When DLB, PD, and PSP masquerade as MSA

An autopsy study of 134 patients

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ABSTRACT

Objective: To determine ways to improve diagnostic accuracy of multiple system atrophy (MSA), we assessed the diagnostic process in patients who came to autopsy with antemortem diagnosis of MSA by comparing clinical and pathologic features between those who proved to have MSA and those who did not. We focus on likely explanations for misdiagnosis.

Methods: This is a retrospective review of 134 consecutive patients with an antemortem clinical diagnosis of MSA who came to autopsy with neuropathologic evaluation of the brain. Of the 134 patients, 125 had adequate medical records for review. Clinical and pathologic features were compared between patients with autopsy-confirmed MSA and those with other pathologic diagnoses, including dementia with Lewy bodies (DLB), Parkinson disease (PD), and progressive supranuclear palsy (PSP).

Results: Of the 134 patients with clinically diagnosed MSA, 83 (62%) had the correct diagnosis at autopsy. Pathologically confirmed DLB was the most common misdiagnosis, followed by PSP and PD. Despite meeting pathologic criteria for intermediate to high likelihood of DLB, several patients with DLB did not have dementia and none had significant Alzheimer-type pathology. Autonomic failure was the leading cause of misdiagnosis in DLB and PD, and cerebellar ataxia was the leading cause of misdiagnosis in PSP.

Conclusions: The diagnostic accuracy for MSA was suboptimal in this autopsy study. Pathologically confirmed DLB, PD, and PSP were the most common diseases to masquerade as MSA. This has significant implications not only for patient care, but also for research studies in MSA cases that do not have pathologic confirmation. *Neurology*® 2015;85:404–412

GLOSSARY

ANOVA = analysis of variance; **CDLB** = Consortium on Dementia with Lewy Bodies; **DLB** = dementia with Lewy bodies; **MSA** = multiple system atrophy; **MSA-OPCA** = multiple system atrophy with predominantly olivopontocerebellar involvement; **MSA-SND** = multiple system atrophy with predominantly striatonigral involvement; **MSA-SND/OPCA** = multiple system atrophy with equally severe involvement of striatonigral and olivopontocerebellar systems; **NFT** = neurofibrillary tangle; **PD** = Parkinson disease; **PSP** = progressive supranuclear palsy; **PSP-C** = progressive supranuclear palsy with cerebellar ataxia; **RBD** = REM sleep behavior disorder.

Multiple system atrophy (MSA) is a sporadic, progressive neurodegenerative disorder characterized by a variable combination of autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal symptoms.[1–3] The current diagnostic criteria for MSA stipulate 3 levels of diagnostic certainty—possible, probable, and definite MSA, with the latter requiring autopsy confirmation.[4] In spite of well-established clinical criteria for MSA, antemortem diagnosis is difficult. Previous autopsy studies revealed a wide range of diagnostic accuracy—between 29% and 86%.[1,5,6] Misdiagnosis has often been with other neurodegenerative diseases that share clinical features with MSA. Difficulty in clinical diagnosis of MSA can also occur when MSA coexists with other neurodegenerative disease processes, such as Alzheimer-type pathology, Lewy-related

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pathology,[7] or tauopathy,[8] a problem that bedevils clinical diagnosis in virtually all of these diseases.

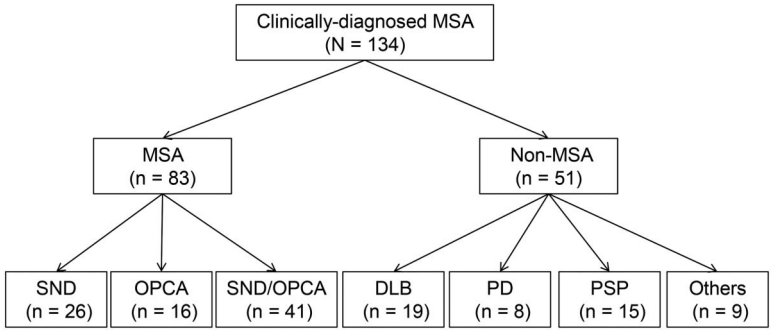
To assess the accuracy of clinical diagnosis of MSA, we examined the neuropathology of 134 patients who were clinically diagnosed with MSA at the time of death. We reviewed medical records to identify possible reasons for misdiagnosis.

METHODS

Subjects. We identified 134 consecutive patients with clinically diagnosed MSA whose brains were sent to the Mayo Clinic brain bank between 1998 and 2014 from 37 states and 1 province of Canada. Brain autopsies were obtained after consent of the legal next of kin and are considered exempt from human subject research. The Mayo Clinic brain bank operates under protocols approved by the Mayo Clinic institutional review board. Most patients were white; 7 were Asian, 1 was Pacific Islander, and 1 was African American. We reviewed medical records of 125 patients with adequate documentation. The study design is shown schematically in the figure.

Neuropathologic assessment. All cases underwent a standardized neuropathologic assessment for Alzheimer-type and Lewy-related pathologies as previously reported.[9] Braak neurofibrillary tangle (NFT) stage[10] and Thal amyloid phase[11] were assigned to each case based upon thioflavin S fluorescent microscopy. Immunohistochemistry for α-synuclein (NACP; 1:3,000) was used to establish neuropathologic diagnosis of MSA.[12] MSA was subclassified as MSA with predominantly striatonigral involvement (MSA-SND), MSA with predominantly olivopontocerebellar involvement (MSA-OPCA), and MSA with equally severe involvement of striatonigral and olivopontocerebellar systems (MSA-SND/OPCA).[7] Lewy-related pathology was assessed in cortex, amygdala, basal forebrain, and brainstem, and classified as brainstem, transitional, or diffuse Lewy body disease.[13] Lewy body subtype and degree of Alzheimer-type pathology were used to classify cases as low, intermediate, or high likelihood of dementia with Lewy bodies (DLB) according to the Third Consortium on Dementia with Lewy Bodies (CDLB) recommendations[14]; a pathologic diagnosis of DLB was assigned to cases with intermediate or high likelihood of CDLB. A pathologic diagnosis of Parkinson disease (PD) required moderate to severe neuronal loss in the substantia nigra and CDLB scores of low likelihood.[15]

Figure Flow chart of study design



DLB = dementia with Lewy bodies; MSA = multiple system atrophy; PD = Parkinson disease; PSP = progressive supranuclear palsy; OPCA = predominantly olivopontocerebellar involvement type of multiple system atrophy; SND = predominantly striatonigral involvement type of multiple system atrophy; SND/OPCA = equally severe striatonigral and olivopontocerebellar involvement type of multiple system atrophy.

Clinical assessment. A neurologist (S.K.) abstracted the following information from medical records collected throughout the course of disease and entered it into a database: sex, age at symptomatic onset, age at death, family history of neurologic disease, initial and final clinical diagnoses, signs and symptoms during the disease course and their timing, and neurologic findings as documented by a neurologist or movement disorder specialist. For each patient, a particular clinical symptom or sign was considered present if specifically stated as present in the clinical records. If clinical symptoms or signs were not described, then for the purpose of analysis, they were considered to be absent, except in the case of levodopa responsiveness. The following symptoms and neurologic signs were abstracted from medical records: orthostatic hypotension, syncope, dizziness, urinary incontinence, constipation, erectile dysfunction, asymmetry of parkinsonism, resting tremor, bradykinesia, axial/limb rigidity, falls, early falls (defined as occurring within 1 year of symptomatic onset), gait ataxia, limb ataxia, nystagmus, vertical gaze palsy, pyramidal signs (spasticity, hyperreflexia, and Babinski sign), cognitive impairment, visual hallucinations, and REM sleep behavior disorder (RBD). Orthostatic hypotension was considered to be positive if there was documented blood pressure drop of at least 30/15 mm Hg (according to MSA criteria[4]) or patients were medicated for orthostatic hypotension (e.g., fludrocortisone, midodrine). Patients were considered to have cognitive impairment if at least short-term memory loss, disorientation, or executive dysfunction were diagnosed by a physician, or there were recorded complaints of these symptoms by the patient or their family members. RBD was positive if found on polysomnography or if it was clinically suspected based upon behavioral descriptions of the bed partner and noted by a physician. The degree of levodopa responsiveness was recorded as no response, partial response, or good response. The information on symptoms was gathered from a combination of medical records, pathology records summarizing clinical history, or a brain bank questionnaire filled out by a close family member. The questionnaire included the clinical diagnosis, age at onset of symptoms, family history, initial symptoms, clinical symptoms (disorientation, agitation, hallucinations, tremors, stiffness, difficulty walking, fluctuating course, violent outbursts, eating disorder, wandering, weight loss, sleep disorder, visual problems, delusions, falls, personality changes, and other noteworthy symptoms), hand dominance, specialty of the physician (neurology, psychology, or psychiatry), and medications. All patients were retrospectively assigned a diagnosis of probable or possible MSA from available clinical information according to the second consensus criteria of MSA.[4]

Given the retrospective nature of the study, the quality of available medical records was variable, and a score was devised to provide a means to assess possible bias that might be related to differential completeness of clinical information with respect to pathologic diagnostic groups: 0, inadequate clinical records; 1, only the brain bank questionnaire; 2, clinical records from general practitioners; 3, clinical records from neurologists; 4, clinical records from movement disorder specialists.

Neuroimaging assessment. To assess MRI findings, the following features were abstracted from both radiology reports and interpretations of the physician of record: atrophy of cerebral cortex, cerebellum, brainstem, and putamen, abnormal signal intensity in putamen, and specific description suggesting a certain diagnosis such as a hot cross bun sign and a hummingbird sign. For the subset of patients evaluated at Mayo Clinic, digitized scans were reviewed.

Statistical analyses. All statistical analyses were performed in SigmaPlot 11.0 (Systat Software, San Jose, CA). A χ^2 test was performed for group comparisons of categorical data. Analysis of variance (ANOVA) on ranks, followed by Dunn post hoc test, or one-way ANOVA, followed by post hoc Holm-Sidak test, were used for analyses of continuous variables as appropriate. p Values <0.05 were considered statistically significant. To adjust for age at death, multivariable logistic regression models were built for each combination of the pathologic groups using the significant pathologic variables from univariate analyses.

RESULTS Brains of 134 patients with a clinical diagnosis of MSA were received by the brain bank in the time frame of the study, and 83 (62%) met pathologic criteria for MSA (figure). Demographic information for the 134 patients is listed in table 1. The breakdown of the 51 misdiagnosed patients by pathologic diagnosis is as follows: DLB in 19 (37%), progressive supranuclear palsy (PSP) in 15 (29%), PD in 8 (15%), and other disorders in 9 (18%) (including 2 corticobasal degeneration and 2 vascular parkinsonism, as well as 5 miscellaneous disorders). The proportion of patients included in final clinicopathologic analyses after exclusion of those with inadequate medical records was similar for the 4 major pathologic groups (i.e., MSA, DLB, PD, and PSP). The diagnostic accuracy was not different between general neurologists (33/53, 62%) and movement disorder specialists (35/56, 63%). After retrospective assessment of clinical features, 49 patients were judged to fulfill the criteria for probable MSA, 35 for possible MSA, and the remaining 41 were not assigned to levels of diagnostic certainty due to lack of adequate clinical information (e.g., levodopa

Table 1 Demographic and pathologic features of pathologically diagnosed MSA compared with non-MSA

		Non-MSA				
Features	MSA	DLB	PD	PSP	Others	p Value
Demographic features						
Number of patients	83	19	8	15	9	
Male, % (n)	60 (50/83)	81 (16/19)	75 (6/8)	60 (9/15)	44 (4/9)	0.12
Patients with clinical records, % (n)	95 (79/83)	93 (18/19)	88 (7/8)	93 (14/15)	78 (7/9)	0.97
Quality of clinical records, median (25th, 75th percentile)	3 (3, 4)	4 (3, 4)	4 (3, 4)	3 (1, 4)	3 (3, 4)	0.73
Age at onset, mean ± SD	57 ± 9	63 ± 10	68 ± 8[a]	66 ± 11[a]	59 ± 4	<0.001
Age at death, mean ± SD	65 ± 8	72 ± 9[a]	77 ± 8[b]	74 ± 9[b]	68 ± 3	<0.001
Symptoms duration, mean ± SD	8.4 ± 3.7	9.0 ± 3.8	9.4 ± 5.5	8.1 ± 3	8.7 ± 4.1	0.95
FH of parkinsonism, % (n)	11 (9/79)	22 (4/18)	0 (0/7)	7 (1/14)	43 (3/7)	0.38
FH of dementia, % (n)	13 (10/79)	22 (4/18)	14 (1/7)	21 (3/14)	0 (0/7)	0.68
Pathologic features						
Brain weight, g, mean ± SD	1,219 ± 142	1,245 ± 167	1,192 ± 96	1,175 ± 236	1,144 ± 209	0.47
Braak NFT stage, median (25th, 75th percentile)	I (0, II)	III (I, III)[a]	II (II, III)[a]	II (I, III)	I (I, II)	0.001
Thal Aβ phase, median (25th, 75th percentile)	0 (0, 1)	2 (1, 3)[a]	2 (0, 2)	0 (0, 3)	0 (0, 1)	0.008
Lewy-related pathology, % (n)	8 (7/83)	100 (19/19)	100 (8/8)	0 (0/14)	22 (2/9)	—
Brainstem subtype, % (n)	86 (6/7)	0 (0/19)	100 (8/8)	—	22 (2/9)	—
Transitional subtype, % (n)	14 (1/7)	63 (12/19)	0 (0/8)	—	0 (0/9)	—
Diffuse subtype, % (n)	0 (0/7)	37 (7/19)	0 (0/8)	—	0 (0/9)	—
Variant of MSA, % (n)						
MSA-SND	31 (26/83)	—	—	—	—	—
MSA-OPCA	19 (16/83)	—	—	—	—	—
MSA-SND/OPCA	49 (41/83)	—	—	—	—	—

Abbreviations: Aβ = β-amyloid; DLB = dementia with Lewy bodies; FH = family history; MSA = multiple system atrophy; MSA-OPCA = multiple system atrophy with predominantly olivopontocerebellar involvement; MSA-SND = multiple system atrophy with predominantly striatonigral involvement; MSA-SND/OPCA = multiple system atrophy with equally severe striatonigral and olivopontocerebellar involvement; NFT = neurofibrillary tangle; PD = Parkinson disease; PSP = progressive supranuclear palsy.
[a] $p < 0.05$, MSA vs DLB, PD, or PSP.
[b] $p < 0.01$, MSA vs PD, or PSP.

responsiveness). The diagnostic accuracy was 71% in probable MSA and 60% in possible MSA. Correctly diagnosed patients with MSA had a younger age at onset and age at death than patients with PD or PSP, but duration of symptoms did not differ.

Although the brain weights did not differ among the 4 groups, Braak NFT stage in both DLB and PD and Thal amyloid phase in DLB were higher than in MSA (table 1). In a multiple logistic regression analysis adjusting for age at death, the difference for Thal amyloid phase was higher in DLB than in MSA (odds ratio 1.5, 95% confidence interval 1.05–2.26, $p = 0.028$), but differences in Braak NFT stage in DLB and PD were not significant. The breakdown of Lewy-related pathology and pathologic variants of MSA is summarized in table 1.

Table 2 lists the frequency of clinical features in autopsy-confirmed MSA, DLB, PD, and PSP. Comparing MSA and DLB, urinary incontinence, limb ataxia, nystagmus, and pyramidal signs were more frequent in MSA. Cognitive impairment and visual hallucinations were more frequent in DLB. Comparing MSA and PD, urinary incontinence was less frequent and visual hallucinations were more frequent in PD. Comparing MSA and PSP, urinary incontinence, constipation, orthostatic hypotension, and RBD were more frequent in MSA. Vertical gaze palsy was more frequent in PSP. Frequency of levodopa responsiveness and average Mini-Mental State Examination score were not different among the groups.

To clarify the factors that led to misdiagnosis, we summarized initial diagnosis, final diagnosis, reasons for diagnosing MSA, and pathologic features in 34 pathologically confirmed patients (18 DLB, 6 PD, and 10 PSP) with the best medical documentation (i.e., scores 3–4), since records with quality scores

Table 2 Clinical features of pathologically diagnosed MSA compared with non-MSA

		Non-MSA				
Features	MSA	DLB	PD	PSP	Others	*p* Value
Symptoms						
Syncope	35 (28/79)	61 (11/18)	29 (2/7)	21 (3/14)	29 (2/7)	0.06
Dizziness	32 (25/79)	56 (10/18)	43 (3/7)	21 (3/14)	29 (2/7)	0.17
Urinary incontinence	84 (66/79)	50 (9/18)[a]	43 (3/7)[a]	50 (7/14)[a]	29 (2/7)	0.001
Constipation	62 (49/79)	50 (9/18)	43 (3/7)	14 (2/14)[a]	29 (2/7)	0.01
Erectile dysfunction	60 (29/48)	33 (5/15)	20 (1/5)	25 (2/8)	50 (2/4)	0.06
Falls	72 (57/79)	72 (13/18)	71 (5/7)	93 (13/14)	57 (4/7)	0.40
Early falls	13 (10/79)	28 (5/18)	0 (0/7)	29 (4/14)	14 (1/7)	0.14
Cognitive impairment	37 (29/79)	89 (16/18)[a]	71 (5/7)	64 (9/14)	71 (5/7)	<0.001
Last available MMSE	28 ± 2 (16/79)	25 ± 3 (9/18)	28 ± 2 (2/7)	28 ± 1 (2/14)	22 ± 6 (2/9)	0.08
Visual hallucinations	13 (10/79)	56 (10/18)[a]	57 (4/7)[a]	29 (4/14)	29 (2/7)	<0.001
RBD	37 (29/79)	28 (5/18)	0 (0/7)	7 (1/14)[a]	0 (0/7)	0.04
Neurologic signs						
Orthostatic hypotension	57 (45/79)	72 (13/18)	71 (5/7)	14 (2/14)[a]	29 (2/7)	0.006
Asymmetric parkinsonism	41 (32/79)	56 (10/18)	29 (2/7)	29 (4/14)	0 (0/7)	0.40
Resting tremor	30 (24/79)	39 (7/18)	43 (3/7)	7 (1/14)	0 (0/7)	0.19
Bradykinesia	68 (54/79)	78 (14/18)	71 (5/7)	36 (5/14)	43 (3/7)	0.07
Rigidity	84 (66/79)	89 (16/18)	86 (6/7)	64 (9/14)	71 (5/7)	0.29
Postural instability	56 (44/79)	67 (12/18)	29 (2/7)	43 (6/14)	43 (3/7)	0.15
Gait ataxia	29 (23/79)	11 (2/18)	0 (0/7)	43 (6/14)	29 (2/7)	0.07
Limb ataxia	48 (38/79)	6 (1/18)[a]	29 (2/7)	43 (6/14)	14 (1/7)	0.009
Nystagmus	23 (18/79)	0 (0/18)[a]	0 (0/7)	7 (1/14)	0 (0/7)	0.04
Vertical gaze palsy	14 (11/79)	22 (4/18)	0 (0/7)	57 (8/14)[a]	29 (2/7)	0.001
Pyramidal sign	41 (32/79)	11 (2/18)[a]	14 (1/7)	14 (2/14)	29 (2/7)	0.02

Abbreviations: DLB = dementia with Lewy bodies; MMSE = Mini-Mental State Examination; MSA = multiple system atrophy; PD = Parkinson disease; PSP = progressive supranuclear palsy; RBD = REM sleep behavioral disorder.
Values are % (n) or mean ± SD (n).
[a] $p < 0.05$, MSA vs DLB, PD, or PSP.

of 2 or less usually did not describe the rationalization for diagnosing MSA (table 3). The most frequent reason for misdiagnosing DLB as MSA was autonomic failure. Seventeen of 18 patients with DLB presented with autonomic failure, which was specifically mentioned as the reason for reaching a clinical diagnosis of MSA in 14 patients. Seven patients were given a diagnosis of MSA as an initial diagnosis because of autonomic failure. Similar to DLB, autonomic failure was the most frequent reason

Table 3 Clinical and pathologic features of 34 patients masquerading as MSA

Pathologic diagnosis	Age, y	Initial diagnosis	Final diagnosis	Reason for diagnosing MSA	Braak NFT stage	Thal Aβ phase	Lewy body type	CDLB
DLB-1	74	Dementia	MSA vs PD	Pism	IV	5	D	High
DLB-2	84	PD	MSA	NA	IV	3	D	High
DLB-3	79	PD	MSA	AF	IV	3	D	High
DLB-4	75	PD	MSA	AF	III	1	D	High
DLB-5	59	MSA	MSA	AF, Pism	II	2	D	High
DLB-6	71	ET	MSA-P	AF	I	4	D	High
DLB-7	63	MSA	MSA	AF, RBD, LDU	I	2	D	High
DLB-8	85	AD	MSA-P	LDU	II	0	T	High
DLB-9	50	PD	MSA	AF, LDU	II	1	T	High
DLB-10	70	PD	MSA	N/A	I	3	T	High
DLB-11	79	MSA	MSA	AF	I	2	T	High
DLB-12	62	MSA	MSA	AF	I	1	T	High
DLB-13	70	MSA	MSA	AF	I	0	T	High
DLB-14	73	MSA	MSA	AF	IV	3	T	Intermediate
DLB-15	77	MSA	MSA-P	AF, LDU, dysphagia	III	5	T	Intermediate
DLB-16	78	TIA	MSA	AF	III	3	T	Intermediate
DLB-17	74	Pism and MND	MSA	AF	III	0	T	Intermediate
DLB-18	69	PD	MSA	AF	III	0	T	Intermediate
PD-1	77	PD	MSA	AF	III	2	B	Low
PD-2	81	MSA	MSA	AF	III	1	B	Low
PD-3	87	PD	MSA	NA	III	0	B	Low
PD-4	80	MSA	MSA	AF	II	0	B	Low
PD-5	62	MSA	MSA	AF	I	2	B	Low
PD-6	70	PD	MSA	AF	I	0	B	Low
PSP-1	83	MSA	MSA	AF	IV	3	—	—
PSP-2	81	MSA	MSA vs SCA	CA	IV	0	—	—
PSP-3	73	PSP	MSA	CA	III	2	—	—
PSP-4	70	PSP vs MSA	PSP vs MSA	LDU	II	0	—	—
PSP-5	70	Pism	MSA-P	AF, LDU	II	0	—	—
PSP-6	87	MSA vs PSP	MSA	CA	II	0	—	—
PSP-7	60	PD	MSA	AF	II	0	—	—
PSP-8	84	PSP vs MSA	PSP vs MSA	CA	I	0	—	—
PSP-9	74	MSA-C	MSA-C	CA	0	0	—	—
PSP-10	71	Alcohol ataxia	MSA	AF	0	0	—	—

Abbreviations: Aβ = amyloid-β; AD = Alzheimer disease; AF = autonomic failure; B = brainstem type; CA = cerebellar ataxia; CDLB = likelihood of dementia with Lewy bodies based on the Third Consortium on Dementia with Lewy Bodies; D = diffuse type; DLB = dementia with Lewy bodies; ET = essential tremor; LDU = L-dopa unresponsiveness; MND = motor neuron disease; MSA = multiple system atrophy; MSA-C = multiple system atrophy with predominant cerebellar ataxia variant; MSA-P = multiple system atrophy with predominant parkinsonism variant; NA = not available; NFT = neurofibrillary tangle; PD = Parkinson disease; Pism = parkinsonism; PSP = progressive supranuclear palsy; SCA = spinocerebellar ataxia; T = transitional type; VH = visual hallucinations.

for misdiagnosing PD as MSA. It is worth noting that 3 patients with PD with severe autonomic failure early in the disease course were diagnosed with MSA. In contrast to DLB and PD, the most frequent reason for misdiagnosing PSP as MSA was the presence of cerebellar ataxia. Three patients with PSP presented with cerebellar ataxia as the initial clinical feature, and 4 other patients developed ataxia (limb ataxia in 6, gait ataxia in 6, and ataxic speech in 2) during the course of the disease. Eight patients with PSP also had signs or symptoms of autonomic failure, and 7 patients had vertical gaze palsy.

We chose patients with at least moderate quality medical records (i.e., scores 2–4) and compared MRI findings in MSA, DLB, PD, and PSP (table 4). Although the frequency of cerebellar atrophy was lower in DLB than in MSA, the frequency of brainstem atrophy, cerebral atrophy, and abnormalities in the putamen (e.g., hyperintensity or hypointensity in lateral putamen on T2-weighted images) were not different among the 4 groups. The duration between performance of MRI and death was shorter in DLB and PD than in MSA (1.9 vs 3.8 years). Hot cross bun sign was noted in 1 patient with MSA, and a hummingbird sign was noted in 1 patient with PSP.

DISCUSSION In this unselected referral autopsy series of patients with antemortem diagnoses of MSA, the diagnostic accuracy was about 62%, which is within the range of other autopsy series.[1,5,6] This study confirms that MSA can be difficult to differentiate from DLB, PD, and PSP not only in early stages, but also at late stages of the disease process. One of the most intriguing results from the present study is that patients with atypical presentations (e.g., ataxia in PSP) or uncommon clinical features (e.g., dysautonomia in DLB and PD) of DLB, PD, and PSP can be misdiagnosed as MSA. Other studies of clinical and autopsy studies have demonstrated that autonomic failure can be a feature of DLB,[16–18] but this fact does not seem to be widely appreciated in clinical practice. Indeed, 6 patients with DLB were initially diagnosed with PD, but the diagnoses were changed to MSA because of developing autonomic failure. Furthermore, 4 patients initially presenting with autonomic failure (orthostatic hypotension in 3 patients) and later developing parkinsonism were diagnosed as MSA. Similar to DLB, 5 patients with PD were misdiagnosed with MSA because of autonomic failure. Three of them had autonomic failure as an initial symptom, adding further evidence that dysautonomia can present another premotor feature of PD.[19–21] Until now, severe dysautonomia in early stages of PD has been considered an exclusion criterion for PD.[22–24] Based on our study, clearly this is not the case. In addition to the autonomic failure, some atypical features in PD (e.g., short duration of symptoms and levodopa unresponsiveness) may also contribute to misdiagnosis as MSA. One patient with DLB and 2 patients with PD developed limb ataxia, usually slight dysmetria on finger-to-nose testing and not severe ataxia seen in MSA. Two patients with ataxia had sensory neuropathy, and sensory ataxia may be the etiology.

In this unselected autopsy series of patients with clinically diagnosed MSA, absent or mild cognitive impairment limited correct diagnosis of DLB defined as intermediate or high likelihood CDLB.[14] This contrasts with findings in prospectively studied cohorts recruited from memory disorder clinics where the CDLB neuropathologic criteria are highly correlated with the DLB clinical syndrome.[25] The results of this study suggest that a subset of patients in a nonspecialty setting with intermediate to high likelihood of DLB pathology (i.e., limbic or diffuse cortical Lewy bodies and minimal Alzheimer-type pathology) may have an atypical parkinsonian syndrome with minimal

Table 4 MRI findings of pathologically diagnosed MSA compared with non-MSA

		Non-MSA			
Features	**MSA**	**DLB**	**PD**	**PSP**	***p* Value**
Patients with MRI findings	67 (53/79)	72 (13/18)	29 (2/7)	57 (8/14)	0.17
Years to death, mean ± SD	3.8 ± 2.3	1.9 ± 2.1[a]	1.5 ± 1.4[a]	4.1 ± 0.6	0.006
Negative findings	38 (20/53)	54 (7/13)	50 (1/2)	25 (2/8)	0.41
Atrophy of cerebellum	42 (22/53)	8 (1/13)[a]	50 (1/2)	38 (3/8)	0.04
Atrophy of brainstem	23 (12/53)	0 (0/13)	50 (1/2)	25 (2/8)	0.19
Abnormality of putamen	13 (7/53)	8 (1/13)	0 (0/2)	13 (1/8)	0.89
Atrophy of cerebrum	15 (8/53)	38 (5/13)	0 (0/2)	25 (2/8)	0.24

Abbreviations: DLB = dementia with Lewy bodies; MSA = multiple system atrophy; PD = Parkinson disease; PSP = progressive supranuclear palsy.
Values are % (n) or mean ± SD (n).
[a] $p < 0.05$, MSA vs DLB or PD.

cognitive impairment that can be misdiagnosed as MSA. In this autopsy series, only 4/18 patients with DLB underwent formal neuropsychological evaluations, and cognitive impairment might have been overlooked. While cognitive impairment was more frequent in DLB than in MSA, the degree of cognitive impairment in patients with DLB thought to have MSA was not sufficient to diagnose dementia and pathologic analyses showed minimal Alzheimer-type pathology (median Braak NFT stage III and Thal amyloid phase 3). These results suggest that pathologically pure DLB can masquerade as MSA because of absent or mild cognitive impairment in combination with features of autonomic failure or limited response to levodopa.

Most patients with PSP masquerading as MSA presented or developed cerebellar ataxia. Although the presence of prominent, early cerebellar symptoms is an exclusion criterion for clinical diagnosis of PSP,[26] 7 patients with PSP in our series had cerebellar ataxia. Furthermore, 3 patients had cerebellar ataxia as an initial and principal symptom. These patients may fit with an atypical form of PSP with cerebellar ataxia (PSP-C).[27,28] Our findings suggest that when cerebellar ataxia is present in a patient with features of an atypical parkinsonian disorder, physicians should consider PSP in addition to MSA. A recent study has shown that older onset, early falls, and vertical gaze palsy without dysautonomia may differentiate PSP-C from MSA-C.[29] Although patients with PSP in our cohort had frequent autonomic failure, older age at onset and the combination of vertical gaze palsy and early falls might be useful in the differential diagnosis of PSP and MSA (33% in PSP vs 4% in MSA).

Even with MRI studies, clinical diagnosis of MSA is challenging. In this retrospective series, 38% of patients with MSA in which imaging results were available had no abnormal MRI findings, and only one had a typical hot cross bun sign. The reason for the low frequency of abnormal findings may be explained by the timing of the MRI. In most cases it was performed relatively early in the disease course, with no clinical indication to repeat scans as the disease progressed. This reflects the nature of clinical practice in America. While longitudinal MRI is frequent in movement disorder research clinics, such is not the case in routine clinical care. In addition, some abnormal findings might have been overlooked because patients were evaluated by general radiologists, whose focus is often on cerebrovascular, traumatic, neoplastic, or other acute processes. Patients with PSP had abnormal findings on MRI at a similar frequency as patients with MSA. Even when a characteristic finding, such as the hummingbird sign, was noted on antemortem MRI, patients with PSP were still misdiagnosed with MSA. Only a few patients with pathologically confirmed DLB had cerebellar atrophy, brainstem atrophy, or abnormality in the putamen, suggesting that MRI may be helpful in differentiating DLB from MSA. Taken together, the results suggest that MRI is helpful in some patients, but is not reliable for diagnosis of MSA if performed too early in the disease course and not repeated later as the disease progresses.

There are some clear limitations of our study. First, it is a retrospective analysis and is not based on standardized prospective clinical evaluations. Therefore, some clinical symptoms and neurologic signs might be underestimated. Hyposmia is an important preclinical sign of PD,[30] but it was not assessed in our study because it was not described in most patients. Second, we restricted the neuroimaging assessment to MRI. Although other modalities such as [^{123}I]-MIBG myocardial scintigraphy are useful for differentiating MSA from other parkinsonian disorders,[31] it is not widely available in clinical practice. Third, the timing of the clinical examinations and autopsy varied among patients. Patients have different clinical features early compared to late in the disease course, and depending upon the records available, some features at either end of the clinical spectrum may have been missed. Although our scoring system of the quality of the medical records does not reflect these issues, records scored in the 3 or 4 range tended to be written later in the disease course. An inherent limitation of any study using autopsy samples is selection bias, with atypical patients being more likely to come to autopsy than typical patients, as shown for parkinsonian syndromes.[6,32]

A notable strength of our study is that many of the patients were derived from the community setting rather than specialty clinics, and therefore, our findings may better represent the state of diagnostic accuracy of MSA in general clinical practice. Another strength is that pathologic diagnostic evaluation used the latest methods for detecting α-synuclein and tau pathologies, and the most current pathologic classification systems for MSA, DLB, PD, and PSP. The results serve as a powerful reminder that the misdiagnosis rate can be high in MSA, and that DLB can be a key culprit in causing this confusion, along with PSP and PD. This has implications not only for patient care, but also for research studies that do not have pathologic confirmation.

AUTHOR CONTRIBUTIONS

Shunsuke Koga: conceptualization, execution of the statistical analysis, execution of the project, writing of the first draft. Naoya Aoki: review and critique of the manuscript. Ryan J. Uitti: review and critique of the manuscript. Jay A. Van Gerpen: review and critique of the manuscript. William P. Cheshire: review and critique of the manuscript. Keith A. Josephs: review and critique of the manuscript. Zbigniew K. Wszolek: review and critique of the manuscript. J. William Langston: review and

critique of the manuscript. Dennis W. Dickson: conceptualization, organization of the research project, review and critique of the manuscript.

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