Disease progression and prognostic factors in multiple system atrophy: A prospective cohort study

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ABSTRACT

Multiple system atrophy (MSA) is a rare neurodegenerative disease, with limited understanding of disease progression and prognostic factors. We leveraged the data of a large prospective cohort of MSA to study both clinical progression and survival and assess their determinants. All consecutive patients seen at the French Reference Centre for MSA since 2007 were included in a prospective cohort with an annual follow-up including the Unified MSA Rating Scale (UMSARS). We used joint models to evaluate the risk of death, the mean trajectory of each UMSARS subscale and to determine the potential factors. Investigated factors included gender, age at baseline, MSA subtype, diagnosis certainty, type of first symptoms and the duration between symptom onset and the first visit. Among the 261 MSA patients included in our cohort, the median duration of clinical follow-up was 2.1 years (up to 10.3 years) and the median survival was 4.0 years since the first visit. Main factors for poor survival were the progression over time of UMSARS score (I + II and IV) and the severity of orthostatic hypotension. MSA subtype had no effect on progression or survival. The UMSARS I + II score progressed faster over time in subjects with autonomic dysfunction as the initial feature and in women. Despite a faster progression, women and men had similar survival. From this large MSA cohort, we confirm the rapid progression and poor prognosis of MSA. We provide additional evidence for a negative impact of early autonomic dysfunction and the severity of orthostatic hypotension on both disease progression and survival.

1. Introduction

Multiple system atrophy (MSA) is a rare progressive neurodegenerative synucleinopathy characterised by combinations of autonomic failure, parkinsonism and cerebellar ataxia, with a prevalence ranging from 1.9–5/100,000 and an annual incidence of 3/100,000 individuals (Bower et al., 1997; Chrysostome et al., 2004; Wenning et al., 2004). Current consensus diagnostic criteria have a high positive predictive value for a clinical diagnosis of MSA, though sensitivity is modest in early disease (Gilman et al., 2008). Diagnostic criteria distinguish between MSA-P and MSA-C subtypes (Gilman et al., 1998).

MSA has a poor prognosis with median or mean survival between 6.2 and 10 years (Coon et al., 2015; Figueroa et al., 2014; Kim et al., 2011; Low et al., 2015; O'Sullivan et al., 2008; Saito et al., 1994; Schrag et al., 2008; Starhof et al., 2016; Tison et al., 2000; Watanabe et al., 2002; Wenning et al., 2013). The clinical factors associated with shorter survival are not consistent across the few studies including the role of MSA subtypes and autonomic dysfunction. Similarly, there are discrepancies regarding the impact of gender and age (Coon et al., 2015; Kim et al., 2011; Low et al., 2015; O'Sullivan et al., 2008; Schrag et al., 2008). Such inconsistencies may have different causes; first, excepting post-mortem studies, studies published before the establishment of clear diagnosis criteria may have included heterogeneous populations; second, most studies comprise only small numbers of patients with

short duration of follow-up; third, progression of disease differs between subjects with a reported range of survival from 3 to 15 years (Figueroa et al., 2014; Goldstein et al., 2015).

Studying disease progression and survival is essential to understand the natural history of MSA. Data is needed for accurate prognostication for patients and for the design of clinical trials. Hitherto, only two prospective studies have described the natural history of MSA with a follow-up of two years for a European cohort and five years for a North American cohort (Low et al., 2015; Wenning et al., 2013). Although providing crucial information, these two studies were limited both by length of follow-up and number of patients. In addition, since MSA is a fatal disease with high rates of death (24% at 2 years in the European cohort and 60% at 5 years in the North American cohort), assessment of disease progression and survival cannot be dissociated, a limitation of both previous studies.

The aims of the study were to describe disease progression and survival in MSA patients, as well as related factors. We leveraged a large prospective cohort comprising more than 250 patients who were annually followed at the French Reference Centre for MSA with a standardized clinical examination including the Unified MSA Rating Scale (UMSARS).

2. Methods

2.1. Study design and clinical characterization

We studied all patients who were enrolled at the Bordeaux site of the French MSA Reference Centre between 2007 and December 2016. Patients had to meet current consensus criteria for a diagnosis of probable or possible MSA and to provide written informed consent in order to be included (Gilman et al., 2008). The constitution of this cohort has been registered with the CNIL (Commission Nationale Informatique et Liberté). All patients were examined by a movement disorder specialist. Once the diagnosis of MSA was confirmed, the patient was included in the cohort and followed up annually. MSA subjects were further categorized into MSA-P or MSA-C based on the predominant clinical findings. Parkinsonism was defined as bradykinesia plus at least one of the following signs: resting tremor, rigidity or postural instability. A cerebellar syndrome was defined as gait ataxia with cerebellar dysarthria, limb ataxia, or cerebellar oculomotor dysfunction. When both parkinsonism and cerebellar ataxia were present at first evaluation, the subtype was assigned based on the predominant symptom. Symptom onset was defined as the initial presentation of any motor symptom (i.e., parkinsonian or cerebellar symptoms) and/or autonomic failure defined by orthostatic hypotension or neurogenic bladder disturbances unless attributable to a non-neurological cause. In males, erectile dysfunction was considered as the presenting symptom only if the onset occurred with motor symptoms or within one year of urinary symptoms. This symptom was included in uro-genital dysfunction. Onset of first symptoms was determined during the patient interview at the first visit. If the patient had difficulties recalling the onset, other sources including relatives and previous medical records were consulted.

All subjects seen at the French Reference Centre for MSA were screened for inclusion at their first visit. The following measures were collected at this visit: demographic information, medical history, neurological examination, diagnostic certainty and subtype according to consensus criteria, and UMSARS scores. Every year, a standardized clinical evaluation was performed including UMSARS and a review of consensus diagnosis criteria. Patients in whom the diagnosis was revised during follow-up to another disorder were removed from the cohort.

2.2. Ascertainment of death

The occurrence of death was systematically sought, especially when

the patient did not consult the Reference Centre for MSA the year following his/her last evaluation. This information was collected from caregivers, general practitioners or town halls (death registry). The cause and the date of death were systematically retrieved and documented. The time to death from the first visit was studied, with the last available follow-up being considered for censored surviving patients.

2.3. Ascertainment of clinical progression

Clinical progression was ascertained using the four UMSARS subscales: I) Activities of Daily Living, II) Motor examination, III) Orthostatic hypotension and IV) Disability. UMSARS I is a functional score based on 12 questions that evaluate symptom severity and ability to undertake activities of daily living. Each question is scored from 0 to 4, with a higher score indicating a lower functional status. UMSARS II is a neurological motor examination comprising 14 questions scored from 0 to 4, 4 being the most severe score. UMSARS III consists of the measurement of supine and standing blood pressure within ten minutes of standing. Supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) were documented after 15 min of rest. UMSARS IV is a disability scale which ranges from 1 (no disability) to 5 (severe disability). To study the progression of the disease, UMSARS I and II (UMSARS I + II) were added to form a score ranging from 0 to 104; higher scores indicating greater impairment. For UMSARS III, in order to provide an index of severity of orthostatic hypotension, we calculated the largest difference between supine SBP and standing SBP (delta SBP) and between supine DBP and standing DBP (delta DBP), both being measured every minute over ten minutes. Finally, we dichotomized UMSARS IV into two categories: lack of or slight disability (answers 1 and 2) and moderate to severe disability (answers 3, 4, and 5).

2.4. Statistical analysis

We assessed the risk of death and its determinants in a Cox model. Considered factors at baseline were gender, age, MSA subtype (MSA-P/MSA-C), diagnosis certainty (possible MSA/probable MSA), type of first symptoms (motor, dysautonomia, orthostatic hypotension/uro-genital dysfunction) and interval between symptom onset and first visit. To account for individual clinical progression, we further adjusted the Cox model for the dynamics of each UMSARS subscale (either through the level of the UMSARS subscale at the time of the risk evaluation for death - thereafter called current UMSARS level -, the current UMSARS slope, or both) in a joint model for survival and longitudinal data (Rizopoulos, 2012). Dynamics of six clinical markers were investigated: UMSARS I + II, supine SBP, supine DBP, delta SBP and delta DBP, and dichotomized UMSARS IV). Using the joint model, we were able to simultaneously describe the mean trajectory over time of each UMSARS subscale by accounting for the informative truncation by death and the interval between two evaluations. Specifically, repeated measures of each subscale score were modelled according to time since the first evaluation using a mixed model (linear mixed model for UMSARS I + II, supine SBP, supine DBP, delta SBP and delta DBP, and a logistic mixed model for dichotomized UMSARS IV). Mixed models systematically included a quadratic function of time (at the population and individuals levels) to capture a possible nonlinear trajectory. They were also adjusted for the same factors as survival both at baseline and in interaction with the quadratic function of time. Models were estimated using R (version 3.5.1) package JM (version 1.4-8) for UMSARS I + II, supine SBP, supine DBP, delta SBP and delta DBP (with a sequential 5 + 15 pseudo-adaptive Gaussian quadrature) and the R package JMBayes for dichotomized UMSARS IV (Rizopoulos, 2010; Rizopoulos, 2012). Parameter estimates were tested at the 5% significance level using univariate or multivariate Wald tests.

Table 1

UMSARS scores at first visit of the French MSA cohort ($n = 261$).

	Overall ($n = 261$)	MSA-P ($n = 171$)	MSA-C ($n = 90$)	p-value[c]
UMSARS I + II (mean, SD)	40.8 (13.9)	42.8 (14.3)	37.1 (12.3)	< 0.01
UMSARS III	2 ND	1 ND	1 ND	
Supine hypertension[a] (n, %)	124 (47.9)	81 (47.6)	43 (48.3)	0.92
Orthostatic hypotension[b] (n, %)	184 (71.0)	123 (72.4)	61 (68.5)	0.52
UMSARS IV (n, %)				
- 1	67 (25.7)	44 (25.7)	23 (25.6)	
- 2	114 (43.7)	68 (39.8)	46 (51.1)	
- 3	56 (21.5)	38 (22.2)	18 (20.0)	0.07
- 4	24 (9.2)	21 (12.3)	3 (3.3)	
- 5	0 (0.0)	0 (0.0)	0 (0.0)	

MSA-P = Multiple system atrophy with predominant parkinsonism, MSA-C = Multiple system atrophy with predominant cerebellar ataxia, NA = Not Done.

[a] Supine hypertension is defined as a systolic blood pressure superior to 140 mmHg and/or diastolic blood pressure superior to 90 mmHg.

[b] Orthostatic hypotension is defined as a difference between supine and standing systolic blood pressure superior to 20 mmHg and/or a difference between supine and standing diastolic blood pressure superior to 10 mmHg.

[c] P-value for the statistical difference between MSA-P and MSA-C, using Student test for UMSARS I and II, and Chi2-test for UMSARS III and IV.

3. Results

3.1. Demographics

A total of 264 patients with MSA were screened for inclusion at their first visit; only three declined inclusion. On the 261 patients included, 197 met consensus criteria for probable MSA and 64 for possible MSA at baseline. The predominant subtype was MSA-P in 171 patients (65.5%) (Table 1). Mean age of onset was 60.8 years (range; 38 to 80 years) and mean age at first visit was 65 years (42.1 to 83.0). Mean time from symptom onset to initial evaluation at the French Reference Centre was 4.5 years (range; 1 to 16 years) and the mean time from symptom onset to diagnosis was 3.7 (range less than one year to 14 years). The median

duration of clinical follow-up was 2.1 years (up to 10.3 years). During follow-up, 36 patients with possible MSA changed to a diagnosis of probable MSA. The diagnosis was confirmed in all 11 patients who underwent post-mortem evaluation.

3.2. Factors associated with survival (Table 2)

Of the 261 patients, 118 died with a median survival of 4.0 years (range 0 to 10.3 years) since the first visit and 9.3 years (range 1.0 to 24.4 years) since symptom onset. At two, four and six years after the first visit, the survival probability was 81%, 49.9% and 22.3%, respectively (Fig. 1). Despite a systematic enquiry, at the time of analysis we have no information (survival or clinical status) on 41 patients (16%).

The only baseline factor associated with mortality, without taking into account clinical progression as measured by UMSARS, was the degree of certainty for probable vs possible MSA patients, with a hazard ratio (HR) of 1.7 (95% confidence interval [1.10; 2.67], $p = .02$). In this analysis, gender, MSA subtype, type of symptom onset or age were not significantly associated with the risk of death (all $p > .32$).

When clinical progression was taken into account, current level of UMSARS I + II and UMSARS IV scores were both associated with an increased risk of death (HR = 2.3 [1.91; 2.77] for a ten-point increase in UMSARS I + II; HR = 1.3 [1.13; 1.49] for UMSARS IV ≥3 versus < 3). Adjusted for UMSARS I + II or UMSARS IV scores, women and subjects with a longer duration between symptom onset and first visit had a better prognosis than the others. Notably, for the same level of impairment, women were twice less likely to die than men (HR = 0.53 [0.35; 0.81]). Regarding UMSARS III, the current level of supine DBP and the current levels of delta SBP and delta DBP were associated with an increased risk of death.

Concerning diagnosis certainty, the association with death was attenuated when the current level of UMSARS I + II and UMSARS IV scores was taken into account in the model (HR = 1.71 [1.10; 2.67] without adjustment and 1.58 [0.98; 2.56] with adjustment for UMSARS I + II progression over time; Table 2).

Table 2

Factors associated with survival with or without accounting for the progression of UMSARS sub-scale scores over time ($n = 261$).

Variable (reference)	Cox model	Survival model adjusted for UMSARS progression[a]					
		I and II[a]	IIIa[a]	IIIb[a]	IIIc[a]	IIId[a]	IV[a]
	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]	HR [95%CI]
Gender (women vs male)	0.98 [0.68; 1.42]	**0.53 [0.35; 0.81]**	0.99 [0.66; 1.49]	1.11 [0.75; 1.64]	1.17 [0.79; 1.72]	1.20 [0.81; 1.80]	**0.43 [0.24; 0.78]**
Diagnosis (MSA-P vs MSA-C)	1.23 [0.82; 1.84]	1.25 [0.80; 1.96]	1.2 [0.80; 1.79]	1.31 [0.87; 1.98]	1.38 [0.91; 2.11]	1.32 [0.87; 2.01]	1.37 [0.80; 2.35]
Certainty (probable vs possible)	**1.71 [1.10; 2.67]**	1.58 [0.98; 2.56]	**1.63 [1.04; 2.56]**	1.55 [0.98; 2.43]	1.39 [0.87; 2.24]	1.31 [0.80; 2.15]	1.47 [0.80; 2.70]
Age at first visit (65 years) in years	1.11 [0.88; 1.39]	0.97 [0.75; 1.24]	1.11 [0.87; 1.41]	1.21 [0.96; 1.52]	1.14 [0.91; 1.43]	1.22 [0.96; 1.56]	1.02 [0.73; 1.41]
Duration since first symptoms (1 year) in years	0.98 [0.91; 1.05]	**0.89 [0.82; 0.97]**	0.97 [0.91; 1.05]	0.99 [0.91; 1.06]	1.01 [0.93; 1.09]	1.01 [0.93; 1.09]	**0.89 [0.80; 0.98]**
Type of symptoms onset (motor)							
Dysautonomia	1.03 [0.46; 2.30]	0.68 [0.28; 1.64]	1.03 [0.46; 2.28]	0.96 [0.42; 2.18]	1.12 [0.50; 2.50]	1.11 [0.49; 2.50]	1.14 [0.40; 3.20]
Motor and dysautonomia	0.81 [0.49; 1.34]	1.03 [0.61; 1.76]	0.77 [0.47; 1.28]	0.85 [0.51; 1.42]	0.97 [0.57; 1.65]	1.07 [0.62; 1.86]	0.96 [0.51; 1.78]
Orthostatic hypotension (absent)	1.09 [0.64; 1.87]	0.65 [0.36; 1.19]	1.04 [0.60; 1.80]	0.81 [0.45; 1.46]	0.76 [0.41; 1.39]	0.66 [0.34; 1.28]	0.73 [0.34; 1.55]
Current level of UMSARS sub-scale		**2.30 [1.91; 2.77]**	1.04 [0.86; 1.25]	**1.44 [1.08; 1.93]**	**1.19 [1.05; 1.35]**	**1.48 [1.10; 1.99]**	**1.30 [1.13; 1.49]**

Bold highlights the statistically significant results.

[a] Adjustment for UMSARS progression was done using a joint shared random effect model (with a baseline hazard approximated by cubic splines). **Joint model I and II** is adjusted on the current level of UMSARS I and II score; **joint model IIIa** on the current level of supine systolic blood pressure (UMSARS III); **joint model IIIb** on the current level of supine diastolic blood pressure (UMSARS III); **joint model IIIc** on the current largest difference between the supine and standing systolic blood pressure (UMSARS III); **joint model IIId** on the current largest difference between the supine and standing diastolic blood pressure (UMSARS III); **joint model IV** on the current underlying level of UMSARS IV score (dichotomized into 1,2 versus 3,4,5). (HR: hazard ratio; 95%CI: 95% confidence interval).
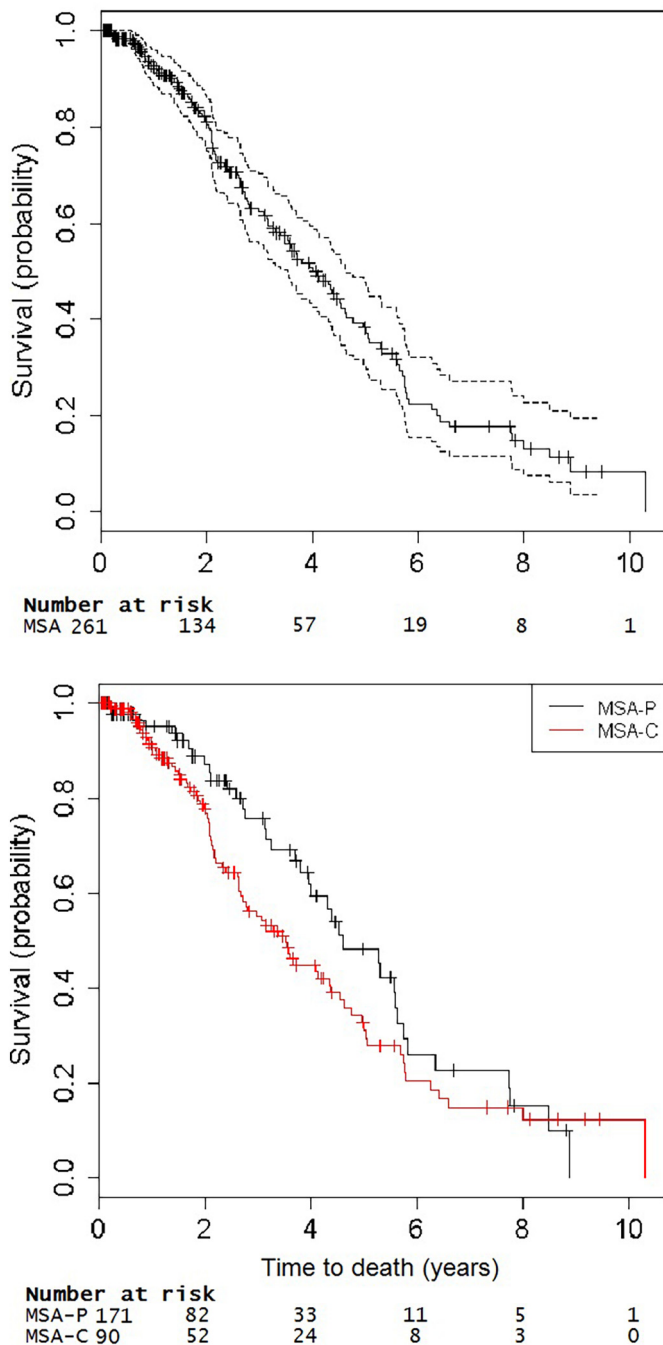
Fig. 1. Survival probability from first visit: Overall (A) and stratified by phenotype (B).

3.3. Progression of UMSARS sub-scores over time

Since most of the UMSARS sub-scores were highly associated with death, we further describe below the progression of these sub-scores in order to have a complete assessment of the progression leading to death. Mean predicted trajectories (Figs. 2, 3, e-1 and e-2) derived from the joint models accounting for death are reported for each marker. Model estimates are provided in supplementary materials (Tables e-1 to e-6).

3.4. UMSARS I and II (Fig. 2, Table e-1)

UMSARS I + II score significantly progressed over time. The MSA

subtype, the level of diagnostic certainty, the age at first visit and the delay since symptom onset were associated with UMSARS I + II level at all times, but not with UMSARS I + II changes over time. Thus, at all time points, patients with MSA-P had a mean UMSARS I + II score that was 4.1 points higher than for MSA-C ($p < .01$), patients with probable MSA had a mean score that was 8.5 points higher than for those with possible MSA ($p < .01$), for a 10-year increase of age at first visit patients had two points more in mean score ($p < .01$); and for a 1-year increase between symptom onset and first visit, they had a 1.5 point higher mean score ($p < .01$). Only two variables modified the progression of UMSARS I + II: gender, with women having a significantly faster progression compared to men, and isolated autonomic dysfunction (uro-genital disturbances or orthostatic hypotension) as first symptom being associated with faster progression (Table 3).

3.5. UMSARS III

3.5.1. Supine SBP and DBP in mmHg (Fig. 3 and Tables e-2 and e-3)

The level of supine SBP and DBP did not substantially change over time whatever the patient profile. At all times, men and patients with probable MSA had higher supine SBP (for men compared to women: mean difference in mmHg (MD) = 7, $p < .01$; for probable compared to possible MSA: MD = 6.9, $p = .01$) and higher supine DBP (for men compared to women: MD = 2.8, $p = .05$; for probable compared to possible MSA: MD = 3.6, $p = .02$). MSA-P patients presented lower supine DBP at any time compared to MSA-C (MD = -3.6, $p = .02$), while supine SBP was not significantly different (MD = -3.3, $p = .20$). Regarding the first symptoms, only subjects with isolated orthostatic hypotension presented higher supine SBP and DBP compared to the other patients (for supine SBP in mmHg: MD = 6.4, $p = .05$; for supine DBP in mmHg: MD = 6.5, $p < .01$).

3.5.2. Maximum difference between supine and standing SBP or DBP (delta SBP and delta DBP) (Fig. e-1, Tables e-4 and e-5)

As results for delta SBP and delta DBP were identical, we only report here the progression of delta SBP over time (Fig. **e-1**). The delta SBP tended to increase over time in all patient profiles with different rates of change. Men, probable MSA and patients who began their disease with orthostatic hypotension had a greater delta SBP compared to the others and this difference persisted over time. By contrast, the subtype of MSA and age had an effect on the progression of delta SBP over time. With time, MSA-C patients tended to have a greater delta SBP compared to MSA-P. Age at first visit had no significant effect during the first years of the disease but after five years, the increase in delta SBP was higher among the oldest (Table e-4). Finally, the delay since symptom onset had no effect on delta SBP.

3.6. UMSARS IV (Fig. e-2 and Table e-6)

The probability of having significant disability as measured by a UMSARS IV score ≥ 3 increased rapidly after the first visit with an odds ratio (OR) of 19.5 per year. Women, probable MSA, subjects with older age at first visit and subjects with a longer delay since symptom onset had a significantly greater probability of having a UMSARS IV score ≥ 3 at any time (for women: OR = 3.5, $p = .03$; for probable MSA: OR = 18.9, $p < .01$; for higher age at first visit: OR = 3.3, $p < .01$ for a ten year difference; for a longer delay since symptom onset and first visit: OR = 1.3, $p = .02$ for a one year difference, respectively). The MSA subtype and the type of symptom onset were not associated with UMSARS IV score, neither at first visit nor over time.

4. Discussion

This prospective cohort study on disease progression and survival factors in MSA is to our knowledge the largest reported, with more than 250 patients followed for up to ten years. The main strengths of our
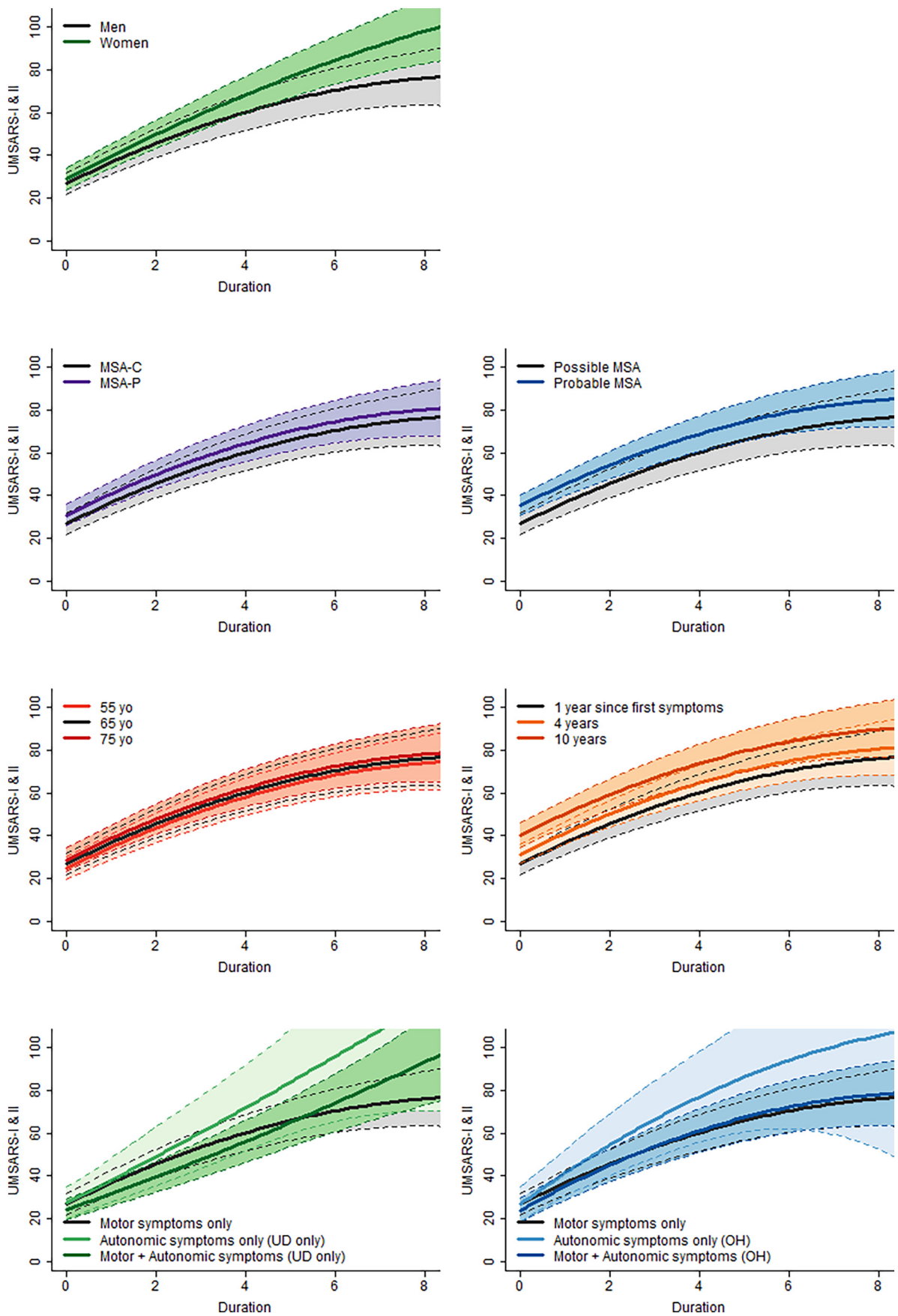
Fig. 2. Mean trajectory of UMSARS I + II score over time according to factors at inclusion. UD: uro-genital dysfunction. OH: orthostatic hypotension.
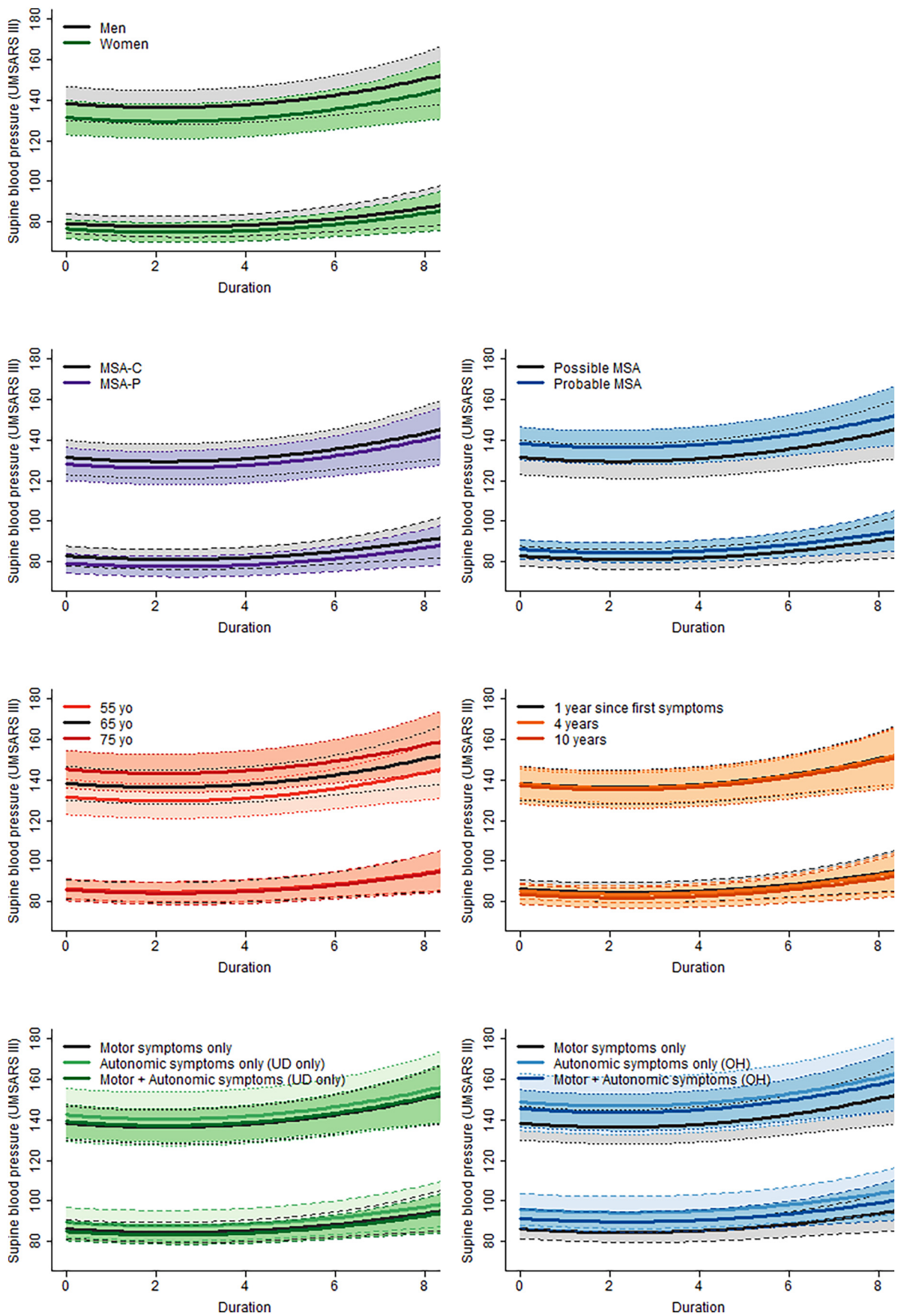
Fig. 3. Mean trajectories of supine systolic (above) and diastolic (below) blood pressure in mmHg over time according to factors at inclusion. UD: uro-genital dysfunction. OH: orthostatic hypotension.

Table 3

Mean progression of UMSARS I + II [with 95% confidence intervals], the first, the second and the third year after the first visit according to gender and type of first symptom predicted by the joint model.

Type of first symptom	Mean progression of UMSARS I + II (in points)		
	First year	Second year	Third year
Among men			
Motor	10.0 [8.1;11.9]	8.9 [7.4;10.5]	7.8 [6.5;9.1]
Urinary dysfunction	10.8 [5.6;16.1]	11.0 [7.0;15.1]	11.3 [7.4;15.1]
Motor and urinary dysfunction	7.5 [5.1;9.8]	7.8 [5.9;9.7]	8.1 [6.4;9.8]
Orthostatic hypotension	14.6 [8.9;20.2]	13.2 [8.8;17.6]	11.9 [7.7;16.0]
Motor and orthostatic hypotension hypotensiaonomic symptoms (OH) sautonomia	11.2 [8.9;13.6]	10.0 [8.0;11.9]	8.7 [7.0;10.3]
Among women			
Motor	10.7 [8.9;12.6]	10.1 [8.6;11.7]	9.5 [8.1;10.9]
Urinary dysfunction	11.5 [6.0;17.1]	12.3 [7.9;16.7]	13.0 [8.9;17.1]
Motor and urinary dysfunction	8.2 [5.9;10.5]	9.0 [7.1;11.0]	9.8 [8.0;11.7]
Orthostatic hypotension	15.3 [9.3;21.3]	14.4 [9.8;19.1]	13.6 [9.3;17.9]
Motor and orthostatic hypotension	12.0 [9.6;14.4]	11.2 [9.2;13.2]	10.4 [8.7;12.1]

study are that (i) all patients were diagnosed and followed at the same centre with a standardized annual evaluation and (ii) the statistical models employed to describe disease progression accounted for the occurrence of death. Furthermore, taking advantage of this long standardized follow-up, we here explored for the first time all four dimensions of the UMSARS scale over time and provided unprecedented information about the progression of supine hypertension and orthostatic hypotension. In our cohort, (i) the mean age of symptom onset was around 60 years, (ii) the MSA-P subtype was predominant in our Caucasian population, (iii) men and women were equally affected, (iv) the median delay between symptom onset and the first visit at our centre was 4.5 years, and (v) the median survival was 9.3 years since symptom onset. These characteristics are consistent with those of other studies (Low et al., 2015; Wenning et al., 2013). Our long follow-up provides additional insights into the high mortality rate of MSA with survival of 81% at 2 years, 50% at 4 years and 22% at 6 years after the first visit, in line with the survival data of the European and North American cohorts, as well as the large treatment trial with riluzole (Bensimon et al., 2009; Low et al., 2015; Wenning et al., 2013).

In our cohort, MSA subtype, type of symptom onset and age at baseline were not associated with the risk of death. The main predictors of survival were not factors at inclusion (i.e. age, MSA subtype, diagnosis certainty or type of first symptoms), but clinical progression over time, especially the current functional or motor impairment and the current level of disability which were strongly associated with risk of death. Furthermore, at equivalent levels of disability, women and those with a longer delay between symptom onset and first visit had a longer survival. Finally, some aspects of progression of autonomic dysfunction over time were also associated with shorter survival, namely current higher supine DBP and current more severe orthostatic hypotension.

By taking advantage of joint models studying functional progression and death simultaneously, we demonstrated that the progression of impairment in activities of daily living, motor function and overall disability were directly associated with a higher risk of death, independently of other factors. Even if MSA-P tended to have a higher level of functional impairment compared to MSA-C, their respective rates of progression and risk of death were similar, confirming observations in the retrospective cohort of MSA patients followed at the Mayo Clinic as well as the North American MSA Natural History Study (Coon et al., 2015; Low et al., 2015). In contrast, the European cohort reported worse survival in MSA-P but the follow-up was only two years (Wenning et al., 2013). As discussed by Coon et al., women had a better survival than men once adjusted for progression of functional disability; this higher tolerance of functional impairment has also been reported in other neurodegenerative diseases (Brodaty et al., 2012; Coon et al., 2015). Finally, the delay between symptom onset and the first visit seems to reflect the aggressiveness of the disease. Thus, whilst this

delay was not associated with the progression of functional or motor scores, for any given level of disability, the shorter this period, the greater the risk of death. Similar results were found in the EMSA study and in a large retrospective study of 230 cases from Japan (Watanabe et al., 2002; Wenning et al., 2013).

Our study has also evaluated the impact of autonomic dysfunction as first symptom on disease progression, and the impact of the progression of autonomic failure over time on the risk of death. We confirmed that the isolated presence of orthostatic hypotension or urogenital dysfunction as first symptom was associated with faster progression of functional and motor scores (Figueroa et al., 2014; Low et al., 2015; Wenning et al., 2013). The availability of longitudinal blood pressure measurements (UMSARS III subscale) for our entire patient cohort is a strength and allowed for a description of its progression over time. We found that supine hypertension and orthostatic hypotension worsened only modestly over time. This may be explained by adjustments of concomitant symptomatic treatments to better control these features. Furthermore, only few variables modified the progression of blood pressure measurements, i.e. MSA-C patients presented only a slight increase in orthostatic hypotension over time, and after five years the same was observed in aged patients. Finally, the severity of orthostatic hypotension was associated with the risk of death and isolated orthostatic hypotension as first manifestation was associated with more rapid progression. Regarding uro-genital dysfunction, we confirmed its poor prognosis observed in other studies (Coon et al., 2015; Wenning et al., 2013). Taken together, these findings indicate that dysautonomia has a significant impact on disease progression and the risk of death in MSA. This further confirms the urgent need for improvements in the management of dysautonomia, especially of orthostatic hypotension, and the evaluation of the impact of this management on survival.

Although this is the largest reported prospective cohort, our study has limitations. First, patients were recruited at a tertiary reference centre, thereby enhancing diagnostic accuracy, but potentially increasing the delay between symptom onset and the first visit. Accordingly, mild disease stages or patients with very early death might be under-represented in our cohort. Patient attrition is another challenge of longitudinal cohort studies. To minimize the number of dropouts, patients who had not been seen for more than one year were systematically contacted to collect the occurrence of a possible death. Despite a systematic enquiry, at the time of analysis we have no information (survival or clinical status) on 41 patients (16%). Second, the identification of the first symptoms was retrospective with a risk of recall bias. To minimize this bias, we determined first symptoms using a predefined minimal data set. Constipation or REM sleep behavior disorder were not considered as symptom onset. We focused on more specific symptoms such as neurogenic bladder (otherwise unexplained

urinary urgency, frequency or incomplete bladder emptying) or orthostatic hypotension, as defined by current consensus criteria. Third, no corrections for multiple comparisons were performed because of the exploratory nature of our study. Finally, while all patients met consensus criteria for probable or possible MSA, and neurologists were movement disorder experts, there is still a risk for a misdiagnosis. However, the diagnosis was confirmed in all eleven patients who underwent post-mortem evaluation.

In conclusion, the results of this large prospective cohort study provide important information on disease progression and survival factors in MSA. The concomitant consideration of progression and death allows a precise estimation of the prognosis to guide patients and their caregivers, as well as the design of future treatment trials.

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Appendix A. Supplementary data

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