



ALMA MATER STUDIORUM  
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE  
DELLA RICERCA

Alma Mater Studiorum Università di Bologna  
Archivio istituzionale della ricerca

Progression and prognosis in multiple system atrophy presenting with REM behavior disorder

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

*Published Version:*

Giannini G., Mastrangelo V., Provini F., Droghini A., Cecere A., Barletta G., et al. (2020). Progression and prognosis in multiple system atrophy presenting with REM behavior disorder. *NEUROLOGY*, 94(17), E1828-E1834 [10.1212/WNL.00000000000009372].

*Availability:*

This version is available at: <https://hdl.handle.net/11585/766212> since: 2020-07-17

*Published:*

DOI: <http://doi.org/10.1212/WNL.00000000000009372>

*Terms of use:*

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).  
When citing, please refer to the published version.

(Article begins on next page)

Manuscript Number: NEUROLOGY/2019/017491

## **Progression and prognosis in Multiple System Atrophy presenting with REM behaviour disorder**

Giulia Giannini, MD\*<sup>1,2</sup>, Vincenzo Mastrangelo, MD\*<sup>2</sup>, Federica Provini MD, PhD<sup>1,2</sup>, Andrea Droghini, MD<sup>2</sup>, Annagrazia Cecere, MSc<sup>1</sup>, Giorgio Barletta, MSc<sup>1,2</sup>, Francesco Mignani, MSc<sup>1</sup>, Pietro Guaraldi MD, PhD<sup>1,3</sup>, Pietro Cortelli MD, PhD<sup>§1,2</sup>, Giovanna Calandra-Buonaura MD, PhD<sup>1,2</sup>

<sup>1</sup> IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica Rete Metropolitana NEUROMET, Bologna, Italy;

<sup>2</sup> Department of Biomedical and NeuroMotor Sciences (DiBiNeM), Alma Mater Studiorum - University of Bologna, Italy;

<sup>3</sup> Neurology Outpatient Clinic, Department of Primary Care, Local Health Authority of Modena.

\*These authors contributed equally to this work.

§ Correspondence to Pietro Cortelli

### **Correspondence to:**

Prof. Pietro Cortelli

IRCCS Istituto delle Scienze Neurologiche di Bologna, Bellaria Hospital

Via Altura 3, 40139 Bologna, Italy

Tel +39 0514966116, Fax +39 0514966098

Email: [pietro.cortelli@unibo.it](mailto:pietro.cortelli@unibo.it)

**E-mail addresses for all coauthors:**

[giulia.giannini15@unibo.it](mailto:giulia.giannini15@unibo.it); [vincenzo.mastrangel2@studio.unibo.it](mailto:vincenzo.mastrangel2@studio.unibo.it);

[federica.provini@unibo.it](mailto:federica.provini@unibo.it); [andrea.droghini@studio.unibo.it](mailto:andrea.droghini@studio.unibo.it);

[annagrazia.cecere@studio.unibo.it](mailto:annagrazia.cecere@studio.unibo.it); [giorgio.barletta@unibo.it](mailto:giorgio.barletta@unibo.it);

[francesco.mignani@ausl.bologna.it](mailto:francesco.mignani@ausl.bologna.it); [pietro.guaraldi@isnb.it](mailto:pietro.guaraldi@isnb.it); [pietro.cortelli@unibo.it](mailto:pietro.cortelli@unibo.it);

[giovanna.calandra@unibo.it](mailto:giovanna.calandra@unibo.it).

**Word counts of the manuscript (excluding abstract, tables, figure legends, references):**

**2408**

**Character counts of the title: 91**

**Word counts of the abstract: 247**

**Number of references: 15**

**Number of Tables: 1**

**Number of Figures: 3**

**Statistical analyses were performed by:**

- Giulia Giannini, MD,  
IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy;  
Department of Biomedical and NeuroMotor Sciences (DiBiNeM), Alma Mater  
Studiorum - University of Bologna, Italy.
- Vincenzo Mastrangelo, MD,  
Department of Biomedical and NeuroMotor Sciences (DiBiNeM), Alma Mater  
Studiorum - University of Bologna, Italy.

**SEARCH TERMS:**

[ 172 ] Multiple system atrophy

[ 1 ] Autonomic diseases

[ 54 ] Cohort studies

[ 58 ] Natural history studies (prognosis)

REM sleep behaviour disorder

**DISCLOSURE**

- Dr. Giannini reports no disclosures.

- Dr. Mastrangelo reports no disclosures.

- Dr. Provini reports no disclosures. Outside the present work, Dr. Provini has received honoraria for speaking engagements or consulting activities from Sanofi, Bial, Fidia, Vanda Pharmaceutical, Zambon, Eisai Japan, and Italfarmaco.

- Dr. Droghini reports no disclosures.

- Dr.. Cecere reports no disclosures.

- Dr. Barletta reports no disclosures.

- Dr. Mignani reports no disclosures.

- Dr. Guaraldi reports no disclosures.

- Dr. Cortelli reports no disclosures.

- Dr. Calandra-Buonaura reports no disclosures.

**STUDY FUNDING:** None.

**ABSTRACT**

**Objectives:** 1) to investigate the prevalence of REM sleep behaviour disorder (RBD) as mode of disease onset in a cohort of Multiple System Atrophy (MSA) patients; 2) to investigate disease progression and prognosis in MSA patients with RBD predating (pre-RBD) and with RBD following (post-RBD) the disease onset.

**Methods:** We retrospectively identified all patients with a clinical diagnosis of MSA evaluated at least once a year during the disease course. Type of onset was defined by the first reported motor or autonomic symptom/sign related to MSA. The occurrence of symptoms/signs and milestone of disease progression, and their latency from disease onset, were collected. Survival data were calculated. RBD was confirmed by video-polysomnography.

**Results:** On a total of 158 patients, pre-RBD represented the mode of disease onset in the 27% of patients, preceding disease onset according to the international criteria with a median of 3 (2-5) years. Comparing pre-RBD and post-RBD patients, the first group showed an increased prevalence of autonomic onset of disease, a reduce prevalence of parkinsonism, an earlier onset of stridor, pyramidal signs, symptomatic orthostatic hypotension, urinary dysfunction, severe dysphagia and wheelchair dependency. The risk of death was higher in patients with pre-RBD.

**Conclusions:** in our MSA cohort, RBD represented the most frequent mode of disease presentation. A more rapid progression of disease was observed in the pre-RBD group. These findings suggested a careful assessment of sleep disorders to early recognize RBD, and a closer follow-up of autonomic dysfunctions and stridor in patients with pre-RBD.

## INTRODUCTION

Multiple System Atrophy (MSA) is a neurodegenerative disease clinically characterized by autonomic dysfunctions (cardiovascular autonomic failure and/or genitourinary dysfunctions) associated with parkinsonism and/or cerebellar impairment. The diagnostic criteria define three degrees of certainty for diagnosis, possible, probable and definite, and two phenotypes, parkinsonian (MSA-P) or cerebellar (MSA-C), according to the predominant feature at the time of evaluation<sup>1</sup>.

Sleep disorders including REM sleep behaviour disorder (RBD), nocturnal stridor and other sleep-disordered breathings are frequently observed in MSA populations and can predate classical motor signs by years<sup>2,3</sup>. RBD is a parasomnia characterized by loss of the normal muscle atonia during REM sleep associated with complex, sometimes violent, and dangerous motor behaviours during which patients act out the content of their dreams<sup>4</sup>. The prevalence of polysomnography-confirmed RBD in MSA ranges from 68.8 to 100%, with an overall prevalence of 88% (95%, CI 79-94%) in a recent meta-analysis<sup>5</sup>. RBD could predate (pre-RBD) or follow (post-RBD) the disease onset (i.e. autonomic or motor onset). Although RBD represents an early clinical marker of neurodegeneration and may be relevant for addressing possible candidates to future neuroprotective therapies, to date video-polysomnography (VPSG) studies investigating RBD in wide cohorts of MSA are still lacking.

The aim of this study was to investigate the prevalence of pre-RBD in a cohort of MSA patients longitudinally evaluated in the Department of Biomedical and Neuromotor Sciences (DiBiNeM), University of Bologna. Furthermore, we aimed to investigate disease progression and prognosis in MSA patients with pre-RBD and post-RBD.

## METHODS

We retrospectively selected all the individuals attending the Movement and Autonomic Disorders Clinic of the DiBiNeM, University of Bologna, between 1991 and June 2018 with a clinical diagnosis of MSA and evaluated at least once a year during the disease course.

Three neurologists expert in movement disorders independently confirmed MSA diagnosis from data available at the last follow-up evaluation according to international criteria<sup>1</sup>; their consensus and absence of non-supporting features for MSA were mandatory for inclusion in the study.

Data were collected as previously described<sup>6,7</sup>. Patients were categorized as probable or possible MSA according to the consensus criteria<sup>1</sup> and classified as MSA-P or MSA-C on the basis of the predominant motor involvement at the time of the last follow-up evaluation. Type of MSA onset was defined by the first reported motor or autonomic symptom or sign that could be related to MSA<sup>1</sup>. Occurrence of other symptoms and signs (parkinsonism, cerebellar and pyramidal involvement, orthostatic hypotension, urinary symptoms, stridor and RBD) and its latency from disease onset was recorded from clinical history and neurological examination. Timing and latency of the milestones of disease progression (frequent falls, wheelchair dependence, severe dysphagia or percutaneous endoscopic gastrostomy, severe dysarthria, urinary catheterization) were also recorded. Disease duration was defined as the interval in years from first symptom onset to death or to the end of this study. Survival data were defined based on time to death from the first symptom of disease.

Orthostatic hypotension (OH) was assessed with blood pressure measurement in the supine position and within 3 minutes of standing or head up tilt test<sup>8</sup>. The neurogenic nature of OH was confirmed by cardiovascular reflex tests<sup>9</sup>. In most cases, OH was assessed in the setting of evaluation for motor symptoms, and its symptomatic onset was retrospectively referred by patients. Patients with symptomatic or asymptomatic isolated neurogenic orthostatic hypotension, confirmed by cardiovascular reflex test, and with normal neurological

examination at disease onset, were recruited from the Autonomic Unit of our Department and were evaluated at least once a year.

Urinary dysfunction included storage disorders (urinary urgency/frequency and incontinence) and voiding disorders (incomplete bladder emptying and urinary retention).

RBD was diagnosed according to the ICSD-3 criteria<sup>4</sup> and confirmed by VPSG in the setting of evaluation for motor and autonomic symptoms. Its onset was retrospectively referred by patient and bed partner, and event registration from VPSG was shown to them to ensure it was the same reported in patient recall. We defined pre-RBD or post-RBD according to its occurrence before or after MSA onset.

#### Standard Protocol Approvals, Registrations, and Patient Consents

The study was conducted in agreement with the principles of good clinical practice. The study protocol was approved by the Local Ethics Committee of the local health service of Bologna, Italy (Cod. CE: 17093). All patients gave their written informed consent to study participation.

#### Data availability

Anonymized data will be shared by request from any qualified investigator.

#### Statistical analysis

Summary statistics are presented as mean  $\pm$  standard deviation or median and interquartile range (IQR) for continuous data, and absolute and relative frequencies for categorical data. Mann-Whitney test and t test were performed to compare continuous variable as appropriate. Categorical variables were compared using the  $X^2$  test. Kaplan-Meier curves were used to analyse survival probability from disease onset, and the log-rank test was performed to compare survival between patient subgroups. Statistical analyses were performed using the statistical software SPSS, version 20. A value of  $p < 0.05$  was considered significant.

## **RESULTS**



A total of 158 patients with MSA (79 MSA-P, 79 MSA-C, 63% male) were included; 3 patients met consensus criteria for definite MSA, 126 for probable MSA and 29 for possible MSA. The mean age at disease onset was  $57 \pm 9$  years, and the median disease (IQR) duration was 7 (5-9) years. Eighty percent of patients were deceased at time of the current study.

Survival curve is shown in **Fig. 1A**.

According to current consensus criteria<sup>1</sup>, at disease onset 40% of patients complained pure motor symptoms (22% cerebellar symptoms, 17% parkinsonism and 1% both), while 34% of patients reported isolated autonomic symptoms (26% urinary involvement, 5% symptomatic OH and 3% both). In 22% of total sample, both motor and autonomic symptoms were present at disease onset (10% with parkinsonism, 9% with cerebellar symptoms and 3% with both).

Additionally, a history of erectile failure in men was present in 80% as first autonomic symptom. In 6 patients (4%) the first symptom of disease was undefined (**Fig. 2**).

History of RBD was reported by 121 patients and diagnosis was confirmed by VPSG in 107.

Among the latter, pre-RBD occurred in 42 patients, which represented the 27% of the total population of 158 patients (**Fig.2**). Conversely, post-RBD was present in 65 patients (41%).

The mean age at pre-RBD onset was  $51 \pm 8$  years, and the median duration before the first autonomic or motor symptom/sign of MSA was 3 (2-5) years. Namely, among patients with pre-RBD 29 presented with history of autonomic failure (25 urinary symptoms, 6 symptomatic OH), 17 with cerebellar syndrome and 6 with parkinsonism (isolated or combined).

Features of MSA population with pre-RBD and post-RBD are compared in **Tab. 1**.

Compared to post-RBD subgroup patients with pre-RBD showed a more frequent autonomic onset of MSA (69% vs. 45%,  $p=0.02$ ) and a less frequent parkinsonism both at disease onset (14% vs. 43%,  $p=0.001$ ) and during the disease course (74% vs. 91%,  $p=0.034$ ). During the course of disease, no significant differences were revealed about the occurrence of cerebellar

symptoms, stridor, symptomatic OH, urinary symptoms and pyramidal signs. Concerning the latency of those symptoms, pre-RBD patients presented earlier stridor [2,5(1-4) vs. 4(3-6),  $p=0.013$ ], pyramidal signs [3(2-4) vs. 4(3-6),  $p=0.027$ ], symptomatic OH [1(0-3) vs. 4(1-6),  $p=0.017$ ] and urinary symptoms [0(0-1) vs. 1(0-4),  $p=0.008$ ] during the disease course (**Fig. 3**). Moreover, compared to post-RBD subgroup, patients with pre-RBD showed a shorter latency of urinary catheterization [4(2-6) vs. 6(5-9) years,  $p=0.016$ ], severe dysphagia [6(4-7) vs. 8(6.5-10.5) years,  $p=0.019$ ] and wheelchair dependency [6(4-7) vs. 7(5-9) years,  $p=0.019$ ]. Median disease duration differed between pre-RBD and post-RBD patients [6(4.75-8) vs. 8(6-10) years,  $p=0.004$ ], and the risk of death estimated by Kaplan-Meier analysis was higher in patients with pre-RBD with a weak statistical significance (log-rank test,  $p=0.05$ ; **Fig. 1B**). In view of these data, we performed a further analysis to investigate if these differences are related to the time of RBD onset or to the presence of RBD per se. Comparing all patients with RBD ( $n=107$ ) to those without ( $n=51$ ), the first group showed: 1- an earlier age at onset ( $56\pm 9$  vs.  $59\pm 8$  years,  $p=0.026$ ); 2- an increased prevalence of stridor (43% vs. 14%,  $p=0.001$ ) without differences in stridor latency; 3- an increased prevalence of dysphagia/PEG (23% vs. 10%,  $p=0.042$ ) but with a longer latency [8 (6-10) vs. 5 (4-6) years,  $p=0.013$ ]; 4- a longer latency of wheelchair dependency [6 (5-8) vs. 5 (4-7) years,  $p=0.04$ ].

## DISCUSSION

This is one of the largest follow-up studies exploring RBD as mode of disease onset in a cohort of MSA patients. This study showed that RBD is the mode of disease presentation in the 27% of patients, preceding the disease onset according to the international criteria with a median of 3(2-5) years. Comparing pre-RBD with post-RBD patients, the first group more frequently presented with autonomic onset and less frequently showed parkinsonism both at disease onset and during the disease course. An earlier onset of stridor, pyramidal signs,

symptomatic OH and urinary dysfunction and a shorter disease duration were also observed in the pre-RBD group.

Moreover, evaluation of milestones, documented a more rapid disease progression in pre-RBD sub-group, with an earlier occurrence of severe dysphagia, need of urinary catheterization and wheelchair dependence. The risk of death estimated by Kaplan-Meier analysis was higher in patients with pre-RBD with a weak statistical significance.

In our cohort roughly one-quarter of patients presented with this sleep disorder (pre-RBD) preceding for years the clinical diagnosis according to current criteria<sup>1</sup>. A recent meta-analysis reported an overall prevalence of clinically suspected RBD of 73% (95% CI, 62-84%) in 324 patients and a prevalence of polysomnography-confirmed RBD of 88% (95%, CI 79-94%) in a sample of 217 patients<sup>5</sup>. However, the prevalence of RBD as initial manifestation in MSA has been poorly investigated. Five studies focused on RBD preceding the disease onset (only 3 diagnosed with VPSG), showing a range of prevalence from 19% to 53.8%<sup>5,10,11,12,13</sup>. The first study evaluating clinical and VPSG data reported that 27 out of 39 MSA patients (69%) had a history of RBD, preceding in 12 (31%) the disease onset<sup>10</sup>. The second one comparing RBD features in MSA and Parkinson Disease patients with VPSG-confirmed RBD, found that the sleep disorder precede the onset of motor symptoms in 14 (53.8%) out of 26 MSA patients<sup>11</sup>. One cross-sectional study based on sleep questionnaires observed that 29 out of 64 MSA patients (45%) presented RBD symptoms before the onset of motor deficits, but the amount of VPSG-confirmed RBD in “pre-RBD” patients is not specified in the article<sup>5</sup>. In a large retrospective study on 685 MSA patients, history of sleep symptoms suggesting RBD was reported in 304 subjects and in 34% of cases sleep symptoms preceded motor and autonomic ones<sup>12</sup>. Finally, in a recent retrospective study on 30 MSA patients, 5 (19%) subjects reported history suggesting RBD as first symptom of disease, which was confirmed by VPSG in 2 patients<sup>13</sup>.

These results are further supported from the additional analysis on patients with and without RBD. This analysis shows that patients with RBD presented more frequently an increased prevalence of dysphagia and stridor but not a shorter latency of stridor, autonomic involvement and milestones of disease progression that are peculiar features of pre-RBD subgroup, determining the observed reduction of disease duration. Therefore, is not the presence of RBD per se but the onset of RBD as first manifestation of disease that is correlated to clinical features and milestones of disease progression involved in survival. In our cohort, patients with pre-RBD showed a more frequent autonomic disease onset and cerebellar predominance, and a shorter latency of autonomic failure, stridor, pyramidal signs and milestones of disease progression. A shorter disease duration was observed in pre-RBD groups compared to post-RBD group and a trend towards shorter disease duration resulted also from the Kaplan-Mayer survival analysis. This could be ascribable, from a clinical point of view, on the high prevalence of early stridor and early autonomic dysfunction in patients with pre-RBD, factors reported as associated with shorter survival<sup>7,12</sup>. These findings could impact the management of patients with pre-RBD suggesting the need of a careful assessment and a closer follow-up of autonomic dysfunctions and stridor in this sub-group. From a pathophysiological perspective, this correlation could be linked to the high topographical and functional interconnection of brainstem neuronal networks (parabrachial nucleus, pre-Botzinger complex, rostral ventrolateral medulla, pontine micturition centre, pedunculopontine tegmental nucleus, sublateralodorsal tegmental nucleus, locus coeruleus) involved in cardiovascular, respiratory and sleep control, whose degeneration in MSA has been widely documented<sup>14,15</sup>. The occurrence of RBD as the first symptom could be the "epiphenomenon" of an early involvement of brainstem nuclei, which leads to early autonomic dysfunctions, stridor and other sleep breathing disorders. This hypothesis, should be confirmed in further prospective multicentre studies on larger samples by mean of

advanced neuroradiological techniques performed at different stage of disease progression (e.g. Ultra High Field magnetic resonance acquisition, diffusion-weighted imaging, diffusion tensor imaging, magnetization transfer imaging, susceptibility-weighted imaging, magnetic resonance spectroscopy) .

Main limitations of the study include its retrospective nature, although some patients derived from the Autonomic and Sleep Centres of our Institute and were evaluated with a closer follow-up before the onset of motor symptoms. Moreover, the present study did not include the systematic assessment of autonomic dysfunction severity and RBD by appropriate scales/questionnaires. Finally, only 3 patients met consensus criteria for definite MSA.

The strengths of our study are that all patients were seen and diagnosed in a single Centre guarantying the uniformity of data and were evaluated at least once a year during the disease course. Moreover, to reduce the recall bias of RBD onset, event registration from VPSG was shown to bed-partners to ensure it was the same reported in patient recall and diagnosis of RBD was retained only when confirmed by VPSG. Finally, cardiovascular autonomic failure and stridor were instrumentally documented.

In conclusion, we showed in a large sample of MSA patients with a systematic clinical and instrumental assessment, that RBD represents the most frequent first symptom of disease in almost a third of cases. As RBD could represent an early marker of central neurodegeneration and could evolve in different synucleinopathies after a variable period of time, this sleep disorder could not be considered alone as criteria of MSA onset. However, given the evidence of a more rapid disease progression related to this "pre-RBD-onset MSA" in our cohort, we suggest a detailed history taking of sleep disorders to recognize RBD early, even in the view of future upcoming neuroprotective trials able to stop or delay the disease progression also in the premotor phase.

Name	Locations	Role	Contribution
Giulia Giannini, MD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Alma Mater Studiorum - University of Bologna, Italy;	AUTHOR	acquisition, analysis and interpretation of data, drafting of the manuscript
Vincenzo Mastrangelo, MD	Alma Mater Studiorum - University of Bologna, Italy;	AUTHOR	acquisition, analysis and interpretation of data, drafting of the manuscript
Federica Provini MD, PhD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Alma Mater Studiorum - University of Bologna, Italy;	AUTHOR	critical revision of the manuscript
Andrea Droghini, MD	Alma Mater Studiorum - University of Bologna, Italy;	AUTHOR	acquisition of data, analysis and interpretation of data
Annagrazia Cecere, MSc	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy;	AUTHOR	acquisition of data, analysis and interpretation of data
Giorgio Barletta, MSc	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Alma Mater Studiorum - University of Bologna, Italy;	AUTHOR	acquisition of data, analysis and interpretation of data
Francesco Mignani, MSc	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy;	AUTHOR	acquisition of data, analysis and interpretation of data
Pietro Guaraldi MD, PhD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Local Health Authority of Modena, Modena, Italy.	AUTHOR	acquisition and interpretation of data, critical revision of the manuscript
Pietro Cortelli MD, PhD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Alma Mater Studiorum - University of Bologna, Italy;	AUTHOR	substantial contributions to conception and design of the study, critical revision of the manuscript
Giovanna Calandra-Buonauro MD, PhD	IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy; Alma Mater Studiorum - University of Bologna, Italy;	AUTHOR	conception and design of the study, supervision of the study, acquisition and interpretation of data, drafting of the manuscript

## REFERENCES

1. Gilman S, Wenning GK, Low PA, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71:670-676.
2. Jecmenica-Lukic M, Poewe W, Tolosa E, Wenning GK. Premotor signs and symptoms of multiple system atrophy. *Lancet Neurol* 2012;11:361-368.
3. Giannini G, Calandra-Buonaura G, Asioli GM, et al. The natural history of idiopathic autonomic failure: The IAF-BO cohort study. *Neurology* 2018;91:e1245-e1254.
4. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine 2014.
5. Palma JA, Fernandez-Cordon C, Coon EA, et al. Prevalence of REM sleep behavior disorder in multiple system atrophy: a multicenter study and meta-analysis. *Clin Auton Res* 2015;25:69–75.
6. Calandra-Buonaura G, Guaraldi P, Sambati L, et al. Multiple system atrophy with prolonged survival: is late onset of dysautonomia the clue? *Neurol Sci* 2013;34:1875-1878.
7. Giannini G, Calandra-Buonaura G, Mastrolilli F, et al. Early stridor onset and stridor treatment predict survival in 136 patients with MSA. *Neurology* 2016;87:1375-1383.
8. Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res* 2011;21:69–72.
9. Baschieri F, Calandra-Buonaura G, Doria A, et al. Cardiovascular autonomic testing performed with a new integrated instrumental approach is useful in differentiating MSA-P from PD at an early stage. *Parkinsonism Relat Disord* 2015;21:477–482.
10. Plazzi G, Corsini R, Provini F, et al. REM sleep behavior disorders in multiple system atrophy. *Neurology* 1997;48:1094–1097.

11. Iranzo A, Santamaria J, Rye DB, et al. Characteristics of idiopathic REM sleep behaviour disorder and that associated with MSA and PD. *Neurology* 2005;65:247–252.
12. Coon EA, Sletten DM, Suarez MD, et al. Clinical features and autonomic testing predict survival in multiple system atrophy. *Brain* 2015;138:3623-3631.
13. McKay JH, Cheshire WP. First symptoms in multiple system atrophy. *Clin Auton Res* 2018;28:215-221.
14. Benarroch EE. Brainstem in Multiple System Atrophy: Clinicopathological Correlations. *Cell Mol Neurobiol* 2003;23:519-526.
15. Benarroch EE. Brainstem integration of arousal, sleep, cardiovascular, and respiratory control. *Neurology* 2018;91:958-966.

## FIGURE LEGENDS

### Figure 1

Title: **Kaplan-Meier survival curves for probability of death from MSA onset.**

Legend: A) All patients with MSA. B) Patients with VPSG-confirmed RBD, grouped in pre-RBD and post-RBD.

### Figure 2

Title: **First clinical presentation in MSA cohort.**

Legend: A= autonomic, P= parkinsonism, C= cerebellar symptoms, pre-RBD= REM sleep behaviour disorder occurred before MSA onset. Data are expressed as percentage of total population. First symptom of disease was unknown in 4% of patients.

### Figure 3

Title: **Latency of symptoms in MSA patients with pre-RBD and post-RBD.**

Legend: Time 0 represents the occurrence of the first motor or autonomic symptom/sign of MSA. Data are expressed as median and interquartile range in years.



**Table 1: Demographic and clinical features of MSA patients with pre-RBD and post-RBD.**

	MSA patients with RBD		p-value
	pre-RBD <i>n</i> =42	post-RBD <i>n</i> = 65	
<b>Males, <i>n</i> (%)</b>	27 (64)	38 (58)	0.547
<b>Age at MSA onset, <i>y</i></b>	55 ± 8	57 ± 9	0.26
<b>Disease duration, <i>y</i></b>	6 (4.75-8)	8 (6-10)	<b>0.004</b>
<b>MSA subtype</b>			<b>0.032</b>
MSA-P, <i>n</i> (%)	15 (36%)	37 (57%)	
MSA-C, <i>n</i> (%)	27 (64%)	28 (43%)	
<b>Symptoms at MSA onset</b>			
Parkinsonism, <i>n</i> (%)	6 (14%)	28 (43%)	<b>0.001</b>
Cerebellar, <i>n</i> (%)	17 (40%)	21 (32%)	0.456
Autonomic, <i>n</i> (%)	29 (69%)	29 (45%)	<b>0.020</b>
<b>Symptoms during the course of disease</b>			
Parkinsonism, <i>n</i> (%)	31 (74%)	59 (91%)	<b>0.034</b>
Latency of parkinsonism, <i>y</i>	3 (1-5)	1 (0-4)	0.051
Cerebellar, <i>n</i> (%)	35 (83%)	55 (85%)	0.675
Latency of cerebellar symptoms, <i>y</i>	1 (0-3)	2 (0-4)	0.152
Pyramidal signs, <i>n</i> (%)	35 (83%)	48 (74%)	0.429

Latency of pyramidal signs, <i>y</i>	3 (2-4)	4 (3-6)	<b>0.027</b>
Urinary symptoms, <i>n (%)</i>	40 (95%)	63 (97%)	0.65
Latency of urinary symptoms, <i>y</i>	0 (0-1)	1 (0-4)	<b>0.008</b>
Symptomatic OH, <i>n (%)</i>	26 (62%)	46 (71%)	0.243
Latency of symptomatic OH, <i>y</i>	1 (0-3)	4 (1-6)	<b>0.017</b>
Stridor, <i>n (%)</i>	21 (50%)	25 (39%)	0.29
Latency of stridor, <i>y</i>	2.5 (1-4)	4 (3-6)	<b>0.013</b>
<b>Milestone of disease progression</b>			
Frequent falls, <i>n (%)</i>	21 (50%)	38 (58%)	0.312
Latency of frequent falls, <i>y</i>	4 (2-6)	5 (3-6)	0.173
Urinary catheterization, <i>n (%)</i>	18 (43%)	26 (40%)	0.955
Latency of urinary catheterization, <i>y</i>	4 (2-6)	6 (5-9)	<b>0.016</b>
Unintelligible speech, <i>n (%)</i>	7 (17%)	23 (35%)	<b>0.025</b>
Latency of unintelligible speech, <i>y</i>	6 (4-8)	7 (5-11)	0.096
Dysphagia/PEG, <i>n (%)</i>	5 (12%)	20 (31%)	<b>0.018</b>
Latency of dysphagia/PEG, <i>y</i>	6 (4-7)	8 (6.5-10.5)	<b>0.019</b>
Wheelchair dependency, <i>n (%)</i>	21 (50%)	42 (65%)	0.056
Latency of wheelchair dependency, <i>y</i>	6 (4-7)	7 (5-9)	<b>0.019</b>

Data are expressed as mean  $\pm$  standard deviation or median (interquartile range).

Legend: MSA-C: Multiple System Atrophy with predominant cerebellar phenotype; MSA-P: Multiple System Atrophy with predominant parkinsonism phenotype ; *n*: sample size; OH= orthostatic

hypotension; PEG= Percutaneous Endoscopic Gastrostomy; RBD: REM sleep behaviour disorder; post-RBD= RBD occurred after MSA onset; pre-RBD= RBD occurred before MSA onset; *y*: years.

*Statistically significant p-values are denoted in bold. Latencies were calculated from disease onset.*