

Increased frontal white matter diffusion is associated with glial metabolites and psychomotor slowing in HIV

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Abstract

Diffusion-weighted imaging (DWI) measures brain water diffusion that is sensitive to microscopic brain injury. A total of 11 HIV seropositive patients were compared to 14 seronegative subjects using DWI, proton magnetic resonance spectroscopy (¹H MRS), and neuropsychological tests. The apparent diffusion coefficient (ADC) was significantly increased in the HIV patients, primarily in the frontal white matter (FWM; +5%, $p=0.01$). Diffusivity correlated positively with the glial marker *myo*-inositol ($r=0.5$, $p=0.008$) and negatively with cognitive performance (NPZ-8 composite score; $r=-0.43$, $p=0.05$). These findings suggest increased brain water diffusion may reflect increased glial activation or inflammation, which in turn, may contribute to the cognitive deficits in HIV patients.

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1. Introduction

HIV encephalitis is characterized by multinucleated giant cells, apoptosis, and viral antigen-positive cells, with the most severe effects found in the white matter and basal ganglia (Bell, 1998). However, clinical assessments of HIV brain injury may be difficult and often rely on noninvasive imaging techniques. Magnetic resonance (MR) imaging may show atrophy of brain parenchyma (Patel et al., 2002) and basal ganglia (Aylward et al., 1993) in patients with HIV dementia, while proton magnetic resonance spectroscopy (¹H MRS) studies have found dementia severity-dependent changes in metabolites that correspond to glial activation and neuronal injury or loss, also primarily in basal ganglia and frontal white matter (FWM; Chang et al., 1999, 2002). Another MR technique, diffusion-weighted imaging (DWI) provides a quantitative measure of the random motion of water molecules. The apparent diffusion coef-

ficient (ADC) obtained with DWI reflects the amount of water diffusion within the tissue in a given region of interest. Because changes in tissue integrity may affect the diffusion of water molecules, changes in ADC may reflect microscopic brain injury. Such changes have been documented in aging (Naganawa et al., 2003; O'Sullivan et al., 2001), Parkinson's disease (Stebbins et al., 2002), vascular dementia (Assaf et al., 2002), Alzheimer's disease (Yoshiura et al., 2002), other dementias (Sullivan and Pfefferbaum, 2003), and stroke (Gass et al., 2004).

One recent DWI study of HIV patients reported an increase in mean diffusivity of frontal and parietal white matter (Filippi et al., 2001). DWI can also be used to assess fiber orientations by measuring the anisotropy that occurs when water motion is not free to move along all directions (diffusion tensor imaging or DTI). DTI demonstrated decreased fractional anisotropy in the frontal white matter and increased anisotropy in the internal capsule of HIV patients (Pomara et al., 2001). Increased diffusion, as measured by ADCs or fractional anisotropy, has been postulated to reflect inflammation, cell membrane breakdown, neuronal loss, or disruption of white matter tracts.

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Because all of these pathologies have been observed in the HIV-infected brain (Berger and Avison, 2001), we hypothesized that HIV-induced microscopic brain injury would result in measurable increases in ADC in the frontal white matter and possibly in the basal ganglia.

HIV-associated brain injury is commonly associated with psychomotor slowing, concentration problems, as well as attention and working memory deficits (Navia et al., 1986). Studies have demonstrated correlations between such cognitive deficits and brain imaging measures, including decreased regional volumes on brain morphometry (Hestad et al., 1993) and elevated glial metabolites on ^1H MRS (Chang et al., 1999, 2002). Psychomotor slowing has been correlated with increased diffusivity on DWI in the white matter of normal aging brain (O'Sullivan et al., 2001) as well as in Parkinson's disease (Stebbins et al., 2002). However, correlations between neuropsychological function and DWI measures have not been evaluated in HIV patients. Therefore, the aims of this preliminary study were to measure changes in brain water diffusion with DWI in HIV patients and seronegative control subjects, and to determine whether brain water diffusion correlates with neuropsychological test performance. To further determine the nature of the injury that maybe related to changes in ADC, we also evaluated whether the ADC changes are related to abnormalities in brain metabolites measured on ^1H MRS.

2. Materials and methods

2.1. Subjects

Twenty-five subjects were studied: 11 HIV-1 seropositive individuals (10 men, mean age of 35 ± 3 years) and 14 HIV-negative (SN) control subjects (11 men, mean age of 31 ± 3 years). Six of the 11 HIV patients were on stable regimens of antiretroviral medications and 5 were antiretroviral-naive. Each subject fulfilled the following inclusion criteria: (1) willingness and ability to give informed consent; (2) men or women of any ethnicity; (3) less than 50 years of age; and (4) for HIV subjects, CD4 count less than $500/\text{mm}^3$. In addition, subjects were excluded if they fulfilled any of the following exclusion criteria: (1) comorbid or history of chronic medical (other than HIV for the seropositive group) or psychiatric illnesses that might confound the outcome measures of the study (e.g., diabetes, schizophrenia, major depression, multiple sclerosis, Parkinson's disease, and degenerative brain diseases); (2) any major structural brain abnormalities (e.g., strokes, vascular malformations); (3) severe hepatic or renal dysfunction; (4) head trauma with loss of consciousness >30 min; (5) metallic objects contraindicated for MRI; and (6) pregnant or breast feeding. All subjects signed an informed consent approved by the Institutional Review Board at Harbor-UCLA Medical Center. All subjects

completed the DWI, and all but one HIV and one control subject completed the ^1H MRS and a battery of neuropsychological tests.

2.2. MR studies

MR scans were performed on a 1.5T GE scanner (General Electric Signa, Milwaukee, WI). The MR protocol included the following sequences: (1) sagittal T1-weighted localizer [echo time (TE)/relaxation time (TR)=11/500 ms, 4-mm slice thickness, 1-mm gap, 24 cm FOV]; (2) axial fast-inversion recovery [TE/inversion time (TI)/TR 32/120/4000 ms, 3.5-mm slices, 24 cm FOV, no gap]; (3) coronal T2-weighted fast spin-echo (TE/TR 102/4000 ms, 5-mm slices, 24 cm FOV, no gap); (4) axial fluid-attenuated inversion recovery (FLAIR, TE/TI/TR 142/2600/11000 ms, 5-mm slices, 24 cm FOV, no gap); (5) axial diffusion MRI using a single-shot spin-echo EPI sequence (TE/TR 109/8000 ms, 5-mm slices, 21 cm FOV, 2 mm gap, 64×64 resolution, ± 100 -kHz bandwidth, b -values 0 and $700 \text{ sec}/\text{mm}^2$ applied separately for each of the three axes); and (6) localized ^1H MRS in two brain regions (frontal white matter and basal ganglia) using a point-resolved spectroscopy (PRESS) sequence (Bottomley, 1987), was optimized for assessing frontal and subcortical brain regions (Ernst and Chang, 1996; TE/TR 30/3000 ms, 64 averages, 2048 acquisitions, and 2.5-kHz bandwidth). The MRS protocol yielded metabolite concentrations of *N*-acetyl compounds (NA), total creatine (CR), choline compounds (CHO), and *myo*-inositol (MI), using a previously described method (Ernst et al., 1993; Kreis et al., 1993), which corrects for the partial volume of CSF (%CSF) in each voxel. Two HIV subjects were scanned twice (before antiretroviral treatment and 3 months after the start of treatment).

2.3. MR data processing

The structural (axial inversion recovery sequence) and diffusion images were segmented and coregistered using a customized program written in C using AVS (Advanced Visual Systems, Waltham, MA; Itti et al., 1996). The logarithm of the intensity ratio between diffusion-weighted and non-diffusion-weighted scans was used to calculate the apparent diffusion coefficient (ADC) for each voxel, separately for each axis. The individual ADC values (x , y , and z) were then averaged to obtain an estimate of the isotropic ADC. Following coregistration and reslicing, regions of interest were drawn manually on each slice of the structural MRI that showed the following regions for both hemispheres: thalamus, caudate, putamen, globus pallidus, and four levels (inferior, middle, superior, and dorsal-lateral) of the frontal white matter (Fig. 1). A semiautomatic program written within SAGE (spectroscopy analyses for General Electrics) was used to analyze the MR spectra (Ernst et al., 1993; Kreis et al., 1993).

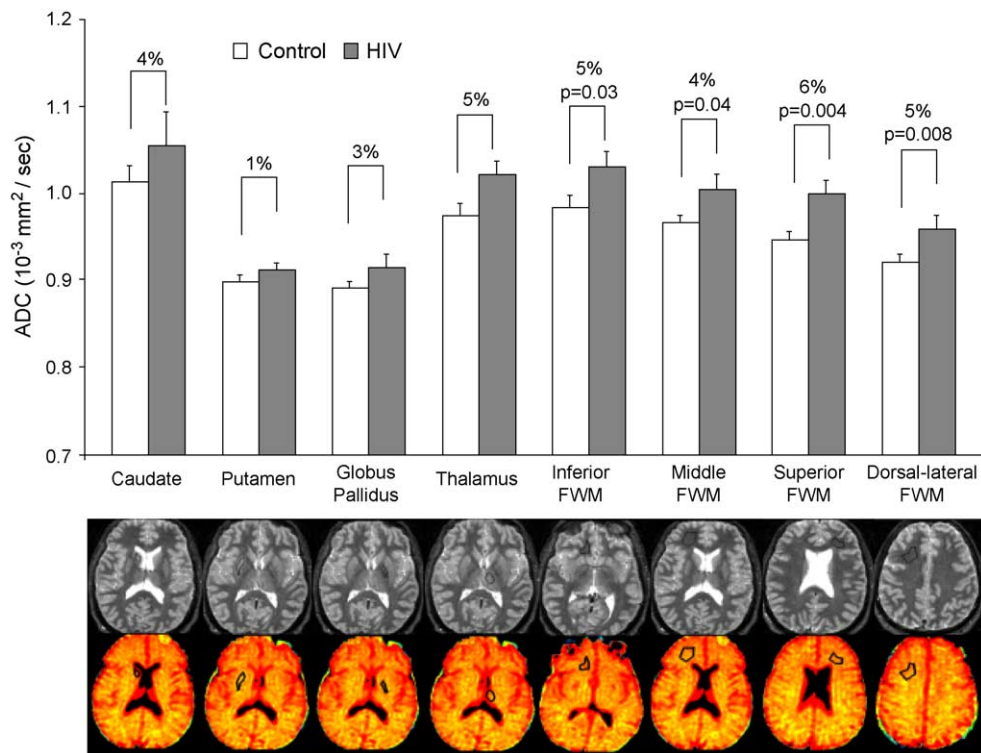


Fig. 1. Diffusion in HIV patients as measured by apparent diffusion coefficients were significantly increased (repeated measures ANOVA, $p=0.01$). Corresponding regions of interest are shown on structural MRI and ADC maps.

2.4. Neuropsychological tests

The neuropsychological battery assessed brain function that might be affected by injury to the frontal lobe and/or basal ganglia. Although a more comprehensive battery of tests were performed, due to the small sample size in the current study, a composite cognitive score, the NPZ-8 (Patel et al., 2002; Sidtis et al., 1993), was calculated to assess cognitive deficits in these subjects. The NPZ-8 included Timed Gait, Grooved Pegboard (dominant and nondominant hand), Trail Making (A and B), Symbol Digit Modalities, and two tests from the California computerized assessment package (CalCAP: choice reaction time and 1-increment).

2.5. Statistics

StatView (SAS Institute, version 5.0.1) was used for all statistical analyses. Regional diffusion values were analyzed with repeated-measures analysis of variance (ANOVA; significance at $p<0.05$), using HIV status as a between variable, region as a within variable, and ADC value as the dependant variable. Post hoc t -tests were performed in regions that were significantly abnormal on ANOVA. Initially, all eight regions and both hemispheres were combined to test for an overall HIV effect on ADCs. Following this, the four levels and two hemispheres in the frontal white matter were combined as frontal white matter, while both hemispheres of the other four regions were

combined as subcortical gray matter to determine HIV effects in frontal white matter and subcortical gray matter specifically.

Correlations between cognitive function (NPZ-8) and brain water diffusion (ADC) were explored using simple regression analysis. Bonferroni corrections were applied to determine significance after multiple correlations. To reduce the number of correlations, these regressions were performed only in brain regions with ADCs that showed significant abnormalities in HIV patients (e.g., averaged frontal white matter). Similarly, only those regions with significant group differences in ADC were correlated with MRS metabolites within the same regions.

3. Results

3.1. Clinical

As a group, the HIV patients had CD4 counts of 191 ± 33 cells/mL, log plasma viral load of 3.7 ± 0.5 copies/mL, Log CSF viral load of 2.8 ± 0.5 copies/mL, AIDS dementia complex stage of 1.3 ± 0.4 (0–4, 0=normal and 3 and 4=severe dementia), HIV dementia scale= 12 ± 1 (0–16, 16=perfect performance), and Karnofsky score= 74 ± 5 (100=no symptoms; Table 1). HIV patients had lower education (12 ± 0.7 years) than the SN control subjects (14 ± 0.5 years), $p=0.01$.

Table 1
HIV patient characteristics

| Patient | Age | Sex | CD4 (cells/ml) | HIV dementia scale | Karnofsky score | ADC stage | Plasma viral load | CSF viral load | Antiretroviral medications |
|---------|-----|-----|----------------|--------------------|-----------------|-----------|-------------------|----------------|----------------------------|
| 1 | 27 | M | 44 | 16 | 90 | 0.0 | 36 870 | 19 855 | none |
| 2 | 29 | M | 327 | 10 | 60 | 3.0 | 133 649 | NA | none |
| 3 | 29 | M | 312 | 15 | 90 | 1.0 | 50 | 50 | D4T, 3TC, NFV |
| 4 | 31 | M | 200 | NA | NA | NA | 1750 | NA | Combivir, Sustiva |
| 5 | 34 | M | 239 | 14 | 70 | 0.5 | 400 | 50 | D4T, 3TC, ABT378 |
| 6 | 37 | M | 5 | 9 | 60 | 1 | 180 109 | 594 | none |
| 7 | 43 | M | 457 | 14 | 90 | 0.5 | 75 476 | 2191 | D4T, 3TC NFV ABT378 |
| 8 | 44 | M | 64 | 8 | 90 | 2.0 | 750 000 | 416 | none |
| 9 | 46 | M | 35 | 15 | 100 | 0.5 | 195 | 50 | none |
| 10 | 48 | M | 230 | NA | NA | NA | 400 | NA | NFV, NRTI AG1549, Combivir |
| 11 | 16 | F | 254 | 16 | 90 | 1.0 | 83 | 140 | D4T, 3TC, NVP |

3.2. MRI

The initial repeated-measures ANOVA, which included both hemispheres of all eight regions evaluated, showed increased diffusion in HIV patients ($p=0.008$; Fig. 1). Post hoc analyses of frontal white matter and subcortical gray matter showed significantly increased diffusion in all the frontal white matter combined (+5%, $p=0.01$), but not in all the combined subcortical gray matter regions (+2%, $p=0.2$) in HIV patients compared to SN controls. While all regions had increased ADCs, post hoc analyses showed significant increases (4–6%, $p\leq 0.05$) in all four levels of frontal white matter (Fig. 2). Due to the significant effects on ADC in the frontal white matter, the t -tests of MRS metabolites were performed in this region. Significant increases in [MI] (SN: 6.8 ± 0.5 mmol/kg; HIV: 8.7 ± 0.4 mmol/kg; +28%, $p=0.007$) and [CHO] (SN: 1.5 ± 0.1 mmol/kg; HIV: 1.8 ± 0.1 mmol/kg; +20%, $p=0.01$) were observed in the HIV patients. No significant changes in [NA] (SN: 7.7 ± 0.2 mmol/kg; HIV: 7.3 ± 0.4 mmol/kg) or [CR] (SN: 5.9 ± 0.2 mmol/kg; HIV: 6.6 ± 0.3 mmol/kg) were observed.

3.3. Correlations

[MI] correlated positively with the average frontal white matter ADC ($r=0.5$, $p=0.008$, Fig. 2). Average frontal white

matter ADCs correlated negatively with cognitive function as measured by the NPZ-8 ($r=-0.43$, $p=0.05$, Fig. 2), indicating that increased diffusion was associated with poorer cognitive performance.

4. Discussion

This small but comprehensive study found significantly increased brain water diffusion (ADC) and glial metabolites (MI and CHO) in the frontal white matter of HIV subjects with mild dementia. The diffusivity correlated positively with the glial marker [MI] and negatively with psychomotor efficiency (NPZ-8). These findings suggest increased brain water diffusion may reflect increased glial activation or inflammation, which in turn, may contribute to the cognitive deficits in HIV patients.

Our findings of increased frontal white matter diffusion are in agreement with two recent DWI studies that evaluated small groups of HIV subjects. These studies found increased mean diffusivity in the frontal and parietal white matter (Filippi et al., 2001) and increased fractional anisotropy in frontal white matter but decreased anisotropy in the internal capsule (Pomara et al., 2001). Only one other study applied both DWI and MRS to study HIV-associated brain injury; however, no significant differences in brain diffusion (ADC)

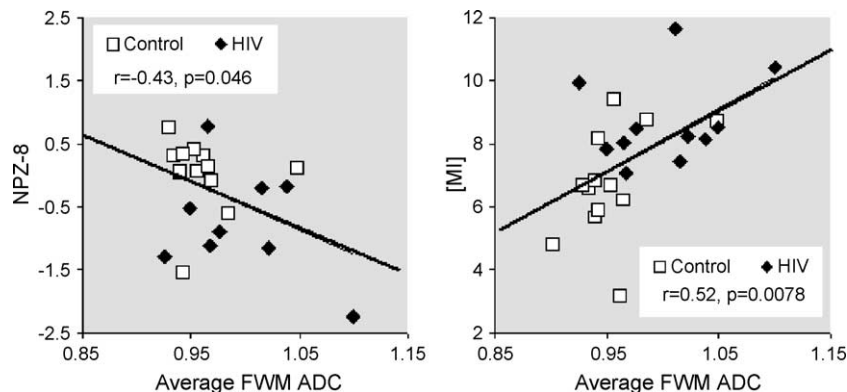


Fig. 2. Frontal white matter (FWM) ADC correlates with measures of psychomotor skill NPZ-8 and MI concentrations.

between patients with no impairment and those with mild or moderate motor disorders were observed, and healthy control subjects were not studied using DWI (Wenserski et al., 2003).

Numerous studies have evaluated the possible mechanism(s) underlying the decreased diffusion observed in ischemic brain injury; however, few studies have been conducted to determine the processes involved in increased brain water diffusion, as observed in aging and several neurodegenerative diseases. Two possible explanations for increased water diffusion are inflammation and breakdown of the extracellular matrix; both of which are evident in HIV (Belichenko et al., 1997). Similar to HIV brain injury, patients with multiple sclerosis typically show increased water diffusion during inflammatory stages (Filippi and Rocca, 2003) along with increased choline and *myo*-inositol (Bitsch et al., 1999). Inflammation has also been implicated in other neurodegenerative diseases (Ringheim and Conant, 2004); some of these diseases have shown increased diffusion measures such as Alzheimer's disease (Yoshiura et al., 2002) and Parkinson's disease (Stebbins et al., 2002). The cytokines and chemokines released as part of the inflammatory response in both Alzheimer's disease (Deb et al., 2003) and HIV (Conant et al., 1998, 1999), in turn, can damage the extracellular matrix. In addition, HIV-1 glycoprotein 120 may induce matrix metalloproteinase-2 activity and protein synthesis, which may further contribute to extracellular matrix degradation (Marshall et al., 1998). One study of acute traumatic injury to rodent cortex showed that ADC decreased in the same regions where extracellular matrix markers were increased, suggesting that increases in extracellular matrix, and therefore increased barriers to diffusion, lead to a decrease in ADC (Vorisek et al., 2002). Although the reverse relationship has not been documented, these findings suggest that decreased extracellular matrix would result in increased ADC.

The current study also found correlations between cognitive function (NPZ-8) and brain water diffusion (ADC) in the frontal white matter, in that poorer task performance was associated with increased diffusion. Because similar associations also have been observed with normal aging (Engelger et al., 2000; O'Sullivan et al., 2001), a Parkinson's variant (Schocke et al., 2002), and Alzheimer's disease (Moseley, 2002; Rose et al., 2000), the increased ADC in HIV brain injury might share some common pathways with those in these other populations. For instance, positive correlations between anterior white matter mean diffusivity and age, as well as slower performance on Trail Making B–A test, were observed in an elderly population (>age 50 years; O'Sullivan et al., 2001). The authors of the study hypothesized that a functional disconnection, or reduction in white matter integrity, with age results in commonly observed cognitive declines with age. A DWI study in Alzheimer's disease patients also showed reduced white matter integrity

(decreased anisotropy or increased ADC) that correlated with poorer cognitive function as measured by the mini mental state examination (Rose et al., 2000). In the HIV-infected brain, direct viral insult and immune responses, such and those described above, may lead to a similar reduction in white matter integrity or increased ADC, hence breakdown of neuronal pathway integrity and cognitive decline.

In the current study, frontal white matter [MI] and [CHO] were significantly elevated, and [MI] correlated positively with ADC. Elevated MI and choline suggest glial proliferation and cell membrane turnover, which in turn may contribute to neuropsychological deficits in HIV (Chang et al., 1999, 2002). *myo*-Inositol is an intracellular osmolyte and has long been considered a glial marker (Brand et al., 1993). Astrocytes, microglia, and macrophages have been shown to increase their levels of the Na⁺/MI cotransporter (SMIT) in response to stress or injury (Aihara et al., 2002; Strange et al., 1994), leading to an accumulation of MI. Due to MI's role in inflammation, the increase in diffusion that corresponds to the increased MI likely reflects, at least in part, inflammation.

Our patient population did not have significantly decreased levels of NA, which is to be expected based on their mild dementia (Chang et al., 1999). Therefore, the increase in ADCs at this early stage, prior to significant neuronal damage or decreased NA, supports the hypothesis that changes in brain water diffusion or inflammation precede neuronal damage. Extended periods of inflammation and the associated macrophage or glial derived cytokines, chemokines, and nitric oxide (Anderson et al., 2002) may lead to gradual breakdown of the ECM, and ultimately neuronal damage and further cognitive decline in later stages of HIV infection. Both inflammation and breakdown of the ECM might lead to elevated ADCs.

In conclusion, increased brain water diffusion (ADC) and its correlation with increase glial metabolite (MI) in the frontal white matter of HIV patients suggest decreased tissue integrity may be related to glial activation or inflammation. The correlations between ADC and MI, as well as higher ADC in those with poorer performance on NPZ-8 further suggest that inflammation-mediated disruption in neuronal pathways may lead to cognitive decline in HIV patients. A larger study to validate these preliminary observations is needed. Future studies also will evaluate the relationships between cytokines and diffusion abnormalities in HIV to further delineate the role of inflammatory responses in the neuropathology of HIV.

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