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Impact of Cerebrovascular Risk Factors and APOE ε4 On Brain Microstructure and Cognition in HIV in the HAART Era

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ABSTRACT

Background: As HIV-infected individuals age, cerebrovascular risk factors and the Apolipoprotein epsilon 4 allele (APOE ε4) may have a greater impact on cognition. Here we characterize the impact of cerebrovascular risk factors and APOE ε4 on brain microstructure, assessed using diffusion tensor imaging (DTI), and cognition in HIV-infected individuals.

Methods: A convenience sample was obtained from a cohort of HIV-infected subjects ≥ 50 years of age recruited to study the effect of ApoE4 on cortical metabolism. Evaluations included demographic/medical history, HIV viral load, CD4+ count, fasting lipid profile, and 2-hour oral glucose tolerance test. A comprehensive neuropsychological battery was performed.

Diffusion-weighted scans were acquired on a Philips 3.0T Achieva scanner. A single-shot echo planar imaging sequence and T2-weighted b0 image was obtained. Tensors were calculated to obtain fractional anisotropy (FA) and mean diffusivity (MD) maps.

Linear regression was used to determine the relationship between z-scores on neuropsychological testing and cerebrovascular risk factors/APOE ε4. For FA and MD maps, statistical comparisons were made between groups with multiple comparison correction for the voxelwise tests using the False Discovery Rate.

Results: Twenty-two subjects were included. Mean age was 58 years (range 50-73). Most (95%) were on HAART. All had CD4+ counts > 200 cells/μL and most (82%) had undetectable viral loads. 60% had impaired glucose tolerance/diabetes; 50% hypertension; 50% elevated LDL; 32% metabolic syndrome; 45% used tobacco; 40% had at least one ApoE4 allele.

On DTI, subjects with impaired glucose tolerance had significant decreases in FA and increases in MD in the caudate. Those with metabolic syndrome had significant increases in MD in the caudate. Elevated blood pressure or hypertension was associated with significant decreases in FA in the hippocampus and increased MD in the thalamus.

Age, impaired glucose tolerance, metabolic syndrome, tobacco use, and the presence of at least one ApoE4 allele were significantly associated with a composite measure of global cognitive function (NPZ-8). The presence of impaired glucose tolerance had a protective effect on NPZ-8, while the other factors had a negative association.

Conclusion: Microstructural changes in the caudate can be detected in older HIV-infected individuals on HAART with impaired glucose tolerance. Further studies are warranted if these changes are additive or synergistic in HIV-infected individuals.

BACKGROUND

- Morbidity from HIV-associated neurocognitive disorders (HAND) continues to be a medical concern despite effective HAART.
- HIV infection *per se* and HAART has been associated with insulin resistance which some believe is the underlying etiology in the pathogenesis of the metabolic syndrome.
- APOE ε4 is associated with about a 3-fold risk of HIV-associated dementia in older HIV-infected individuals.
- As HIV-infected individuals age, understanding how components of the metabolic syndrome and APOE ε4 influence the microstructure of the brain and HAND will become increasingly important.

AIMS/OBJECTIVES

- To characterize the microstructural changes on diffusion tensor imaging and the neuropsychological profile associated with the metabolic syndrome and APOE ε4 in a cohort of older HIV-infected individuals.
- Hypothesis: The brain microstructure on diffusion tensor imaging will differ in older HIV-infected individuals with and without components of metabolic syndrome or APOE ε4. HIV-infected individuals with components of the metabolic syndrome or APOE ε4 will perform worse on composite neuropsychological measures of global cognitive function, memory, and psychomotor function compared to those without components of the metabolic syndrome or APOE ε4.

METHODS

- **Study design:** HIV-seropositive subjects, 12 with and 12 without at least one APOE ε4 allele were identified from a cohort of subjects previously recruited to study the effect of APOE ε4 on cortical metabolism with positron emission tomography (PET).
- **Study population:** Subjects were ≥50 years and spoke English as a primary language. Subjects with a history of learning disability, head injury, active psychosis or uncontrolled major affective disorder, current substance abuse or dependence, and brain opportunistic disease were excluded.
- **Clinical assessment:** Evaluations included demographic and medical intake data, self-reported lowest ever CD4+ count, current antiviral therapy, height, weight, waist circumference, blood pressure, plasma HIV viral load, CD4+ lymphocyte cell count, APOE ε4 genotype, fasting lipid profile, fasting plasma glucose, and 2-hour oral glucose tolerance test (OGTT).
- **Diffusion tensor imaging:** Diffusion-weighted scans were acquired on a Philips 3.0T Achieva scanner. A single-shot echo planar imaging sequence and T2-weighted b0 image were obtained. Tensors were calculated to obtain fractional anisotropy (FA) and mean diffusivity (MD) maps.
- **Neuropsychological testing:** Neuropsychologic composite z-scores were calculated using the arithmetic means of various individual z-scores. NPZ-8 is a measure of global cognitive function and included Trailmaking Test – Part A, California Computerized Assessment Battery, Choice and Sequential, WAIS-III Digit Symbol Subtest, Trailmaking Test – Part B, Grooved Pegboard Test, Dominant and Nondominant , Timed Gait. NPZ-3-mem is a measure of memory and included Rey Auditory Verbal Learning Test – Trial 5, Rey Auditory Verbal Learning Test, Delayed Recall, and Rey-Osterreith Complex Figure Test, Delayed Recall. NPZ-3-pm is a measure of psychomotor speed and included WAIS-III Digit Symbol Subtest, Trailmaking Test – Part B, Grooved Pegboard Test, Non-dominant.
- **Statistical analysis:** Linear regression was used to determine the relationship between z-scores on neuropsychological testing and cerebrovascular risk factors/APOE ε4. For FA and MD maps, statistical comparisons were made between groups with multiple comparison correction for the voxelwise tests using False Discovery Rate < 0.05.

RESULTS

- Twenty-two of these subjects had an MRI and were included in our sample.

Table 1. Demographics and clinical characteristics

	N = 22
Mean age, years (SD)	58 (6)
% males	86
% white	77
% on HAART	95
%on protease inhibitor	9
% with undetectable HIV viral load	82
Mean CD4+ nadir	210 (171)
Mean body mass index, kg/m^2 (SD)	24 (3)
% with abdominal obesity	0
Mean waist circumference, cm (SD)	91 (7)
% with impaired glucose tolerance	40
% with diabetes	20
% with hypertension	50
Mean systolic blood presssure, mm Hg (SD)	126 (18)
Mean diastolic blood pressure, mm Hg (SD)	74 (10)
% with fasting LDL ≥ 100 mg/dL	50
Mean fasting LDL, mg/dL (SD)	40 (19)
% with fasting triglycerides ≥ 150 mg/dL	36
% with fasting HDL < 40 mg/dL in men, < 50 mg/dL in women	40
% with metabolic syndrome	32
% with past or present tobacco use	45
Mean pack years (SD)	19 (11)
% with at least one ApoE4 allele	40

Table 2. Association of vascular risk factors and diffusion tensor imaging parameters

Vascular risk factors	Regions of interest	Anisotropy	FDR p-value
Glucose intolerance	Caudate	Decreased FA Increased MD	p = 0.002 p = 0.008
Metabolic syndrome	Caudate	Increased MD	p = 0.001
Elevated blood pressure or hypertension	Hippocampus	Decreased FA	p = 0.004
Elevated blood pressure or hypertension	Thalamus	Increased MD	P = 0.002

Table 3. Multivariate analysis of the association of vascular risk factors / APOE ε4 and neuropsychological composite scores

	NPZ-8	NPZ-3-mem	NPZ-pm
Age	**- 0.05 (p = 0.02)**	0.02 (p = 0.60)	- 0.04 (p = 0.23)
Glucose intolerance	**0.92 (p < 0.01)**	**0.75 (p = 0.16)**	**0.58 (p = 0.10)**
Metabolic syndrome	**- 0.81 (p < 0.01)**	- 0.60 (p = 0.41)	0.33 (p = 0.46)
Tobacco use	**- 0.51 (p = 0.03)**	0.34 (p = 0.54)	- 0.33 (p = 0.38)
At least one ApoE4 allele	**- 0.81 (p < 0.01)**	**- 0.94 (p = 0.12)**	**- 0.86 (p = 0.07)**

DISCUSSION

- Diffusion tensor parameters (MD and FA) can detect microstructural differences between the brains of HIV-infected subjects with and without some components of the metabolic syndrome.
- The negative association between age and APOE ε4 and cognitive function is consistent with prior studies (Valcour et al., 2004). The negative association between the metabolic syndrome and cognitive function is consistent with that seen in the HIV-seronegative population (Awad et al., 2004). Further studies are warranted to determine if the association between the metabolic syndrome and cognitive function is additive or synergistic in HIV-infected individuals.

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