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Clinicopathological correlates of pyramidal signs in multiple system atrophy

Chi-Ying R. Lin[1], Anisha Viswanathan[2,3], Tiffany X. Chen[2,3,4], Hiroshi Mitsumoto[2,5], Jean P. Vonsattel[6], Phyllis L. Faust[6] & Sheng-Han Kuo[2,3]

[1]Department of Neurology, Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, Texas, USA
[2]Department of Neurology, Columbia University Irving Medical Center and the New York Presbyterian Hospital, New York, New York, USA
[3]Initiative for Columbia Ataxia and Tremor, Columbia University Irving Medical Center, New York, New York, USA
[4]Department of Biomedical Engineering, Whiting School of Engineering, Johns Hopkins University, Baltimore, Maryland, USA
[5]Eleanor and Lou Gehrig ALS Center, Columbia University Irving Medical Center, New York, New York, USA
[6]Department of Pathology and Cell Biology, Columbia University Irving Medical Center and the New York Presbyterian Hospital, New York, New York, USA

Correspondence
Chi-Ying R. Lin, Department of Neurology, Baylor College of Medicine, Houston, TX, USA. Tel: 713-798-2273; Fax: 713-798-7434; E-mail: chi-ying.lin@bcm.edu

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Abstract

Objective: Pyramidal signs are common but often under-recognized in multiple system atrophy (MSA). The clinicopathological correlates of pyramidal signs in MSA are not well characterized. The present study aims to understand the role of pyramidal signs in MSA. **Methods**: We examined 40 autopsy-confirmed MSA cases in New York Brain Bank. The pyramidal signs were quantified by an established rating scale, summarized as the pyramidal score. We assessed whether pyramidal scores are associated with autonomic, parkinsonism, and cerebellar features and survival. We also examined whether the density of glial cytoplasmic inclusions (GCIs) in the motor cortex and its underlying white matter is associated with the pyramidal score. **Results**: MSA parkinsonian type cases have higher pyramidal scores compared to cerebellar type cases ($p = 0.017$). MSA cases with high pyramidal scores are more likely to have laryngeal stridor (OR = 4.89, $p = 0.022$), but less likely to have orthostatic hypotension (OR = 0.11, $p = 0.006$) and erectile dysfunction (OR = 0.05, $p = 0.018$). MSA cases with high pyramidal scores do not differ from those with low pyramidal scores in terms of bowel dysfunction, dry eyes and mouth, and survival. Finally, MSA cases with more GCIs in the motor cortex have higher pyramidal scores compared to those with few GCIs ($p = 0.017$). **Interpretation**: Pyramidal signs in MSA are associated with the parkinsonian subtype, laryngeal stridor, and certain autonomic dysfunction.

Introduction

Multiple system atrophy (MSA) is an adult-onset, sporadic, and relentlessly progressive neurodegenerative disease.[1,2] The neuropathological hallmark for MSA is the glial cytoplasmic inclusion (GCI), reflecting alpha-synuclein deposition in glial cells in the nigrostriatal or/and olivo-ponto-cerebellar systems,[3] leading to parkinsonism (MSA-P), and cerebellar ataxia (MSA-C) subtypes. MSA-P may have a faster disease progression than MSA-C,[4] indicating that the predominant symptoms of MSA may have prognostic value. Another core feature for MSA is autonomic dysfunction, which occurs early and persists throughout the disease course.[3]

In addition to the above-mentioned three domains of MSA (parkinsonian, cerebellar, and autonomic), the fourth domain of neurological symptoms in the originally described MSA is in the pyramidal system, manifesting as pyramidal signs, such as hyperreflexia, extensor plantar responses, and spasticity.[5–8] These pyramidal signs can provide important diagnostic clues for MSA in both parkinsonian and cerebellar subtypes.[2,9–12] Pyramidal

signs are due to damage in the pyramidal system from the motor cortex to corticospinal tract. These clinical observations can also be reflected in structural imaging studies, demonstrating pyramidal system degeneration in MSA.[9] Neuropathological examination in the MSA motor cortex demonstrates astrocytosis, loss of Betz cells, and GCIs, along with reduced number of myelinated fibers in the spinal cord,[11] which all supports the pyramidal involvement. In summary, these data support that this fourth domain of MSA may be part of the core clinical and pathological features.

Despite clear involvement of the pyramidal system in MSA, there is no study, to our knowledge, that investigates associations between pyramidal signs and other clinical landmarks in MSA. Additionally, there have been no studies evaluating pathologic correlates of clinical pyramidal signs in MSA. To address these knowledge gaps, we thus studied the associations between the pyramidal signs with other clinical features and pathological alterations in autopsy-confirmed MSA cases.

Methods

We studied autopsy-confirmed MSA cases from the New York Brain Bank at Columbia University.[13] The study was approved by Columbia University Institutional Review Boards and the informed consents for brain donations were obtained for all cases. The presence of GCIs was confirmed by the standard alpha-synuclein immunohistochemistry staining (clone KM51, Novocastra Antibodies) and clear documentation by neuropathologists at Columbia University.[13] Up until January 2021, the New York Brain Bank contains 40 MSA cases, and all of the cases were followed up in our Center for Parkinson's disease and Other Movement Disorders Clinic during life. We conducted a retrospective review for all these 40 MSAs and recorded their clinical features in detail,[7] including the pre-mortem diagnoses, dysautonomia (i.e., autonomic failure or dysfunction as defined by the MSA diagnostic consensus[7]), rapid eye movement behavior disorder (RBD, i.e., sleep behaviors such as arm thrashing, leg kicking, or falling out of bed in the context of dream enactment scenes; based on self-report or via sleep studies), stridor (i.e., based on physician's questioning and/or patient's self-report, described as a high-pitched, harsh, or strained breathing sound during inspiration either during sleep or wakefulness[14]), dysarthria (i.e., change of the speech articulation clarity), and dysphagia (i.e., reported symptoms indicative of swallowing difficulty, such as "food stuck in the throat"), and the presence of dry eyes (i.e., patient's self-report of dry-eye-related description, including but not limited to "a feeling of gravel, pain, dryness, or gravel) and dry mouth (i.e., patient's self-report of dry mouth-related description, including but not limited to "a feeling of dryness, lack of saliva, burning of mouth").[15]

Assessment of pyramidal signs

To quantitatively measure the severity of pyramidal signs, we used a published scale (i.e., pyramidal scores) developed for amyotrophic lateral sclerosis (ALS).[16] In clinical practice, it could be difficult to assess whether the increased muscle tone is fully attributed to pyramidal involvement, especially for MSA-P cases who have rigidity. Thus, to avoid overestimating the assessment, we modified the scale by excluding the "muscle tone" domain. The details of this scale are listed in Table S1. We quantified deep tendon reflexes for each extremity and also counted the total numbers of Babinski signs, Tromner signs, brisk facial, and jaw jerks and forced yawn signs. The highest possible score is 20; we then divided the sum of the scores in each case by 20 to calculate the percentage as the "*pyramidal scores*."[16] Each case is categorized into high pyramidal scores (P_H: score ≥ 50) or low pyramidal scores (P_L: score < 50). We compared the severity of pyramidal signs between MSA-P and MSA-C, as well as probable MSA and possible MSA, diagnosed during life.

Neuropathologic investigation

To determine the association between pyramidal scores and the density of GCIs, we developed a semi-quantitative scale for GCI density in the motor cortex as well as the white matter underlying the motor cortex (Brodmann area 4 and 6): GCI score 0 = none, 1 = scanty/rare, 2 = scattered, and 3 = widespread (Fig. 1). We divided MSA cases into those with a higher GCI density (GCI_H: GCI score ≥ 2) and those with low GCI density (GCI_L: GCI score < 2). Considering that MSA has pathological involvement in the olivo-ponto-cerebellar systems, we also examined the presence of GCIs in the pontine base, inferior olivary nucleus, and cerebellar dentate as well as its adjacent white matter. The severity of the neuronal loss of motor cortex (0 = normal, 1 = relatively spared though not normal/mild loss, 2 = moderate loss, and 3 = marked/severe loss) and the neuronal cytoplasmic inclusion density of inferior olivary nucleus were also rated (0 = none, 1 = scanty/rare, 2 = scattered, and 3 = widespread). In addition, we studied the co-existent Alzheimer-type pathology using Braak and Braak Alzheimer's Disease (AD) staging for neurofibrillary tangles[17] and The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) staging[18]—a

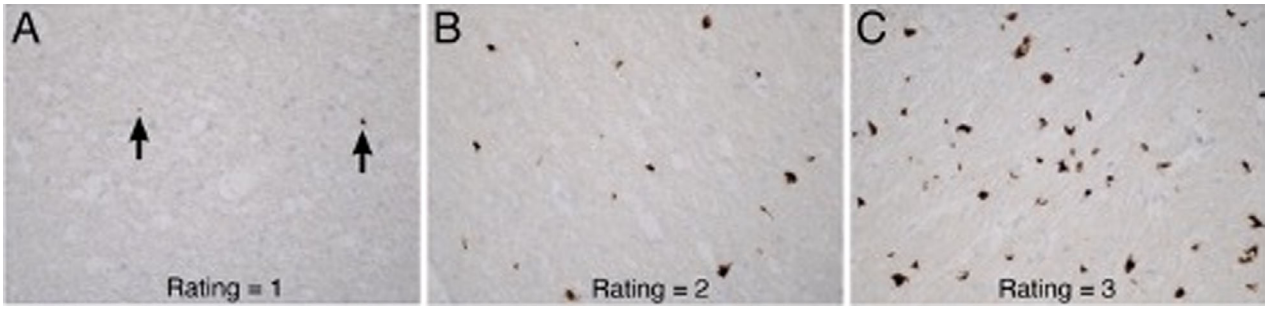

Figure 1. Representative images of glial cytoplasmic inclusions in white matter underlying the primary motor cortex/Brodmann area four in multiple system atrophy demonstrated by alpha-synuclein immunohistochemistry staining. (A) scanty and rare distribution (GCI score = 1), (B) scattered to numerous (GCI score = 2), and (C) widespread (GCI score = 3). *GCI = glial cytoplasmic inclusion.

National Institute of Aging-Reagan category (low, intermediate, and high probability of AD) was then assigned.[19] We also studied the Lewy body disease pathology using Braak Lewy body staging.[20] The pathological quantification was first performed by two neuropathologists when the brain was examined at the New York Brain Bank, and underwent a secondary inspection by experienced neuropathologists (P.L.F. and J.P.V.) before determining the final grading.

Statistical analysis

We investigated if P_H and P_L cases are more likely to have different subtypes of MSA (MSA-P vs. MSA-C) using chi-squared test. We also examined whether pyramidal scores differ between MSA-P and MSA-C using independent two-sample t-test. We conducted multivariable linear regression models to determine if the pyramidal scores are associated with survival, defined by the length of time in years from the time of diagnosis to the end of life, taking into account age, sex (male = 0, female = 1), and MSA types (MSA-C = 0, MSA-P = 1). We conducted logistic regression to examine whether the pyramidal scores are associated with other clinical features in MSA (P_L = 0, P_H = 1). We determined whether cases with higher GCI density (GCI_H: GCI score $\geq$ 2) in the motor cortex and adjacent white matter as well as the olivo-ponto-cerebellar system have higher pyramidal scores compared to cases with low GCIs (GCI_L: GCI score < 2) using a chi-squared test. We also studied if the GCIs density in the motor cortex are different between MSA-P and MSA-C cases using independent two-sample *t*-test. To address whether pyramidal signs are correlated specifically with pathological changes in the motor cortex, we used Pearson's correlation to examine the association between pyramidal scores and the pathological alterations in motor cortex. As the design of the present study is of exploratory nature, multiple comparisons were not planned in order not to underestimate the statistical significance in a small-sample size analysis. All analyses were conducted using GraphPad Prism v8.

Results

Demographics

In 40 autopsy-confirmed MSA cases, the average age of symptoms onset was 60.8 ± 7.7 years, and the age of death was 68.4 ± 7.2 years, with disease duration of 7.9 ± 2.7 years. There were 15 (35%) men and 25 (65%) women. The average pyramidal scores were 50.9 ± 16.7. In this cohort, the number of individuals with MSA-P (n = 27, 67.5%) was approximately twice of that of individuals with MSA-C (n = 13, 32.5%). Interestingly, the pyramidal scores were higher in MSA-P cases when compared to MSA-C cases (60.0 ± 7.5 vs. 41.9 ± 17.9, p = 0.017) (Table 1), indicating that MSA-P cases have more pyramidal signs, when compared to MSA-C cases. Consistently, hyperreflexia and Babinski sign were also more frequently seen in MSA-P cases (hyperreflexia: MSA-P 44% vs. MSA-C 15%; Babinski sign: MSA-P 48% vs. MSA-C 23%; Table S2). We found that the severity of pyramidal signs did not significantly differ between the

Table 1. Pyramidal score difference in multiple system atrophy parkinsonism and cerebellar types.

	MSA-P(n = 13)	MSA-C(n = 27)	p-value
Age[1]	68.1 ± 7.9	69.0 ± 5.9	0.732
Sex (M/F)[2]	9/18	6/7	0.785
Age at onset[1]	60.0 ± 7.5	62.4 ± 8.1	0.371
Disease duration (years)[1]	8.1 ± 2.7	7.3 ± 2.8	0.382
Pyramidal score[1]	60.0 ± 7.5	41.9 ± 17.9	*0.017*

MSA-C, multiple system atrophy cerebellar type; MSA-P, multiple system atrophy parkinsonian type.
p < 0.05 are in italics.
[1]Independent two sample *t*-test.
[2]Chi-squared test.

diagnosis of probable MSA and possible MSA during life (Table S3). We were able to study 38 cases' AD type changes (Braak neurofibrillary tangle and CERAD staging) and Braak Lewy body staging. Our results showed that majority of cases examined did not have co-existent Alzheimer-type pathology (CERAD = 0 in 32 cases, A in three cases, B in two case, and C in one case; Braak neurofibrillary tangle staging = zero in six cases, I in 11 cases, II in 10 cases, III in five cases, IV in five cases, and V in one case; NIA-Reagan probability of AD: no evidence of AD for 32 cases, low evidence for three cases, intermediate evidence for two cases, and high evidence for one case) or Lewy body pathology (Braak Lewy body staging = 0 in 34 cases, 2 in two cases, 3 in one case, and 4 in one case).

We next stratified patients into those with high pyramidal scores ($P_{H:}$ score ≥ 50) or low pyramidal scores (P_L: score < 50). We found that P_H and P_L cases were similar in age of death, gender, age of symptoms onset, or disease duration (Table 2).

Clinical correlates with pyramidal scores

We next examined whether the pyramidal scores are associated with features of MSA. We found that, when compared to P_L cases, P_H cases are more likely to have stridor (OR = 4.89, $p = 0.022$), but less likely to have orthostatic hypotension (OR = 0.11, $p = 0.006$) and erectile dysfunction (OR = 0.05, $p = 0.018$), both of which belong to the autonomic dysfunction (Table 3). P_H cases did not have increased odds of having bowel dysfunction (constipation or fecal incontinence), RBD, dry eyes/mouth, dysarthria, and dysphagia compared to P_L cases (all $p > 0.05$).

Table 2. Clinical features of multiple system atrophy cases, stratified by clinical pyramidal scores.

	Clinical pyramidal scores		
	P_H(n = 20)	P_L(n = 20)	p-value
Age[2]	68.4 ± 5.5	68.45 ± 8.75	0.983
Sex (M/F)[1]	14/6	11/9	0.327
Age at onset[2]	60.4 ± 5.2	61.3 ± 9.6	0.715
Disease duration (years)[2]	7.9 ± 2.7	7.9 ± 2.9	0.978
Pyramidal score[2,*]	64.3 ± 9.3	37.3 ± 9.0	<0.001*

Abbreviations: F, female; GCI, glial cytoplasmic inclusion; GCI_H, GCI deposition is none (GCI = 0) or scanty/rare (GCI = 1); GCI_L = GCI deposition is scattered/numerous (GCI = 2) or widespread/everywhere (GCI = 3); M, male; MSA, multiple system atrophy; P/C, parkinsonism type/cerebellar type; P_H, high pyramidal scores (≥50); P_L, low pyramidal score (<50).
*$p < 0.05$.
[1]Independent two sample t-test.
[2]Chi-squared test.

Table 3. Logistic regression analyses investigating the association between the pyramidal score and the core features seen in multiple system atrophy.

Features	Odds ratio	p-value
Urinary incontinence	2.25	0.206
Orthostatic hypotension	0.11	*0.006*
Erectile dysfunction[1]	0.05	*0.018*
Bowel dysfunction[2]	0.80	0.736
RBD	0.58	0.465
Stridor	4.89	*0.022*
Dry eyes	0.75	0.105

Odds ratio of cases with high versus low pyramidal scores are displayed. Dependent variable: pyramidal score < 50 = 0, pyramidal score ≥ 50 = 1. RBD, rapid eye movement behavioral disorders.
$p < 0.05$ are in italics.
[1]Females excluded.
[2]Bowel dysfunction includes constipation and fecal incontinence.

Table 4. Multivariable linear regression examines the association between the disease survival and clinical features.

Clinical features	β	p-value
Age	0.07	0.253
Sex[1]	0.26	0.780
MSA type[2]	0.92	0.359
Pyramidal score[3]	−0.24	0.797

[1]Male = 0, Female = 1.
[2]Cerebellar type = 0, parkinsonism type = 1.
[3]Pyramidal score < 50 = 0, pyramidal score ≥ 50 = 1.

Finally, we determined whether pyramidal signs are associated with survival: we found P_H and P_L cases are not different in survival (P_H vs. P_L = 7.9 ± 2.7 years vs. 7.9 ± 2.9 years, $p = 0.978$). The results did not change after we stratified the MSA cases into MSA-P (P_H vs. P_L = 7.8 ± 2.7 years [n = 16] vs. 8.6 ± 2.8 years [n = 11], $p = 0.870$; $\beta = -1.08$, $p = 0.322$) and MSA-C (P_H vs. P_L = 8.3 ± 3.1 years [n = 4] vs. 6.9 ± 2.8 years [n = 9], $p = 0.703$; $\beta = 1.20$, $p = 0.574$). In addition, using multivariable regression analysis, we also found no association between pyramidal scores and survival ($\beta = -0.24$, $p = 0.797$, Table 4).

Neuropathological correlates with pyramidal scores

We next studied clinicopathological correlates by investigating if GCI density in the motor cortex and the adjacent white matter is associated with pyramidal scores. We found indeed that GCI_H cases have higher pyramidal scores compared to GCI_L cases (54.0 ± 14.7 vs. 39.4 ± 18.6, $p = 0.017$). Consistently, GCI_H cases have a

Table 5. Neuropathological assessments of multiple system atrophy cases, stratified by glial cytoplasmic inclusion density.

	GCI density		
	GCI_H	GCI_L	*p*-value
Age at death[1]	68.1 ± 7.3	69.4 ± 7.4	0.637
Sex (M/F)[2]	11/20	4/5	0.625
Age at onset[1]	60.2 ± 8.0	62.9 ± 6.3	0.359
Disease duration/survival (years)[1]	8.3 ± 2.4	6.5 ± 3.4	0.091
Pyramidal score[1]	54.0 ± 14.7	39.4 ± 18.6	*0.017*
MSA subtype (P/C)[2]	24/7	3/6	*0.013*
GCI density – motor cortex[1]	2.6 ± 0.5	1.0 ± 0.0	*<0.001*
GCI density – pontine base[1]	2.7 ± 0.8	2.0 ± 0.7	0.095
GCI density – ION[1]	2.0 ± 0.8	1.4 ± 0.5	0.154
GCI density – cerebellar dentate and its adjacent white matter[1]	2.5 ± 0.9	2.3 ± 0.5	0.612
Motor cortex neuronal loss level[1]	1.3 ± 0.9	0.4 ± 0.9	0.084
NCI density – ION[1]	1.7 ± 0.8	1.3 ± 1.0	0.480

CERAD, The Consortium to Establish a Registry for Alzheimer's disease; F, female; GCI, glial cytoplasmic inclusion; GCI_H, cases with GCI deposition in the motor cortex and its adjacent white matter rated as none (GCI = 0) or scanty/rare (GCI = 1); GCI_L, cases with GCI deposition in the motor cortex and its adjacent white matter rated as scattered/numerous (GCI = 2) or widespread/everywhere (GCI = 3); the same method was applied to quantify the GCI density in other brain regions listed in the table; ION, inferior olivary nucleus; M, male; MSA, multiple system atrophy; NCI, neuronal cytoplasmic inclusion; P/C, parkinsonism type/cerebellar type; P_H, high pyramidal scores (≥50); P_L, low pyramidal score (<50).
$p < 0.05$ are in italics.
[1]Independent two sample *t*-test.
[2]Chi-squared test.

trend toward more severe neuronal loss in the motor cortex when comparing to GCI_L cases, although not statistically significant (1.3 ± 0.9 vs. 0.4 ± 0.9, $p = 0.084$, Table 5). Our results showed that GCI_H cases were more likely to be clinically diagnosed with MSA-P (MSA-P/MSA-C in GCI_H = 24/7, MSA-P/MSA-C in GCI_L = 3/6, $p = 0.013$), consistent with clinical findings (Table 1). Interestingly, the GCI_H and GCI_L cases had no significant differences in the GCI severity in the olivo-ponto-cerebellar regions (Table 5), demonstrating specificity. The neuronal cytoplasmic inclusion density in the inferior olivary nucleus is not significantly different in GCI_H versus GCI_L (Table 5). Finally, GCI_H and GCI_L cases have no difference in survival (Table 5).

Discussion

While the pyramidal system is one of the major domains frequently involved in MSA, the association between pyramidal signs and other clinical features has not been well studied. Our results demonstrate that pyramidal signs are more frequent in MSA-P than in MSA-C, and MSA patients with pyramidal signs are more likely to have comorbid laryngeal stridor. Laryngeal stridor, which can be partly explained by the pyramidal hyperactivity of respiratory adductor muscles,[21] has been reported in ALS.[22] ALS is a classic disease with pyramidal system involvement, which resonates with our study findings. Interestingly, the presence of pyramidal signs does not appear to affect patient survival. Finally, pyramidal signs correlate with GCI pathology in the motor cortex and the adjacent white matter.

The association between pyramidal signs and autonomic dysfunction in MSA is complex and requires future exploration. Specifically, we found that patients with high pyramidal scores are less likely to have orthostatic hypotension and erectile dysfunction. These observations may be partly explained by the fact that autonomic dysfunction in MSA can result from the pathological involvement of the preganglionic neurons of the central autonomic pathway at different levels, creating diverse autonomic symptoms.[23,24] The finding of less erectile dysfunction may imply less parasympathetic involvement in MSA cases with higher pyramidal scores.

MSA pathology was hypothesized to have a prion-like spreading pattern.[25] How do we factor our findings into the prion-like spreading of MSA pathology in the central nervous system? Since we have identified that MSA-P cases are more likely to have higher pyramidal scores, which correlate with the density of GCIs in the motor cortex, it is plausible that alpha-synuclein pathology in the nigrostriatal pathway is more likely to reach the motor cortex, possibly via retrograde connection, given the direct connection between the motor cortex and basal ganglia.[26] On the other hand, alpha-synuclein deposits in the cerebellum may need to go through several relays of brain areas such as the thalamus to reach the motor cortex. The other possibility is that MSA-P and MSA-C may have different alpha-synuclein "strains",[27,28] which potentially have differential properties to spread to the motor cortex. Further examination in experimental models will yield additional insight and help us to understand the pathomechanism of MSA.

A strength of this study is that all MSA cases are pathologically confirmed. To our knowledge, this is the first study unveiling the association between pyramidal signs and other clinical features in MSA. This is also the first study demonstrating the correlations between the pathologic burdens of GCIs in the motor cortex with pyramidal signs in MSA. There are several limitations of the present study. First, we do not have neuropathologic examination in the spinal cord, which is not included in the standard

protocol in the New York Brain Bank for MSA cases. Therefore, we were not able to examine the sacral Onuf's nucleus and interomediolateral column, both of which contain neurons for autonomic function. Along this line, we were not able to examine the lateral corticospinal tract, which would be an additional correlate of pyramidal signs. Our study did not detect a statistically significant correlation between neuronal loss in motor cortex and GCI_H versus GCI_L density. However, despite an often-high density of GCIs in motor cortex and its adjacent white matter, other pathological changes in motor cortex may be relatively unnoticeable, including that only up to ~20% neuronal loss could be detected.[29,30] In addition, neuronal loss could be a relatively late manifestation.[30] Thus, pyramidal tract dysfunction in MSA might be largely explained by the location of GCIs in oligodendrocytes,[30] affecting the integrity of myelin, and transduction of action potentials along axons even before neuronal cell body loss is appreciable. Second, we studied the clinical features based on a retrospective review, rather than prospective, standardized assessment. Nonetheless, all medical records in these MSA cases were documented comprehensively by movement disorders neurologists in a single center at Columbia University with sufficient clinical data for the presence or absence of the clinical variables stated in the methodology. Lastly, while we found higher pyramidal scores are related to less parasympathetic involvement in MSA, we should cautiously interpret this finding, which may also reflect the variability in reporting symptoms such as erectile dysfunction from patients. Future studies should focus on detailed clinical-radiological studies to examine the degenerative patterns and more comprehensive neuropathologic investigations, such as neurofilament immunohistochemistry, to examine extent of axonal degeneration in the pyramidal system to fully characterize this under-recognized clinical domain for MSA.

Conclusions

Our study suggests that MSA cases with prominent pyramidal signs could belong to a rather distinct type with different constellations of autonomic, parkinsonian, and cerebellar symptoms.

Conflict of Interest

Authors report nothing to disclose.

Author Contribution

Chi-Ying R. Lin: study concept, data acquisition and interpretation, manuscript draft and revision. Anisha Viswanathan: extensive chart review and literature search. Tiffany X. Chen: comprehensive statistical analysis and data interpretation. Hiroshi Mitsumoto: critical revision of the manuscript for important intellectual content. Jean P. Vonsattel: data acquisition and interpretation. Phyllis L. Faust: study supervision, critical revision of the manuscript for important intellectual content. Sheng-Han Kuo: study concept, data interpretation, critical revision of the manuscript for important intellectual content, and study supervision.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Scale for clinical pyramidal burden applied in the present study.
Table S2. Prevalence of each clinical variables of interest.
Table S3. Severity of hyerreflexia and upper motor neuron signs between probable versus possible multiple system atrophy.

