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Marked relationship between matrix metalloproteinase 7 and brain atrophy in HIV infection

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Abstract Circulating levels of matrix metalloproteinases (MMP-1 and 7) have been found to correlate with the severity of brain injury in HIV-infected subjects. This study used high-resolution neuroanatomic imaging and automated segmentation algorithms to clarify this relationship. Both metalloproteinases were significantly correlated with increased cerebrospinal fluid volume fraction. Comprehensive brain volumetric analysis revealed a more marked relationship with atrophy for MMP-7, which was significantly correlated with neural injury in multiple brain regions and nearly all ventricular measurements. MMP-7 was also correlated with measures of virologic and cognitive status.

Keywords HIV-dementia · MMP-1 · MMP-7 · NeuroAIDS · Quantitative MRI

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Introduction

Human Immunodeficiency virus (HIV) infection is associated with considerable risk of injury to the brain, including irreversible neuronal loss, e.g., (Thompson et al. 2005). Direct infection of neurons, however, does not appear to be the primary mechanism underlying brain atrophy. Interest in matrix metalloproteinases (MMPs) follows from evidence implicating systemic monocyte activation and brain monocyte trafficking in HIV Dementia, e.g., (Gartner 2000; Pulliam et al. 1997). Metalloproteinases are products of activated monocytes and involved in monocyte migration, blood–brain barrier permeability, and pathogen clearance (Parks et al. 2004). MMPs, which are generally undetected in the healthy brain, are elevated in subjects with HIV-dementia (Conant et al. 1999). Circulating levels of MMP-1 (collagenase-1) and MMP-7 (matrilysin) have been found to correlate with aggregate microstructural brain alterations quantified by diffusion tensor imaging and with the severity of atrophy determined by brain volumetry (Ragin et al. 2009). This study was undertaken to evaluate whether MMPs correlate with changes in specific brain regions. High-resolution neuroanatomic images were acquired at a higher magnetic field strength (3 Tesla), and fully automated segmentation algorithms (Fischl et al. 2002) were used to

derive volumetric measurements for approximately 42 regions and structures.

Eight well-characterized, medically stable subjects (six males, two females; mean age, 50.9±7.2 years) were enrolled from a larger cohort study of advanced HIV infection (Sevigny et al. 2004). Exclusion criteria for cohort study entry included history of neurological disorder, stroke, head trauma, opportunistic CNS infection, or psychosis. Magnetic Resonance (MR) contraindication was a specific exclusion criterion for this neuroradiological study. Seropositivity was confirmed by ELISA and Western blot. All subjects met criteria for AIDS (CD4 cell counts, 50 to 777/mm^3; plasma viral load, undetectable to 55,300 copies/mL) and were on antiretroviral regimens (mean CD4, 400.4±290). Subjects were followed with annual standardized clinical examinations and tests of psychomotor function and timed gait, as detailed elsewhere (Sevigny et al. 2004). Clinical and demographic characteristics of the sample are presented in Table 1. MMP-1 and MMP-7 levels were determined according to the manufacturer's instructions using commercial kits available through R & D Systems (Minneapolis, MN).

Brain images were obtained using an eight-channel phased array coil (MRI Devices, Gainesville, FL) on a 3 Tesla General Electric (Waukesha, WI) HDx system. 3D images were acquired using MP-RAGE with the following parameters: repetition time (TR), 7.4 ms; echo time (TE), 3 ms; inversion time, 450 ms; 12-degree flip angle; bandwidth, 244 kHz; field of view, 240 mm; and slice thickness, 1.5 mm resulting in isotropic voxel volume of $0.9375\times0.9375\times1.5$ mm^3 with 116 slices covering the whole brain. Images were transferred to a Linux workstation for post-processing and analyzed using the fully automated Freesurfer algorithm (Fischl et al. 2002). The approach utilizes an affine rigid linear transformation, combining information concerning voxel intensity relative to a probability distribution for tissue classes and information concerning the spatial relationship of the voxel to location of neighboring structures from an integrated a priori anatomic atlas (Fischl et al. 2002). Systematically restricting the focus to more localized brain regions with less signal variation enhances the accuracy of brain segmentation. The Freesurfer algorithm fully automates segmentation and labeling of brain neuroanatomical features, including subcortical structures such as caudate, putamen, amygdala, and hippocampus, as well as smaller regions. This eliminates the necessity of labor-intensive, manual outlining across multiple brain images by expert operators. The sensitivity of this approach for systematically evaluating localized changes throughout the brain, particularly in subcortical brain regions, is a considerable advantage. Figure 1 illustrates the segmentation methods and selected brain structures are shown in 3D. To calculate the relative volumes, the volume for each structure of interest was determined in cubic millimeters and expressed as a percentage of the individual intracranial cavity volume.

Statistical analyses Primary variables for analysis included serum MMP levels and the brain volumetric measurements expressed as a fraction of the individual intracranial cavity volume to adjust for individual differences in head size. Clinical markers of HIV disease progression included CD4 cell count and plasma HIV RNA copies per milliliters (viral load) measured concurrently, at first available clinical visit (baseline) and averaged across the period of available clinical follow-up (approximately 5 years in this sample). Cognitive status measures included digit symbol and timed gait measurements from standardized neuropsychological assessments. For all variables, distributional assumptions were evaluated prior to analysis. Pearson correlation coefficients were used to evaluate relationships between MMPs and the MR measurements. The significance level used for analyses was 0.05. Analyses were executed with PASW 18.0.0 (Chicago, IL).

Mean values of 1.39 (±0.84) were obtained for MMP1 and of 0.289 (±0.25) for MMP7 in this sample of HIV+ subjects. MMP correlations with the volumetric brain

Table 1 Clinical characteristics and MMP levels

Subject	Age	Educ	CD4	Nadir CD4[a]	Viral load	Avg. viral load[a]	CD8	BMI	Hemoglobin	MMP-1	MMP-7
1	45	12	367	108	152	756	1056	21.9	13.3	2.308	0.252
2	52	16	777	13	Lt 50	77494	1018	24.3	12.4	3.396	0.807
3	62	17	74	10	351	1014	684	21.4	13.5	1.94	0.051
4	41	14	737	176	Lt 50	24	1536	27.7	15.0	1.132	0.164
5	57	20	649	119	Lt 50	1853	1766	18.0	15.7	6.142	0.363
6	55	16	350	187	Lt 50	10245	1213	32.9	14.0	2.504	0.002
7	44	12	50	24	55300	57440	462	31.6	14.8	0.944	0.289
8	51	14	199	61	Lt 50	51963	1176	27.7	13.3	3.882	0.385

[a] Based, on available clinical information for an average of five prior years

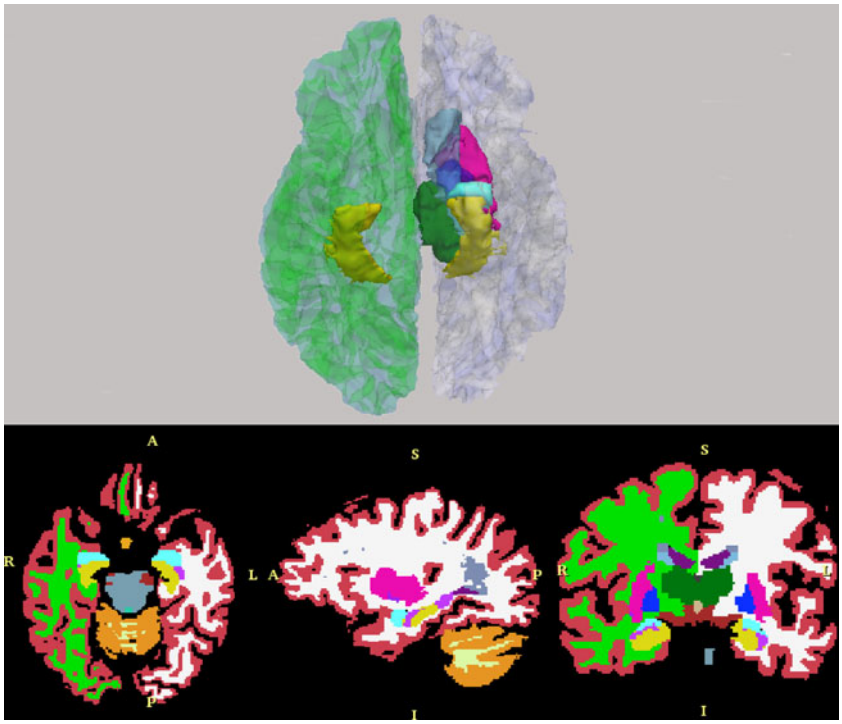

Fig. 1 Delineation of specific brain regions using fully automated brain segmentation (*bottom*). Segmentation results in axial, sagittal, and coronal spatial orientations. Brain regions are color-coded; all voxels within a region are assigned the same digital value. Segmentation results for selected brain structures are reconstructed and shown in 3D (*top*)

measurements are shown in Tables 2 and 3. For both MMP-1 and MMP-7, significant or nearly significant relationships were observed with cerebrospinal fluid (CSF) volume (Table 2), a measure of overall brain atrophy (MMP-1, r=0.68; p=0.06; MMP-7, r=0.82; p=0.01). The relationship with atrophy was more pronounced for MMP-7 as indicated by the pattern of significant correlations with nearly all ventricular volumetric measurements (Table 2), including third ventricle (r=0.84; p=0.009), fourth ventricle (r=0.79; p=0.019), inferior lateral ventricles (left, r=0.80; p=0.016 and right, r=0.83; p=0.011), lateral ventricles (left, r=0.94; p=0.001 and right, r=0.94; p=0.001), and choroid plexus (left, r=0.78; p=0.023 and right, r=0.87; p=0.005) measurements. MMP-7 was also significantly correlated with losses in bilateral in cerebral white matter (left, r=−0.90; p=0.003 and right, r=−0.92; p=0.001), left pallidum (left, r=−0.78; p=0.021), and right ventral diencephalon (r=−0.73; p=0.039). In addition, correlations of MMP-7 with left putamen (r=−0.67; p=0.067), bilateral hippocampi (left, r=−0.68; p=0.062 and right, r=−0.63; p=0.092), and left ventral diencephalon (r=−0.65; p=0.081) approached significance (Table 3). For cognitive measures, MMP-7 was also significantly correlated with reduced psychomotor speed (digit symbol, r=−0.73; p=0.040) and nearly significantly correlated with slowed timed gait (r=0.63; p=0.090).

No significant correlations were found between the MMPs and concurrent CD4 cell count or plasma HIV RNA copies per milliliters (Table 4). Elevated MMP-7, however, was significantly correlated with higher average HIV RNA copies per milliliter across the clinical course (r=0.75; p=0.031).

Discussion

This investigation replicates the reported relationship between matrix metalloproteinase levels and the severity of brain injury in HIV infection (Ragin et al. 2009). Both

Table 2 Correlations of MMPs with CSF and ventricular measurements

Volumetric measurement	MMP-1	MMP-7
Total CSF	0.68	0.82**
Third ventricle	0.33	0.84**
Fourth ventricle	−0.12	0.26
Fifth ventricle	0.06	0.79*
L inferior lateral ventricle	0.11	0.80**
R inferior lateral ventricle	0.23	0.83**
L lateral ventricle	0.30	0.94**
R lateral ventricle	0.22	0.94**
L choroid plexus	0.04	0.78*
R choroid plexus	0.11	0.87**

L left, *R* right

*Pearson correlation coefficients significant at the 0.05 level

**Significant at the 0.01 level

Table 3 Correlations of MMPs with brain volumetric measurements

Region	MMP-1	MMP-7	Region	MMP-1	MMP-7
L cerebral cortex	−0.24	−0.17	R cerebral cortex	−0.26	−0.19
L cerebral white matter	−0.10	−0.90**	R cerebral white matter	−0.17	−0.92**
L caudate	0.33	0.25	R caudate	0.11	0.26
L putamen	−0.360	−0.67	R putamen	−0.55	−0.56
L pallidum	0.30	0.94**	R pallidum	−0.10	−0.61
L accumbens	−0.02	0.19	R accumbens	0.13	−0.03
L amygdala	−0.34	−0.64	R amygdala	0.11	−0.56
L hippocampus	−0.29	−0.68	R hippocampus	−0.13	−0.63
L thalamus	−0.20	0.18	R thalamus	−0.20	0.41
L cerebellum cortex	−0.25	0.16	R cerebellum cortex	−0.49	−0.10
L cerebellum white matter	−0.44	−0.28	R cerebellum white matter	−0.68	−0.25
L ventral diencephalon	−0.47	−0.65	R ventral diencephalon	−0.41	−0.73*
Brain stem	−0.50	−0.24	CC ante	0.24	−0.24
CC central	−0.11	−0.03	CC mid-ante	−0.06	0.03
CC mid-Post	−0.55	−0.47	CC post	0.26	0.07
Optic chiasm	−0.17	−0.27	WM hypointensities	0.00	0.53

L left, *R* right, *WM* white matter

Pearson correlation coefficients: significant at the *0.05 level, and **at the 0.01 level

MMP-1 and MMP-7 were significantly correlated with the extent of atrophy, as indicated by increased percentage volume of CSF. A more marked pattern of relationship with brain injury was indicated for MMP-7. MMP-7 was correlated with reductions in cerebral white matter, pallidum, diencephalon, putamen, and hippocampus with expansion in nearly all ventricular measurements (third, fourth, as well as bilateral inferior lateral, lateral, and choroid plexus). Significant relationships with higher mean viral load and with psychomotor impairment, a diagnostic hallmark of HIV-associated neurocognitive disorder (Antinori et al. 2007), were also identified, specifically for MMP-7.

MMPs are involved in extracellular matrix degradation in physiological and pathological conditions (Sternlicht and Werb 2001). Levels are elevated in the injured brain (Milward et al. 2007; Parks et al. 2004) and other findings have implicated MMPs in neuronal injury (Conant et al. 2004; Gu et al. 2002; Vos et al. 2000; Zhang et al. 2003a, b). Dysregulated MMP activity may pose considerable risk of tissue destruction. MMPs may degrade constituents of the extracellular matrix, alter biologic activity of cytokines and chemokines (Lugli et al. 2005; Schlondorff and Blobel 1999), and modulate the neurotoxicity of HIV viral proteins (Johnston et al. 2001; Rumbaugh et al. 2006).

This exhaustive volumetric analysis revealed an extensive pattern of relationship between MMP-7 and atrophic brain changes. MMP-7 has been found to influence synaptic morphology and neuronal survival (Bilousova et al. 2006; Bozzo et al. 1997; Patton et al. 1998) and is characterized by broad-spectrum proteolytic activity against extracellular substrates, including proteoglycans (Yu and Woessner 2000), a major constituent of the CNS (Parks et al. 2004). As more has been learned, MMP physiologic significance appears to extend to involvement in regulating and modulating inflammation, for example, through proteolysis of chemokines (McQuibban et al. 2002; Parks et al. 2004; Van Lint and Libert 2007). In this regard, MMP-7 may be particularly relevant to self-reinforcing cycles of chronic immune activation and cytokine/chemokine-mediated neurotoxicity. Unlike many MMPs, MMP-7 is characterized by inability to process monocyte chemoattractant protein 1 (MCP-1 or CCL2) (McQuibban et al. 2002), a chemokine that has been implicated in HIV-associated brain injury (Avison et al. 2004a, b; Chang et al. 2004; Cinque et al. 1998; Kelder et al. 1998; Sevigny et al. 2004). MCP-1 enhances neuroinvasion of blood-borne monocytes, the presumed vehicle for brain viral entry (Conant et al. 1999; Langford and Masliah 2001; Persidsky et al. 1999, 2000; Sasseville et al. 1994; Weiss et al. 1999). Blood-borne and

Table 4 Correlations of MMPs with clinical variables

	MMP-1	MMP-7
CD4+ cell count	0.36	0.48
Concurrent HIV RNA	−0.44	−0.00
Average HIV RNA	0.00	0.75*
Psychomotor (digit symbol)	−0.13	−0.73*
Timed gait	−0.09	0.63

*Significant at the 0.05 level

infiltrating monocytes express MMP-7 (Busiek et al. 1995). Increased MMP-7 expression has been shown by cells expressing the HIV viral protein (*tat*) (Johnston et al. 2001) and by cytokine-stimulated cells in the brain (Conant et al. 1999). Mice deficient in MMP-7 are resistant to neuroinflammatory injury (Buhler et al. 2009).

Levels of endogeneous metalloproteinase inhibitors are also reduced in HIV-dementia (Dhar et al. 2006; Suryadevara et al. 2003). MMP-7 lacks the domain to which MMP inhibitors bind; this domain is present, however, in MMP-1. Chronic immune activation may be associated with reduced capacity to counter potentially destructive effects of MMPs (Dhar et al. 2006). Prolonged activation of astrocytes has been associated with reduced MMP inhibitor levels and sustained MMP elevations (Suryadevara et al. 2003). Other factors implicated in HIV cognitive deterioration (e.g., FasL, TNFα, apolipoprotein E, defensin, microbial translocation) are regulated by, or are substrates, of MMP-7 (Haro et al. 2000; Hwang et al. 2004; Powell et al. 1999; Sevigny et al. 2004; Towfighi et al. 2004; Valcour et al. 2004).

Elevations in MMP levels among the HIV-infected participants studied in this investigation (all met criteria for AIDS) were consistently correlated with greater brain tissue loss. Because healthy controls were not available, this study cannot definitely determine whether these levels reflect an increase or decrease relative to normative levels. While very limited MMP data is available for healthy subjects, serum MMP7 levels in patients with other chronic diseases (e.g., coronary artery disease, diabetes) are increased compared with controls and correlate with disease severity (Ban et al. 2010; Nilsson et al. 2006). It is also important to appreciate that MMPs orchestrate both protective and destructive effects in the context of a dynamic protease web. The substrates and repertoire of individual MMPs have not been completely characterized and many factors influence their activity. In the setting of HIV infection, for example, enzymatic cleavage by MMP-1 may degrade and decrease *tat*-induced neurotoxicity (Rumbaugh et al. 2006). Findings from this investigation clearly demonstrate the relevance of circulating MMPs, particularly MMP-7, to an understanding of brain injury in HIV infection. Further study of these dynamics may yield insights into underlying mechanisms and inform neuroprotective intervention.

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