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CSF Biomarkers Correlate with Magnetic Resonance Spectroscopy Metabolites during HIV disease

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Background & Significance

HIV-associated neurocognitive disorders (HAND) remain common in the current treatment era and can adversely affect quality of life, employment, and survival.[1] The pathogenesis of HAND is not fully understood but Magnetic Resonance Spectroscopy (MRS) and structural MR imaging evidence cerebral inflammation and neuronal loss even during suppressive cART.[2,3]

Multiple immune biomarkers in cerebrospinal fluid (CSF) have been associated with HAND. These include markers of monocyte/macrophage activation such as soluble CD14 (sCD14) and chemotactic cytokines such as monocyte chemotactic protein-1 (MCP-1), interferon inducible protein-10 (IP-10), and stromal cell derived growth factor-1α (SDF-1α).[4-6]

Previous studies have identified associations between CSF biomarkers and MRS metabolites[7] but the majority of these studies have been limited by their relatively small sample size and cross-sectional design.[8] This is the initial report of cross-sectional findings from a longitudinal project comparing CSF biomarkers and MRS metabolites.

Objective and Hypotheses

- Determine the associations between CSF biomarkers and regional cerebral metabolites in a multicenter cohort of HIV-infected individuals
- We hypothesized that biomarkers of immune activation would be associated with evidence of membrane remodeling and neuronal injury

Methods

Data from 91 HIV seropositive participants from five CHARTER sites (Galveston, Baltimore, New York, Seattle, and San Diego) were analyzed (**Table 1**). CSF biomarkers were measured by immunoassay or bead array.

Image Acquisition

- All sites GE 1.5T
- Point-resolved spectroscopy
- TE=35, TR=3000, autoshimmed
- Three voxels acquired
- FGM 20mm^3, 64 acq
- FWM 20mm^3, 64 acq
- BG 15mm^3, 96 acq

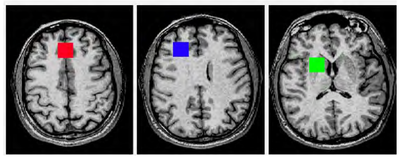


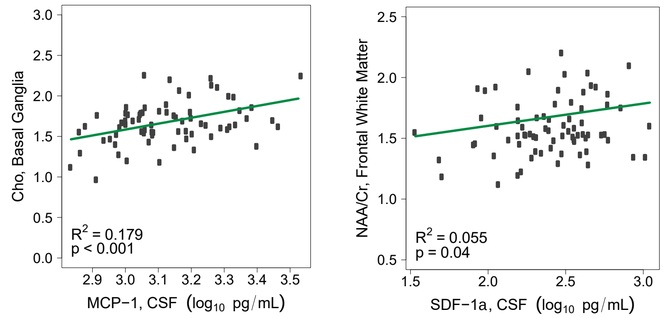
Figure 1. Axial T1 sections with MRS voxels: Frontal Gray (**FGM**) & White (**FWM**) Matter; and Basal Ganglia (**BG**).

Image Processing: MRS concentrations of N-acetylaspartate (**NAA**), choline (**Cho**), myo-inositol (**MI**), and creatine (**CR**) were quantified using LCModel[9] with water suppression

Statistical Analysis: Effects sizes of associations between biomarkers and MRS metabolites were measured by R^2 values, which were estimated from multivariable models that accounted for demographic (age, race, gender) and disease (Nadir CD4, HCV) characteristics as well as the proportion of relevant tissue volume within each voxel (e.g., amount of gray matter in FGM).

Results

Figures 2 and 3. Associations between selected CSF biomarkers and cerebral metabolites.



Associations: Biomarkers and absolute MRS metabolites (Table 2)

- Higher levels of MCP-1 and IP-10 were each associated with higher levels of MI and Cr in FWM
- The strongest correlation was between higher MCP-1 and higher Cho in BG (Figure 2) while a weaker association was found between lower IP-10 and lower NAA in FWM
- No statistically significant associations were present between either sCD14 or SDF-1α and cerebral metabolites

Associations: Biomarkers and MRS metabolite/Cr ratios (Table 3)

- Higher levels of MCP-1 were associated with higher Cho/Cr ratio in BG and lower NAA/Cr ratio in FWM
- Higher levels of sCD14 were associated with lower ratios of both NAA/Cr in FGM and Cho/Cr in FGM
- Lower levels of SDF-1α were associated with lower NAA/Cr in FWM (Figure 3)
- IP-10 was not associated with any cerebral metabolite ratios

Table 1: Characteristics of 91 participants. [1]Mean (SD) [Range]; [2]Median [IQR]

Age[1]	45 (7.6) [27-62] years	Current CD4[2] (cells/mm^3)	458 [311, 600]
Ethnicity	47% European American 43% African American 10% Other	Nadir CD4[2] (cells/mm^3)	145 [24, 238]
Gender	84% male	Plasma HIV RNA	50% > 50 c/mL
Duration HIV[1]	134 (72) [7-285] mos	CSF HIV RNA	34% > 50 c/mL
ART	76% On 16% Off 8% Naive	Cognitively Impaired	23% ANI 11% MND/HAD 8% Confounded
AIDS	69%	HCV seropositive	26%

Conclusions

- **CSF biomarkers of monocyte chemotaxis (MCP-1) and antiviral immune responses (IP-10) were associated with cerebral metabolites reflecting: a)membrane remodeling (high Cho), b) neuronal damage (low NAA), and c) glial proliferation (high MI) in frontal white matter and basal ganglia.**
- **Cr, an indicator of energy metabolism often used in MRS ratios was associated in higher IP-10 and MCP-1 levels in FWM**
- **Incorporation of Cr into MRS ratios (per convention) altered several associations between CSF biomarkers and cerebral metabolites, in some cases reversing the direction of the association identified using unadjusted metabolites**

Table 2: Values are adjusted R^2 (P value). All R^2 values were positive.*

CSF biomarker	MRS metabolite			
	NAA FWM	Cr FWM	Cho BG	MI FWM
IP-10	0.045 (0.046)	0.106 (0.003)	-	0.05 (0.036)
MCP-1	-	0.075 (0.01)	0.179 (<0.001)	0.137 (0.002)

Table 3: Values are adjusted R^2 (P value). Green indicates positive association, red indicates negative association.*

CSF biomarker	MRS metabolite			
	NAA/Cr FWM	NAA/Cr FGM	Cho/Cr BG	Cho/Cr FGM
sCD14		0.068 (0.019)	-	0.177(<0.001)
MCP-1	0.102 (0.005)	-	0.073 (0.019)	
SDF-1α	0.056 (0.037)	-	-	-

* Statistically insignificant results are not shown.

References

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