Correlation of In Vivo Neuroimaging Abnormalities With Postmortem Human Immunodeficiency Virus Encephalitis and Dendritic Loss

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Background: In the absence of significant opportunistic infection, the most common alterations on neuroimaging in the brains of patients with AIDS include enlarged cerebrospinal fluid spaces, white-matter loss, volume loss in striatal structures, and white-matter signal abnormalities. Although previous studies have linked brain viral levels to these alterations, other neuropathological mechanisms might also contribute to them.

Objective: To examine the relationship between findings on premortem magnetic resonance images and postmortem neuropathologic evidence of human immunodeficiency virus (HIV) encephalitis and neurodegeneration.

Design: Morphometric analysis of magnetic resonance imaging in seropositive cases with matched seronegative controls, and the correlation of these volumes to neuropathological measures in autopsied seropositive cases.

Setting: University of California, San Diego, HIV Neuropsychiatric Research Center.

Subjects: Twenty-one seropositive subjects studied at autopsy and 19 seronegative cases.

Main Outcome Measures: In vivo structural magnetic resonance imaging data analyzed by quantitative methods, with comparison of volumes from magnetic resonance imaging and neuropathological data from autopsies.

Results: The HIV-seropositive subjects demonstrated cerebrospinal fluid increases relative to seronegative controls. These increases were associated with a significant decrease in the volumes of cerebral and cerebellar white matter, caudate nucleus, hippocampus, and, to a lesser extent, cerebral cortex. The volume of cerebral white-matter tissue with elevated signal was also increased. This signal elevation in white matter predicted the autopsy diagnosis of HIV encephalitis, as well as the extent of dendritic loss as assessed by analysis of microtubule-associated protein 2 immunoreactivity.

Conclusions: White-matter and cortical damage resulting from HIV disease are closely related. In vivo magnetic resonance imaging may be a valuable adjunct in the assessment of patients at risk for developing HIV encephalitis.

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Despite the advent of combination antiretroviral therapy, damage to the central nervous system (CNS) by human immunodeficiency virus (HIV) continues to be a significant problem. Infiltration of HIV-infected monocytes begins at early stages of the disease and ultimately leads to microglial activation, diffuse white-matter injury, and neurodegeneration, primarily in patients with advanced immunosuppression (for review see Langford and Masliah). These neuropathological findings, collectively known as HIV encephalitis (HIVE), are often associated with cognitive alterations. Neuropsychological impairment related to HIV has a deleterious effect on the quality of life and everyday functioning of individuals living with AIDS and is associated with increased mortality.

Identification of in vivo markers of HIVE would permit discrimination of individuals at risk of developing CNS abnormalities and facilitate early treatment. Previous studies have shown that persistent viral infection of the CNS by HIV results in structural alterations that are detectable by magnetic resonance (MR) imaging. In our own cross-sectional and longitudinal studies using MR morphometric techniques, our group demonstrated brain parenchymal loss in HIV-infected subjects, increases in cerebrospinal fluid (CSF) volume, decreases in striatal grey-matter volume, and decreases in cerebral white-matter volume. In those studies, de-
HIV Status

<table>
<thead>
<tr>
<th>HIV Status</th>
<th>Positive (n = 21)</th>
<th>Negative (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>40.4 (60.7)</td>
<td>39.1 (100.2)</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>20/1</td>
<td>17/2</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>14.3 (20.6)</td>
<td>15.4 (20.4)</td>
</tr>
<tr>
<td>Time from MR imaging to autopsy, mo</td>
<td>Mean (SD)</td>
<td>6.6 (30.6)</td>
</tr>
<tr>
<td>Range</td>
<td>0.8-150.6</td>
<td>NA</td>
</tr>
<tr>
<td>CD4 T cells/mL</td>
<td>Mean (SD)</td>
<td>36.9 (540.9)</td>
</tr>
<tr>
<td>Range</td>
<td>1.6-2370.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; MR, magnetic resonance; NA, not applicable.

Table 2. Characteristics of Autopsy Cases With and Without HIV Encephalitis

<table>
<thead>
<tr>
<th>HIV Encephalitis</th>
<th>Positive (n = 11)</th>
<th>Negative (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, mean (SD), y</td>
<td>42.8 (5.7)</td>
<td>37.8 (7.0)</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>9/2</td>
<td>10/0</td>
</tr>
<tr>
<td>Risk factor</td>
<td>6 SM, 4 DU, 0 BT</td>
<td>6 SM, 4 DU, 0 BT</td>
</tr>
<tr>
<td>Cause of death, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Cachexia, KS, CMV, MAC</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diagnosis of HIV dementia, No.</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Postmortem diagnosis of CMV encephalitis, No.</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: BT, blood transfusion; CMV, cytomegalovirus; DU, drug use; HIV, human immunodeficiency virus; KS, Kaposi sarcoma; MAC, mycobacterial atypical; SM, sex with men.

The sample of seropositive cases was identified in a review of the autopsy cases examined in a longitudinal study at the University of California San Diego HIV Neurobehavioral Research Center. This review showed that 22 seropositive cases had been studied with structural MR imaging within 16 months of death (in 17 cases within 9 months). One case was excluded because a course of combination antiretroviral therapy had been initiated shortly after the imaging session and continued until death. In this case it was thought that viral levels in the brain at autopsy may have been quite different than at the time of the imaging session before treatment. A previous longitudinal study demonstrated regression of T2 signal hyperintensities on brain MR images with combination antiretroviral therapy. In the remaining cases, there were no significant changes in treatment between imaging and autopsy.

Nineteen seronegative cases were then identified that, as a group, matched the 21 included cases studied by autopsy in distribution of age, sex, and education at the time of imaging (Table 1). This study was approved by the University of California, San Diego, Human Research Protections Program, and informed consent was obtained for all participants.

Exclusion criteria for HIV Neurobehavioral Research Center studies include a history of non–HIV-related neurologic disorder or medical disorder affecting the CNS (eg, head trauma with >30 minutes’ loss of consciousness, neurosyphilis) and schizophrenia. Participants with CMV, HIV dementia, or peripheral neuropathies were not excluded. All autopsy cases selected had detailed antemortem neuromedical and neuropsychological examinations by means of previously described protocols. On the basis of blind clinical ratings of a comprehensive neuropsychological test battery, 9 of the subjects studied by autopsy had been classified as neurocognitively normal and 12 as impaired. Of the 12 subjects with impairment, 2 were diagnosed as having HIV dementia, 4 minor cognitive motor disorder, and 6 other neuropsychological impairment. Information obtained from available neuropathological data was used to exclude cases with opportunistic infections other than CMV (4 cases had CMV encephalitis), malignant neoplasms in the CNS, and anoxic brain injury. In most cases, patients died as a result of acute bronchopneumonia and/or sepsisemia, and the autopsy was performed within 24 hours of death (Table 2).

MR IMAGING PROTOCOL AND IMAGE ANALYSIS.

Three whole-brain image series were collected for each participant. The first 2 series were fast spin-echo acquisitions yield-
ing 2 separate 4-mm coronal image sets: repetition time (TR) of 3000 milliseconds, echo time (TE) of 17 milliseconds, and echo train (ET) of 4; and TR of 3800 milliseconds, TE of 102 milliseconds, ET of 8, and field of view (FOV) of 24 cm. The third was a sagittal gradient-echo T1-weighted series with TR, 24 milliseconds; TE, 5 milliseconds; number of excitations, 2; flip angle, 45°; section thickness, 1.2 mm; no gaps; and FOV, 24 cm. The image-analytic approach is similar to that used in our previous anatomic studies but represents a significant elaboration of these methods as described previously. 

Trained anatomists who were blind to subject diagnosis, age, sex, or any other identifying information subjected each image dataset to the following image analysis procedures: (1) interactive isolation of intracranial regions from surrounding extracranial tissue, (2) 3-dimensional digital filtering of the matrix of pixel values representing brain voxels to reduce inhomogeneity artifact, (3) reslicing of the volume to a standard orientation, (4) tissue segmentation using semiautomated algorithms, and (5) neuroanatomic region-of-interest analysis.

First the brain was isolated from extracranial areas in the image, ie, from surrounding tissue that was in some instances contiguous with brain tissue and similar in signal value. Filtering was applied to reduce nonbiological signal drift across the FOV, which is presumably due to field inhomogeneity and susceptibility effects. A 3-dimensional, high-pass filter was applied, with 2 iterations, separately to the “stripped” proton density–weighted and T2-weighted fast spin-echo image volumes.

The tissue classification procedure is an interactive, supervised process. Trained operators manually designate the positions of 3 sets of tissue samples, one for each of the target tissues (gray, white, and CSF). Samples are selected in locations that appear to be homogeneous and free of signal abnormalities. Sample voxel values are then analyzed by simple regression techniques to separate first all brain parenchymal voxels from CSF voxels, and then gray-matter voxels from white-matter voxels. The regression coefficients obtained in these simple analyses are then applied to classify each voxel within the volume as most similar to CSF, gray matter, or white matter.

Datasets were aligned to a standardized stereotactic space defined relative to the decussations of the anterior and posterior commissures and the structural midline. Anatomists circumscribed regions on tissue-segmented images. Standardized rules were applied for delineating a set of subcortical and cortical regions within the cerebrum, as well as gray matter, white matter, and CSF in the cerebellum (Figure 1).

For the present study, the cerebral subcortical structures that were evaluated included the cerebral ventricles, the caudate nucleus, the nucleus accumbens, the lenticular nucleus, the thalamus, the amygdala (and adjacent entorhinal and perirhinal cortex), the hippocampus, and a region referred to as basomesial diencephalon (which includes septal nuclei, mammillary bodies and other hypothalamic structures, the bed nucleus of the stria terminalis, and the diagonal band of Broca). The cerebral cortex, cerebral white matter, and CSF in the subarachnoid spaces were also measured separately, as were the gray matter, white matter, and CSF of the cerebellum. All volume estimates were expressed as proportions of either the volume of the total supratentorial (cerebral) vault or the total infratentorial (cerebellar) vault.

**Figure 1.** Fully processed magnetic resonance images.
ABNORMAL WHITE MATTER

Within the regions designated anatomically as “cerebral white matter,” some voxels had signal values that exceeded those of the voxels selected for the samples of normal white matter. Because of their higher signal values, many of these voxels were classified with our tissue segmentation methods as “gray matter,” but were isolated from true gray-matter voxels in the anatomic analysis described in the preceding section. Such voxels (with elevated signal values) were coded as abnormal white matter and summed separately. Thus, the abnormal white-matter volume represents areas in white matter with subtle elevation of signal as well as frank hyperintensities. Figure 2 illustrates the results of the anatomic methods applied, as well as the appearance of the abnormal white-matter regions in 2 subjects from the present study.

NEUROPATHOLOGICAL ANALYSIS

Brains were removed rapidly, and, after macroscopic examination, tissue blocks from the midfrontal cortex, temporal cortex, parietal cortex, cingulate cortex, hippocampus, basal ganglia, mesencephalon, pons, medulla, and spinal cord were obtained, immersion-fixed in 4% formalin, and embedded in paraffin. For routine analysis, paraffin blocks were sectioned and stained with hematoxylin-eosin, luxol fast blue, Bodian stain, and Prussian blue stain for ferric iron. Additional paraffin sections of frontal neocortex, basal ganglia gray matter, and subcortical white matter (centrum semiovale) were used for immunocytochemical analysis with a mouse monoclonal antibody against HIV-gp41 (Genetics Systems, Seattle, Wash), as previously described.28,29 A semiquantitative score of HIV viral burden was assigned to each area, based on the number of gp41-immunoreactive cells present, and scores from the 3 areas were added to derive a summary score of 1 to 6.28,30,31 The HIV-seropositive cases were characterized, on the basis of the presence of activated microglia and multinucleated giant cells and gp41 summary scores, as HIVE positive or HIVE negative.

Additional paraformaldehyde-fixed tissue blocks from the midfrontal cortex were serially sectioned at 40 µm with the Vibratome 2000 (Leica; Bannockburn, Ill) for immunocytochemical and computer-aided laser scanning confocal microscopic analysis. Briefly, as previously described,5,28 sections were incubated overnight with monoclonal antibodies against microtubule-associated protein 2 (MAP-2, dendritic marker; Chemicon International, Temecula, Calif), parvalbumin (marker of interneurons; Sigma-Aldrich Corp, St Louis, Mo), or SMI312 (axonal marker; Sternberger Monoclonals, Baltimore, Md). Additional sections were also immunostained with monoclonal antibodies against glial fibrillary acidic protein (astroglial marker; Chemicon International) and CD45 (microglial marker; DAKO, Copenhagen, Denmark). After an overnight incubation with primary antibodies, sections were incubated for 1 hour at room temperature in fluorescein isothiocyanate–conjugated horse anti–mouse IgG (Vector Laboratories, Burlingame, Calif). Sections were then transferred to SuperFrost charged slides (Fisher Scientific, Pittsburgh, Pa), mounted under glass coverslips with antifading medium (Vector Laboratories), and analyzed with the laser scanning confocal microscope (MRC1024; BioRad, Hercules, Calif), as previously described.26 All sections were processed simultaneously under the same conditions, and experiments were performed twice to assess reproducibility.

To determine the severity of dendritic pathology, computer-aided assessment of the percentage area of the neuropil within the cortical ribbon covered by MAP-2–
The percentage area covered, cases were divided into the following categories: (1) normal dendritic complexity (≥20%); (2) mild to moderate damage (15%-19%); and (3) severe damage (<15%). Similarly, the National Institutes of Health Image 1.43 software was used to determine the percentage area of the white matter covered by parvalbumin- or SMI312-immunoreactive fibers and the levels of CD45 and glial fibrillary acidic protein immunoreactivity (pixel intensity) in the white matter.

**STATISTICAL ANALYSES**

Structural MR imaging measures were compared between the HIV-seronegative and the HIV-seropositive groups with 2-group t tests. The smaller groups of cases with and without HIVE were compared by nonparametric Mann-Whitney tests. Pearson correlations were used for comparison of neuroimaging, clinical, and neuropathological markers. Because of the long time between the in vivo imaging session and death in 4 of the seropositive participants, the significant findings for this group were reexamined post hoc in the 17 cases in which the time between imaging and autopsy was less than 9 months.

**RESULTS**

**GRAY- AND WHITE-MATTER TISSUE LOSS IN SEROPOSITIVE PATIENTS**

Compared with the HIV-seronegative control group, the HIV-seropositive group had increased sulcal, ventricular, and cerebellar CSF volumes (Table 3). These CSF increases were associated with a significant decrease in the volumes of cerebral and cerebellar white matter, caudate nucleus, hippocampus, and, to a lesser extent, the cerebellar cortex. In contrast, the volume of the amygdala was elevated in the HIV-seropositive group compared with the HIV-seronegative controls. The volume of cerebral white-matter tissue with elevated signal (white-matter abnormality) was also significantly increased in the HIV-seropositive group compared with the HIV-seronegative controls (Table 3).

**ASSOCIATION BETWEEN WHITE-MATTER SIGNAL INTENSITY AND HIVE AND DENDRITIC DAMAGE**

Compared with HIV-seropositive patients who were HIVE negative, individuals with a diagnosis of HIVE at autopsy had significantly more abnormal white-matter tissue, as reflected by signal elevation on the in vivo structural MR images (Table 4). Consistent with this finding, viral burden in the brain (gp41 immunoreactivity) was significantly related to the amount of abnormal white matter in the in vivo MR images (r = 0.48, P = 0.03). Furthermore, volume of abnormal white-matter tissue on in vivo MR images was inversely correlated with dendritic density (MAP-2) in the neocortex (r = −0.60, P = 0.004). Both of these results remained significant when 4 cases with CMV encephalitis were removed from the analyses. However, significant correlations could not be demonstrated between volume of abnormal white-matter tissue and levels of astrogliaosis or microglialosis as measured by glial fibrillary acidic protein and CD45 immunocytochemistry, respectively.

Cases with severe dendritic damage (MAP-2, <15%) and HIVE had widespread white-matter abnormality by in vivo MR imaging (Figure 3). However, many individuals with moderate dendritic damage (MAP-2, 15%-19%), most of whom had no evidence of HIVE, did not display significant white-matter abnormality. Of note, 3 of the patients with HIVE who did not have signal eleva-
tion in the white matter also had no evidence of dendritic damage (MAP-2, %). To assess whether the time elapsed between imaging and autopsy influenced the observed relationships, linear regression analyses were performed using both the time from imaging to death and neuropathological measures to predict the morphometry measures. In all cases, significant relationships between neuropathological measures and MR imaging measures remained significant when controlling for time elapsed. In addition, post hoc analyses within the 17 cases in which the time lag was less than 9 months showed similar significant findings. Subjects with and without neuropsychological impairment at the last assessment did not differ significantly on the MAP-2 measure or MR imaging measures.

TISSUE LOSS IN PATIENTS WITH AND WITHOUT HIVE

Table 4 compares the HIVE groups on the key in vivo MR imaging measures. As described earlier, patients who met criteria for HIVE at autopsy did show significantly more abnormally elevated signal in white matter. However, on the measures of tissue volume loss and the resulting increases in CSF compartments, the HIVE negative cases exhibited as much evidence of global atrophy as cases that met criteria for HIVE. Neuropsychological impairment at the last assessment before death was not associated with evidence of HIVE at autopsy.

This study showed that in HIV-infected patients without other brain infections, the pathological stigmas of HIVE, high levels of HIV-gp41 immunoreactivity, and dendritic loss at autopsy were associated with abnormal MR signal in cerebral white matter shortly before death. A previous in vivo structural MR imaging study in HIV-infected patients showed that diffuse white-matter hyperintensity was well correlated with leukoencephalopathy, defined by the light microscopic appearance of myelinated tracts in postmortem material. In that study, however, patients with HIV and CMV encephalitis, lymphoma, progressive multifocal leukoencephalopathy, and other CNS infections were included. The present study extends these findings by showing that diffuse white-matter hyperintensity is specifically associated with high levels of HIV coat protein and loss of dendritic arbor at autopsy in patients without CNS opportunistic infections other than CMV.

Although cerebral white-matter hyperintensity during life was predictive of an autopsy diagnosis of HIVE, many of the most consistent in vivo markers of HIV-related neurodegeneration were not. Neither the measures of tissue loss in cerebral white matter or caudate nucleus, nor increases in cerebral CSF, distinguished patients diagnosed as having HIVE from those free of HIVE. More important, the HIVE-negative group exhibited tissue loss as severe as that observed in the HIVE-positive group. Even if the lack of correlation could be accounted for by the emergence of HIV encephalitis in the period between imaging and autopsy, this would not account for the severity of tissue loss in the HIVE-negative group. While 8 of 11 HIVE-positive cases had significant loss of dendritic area in midfrontal cortex, 7 of 10 HIVE-negative cases also had losses in this range. These observations have several possible explanations. Tissue volume loss in the HIVE-negative patients may

<table>
<thead>
<tr>
<th>Cerebral Proportions</th>
<th>Positive (n = 11)</th>
<th>Negative (n = 10)</th>
<th>U*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulcal CSF</td>
<td>0.120 (0.042)</td>
<td>0.124 (0.038)</td>
<td>52</td>
<td>.83</td>
</tr>
<tr>
<td>Ventricular CSF</td>
<td>0.028 (0.014)</td>
<td>0.024 (0.007)</td>
<td>52</td>
<td>.83</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>0.492 (0.037)</td>
<td>0.499 (0.040)</td>
<td>50</td>
<td>.72</td>
</tr>
<tr>
<td>Cerebral white matter</td>
<td>0.329 (0.044)</td>
<td>0.322 (0.024)</td>
<td>47</td>
<td>.57</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0.005 (0.001)</td>
<td>0.006 (0.001)</td>
<td>55</td>
<td>.99</td>
</tr>
<tr>
<td>Cerebral abnormal white matter</td>
<td>0.022 (0.014)</td>
<td>0.12 (0.004)</td>
<td>26</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus.

* Mann-Whitney statistic.
have occurred as a result of previous bouts of HIVE that were in remission at the time of death. If so, these findings, like previous findings, suggest that MR hyperintensities and the pathological stigmata of HIVE may exhibit a waxing and waning course in treated patients with AIDS. Another possibility is that much of the cerebral tissue damage sustained in patients with AIDS is mediated by processes other than HIVE, such as cytokine expression: so much, in fact, that the overall loss of tissue is as great in patients without HIVE as in those with HIVE.

Although HIV-mediated white-matter damage is common in patients with AIDS, the mechanism is unclear. Previous studies have suggested that myelin toxic effects may be mediated by cytokines produced by HIV-infected mononuclear cells trafficking into the CNS, and release of HIV toxic products, such as gp120 and Tat, may play a role. In this regard, viral RNA burden tends to be highest in the white matter and cdate, compared with other brain regions. Alternatively, breakdown of the blood-brain barrier and leakage of myelinoxic serum components in combination with ischemic injury may also be involved. Although all of these factors might act together to promote myelin injury, special attention has been paid to the potential role of gp160 sequences that increase monocyte trafficking into the brain.

Diffuse damage to the cerebral white matter has been correlated with the cognitive alterations in patients with AIDS. However, other structural alterations might mediate the cognitive impairment. Among them, simplification of neuronal dendritic arbor and loss of interneurons have been suggested to play a role. The present study demonstrated that the severity of the white-matter alterations in the in vivo MR image was associated with the severity of dendritic damage. Two mechanisms might link the white- and gray-matter damage. Myelin and axonal damage might be followed by retrograde damage to pyramidal neurons and secondary dendritic atrophy. Alternatively, factors damaging the myelin sheath might also affect the dendritic arbor. Both longitudinal MR imaging studies in humans and experimental studies in the simian immunodeficiency virus encephalitis model suggest that white-matter damage may precede cortical loss, although these alterations are closely associated.

In summary, this study illustrates that white-matter alterations demonstrable by in vivo MR imaging are associated with HIV and dendritic damage, suggesting that white-matter and cortical damage are closely related. Furthermore, these results support the notion that in vivo MR imaging may be a valuable adjunct in the assessment of patients at risk for developing HIVE.

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