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Autopsy confirmed multiple system atrophy cases: Mayo experience and role of autonomic function tests

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Abstract

Background—Multiple system atrophy (MSA) is a sporadic progressive neurodegenerative disorder characterised by autonomic failure, manifested as orthostatic hypotension or urogenital dysfunction, with combinations of parkinsonism that is poorly responsive to levodopa, cerebellar ataxia and corticospinal dysfunction. Published autopsy confirmed cases have provided reasonable neurological characterisation but have lacked adequate autonomic function testing.

Objectives—To retrospectively evaluate if the autonomic characterisation of MSA is accurate in autopsy confirmed MSA and if consensus criteria are validated by autopsy confirmation.

Methods—29 autopsy confirmed cases of MSA evaluated at the Mayo Clinic who had undergone formalised autonomic testing, including adrenergic, sudomotor and cardiovagal functions and Thermoregulatory Sweat Test (TST), from which the Composite Autonomic Severity Score (CASS) was derived, were included in the study.

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Results—Patient characteristics: 17 men, 12 women; age of onset 57 ± 8.1 years; disease duration to death 6.5 ± 3.3 years; first symptom autonomic in 18, parkinsonism in seven and cerebellar in two. Clinical phenotype at first visit was MSA-P (predominant parkinsonism) in 18, MSA-C (predominant cerebellar involvement) in eight, pure autonomic failure in two and Parkinson's disease in one. Clinical diagnosis at last visit was MSA for 28 cases. Autonomic failure was severe: CASS was 7.2 ± 2.3 (maximum 10). TST% was $65.6 \pm 33.9\%$ and exceeded 30% in 82% of patients. The most common pattern was global anhidrosis. Norepinephrine was normal supine (203.6 ± 112.7) but orthostatic increment of $33.5 \pm 23.2\%$ was reduced. Four clinical features (rapid progression, early postural instability, poor levodopa responsiveness and symmetric involvement) were common.

Conclusion—The pattern of severe and progressive generalised autonomic failure with severe adrenergic and sudomotor failure combined with the clinical phenotype is highly predictive of MSA.

INTRODUCTION

Multiple system atrophy (MSA) is a sporadic progressive neurodegenerative disorder characterised by autonomic failure (AF), manifested as orthostatic hypotension (OH) or urogenital dysfunction, with combinations of parkinsonism that is poorly responsive to levodopa, cerebellar ataxia and corticospinal dysfunction.^{1–4} Consensus criteria² and its update¹ have improved the clinical diagnosis. These require the presence of urinary dysfunction or OH with a decrease in blood pressure of at least 30 mm Hg systolic or 15 mm Hg diastolic within 3 min after standing up, as well as a motor syndrome that includes parkinsonism with a poor response to levodopa or a cerebellar syndrome.

The most difficult differential diagnoses are in patients with phenotypic features that lead to misdiagnoses such as Parkinson's disease, progressive supranuclear palsy (PSP) or other forms of parkinsonism, such as corticobasal degeneration (CBD)⁵ and diffuse Lewy body disease. On the other hand, patients with diffuse autonomic impairment but with minimal or no motor signs may receive a diagnosis of pure autonomic failure (PAF).

AF is a central feature of MSA,^{6–8} mainly neurogenic bladder and OH.¹⁹ However, the presence of OH alone does not distinguish MSA from Parkinson's disease (PD).¹⁰ A major limitation of published studies on MSA is that the diagnosis has been assumed and not confirmed. A definitive diagnosis requires the neuropathological findings of widespread CNS α -synuclein positive glial cytoplasmic inclusions associated with neurodegenerative changes in striatonigral or olivopontocerebellar structures.¹¹ There are few reports of autopsy confirmed MSA cases. Published autopsy confirmed cases have provided reasonable neurological characterisation but have lacked adequate autonomic function testing.¹² To fill this niche, we reviewed the records of autopsy confirmed MSA patients seen at the Mayo Clinic, Rochester, Minnesota, USA, who underwent full autonomic function tests. We had undertaken a prospective study documenting that autonomic function tests will distinguish MSA from PD and controls with sensitivity and specificity.¹³ The specific aims of this study were: (1) to evaluate if the severity and distribution of autonomic failure, as previously described,¹³ applies to autopsy confirmed MSA; and (2) to evaluate if consensus criteria are validated by autopsy confirmation.

METHODS

We undertook a retrospective study of patients who received an autopsy confirmed diagnosis of MSA according to the current criteria.¹¹

Clinical data abstracted from the patients' medical records included disease onset and disease duration, as defined below, and clinical features (autonomic, cerebellar, parkinsonian and pyramidal symptoms and signs) at the first and last visit at the Mayo Clinic (see table 1).

Disease onset

Disease onset was defined as the initial presentation of any motor problem, whether parkinsonian or cerebellar, or autonomic features, as defined in the criteria for possible MSA.¹

MSA categories

Patients were classified into two clinical phenotypes based on the predominant motor features, as defined by the second MSA consensus¹: predominant parkinsonism (MSA-P) or predominant cerebellar involvement (MSA-C).

Diagnostic categories

A diagnostic category of possible or probable was defined for each patient at the first and last Mayo visit according to the current MSA consensus.¹

Autonomic phenotype

Recorded investigations included autonomic function tests (autonomic reflex screen, Thermoregulatory Sweat Test (TST), and supine and standing plasma catecholamine levels (see table 2)).

Autonomic function tests—Cardiovagal, cardiovascular, adrenergic and postganglionic sudomotor functions were assessed as follows: the Quantitative Sudomotor Axon Reflex Test (QSART) evaluated the postganglionic sympathetic sudomotor axon¹⁴ and the sweat response was recorded routinely from four sites (the forearm and three leg sites). Control values were derived from studies on 223 healthy subjects aged 10–83 years.¹⁵ Heart rate response to deep breathing and Valsalva ratio were used to evaluate cardiovagal function.¹⁵ Control values were based on 157 healthy subjects aged 10–83 years.¹⁵ Cardiovascular adrenergic function was evaluated by the blood pressure and heart rate response to the Valsalva manoeuvre and headup tilt. Beat to beat blood pressure was monitored continuously (Finapres monitor; Ohmeda, Englewood, Colorado, USA).¹⁶

Composite Autonomic Severity Score (CASS) is derived from the autonomic reflex screen as previously described¹⁷ and provides an evaluation of severity and distribution of autonomic failure. Patients with autonomic failure were graded as follows: 1–3, mild autonomic failure; 4–6 moderate autonomic failure; and 7–10, severe autonomic failure.¹⁷

Thermoregulatory Sweat Test—The TST assesses the pattern of sweat loss and provides a quantitative evaluation of per cent of anterior body surface anhidrosis.¹⁸ The TST was performed in a cabinet with a hot and humid environment (45–50°C air temperature; 35–40% relative humidity) and sweating was demonstrated by an indicator powder. The percentage of anhidrosis on the anterior body surface was calculated from images created from digital photographs of the sweat distribution. Results were expressed as the percentage of body surface area that did not sweat (100% indicates complete anhidrosis).¹⁹

Plasma catecholamine—Recorded investigations also included supine and standing plasma catecholamine levels (see table 2).

RESULTS

We identified 29 patients with autopsy confirmed MSA who had undergone autonomic function testing. Age at onset, at death and disease duration are listed in table 1.

Neurological phenotype

Autonomic symptoms were the most common disease presentation occurring in 18 patients (table 1).

First evaluation at the Mayo Clinic—Of the 29 MSA cases at the first evaluation at the Mayo Clinic, 18 had MSA-P, eight had MSA-C, two had PAF and one had PD-like (table 2). Twenty-four patients fulfilled the criteria for probable MSA at the first visit. Cognition was intact in all patients.

MSA-P phenotype: The presenting motor disorder characterised by bradykinesia and rigidity was present in all MSA-P patients but one. Resting tremor was present in 3/18 (16.6%) patients and action tremor in 4/18 (22.2%) patients. Stooped posture was present in 9/14 patients (64.2%) and laterocollis in one patient. Speech was impaired in 13/18 patients (72.2%). An associated cerebellar feature, including gait ataxia with limb ataxia, or cerebellar oculomotor dysfunction was present in three patients. Mean disease duration was 5 ± 1.8 years.

MSA-C phenotype: Ataxia of gait was present in 6/8 (75%) patients, dysarthria in 5/8 (62.5%), limb ataxia in 4/8 (50%) and gaze-evoked nystagmus in 3/8 (37.5%) patients. One patient received a diagnosis of MSA-C at his first visit outside the Mayo Clinic. Mean disease duration was 8 ± 3.6 years.

Pure autonomic failure: Two patients had a phenotype of PAF with severe autonomic failure and without additional motor impairment suggestive of parkinsonism or cerebellar syndrome. Their mean disease duration was 13 ± 4.2 years. These two patients later developed parkinsonism (see atypical cases below for more details).

Parkinson's disease-like: One patient had a diagnosis of idiopathic PD at his first Mayo Clinic visit. His detailed clinical phenotype is described below.

Autonomic failure: A summary of autonomic features and laboratory characteristics of the patients is provided in tables 2 and 3. Symptoms of orthostatic intolerance (OI) and bladder dysfunction were especially common, as was bowel and sexual dysfunction. All patients underwent autonomic reflex screen. The mean CASS total score was 7.2 ± 2.3 , indicating severe generalised autonomic failure. A low CASS total score (CASS total < 3) was present in two patients, indicating that, in a minority of cases, autonomic failure can be mild (table 3). OH was present in 21 patients and symptomatic in 19. Among the remaining patients who did not have OH at the first Mayo Clinic visit (seven patients), the only one who underwent follow-up autonomic studies was found to have developed OH.

Sudomotor function: The QSART was performed in all patients, of whom eight had normal findings, 10 had reduced widespread postganglionic sudomotor function and the remaining had either patchy (4/29 patients, 13.7%), distal or length dependent (3/29 patients, 10.3%), or focal (1/29 patients, 3.4%) (table 3).

TST was performed in 22 patients, of whom only two had normal results; 20/22 had anhidrosis and 18 had TST% anhidrosis $> 30\%$ (82% of patients) (table 3, figure 1). The

most common pattern was a global pattern of anhidrosis (10/22 patients, 45%). The remainder had either a mixed (6/22 patients, 27%), regional (3/22 patients, 13.6%) or segmental pattern (1/22 patients, 4.5%) of sweat loss. Mean TST% anhidrosis was $65.6 \pm 33.9\%$.

Plasma norepinephrine: Standing and supine catecholamine levels were measured in 10 patients. Median supine norepinephrine was 203.6 ± 112.7 (70 to 415) pg/ml. Median standing norepinephrine was 258.7 ± 137 (97 to 519.8) pg/ml. The difference between standing–supine norepinephrine was 55.1 ± 51.7 (–5 to 182.4) and the percentage increase in norepinephrine was 33.5 ± 23.2 (–1.20 to 64.6) (table 3).

Levodopa response: Twelve patients (11 MSA-P, one MSA-C) were treated with levodopa and only two had a transient positive response with improvement in parkinsonian features (table 3).

MRI of the brain: MRI findings were available for 11 patients and details are provided in table 3. Cerebellar atrophy was the most common finding (10/16 patients) and the hot cross bun sign was present in two patients.

Last evaluation at Mayo: Clinical diagnosis at the last visit was MSA for 28 cases. One case was diagnosed as PAF at his last (and only) Mayo Clinic visit (see atypical cases below).

Clinical red flags—Rapid progression was characteristic, with gait impairment being present at motor onset in 75% of cases; 93% of patients progressed from motor onset to wheelchair dependency within 5 years. Another characteristic was early postural instability with mean time to first fall of 21 ± 17 months. Retropulsion on the Pull Test was positive in 92% of patients when it was done at 21 ± 18 months from onset of symptoms. A rest tremor was uncommon, being present in 10% of patients. Symmetric motor involvement was the rule; symmetric bradykinesia in 78% and rigidity in 80%. Levodopa responsiveness was poor or poorly sustained in 80%. Antecollis was noted in six patients.

Atypical cases

Pure autonomic failure

Case No 1: This 55 year old presented with a longstanding history of OH, with onset at age 45 years. Other manifestations were bladder retention, constipation, sexual dysfunction, nocturnal stridor (10 years after disease onset) and sleep apnoea. No additional motor impairment suggestive of parkinsonism or cerebellar syndrome was noted by history or by neurological examination. OH occurred with severe exercise and did not require medications to control it at that time. The autonomic reflex screen showed normal postganglionic sympathetic and vagal functions, and severe cardiovascular adrenergic failure (CASS adrenergic 4). TST% anhidrosis was 60%. In the 6 subsequent years, the condition evolved into full blown MSA-P, a diagnosis that was confirmed by the local neurologist antemortem.

Case No 2: This 47 year old presented with a 3 year history of OH. Other autonomic manifestations were bladder symptoms, including urgency and frequency and variable diarrhoea without incontinence. OI developed after about 5 min of standing; symptoms included orthostatic headache and lightheadedness. No additional neurological signs were present at the first visit and a provisional diagnosis of PAF was made. The autonomic reflex screen showed severe generalised autonomic failure (CASS total=9); TST% was 36%. At the 10 month follow-up, there was worsening of sudomotor dysfunction; TST% had increased to 65% anhidrosis.

Over the subsequent 4 years, the patient developed parkinsonian features affecting initially the left upper extremity and then both upper extremities. The patient also developed masked facies, a flexed posture, psychomotor slowing, and faecal and urinary incontinence. The patient continued to have multiple episodes of syncope. The patient was started on levodopa/carbidopa with mild benefit and without aggravation of her OH. By the last follow-up visit (8 years from the onset), the patient had a full blown parkinsonian syndrome. The patient died 2 years later, and neuropathological examination confirmed the diagnosis of MSA.

For case No 1, the normal QSART and anhidrotic TST localized the site of the lesion to the central/preganglionic site. However, the long history of autonomic failure without parkinsonian or cerebellar features mandated the diagnosis of PAF at the initial visit. In the 6 subsequent years, it evolved into full blown MSA-P, a diagnosis that was confirmed by the local neurologist. Both cases exemplify the progression from a PAF phenotype to MSA-P. Neuropathological examination confirmed the diagnosis of MSA in both cases.

Possible corticobasal degeneration phenotype

Case No 3: This 74 year old presented with left-sided hypokinesia and profound inability to use the left limbs as if they were not under voluntary control. There was also dystonia on the left with spontaneous left foot posturing and extension of the great toe. The right side was unaffected. Cognition was intact. Bladder, bowel and sweating functions were normal. The patient has been using levodopa/carbidopa without any benefit. The patient had symptoms of OH. Past clinical history was complicated by a significant neck surgery with scarring and requiring a tracheostomy.

Autonomic reflex screen documented severe generalised autonomic failure with a CASS total of 8. TST was normal. Supine and standing norepinephrine levels were 154 and 214.2, respectively. The diagnosis of CBD was considered but, in the context of severe generalised autonomic failure, was diagnosed as MSA-P. Two years after first evaluation at the Mayo Clinic, the patient died and neuropathological examination was diagnostic of MSA.

Progressive supranuclear palsy versus multiple system atrophy

Case No 4: This 66 year old developed difficulty with bladder emptying and urinary retention necessitating self-catheterisation at age 64 years. One year later, clear impairment of gait was evident. A diagnosis of PD was made followed by treatment with levodopa/carbidopa without benefit. A thoracic syrinx on MRI was subsequently found and was treated with a thoracic syrinx shunt procedure. After the surgery, the patient developed speech disturbance (hypophonia), tendency to fall and a festinating gait. Supine hypertension was noted.

On examination, the patient had masked face, flexed posture, axial as well as appendicular rigidity, limitation of vertical gaze and hypokinetic dysarthria.

Autonomic function tests showed severe generalised autonomic failure (CASS total=7) without OH. Plasma catecholamine levels were normal supine but failed to increase on standing (norepinephrine supine 415, norepinephrine standing 410). TST was not performed. Nocturnal stridor (3 years after disease onset) subsequently developed. The patient also had severe constipation.

The diagnosis of PSP was considered, but given the clinical features of nocturnal stridor and severe generalised autonomic failure, the most likely diagnosis was considered to be MSA. The patient died 2 years later and neuropathological examination confirmed the diagnosis of MSA.

Parkinson's disease-like

Case No 5: This 67 year old developed mild tremor of the right hand at age 64 years, followed by difficulty of gait and a stooped posture. A diagnosis of PD was made and the patient was started on pergolide with mild benefit. Dysautonomia consisted of urinary hesitancy followed by urinary retention. On examination, the patient had mildly stooped posture and bilateral reduction of arm swing (right > left). Stride length was mildly reduced and there was mild generalised bradykinesia. Rigidity was present in all four limbs, the right greater than the left. A mild resting tremor of the right hand was evident. Alternate motion rate was moderately to markedly reduced in the right hand and mildly reduced in the other three limbs. There was no evidence of appendicular ataxia or pyramidal signs. A diagnosis of idiopathic PD was made followed by treatment with levodopa. Two years later, the patient reported worsening of his symptoms, including developing severe anterocollis, constipation, back pain and poor response to levodopa. Autonomic function tests showed moderate autonomic failure (CASS total=5) without OH and a TST% anhidrosis of 67%. At that time, a diagnosis of MSA-P was made. The patient died 1 year later and neuropathological examination confirmed the diagnosis of MSA.

DISCUSSION

The main findings are as follows: (1) the consensus criteria coupled with autonomic function tests showing severe generalised autonomic failure are highly predictive of autopsy confirmed MSA; (2) autonomic dysfunction is the most frequent presenting clinical feature of MSA in both MSA-P and MSA-C. Bladder dysfunction was the most frequent autonomic manifestation, followed by constipation and OH; (3) autonomic symptoms are supported by autonomic tests showing severe generalised autonomic failure (CASS total score was 7.2 ± 2.3 in 27 patients) and widespread anhidrosis on TST (anhidrosis >30% in 82% of patients); and (4) the present study, with autopsy confirmation, confirm our recent findings that the severity and distribution of anhidrosis distinguished MSA from PD.¹³ It also confirms earlier reports that clinical features of rapid progression, early postural instability, symmetric disease and inadequate levodopa responsiveness are characteristic of MSA.³⁴⁸²⁰

The most frequent clinical phenotype was MSA-P, as previously reported.¹⁴²¹ Of interest is the observation that there was a trend towards an increase in disease duration and a less progressive clinical course going from MSA-P to MSA-C to PAF phenotypes. Mean disease duration for the phenotypes were 5 ± 1.8 to 8 ± 3.6 to 13 ± 4.2 years, respectively.

AF is a well recognised feature in MSA and atypical parkinsonian syndromes. However, OH is also a common finding in PD patients.^{7132022–24} The differential diagnosis clinically between MSA and PD with autonomic failure can sometimes be difficult. It is often also difficult to distinguish MSA from DLB. REM sleep disorder, parkinsonism and autonomic failure are common to both conditions although the severity and distribution of AF is generally less in DLB.²⁵ The clinical diagnosis of PAF may be made in a patient who is in fact in an early stage of MSA. Therefore, making the right diagnosis at an early stage of the disease has not been satisfactorily addressed.

PAF is phenotypically distinct from MSA. Some cases remain throughout the lifetime of the patient as PAF while others evolve into MSA.^{26–28} It is clearly desirable to be able to differentiate cases that remain as PAF from those that will evolve into MSA or diffuse Lewy body disease, especially with the potential of neuroprotective therapies for MSA. A definitive answer must await long term prospective studies. However, there are some clues on prognosis. PAF that does not evolve is usually characterised by: (1) gradually progressive autonomic failure (neurogenic OH, neurogenic bladder) in the absence of cognitive, motor or sensory impairment²⁷; and (2) absence of respiratory dysfunction such as sleep apnoea or

stridor.²⁸ PAF is characterised by a distinctly postganglionic site of both sudomotor and adrenergic denervation, manifest as widespread anhidrosis on TST and absent QSART responses⁶; postganglionic cardiac denervation on MIBG and fluorodopa or hydroxyephedrine positron emission tomography scan of the heart²⁹; there is markedly reduced supine and orthostatic plasma norepinephrine; and denervation supersensitivity is characteristic.^{30,31} In contrast, some cases that evolve into MSA may demonstrate red flags. In one patient (case No 1), normal QSART combined with anhidrosis on TST localised the site of lesion to the preganglionic pathway, providing a red flag for MSA. The combined use of QSART and TST is helpful in localising the site of the lesion, distinguishing MSA (preganglionic) from PAF (postganglionic). Another characteristic of MSA is inexorable progression.¹³ The second PAF case (case No 2) had severe and progressive autonomic failure (CASS total=9) and TST% anhidrosis of 36%. At the 10 month follow-up, TST% has increased to 65% anhidrosis. However, disease duration alone may be unreliable. Two of our patients had a longstanding history of PAF. Both patients had long disease duration (10 and 16 years). The occasional patient has been described developing features of PD or dementia with Lewy body with disease duration of over 20 years.³²

One patient received an initial misdiagnosis of idiopathic PD at the first Mayo Clinic visit (case No 5) and developed worsening of symptoms and a poor levodopa response after 2 years. At that time, the autonomic function tests showed moderate autonomic failure (CASS total=5) without OH and a degree of anhidrosis of 67%. The clues to diagnosis of MSA-P were the early loss of levodopa responsiveness and the presence of autonomic failure with diffuse sudomotor failure. The sudomotor impairment confirms our previous report¹³ that the distribution and TST% anhidrosis are significantly different between MSA and PD patients and can be very helpful in the diagnosis of MSA. This patient additionally developed severe anterocollis, a red flag for the diagnosis of MSA.¹ The rapid clinical progression associated with worsening of autonomic function tests is an important index suggesting the diagnosis of MSA.

In one patient (case No 3), a diagnosis of CBD was entertained because of unilateral involvement, lack of levodopa responsiveness and possible 'alien limb'. However, severe generalised AF (CASS total=8) suggested MSA-P as the most likely diagnosis. OH has not been recorded in patients with CBD^{12,33} and severe generalised autonomic failure should suggest the diagnosis of MSA to the clinician.

One patient presented with parkinsonism associated with limitation of vertical gaze and frequent falls. The diagnosis of PSP was considered but given the additional clinical feature of nocturnal stridor, red flag supporting the diagnosis of MSA¹ and autonomic failure (CASS total=7), the most likely diagnosis was considered to be MSA. PSP is characterised by prominent postural instability, including falls, supranuclear gaze palsy, pseudobulbar palsy, little or no response to levodopa and frequently cognitive impairment. There are conflicting data on the presence of autonomic dysfunction in PSP patients. Asymptomatic OH has been reported^{7,34} and symptoms suggestive of OH were reported in a large proportion of post mortem confirmed PSP (78%).¹² In contrast, a prospective study found that OH was absent and cardiovascular adrenergic function was intact in PSP patients.³⁵

In conclusion, our study showed that the presence of severe generalised autonomic failure, widespread anhidrosis, and rapid progression of autonomic failure is highly predictive of MSA. There is a suggestion that different MSA phenotypes (MSA-P, MSA-C or PAF-like) may have different clinical courses with a less progressive clinical course in PAF-like patients.

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Figure 1.

Characteristics of sudomotor autonomic failure in multiple system atrophy. Left: Preserved postganglionic sweat responses (Quantitative Sudomotor Axon Reflex Test (QSART)) with complete anhidrosis on the Thermoregulatory Sweat Test (TST), suggesting a central or preganglionic lesion. Right: Rapid progression (from 0% to 66% body surface anhidrosis) in only 1 year (sweating in shaded areas).

Table 1

Patients characteristics

Characteristic	Mean (SD) or
No of patients (M/F)	29 (17/12)
Age at onset (years)	57±8.1
Age at death (years)	62.5±8.4
Disease duration (years)	6.5±3.3
Symptoms onset (n)	
Autonomic	18
Parkinsonism	7

Table 2

First evaluation at the Mayo Clinic

Clinical phenotype	No of patients
MSA-P	18
MSA-C	8
PAF	2
PD	1
Autonomic dysfunction	% of patients
OI	75
Bladder dysfunction	89
Urinary incontinence	44.4
Urinary retention	26
Urinary frequency	18.5
Sweating dysfunction	40
Bowel dysfunction	77
Constipation	46
Faecal incontinence	27
Sexual dysfunction	64
REM BD	54
Sleep apnoea	37
Nocturnal stridor	30

BD, behaviour disorder; MSA-C, multiple system atrophy with predominant cerebellar involvement; MSA-P, multiple system atrophy with predominant parkinsonism; OI, orthostatic intolerance; PAF, pure autonomic failure; PD, Parkinson's disease.

Table 3

Laboratory characteristics of the patients

Clinic phenotype at the last evaluation	Sex/age at onset (years)	CASS Total	QSART pattern	TST % Anhidrosis	NE supine/Upright	Levodopa Response	MRI
MSA-P	F/77	10	Widespread	99	NA	Yes	Atrophy of pons and cerebellum
MSA-P	M/63	7	Distal	NA	415/410	No	Cerebellum and brainstem atrophy
MSA-P	F/61	6	Normal	0	NA	NA	NA
MSA-P	F/58	10	Widespread	51	162/205	NA	Cerebellar atrophy
MSA-P	M/49	4	Distal	NA	NA	No	Mild cerebellar atrophy
MSA-P	M/42	9	Widespread	97	NA	No	Hot cross bun sign in the pons; cerebellar atrophy
MSA-P	F/57	9	Widespread	99	NA	No	NA
MSA-P	F/61	7	Normal	39	NA	No	Normal
MSA-P	M/52	9	Widespread	NA	150/201	NA	NA
MSA-P	M/?	8	Length Dependent	NA	NA	No	NA
MSA-P	F/52	7	Focal	62	NA	No	NA
MSA-P	M/57	8	Distal	93	373/408	NA	Hypodensity of caudate and mild atrophy of cortex and cerebellum
MSA-P	M/45	8	Normal	99	70/97	NA	NA
MSA-P	M/52	3	Normal	9	126.5/208.3	NA	Early penguin sign, relative atrophy of the midbrain compared with the pons
MSA-P	F/72	8	Patchy	1	154/214.2	No	NA
MSA-P	F/57	6	Patchy	97	337.4/519.8	Yes	Normal
MSA-P	M/62	6	Normal	42	NA	NA	NA
MSA-P	M/?	6	Patchy	91	NA	NA	NA
MSA-P	M/63	5	Widespread	67	NA	No	Normal
MSA-P	F/44	9	Widespread	36	NA	NA	NA
MSA-C	M/62	6	Normal	NA	NA	No	Cerebral and cerebellar atrophy
MSA-C	M/62	9	Length dependent	NA	NA	NA	Mild cerebral atrophy and cerebellar atrophy
MSA-C	F/51	10	Widespread	92	143/153	NA	Cerebellar and pontine atrophy
MSA-C	M/48	6	Widespread	35	105/171	NA	Normal
MSA-C	M/53	10	Length dependent	99	NA	NA	NA
MSA-C	F/51	8	Patchy	13	NA	NA	Marked atrophy of the cerebellum and some pontine atrophy
MSA-C	F/60	10	Widespread	98	NA	NA	Cerebellopontine atrophy + hot cross bun sign

Clinic phenotype at the last evaluation	Sex/age at onset (years)	CASS Total	QSART pattern	TST % Anhidrosis	NE supine/Upright	Levodopa Response	MRI
MSA-C	M/?	0	Normal		NA	NA	NA
PAF	M/45	4	Normal	60	NA	NA	NA

CASS, Composite Autonomic Severity Score; MSA-C, multiple system atrophy with predominant cerebellar involvement; MSA-P, multiple system atrophy with predominant parkinsonism; NA, not applicable (referred to investigation not performed or findings not available); NE, norepinephrine; PAF, pure autonomic failure; QSART, Quantitative Sudomotor Axon Reflex Test; TST %, Thermoregulatory Sweat Test.