Relationship between N-acetylaspartate and neurofilament light chain in multiple system atrophy

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OBJECTIVE

- To evaluate the relationship between N-acetylaspartate (NAA) as measured using magnetic resonance spectroscopy (MRS) and neurofilament light chain in patients with multiple system atrophy (MSA).

INTRODUCTION

- MSA is pathologically characterized by glial cytoplasmic inclusions, neuronal loss, axonal degeneration, microglial activation and astrogliosis in the basal ganglia.
- Early diagnosis of MSA is vital for preserving neuronal function with disease modifying therapies, and thus identifying biomarkers for early pathology is critical.
- Neurofilament light chain (NfL) in cerebrospinal fluid (CSF) and plasma is gaining interest as a marker of axonal damage in MSA.[1]
- Magnetic resonance spectroscopy (MRS) is a non-invasive technique that allows for metabolite quantification, including N-acetylaspartate (NAA) as a marker of neuronal integrity given its role in cellular energetics and myelin synthesis.[2]
- In this study, we tested the hypothesis that the quantity of NAA measured using MRS is correlated with NfL levels.

METHODS

- Participants completed neurologic examination including clinical assessment with the Unified Multiple System Atrophy Rating Scale (UMSARS) and Natural History and Neuroprotection in Parkinson Plus Syndromes (NNIPPS).
- MRS was obtained from the right putamen using a PRESS sequence on a 3T scanner (**Fig. 1**).
- Data processing was performed using Osprey[3], and the tissue-corrected water-scaled NAA (NAA/water) estimates were obtained.
- CSF NfL was assessed with an Enzyme-linked immunosorbent assay (ELISA).
- Spearman correlation was used to evaluate the relationships between putamen NAA and NfL levels in CSF.

RESULTS

- 13 early MSA patients (symptom onset ≤ 4 years) were assessed.
- The MSA diagnosis was supported by fluid biomarkers. For all participants, the α-Synuclein Seed Amplification Assay diagnostic result indicated MSA, CSF NfL > 2000, and plasma NfL > 20.

N	13
Sex (M/F)	5/8
Age (years), mean ± SD	61.2 ± 7.9
UMSARS Total score, mean ± SD	39.7 ± 15.1
NNIPPS Total score, mean ± SD	78.1 ± 33.8

Table 1. Demographic and Clinical Data

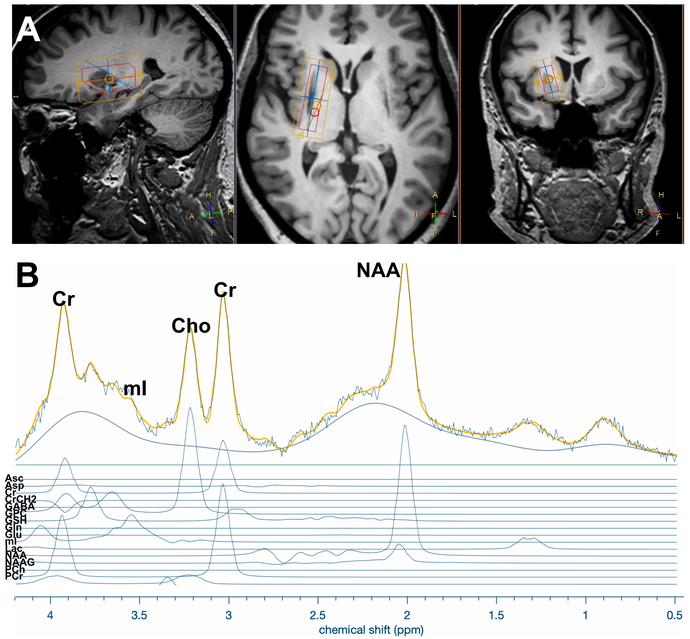

Fig. 1. Single-voxel MRS from right putamen. A) Sagittal, coronal, and axial views of T1-weighted image showing the location of the MRS voxel in the putamen (red). B) Example fit with contributions from individual metabolites.

RESULTS

- CSF NfL levels ranged from 2869 to 9880 pg/mL.
- NAA/water was significantly negatively correlated with CSF NfL (**Fig. 2**).

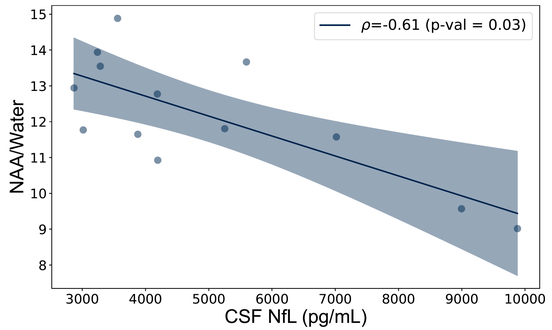

Fig. 2. Relationship between NAA/water and CSF NfL. Scatter plot and linear regression showing the association between NAA/water and NfL levels.

CONCLUSIONS

- We provide evidence that NAA is negatively correlated with CSF NfL levels in patients with early MSA.
- The results suggest that NAA concentration by MRS may reflect the degree of axonal integrity in these subjects.
- NAA is potentially a novel biomarker for neuronal viability in the disease course of MSA, and NAA and CSF NfL evaluation may be useful for assessing disease severity and optimizing patient stratification in clinical trials.

REFERENCES

1. Singer W, et al. Neurofilament light chain in spinal fluid and plasma in multiple system atrophy: a prospective, longitudinal biomarker study. Clin Auton Res. 2023. doi: 10.1007/s10286-023-00974-6
2. Moffett JR, et al. N-Acetylaspartate in the CNS: from neurodiagnostics to neurobiology. Prog Neurobiol. 2007;81(2):89-131.
3. Oeltzschner G, et al. Osprey: Open-source processing, reconstruction & estimation of magnetic resonance spectroscopy data. J Neurosci Methods. 2020;343:108827

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