSF. However, because this period is highly dynamic, longitudinal study design is a prerequisite for understanding (1) the extent and (2) the types of neurochemical changes, (3) their prevalence, and (4) to what extent individuals improve once antiretroviral therapy (ART) is initiated.

In this issue of *Neurology*®, Young et al.[6] provide new data on points 1, 2, and 4. They conducted ^{1}H-MRS in 53 adult men (5 had a history of ART, the others were treatment-naive) who were recruited at a median of 3.7 months post HIV transmission and who were followed up for a median of 6 months. Importantly, only 23 participants initiated ART during follow-up as prescribed by their treating doctor (i.e., a nonrandomized design). In relation to points 1 and 2, the authors found, within a few months of HIV infection, evidence of progressive inflammation and gliosis (increasing choline/creatine and myo-inositol/creatine ratios) in the frontal white matter, parietal gray matter, and potential excitotoxicity (increased baseline glutamate/creatine ratio) in the basal ganglia. These results represent the largest longitudinal investigation of brain neurochemical change during PHI (n = 53) and show that early inflammation and gliosis are widespread across the brain and that the changes do not include dramatic change to neuronal integrity (*N*-acetylaspartate was not significantly reduced). However, the basal ganglia appeared to be affected by glutamate excitotoxicity, which is one of the most devastating forms of brain toxicity, and usually precedes neuronal damage. Therefore, there are several parallel neuropathologic processes of early brain damage in PHI with a regional affinity that CSF studies cannot detect. The study also provides in vivo regional timeline of these events. HIV-related damage is rapid; in particular, glutamate excitotoxicity is concerning, even in the absence of major neuronal damage in the current study. The scanning timeline seems important in the detection of any early neuronal damage; another longitudinal ^{1}H-MRS study conducted in Thailand[7] found *N*-acetylaspartate reduction in addition to choline increase in the basal ganglia. In the latter, study participants were identified with acute HIV infection (n = 31) and scanned within a median of 14 days after HIV transmission. Both studies therefore indicate that neurochemical changes are highly dynamic, following complex nonlinear patterns.

On to point 4: the authors chose a "2-phase linear mixed model" in order to use all the longitudinal data collected in the 53 participants between baseline and pre-ART scans, from which they estimated how the cerebral metabolites changed without ART (they found an abnormal increase in some brain metabolites in the first phase); they then (second phase) assessed if these changes, seen in the 23 ART-initiated participants, remained (different from zero rate change or not). While this model ingeniously used all the available data, it actually represents a null-hypothesis model rather than an attenuation model per se. An alternative model that would demonstrate actual attenuation of neurochemical abnormalities would have involved direct comparison of brain metabolites' changes on vs off ART (ideally with randomized arms). Overall, the current study design does not solve the question as to whether or not ART initiation is of any clinical benefit, because the magnitude of metabolites' changes is unclear and not optimally controlled in the design. Despite its limitations, however, the current study provides a strong

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From UNSW Australia (L.A.C., K.K.K.); Neuroscience Research Australia (L.A.C.); St. Vincent's Hospital & St. Vincent's Centre for Applied Medical Research (L.A.C., K.K.K.); and The Kirby Institute (K.K.K.), UNSW Medicine, UNSW Australia, Sydney.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

incentive for conducting a randomized clinical trial. Larger sample sizes (also inclusive of women and minorities) are needed because there are known individual variations in brain viral entry timelines and tropisms, trafficking, host genetic factors, and presence of neurologic illness at seroconversion. Furthermore, relating back to point 3: the current data did not clarify the prevalence of neurochemical abnormalities in PHI. One cross-sectional study suggested that only a subset of individuals may have altered neurochemistry.[5] This is an important consideration for a randomized trial design. Also, future investigations into the effects of early therapy on brain pathology would benefit from the inclusion of assessments of viral reservoirs (but innovative technology is needed to assess in vivo CNS reservoirs), as these results would constructively inform the debate on possible brain HIV eradication[8] in addition to curbing early brain damage. Integrated HIV DNA in CD4 T+ cells accumulates in peripheral blood according to the duration of untreated HIV infection[9] and it is conceivable that a similar dynamic of HIV accumulation occurs in the brain (more specifically in microglia and long-lived cells: macrophages and astrocytes[8]). This can consequently impact on the future course of HAND. Finally, the current study lends strong support for the use of ^{1}H-MRS as a method of choice for assessing early HIV-related brain damage and response to ART during PHI. Pending further study, this method could become a screen, as suggested by the authors. This would be particularly timely as there is an international effort to develop guidelines for optimal clinical ^{1}H-MRS protocols.[10] Conducting such studies will ultimately be critical for improving the management of neurologic disorders in HIV-infected persons.

AUTHOR CONTRIBUTIONS

Lucette A. Cysique: drafting/revising the manuscript, analysis or interpretation of data. Kersten K. Koelsch: drafting/revising the manuscript.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

L. Cysique is funded by a National Health and Medical Research Council of Australia Career Development Fellowship APP1045400; receives research support from Abbvie Ltd., ViiV Healthcare, and the Australian National Association of People Living with HIV/AIDS (NAPWA); has received honoraria from Abbvie Ltd., CogState Ltd., and ViiV Healthcare; and received partial salary support in 2012 from Merck Sharp Dome and CogState Ltd. K. Koelsch has received honoraria from Bristol Myers Squibb. Go to Neurology.org for full disclosures.

REFERENCES

1. Pilcher CD, Shugars DC, Fiscus SA, et al. HIV in body fluids during primary HIV infection: implications for pathogenesis, treatment and public health. AIDS 2001; 15:837–845.
2. Cysique LA, Lane T, Moffat K, et al. HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a ^{1}H-MRS study. PLoS One 2013;8:e61738.
3. Lentz MR, Kim WK, Kim H, et al. Alterations in brain metabolism during the first year of HIV infection. J Neurovirol 2011;17:220–229.
4. Letendre SL, Zheng JC, Kaul M, et al. Chemokines in cerebrospinal fluid correlate with cerebral metabolite patterns in HIV-infected individuals. J Neurovirol 2011;17: 63–69.
5. Peluso MJ, Meyerhoff DJ, Price RW, et al. Cerebrospinal fluid and neuroimaging biomarker abnormalities suggest early neurological injury in a subset of individuals during primary HIV infection. J Infect Dis 2013;207: 1703–1712.
6. Young AC, Yiannoutsos CT, Hegde M, et al. Cerebral metabolite changes prior to and after antiretroviral therapy in primary HIV infection. Neurology 2014; 83:1592–1600.
7. Sailasuta N, Ross W, Ananworanich J, et al. Change in brain magnetic resonance spectroscopy after treatment during acute HIV infection. PLoS One 2012;7: e49272.
8. Brew BJ, Gray L, Lewin S, Churchill M. Is specific HIV eradication from the brain possible or needed? Expert Opin Biol Ther 2013;13:403–409.
9. Murray JM, McBride K, Boesecke C, et al. Integrated HIV DNA accumulates prior to treatment while episomal HIV DNA records ongoing transmission afterwards. AIDS 2012;26:543–550.
10. Oz G, Alger JR, Barker PB, et al. Clinical proton MR spectroscopy in central nervous system disorders. Radiology 2014;270:658–679.