Diagnosing Premotor Multiple System Atrophy: Natural History and Autonomic Testing in an Autopsy Confirmed Cohort

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Abstract

Background and Objectives: Non-motor features precede motor symptoms in many patients

with multiple system atrophy (MSA). However, little is known about differences between the

natural history, progression and prognostic factors for survival in MSA subjects with non-

motor versus motor presentations. We aimed to compare initial symptoms, disease

progression and clinical features at final evaluation and investigate differences in survival and

natural history between MSA patients with motor and non-motor presentations.

Methods: Medical records of autopsy-confirmed MSA cases at Queen Square Brain Bank

who underwent both clinical examination and cardiovascular autonomic testing were

identified. Clinical features, age at onset, gender, time from onset to diagnosis, disease

duration, autonomic function tests and plasma noradrenaline levels were evaluated.

Results: 47 autopsy-confirmed MSA patients (60$\pm$8 years; 28 males) were identified. Time from symptom onset to first autonomic evaluation was 4$\pm$2 years and disease duration was 7.7$\pm$2.2 years. Fifteen (32%) patients presented with non-motor features including genitourinary dysfunction, orthostatic hypotension or REM sleep behaviour disorder prior to developing motor involvement (median delay 1-6 years). A third (5/15) were initially diagnosed with pure autonomic failure (PAF) before evolving into MSA. All these patients had normal supine plasma noradrenaline levels (332.0$\pm$120.3 pg/ml) with no rise on head-up tilt (0.1$\pm$0.3 pg/ml).

MSA patients with early cardiovascular autonomic dysfunction (within 3 years of symptom onset) had shorter survival compared to those with later onset of cardiovascular autonomic impairment (6.8 years [5.6-7.9] vs 8.5 years [7.9-9.2]; p=0.026).

Patients with early urinary catheterisation had shorter survival than those requiring catheterisation later (6.2 years [4.6-7.8] vs 8.5 years [7.6-9.4]; p=0.02). The survival of MSA patients presenting with motor and non-motor symptoms did not differ (p>0.05).

Discussion: Almost one-third of MSA patients presented with non-motor features, which could predate motor symptoms by up to 6 years. Cardiovascular autonomic failure and early urinary catheterisation were predictors of poorer outcomes. A normal supine plasma noradrenaline level in patients presenting with PAF phenotype is a possible autonomic biomarker indicating later conversion to MSA.

Keywords: multiple system atrophy, pure autonomic failure, autonomic testing, non-motor features, premotor phase multiple system atrophy

Abbreviations: MSA, Multiple system atrophy; PAF, pure autonomic failure; ILOCA, Idiopathic late-onset cerebellar ataxia; PSP, Progressive supranuclear palsy; RBD, Rapid eye movement sleep behaviour disorder; OH, Orthostatic hypotension; HUT, head-up tilt test; AFT, Cardiovascular autonomic function tests;

Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by autonomic failure, parkinsonism, and cerebellar signs. Non-motor features, including cardiovascular, respiratory, urogenital, gastrointestinal, sudomotor dysfunction and REM sleep behaviour disorder (RBD), can be presenting symptoms and often precede the motor symptoms in MSA[1]. MSA patients presenting with non-motor features are often misdiagnosed with other conditions. A previous study has shown that more than 40% of MSA patients who presented with urogenital dysfunction were misdiagnosed with prostatic hypertrophy or bladder dysfunction and underwent urological surgery with poor outcome[2], and patients with MSA initially presenting with orthostatic hypotension (OH) were usually diagnosed with pure autonomic failure (PAF) before the development of other hallmark MSA features[3].

Pure autonomic failure (PAF) is a sporadic alpha-synucleinopathy disorder characterized by autonomic failure without other neurological symptoms and signs[4]. A recent natural history study showed that up to 8% of PAF subjects presenting with isolated cardiovascular autonomic failure eventually evolve into MSA within 4 years after symptom onset[3]. Another, retrospective, study demonstrated that approximately 12% of PAF patients evolve into other neurodegenerative disorders, and more than half (59%) were diagnosed with MSA within the first 3 years after the initial diagnosis of PAF[5].

Cardiovascular autonomic dysfunction is an integral part of MSA diagnostic criteria[6], and is also likely to be a key factor influencing survival in MSA[7]. Two recent autopsy-confirmed studies have identified unfavourable prognostic factors in MSA[7, 8] including early development of generalised cardiovascular autonomic dysfunction[9], urinary catheterisation[7], severe autonomic dysfunction[7, 10], later age of onset[11], parkinsonian subtype of MSA[12, 13] and stridor[14]. However, the survival rate and disease progression have not been previously investigated in autopsy-proven cases presenting with motor vs non-motor features of MSA.

Therefore, the aim of this study was: 1) to characterize the initial symptoms, disease progression and clinical features at last evaluation in a large UK cohort of autopsy-confirmed MSA and 2) to investigate whether there are any differences in survival, clinical features and natural history between MSA patients with motor and non-motor presentations.

Methods

We retrospectively evaluated autopsy-confirmed MSA cases at the Queen Square Brain Bank, who underwent full autonomic function testing at the Autonomic Unit, National Hospital for Neurology and Neurosurgery, Queen Square (NHNN) between 1992 and 2012.

All were reviewed by movement disorder and autonomic specialists. Exclusions included concomitant diseases potentially affecting the autonomic nervous system (such as diabetes mellitus, heart diseases, cancer, hypothyroidism).

Clinical history, disease onset and clinical presentation

Medical records of MSA patients were systematically reviewed. History and relevant information of each patient was evaluated, including: age at evaluation, gender, age at onset, presenting symptoms, time from presenting symptoms to date of autonomic testing, dopaminergic medications, disease duration (time from symptom onset to death), and clinical diagnosis at first and last evaluation at NHNN.

Patients were divided into non-motor onset and motor onset, based on the first presenting symptoms according to the information recorded by the treating clinician on the medical notes. Non-motor presenting features included any of the following: cardiovascular autonomic symptoms (e.g. dizziness, light-headedness, visual disturbances, syncope and coat-hanger pain) [15], bladder dysfunction (urinary incontinence, frequency, urinary retention, urinary catheterisation), erectile dysfunction, gastrointestinal (GI) dysfunction, swallowing difficulties, stridor and REM sleep behaviour disorders (RBD).

Neurogenic bladder was defined as urinary incontinence or retention not attributable to urological or gynaecological pathology. Motor presenting features comprised of parkinsonism and/or cerebellar symptoms.

Cardiovascular autonomic testing

Cardiovascular autonomic function tests (AFT) were performed using Autonomic Unit, Queen Square autonomic protocols [16]. AFT data, including blood pressure (BP) and heart rate (HR) responses to head-up tilt test (HUT), Valsalva manoeuvre (VM), and HR response to deep breathing were collected. HUT was performed at 60° for 10 minutes. OH was defined as a drop of >30 mmHg in systolic blood pressure or >15 mmHg in diastolic blood pressure on HUT according to the MSA second consensus criteria[6]. Deep breathing was performed at a rate of 6 breaths per minute for one minute, and VM was performed by blowing against a fixed resistance of 40 mmHg for 15 seconds in the supine position. Supine and tilted plasma noradrenaline levels were included when available. To define the degree of cardiovascular autonomic dysfunction, we used the following criteria below:

- Isolated sympathetic dysfunction (OH and abnormal blood pressure responses during VM).

- Isolated parasympathetic dysfunction (abnormal Valsalva ratio and heart rate responses to deep breathing)

- Generalised cardiovascular autonomic dysfunction (Both sympathetic and parasympathetic autonomic dysfunction; OH with abnormal blood pressure responses during VM, abnormal Valsalva ratio and heart rate responses to deep breathing)

- No cardiovascular autonomic dysfunction

Statistical methods

Continuous data are presented as mean (± 1 SD) and categorical data as number (percentage). Mann-Whitney U tests were used to compare continuous variables between the 2 groups e.g., patients presenting with non-motor features vs motor (parkinsonian or cerebellar features) for

non-normally distributed data and unpaired t-tests for normally distributed data. Chi-square analyses were used for analysis of categorical variables.

Disease duration (time from first symptom to death) was considered as a dependent variable. Other relevant variables, including cardiovascular autonomic measures (such as blood pressure falls during HUT, HR responses to deep breathing etc.), age at onset, gender, MSA subtype (cerebellar subtype; MSA-C and parkinsonian subtype; MSA-P), the presence of stridor, respiratory involvement, swallowing difficulties, supine hypertension, early cardiovascular autonomic dysfunction, early neurogenic bladder ($\leq$3 years after onset), urinary catheterisation (either indwelling or intermittent), and plasma noradrenaline levels, were included as determinants in the model.

Multiple linear regressions were performed to assess the relationship between explanatory variables and disease duration. Kaplan-Meier curves were used to graphically estimate the median time to death and the log-rank test was used to compare the median time to death among the prognostic factors. Statistical analyses were carried out using STATA 11.0 (STATA Corporation, College station, Texas, USA). All tests were 2-sided and a p-value of $\leq$ 0.05 was considered significant

Standard Protocol Approvals, Registrations, and Patient Consents

The brain donor programme and protocols were approved by the NRES Committee London-Central (18/LO/0721) and tissue wa stored for research under a license issued by the Human Tissue Authority (No.12198). Written informed consent was obtained from all donors.

Data Availability

Due to the sensitive nature of the data collected for this study, anonymized data pertaining to the research presented will be made available upon reasonable request from external qualified investigators.

Results

Patient characteristics

Forty-seven patients (M: F, 28:19) with autopsy-confirmed MSA were included in the final analysis. Their mean age at onset was 56 ± 8 years and their mean disease duration (time from onset to death) was 7.9 ± 2.2 years.

The average time from symptom onset to the first evaluation at the NHNN was 4.2 ± 1.8 years. The final clinical diagnoses included MSA-C (n=24), MSA-P (n=21) and progressive supranuclear palsy (n=2). There were no significant differences in age, disease duration and gender between patients with MSA-C and MSA-P.

MSA patients with motor onset

Thirty-two (68%) patients presented with motor symptoms including parkinsonism or cerebellar features at onset (Upper panel, figure 1). Parkinsonism was more common than cerebellar features among MSA patients with motor onset. Patients with motor onset reported urinary symptoms within a median of 3 years (range 2-4 years) and cardiovascular autonomic dysfunction within 4 years (range 3-6 years) after symptom onset, respectively (see Table 1 and Figure 1). Bladder dysfunction eventually developed at some point during disease progression and was reported in all patients. These MSA patients presented with motor symptoms including tremor, and movement and balance problems, and were initially diagnosed with Parkinson's disease (PD), MSA, atypical parkinsonian disorders) or

idiopathic late onset cerebellar ataxia (ILOCA) at NHNN. These patients subsequently underwent cardiovascular autonomic testing before the diagnosis was subsequently refined to MSA in 96% (45/47) (eFigure).

Two patients were diagnosed clinically with progressive supranuclear palsy with predominant parkinsonism (PSP-P). Both patients presented with asymmetrical parkinsonism in their early 60s and were initially diagnosed with Parkinson's disease. Limitation of vertical gaze and slow vertical saccadic eye movements were documented in both patients. Urinary incontinence was reported within the first two years in both cases, followed by urinary retention. Urinary catheterisation was required at 4-5 years after the first symptom onset. Cardiovascular autonomic testing was performed at 2-4 years after first symptom onset. There was isolated cardiovascular parasympathetic dysfunction in both cases. The other patients' demographic data and features are presented in Table 1.

MSA patients with non-motor onset

15/47 (32%) patients initially presented with non-motor symptoms which preceded motor involvement. Erectile dysfunction and bladder dysfunction were the most two common initial symptoms (47% and 40% respectively) among patients with non-motor onset.

Symptomatic orthostatic hypotension (postural lightheadedness and syncope) and REM sleep behaviour disorder (RBD) occurred as an initial presentation in one patient each. Five of six (83%) female patients had bladder dysfunction as a presenting feature. The median time to subsequent development of motor features (either parkinsonism or cerebellar features) was three years (range, 1-5 years) (Figure 1).

Of the patients with non-motor onset (n=15), five presented with cardiovascular autonomic failure, erectile and bladder dysfunction with no motor features, and were diagnosed with

PAF during the first assessment at NHNN. (eTable; patient case numbers 3, 6, 9, 11 and 14). Three patients were initially given a clinical diagnosis of ILOCA and two with PD before their diagnosis was changed to MSA. The remaining five patients developed other features including poor levodopa response parkinsonism or cerebellar signs, and were subsequently diagnosed with MSA at first evaluation at NHNN.

Motor versus Non-motor onset: differences in autonomic and clinical features

There were no differences in age at onset (p=0.88) and disease duration (p=0.67) between patients with motor and non-motor onset. Patients with non-motor onset had a significant delay in clinical diagnosis compared to those with motor onset (4.8+2.0 years vs 3.5+1.8 years; p=0.03) (Table 1).

At last evaluation, there were no differences in reported symptoms including bladder dysfunction, requirement for urinary catheterisation, stridor, swallowing difficulty and constipation (all p>0.05) between patients with motor and non-motor onset. OH was present in all patients with non-motor onset and 75% (24/32) of patients with motor onset (p=0.03). In contrast, RBD was more commonly reported in patients with motor onset MSA in comparison to those with non-motor onset (odds ratio 4.3; 95% CI 1.00-18.36, p=0.05) (Figure 1).

Cardiovascular autonomic testing

All patients underwent comprehensive cardiovascular autonomic testing, which showed: 1) generalised autonomic failure (both sympathetic and parasympathetic autonomic dysfunction) in 20 (43%) patients; 2) isolated sympathetic dysfunction (OH and abnormal blood pressure

responses during VM) in 19 (40%) patients; 3) isolated parasympathetic dysfunction in 5 (11%); 4) no cardiovascular autonomic dysfunction at the first evaluation in 3 (6%) patients (Table 2).

MSA patients with isolated sympathetic impairment were significantly younger and had an earlier onset than those with generalised cardiovascular autonomic dysfunction (p<0.05; Table 2).

There were no differences in supine systolic blood pressure (SBP) between MSA patients with isolated sympathetic impairment compared to those with generalised cardiovascular autonomic dysfunction.

Orthostatic hypotension was documented in 83% (39/47) on head-up tilt (HUT). Supine hypertension, defined as supine systolic blood pressure ≥150 mmHg or diastolic blood pressure ≥90 mmHg, was present in 21% (10/47 patients) at first evaluation. The degree of OH (Δsupine ‐ head-up tilt BP) was not significantly different in patients with MSA with isolated sympathetic impairment compared to those with both sympathetic and parasympathetic impairment (p>0.05).

20/47 patients (43%) had plasma noradrenaline (NA) measurements both on supine and head-up tilt. Mean supine plasma noradrenaline was 345.0 ± 145.6 pg/ml with a minimal rise on HUT (increase of 34.7 ± 51.0 pg/ml). There were no differences in supine plasma noradrenaline levels between motor and non-motor presenting MSA patients (motor vs non-motor; 350 ± 156pg/ml vs 332 ± 120pg/ml, p=0.8).

All MSA patients with initial PAF phenotype had normal supine plasma noradrenaline levels with no rise on head-up tilt (mean supine plasma noradrenaline 357.6 ± 165.4 with a change of -11.8 ± 27.8 pg/ml on head-up tilt; normal supine plasma noradrenaline 200-500 pg/ml).

Prognostic factors for survival

There was no difference in survival between MSA presenting with motor and those with non-motor symptoms (p>0.05; Table 1). MSA patients with early cardiovascular autonomic dysfunction (within 3 years of symptom onset) had shorter disease survival compared to those with later onset of cardiovascular autonomic impairment (6.8 years [5.6-7.9] vs 8.5 years [7.9-9.2]; p=0.026) (Figure 2).

Thirty-two of 47 (68%) reported urinary symptoms (urinary frequency, incontinence or retention) and 10/30 (33%) had severe bladder dysfunction requiring indwelling or intermittent catheterisation within 3 years of symptom onset. MSA patients with early urinary catheterisation (within 3 years of symptom onset) had shorter survival in comparison to patients who had catheterisation later in disease progression (6.2 years [4.6-7.8] vs 8.5 years [7.6-9.4]; p=0.019) (Figure 2).

MSA patients with older age at onset ≥51 years had shorter disease duration compared to those with a younger age of onset (7.3 years [6.5-8.0] vs 9.1 years [8.2-9.9]; p=0.018).

There was a significant inverse correlation between the age of onset and disease duration in patients with generalized cardiovascular autonomic failure (sympathetic and parasympathetic cardiovascular autonomic dysfunction) (r=-0.71, p<0.01), but not in other groups with less severe autonomic dysfunction (all p>0.05) (Figure 3).

Amongst the minority of patients with MSA with no cardiovascular autonomic dysfunction (n=3) at first evaluation, disease duration ranged from 9-10 years, which appeared to be longer than those with cardiovascular autonomic dysfunction (Table 2). However, statistical analysis was not performed due to limited subgroup sample size. Balance problems and parkinsonism were presenting features in these patients and the diagnosis of MSA was made

at a time when patients presented with a combination of cerebellar features/parkinsonism, erectile dysfunction, severe bladder dysfunction leading to urinary catheterisation or other features according to the MSA consensus criteria (stridor, sleep apnoea or severe dysphagia). These patients had no cardiovascular dysfunction on repeat testing up to even 6 years after the first autonomic evaluation.

There was no association between MSA subtype, the presence of stridor, respiratory involvement, swallowing difficulties, supine hypertension, plasma noradrenaline levels and early neurogenic bladder (within 3 years after disease onset), excluding severe neurogenic bladder needing catheterization) (all p>0.05). There was also no association between non-motor presenting features, including erectile dysfunction, RBD, bladder dysfunction or orthostatic hypotension, and disease duration (p>0.05).

Discussion

The main finding of this study is that almost a third of our MSA patients presented with non-motor features at the onset. Among these patients, all but one who reported RBD as their initial symptom, presented with autonomic features, including erectile failure, bladder dysfunction, and/or OH. These findings are consistent with a recent study looking at initial symptoms in non-autopsy confirmed MSA[17]. The patients developed other features including poorly levodopa responsive parkinsonism, cerebellar signs, OH, or severe neurogenic bladder dysfunction during disease progression, and subsequently their diagnoses were changed to MSA.

In our cohort, MSA patients with motor onset usually developed bladder and cardiovascular autonomic dysfunction within 3 and 4 years respectively. The mean interval from the onset of

bladder symptoms to motor features in our study is in concordance with a large prospective study in MSA patients who initially presented with bladder dysfunction[18].

Two patients were initially diagnosed with Parkinson's disease, and three with idiopathic late onset cerebellar ataxia (ILOCA) before being re-diagnosed with MSA. A previous study has demonstrated that approximately a quarter of patients with a diagnosis of olivopontocerebellar atrophy will evolve to multiple system atrophy within 5 years[19].

Our findings demonstrated that non-motor features can predate motor symptoms by up to 6 years. These figures are comparable to previous studies[1, 20, 21], and emphasize the importance of regular monitoring for emerging features in these patients. We found that the final diagnosis of MSA was delayed by over a year in non-motor onset, compared to patients presenting with motor onset.

RBD was more frequently reported at final evaluation in patients with motor than non-motor onset MSA. It is a well-known feature that can predate other neurological symptoms in patients with synucleinopathies[22]. Its higher occurrence in motor onset MSA patients may reflect the selective vulnerability and differential involvement of key networks between these subgroups[23]. The anatomical substrate and pathophysiology of RBD is not completely understood. Several anatomical structures including dorsal midbrain, pons [24], in particular peri-locus coeruleus and sublaterodorsal nucleus as well as basal ganglia, substantia nigra and frontal cortex, have been proposed to play a crucial role in RBD[25]. Interestingly, imaging studies have linked idiopathic RBD with locus coeruleus-noradrenergic dysfunction [26].Quantitative pathological study in this area could shed some light on the differences in progression of autonomic pathology between these subgroups of MSA.

In contrast, OH was more common in MSA patients with non-motor onset than those with motor onset. Previous studies have reported a correlation between the loss of pre-ganglionic

neurons in the intermediolateral (IML) column and the degree of OH[27], and the depletion of C1 catecholaminergic neurons in the rostral ventrolateral medulla is thought to be partly responsible for the pathogenesis of OH in MSA[28]. Certain areas of the central autonomic network may be more vulnerable in patients with non-motor onset MSA.

These differences warrant further pathological studies on the distinct initial loci of α-synuclein pathology deposition influencing the evolution of clinical features and disease progression between MSA patients with motor and non-motor onset. A recent study has reported a subgroup of MSA patients who presented with isolated urinary retention requiring urinary catheterisation, sexual and bowel dysfunction, and abnormal anal sphincter electromyography (EMG) even before developing motor signs[29]. These findings raise the possibility that the pathological substrate for non-motor onset patients may start from the spinal cord before involving other regions of the central nervous system[29].

It is well recognized that a proportion of MSA patients may initially present with a 'PAF phenotype' before motor features emerge. Our study has demonstrated that at least 10% of MSA patients start with the 'PAF phenotype' before evolving into classical MSA features, with an average conversion time of 3 years. This is consistent with a recent study looking at the predictors of conversion from PAF to either MSA or PD/DLB [5]. Previous case reports have shown that autonomic failure can predate motor features for more than a decade in a subgroup of MSA patients [8, 30]. Our findings revealed that MSA patients who presented with PAF features had normal supine plasma noradrenaline levels (200-500 pg/ml) with no significant rise on head-up tilt, which is in line with a prospective cohort study on the natural history of PAF[3]. A normal supine plasma noradrenaline level in patients with PAF may indicate the likelihood of MSA conversion. This raises the possiblity that autonomic dysfunction and RBD is a prodomal phase of MSA[31].

Two patients with a clinical diagnosis of PSP at final evaluation were found to have MSA at post-mortem. They presented with asymmetrical parkinsonism with poor responses to levodopa, bladder symptoms, limitation of vertical gaze with slow vertical saccadic eye movements, and isolated parasympathetic dysfunction on cardiovascular autonomic testing. Recent studies have also described some patients with PSP-like presentation, who were subsequently found to have MSA at post-mortem[8], and almost 6% of patients with autopsy-confirmed PSP were misdiagnosed with MSA in life[32].

Mild autonomic impairment in PSP is thought to be linked with tau deposition in selected brainstem nuclei involved in the regulation of cardiovascular function and micturition[33]. Onuf's nucleus was reported to be involved in autopsy-confirmed PSP cases[34]. Pathological involvement of key autonomic structures in both MSA and PSP may give rise to a substantial overlap in the clinical presentation of some patients with MSA-P and PSP-P. However, the presence of severe cardiovascular autonomic and bladder dysfunction (indicated by time from onset to urinary catheterisation) and early autonomic dysfunction are more suggestive of MSA, as opposed to PSP [35].

Our study found no difference in survival between MSA patients presenting with motor and non-motor features. Nevertheless, selected characteristics and non-motor features including early urinary catheterisation (within 3 years of disease onset) and later age at onset (over 51 years) were associated with poor survival in MSA patients. These findings are consistent with both previous autopsy-confirmed [7, 11] and non-autopsy MSA studies[9, 20, 30]. Our study confirmed that MSA patients with cardiovascular autonomic dysfunction had shorter survival than those without, as previously reported in another autopsy-confirmed study[7].

Cardiovascular autonomic testing plays an important role in diagnosing MSA. 45/47 (96%) fulfilled Gilman diagnostic criteria for probable MSA after the autonomic testing at NHNN.

Some patients with MSA may only have isolated parasympathetic dysfunction (i.e., abnormal heart rate responses to deep breathing without OH on head up tilt) on cardiovascular autonomic testing. We propose that formal cardiovascular autonomic assessments should be performed in all patients with suspected MSA, as isolated parasympathetic deficits are unlikely to be detected by bedside cardiovascular autonomic testing. In our series, approximately 6% of MSA patients had normal cardiovascular autonomic function on testing up to 6 years after symptom onset, suggesting that although cardiovascular autonomic dysfunction is a key feature in MSA patients, normal cardiovascular function does not necessarily exclude a diagnosis of MSA.

There are some limitations of our study. First, the clinical history and data obtained retrospectively from the medical notes with lack of standardised autonomic questionnaires may result in an incomplete record of certain clinical features, such as RBD, olfactory function, gastrointestinal symptoms (i.e., constipation) and respiratory sighs/stridor in some patients, or these symptoms being underreported. RBD was less frequently reported in the clinical history prior to knowledge of its importance in synucleinopathies, and the frequency of RBD in our patients is also based on clinically suspected but not polysomnography-confirmed cases. Furthermore, we have no quantitative sudomotor function data in these patients, as this was not routinely performed in our department.

Moreover, we have limited information regarding the actual causes of death, including sudden unexpected death or unrelated concurrent medical conditions. These are often reported in MSA patients[36], and may have influenced the disease duration in our subjects. Finally, the patients in our cohort were all referred to a tertiary neurosciences unit and may represent more severe cases of MSA leading to poorer survival rate. The strength of our study is a large cohort of neuropathologically confirmed cases. Furthermore, these patients were referred from local neurologists, neurogeneticists (ataxia clinic), movement disorder and

autonomic specialists at NHNN. Also, in all our subjects comprehensive cardiovascular autonomic testing and detailed autonomic symptom profile were recorded during their disease course by specialists and clinical autonomic scientists.

In summary, non-motor features, particularly genitourinary and cardiovascular autonomic dysfunction, are common presenting symptoms in MSA. Almost a third of MSA patients in our cohort presented with non-motor features before developing motor involvement within 6 years. MSA patients with later age of onset and early impairment of cardiovascular autonomic function or bladder dysfunction requiring urinary catheterisation have shorter survival. A proportion of MSA patients start with PAF phenotype before developing motor features. Normal supine plasma noradrenaline levels in patients presenting with PAF is a red flag that may raise the possibility of subsequent conversion to MSA. The discrepancy in frequencies between RBD and OH in motor onset and non-motor onset MSA may indicate impairment of different brain areas. Understanding these differences may shed light on the selective vulnerability of brain and spinal cord nuclei in subtypes of MSA, and aid potential means for intervention or treatment at an earlier and thus modifiable stage of the disease.

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Figure Legends

Figure 1. Clinical features from onset to last clinical evaluation in MSA patients with motor (upper panel) and non-motor onset (lower panel), [*]median, range in years, [**]p<0.05. RBD=REM sleep behaviour disorder.
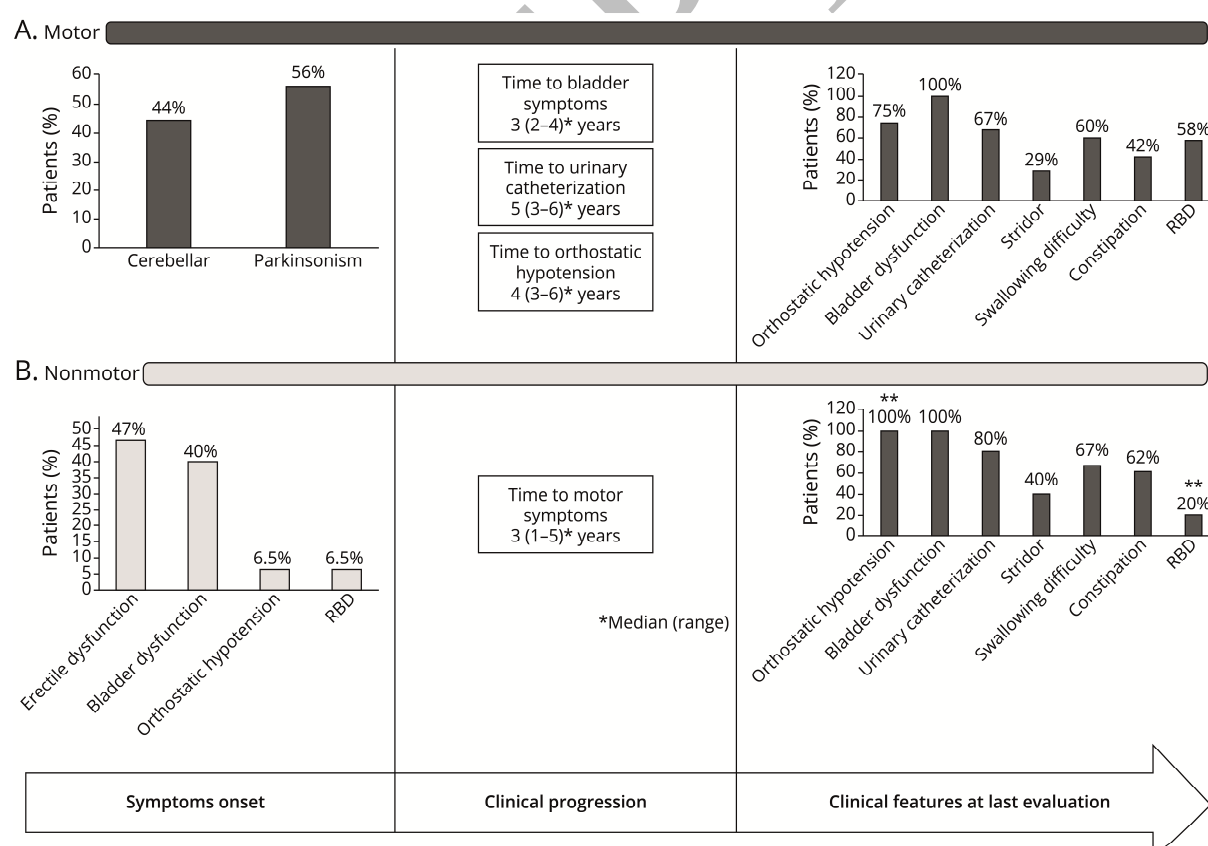

Figure 2. Kaplan-Meier curves for survival outcome (A) symptom onset to death comparing between patients who developed early cardiovascular autonomic dysfunction

(within 3 years of disease onset; p=0.026); **(B)** symptom onset to death comparing between patients who developed early urinary catheterisation (within 3 years of disease onset; p=0.019) and **(C)** symptom onset to death comparing between patients who developed early bladder dysfunction (within 3 years of disease onset; p=0.67).

A. Time from onset to autonomic dysfunction
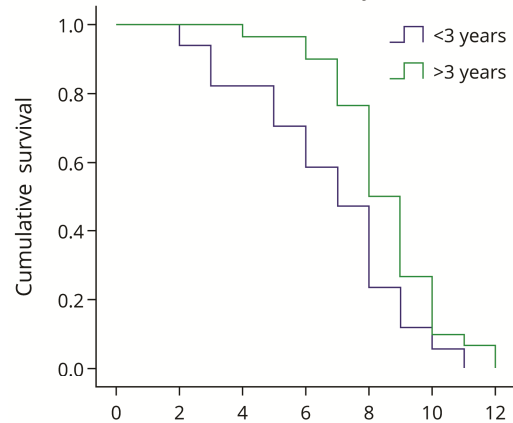
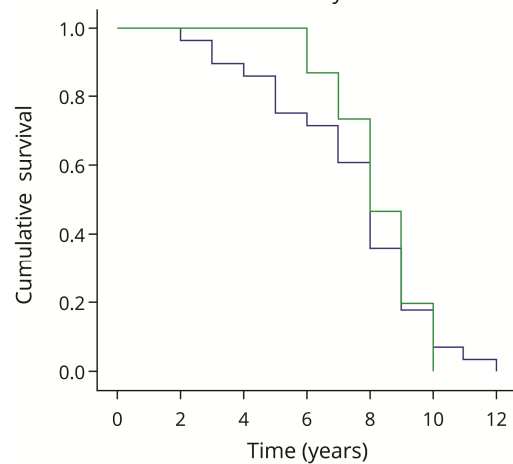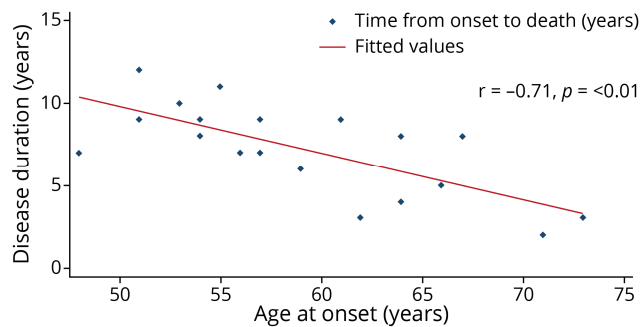B. Time to catheterization
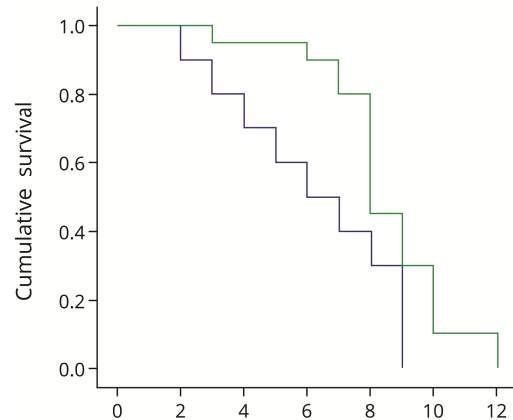
C. Time from onset to bladder dysfunction

Figure 3. Scatter plot showing the correlation between Time from onset to death (disease duration- Y axis) and Age at onset (X axis) in MSA patients with generalised cardiovascular autonomic dysfunction (both sympathetic and parasympathetic impairment) on autonomic testing.

Tables

Table 1. Demographic data and clinical features in MSA patients with motor and non-motor onset

	Presenting features	
	Motor (n=32)	**Non-motor (n=15)**
Age at onset (yrs.)	56+8	55+7
Age at first evaluation (yrs.)	60+8	59+7
Male% (n)	59% (19/13)	60% (9/6)
Time from onset to diagnosis of MSA (yrs)	3.5+1.8	4.8+2.0[#]
Time from onset to first evaluation (yrs)	4.0+1.8	4.9+1.7
Final clinical diagnoses (MSA-C:MSA-P: PSP)	14:16:2	10:5:0
Disease duration (Time from onset to death; years)	8.0+2.2	7.7+2.4
Early generalised*cardiovascular autonomic dysfunction (<3 year from onset), % (n/n)	41% (12/29)	41% (12/29)
Early cardiovascular sympathetic autonomic dysfunction (<3 year from onset), % (n/n)	50% (12/24)	40% (6/15)
Early bladder dysfunction (<3 year from onset), % (n/n)	63% (20/32)	80% (12/15)
Early urinary catheterisation (< 3 years from onset), % (n/n)	28% (5/18)	42% (5/12)
*Values are mean+SD unless stated, *sympathetic and parasympathetic; [#]p<0.05*		

Table 2. Cardiovascular autonomic measures in MSA according to the severity of cardiovascular autonomic dysfunction at first evaluation

	MSA with no CV autonomic dysfunction (n=3)	MSA with CV autonomic dysfunction		
		Sympathetic (n=19)	Both sympathetic and parasympathetic (n=20)	Parasympathetic (n=5)
Age at first evaluation (Mean±SD)	59±9	55±7 [$]	63±7	65±3
Male% (n/n)	66(2/1)	79(15/4)	50(10/10)	20(1/4)
Age at onset (Years; Mean±SD)	55±9	52±7 [$]	59±7	61±3
Disease duration (Years; Mean±SD)	10±1	8±2	7±3	8±1
Time from testing to death (Years; Mean±SD)	5.7±0.6	4.8±2.2 [$]	2.8±2.3	3.6±1.5
Values are mean±SD unless stated, [$]p<0.05 vs. MSA with both sympathetic and parasympathetic cardiovascular autonomic dysfunction, HUT=Head-up tilt				