Journal of Integrative Neuroscience, Vol. 6, No. 1 (2007) 1–14

Imperial College Press
www.icpress.co.uk

NEUROPSYCOLOGICAL AND NEUROIMAGING OUTCOME OF HIV-ASSOCIATED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPHATHY IN THE ERA OF ANTIRETROVIRAL THERAPY

ROBERT H. PAUL

University of Missouri – St. Louis
Behavioral Neuroscience, St. Louis, MO 63121
paulro@umsl.edu
http://www.umsl.edu

DAVID LAIDLAW

Brown University, Department of Computer Science
Providence, RI 02906

DAVID F. TATE

Harvard Medical School, Cambridge MA, 02115

STEPHANIE LEE

Brown University, Department of Computer Science
Providence, RI 02906

KARIN HOTH

Brown Medical School, Department of Psychiatry
Providence, RI 02906

JOHN GUNSTAD

Kent State University, Department of Psychology
Kent, OH 44242

SONG ZHANG

Brown University, Department of Computer Science
Providence, RI 02906

JEFFREY LAWRENCE

Brown Medical School, Department of Psychiatry
Providence, RI 02906

TIM FLANIGAN

Brown Medical School, Center for AIDS Research
Providence, RI 02906

Received 16 October 2006
Accepted 30 November 2006

Aims: The purpose of the present case is to describe the functional outcome of a patient with human immunodeficiency virus (HIV) and progressive multifocal leukoencephalopathy (PML) on treatment with antiretroviral therapy using a multidisciplinary approach.

Methods: Neuropsychological tests and diffusion tensor imaging (DTI) were obtained at baseline and after 12 months to define the severity of white matter damage. Neuropsychological and neuroimaging data were compared to an HIV-infected patient without PML and with good immune system health, and to a second HIV-infected patient without PML but with notable immunosuppression.

Results: Review of the HIV/PML patient's cognitive data at both time points revealed significant impairments compared to the control subjects. Similarly, the HIV/PML patient's white matter lesion load and whole brain volume were markedly different from the control subjects at both time points. The tractography-defined metrics suggest significant white matter fiber loss associated with HIV/PML that was not evident in either HIV control patient.

Discussion: Our findings suggest that PML is associated with marked cognitive and neuroimaging abnormalities in the context of antiretroviral therapy.

Integrative Significance: To our knowledge this is the first study to integrate both quantitative DTI and cognitive assessment to define white matter damage associated with HIV and PML. This integrative approach provides a robust methodology to examine the integrity of brain systems mediating cognitive function.

Keywords: HIV; PML; neuropsychology; neuroimaging; diffusion tensor imaging.

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a potentially terminal illness that develops in the context of significant immunosuppression. The disease is caused by a reactivation of the JC virus, which targets and eventually destroys oligodendrocytes via lytic infection [12]. PML is characterized by aggressive deterioration of white matter pathways throughout the subcortical brain parenchyma. The white matter damage can be visualized on standard magnetic resonance imaging (MRI), particularly using acquisition sequences sensitive to white matter alterations (e.g., fluid attenuated inversion recovery; FLAIR).

PML has been a complicating factor associated with human immunodeficiency virus (HIV), however, antiretroviral treatment (ART) has significantly modified the natural course of PML. ART has improved the mortality rate from 90% to approximately 50%[1, 12]. The prevalence of PML associated with HIV has also declined significantly in the era of ART [14], yet a number of patients remain infected with the virus and the neurological and functional outcome remains unclear. Several studies have demonstrated regression of MRI abnormalities after therapy with ART [6, 7, 13] and neurological function improves in approximately 50% of patients [4]. Little is known, however, about the cognitive outcome of HIV-infected patients who are living with PML over an extended period of time.

In the present case report, we describe the cognitive and neuroimaging outcome of an HIV-infected patient with PML who had been treated with ART. The case report is novel in three respects. First, we describe 12-month longitudinal

neuropsychological outcome of a patient with PML *treated with ART*. Second, we used two different *in vivo* imaging modalities (FLAIR) and diffusion tensor imaging — DTI to quantify and visualize severity of white matter damage in this patient. Third, we compared the cognitive performances and severity of white matter damage in this patient to two demographically-matched HIV-infected patients without PML who differed in terms of the degree of immunesuppression.

2. Methods

2.1. *Participants*

HIV/PML Patient: The patient is a 42 year-old male who was enrolled in a study of cognitive dysfunction and neuroimaging abnormalities associated with HIV. He was also co-enrolled in a study of CSF abnormalities associated with PML at a separate academic institution [8]. At the time of involvement in the cognitive study, the patient's CD4 cell count was 120 cells/mm^3, and his plasma viral load was 6,000 copies per ml. A nadir CD4 count of 63 was recorded in 2001. JC viral infection was initially defined by neuroradiographic and clinical evaluation. However, he was subsequently enrolled in study of PML at a regional academic center, and was found to exhibit JC-specific cytotoxic T lymphocytes in peripheral blood mononuclear cells. There was no history of opportunistic infections other than the JC virus. The patient had become infected with HIV via sexual contact, and he denied a history of intravenous drug abuse. The patient did have a history of marijuana use, however, his use did not meet DSM–IV criteria [2] for abuse. Similarly, he did not meet DSM-IV criteria for current affective disorder, though he was receiving treatment with an antidepressant. The patient had been diagnosed with HIV in 1984 and diagnosed with PML in 1999 at which time he presented with gait imbalance and multiple falls, as well as multiple white matter lesions on MRI. Medical records reveal that his neurological symptoms improved briefly but deteriorated again by 2002. A neurological exam at that time revealed that he was alert, oriented, with good psychomotor speed, memory, and speech, but "marked" impairment in attention and constructive apraxia, as well as multiple errors on a test of antisaccadic eye movements. At the time of his enrollment in the current study (2002), his treatment regimen included Efavirenz, Lamivudine, Stavudine Cotrimoxazole, Fluconazole, Alprazolam and Fluoxetine. He completed 12 years of high school and was employed at the time of participation, working as a local community advocate on a part-time basis.

HIV-positive comparison patients: The immunologically healthy individual was a 49 year-old male enrolled in the same parent study described above. At study enrollment, his CD4 lymphocyte count was 864 cells/mm^3 and his plasma viral load was 23 copies per ml. His nadir CD4 count of 272 was recorded in 2002. He had no history of opportunistic infections. He had been diagnosed with HIV for approximately 24 months and his current treatment regimen included Efavirenz,

Lamivudine and Zidovudine. Psychosocial and psychiatric histories were unremarkable. He completed 12 years of education and was employed as a cook at the time of study participation.

The immunecompromised patient included a 51 year-old male. At study enrollment, his CD4 lymphocyte count was 225 cells/mm^3 and his plasma viral load was <75 copies per ml. His nadir CD4 count of 36 was recorded in 1997, at which time he presented with an oral leukoplakia and thrush, but no CNS opportunistic infection. The patient was positive for hepatitis C. He had been diagnosed with HIV and hepatitis C since 1997. His current treatment regimen was Cotrimoxazole, Norvir, Lamivudine, Zidovudine, and Saquinavir. His psychosocial and psychiatric histories were unremarkable. He completed 13 years of education and was unemployed at the time of participation.

A reference group of 25 seronegative healthy male subjects from the Brain Resource International Brain Database (BRID; [10]) was also included to compare neuropsychological performances. The healthy control sample reported no history of learning disability, head injury, or any medical/psychiatric history that could confound cognitive function. The healthy sample had been recruited from the community, and averaged 44.8 (3.6) years of age, and 12.9 (1.7) years of education.

2.2. *Cognitive assessment*

All three patients completed the BRID computerized battery of cognitive measures. The computerized battery is both reliable [20] and valid [15]. The computerized battery was administered on a touch-screen (NEC MultiSync LCD 1530V).The cognitive tests were administered using standardized task instructions presented via headphones and visual screen display. All responses to the tests were recorded via the touch-screen or recorded as .wav files. Each cognitive test was preceded by a practice trial and participants were required to successfully complete the practice trial prior to the test trial for each measure. In the event that an individual failed a practice trial, the computerized battery immediately moved on to the next test in the battery. The battery included tests examining motor tapping, sustained attention, psychomotor speed, cognitive flexibility, and response inhibition. The HIV/PML patient repeated the computerized tests after one year, using an alternate version of each measure except the motor tapping task. These domains are known to be sensitive to cognitive impairments associated with HIV and white matter damage [16].

2.3. *Neuroimaging*

Neuroimaging was acquired using a Siemens 1.5 Tesla Symphony scanner. The imaging sequence consisted of a sagittal MPRAGE T1, an axial FLAIR, and a sagittal diffusion imaging sequence. The results of the MPRAGE T1 sequence were visually inspected for any neurological abnormalities including lesions and/or tumors that might significantly alter cognitive and imaging findings. The FLAIR sequence

was a clinical sequence with the following parameters: TE = 105, TR = 6000, 192×256 matrix, 5 mm thick slices, 2 mm gap, one excitation. The commercial program ANALYZE was used to quantify the hyperintensities in the FLAIR images for all three patients separately in three anatomical regions; 1) hyperintensities in the centrum semiovale (CSH), 2) hyperintensities in the periventricular region (PVH, those confluent with the lateral ventricles), and 3) hyperintensities in the area of the subcortical nuclei (SCH, those adjacent to or in the area of the caudate, lentiform, or thalami nuclei). Using a trained rater and a thresholding technique, the hyperintense regions from surrounding parenchyma for each patient were identified. The number of pixels were counted for each slice and summed separately for each of the anatomical regions. Whole brain volume was also calculated by summing the segmented pixels classified as brain tissue across all slices.

2.3.1. *Diffusion tensor imaging*

For diffusion tensor imaging, we used the Siemens MDDW protocol with no partial echos to image the entire brain. These co-registered sagittal double spin-echo, echo planar diffusion-weighted images were collected using the following parameters: TR = 7200; TE = 156; three acquisitions with offset in slice direction by 0.0 mm, 1.7 mm, and 3.4 mm; 5 mm thick slices; 0.1 mm inter-slice spacing, 30 slices per acquisition; 128×128 matrix; 21.7 cm FOV. Diffusion gradients were applied in 12 non-colinear directions with two b magnitudes (0 and 1000 $\mathrm{mm/s^2}$, NEX = 3). The three acquisitions were interleaved to provide isotropic 1.7 mm sampling.

2.3.2. *ROI analysis*

A region of interest (ROI) method using ANALYZE 6.0® was employed to examine DTI scalar metrics within defined neuroanatomical regions. Fractional anisotropy (FA) maps were reoriented along the ACPC axis then registered with the T1 MPRAGE sequence for accurate placement of ROIs. ROIs were sampled in three adjacent axial slices where the caudate was widest. Small 3 mm by 3 mm wide ROIs were placed in genu and splenium of the corpus callosum, right and left frontal forceps minor, right and left anterior limb of the internal capsule, right and left posterior limb of the internal capsule, and the right and left genu of the internal capsule (see Fig. 1). FA for each of the ROIs was back-calculated using the scan parameters.

2.3.3. *Tractographic analysis*

Integral paths along the direction of fastest diffusion were calculated through the DTI data starting at randomly selected points near each point in a grid with 1.7 mm spacing in all three coordinate directions. Paths were integrated in both directions as long as linear anisotropy was greater than 0.1 [20]. Short paths and those similar to paths already generated were culled, typically leaving several thousand paths [18].

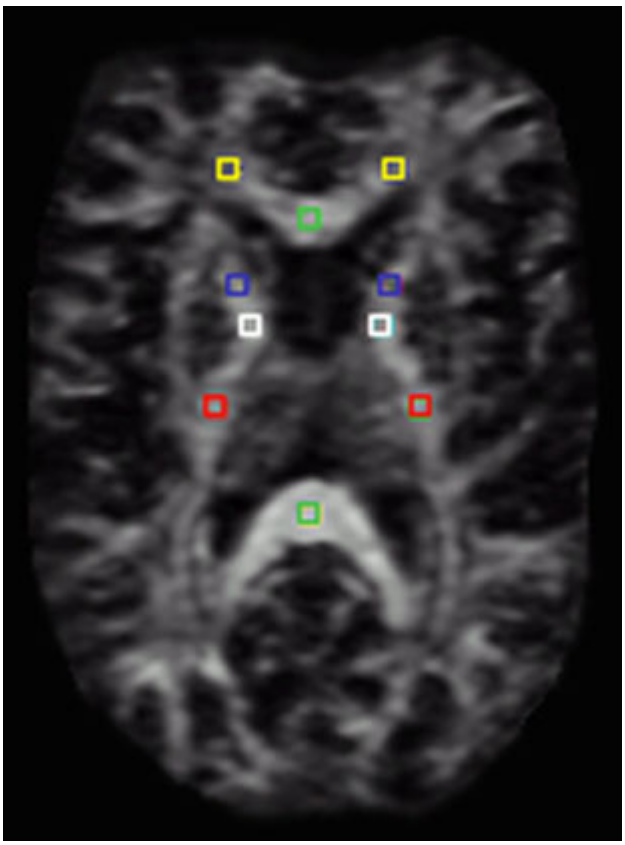

Fig. 1. Region of interest placement to quantify diffusion tensor data.

All resulting paths as well as paths with an average linear anisotropy greater than 0.25 were visualized on a 3D display together with a visual representation of the lateral ventricles. Tracts of interest (TOI) were interactively selected using a method similar to the volume of interest (VOI) approach of Sherbondy and colleagues [17]. The entire brain was treated as one such tract; a second TOI was defined as those paths that crossed the midplane. For each TOI, the following metrics were calculated: number of paths, total length of paths, and total length of paths weighted by linear anisotropy. The same three metrics were calculated including only those paths for which the average linear anisotropy was greater than 0.25.

3. Results

3.1. *Neuropsychological comparisons*

Review of the baseline cognitive data revealed that all three HIV-infected patients earned mean scores more than 1.5 standard deviations below average on multiple tests compared to the healthy control sample, suggesting a significant effect of HIV status on cognitive function (Table 1). Compared to the healthy control sample,

Table 1. Cognitive performances for the healthy controls, the HIV/PML patient and the HIV patients.

		HIV		HIV		HIV/PML			
	Healthy Controls	CD4 = 864 cells/mm^3 (good immune health)		CD4 = 225 cells/mm^3 (poor immune health)					
	Baseline	Baseline		Baseline		Baseline		1 Year	
Cognitive Measure	Mean (SD)	Raw (T-score)	Range	Raw (T-score)	Range	Raw (T-score)	Range	Raw (T-score)	Range
Motor tapping (total)									
# Dominant hand	181 (15.8)	71 (<1)	Sev. Impaired	164 (<1)	Sev. Impaired	94 (<1)	Sev. Impaired	125 (<1)	Sev. Impaired
Sustained attention									
# False alarms	.62 (1.4)	0 (54)	Average	1 (47)	Average	19 (<1)	Sev. Impaired	19 (<1)	Sev. Impaired
# Omissions	1.5 (2.5)	2 (48)	Average	4 (40)	Low Average	6 (32)	Mild Impaired	6 (32)	Mild Impaired
Psychomotor speed									
Completion time (s)	13.7 (4.0)	24 (24)	Mod. Impaired	17.2 (41)	Low Average	31 (7)	Sev. Impaired	43 (<1)	Sev. Impaired
Cognitive flexibility									
Completion time (s)	29.5 (8.6)	56 (19)	Sev. Impaired	44.5 (33)	Borderline	>60 (<10)	Sev. Impaired	>60 (<10)	Sev. Impaired
Connection time (s)		2.1				3.6		3.1	
Reading speed									
Total # correct	17.2 (2.2)	16 (45)	Low Average	13 (31)	Borderline	10 (17)	Sev. Impaired	10 (17)	Sev. Impaired
Executive Function									
# Maze errors	37.3 (20.2)	50 (44)	Low. Average	83 (27)	Mild Impaired	154 (<1)	Sev. Impaired	187 (<1)	Sev. Impaired
# Overruns	2.3 (0.7)	23 (<1)	Sev. Impaired	40 (<1)	Sev. Impaired	90 (<1)	Sev. Impaired	140 (<1)	Sev. Impaired

the HIV/PML patient performed in the severely impaired range on all cognitive measures. The observation that the HIV/PML patient performed markedly worse than the age- and education-matched HIV patients suggests that poor cognitive performances evident by the HIV/PML patient were not due to HIV alone. The follow-up assessment of the PML patient, completed 12 months later, revealed consistent deficits across cognitive domains, with evidence of poorer function on measures of executive function and psychomotor speed, yet improved performance on measures of sustained attention and motor tapping.

3.2. *Structural neuroimaging*

Structural imaging data also revealed notable differences between the three HIV patients at the baseline assessment (Table 2). The HIV/PML patient exhibited a lower brain volume compared to the two HIV patients, and the HIV/PML patient exhibited notably greater lesion load in the white matter compared to the HIV patients on the FLAIR sequence; note we did not identify any clear evidence of white matter abnormalities in the HIV patient with good immunological health. A repeat FLAIR conducted approximately 12 months later demonstrated notably increased white matter involvement for the HIV/PML patient.

3.3. *Diffusion tensor imaging*

ROI Analysis of the DTI data revealed decreased FA values for the HIV/PML patient in the forceps minor, anterior limb of the internal capsule, and the splenium of the corpus callosum compared to the other two HIV patients (Table 3). There was no noticeable change in the genu of the corpus callosum, genu of the internal capsule, or the posterior limb of the internal capsule. Examination of the novel DTI metrics revealed a dose-dependent relationship across the three subjects on each of the dependent variables (Table 4; Fig. 2). Specifically, the HIV patient with good

Table 2. Neuroimaging comparisons between the HIV patients and the HIV/PML patient.

	HIV CD4 = 864 cells/mm^3 (good immune health)	HIV CD4 = 225 cells/mm^3 (poor immune health)	HIV/PML	
MRI Measure	Baseline	Baseline	Baseline	1 Year
SH lesion load				
Centrum semiovale	0	0	1.12*	1.05
Periventricular hyperintensities	0	0	0.24	0.49
Subcortical hyperintensities	0	0	0.02	0.03
WBV	963.63 cm^3	950.20 cm^3	841.74 cm^3	899.86 cm^3

*Ratio to WBV. SH = subcortical hyperintensities, WBV = whole brain volume

Table 3. Fractional anistropy values for each ROI.

	Forceps Minor		Gene of the Internal Capsule		Posterior Limb of the Internal Capsule		Anterior Limb of Internal Capsule		Corpus Callosum	
	Left	Right	Left	Right	Left	Right	Left	Right	Splenium	Genu
HIV/PML	0.22	0.43	0.36	0.42	0.71	0.70	0.67	0.69	0.20	0.88
HIV healthy	0.52	0.48	0.72	0.72	0.66	0.64	0.73	0.78	0.83	0.91
HIV immune compromised	0.62	0.45	0.54	0.63	0.68	0.70	0.75	0.67	0.76	0.80

Table 4. Streamtube-based metrics.

	Unthresholded			Thesholded (minimum linear anisotropy = 0.25)		
	Number of Paths	Total Length (mm)	Weighted Length (mm)	Number of Paths	Total Length (mm)	Weighted Length (mm)
HIV good immune health	5290	118606	28804	1011	46553	14808
HIV poor immune health	5304	116619	27432	844	37523	11968
HIV/PML	4250	84837	19687	804	29679	9090

immune health exhibited more streamtube paths, greater fiber length and greater weighted fiber length compared to the other two patients. Similarly, the HIV patient with poor immune health had superior results on these same indices compared to the HIV/PML patient. These results suggest that HIV/PML was characterized by the greatest DTI abnormalities on both standard metrics (FA) and the novel metrics presented in the current study.

4. Discussion

This is the first report of neuropsychological, structural neuroimaging, and DTI in a patient with HIV and PML treated with ART. We observed significant global cognitive impairment on neuropsychological tests in the patient infected with both HIV and JC virus and the severity was far greater than that observed in control patients infected with HIV but not PML, regardless of the degree of immunosuppression. Consistent with the pathophysiology of PML, the co infected individual exhibited significant white matter abnormalities on FLAIR imaging. However, the extent of white matter damage was best appreciated using DTI, which revealed abnormalities in multiple white matter regions that could not be identified readily using the FLAIR sequence.

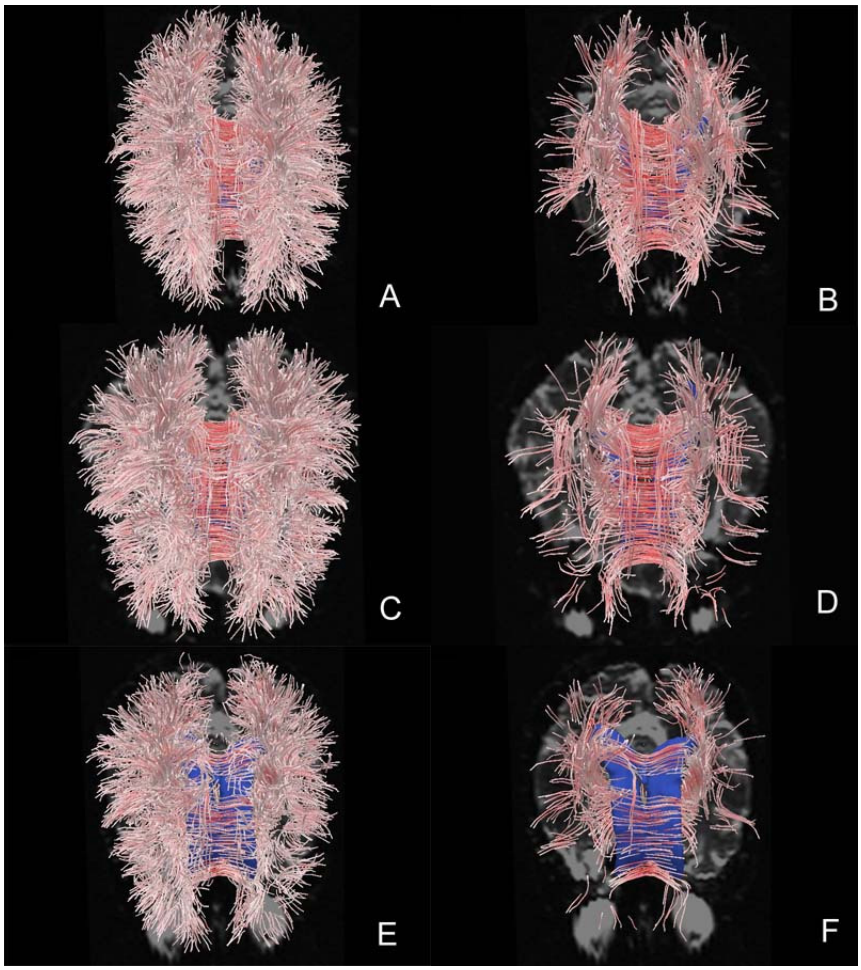

Fig. 2. Axial views of unthresholded and thresholded streamtube models for the immunologically healthy HIV patient (A and B, respectively), the immunecompromised patient (C and D), and the HIV patient with PML (E and F).

Historically, activation of the JC virus in the context of HIV offered little therapeutic hope with mortality rates near 100%. ART has significantly increased life expectancy associated with this condition [3], but the neurological outcome among survivors has not been well defined. Previous case control studies have demonstrated improvement in cognitive function and regression of white matter abnormalities visualized on structural MRI among HIV/PML patients treated with ART [6, 7, 14]. We did not have access to remote clinical and neuroimaging data to examine changes across more than two time points following treatment in the patient, and this is a limitation of our study as we cannot fully describe the development and progression of his symptoms from disease onset. However, our data demonstrate that in the context of ART, individuals with HIV/PML are likely to experience very significant residual cognitive symptoms and evidence of white matter damage on MRI. These

findings are very similar to Gasnault *et al.* who reported increased survival following HIV treatment (particularly with protease inhibitors) but no effective neurologic improvement [9].

The degree of cognitive impairment exhibited by the HIV/PML patient compared to healthy controls and the HIV control subjects was quite severe, and the nature of the deficits remained consistent over the course of the year. The severity of his cognitive difficulties likely impacts his ability to independently complete activities of daily living. We did not have information on memory function to document a diagnosis of dementia. However, the observation that executive deficits are more significant predictors of activities of daily living than memory deficits [5], argues that this patient's cognitive deficits were of significant clinical importance. It is of note that this individual became lost on multiple occasions driving to our site for the assessments, and this may represent evidence of functional impairment.

The neurophysiology of cellular dysfunction associated with the JC virus is characterized by apoptosis of oligodendrocytes. Richardson-Burns and colleagues [17] have shown that neuronal cells and oligodendrocytes distant from regions of JC viral presence at autopsy are not apoptotic, suggesting that the impact of the virus on brain tissue is focal. We obviously do not have pathology data to confirm the anatomical location of his virus within the brain. Given the sensitivity of DTI of microstructural brain changes, future studies attempting to correlate antemortem and postmortem findings would benefit from the application of DTI data. Use of the weighted streamtube length metric described in the current study may help to define whether neuronal diaschesis occurs among patients with active PML.

The novel DTI scalar metrics (number of paths, length of paths and weighted length of paths) included in the current study revealed robust differences in white matter integrity across the three HIV patients. These differences were evident in a dose-dependent manner with the most severe white matter damage observed in the HIV/PML patient, followed by the immunologically impaired patient and finally the immunologically healthy patient. This pattern provides some support for the validity of these novel metrics, however, additional studies will be needed to more definitively determine the relative value of these metrics compared to standard DTI variables such as regional FA and MD. These studies are currently underway by members of our group (DL) using various patient groups as model systems.

In summary, PML associated with HIV has become less common in the era of ART, and treatment with retroviral medications has been shown to improve clinical indicators in previous case reports. Our results are based on a single case of PML and therefore caution must be exercised in interpreting too much from the data. Nevertheless, the findings indicate that for some patients with HIV and PML, severe cognitive difficulties and neuroimaging abnormalities may remain despite treatment with ART. Evidence that AIDS-related PML may arise from immune reconstitution inflammatory syndrome in the current era of HAART [11] emphasizes the need to further understand the functional impact of this condition. Further, as patients experience increased life expectancy it will be important to direct clinical care on

the impact of residual cognitive deficits on quality of life and ability to complete basic activities of daily living (driving, medication adherence, etc.).

4.1. *Integrative significance*

To our knowledge, this is the first study to integrate quantitative DTI, structural imaging and cognitive assessment to define white matter damage associated with HIV and PML. This integrative approach provides a robust methodology to examine the integrity of brain systems that mediate cognitive function, and this is particularly true regarding PML, HIV, and other diseases affecting the white matter (e.g., subcortical ischemic disease, multiple sclerosis). The white matter accounts for substantial volume of overall brain parenchyma yet our understanding of the impact of microstructural and macrostructural damage to the large and distributed neural networks within the white matter remains incomplete. Integration of cognitive, structural imaging and quantified tractography will likely enhance our understanding of these important brain systems beyond what is possible by any one of these methodologies applied in isolation.

Acknowledgments

We acknowledge the support of the Brain Resource International Database (under the auspices of The Brain Resource Company — www.brainresource.com) for use of the normative data. We also thank the individuals who gave their time to take part in the study. All scientific decisions are made independent of any BRC commercial decisions via the independently operated scientific division, BRAINnet (www.brainnet.org.au), which is overseen by the independently funded Brain Dynamics Center and scientist members.

References

[1] Albrecht H, Hoffman C, Degen O, Stoehr A, Plettenberg A, Mertenskotter T, Eggers C, Stellbrink HJ, Highly active antiretroviral therapy significantly improves the prognosis of patients with HIV-associated progressive multifocal leukoencephalopathy, *AIDS* **12**(10):1149–1154, 1998.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. American Psychiatric Press Inc, Washington DC, 1994.

[3] Antinori A, Cingolani A, Lorenzini P, Giancola ML, Uccella I, Bossolasco S, Grisetti S, Moretti F, Vigo B, Bongiovanni M, Del Grosso B, Arcidiacono MI, Fibbia GC, Mena M, Finazzi MG, Guaraldi G, Ammassari A, d'Arminio Monforte A, Cinque P, De Luca A; Italian Registry Investigative Neuro AIDS Study Group. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: Data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol* **9**:47–53, 2003.

[4] Berenguer J, Miralles P, Arrizabalaga J, Ribera E, Dronda F, Baraia-Etxaburu J, Domingo P, Marquez M, Rodriguez-Arrondo FJ, Laguna F, Rubio R, Lacruz Rodrigo

J, Mallolas J, de Miguel V; GESIDA 11/99 Study Group, Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy, *Clin Infect Dis* **36**(8):1047–1052, 2003.

[5] Boyle P, Paul R, Moser D, Cohen R, Executive impairments predict functional declines in vascular dementia, *Clin Neuropsychol* **18**(1):75–82, 2004.

[6] Cardenas RL, Cheng KH, Sack K, The effects of cidofovir on progressive multifocal leukoencephalopathy: an MRI case study, *Neuroradiology* **43**(5):379–382, 2001.

[7] Cinque P, Koralnik IJ, Clifford DB. The evolving face of human immunodeficiency virus-related progressive multifocal leukoencephalopathy: defining a consensus terminology, *J Neurovirol* **9** (suppl 1):S88–S92, 2003.

[8] Du Pasquier RA, Autissier P, Zheng Y, Jean-Jaques J, Koralnik IJ, Presence of JC virus-specific CTL in the cerebrospinal fluid in PML patients; rationale for immune-based therapeutic strategies, *AIDS* **19**:2069–2075, 2005.

[9] Gasnault J, Taofik Y, Goujard C, Kousignian P, Abbed P, Boue F, Dussaix E, Delfraissy JF, Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on potent combined antiretroviral therapy, *J Neurovirol* **5**:421–429, 1999.

[10] Gordon E, Integrative neuroscience, *Neuropsychopharmacol* **28**:52–58, 2003.

[11] Gray F, Bazille C, Adle-Biassette H, Mikol J, Moulignier A, Scaravelli F, Central Nervous system immune reconstitution disease in acquired immunodeficiency syndrome patients receiving highly active antiretroviral therapy, *J Neurovirol* **11** S3:16–22, 2005.

[12] Koralnik I, Overview of the cellular immunity against JC virus in progressive multifocal leukoencephalopathy, *J Neurovirol* **8**:S59–S65, 2002. Leukoencephalopathy with highly active antiretroviral therapy, *AIDS* **12**(18):2467–2472, 1998.

[13] Miralles P, Berenguer J, Garcia de Viedma D, Padilla B, Cosin J, Lopez-Bernaldo de Quiros JC, Munoz L, Moreno S, Bouza E, Treatment of AIDS-associated progresive multifocal.

[14] Neuenburg J, Brodt H, Herndier B, Bickel M, Bacchetti P, Price RW, Grant RM, Schlote W, HIV-related neuropathology, 1985–1999: Rising prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy, *J Acquir Immune Defic Syndr* **31**(2):171–177, 2002.

[15] Paul R, Lawrence J, Williams L, Richard CC, Cooper N, Gordon E, Preliminary validity of IntegNeuro: A new computerized battery of neurocognitive tests, *Int J Neurosci* **115**(11):1549–1567, 2005.

[16] Paul R, Cohen R, Stern R, Neurocognitive manifestations of human immunodeficiency virus. *CNS Spectr* **7**(12): 860–866, 2002.

[17] Richardson-Burns S, Kleinschmidt-DeMasters, B, DeBiasi R, Tyler K, Progressive multifocal leukoencephalopathy and apoptosis of infected oligodendrocytes in the central nervous system of patients with and without AIDS, *Arch Neurol* **59**:1930–1936, 2002.

[18] Sherbondy A, Akers D, Mackenzie R, Doughtery R, Wandell B. Exploring connectivity of the brain's white matter with dynamic queries, *Proc IEEE Visualization*: **11**(4):419–30, 2005.

[19] Westin C, Peled S, Gubjartsson H, *et al.*, Geometrical diffusion measures for MRI from tensor basis analysis, *Proceedings of the International Society for Magnetic Resonance in Medicine*, 1997.

[20] Williams L, Simms E, Clark C, Paul R, Rowe D, Gordon E, The reproducibility of a standardized and integrated neurophysiological and neuropsychological test battery, *Int J Neurosci* **115**(12):1605–1630, 2005.

[21] Zhang S, Laidlaw D, Demiralp C, Visualizing diffusion tensor MR images using streamtubes and streamsurfaces, *IEEE Trans on Vis and Comp Graphics* **9**:454–462, 2003.