A Multimodal Approach is Needed to Accurately Diagnose Early Multiple System Atrophy (MSA)

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OBJECTIVE

- To describe the use of neuroimaging and fluid biomarkers to improve the clinical diagnosis of early MSA.

INTRODUCTION

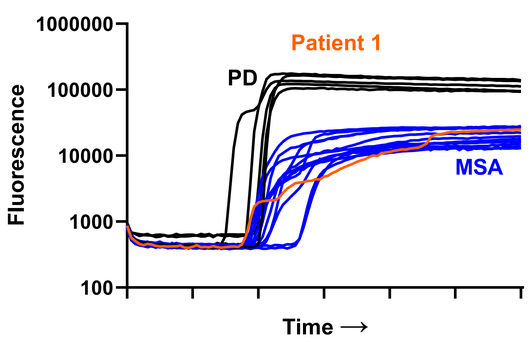
- MSA often presents similarly to Parkinson disease (PD)
- The revised MDS diagnostic criteria use MRI findings for defining clinically established but not clinically probable MSA.[1]
- Specialized MRI and fluid biomarkers have promise in improving the specificity of MSA diagnosis early in the disease course.
- We describe 3 clinically probable MSA patients with divergent MRI and fluid biomarker data, supporting the use of biomarkers to improve diagnostic accuracy in early MSA.

METHODS

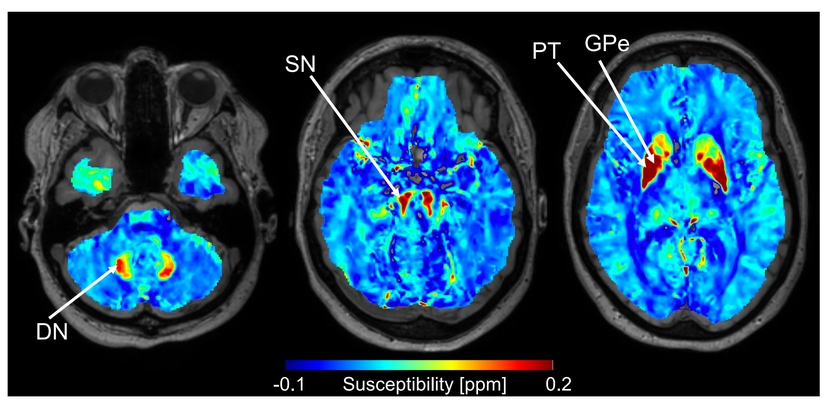
- Participants enrolled in the biomarkers of progression in MSA (bioMUSE) natural history study were diagnosed with early MSA (<3 years of motor symptoms) by clinical assessment.
- Neurologic exam was assessed at baseline (BL) and 3, 6, 9 and 12 months and neuroimaging and fluid biomarkers at BL, 6 and 12 months.
- MRI with quantitative susceptibility mapping (QSM) was used to measure iron content in the putamen (PT), substantia nigra (SN), globus pallidus (GP), and dentate nucleus (DN).
- CSF α-synuclein aggregation kinetics were assessed using a seed amplification assay[2].
- Plasma and CSF neurofilament light chain (NfL) levels were assessed.

PATIENT 1 - MSA

- 53-year-old female presented with a 3-year history of urinary and orthostatic hypotension [OH] symptoms, parkinsonism, and REM behavior disorder .
- Clinical exam noted Babinski sign, myoclonic tremor, limb ataxia, ataxic dysarthria and axial dystonia.
- QSM : increased iron in the putamen, globus pallidus externa (GPe), and substantia nigra.
- The Agg-α syn pattern indicated MSA pattern.

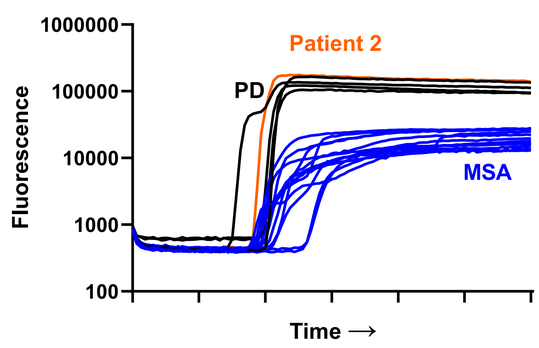


- CSF NfL: 4001.8 pg/mL
- α-syn profile: MSA

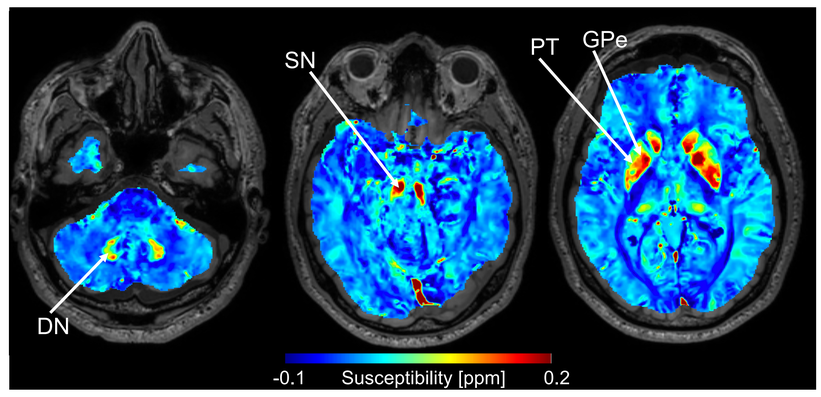


PATIENT 2 - PD

- 65-year-old male presented with a 2-year history of unexplained voiding difficulties with post void residual, OH and RBD.
- Clinical exam noted parkinsonism, asymmetric resting and myoclonic tremor and ataxic gait.
- QSM showed evidence of increased iron only in the substantia nigra.
- The Agg-α syn pattern indicated PD pattern

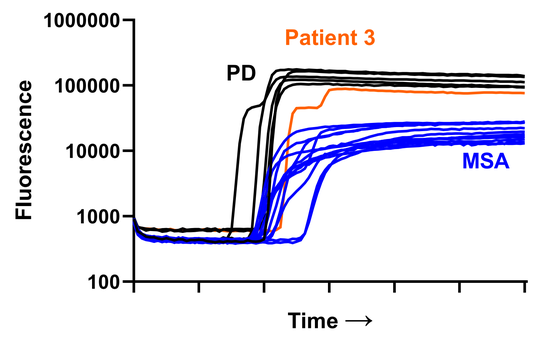


- CSF NfL:1297.6 pg/mL
- α-syn profile: PD

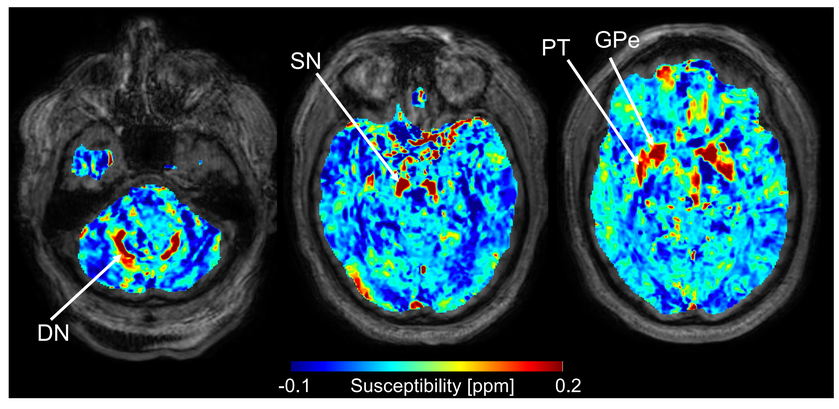


PATIENT 3 - MSA

- 53-year-old male presented with a 2-year history of unexplained voiding difficulties, OH, poorly responsive parkinsonism, gait dysfunction, RBD.
- Clinical exam noted parkinsonism, ataxia, Babinski sign and ataxic dysarthria.
- QSM showed increased iron in the putamen, GPe, substantia nigra and dentate.
- The Agg-α syn pattern was indeterminate with a PD and MSA pattern noted.



- CSF NfL: 2869.2 pg/mL
- α-syn profile: heterogenous, with MSA and PD patterns



CONCLUSIONS

- The diagnosis of early MSA based solely using clinical criteria is challenging.
- The presented cases demonstrate that no single biomarker can be relied on to aid in the diagnosis of early MSA.
- Divergent clinical and biomarker findings in this case series suggests a multimodal clinical-biomarker approach is required for accurate diagnosis of clinically probable or early MSA.
- These examples support application of clinical and quantitative biomarkers in clinical trials evaluating disease-modifying treatments for early MSA.

1. Wenning, et al. The MDS Criteria for the Diagnosis of Multiple System Atrophy. Mov. Disord. 2022. doi: 10.1002/mds.2900
2. Siderowf, Concha-Marambio, et al. Assessment of heterogeneity in the PPMI cohort using α-synuclein seed amplification. Lancet Neurol. 2023. doi: 10.1016/S1474-4422(23)00109-6

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