Neuroimaging Markers of HIV Disease in the Central Nervous System: A Role For Diffusion Tensor Imaging and Diffusion Distribution Maps

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Introduction

The human immunodeficiency virus (HIV) is neurotropic, and most HIV-positive patients develop neuropsychiatric impairment during the course of their illness, which ranges from HIV-associated minor cognitive motor deficit (MCMD) to HIV-associated dementia (HAD).[1,2]

Reports have shown that patients on highly active antiretroviral therapy (HAART) experience decreases in viral load level[3], reversal of white matter lesions on MR[4], and improvements in neuropsychological test performance[5], but others continue to have progressive neurological impairment despite the HAART regimen and low viral load levels.[6] Since the central nervous system (CNS) is likely a reservoir site for HIV[7], this may allow for the development of viral resistance and reseeding the peripheral circulation with drug-resistant virus.

Initial studies in HIV-positive patients have shown that MR tensor imaging can detect white matter abnormalities even when brain MR scans are normal.[8] The purpose of this study was to determine whether abnormalities detected on magnetic resonance diffusion tensor imaging (MRDTI) and diffusion distribution maps in HIV-positive patients correlated with viral load levels and adequate HAART regimens. The development of a neuroimaging marker of HIV disease in the CNS may allow for the earliest possible detection of cognitive impairment, and could be used to assess HAART efficacy.

Methods

20 HIV-positive patients (11 men, 9 women, mean age 44.5 yrs) were prospectively studied over a two year period. All of these patients had routine MR imaging including diffusion weighted axial imaging (TR 10000/TE 100/1 NEX) using an echoplanar multislice sequence of 30 interleaved slices of 5mm thickness, matrix 128 X 128, FOV 22cm. Diffusion was measured in three directions with a b-value of 100,000 s/cm^2 for each direction. Using diffusion-weighted images in three orthogonal directions, an orientation-independent diffusion-weighted image (DWI_{trace}) is obtained on scanner as follows: $DWI_{trace} = (DWI_x DWI_y DWI_z)^{1/3}$.

This trace-weighted image and image without diffusion weighting (S_0) are transferred to a workstation. A C program employing the equation ($DWI_{trace}=S_0\exp(-bD_{av})$) is used to calculate the orientation-independent average diffusion maps (D_{av}=Trace/3) on a pixel-by-pixel basis.[8]

We measured the D_{av} values of the periventricular white matter, corona radiata, centrum semiovale, genu and splenium of the corpus callosum, and the anterior and posterior limbs of the internal capsule using region-of-interest (ROI) analysis. Typically 20 ROIs (125mm^3) were placed. Values were compared to normative data (age-matched controls).[9]

We calculated diffusion distribution maps (histograms) from the entire brain using a C-program. The program distributes the pixels to 250 bins with bin widths of 0.02 x 10^{-5}cm^2/s. This distribution map was fitted to a three compartment model of i) brain tissue, ii) cerebrospinal fluid, iii) partial volume using the curve below:

$(C_1\exp[(D_{av}-BD_{av}/s)]^2+ C_2\exp[(D_{av}-D_2/s_2)]^2+ C_3\exp[(D_{av}-D_3/s_3)]^2$. Peak location ($BD_{av}$) and peak width (s) of the brain tissue compartment were determined from the fitted data.

Comparisons of BD_{av} and D_{av} for anatomic structures were done using 2-tailed student t-test assuming unequal variance.

Results

All 20 patients had normal brain MR exams except for mild cerebral atrophy. 12 patients had undetectable viral load levels (<400 HIV mRNA copies/mm^3). 8 patients had elevations in viral load from 10K to 100K HIV mRNA copies/mm ^{3}, and these patients had significantly higher diffusion values compared to the other patients and normals, which are tabulated (Table I). Figure shows comparison of diffusion maps in a patient with undetectable viral load versus a patient with elevated viral load.

Discussion

In HIV-positive patients, diffusion histograms and diffusion constant (D_{av}) calculations can detect abnormalities within the periventricular white matter, corpus callosum, internal capsule, and centrum semiovale that are not appreciated on routine brain MR. Furthermore, patients with elevated viral load levels, who were not on adequate HAART regimens, compared to those with undetectable viral load levels, all of whom were on HAART regimens, had statistically significant elevations in the BD_{av} and increases in the diffusion constant in the periventricular white matter, corpus callosum, internal capsule, and centrum semiovale bilaterally. Thus, MRDTI and diffusion distribution analysis may have a role as a marker of HIV disease progression and HAART efficacy.

Acknowledgments

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Table I: Diffusion Measurements (10^{-5} cm^2/s)

	Patients with Undetectable Viral Load (n=12)	Patients with Elevated Viral Loads (n=8)	P-value
PVWM right	0.820	0.877	P <.050
PVWM left	0.832	0.914	P <.015
genu CC	0.809	0.927	P <.042
PLIC right	0.755	0.804	P <.035
PLIC left	0.744	0.817	P <.003
Centrum Semiovale left	0.749	0.804	P <.015
Centrum semiovale right	0.746	0.800	P <.026
BDav	0.742	0.782	P <.001