The MSA Atrophy Index: A Marker of Clinical Progression in Multiple System Atrophy

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OBJECTIVE

To develop a specific brain atrophy marker to track disease progression in multiple system atrophy (MSA) patients over one year and to assess its association with clinical measures of disease progression.

INTRODUCTION

- MSA is a rapidly progressing neurodegenerative disorder characterized by autonomic failure, Parkinsonism (MSA-P), and/or cerebellar ataxia (MSA-C).
- Reliable biomarkers for tracking disease progression are lacking, in part due to MSA's significant clinical and pathological heterogeneity.
- Previous MRI studies have reported brain volume reductions in regions implicated in MSA, but tracking these changes reliably has been challenging.
- We introduce the MSA Atrophy Index (MSA-AI), a composite atrophy marker derived from the lentiform nucleus (LN, putamen and globus pallidus) and olivopontocerebellar (OPC, cerebellum and brainstem) regions, as a potential biomarker for assessing MSA progression.

METHODS

- **Participants:** Seventeen participants with clinically probable MSA were recruited from the bioMUSE natural history study.
- **Data Collection:** Fluid biomarker analysis, 3T MRI, and neurological exams were conducted at baseline, 6 months, and 12 months. Clinical assessments included UMSARS and NNIPPS rating scales.
- **Regions of Interest (ROIs):** AssemblyNet, a deep learning model, was used to segment the putamen, globus pallidus, cerebellum and brainstem. Regional volumes were normalized to total intracranial volume and expressed as %TICV.
- **Z-scores** for the LN and OPCA were derived using the reference data from age-matched healthy adults from the Human Connectome Project (n=489, ages 46-82).
- **MSA Atrophy Index (MSA-AI):** The MSA-AI was derived by averaging the z-scores of LN and OPCA.
- **Group Differences:** Baseline volumes and MSA-AI values were compared between MSA and PD/DLB participants using two-sample Wilcoxon tests.
- **Longitudinal Changes:** Linear mixed-effects models were used to assess volume changes over time, controlling for age and sex.
- **Clinical Correlation:** Associations between volume changes and disease progression (Unified Multiple System Atrophy Rating Scale, UMSARS) were examined using Spearman correlation.

RESULTS:MSA PARTICIPANTS

Fluid and imaging biomarkers, along with clinical manifestations, were used to classify patients as MSA (n=10: 6 MSA-P, 4 MSA-C) or PD/DLB (n=5). Patients who tested negative for alpha-synuclein (n=2) were excluded from the analyses.

	MSA	PD/DLB
N	10	5
Sex (M/F)	4/6	4/1
Age (years), mean ± std	60 ± 8	67 ± 7
UMSARS Total, mean ± std	34 ± 11	25 ± 9
PPS Total score, mean ± std	59 ± 20	50 ± 27

Table 1. Demographic and Clinical Data at baseline

RESULTS:BRAIN VOLUMES

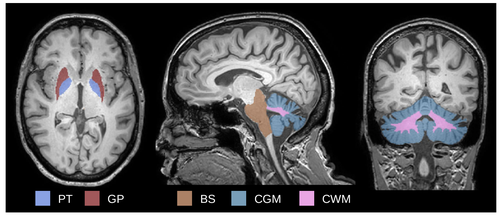

Fig. 1. Regions of Interests (ROIs) Example of ROIs segmented using AssemblyNet, including the putamen (PT), globus pallidus (GP), brainstem (BS), cerebellar grey matter (CGM), and cerebellar white matter (CWM).

Baseline Group Differences:

MSA patients had significantly lower LN and OPC volumes compared to PD/DLB participants (p=0.074 and p=0.007, respectively). The **MSA-AI** was also significantly lower in MSA patients compared to PD/DLB (p<0.001).

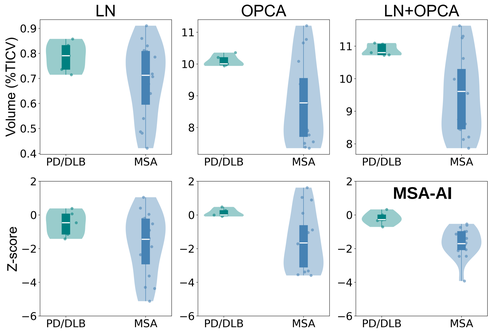

Fig. 2. Group differences.
Top row: Normalized volumes (%TICV) for the LN, OPCA and combined (LN+OPCA).
Bottom row: Z-scores.
Z-score interpretation: 0 = no difference from reference group, more negative values indicate greater atrophy, with -1 representing one standard deviation below controls. Progressively lower z-scores indicate more atrophy relative to controls.

RESULTS: LONGITUDINAL CHANGES

Longitudinal Changes Over 12 Months:

- MSA patients experienced significant volume reductions reductions in LN, OPC, and MSA-AI at 12 months (p=0.001, p<0.001, and p<0.001).
- PD/DLB participants showed no significant volume changes.

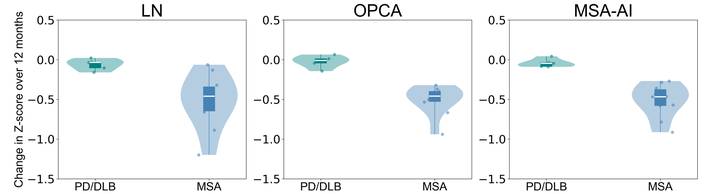

Fig. 3. Longitudinal changes over 12 months. Violin plots showing the changes in z-scores over 12 months. MSA patients showed significant reductions.

Correlation with Clinical Measures:

- Decreases in LN, OPCA, and MSA-AI z-scores were associated with increases in total UMSARS scores, suggesting a correlation between brain atrophy and disease progression.

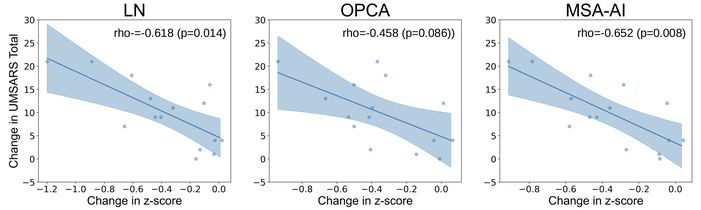

Fig. 4. Association between volumes changes and clinical scores. Scatter plot illustrating the association between decreases in LN, OPCA, and MSA-AI z-scores with increases in UMSARS scores over a 12-month period..

CONCLUSIONS

- The MSA-AI is a promising biomarker for tracking progression in MSA.
- Significant reductions in brain volume over 12 months correlate with clinical progression, underscoring the utility of structural MRI in monitoring MSA.
- MSA-AI z-scores provide objective interpretation by representing deviations from a normative population, in contrast to raw or normalized volumes that require reference data for context.
- Future longitudinal studies with automated segmentation could enhance the understanding of MSA progression and support the use of brain volume endpoints for the evaluation of of disease-modifying therapies.

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