IDENTIFICATION OF CSF BIOMARKERS OF COGNITIVE IMPAIRMENT AND CEREBELLAR DYSFUNCTION IN MULTIPLE SCLEROSIS

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INTRODUCTION

- Cerebellar and cognitive deficits are common symptoms in multiple sclerosis (MS), contributing to significant disability in a subset of patients. The underlying pathology behind this symptom complex is poorly understood and is typically refractory to standard MS treatments.
- We hypothesize that biomarkers in the cerebrospinal fluid (CSF) may be useful indicators of cognition impairment and cerebellar dysfunction in patients with MS.
- Identification of biomarkers of cerebellar/cognition deficits may allow further insight into pathophysiological mechanisms underlying this system complex, and potentially help identify new therapeutic targets.

OBJECTIVE

To identify and validate CSF biomarkers of cognitive impairment and cerebellar dysfunction in MS

DESIGN AND METHODS

❖ CSF samples were obtained by standard lumbar puncture from MS patients with or without co-existing cerebellar dysfunction and cognition impairment, which were determined by neurological exam and cognitive screening test battery, respectively.

	MS with normal cognition/cerebellar function	MS with cognition/cerebellar deficits
SCREENING COHORT		
# patients	n=5	n=5
Age (range) in yrs	51 (38-66)	47 (30-60)
Female:male ratio	2:3	3:2
Disease duration	13 (8-21)	18 (17-19)
Current treatment	no treatment (n=5)	no treatment (n=2), β-interferons (n=2), glatiramir acetate (n=1)
VALIDATION COHORT		
# patients	n=17	n=20
Age (range) in yrs	50 (30-66)	48 (30-60)
Female:male ratio	13:4	14:6
Disease duration	13 (8-21)	18 (17-19)
treatment	no treatment (n=12), β-interferons (n=5)	no treatment (n=12), β-interferons (n=4), glatiramir acetate (n=4)

❖ Candidate CSF biomarkers in screening cohort were identified by mass spectrometry-based MRM technology (NextGen Sciences) which simultaneously quantifies 82 proteins in CSF. Experimental samples were compared to 3 normal CSF controls (NextGen Sciences).

❖ Biomarkers were validated in CSF from validation cohort. CSF APLP2 and APP were assayed by ELISA , Aβ40/42 and tau were assayed by bead-based Luminex assays.

❖ Protein content was measured in all samples by BCA assay to confirm uniform protein levels.

❖ Statistical significance was analyzed using two-tailed Student's T test.

RESULTS

Candidate biomarkers identified in MS cog/cereb CSF samples		Levels in MS Cog/Cereb CSF	p value
APLP2	Amyloid beta (A4) precursor-like protein 2	decreased	0.030
C2	Complement 2	increased	0.016
C3	Complement 3	increased	0.011
CHGB	Chromagenin B	decreased	0.010
CP	Ceruloplasmin (ferroxidase)	increased	0.002
HABP2	Hyaluronan-binding protein 2	increased	0.021
HPX	Hemopexin	increased	0.013
KNG1	Kininogen 1	increased	0.018
LRG1	Leucine-rich alpha-2-glycoprotein 1	increased	0.044
LUM	Lumican	increased	0.042
ORM1	Alpha-1-acid glycoprotein	increased	0.022
PLG	Plasminogen	increased	0.016
PON1	Paraoxonase 1	increased	0.012
SERPINA3	Alpha-1-anti-chymotrypsin	increased	0.004
SERPINA6	Corticosteroid-binding globulin precursor	increased	0.016
SERPINA1	alpha-1 antiproteinase, antitrypsin	increased	0.040

Table 1. Identification of candidate biomarkers. CSF from MS patients with normal (n=5) or with severe cognitive and cerebellar symptoms (n=5) were screened for quantitative differences within 82 CSF biomarkers using LS/MRM-mass spectrometry. 16 proteins were significantly increased or decreased in CSF samples from MS patients cognitive/cerebellar dysfunction. All samples were corrected for protein content.

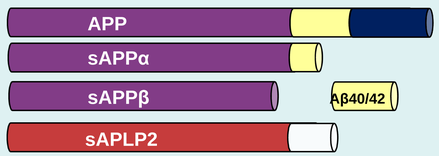

Figure 1. Schematic of APP/APLP2 cleavage products. Amyloid precursor protein (APP) and APP-like protein-2 (APLP2) are released from the cell membrane after cleavage by α-, β-, and γ-secretases. APLP2 lacks the Aβ domain.

RESULTS

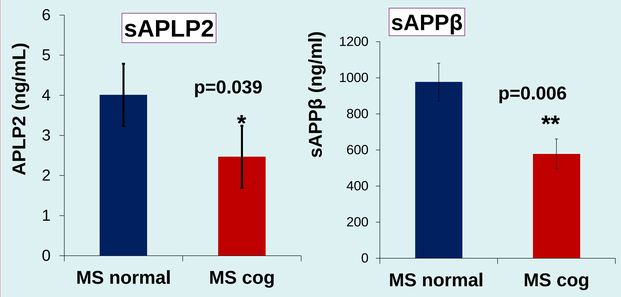

Figure 2. Validation results: sAPLP2, sAPPβ, Aβ40, and Tau levels are reduced in CSF from MS patients with cognition/cerebellar deficits. Analytes were measured by ELISA or by Luminex assay in the validation cohort.

RESULTS

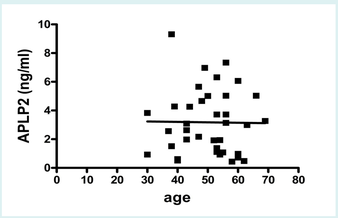

Figure 3. Lack of correlation between APLP2 or sAPPβ and patient age. CSF analyte levels did not correlate with patient age, suggesting that APLP2 and sAPPβ are correlated to MS-specific cognitive deficit.

CONCLUSIONS

❖ **The results of our preliminary study suggest that reduced levels of APP proteins in CSF may serve as useful biomarkers of cognition/cerebellar dysfunction in MS.**

❖ **Specifically, CSF levels of sAPLP2, sAPPβ, Aβ40, and total Tau were reduced in the MS group exhibiting severe cognition/cerebellar abnormalities.**

❖ **These findings will require further validation in a larger number of MS patients.**

❖ **Whether or not the APP pathway plays a pathological role in MS-related cognitive decline and cerebellar dysfunction remains to be determined.**

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