Preliminary evidence for evolution of myoinositol and N-acetylaspartate as biomarkers of disease severity in early-stage Multiple System Atrophy

Paula Trujillo[1], Jessica Iregui[1], Kilian Hett[1], Amy Wynn[1], Manus J. Donahue1, Cynthia Wong[2], David Stamler[2], Daniel O. Claassen[1] Vanderbilt University Medical Center, Nashville, TN, 2 Alterity Therapeutics, Newark, CA

OBJECTIVE

- To quantify the longitudinal evolution of metabolic indicators of gliosis and neuronal integrity in patients with multiple system atrophy (MSA) over 1 year.

INTRODUCTION

- MSA is pathologically characterized by glial cytoplasmic inclusions, neuronal loss, axonal degeneration, microglial activation and astrogliosis in the basal ganglia.
- Diagnosis of early of MSA is vital for maximizing neuronal preservation with disease modifying therapies, and thus identifying biomarkers for early pathology is critical.
- Magnetic resonance spectroscopy (MRS) is a non-invasive MRI technique that allows metabolite quantification in the brain, including myoinositol (a marker of gliosis) and N-acetylaspartate (NAA; a marker of neuronal integrity).
- We applied MRS longitudinally to test the hypothesis that these neuro-chemical biomarkers are associated with clinical measures of disease severity in MSA.

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) rating scales at baseline, 6 and 12 months.
- MRS was obtained from the right putamen using a PRESS sequence on a 3T MRI scanner (**Fig. 1**).
- Data processing was performed using Osprey[1], and the tissue-corrected water-scaled myoinositol (mI/water) and NAA (NAA/water) estimates were obtained.
- Spearman correlation was used to evaluate the relationships between metabolite concentration and clinical scores.
- Wilcoxon paired test was used to compare the results between baseline and follow up.

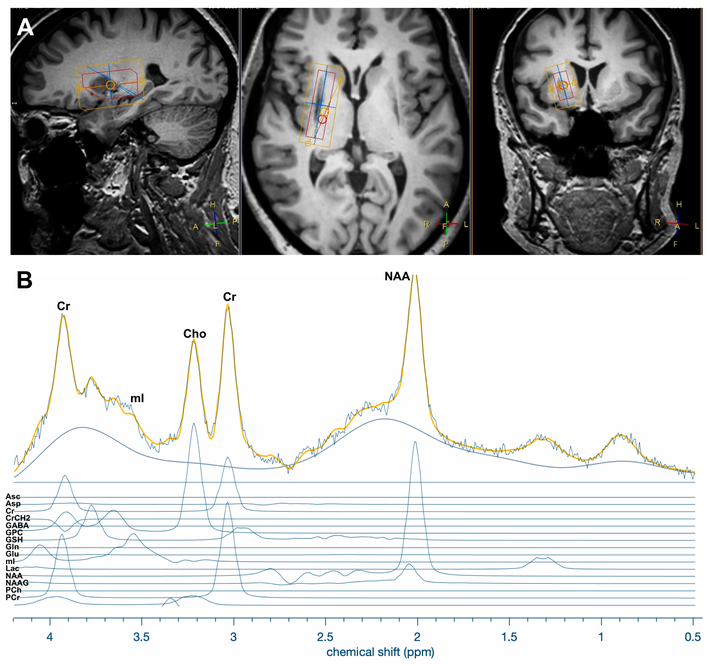

Fig. 1. Single-voxel MRS from right putamen. A) Sagittal, coronal, and axial views of T1-weighted image showing the location of the MRS voxel in the putamen (red). B) Example fit with contributions from individual metabolites.

RESULTS

- 13 early MSA patients (motor symptoms ≤ 3 yrs) were assessed at baseline; 10 patients completed the 6-month visit and 8 patients completed the 12-month visit.
- For all patients, MSA diagnosis was based on clinical parameters[2] and fluid biomarkers (α-synuclein SAA positive for MSA, CSF NfL > 2000), and quantitative MRI sensitive to iron deposition[3].

	Baseline	6 months	12 months
N	13	10	8
Sex (M/F)	5/8	4/6	2/6
Age (years), mean	60.7	59.9	59.8
UMSARS Total score, mean	34.1	40.5	48.0
NNIPPS Total score, mean	65.8	76.7	91.1

Table 1. Demographic and Clinical Data

RESULTS

- mI/water was positively correlated (P<0.05) with UMSARS and NNIPPS total scores (**Fig. 2**).

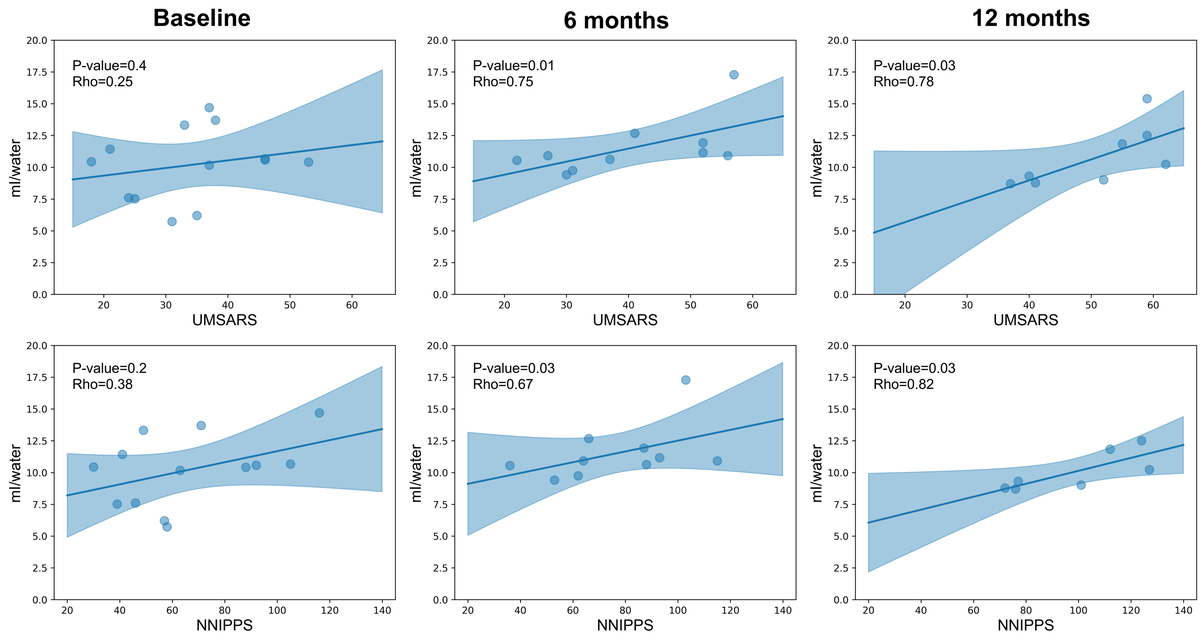

Fig. 2. Correlation between mI/water and clinical scores. Scatter plot and linear regression showing the positive relationship between mI/water (single-voxel, right putamen) and A-C) UMSARS, and D-F) NNIPPS, for baseline, 6 months and 12 months.

- NAA/water trended inversely with the clinical scores at 12 months, but these correlations did not reach statistical significance (**Fig. 3**).

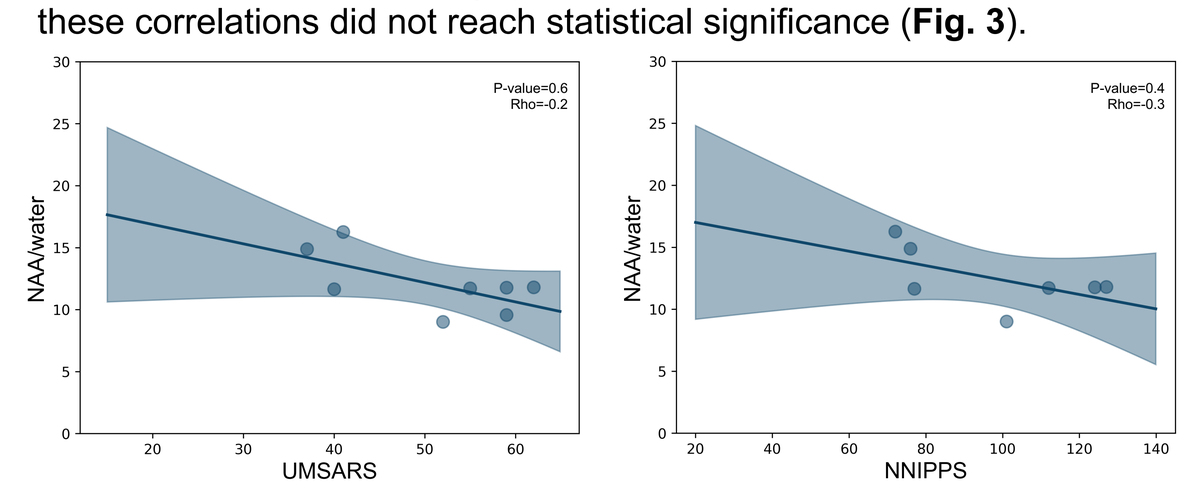

Fig. 3. Relationship between NAA/water and clinical scores at 12 months. Scatter plot and linear regression showing the negative association between NAA/water and disease severity.

- mI/water increased over 12 months, while NAA/water decrease over this period, but these changes were not statistically significant (**Fig. 4**).

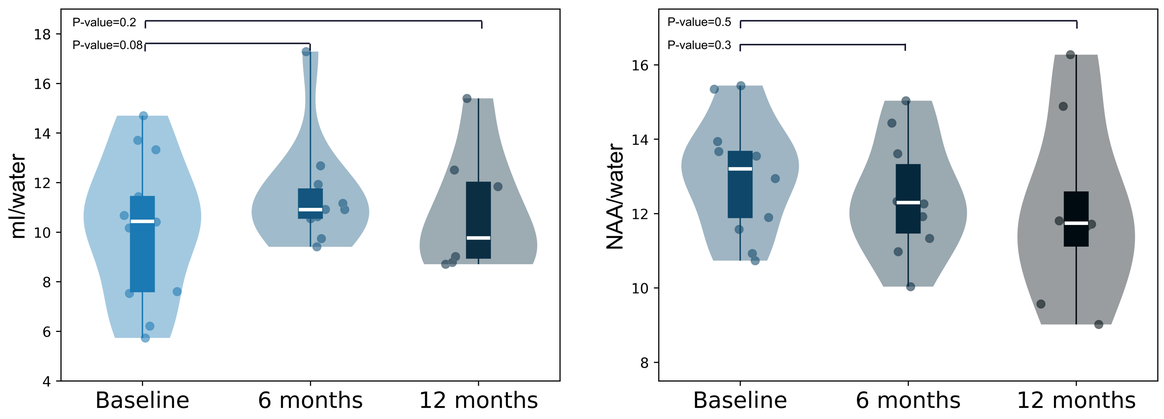

Fig. 4. Evolution of the metabolites over time. Violin and box plots showing the distribution of values for mI/water and NAA/water for baseline, 6 months and 12 months.

CONCLUSIONS

- mI/water, as a marker of gliosis, was significantly correlated with disease severity.
- NAA/water, as a marker of neuronal integrity, was negatively associated with disease severity but did not reach statistical significance. Lack of significance may be based on small patient numbers and limited follow up.
- Our results suggest that mI/water increases, while NAA/water decrease over one-year in patients with MSA, consistent with MSA pathology.
- These findings suggest that metabolite concentration by MRS may be useful biomarkers for assessing disease severity and treatment response In MSA.

[1] Oeltzschner G, et al. J Neurosci Methods. 2020;343:108827
[2] Wenning, G, et al. Mov. Disord. 2022; 37:1131
[3] Lancione, M, et al. Neuroimage Clin. 2022;34:102989

International Congress of Parkinson's Disease and Movement Disorders. Copenhagen, August 27-31, 2023.
Abstract No. 181