Novel Multiple System Atrophy Subtypes Identified Using Unsupervised Machine Learning Algorithms

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ABSTRACT

OBJECTIVE
To identify a novel disease subtype of multiple system atrophy (MSA) by applying machine learning algorithms to a large cohort of autopsy-confirmed MSA.

BACKGROUND
MSA shows various degrees of degeneration in striatonigral and olivopontocerebellar systems; however, its progression remains to be elucidated. Recently, probabilistic disease progression models have been developed, yet this approach has not been applied to MSA.

METHODS
We analyzed 167 autopsy-confirmed MSA patients. Neuronal loss in five regions (putamen, substantia nigra, pontine nucleus, inferior olivary nucleus, and cerebellar Purkinje cells) was semi-quantitatively assessed using a 4-point scale for input into an unsupervised learning algorithm (Subtype and Stage Inference - SuStaIn). Clinical information was collected from medical records. The immunoreactive area of α-synuclein immunohistochemistry (IHC) was quantitatively measured using a color deconvolution algorithm in the putamen, substantia nigra, pontine nucleus, inferior olivary nucleus, and cerebellar dentate nucleus. We examined correlations between SuStaIn subtyping results and both clinical information and pathological findings.

RESULTS
The SuStaIn algorithm classified patients into three subtypes: subtype 1 (S1, n=86), subtype 2 (S2, n=44), and subtype 3 (S3, n=30). S1 showed initial neuronal loss in the striatonigral system, S2 in the olivopontocerebellar system, while S3 exhibited early neuronal loss in both systems. These patterns were validated by stained area analysis with S3 showing greater areas in the putamen compared to S2 (P = 0.02) and in the pontine and dentate nuclei compared to S1 (P = 0.001 and P = 0.016). Parkinsonism was predominant in 97% of S1 and 63% of S3, while cerebellar symptoms were predominant in 66% of S2 (P < 0.0001). S3 demonstrated shorter disease duration (6±2 years) compared to S1 and S2 (both 8±3 years; P < 0.05), more frequent rapid progression and early falls, and less frequent cognitive impairment. A positive correlation was observed between the SuStaIn stage and disease duration (r = 0.25, P = 0.0014).

CONCLUSIONS
This study identified a unique MSA subtype characterized by early involvement of both striatonigral and olivopontocerebellar pathology and poor prognosis. The SuStaIn algorithm shows promise for novel classifications of MSA subtypes.

OBJECTIVE

- To explore novel subtypes of MSA using an unsupervised machine learning algorithm based on the pathological severity of affected brain regions in a cohort of autopsy-confirmed MSA.

METHODS

- From 2015 to 2022, we identified 214 consecutive autopsy patients with a pathological diagnosis of MSA from the Mayo Clinic brain bank.
- After excluding 47 patients lacking adequate clinical information, the final study cohort comprised 167 patients[1,2].
- Neuronal loss was semi-quantitatively assessed on H&E-stained sections using a 4-point scale[3] in five regions: putamen, substantia nigra pars compacta, pontine nucleus, inferior olivary nucleus, and cerebellar Purkinje cells.
- α-Synuclein immunoreactive areas were quantitatively measured using color deconvolution in five brain regions.
- Ordinal SuStaIn algorithm[4] was performed using neuronal loss scores.

RESULTS 1

Table 1 Characteristics of patients

	All patients N = 167
Female	81 (49%)
Age at onset (years)	59.5 ± 8.7
Age at death (years)	67.0 ± 8.0
Disease duration (years)	7.5 ± 3.4
Clinical subtypes	
MSA-P	122 (73%)
MSA-C	45 (27%)
Antemortem clinical diagnosis	
MSA	136 (81%)
MSA or other diseases	13 (8%)
Other than MSA	18 (11%)
Parkinson's disease	11 (7%)
Corticobasal degeneration	4 (2%)
Progressive supranuclear palsy	3 (2%)

RESULTS 2

FIGURE 1 Three-subtypes

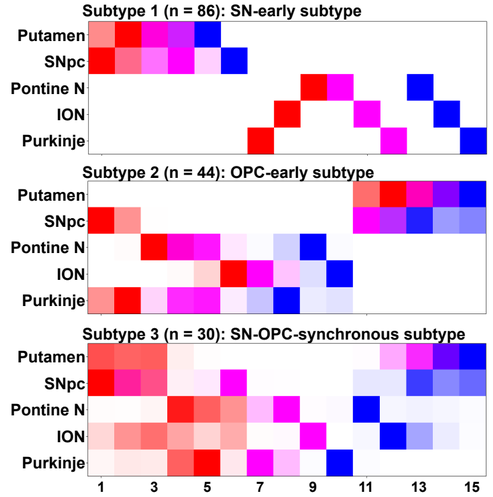


Table 2 Clinical characteristics of 3 subtypes

	S1 n = 86	S2 n = 44	S3 n = 30	p-value
Female	48 (56%)	14 (32%)	17 (57%)	**0.024**
Age at onset (years)	59.6 ± 8.7	56.6 ± 7.4	62.4 ± 7.2	**0.011**
Age at death (years)	67.6 ± 8.5	64.5 ± 6.5	68.7 ± 6.6	**0.036**
Duration (years)	7.8 ± 3.5	8.0 ± 3.1	6.3 ± 1.9	**0.034**
Clinical subtypes				**< 0.0001**
MSA-P	83 (97%)	15 (34%)	19 (63%)	
MSA-C	3 (3%)	29 (66%)	11 (37%)	
Clinical Dx = MSA	64 (74%)	42 (95%)	26 (87%)	**0.007**
Autonomic onset	15 (17%)	7 (16%)	10 (33%)	0.26
Rapid progression	21 (24%)	18 (41%)	17 (57%)	**0.0048**
Early falls	31 (36%)	22 (50%)	21 (70%)	**0.0039**
Stridor	16 (19%)	12 (27%)	9 (30%)	0.33
Pseudobulbar affect	13 (15%)	12 (27%)	5 (17%)	0.23
Jerky myoclonic tremor	10 (12%)	4 (9%)	3 (10%)	0.89
Cognitive impairment	32 (37%)	19 (43%)	4 (13%)	**0.021**

FIGURE 2 SuStaIn stage and clinical parameters

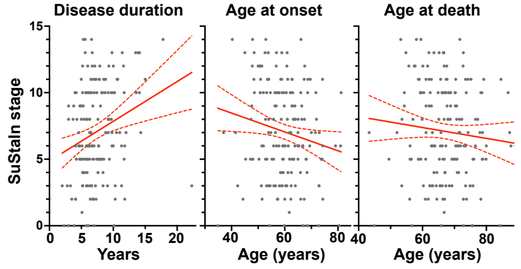


FIGURE 3 α-Synuclein stained areas

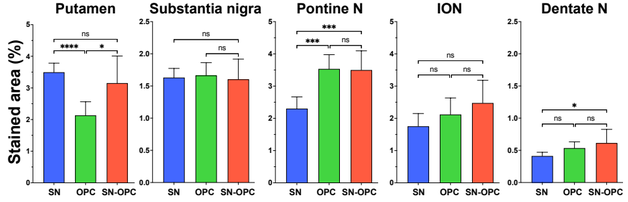
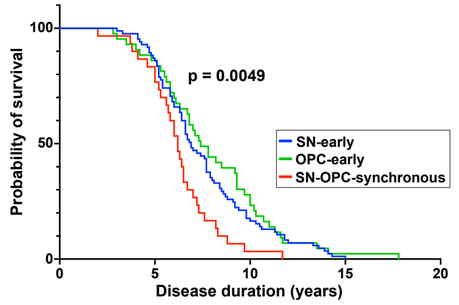


FIGURE 4 Survival analysis among MSA subtypes



Abbreviations
Dx, diagnosis; H&E, hematoxylin and eosin; ION, inferior olivary nucleus; MSA, multiple system atrophy; N, nucleus; OPC, olivopontocerebellar; SN, striatonigral; SNpc, substantia nigra pars compacta; SuStaIn, Subtype and Stage Inference

DISCUSSION

- Neuronal loss selectively progressed early in the SN system in subtype 1 (SN-early) and in the OPC system in subtype 2 (OPC-early), followed by progression to the other system.
- In contrast, subtype 3 showed concurrent neuronal loss in both systems from the early stages (SN-OPC synchronous).
- Patients in the SN-OPC-synchronous subtype showed a significantly higher proportion of patients with rapid progression and early falls compared to other subtypes.
- Cognitive impairment was significantly less frequent in the SN-OPC-synchronous subtype.
- The SN-OPC-synchronous subtype had significantly shorter disease duration compared to both SN-early (p = 0.0010) and OPC-early (p = 0.0093) subtypes.
- The SN-OPC-synchronous subtype demonstrated the most widespread α-synuclein pathology, validating SuStaIn subtypes using α-synuclein immunostaining in addition to neuronal loss.

CONCLUSIONS

- The present study identified a unique SN-OPC-synchronous subtype of MSA characterized by poor prognosis and early neuronal loss in both the SN and OPC systems.
- The SuStaIn algorithm has the potential to contribute to novel classification of MSA and a better understanding of the disease.

REFERENCES

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