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Brain Structural and Functional Recovery Following Initiation of Combination Anti-Retroviral Therapy

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Abstract

NeuroAIDS persists in the era of cART. We describe here recovery of brain structure and function following after 6 months of therapy in a treatment-naïve patient presenting with HIV-Associated Dementia. The patient's neuropsychological test performance improved, and his total brain volume increased by more than 5%. Neuronal functional connectivity measured by magnetoencephalography changed from a pattern identical to that observed in other HIV-infected individuals, to one that was indistinguishable from that of uninfected control subjects. These data suggest that at least some of the effects of HIV on the brain can be fully reversed with treatment.

Keywords

HIV Disease; NeuroAIDS; Magnetoencephalography; Functional Connectivity

Introduction

In spite of changes in the treated history of HIV disease following the introduction of combination therapies (cART), there have been few detailed descriptions of the recovery of brain structure and function that occur following treatment initiation. We describe here a 54 year old man who first presented for treatment with HIV Associated Dementia (HAD), neuropathy and myelopathy who had significant recovery documented with neurobehavioral exams, brain structural data from magnetic resonance imaging (MRI), and functional connectivity of neuronal networks using magnetoencephalography (MEG).

Methods

Case Summary

PG is a 54-year-old, high-school educated, right-handed, African American man who was admitted to a local hospital and diagnosed with *Pneumocystis jirovecii* pneumonia and found to be HIV-infected. His family learned that he was unable to live independently, that he had been fired from his job and that he had been evicted from his apartment due to memory loss, confusion and the inability to care for himself. PG moved to live with his extended family and to establish care with an HIV specialty clinic (March 2010). At that time they reported that he was confused, having problems with both short- and long-term memory and was unsteady on his feet resulting in several falls. He had lost 40 pounds over 5 months.

His CD4+ count in March 2010 was 12 cells/mm³ (1%) with an HIV-1 RNA level of 638,000 copies/ml (log₁₀ 5.80); therapy was started using the daily fixed-dose combination of efavirenz-emtricitabine-tenofovir. He returned to clinic one month later at which time both he and his family reported that he was functioning more independently; His CD4+ count was 236 cells/mm³ (8%) and the HIV-1 RNA level was 7,510 copies/ml (log₁₀ 3.88). In May 2010, his viral load was 412 (log₁₀ 2.61), he was more independent, and he was intermittently using a cane to ambulate.

A clinical neuropsychological assessment was completed in May 2010 that revealed evidence of HAD, including moderate to severe deficits in cognitive functions. He was approached by his treating physician about his willingness to participate in a study of the utility of MEG as a biomarker in HIV disease. He consented to enroll, and his data were compared with that of 9 HIV-infected individuals and 7 uninfected control subjects. With the exception of the Executive Domain Rating score from the neuropsychology test battery, there were significant differences between the two comparison groups (HIV+ vs. HIV-), so the data from all 16 participants were combined. The mean age (50.2 ± 5.0) and education level (14.7 ± 1.9) compared well with PG.

Procedures

A neuropsychological examination was completed in May 2010, and again 6 months later, and included measures from multiple cognitive domains including Memory, Language, Visual-Construction, Psychomotor Speed, Motor and Executive functions. PG underwent a semi-structured diagnostic interview, and completed questionnaires concerning psychiatric symptomatology (See, Becker, et al. ¹ for details).

MRI Study—PG had an MRI exam of the brain on a Siemens 3T TIM Trio using the protocol that was modified from that of the Alzheimer's Disease Neuroimaging Initiative ². The parameters of the sagittal Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence were: FOV = 256 mm; slices = 160; TR = 2300ms; TE = 2.91 ms; TI = 900ms; Flip angle = 9 degrees; slice thickness = 1.2 mm. The MRI data were processed using SIENA, a fully automated method to measure the change between two MR images taken at different time points. The output from SIENA is the mean perpendicular edge motion across the entire brain surface converted into a percentage brain volume change estimate.

Magnetoencephalography—*Elekta Neuromag® Vectorview* (Elekta Oy, Helsinki, Finland) uses 306 MEG channels for registering the neuromagnetic signatures of the intracranial neural currents. The MEG acquisition included 5 minutes of “eyes open” and 5 minutes of “eyes closed” resting state; for this report we analyzed only the eyes closed data

as there were fewer artifacts (e.g., eye blinks) compared to eyes-open. The MEG procedures and data preprocessing are detailed elsewhere ¹.

The MEG data were filtered on-line to 0.1–330 Hz and sampled at 1 kHz. For analysis, we filtered the data to 0.1–60 Hz and calculated the Mutual Information (MI) ³ between the 102 sensor units (magnetometers and gradiometers) which gave us a symmetric and weighted correlation matrix of 102×102 elements for each analysis. We computed a “MI score” by taking the mean MI between the two groups of sensors where we have previously found significant statistical differences in the gradiometers (See Figure 1b) ⁴.

Results

The change in PG's test scores over the six-month interval was compared with the change observed in the comparison group (See Table 1). Significant improvements were observed on tasks of cognitive and motor speed; there were no significant changes in his performance on measures of either learning or memory.

The neuropsychological test data were reduced to Domain and Global ratings of performance based on standardized and normative procedures ⁵. The scores have a range from 1 (Superior) to 9 (Severely Impaired); 1–3 is considered Normal, 4 is considered Borderline, and scores of 5 and greater are considered abnormal. With the exception of the Memory and Learning ratings, his test performance improved from Impaired to Borderline and Normal after 6 months of cART (See Table 1).

The mean change in whole brain volume in the comparison group was –0.29% (SD = 0.97). The percent change in brain volume in PG was 5.87% (i.e., an increase in volume), which is significantly greater than that expected based on the comparison group ($Z = 6.36$) (See Figure 1a). There is evidence of both expansion of gray matter (indicated in yellow and red in Fig. 1), reduction of ventricular volume, and widening of the gyri.

Figure 1b presents the results of the analysis of the MEG data. The left hand graphs shows the functional connectivity “map” between the MEG sensors; the right hand graphic shows the MI score for each subject – PG and the comparisons group. The MI score for PG is shown as two points connected by a line. As can be seen from this figure, his MI score at baseline was near the mean for the infected participants, while at the end of six months, his score had changed to a value close to the mean of the uninfected individuals.

Discussion

In spite of the declining incidence of HAD ⁶, cognitive dysfunction persists even with the use of cART ⁷. Severe immunosuppression is not a requirement for HAD ⁸, Undetectable CSF HIV does not prevent the progression of disease ⁹, and even with effective viral suppression there is a high rate of the milder forms of HAND ¹⁰. These studies report group-level data; ours is one of the few reports of recovery of function among an individual diagnosed with HAD who had detailed cognitive testing, MR imaging, as well as an analysis of neuronal functional connectivity using MEG.

PG had virtual elimination of viral replication in the periphery (<50 copies at second visit), as well as a significant improvement in his CD4+ cell counts. His performance on the neuropsychological tests improved, and his overall brain volume increased more than 5% with gyral widening and reduction in the size of the lateral ventricles. What was most striking, however, was the “normalization” of his neuromagnetic signature. The MI score derived from the functional connectivity analysis of the MEG data reflects the extent to which the neuronal populations near the sensor nodes were functionally connected, and

differentiated infected from uninfected individuals. Over the course of treatment, his MI score changed from one that was virtually identical to that of other infected subjects, to one that was indistinguishable from the uninfected controls, suggesting that CNS function was returning to normal.

With one exception, the HIV-infected individuals included in the comparison group had been infected for at least 10 years, had endured periods of uncontrolled viral replication, and had survived long enough to enjoy the benefits of cART. We speculate that the long-term uncontrolled or poorly controlled viral replication in the brain may have resulted in a permanent alteration in the functional networks, which is reflected in the MEG signature. PG's data suggests the possibility that all of the HIV-infected individuals in the comparison group at one time had the *potential* to have their functional connectivity return to normal, if effective therapy had been available to them.

In summary, we report the changes in CNS structure and function that occurred in a patient whose initial presentation and AIDS-defining illnesses included HAD following effective viral suppression. The recovery included a normalization of a functional brain network identified with MEG imaging, suggesting that MEG may be a useful tool in monitoring response to HIV therapeutics ¹¹.

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1.

(A) The results of the SIENA analysis (upper panel); the images show the changes in brain surface over the course of six months (top row – sagittal plane; bottom row – coronal row). Expansion of the brain (indicated in yellow and red) indicates a narrowing of the sulci (i.e., widening of the gyri) as well as shrinkage of the ventricles. (B) The results of the analysis of the MEG data are shown in the lower panel. On the left is a graph of the functional network that maximally differentiated HIV-infected from uninfected individuals. On the right is a graph of the MI score for each individual subject. The green circles indicate uninfected participants in the comparison group, and the red circles indicate HIV-infected participants. The MI score for PG is shown as two points connected by a line.

Table 1

Change in Neuropsychological Test Performance in PG

	Comparison Group ¹		Patient PG ²		Statistics ³	
	Baseline	Follow-Up	Baseline	Follow-Up	Z-Score	p
Domain/Measure						
Fluency						
Letters	54.4 (8.4)	54.1 (8.9)	36	54	2.29	.02
Animals	57.5 (9.4)	57.1 (8.9)	43	58	1.90	.04
<i>Domain Score</i>	2 (1-4) ⁴	2 (1-4) ⁴	5	2		
Executive						
Trail Making B	67.3 (11.2)	64.4 (13.4)	31	43	1.29	.07
<i>Domain Score</i>	2 (1-4)	1 (1-5)	6	4		
Speed of Processing						
Digit-Symbol Substitution	53.5 (9.3)	54.2 (9.0)	31	39	-0.25	.12
Trail Making A	73.2 (11.4)	70.1 (11.7)	21	42	1.46	.02
<i>Domain Score</i>	1 (1-3)	2 (1-4)	8	4		
Spatial Skills						
Block Design	59.8 (9.2)	61.6 (12.7)	25	33	2.67	.03
<i>Domain Score</i>	1 (1-5)	1 (1-3)	7	6		
Learning						
HVLT-TR	49.3 (12.8)	51.3 (8.8)	20	32	0.85	.46
<i>Domain Score</i>	2 (1-9)	2 (1-7)	8	6		
Memory						
HVLT-Delay	46.5 (13.3)	51.6 (8.5)	20	23	-0.22	.07
<i>Domain Score</i>	2 (1-9)	2 (1-7)	8	8		
Motor						
Grooved Pegboard	56.2 (8.7)	54.6 (8.0)	29	46	2.61	.02
<i>Domain Score</i>	1 (1-5)	2 (1-2)	7	2		
<i>Global Impairment Rating</i>	4 (1-9)	4 (1-7)	9	8		

- ¹ Means and standard deviations of age, education, sex and race adjusted T-scores ¹²
- ² Individual t-scores for each performance measure
- ³ Z-scores and p-values of difference between predicted change (from comparison group) and that of PG ¹³
- ⁴ Median and range of Domain Scores; n.b., higher scores (i.e., 5-9) indicate impaired performance