Correlation of Magnetization Transfer Ratio with Cognitive Impairment in HIV

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Purpose: Patients infected with Human Immunodeficiency Virus (HIV) are vulnerable to brain injury and cognitive deterioration. Postmortem studies of HIV-Dementia patients indicate extensive neuropathology in subcortical brain regions (1). Magnetization Transfer (MT) Imaging can be used to probe microstructural brain tissue integrity and MT measurements have been shown to correspond to postmortem findings of myelin damage, reduced axonal density and increased inflammatory extracellular water content (2). Studies in HIV infection (3, 4) and in other CNS diseases (5) indicate relationships between global MTR alterations and clinical neuropsychological status. MTR measurements can be acquired in vivo and may afford a mechanism for studying ongoing changes in localized brain regions and the relationship to deterioration in specific cognitive functions. In this investigation, MT measurements were determined for white matter (corpus callosum, frontal white matter and centrum semiovale) and gray matter (caudate, putamen, thalamus) regions in HIV infected and control subjects. Global MT measurements of intracranial brain tissue were also calculated. The regional and global MT measurements were compared in the two groups and examined for patterns of relationship to dementia severity and to deficits in specific cognitive functions as determined by a concurrent neurological and neuropsychological evaluation.

Methods: Participants included 11 well-characterized HIV patients (mean±sd: 49.4±7.27) and 12 healthy controls (43.0±10.36). The groups did not differ in years of education (15.5±2.4 vs. 15.5±2.7). Dementia severity was determined according to operationalized criteria based on the Memorial Sloan Kettering (MSK) rating system (6). A comprehensive neuropsychological battery was used to evaluate impairment in attention, memory, constructional, motor and executive functions. Scores were calculated for each cognitive domain based on composites of relevant individual subtests (6). Subjects were scanned using a GE 1.5T MR system with a fast gradient echo (TR=1000ms /flip angle= 20°). This sequence was repeated with (Ms) and without (Mo) an off-resonant saturation pulse (frequency=1200 HZ/ duration= 16 msec). The MT Ratio (MTR) was defined as (Mo-Ms)/Mo. Whole brain MTR histograms of the intracranial brain tissue were constructed offline using custom software. The normalized peak height (normalized by total number of intracranial pixels) and histogram mean MTR were calculated. MTR maps were generated and mean MTR values were determined for each ROI (30 mm^2) using an advanced workstation (GE, Milwaukee) (Figure 1).

Results: Reduced whole brain MTR values, including normalized histogram peak height ($F(1,20)=5.89$; $p=0.025$) and histogram mean MTR ($F(1,20)=6.82$; $p=.017$) were identified in the HIV patients as determined by analysis of covariance (age as a covariate). The localized MTR measures were evaluated with separate repeated measures analysis of variance models (with age as a covariate) for the white matter and for gray matter regions. Significant main effects for group were also found for both white matter ($F(1,20)=6.13$; $p=.02$) and for gray matter ($F(1,20)=4.33$; $p=.05$). Planned comparisons indicated significantly lower MTR measurements in the HIV patients in all regions studied, shown in Figure 3. Correlations between MTR measurements and the cognitive status measures are presented in Table 1.

Conclusion: MTR evaluation for whole brain and for ROIs detected microstructural brain alterations in HIV subjects. The reduction in MTR observed for all studied regions is consistent with diffuse brain involvement in the HIV patients. In addition, significant correlations between MT measurements and dementia severity were indicated for whole brain and nearly all studied white and gray matter regions (Table 1). Significant relationships were identified between whole brain MTR values and cognitive status in working memory, verbal memory, visual Memory and motor speed. For the localized values, the observed pattern indicated neuropsychological correlates involving visual memory (genu, splenium, centrum semiovale), visuoconstruction (genu, frontal white matter and centrum semiovale) and motor speed (splenium). Among gray matter regions, only nearly significant relationships were noted between thalamus and motor speed (p=.06) and between caudate and visuoconstruction (p=.07). The findings suggest that white matter alterations are more prominently implicated in specific cognitive deficits, possibly due to white matter functional disconnection between different cortical areas (5). The results indicate that both global and localized MTR measurements are sensitive to the neuropathological substrate of HIV infection and this MR strategy may have potential utility for monitoring brain injury underlying neurocognitive impairment in HIV infection.

Figure 1

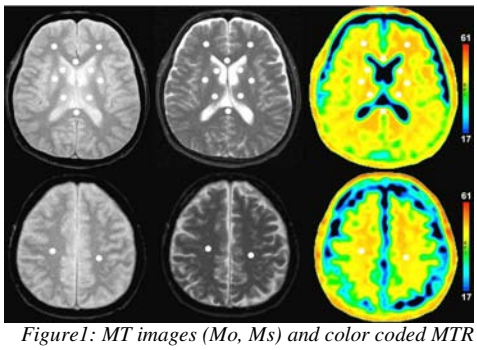

Figure 2

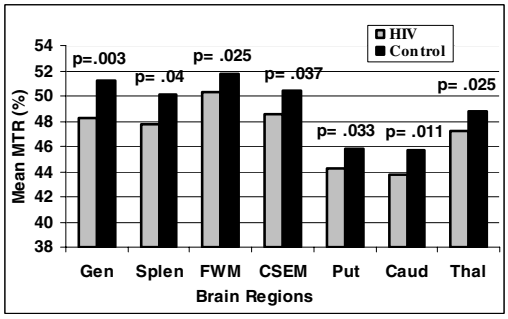

Figure 3

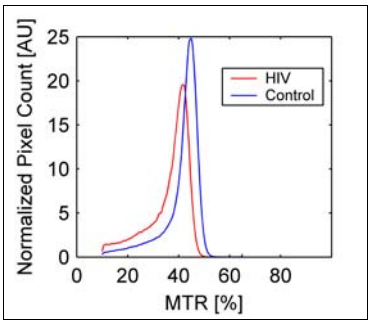

Figure1: MT images (Mo, Ms) and color coded MTR maps showing ROI regions. Figure2: Mean MTR and P value for ROIs in HIV and control groups. Figure3: Global MTR histograms of an HIV and a control subject. AU= arbitrary unit.

Table 1: Correlations between MTR and the cognitive status measures

	Regional MTR							Whole Brain MTR	
	Gen	Splen	FWM	CSEM	Put	Caud	Thal	Peak Height	Mean MTR
MSK	-.61**	-.53**	-.46*	-0.38	-.43*	-0.39	-.42*	-.57**	-.70**
Working Memory	0.11	0.29	0.25	0.31	0.06	0.08	0.09	-.51*	0.03
Verbal Memory	-0.23	-0.01	-0.28	-0.32	-0.02	-0.33	-0.05	.51*	-0.14
Visual Memory	.48*	.48*	0.42	.46*	0.10	0.30	0.3	0.18	.47*
Visuoconstruction	.49*	0.20	.56*	.54*	0.28	0.41	0.37	-0.05	0.43
Psychomotor	0.24	0.19	0.04	-0.12	0.15	-0.25	0.23	0.27	0.11
Motor Speed	0.24	.54*	0.24	0.11	0.26	0.05	0.42	.46*	0.40
Executive Function	-0.37	-0.14	-0.26	-0.22	-0.36	-0.24	-0.16	0.14	-0.26

*Pearson correlation coefficients for ROIs; Spearman correlation coefficients for whole brain. * $p < .05$; ** $p < .01$. MSK= dementia severity measure. Gen= Genu. Splen= splenium. FWM = frontal white matter. CSEM= centrum semiovale. Put= putamen. Caud= caudate. Thal= thalamus.*

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