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Multiple System Atrophy Without Dysautonomia

An Autopsy-Confirmed Study

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Abstract

Background and Objectives

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by 3 core symptom complexes: parkinsonism, cerebellar syndrome, and dysautonomia. Recent Movement Disorder Society (MDS) criteria allow for the clinical diagnosis of MSA based solely on motor symptoms, without requiring dysautonomia. This study aimed to evaluate the frequency and disease trajectory of MSA patients without dysautonomia compared with those with autonomic involvement.

Methods

A multicenter cohort of autopsy-confirmed patients with MSA was analyzed for demographic characteristics, symptom onset, and progression of parkinsonism, cerebellar syndrome, and dysautonomia. Clinical data were collected through standardized chart reviews across participating centers and categorized using the MDS-MSA criteria. Patients were grouped according to their initial symptom complex and tracked for the evolution of additional symptoms. Analyses included time to development of further symptom complexes, age at symptom onset, disease duration, and phenotype at the last recorded visit. Patients with motor symptoms only were matched to patients with similar demographics but with dysautonomia. Statistical methods included ANOVA, *t* tests, Welch *t* tests, and χ^2 tests, with significance set at $p < 0.05$.

Results

Among 140 patients (mean age at onset 62.3 ± 8.9 years; 44% female), 81 (58%) initially presented without dysautonomia (57 with parkinsonism only, 17 with cerebellar syndrome only, 7 with both). At final follow-up, 12 patients (9%) had not developed dysautonomia. These patients showed significantly longer disease duration (mean 8.1 ± 2.1 years) than matched patients with dysautonomia (mean 6.3 ± 2.6 years; $p = 0.035$). Overall, 51% of patients developed all 3 symptom complexes. Patients with cerebellar onset progressed more rapidly to

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Supplementary Material

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Glossary

A = autonomic dysfunction; **C** = cerebellar syndrome; **C+A** = cerebellar syndrome and autonomic dysfunction; **F** = female; **M** = male; **MDS** = Movement Disorder Society; **MSA** = multiple system atrophy; **P** = parkinsonism; **P+A** = parkinsonism and autonomic dysfunction; **P+C** = parkinsonism and cerebellar dysfunction; **P+C+A** = parkinsonism and cerebellar syndrome and autonomic dysfunction; **SEM** = standard error of the mean.

multisystem involvement than those with parkinsonian onset (mean interval to second symptom: 2.0 vs 3.4 years; $p < 0.05$).

Discussion

The MDS-MSA criteria expand the diagnostic scope by identifying a motor-only subgroup with a distinct and potentially slower disease course. These findings underscore the importance of including motor-only patients in natural history and interventional studies. Limitations include retrospective data collection and potential variability in symptom documentation.

Introduction

Multiple system atrophy (MSA) is a rare, rapidly progressing neurodegenerative disease characterized by a variable combination of parkinsonism, cerebellar ataxia, and autonomic dysfunction.[1-3] Histologic hallmarks of MSA include glial cytoplasmic inclusions and neuronal cytoplasmic aggregates, each primarily containing misfolded alpha-synuclein.[4] The accumulation of alpha-synuclein protein leads to neuronal degeneration in various brain regions, including the substantia nigra, striatum, inferior olivary nucleus, and cerebellum. The peripheral and autonomic nervous system may also be affected, highlighting the multisystemic nature of the disease.[5,6] This results in a variable presentation of primary symptoms—parkinsonism, cerebellar syndrome, and autonomic dysfunction—which complicates clinical diagnosis, especially in the early stages of the disease.[7,8]

The International Parkinson and Movement Disorder Society (MDS) criteria for the clinical diagnosis of MSA were proposed in 2022 to improve early and accurate diagnosis and have since been validated against the neuropathologic diagnostic gold standard in independent reports.[3,7,9,10] A notable innovation of the MDS-MSA diagnostic criteria is the possibility of diagnosing clinically probable MSA in patients presenting with motor symptoms in the absence of dysautonomia. As patients with MSA lacking autonomic features did not receive a formal clinical diagnosis of MSA before the publication of the MDS-MSA criteria, this subgroup has historically not yet been included in natural history and interventional studies.[11-14] A few cases of a possible predominant motor subtype of MSA with extended disease duration are documented.[15] As the autonomic symptom orthostatic hypotension is a known side effect of dopaminergic therapy,[11,16] we examined the distribution of Levodopa usage across groups with and without autonomic symptoms.

Therefore, we evaluate MSA with and without autonomic dysfunction in a large retrospective multicenter cohort study of autopsy-confirmed patients with MSA.

Methods

Patients and Clinical Data

The cohort has been described in previously published work, comprising 144 patients with a pathologic diagnosis of MSA.[9,17] Cases with a pathologic diagnosis of MSA and detailed longitudinal information in their clinical charts were identified from collaborating brain branks (Ludwig-Maximilians-University, Munich, Germany; King's College, London, UK; Lund University, Lund, Sweden; Erasmus Medical Center, Rotterdam, the Netherlands; Hospital Clinic-August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain; Johns Hopkins University, Baltimore, MD; University of Pennsylvania, Philadelphia, PA; University of Toronto, Toronto, ON, Canada; sample overview: Supporting information eTable 1). Patients had been regularly assessed by specialists in movement disorders throughout their disease course, and clinical diagnosis ante mortem had been established by specialists in movement disorders in secondary/tertiary care settings. Comprehensive clinical data for each case were collected through a standardized retrospective review of medical charts by a movement disorder specialist, according to the 2022 MDS-MSA diagnostic criteria. Data extraction from patients' medical records focused on autonomic, parkinsonian, and cerebellar features, as defined by the 2022 MDS criteria for the diagnosis of MSA.[7] Symptoms of autonomic dysfunction were categorized into 3 main groups: urinary retention, defined as voiding difficulties with a postvoid residual volume >100 mL; unexplained urinary urge incontinence; and neurogenic orthostatic hypotension, defined as a sustained blood pressure drop of ≥20 mm Hg systolic or ≥10 mm Hg diastolic within 3 or 10 minutes of standing or during a head-up tilt test. A detailed list of symptom categories and corresponding clinical documentation is provided in eTable 2. The motor or autonomic symptoms initially reported by patients were identified as marking the onset of the disease. In addition, sex, age at onset of the clinical documentation, age at death, disease duration, and whether the patient received Levodopa treatment were documented.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval has been obtained from all responsible ethics committees. All donors and/or relatives provided written informed consent for the scientific use of their brains and medical records. The study conforms to the Declaration of Helsinki, and with national and institutional legal and ethical requirements.

Analysis of Clinical Phenotypes at Disease Onset

Patients were categorized into groups based on the first documented symptom.

Most patients could be categorized in groups with 1 symptom complex at disease onset: "autonomic dysfunction" (A), "parkinsonism" (P) or "cerebellar syndrome" (C). These groups were compared for the following parameters: age at onset of the clinical documentation, age at death, and disease duration. Patients initially presenting with more than 1 symptom complex, that is, "parkinsonism and autonomic dysfunction" (P+A), "cerebellar syndrome and autonomic dysfunction" (C+A), "parkinsonism and cerebellar syndrome" (P+C), or a combination of "parkinsonism, cerebellar syndrome, and autonomic dysfunction" (P+C+A), were excluded from the first comparative analysis because the initial symptom could not be reliably determined in these cases. In addition, to investigate the influence of sex on the disease course, we compared all male and female patients with MSA according to the basic parameters. To investigate the influence of Levodopa treatment, that might cause signs of dysautonomia on the disease course,[16] we compared patients with and without Levodopa treatment according to the basic parameters.

Analysis of Subgroups Over Disease Progression

To investigate how disease progression related to the phenotype at onset, each new clinical symptom was assessed for each group (A, P, C). Patients were categorized into new subgroups according to their second symptom. For example, patients with the initial phenotype "P" were hence grouped into "P+A" or "P+C." Across these subgroups, the duration between onset of the clinical documentation until development of a second symptom in years was calculated and compared.

To compare all patients with a combination of 2 symptoms, the aforementioned subgroups were then combined with the previously excluded subgroups with 2 symptoms at onset, for example, P+A, C+A, and P+C. The resulting groups were compared for basic parameters. In this analysis, we excluded patients with all 3 symptom complexes combined because it was not clear from retrospective chart review, in which order the patients developed their symptoms and what had been the second symptom.

Analysis of Clinical Phenotypes at the Final Clinical Visit

In the final step, patients who developed a third symptom were grouped into the category P+C+A. At the final clinical visit available in the record, all patients were categorized in the group P+A, C+A, P+C, or P+C+A. We compared if patients who developed all 3 symptom complexes had a faster disease progression than those who "only" developed 2 symptoms, respectively.

To examine whether the subgroup without autonomic symptoms at the end of record showed a longer disease duration, we compared the subgroup P+C at the end of record (without autonomic symptoms) with a comparable group of 12 patients with autonomic symptoms. Therefore, we performed a matched sampling: out of the large group "patients with autonomic symptoms at the end of record," we selected those patients (as potential controls) most similar (individually matched) to each patient in the small group P+C at the end of record ("patients with exclusively motor symptoms at the end of record"). Matching variables were sex (exact match), age at onset (±1 year), and number of showed symptom categories (±1 symptom category). The resulting matched sample consisted of 12 pairs. All matched pairs have the same sex. In 10 of the 12 pairs, patients had the same age at onset; in the remaining 2 pairs, the difference was within ±1 year. Similarly, in 10 of the pairs, patients had the same number of affected symptom categories; in the remaining 2 pairs, the number differed by only 1 domain. To investigate the relationship between Levodopa treatment and autonomic symptoms at the end of record, we compared Levodopa treatment status in the matched groups.

Statistical Analysis

Demographic data were presented as means ± SD, ranges, and medians. To compare the basic parameters (age of onset, age of death, and disease duration) in the subgroups, we performed 1-way ANOVAs along with appropriate post hoc tests. Therein, we followed the recommendations of ruxton[18] and performed unequal variance *t* tests (Welch tests). To compare the basic phenotype parameters in women vs men and in patients with vs without Levodopa treatment, we performed independent *t* tests and adjusted the alpha error according to the performed 3 tests each. Chi-square tests of independence were conducted to examine associations of sex and Levodopa treatment with phenotype classification. Significance was set at $p < 0.05$. All statistical analyses were performed using SPSS software, versions 23.0 and 28.0.1.1 (SPSS Inc., Chicago, IL).

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Characteristics of Patients and of Clinical Phenotypes at Disease Onset

We included a total of 140 autopsy-confirmed patients with MSA who had sufficient clinical data regarding disease progression in the analysis. The demographic characteristics and

basic parameters of the study population are summarized in Table 1. No significant differences were observed among the subgroups A, P, and C nor among women (f) vs men (m) nor among patients with vs without Levodopa treatment in disease duration, age at onset, or age at death. A significant association was found between sex and phenotype A, P, and C at onset, $\chi^2(2, N = 101) = 7.015$, $p = 0.030$, indicating a higher prevalence of P in women (n = 20 m vs n = 37 f) and of C (n = 11 m vs n = 6 f) and A (16 m vs 11 f) in men. In addition, a significant association was found between Levodopa treatment and phenotype A, P, and C at onset, $\chi^2(2, n = 99) = 10.271$, $p = 0.006$, indicating a higher Levodopa treatment in P (n = 45 with vs n = 10 without) than in A (n = 15 with vs n = 12 without) and C (n = 8 with vs n = 9 without).

Disease Progression by Initial Symptom Complex

In the group of patients with autonomic dysfunction at onset (A) (n = 27), 8 patients (30%) developed parkinsonism and 8 patients (30%) cerebellar symptoms. Eleven patients (41%) seemed to simultaneously develop the full combination of all 3 symptom complexes subsequently. At the final visit, 21 patients (78%) of the initial A group exhibited all 3 symptom complexes (Figure).

In group P at onset (n = 57), the majority (n = 39, 68%) developed autonomic symptoms subsequently. Twelve patients (21%) developed cerebellar syndrome, while 6 patients (11%) developed both autonomic dysfunction and cerebellar syndrome. At the final visit, 20 patients (35%) of the initial P group exhibited all 3 symptom complexes, whereas 30 patients (53%) exhibited "only" P+A and 7 patients (12%) only P+C (Figure).

In group C at onset (n = 17), the majority (n = 11, 65%) subsequently developed autonomic symptoms, 4 patients (24%) developed parkinsonism, and 2 patients (12%) developed both. At the final visit, 12 patients (71%) of group C had developed all 3 symptom complexes, whereas 3 patients (18%) exhibited only C+A and 2 patients (12%) only P+C (Figure).

The mean time interval until manifestation of a second symptom complex was calculated for patients who were initially in group A, P, or C. The mean time differed across groups, $F(2, 79) = 4.129$, $p < 0.01$. In group C, the mean time to develop a second symptom complex was 2 ± 1.36 years (range: 1–5), which was significantly shorter than the interval observed in group P (3.4 ± 1.8 years, range: 1–8; P vs C: $T(30.61) = 3.10$; $p < 0.05$). In group A, the mean time 2.5 ± 1.7 years (range: 1–7) lies in between the groups C and P.

Analysis of Phenotypes at Final Visit

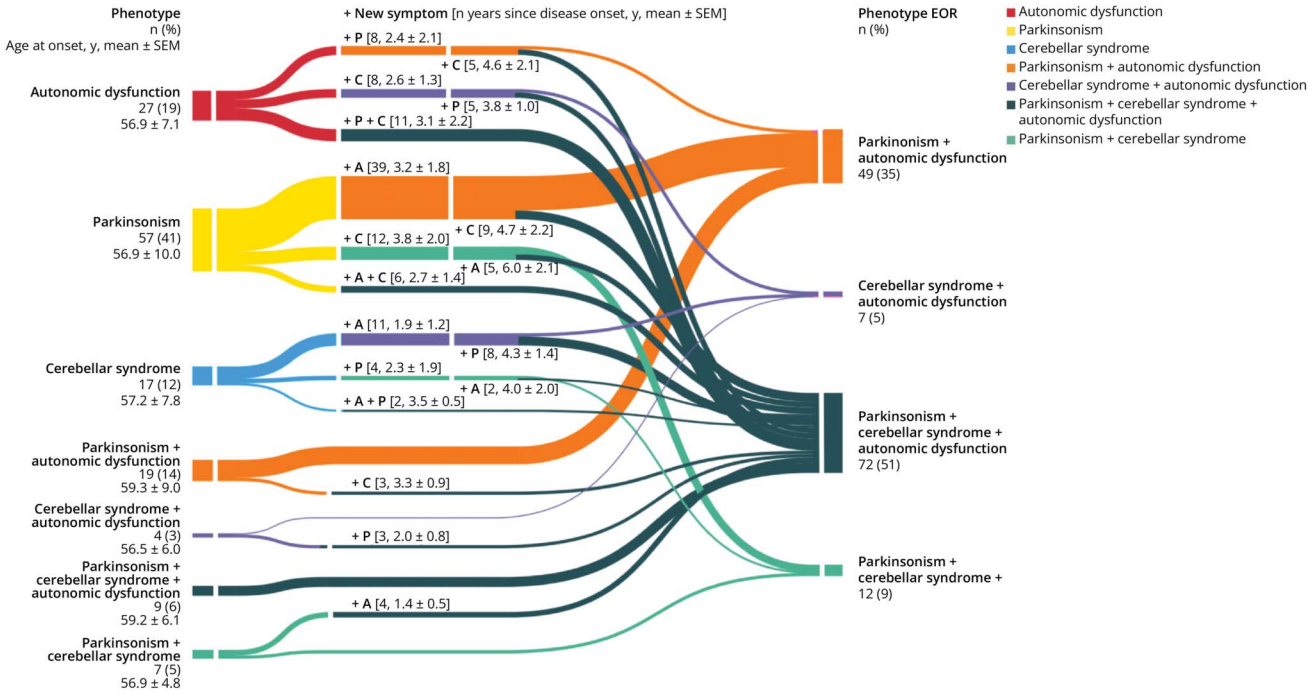
At the final visit, all patients showed either a combination of 2 or 3 symptom complexes. 72 patients (51%) exhibited a combination of all 3 symptom complexes. Fifty patients (36%) showed only P+A, 12 (9%) only P+C, and 7 (5%) only

Table 1 Demographic Data

	All patients	A	P	C	P + A	C + A	P + C	P + C + A
Phenotype at onset n [%]	140	27 [19]	57 [41]	17 [12]	19 [14]	4 [3]	7 [5]	9 [6]
M:F, n [%]	59:81 [42:58]	16:11[a] [59:41]	20:37[a] [35:65]	11:6[a] [65:35]	5:14 [26:74]	2:2 [50:50]	3:4 [37:63]	2:7 [22:78]
Age at onset, y, mean ± SEM [range; median]	57.4 ± 8.5 [35–80; 57.5]	56.9 ± 7.1 [44–68; 58]	56.9 ± 10 [38–80; 55]	57.2 ± 7.8 [46–77; 57]	59.3 ± 9 [35–76; 60]	56.5 ± 6 [49–63; 57]	56.9 ± 4.8 [48-61; 58]	59.2 ± 6.1 [53–71; 59]
Age of death, y, mean ± SEM [range; median]	64.8 ± 7.7 [40–90; 64.5]	64.4 ± 6.9 [50–77; 66]	65.4 ± 8.4 [50–90; 65]	64.9 ± 7.2 [52–81; 66]	64.4 ± 9.5 [40–79; 65]	61.3 ± 6.13 [54–69; 61]	64.1 ± 3.48 [59–69; 63.5]	65 ± 6.5 [58–76; 64]
Disease duration, y, mean ± SEM [range; median]	7.4 ± 3 [2–20; 7]	7.5 ± 2.3 [2–12; 8]	8.5 ± 3.4 [3–20; 8]	7.7 ± 2.4 [4–13; 8]	5.2 ± 2.4 [2–10; 5]	4.8 ± 1.9 [2–6; 5.5]	7.3 ± 2.3 [4–11; 8]	6 ± 1.7 [4–10; 5]
Phenotype at final visit N [%]					49 [35]	7 [5]	12 [9]	72 [51]
M:F n [%]					18:31 [37:63]	6:1 [86:14]	7:5 [58:42]	28:44 [39:61]
Age at onset, y, mean ± SEM [range; median]					57.5 ± 10.8 [35–80; 58]	55.9 ± 8.1 [46–66; 54]	59.7 ± 6.9 [53–77; 59]	57.3 ± 6.9 [38–78; 57.5]
Age of death, y, mean ± SEM [range; median]					65.3 ± 9.6 [40–90; 65]	63 ± 7.4 [53–73; 64]	67.8 ± 6.2 [60–81; 68]	64.3 ± 6.4 [50–82; 64]
Disease duration, y, mean ± SEM [range; median]					7.9 ± 4 [2–20; 7]	7.1 ± 3 [4–13; 6]	8.1 ± 2.1 [4–12; 8]	7 ± 2.4 [2–12; 7]

Abbreviations: A = autonomic dysfunction; C = cerebellar syndrome; C+A = cerebellar syndrome and autonomic dysfunction; F = female; M = male; MSA = multiple system atrophy; P = parkinsonism; P+A = parkinsonism and autonomic dysfunction; P+C = parkinsonism and cerebellar dysfunction; P+C+A = parkinsonism and cerebellar syndrome and autonomic dysfunction; SEM = standard error of the mean.
Note: Demographic data of all autopsy-confirmed patients, grouped according presenting clinical symptoms.
[a] Chi-square test of independence showed a significant association between sex and phenotype distribution.

Figure Development of Clinical Multiple System Atrophy Phenotypes



Note: Disease course of all autopsy-confirmed patients, subgrouped according to present clinical symptoms. A = autonomic dysfunction; C = cerebellar syndrome; EOR = final visit; F = female; M = male; MSA = multiple system atrophy; P = parkinsonism; SEM = standard error of the mean.

C+A, Table 1. When comparing whether patients who showed all 3 symptom complexes (n = 72) had a more rapid disease course than patients with 2 symptom complexes (n = 68), no significant differences were found.

Furthermore, to examine whether the subgroup without autonomic symptoms at the end of record showed a more rapid disease course, we compared the subgroup P+C at the end of record (without autonomic symptoms) with a comparable group of 12 patients with autonomic symptoms. The comparison of the subgroup without autonomic symptoms at the final visit (only P+C at the end of record) with a group of patients with autonomic symptoms showed that patients with "exclusively motor symptoms at the final visit" (only P+C, n = 12) showed a longer disease duration (mean: 8.1 ± 2.1) than a group of 12 patients with "autonomic symptoms at the final visit" (mean: 6.3 ± 2.6), T = −1.914, df = 20.93, p = 0.035 (one-tailed).

We examined whether the absence of autonomic symptoms in patients with exclusively motor manifestations could be attributed to lower Levodopa exposure. However, 83% (n = 10) of the 12 patients without dysautonomia had received Levodopa treatment, compared with 68% (n = 84) of those 124 patients with dysautonomia. No significant association was found between Levodopa treatment (with vs without) and autonomic symptoms at the final visit (yes vs no). As one of the expected cell frequencies was below 5, an exact Fisher test was applied.

Discussion

The introduction of the Movement Disorder Society Criteria for the diagnosis of MSA enables the diagnosis of clinically probable MSA based solely on motor symptoms.[3,7,9,10] This is a significant shift because prior diagnostic frameworks would have excluded such patients despite pathologic confirmation of MSA.[7,13,15] This study highlights the clinical relevance of this broader definition by analyzing phenotypic development in an autopsy-confirmed cohort.

In our cohort, parkinsonism with autonomic dysfunction was the most common phenotype, consistent with data suggesting a higher prevalence of the parkinsonian subtype (MSA-P) in White populations compared with East Asian cohorts.[19-22] It is important that 51% of patients developed all 3 symptom complexes (parkinsonism, cerebellar syndrome, and autonomic dysfunction), emphasizing the multisystemic nature of MSA.[23,24] Patients with cerebellar symptoms at onset progressed more rapidly to multisystem involvement than those with parkinsonism, without significant differences in disease duration, in line with previous studies which did not describe differences between survival in MSA-P and MSA-C.[11,25]

Notably, 58% of patients in our cohort initially presented without dysautonomia and would have been excluded under previous diagnostic criteria.[2] At the final visit, 12 patients (9%) remained free of dysautonomia despite a mean disease duration of 8.1 ± 2.1 years, which was longer than that of

a matched group with autonomic symptoms (6.3 ± 2.6 years), suggesting a more favorable prognosis. These findings align with earlier reports indicating that delayed-onset or absent dysautonomia may correlate with slower disease progression and a more favorable prognosis.[2] Previous studies have described MSA patients with a prolonged disease duration (>15 years) and latency of more than 11 years before autonomic symptoms emerged, most of whom initially presented with parkinsonism and showed a slow progression of symptoms.[15] The patients (n = 12, 9%) in our motor symptom-only subgroup did not develop any dysautonomia, but might have reached the terminal stages of the disease before autonomic symptoms could have manifested. Alternatively, severe motor disability at advanced disease stages may have prevented accurate detection of dysautonomia in some patients, who might have been using wheelchair and immobile. Nevertheless, those patients still exhibited a considerable delay in development of autonomic dysfunction.

Complementary to our findings, an earlier onset of dysautonomia in MSA seems to be associated with faster disease progression and worse prognosis.[13,24,26,27] Furthermore, the severity and type of dysautonomia seem to influence prognosis in MSA.[11] For instance, bladder dysfunction requiring catheterization within 3 years has been linked to significantly reduced survival, while orthostatic intolerance as well exerts a measurable, though less pronounced, effect.[11,28]

When examining the relationship between specific autonomic features and MSA-phenotypes, orthostatic intolerance has been reported to occur more frequently in MSA-P,[11] potentially due to more common Levodopa treatment in this group. We observed a similar trend in our cohort in which patients with predominant parkinsonism as the initial symptom more often received Levodopa. However, no significant association was found between Levodopa treatment and the presence or absence of autonomic symptoms at the final visit. In addition, a post hoc analysis revealed no consistent pattern or predominance of specific autonomic features across the clinical subgroups with dysautonomia. Nevertheless, larger prospective studies are needed to investigate the development of specific autonomic features and to examine the various patterns that emerge among different clinical subgroups with dysautonomia.

The study's retrospective multicenter design presents inherent limitations, such as variability in clinical documentation and a potential selection bias. Although the inclusion of autopsy-confirmed cases strengthens diagnostic accuracy, milder or atypical cases may have been excluded. The absence of disease controls limits the ability to assess the specificity of phenotype combinations for MSA diagnosis. However, diseases presenting with both parkinsonism and cerebellar syndrome, such as certain spinocerebellar ataxias, are rare in clinical practice and pathologic validation.[29-31] Future prospective multicentric studies with standardized diagnostic and follow-up, protocols are needed to validate our findings.

In summary, our results confirm the diagnostic utility of the MDS-MSA criteria, which enable the diagnosis of MSA even in the absence of dysautonomia. Diagnosing this previously unrecognized subgroup marks a pivotal advancement in capturing the full clinical spectrum of MSA. It is important that it underscores the need to actively include patients with a motor-only phenotype in natural history studies—particularly given their distinct, and possibly more protracted, disease course.

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Author Contributions

I. Wilkens: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. S. Bebermeier: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Heine: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. V.C. Ruf: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. Y. Compta: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. L. Molina Porcel: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Troakes: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Vamanu: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Downes: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. D.J. Irwin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Cohen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E.B. Lee: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.F. Nilsson: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E.M. Englund: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Nemati: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Katzdobler: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Levin: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.M. Bernhardt: drafting/revision of the manuscript for content,

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Disclosure

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