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RESEARCH PAPER

New insights into orthostatic hypotension in multiple system atrophy: a European multicentre cohort study

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ABSTRACT

Objectives Orthostatic hypotension (OH) is a key feature of multiple system atrophy (MSA), a fatal progressive neurodegenerative disorder associated with autonomic failure, parkinsonism and ataxia. This study aims (1) to determine the clinical spectrum of OH in a large European cohort of patients with MSA and (2) to investigate whether a prolonged postural challenge increases the sensitivity to detect OH in MSA.

Methods Assessment of OH during a 10 min orthostatic test in 349 patients with MSA from seven centres of the European MSA-Study Group (age: 63.6 ±8.8 years; disease duration: 4.2±2.6 years). Assessment of a possible relationship between OH and MSA subtype (P with predominant parkinsonism or C with predominant cerebellar ataxia), Unified MSA Rating Scale (UMSARS) scores and drug intake.

Results 187 patients (54%) had moderate (≥20 mm Hg (systolic blood pressure (SBP)) and/or ≥10 mm Hg (diastolic blood pressure (DBP)) or severe OH (≥30 mm Hg (SBP) and/or ≥15 mm Hg (DBP)) within 3 min and 250 patients (72%) within 10 min. OH magnitude was significantly associated with disease severity (UMSARS I, II and IV), orthostatic symptoms (UMSARS I) and supine hypertension. OH severity was not associated with MSA subtype. Drug intake did not differ according to OH magnitude except for antihypertensive drugs being less frequently, and antihypotensive drugs more frequently, prescribed in severe OH.

Conclusions This is the largest study of OH in patients with MSA. Our data suggest that the sensitivity to pick up OH increases substantially by a prolonged 10 min orthostatic challenge. These results will help to improve OH management and the design of future clinical trials.

INTRODUCTION

Multiple system atrophy (MSA) is a sporadic adult onset neurodegenerative disorder characterised by varying severity of parkinsonism, cerebellar ataxia, autonomic failure and corticospinal impairment.[1] Autonomic failure results in orthostatic hypotension (OH) and/or urogenital symptoms, key features of current diagnosis criteria. Autonomic failure is an independent predictive factor for rapid disease progression and shorter survival.[2] OH is defined by consensus as a drop of systolic blood pressure (SBP) ≥20 mm Hg and/or of diastolic BP (DBP) ≥10 mm Hg within 3 min in upright position.[3] A more pronounced drop (≥30 mm Hg for SBP and/or ≥15 mm Hg for DBP) is often reported in MSA and is one of the criteria for 'probable' MSA.[1] OH symptoms can cause significant disability for activities of daily living that require standing or walking. OH increases the risk of falls and associated morbidity.[4 5] Several studies have dealt with OH in patients with Parkinson's disease (PD) and atypical parkinsonian syndromes. These studies, which generally included a large number of patients with PD, showed that advancing age, disease severity and duration were related to OH in PD. In addition, non-specific predisposing factors may favour OH such as fluid depletion, medication intake, food ingestion, increased room temperature and physical deconditioning. However, none of these studies on the epidemiology and predisposing factors of OH focused on a large number of patients with MSA.

Jamnadas-Khoda *et al*[6] observed, in patients with PD, that OH frequently occurs after 3 min in upright position. Patients with PD and MSA can also remain asymptomatic despite large decreases in BP, and some orthostatic symptoms have low specificity.[4 5] These observations call for an optimisation of OH detection.

The study objectives were to analyse factors that may influence OH magnitude such as disease duration, disease severity, MSA phenotype (P with predominant parkinsonism or C with predominant cerebellar ataxia) and drug intake. We also evaluated the interest of a 10 min orthostatic test to detect delayed OH, and assessed the relation between OH and orthostatic symptoms in patients with MSA recruited into a large multicentre European cohort study.

METHODS

Patients

We studied 373 patients with 'possible' or 'probable' MSA from seven centres of the EMSA (European MSA)-Study Group (EMSA-SG); 349 patients with adequate BP measurements were included between 1995 and 2012 (Bologna

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(n=34), Bordeaux (n=106), Innsbruck (n=23), Rome (n=5), Strasbourg (n=13), Tel-Aviv (n=57) and Toulouse (n=111)). Data were collected retrospectively in Bologna, Innsbruck, Rome, Strasbourg and Tel-Aviv, while patients of the French reference centres in Bordeaux and Toulouse are part of a prospective longitudinal natural history study of MSA that has received ethics approval (CNIL, n° 1 338 780; CCTIRS, n° 10.065). Approval from an ethical standards committee was received to conduct the study on retrospective data. The diagnosis of 'possible' or 'probable' MSA was based on consensus diagnosis criteria for MSA.[1] Patients were further divided into MSA-P or MSA-C, according to the predominant motor feature.

Orthostatic challenge test

BP recordings were carried out with a sphygmomanometer (arm cuff) in routine examination. Some patients (n=34) had a continuous digital BP measurement (Finapres®); in this case, BP values were averaged every minute. Resting BP measurements were performed in supine position. The patients were then asked to stand up (n=287) or were tilted at 80° head up tilt (HUT) position (n=62), with BP being recorded, if possible, for 10 min in upright position. Patients unable to stand in upright position (even with support) and patients for which the stand test was interrupted for a reason other than OH, were excluded from the study. BP measurements were taken every minute (n=214) or at least at minute 3, 5 and 10 (n=135) in upright position, and were compared with the last measurement in supine position (baseline). OH was only considered if confirmed by at least two consecutive BP measurements.

We calculated the number of patients who had moderate OH (drop of SBP $\geq$20 mm Hg and/or DBP $\geq$10 mm Hg) and severe OH (drop of SBP $\geq$30 mm Hg and/or DBP $\geq$15 mm Hg) within 3, 5 and 10 min in upright position. We also calculated the number of patients who had mild non-significant OH (drop of SBP >10 and <20 mm Hg), since mild OH may already indicate minor sympathetic impairment.

Data on orthostatic symptoms reported by the patients during the test were not systematically recorded and were therefore excluded from the analysis. By contrast, the severity of OH symptoms was assessed in 228 patients (65%) by the corresponding item 9 of the Unified MSA Rating Scale (UMSARS) I[7] (see next paragraph).

Disease characteristics

Disease severity was evaluated in 65% (n=228) of the patients by means of the UMSARS[7] at the same visit as for BP measurements. The UMSARS is a validated, MSA-specific scale that assesses activities of daily living (UMSARS I, 12 items), motor impairment (UMSARS II, 14 items) and global disability (UMSARS IV). Higher scores indicate greater disease severity. Other autonomic symptoms such as bladder and sexual dysfunction as well as gastrointestinal impairment are assessed by UMSARS I items 10–12.

As supine hypertension is a hallmark of cardiovascular autonomic failure that is frequently associated with OH, we studied the relation between OH magnitude and supine hypertension severity assessed on the last BP measurement in supine position. The severity level was defined according to European guidelines.[8]

Correlation with drug intake

Patients were assessed on regular therapy, which included treatments of OH for some. Where information on treatment was available, we studied if OH was associated with drug intake (n=278). All medications were coded according to the WHO Anatomical Therapeutic Chemical classification system (WHO-ATC). Only medications susceptible to significantly influence BP were analysed (mainly hypotensive and hypertensive treatment, and antidepressant, levodopa (L-dopa) and dopamine agonists).

Statistics

Statistical analysis was performed using SAS (V.9.2). Quantitative variables are indicated by means and SDs, and qualitative ones by number of cases and percentages. Patients were classified in three categories according to the magnitude of the OH (no significant OH/moderate OH/severe OH). The association between the magnitude of OH and the different variables was studied using a χ^2 test or a Fisher exact test for qualitative variables, or using the Spearman's r test for quantitative variables. We also studied the association between the magnitude of OH and the different variables in patients with mild OH using four categories including (no OH/mild OH/moderate OH/severe OH; see online supplementary material). The two groups with early (within 3 min) or delayed OH (after 3 min) were compared by t test or rank test for quantitative variables and by a χ^2 test for qualitative variables. Frequency of drug exposition was compared by χ^2 test or by Fisher test. Quantitative variables were compared by t test with adjustments for variance heterogeneity, if found necessary.

Multivariate analyses were performed by logistic regressions. An ordinal logistic regression was used to determine the risk factors for developing OH within 10 min. All tests are two sided at 0.05 level.

RESULTS

Patients characteristics

Three hundred and forty-nine patients (184 male and 165 female) were included for prolonged (10 min) orthostatic test analysis. Mean age was 63.6±8.8 years. According to current consensus diagnosis criteria, MSA was 'probable' in a large number of patients (77%) and 'possible' in the others; 67% were classified as having MSA-P and 33% as having MSA-C. Mean disease duration was 4.2±2.6 years.

OH challenge test

When defining OH by a drop of BP on at least two consecutive BP measurements, 187 patients (54%) had moderate or severe OH within 3 min, 223 patients (64%) within 5 min and 250 patients (72%) within 10 min (figure 1). Thus, 63 additional patients (18%) were diagnosed as having significant OH when orthostatic testing was extended from 3 to 10 min. Forty-six additional patients (13%) had mild non-significant OH.

No statistical difference in OH onset or magnitude was observed between the standing test and the HUT test (p=0.6483). Sixty-five tests (19% of patients) were interrupted because of significant orthostatic intolerance. OH magnitude was associated with UMSARS I orthostatic symptom subscores (item 9; table 1).

In the ordinal regression model, orthostatic symptom severity remained significantly associated with OH magnitude (table 2).

OH and disease characteristics

As shown in table 1, OH magnitude was not associated with age or MSA subtype (P vs C). As expected, OH was more pronounced in 'probable' MSA. OH was more frequent in males (n=143 (57%)) than in females (n=107 (43%)) and was associated with increased disease severity (UMSARS I and II) and

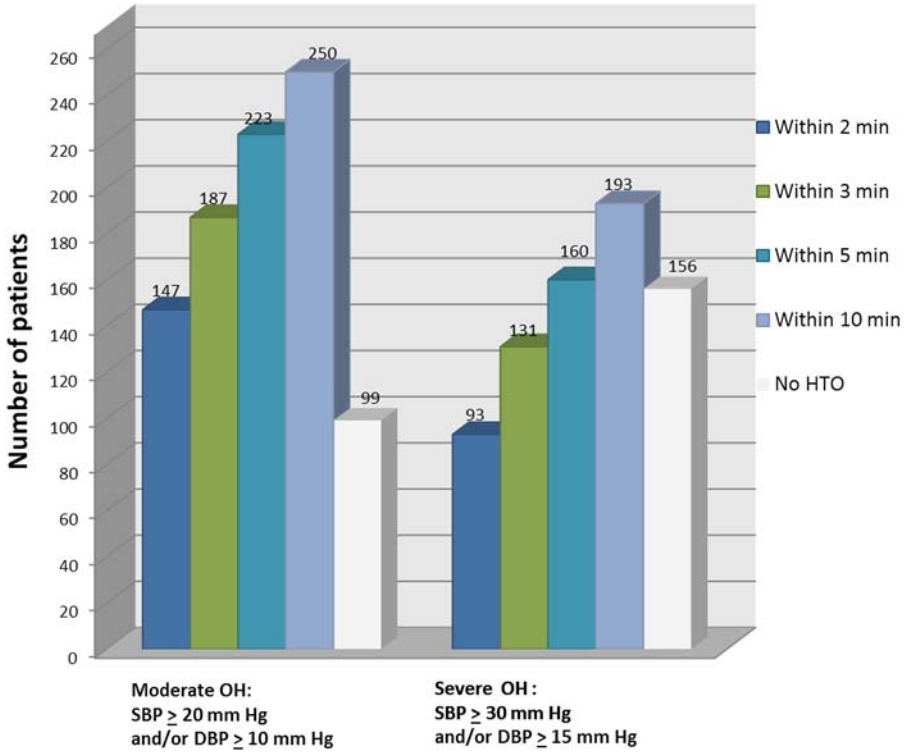

Figure 1 Number of patients with moderate or severe orthostatic hypotension (OH) according to OH onset time.

global disability (UMSARS IV). OH magnitude was associated with other autonomic symptoms (bladder and sexual dysfunction), while no association was found with gastrointestinal symptoms. The significant associations with disease characteristics did not differ when considering four OH magnitude categories (no significant OH/mild OH/moderate OH/severe OH; see online supplementary table). The post hoc analysis showed that UMSARS I bladder and sexual dysfunction were significantly associated only with severe OH. Interestingly, item scores of bladder and sexual dysfunction were already higher in patients with mild OH compared with patients without OH (see online supplementary table). For bladder dysfunction, the item score was 2.0±0.9 in patients with mild OH (n=36) versus 1.3 ±0.9 in patients without OH (n=25) and 2.0±1.0 in patients with moderate OH (n=40). Same results were observed for sexual dysfunction: 2.7±1.5 in patients with mild OH (n=33) versus 1.7±1.5 in patients without OH (n=24) and 2.7±1.5 in patients with moderate OH (n=35).

The association between OH magnitude and the severity of supine hypertension (classified in 5 categories according to European recommendations) was highly significant.

In an ordinal logistic regression model, the factors that remained associated with OH severity (within 10 min) were orthostatic symptom severity (UMSARS I item 9), diagnosis

Table 1 Patient characteristics with regard to three OH magnitude categories within 10 min

	No significant OH n=99 (28%) n (%) or mean±SD	Moderate OH n=57 (16%) n (%) or mean±SD	Severe OH n=193 (56%) n (%) or mean±SD	p Value*
Gender (M vs F)	41 vs 58 (41 vs 59)	29 vs 28 (51 vs 49)	114 vs 79 (59 vs 41)	**0.0160**
Age	63.2±9.0	63.3±8.0	63.8±9.0	0.8453
Disease duration	3.9±2.7 (n=97)	3.8±2.6 (n=57)	4.5±2.5 (n=192)	**0.0193** $^{0-2,\ 1-2}$
MSA type (P vs C)	66 vs 28 (70 vs 30)	36 vs 18 (67 vs 33)	122 vs 66 (65 vs 35)	0.6710
Diagnosis certainty ('probable' vs 'possible')	59 vs 36 (62 vs 38)	38 vs 16 (70 vs 30)	161 vs 27 (86 vs 14)	**<0.0001**
UMSARS I	17.6±7.4 (n=60)	18.6±6.5 (n=37)	21.5±7.7 (n=125)	**0.0030** $^{0-2}$
Orthostatic symptoms (item 9)	0.8±0.8 (n=61)	0.9±0.9 (n=40)	1.4±1.2 (n=127)	**0.0005** $^{0-2,\ 1-2}$
Bladder dysfunction (item 10)	1.7±1.0 (n=61)	2.0±1.0 (n=40)	2.2±1.1 (n=128)	**0.0098** $^{0-2}$
Digestive dysfunction (item 11)	1.4±1.0 (n=61)	1.4±0.9 (n=40)	1.5±0.9 (n=128)	0.6724
Sexual dysfunction (item 12)	2.3±1.6 (n=57)	2.7±1.5 (n=35)	3.0±1.4 (n=121)	**0.0073** $^{0-2}$
UMSARS II	21.7±8.3 (n=62)	23.1±7.9 (n=39)	24.1±7.8 (n=127)	**0.0276** $^{0-2}$
UMSARS IV	2.1±1.0 (n=61)	2.0±0.9 (n=39)	2.5±1.0 (n=127)	**0.0018** $^{0-2,\ 1-2}$
Supine hypertension severity†	1.1±1.0	1.4±1.0	1.9±1.2	**<0.0001** $^{0-2,\ 1-2}$

$^{0-2}$ Pairwise comparisons (Bonferroni test): 0–2 means difference between 0 (no OH) and 2 (severe OH).
*χ^2 or exact Fisher test for qualitative variables and Spearman's ρ test for quantitative variables.
†According to European guidelines.
F, female; M, male; MSA, multiple system atrophy; OH, orthostatic hypotension; UMSARS, Unified MSA Rating Scale.

Table 2 ORs and confidence limits for having OH within 10 min in upright position

	Model with UMSARS I		Model with items of UMSARS I	
	OR	95% CI	OR	95% CI
Gender (F vs M)	0.652	0.316 to 1.304	0.642	0.316 to 1.304
Age (years)	0.996	0.966 to 1.031	0.998	0.962 to 1.037
MSA type (C vs P)	1.091	0.572 to 2.129	1.104	0.572 to 2.129
Disease duration	1.092	0.966 to 1.234	1.094	0.963 to 1.243
Diagnosis certainty ('possible' vs 'probable')	**0.315**	**0.150 to 0.662***	**0.367**	**0.165 to 0.817***
UMSARS I	1.042	0.973 to 1.115	–	–
Orthostatic symptoms (item 9)	–	–	**1.659**	**1.124 to 2.267***
Bladder dysfunction (item 10)	–	–	1.224	0.893 to 1.678
Digestive dysfunction (item 11)	–	–	1.082	0.764 to 1.532
Sexual dysfunction (item 12)	–	–	1.065	0.846 to 1.340
UMSARS II	0.971	0.916 to 1.029	0.984	0.931 to 1.040
UMSARS IV	1.418	0.880 to 2.286	1.306	0.821 to 2.079
Supine hypertension severity	**1.822**	**1.373 to 2.417***	**1.783**	**1.337 to 2.378***

*p<0.05—Ordinal logistic regression—patients were classified in three categories according to the magnitude of OH as clinically defined. 0: No significant OH, 1: moderate OH, 2: severe OH.
F, female; M, male; MSA, multiple system atrophy; OH, orthostatic hypotension; UMSARS, Unified MSA Rating Scale.

certainty ('probable' vs 'possible') and supine hypertension severity (table 2).

OH onset within 3 min (compared with a delayed onset after 3 min) was more often reported in patients with OH symptoms (UMSARS I item 9), more severe disability (UMSARS IV) and, as expected, in those with 'probable' MSA (table 3). OH onset within 3 min was not related to disease duration or disease subtype.

Drug intake

The distribution of potentially hypotensive drugs according to OH magnitude (over 10 min) is shown in table 4.

A large number of patients received potentially hypotensive treatments (between 81% and 84%). Drug intake did not differ between the three groups except for antihypertensive drugs, which were less prescribed in patients with severe OH, and the number of potentially hypotensive drugs, which was slightly lower in patients with severe OH compared with both other groups. The variations in SBP and DBP in upright position were studied with respect to drug intake (those likely to influence BP) and showed a less pronounced drop in BP in patients receiving antihypertensive drugs. The drop in BP after 10 min in upright position remained high in patients who were receiving antihypotensive therapy. The drop in BP was particularly high in patients taking fludrocortisone (generally prescribed as second line; table 5).

DISCUSSION

This large multicentre cohort study is the first to determine the prevalence and the factors of OH in MSA, a key symptom of cardiovascular autonomic failure. Further, we show that by a modest extension of the orthostatic challenge from 3 to 10 min, an additional 20% of patients with MSA with significant OH can be identified.

OH characteristics and assessment

OH was observed within 3 min in upright position in 54% of patients with MSA, which is in accordance with a prospective European cohort study where OH was found in 57% of patients

Table 3 Patient characteristics with regard to the time of OH onset (within or after 3 min in upright position)

	Significant OH within 3 min n=187 (75%) n (%)	Significant OH after 3 min n=63 (25%) n (%)	p Value*
Gender (M vs F)	110 vs 77 (59 vs 41)	33 vs 30 (52 vs 48)	0.3714
Age (years)	64.3±9.2	63.5±8.6	0.5316
MSA type (P vs C)	120 vs 60 (67 vs 33)	38 vs 24 (61 vs 39)	0.4431
Disease duration	4.3±4.0 (n=186)	4.4±3.7	0.7922
Diagnosis certainty ('probable' vs 'possible')	157 vs 23 (87 vs 13)	42 vs 20 (68 vs 32)	0.0005
UMSARS I	21.3±7.7 (n=123)	19.5±6.7 (n=39)	0.1694
Orthostatic symptoms (item 9)	1.4±1.2 (n=127)	1.0±1.0 (n=40)	0.0164
Bladder dysfunction (item 10)	2.0±1.1 (n=128)	2.2±1.1 (n=40)	0.4755
Digestive dysfunction (item 11)	1.5±0.9 (n=128)	1.5±0.9 (n=40)	0.6966
Sexual dysfunction (item 12)	2.9±1.4 (n=120)	2.9±1.5 (n=36)	0.9311
UMSARS II	24.0±7.8 (n=126)	23.4±8.0 (n=40)	0.6774
UMSARS IV	2.5±1.0 (n=126)	2.1±0.9 (n=40)	**0.0376**
Supine hypertension severity	1.8±1.2	1.6±1.1	0.2294

*t test or Wilcoxon test for quantitative data or by χ^2 for qualitative variables.
F, female; M, male; MSA, multiple system atrophy; OH, orthostatic hypotension; UMSARS, Unified MSA Rating Scale.

Table 4 Exposure to potentially hypotensive/hypertensive drugs in patients with multiple system atrophy patients with or without orthostatic hypotension (OH) as defined by extended criteria (moderate or severe)

	No significant OH (n=79) n (%) or mean±SD	Moderate OH (n=57) n (%) or mean±SD	Severe OH (n=142) n (%) or mean±SD	p Value
Number of drugs	4.7±0.4	5.1±0.4	4.5±0.2	0.6
Polypharmacy*	29 (40)	24 (44)	40 (29)	0.1
Any antihypertensive drug	24 (30)	23 (40)	21 (15)†‡	**0.001**
Any antihypotensive treatment	10 (12)	9 (16)	58 (41)†‡	**0.001**
Midodrine	8 (10)	9 (16)	53 (37)†‡	**0.001**
Fludrocortisone	2 (2)	0	18 (13)†‡	**0.001**
Any α-adrenergic blocker	9 (12)	4 (7)	14 (10)	0.6
Levodopa	51 (65)	38 (67)	85 (60)	0.7
Dopamine agonists	18 (23)	13 (24)	18 (13)	0.7
Monoamine oxydase B (MAO-B) inhibitors	7 (9)	7 (13)	12 (9)	0.7
Any antidepressant	33 (42)	22 (40)	64 (45)	0.8
Number of potentially hypotensive treatments	1.9±0.2	2.0±0.2	1.6±0.1	**0.05**
Any potentially hypotensive treatment	66 (84)	48 (84)	115 (81)	0.8

OH was calculated over the maximal blood pressure fall on two consecutive recordings over 10 min. Groups were compared by χ^2.
*Co-administration of five or more drugs.
†p<0.05 versus no significant OH.
‡p<0.05 versus moderate OH (χ^2 or analysis of variance with Bonferroni correction).

with MSA.[9] The prevalence of OH increased to 72% when BP measurements in upright position were continued over 10 min. Our findings have significant implications for clinical practice. Using a prolonged orthostatic challenge test may facilitate earlier recognition of patients with MSA. Further, effective antihypotensive therapies can be implemented, resulting in direct patient benefit by alleviating orthostatic intolerance, improving quality of life[10] and preventing fall-related injuries. The duration of the BP drop that defines OH is not specified by current consensus criteria of OH. When considering OH as a drop in BP on one single measurement (instead of on two consecutive measurements), the prevalence increased to 67% within 3 min and to 79% within 10 min (results not shown). Others have already stressed the need for a better definition of the timing of BP measurements instead of 'within 3 min of standing',[11] and OH is defined as a sustained fall in BP in a revised consensus statement on OH.[12 13]

Different clinical variants of orthostatic intolerance have been described, including initial OH (within the first 30 s), 'classical' OH (within 3 min) and delayed OH (3–45 min).[12 13] Baroreceptor and chemoreceptor reflexes are the main mechanisms to maintain BP within the first 3 min of standing, whereas neurohumoral factors (notably the renin–angiotensin system) and a capillary fluid shift have more critical roles during prolonged standing. In the first 10 min in upright position, there is a progressive transition and overlap of these different mechanisms. Delayed OH has already been reported in patients with autonomic failure.[6 12 14] For instance, Jamnadas-Khoda *et al*[6] observed delayed OH during a head-up tilt test in 55% of patients with PD with OH. Gibbons and Freeman[14] showed that delayed OH is associated with milder sympathetic adrenergic dysfunction, suggesting that this disorder may be a mild or early form of sympathetic adrenergic failure. Chang *et al*[15] also showed a decreased vasomotor response in patients with MSA, using a 10 min orthostatic challenge test. In addition, some studies have shown blunted renin responses to postural stimuli in patients with autonomic failure, which may also favour delayed OH.[16] The pattern of BP fall in upright position provides additional information on the magnitude of autonomic failure since patients with a progressive decline in BP in upright position have more severe adrenergic impairment.[17] This is illustrated by the significant larger drop in mean BP in patients

Table 5 Variations in SBP and DBP during orthostatic test according to treatment

		3 min SBP	3 min DBP	5 min SBP	5 min DBP	10 min SBP	10 min DBP
Any treatment for OH	N (n=185)	−15.8±1.3	−6.3±0.8	−16.9±1.3	−6.9±0.8	−17.4±1.3	−6.8±0.8
	Y (n=74)	−37.6±3.7**	−17.7±2.3**	−35.6±3.6**	−16.2±2.4**	−38.1±3.6**	−16.9±2.9**
Midodrine	N (n=192)	−16.2±1.3	−6.5±0.8	−17.2±1.3	−7±0.8	−17.7±1.3	−7±0.9
	Y (n=67)	−38.6±4**	−18.1±2.5**	−36.8±3.8**	−16.9±2.5**	−39.5±3.8**	−17.5±3.1**
Fludrocortisone	N (n=240)	−19.5±1.4	−7.9±0.9	−19.9±1.2	−8.1±0.8	−20.8±1.4	−8.2±0.9
	Y (n=19)	−52±9.0**	−29.2±5.1**	−47.8±10.6**	−26.4±5.6**	−44.7±9.3**	−24.1±5.7**
Any antihypertensive	N (n=195)	−23.9±1.8	−11±1.2	−24.1±1.7	−10.6±1.1	−25±1.7	−10.2±1.2
	Y (n=64)	−15.7±2.3**	−4.8±1.2**	−14.6±2.1**	−5.4±1.4**	−13±2.2**	−5.6±1.6*
Any antiparkinsonian	N (n=76)	−25±3.3	−11.2±2.1	−25.3±3	−11.8±2	−24.2±2.7	−10.6±1.8
	Y (n=183)	−21.1±1.8	−9.3±1.1	−20.7±1.6	−8.9±1	−21.6±1.7	−9±1.2
Any antidepressant	N (n=144)	−22.5±2.2	−9.5±1.4	−23.3±2.1	−10.3±1.4	−23.3±2.1	−9.7±1.5
	Y (n=115)	−21.3±2	−9.6±1.3	−19.7±1.7	−7.9±1	−20.6±1.9	−8.3±1.1

*p<0.05, **p<0.01 versus patients not exposed to the treatment—comparison by t test.
DBP, diastolic blood pressure; N, no; OH, orthostatic hypotension; SBP, systolic blood pressure; Y, yes.

with early OH onset (within 3 min) compared with patients with late OH onset (after 3 min; 25.9±16.4 mm Hg at minute 3 vs 15.4±8.5 mm Hg at minute 10). Mild OH observed in an additional 13% of the patients might reflect early sympathetic impairment. In MSA, the loss of sympathetic preganglionic neurons in the intermediolateral spinal cord and supraspinal lesions of areas involved in central autonomic control (notably in the brainstem) contribute to autonomic failure.[18 19]

A limitation of this retrospective study is the use of both active standing and passive tilting to assess orthostatic tolerance; passive tilting was performed in 62 patients (17.7%). Passive tilting is considered more sensitive to detect OH than the standing test.[6] However, we did not find significant differences in OH onset or magnitude between stand test and HUT in this cohort of patients with MSA. An additional multilevel analysis performed to check the effects of OH assessment on the main study outcomes did not show any difference between the two methods (stand test and tilt test; not shown).

Association with orthostatic symptoms

OH symptoms are not specific and not always well correlated with the fall in BP. The impact of orthostatic symptoms on activities of daily living was significantly associated with the magnitude of the drop in BP; this association remained significant in the ordinal logistic regression model. Patients with OH onset within 3 min had more impaired activities of daily living than those with delayed OH; this is consistent with the hypothesis that delayed OH might represent a milder form of OH. Although data on orthostatic symptoms were not systematically recorded, 19% of the orthostatic tests were interrupted because of symptomatic OH. This is in accordance with the 20% of presyncopal symptoms reported in the European EMSA-SG MSA cohort.[9 20]

OH and MSA characteristics

General population characteristics

As expected, according to MSA consensus diagnosis criteria,[1] OH magnitude was larger in 'probable' MSA. Early OH onset within 3 min was also more frequent in 'probable' MSA. Besides diagnosis certainty, the characteristics of patients with OH onset within or after 3 min did not differ except for UMSARS I item 9 and UMSARS IV global disability scores; patients with OH onset within 3 min had more orthostatic symptoms and were more disabled. No differences were found with regard to motor impairment, disease duration and disease subtype.

When looking at the entire cohort, OH magnitude was significantly associated with disease duration, motor impairment and global disability. The association with disease duration is in accordance with the timeline of autonomic disturbances and the late occurrence of OH reported in other studies.[21 22]

In contrast to the usually reported association of OH with female gender,[23] OH magnitude was associated with male gender. This association may be favoured by the more frequent use of α-blockers for urological symptoms in men (17% in men and 2% in women—p<0.001).

Disease subtype

Only a few studies have compared OH between MSA-P and MSA-C subtypes. Wenning *et al*,[24] in a small study, found that OH frequency and severity were more frequent in MSA-C (n=16) compared with MSA-P (n=17). In our large cohort of patients with MSA, no significant association was found between OH and MSA subtype.

Other autonomic symptoms

Autonomic failure is a prominent clinical feature and is mandatory for the diagnosis of MSA. The magnitude of OH was associated with the severity of other autonomic symptoms, namely bladder and sexual dysfunction. However, even patients with mild OH had greater bladder and sexual dysfunction compared with patients with no OH. This illustrates the extent and severity of autonomic failure in MSA. Early onset of urogenital symptoms was described in several studies of MSA[21] and urinary symptoms were more commonly reported (88%) than OH (57%) in the cohort of the EMSA-SG.[9] No association was found with subscores of UMSARS I item 12 (digestive symptoms), which only focuses on the severity of constipation. This may be related to the lack of specificity of this symptom.

Supine hypertension

At least half of patients with primary autonomic failure and OH exhibit supine hypertension despite profound impairment in sympathetic activity.[16 25–27] Supine hypertension increases nocturnal natriuresis, which worsens morning OH. Baroreceptor reflex impairment favours supine hypertension;[25–27] however, the mechanisms of supine hypertension are not well known. Recent results suggest increased angiotensin 2 levels as a possible pathophysiological mechanism providing a rationale for the use of Angiotensin 2 receptor type 1 (AT1) receptor blockers to treat supine nocturnal hypertension in MSA.[16]

Drug intake

A large number of patients received at least one potentially antihypotensive drug (81% in patients with severe OH and 84% in others). Most patients received L-dopa and/or dopamine agonists for their parkinsonism.[28] While L-dopa and dopaminergic drugs may cause or worsen pre-existing OH in PD,[29] we did not find a significant effect on OH in this cohort of patients with MSA. Several previous studies in patients with PD have shown that acute or chronic administration of oral L-dopa produces mild OH and lowers resting BP;[30] this had never been specifically studied in patients with MSA. In our study, drug intake did not differ with regard to OH severity, except for antihypertensive drugs, which were less prescribed in patients with severe OH, and the number of potentially hypotensive drugs, which was slightly lower in patients with severe OH.

Indeed, the association of supine hypertension and OH complicates the management of these patients, and may limit the use of antihypertensive agents including at night time.[16 27] The reduced use of antihypertensive agents in patients with severe OH also explains the less pronounced drop in BP in patients with MSA receiving antihypertensive agents that usually favour OH.

Only 28% of the patients suffering from OH received specific antihypotensive treatment. As expected, antihypotensive treatment was more frequently prescribed in severe OH; however, less than one patient out of two was treated (41%). Fludrocortisone, which is usually prescribed as second line after midodrine, was more frequently prescribed in severe OH. However, the drop in BP in patients who were receiving treatment against OH remained high. This illustrates the need for new drugs against OH. Droxidopa, currently marketed in Japan, recently received Food and Drug Administration (FDA) approval for the treatment of symptomatic neurogenic OH. Droxidopa (L-threo-3,4-dihydroxyphenylserine) is an orally administered artificial amino acid converted both peripherally and centrally into norepinephrine.[31] Only midodrine and

droxidopa were found to be efficient for neurogenic hypotension in double-blind controlled studies,[31–34] whereas other treatments such as fludrocortisone are off label treatments. However, trials assessing droxidopa effects on neurogenic OH included a limited number of patients suffering from MSA; a study focusing on patients with MSA is ongoing (clinicaltrials.gov NCT02071459).

This retrospective study has some limitations: the potential effects of different methods of OH assessment (tilt test or stand test) were already discussed. Some data such as UMSARS scores and drug intake were not available in all patients, and detailed dosage of drug intake could not be studied.

In conclusion, the present results show that OH magnitude was significantly associated with disease duration, motor impairment and global disability, but not related to the MSA subtype. This study also illustrates the poor or partial efficiency of current treatments against OH and highlights the need for new drugs. In addition, these results suggest that the amplitude of the BP fall and the time required to develop OH are both relevant for a diagnosis of cardiovascular autonomic failure in MSA, notably in possible MSA cases. Therefore, we recommend performing orthostatic testing over 10 min, since this allows detecting OH in a significant number of additional patients with MSA. Early recognition and treatment of OH is paramount to alleviate the disabling symptoms of orthostatic intolerance in patients with MSA who are also disabled by treatment-resistant progressive parkinsonism and ataxia. This study in a large cohort of patients with MSA provides new insights on factors influencing OH, and helps to improve OH management and the design of future clinical trials.

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REFERENCES

1 Gilman S, Wenning GK, Low PA, *et al*. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71:670–6.
2 O'Sullivan SS, Massey LA, Williams DR, *et al*. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain* 2008;131(Pt 5):1362–72.
3 No authors listed]. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. *Neurology* 1996;46:1470.
4 Rose KM, Eigenbrodt ML, Biga RL, *et al*. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk In Communities (ARIC) Study. *Circulation* 2006;114:630–64.
5 Benvenuto LJ, Krakoff LR. Morbidity and mortality of orthostatic hypotension: implications for management of cardiovascular disease. *Am J Hypertens* 2011;24:135–44.
6 Jamnadas-Khoda J, Koshy S, Mathias CJ, *et al*. Are current recommendations to diagnose orthostatic hypotension in Parkinson's disease satisfactory. *Mov Disord* 2009;24:1747–51.
7 Wenning GK, Tison F, Seppi K, *et al*. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). *Mov Disord* 2004;19:1391–402.
8 Mancia G, De Backer G, Dominiczak A, *et al*. 2007 guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2007;28:1462–536.
9 Wenning GK, Geser F, Krismer F, *et al*; European Multiple System Atrophy Study Group. The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol* 2013;12:264–74.
10 Arnold AC, Shibao C. Current concepts in orthostatic hypotension management. *Curr Hypertens Rep* 2013;15:304–12.
11 Braam EA, Verbakel D, Adiyaman A, *et al*. Orthostatic hypotension: revision of the definition is needed. *J Hypertens* 2009;27:2116–20.
12 Wieling W, Schatz IJ. The consensus statement on the definition of orthostatic hypotension: a revisit after 13years. *J Hypertens* 2009;27:935–93.

13 Freeman R, Wieling W, Axelrod FB, *et al*. Consensus statement on the definition of orthostatic hypotension, neutrally mediated syncope and the postural tachycardia syndrome. *Clin Auton Res* 2011;21:69–72.
14 Gibbons CH, Freeman R. Delayed orthostatic hypotension: a frequent cause of orthostatic intolerance. *Neurology* 2006;67:28–32.
15 Chang KV, Chen WS, Wu RM, *et al*. Pulsed wave Doppler ultrasound is useful to assess vasomotor response in patients with multiple system atrophy and well correlated with tilt table study. *Sci World J* 2012;2012:548529.
16 Arnold AC, Okamoto LE, Gamboa A, *et al*. Angiotensin II, independent of plasma renin activity, contributes to the hypertension of autonomic failure. *Hypertension* 2013;61:701–6.
17 Gehrking JA, Hines SM, Benrud-Larson LM, *et al*. What is the minimum duration of head-up tilt necessary to detect orthostatic hypotension? *Clin Auton Res* 2005;15:71–5.
18 Benarroch EE. Brainstem in multiple system atrophy: clinicopathological correlations. *Cell Mol Neurobiol* 2003;23:519–26.
19 Benarroch EE. New findings on the neuropathology of multiple system atrophy. *Auton Neurosci* 2002;96:59–62.
20 Stefanova N, Bücke P, Duerr S, *et al*. Multiple system atrophy: an update. *Lancet Neurol* 2009;8:1172–8.
21 Jecmenica-Lukic M, Poewe W, Tolosa E, *et al*. Premotor signs and symptoms of multiple system atrophy. *Lancet Neurol* 2012;11:361–8.
22 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;34:1875–8.
23 Fedorowski A, Stavenow L, Hedblad B, *et al*. Orthostatic hypotension predicts all-cause mortality and coronary events in middle-aged individuals (The Malmo Preventive Project). *Eur Heart J* 2010;31:85–91.
24 Wenning GK, Granata R, Krismer F, *et al*. Orthostatic hypotension is differentially associated with the cerebellar versus the parkinsonian variant of multiple system atrophy: a comparative study. *Cerebellum* 2012;11:223–6.
25 Biaggioni I, Robertson RM. Hypertension in orthostatic hypotension and autonomic dysfunction. *Cardiol Clin* 2002;20:291–301.
26 Goldstein DS, Pechnik S, Holmes C, *et al*. Association between supine hypertension and orthostatic hypotension in autonomic failure. *Hypertension* 2003;42:136–42.
27 Shannon J, Jordan J, Costa F, *et al*. The hypertension of autonomic failure and its treatment. *Hypertension* 1997;30:1062–7.
28 Flabeau O, Meissner W, Tison F. Multiple system atrophy: current and future approaches to management. *Ther Adv Neurol Disord* 2010;3:249–63.
29 Senard JM, Brefel-Courbon C, Rascol O, *et al*. Orthostatic hypotension in patients with Parkinson's disease: pathophysiology and management. *Drugs Aging* 2001;18:495–505.
30 Asahina M, Vichayanrat E, Low DA, *et al*. Autonomic dysfunction in parkinsonian disorders: assessment and pathophysiology. *J Neurol Neurosurg Psychiatry* 2013;84:674–80.
31 Kaufmann H, Freeman R, Biaggioni I, *et al*. Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. *Neurology* 2014;83:328–35.
32 Kaufmann H. L-dihydroxyphenylserine (droxidopa): a new therapy for neurogenic orthostatic hypotension: the US experience. *Clin Auton Res* 2008;18(Suppl 1): 19–24.
33 Low PA, Gilden JL, Freeman R, *et al*. A randomized, double-blind multicenter study. Midodrine Study Group. *JAMA* 1997;277:1046–51.
34 Wright RA, Kaufmann HC, Perera R, *et al*. A double-blind, dose-response study of midodrine in neurogenic orthostatic hypotension. *Neurology* 1998;51:120–4.

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