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Progression of Multiple System Atrophy (MSA): A Prospective Natural History Study by the European MSA Study Group (EMSA SG)

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Abstract: The disease-specific Unified Multiple System Atrophy Rating Scale (UMSARS) has been developed recently and validated for assessing disease severity in multiple system atrophy (MSA). Here, we aimed at (1) assessing rates of disease progression in MSA and (2) validating UMSARS for sensitivity to change over time. Impairment was assessed at two time points 12 months apart using UMSARS Part I (historical review), UMSARS Part II (motor examination), as well as measures of global disease severity, including UMSARS Part IV, Hoehn and Yahr (HY) Parkinson's disease staging, Schwab England Activities of Daily Living (SE ADL), and a three-point global Severity Scale (SS3). Fifty patients (male:female ratio, 1:0.9; possible MSA, 16%; probable MSA, 84%; MSA-parkinsonian, 58%; MSA-cerebellar, 42%) were assessed twice with an interval of 12.3 months. UMSARS II scores progressed by 57.3% ($P < 0.0001$) and UMSARS I scores by 35.6% ($P < 0.0001$) in relation to the respective baseline scores with no differences between motor subtypes, diagnostic categories and gender. Significant inverse correlations between (1) UMSARS I or UMSARS II progression and (2) baseline disability measures (i.e., the respective UMSARS or SS3 scores) and disease duration were found. Furthermore, the increases in HY staging, SE ADL and SS3 correlated significantly with UMSARS I, UMSARS II, and UMSARS IV progression. This report is the first prospective study showing rapid annual UMSARS rates of decline in MSA. Our data contribute to the ongoing validation process of UMSARS, and they facilitate the planning and implementation of future neuroprotective intervention trials. © 2005 Movement Disorder Society

Key words: multiple system atrophy; Unified MSA Rating Scale; progression; sensitivity to change

Multiple system atrophy (MSA) is a sporadic progressive neurodegenerative disorder characterized clinically by various combinations of parkinsonian, autonomic, cerebellar, or pyramidal signs and pathologically by cell loss, gliosis, and α-synuclein–positive glial cytoplasmic inclusions in several brain and spinal cord structures.[1] Two major motor presentations can be distinguished clinically with a predominance of parkinsonian features in 66% of patients (MSA-P subtype) or cerebellar ataxia in 34% of patients (MSA-C subtype) according to a recent survey.[2] Compared to Parkinson's disease (PD), disease progression is much faster in MSA.[3–10] However,

[†]A full list of study members is presented in the Appendix.

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the rates of decline may vary considerably between individual MSA patients.[3,11] Studies prospectively defining rates and predictors of progression in MSA are lacking, except for one based on the Unified Parkinson's Disease Rating Scale (UPDRS).[10] Therefore, the European MSA Study Group (EMSA SG) launched a natural history study incorporating serial 6-monthly ratings using the novel Unified MSA Rating Scale (UMSARS)[12] as well as a range of additional scales throughout a 2-year follow-up period. To complete the UMSARS validation process, here we report an interim analysis on annual UMSARS rates of decline and their predictors in a cohort of 50 European MSA patients. Furthermore, we assess the sensitivity of UMSARS to determine the change of disability during the time course of MSA.

PATIENTS AND METHODS

Data collection

A cohort of European Caucasian MSA patients was recruited consecutively at eight EMSA SG centers. Patients were diagnosed as MSA-P or MSA-C according to established criteria.[13] Clinical assessments were made at baseline and after 12 months of follow-up and included basic clinical data (EMSA SG Minimal Data Set, MDS), the UMSARS, as well as scales of global disease severity. The MDS comprises demographic features, patients' clinical presentation (Parkinsonism, dysautonomia, cerebellar ataxia, and so on), and results of ancillary investigations (e.g., magnetic resonance imaging, single photon emission computed tomography, autonomic function tests) plus data on current therapy. At site visits, the UMSARS, Hoehn and Yahr Parkinson's disease staging (HY staging), Schwab and England Activities of Daily Living (SE ADL) scale, and a three-point global disease severity scale (SS3) were completed by neurologists with particular expertise in the field of movement disorders. An abbreviated version of the UMSARS Part I (Historical Review) and UMSARS II (Motor Examination Scale) showing the items without the different categories, as well as UMSARS Part III (Autonomic Examination) and UMSARS Part IV (Global Disability Scale) is depicted in Table 1. Follow-up examination was performed independently by the same rater in each center, blinded to the result of the baseline visit.

This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983), and the 41st (Hong Kong, 1989) World Medical Assemblies, as well as the European Guidelines for Good Clinical Practice (ISBN 92-825-9563-3). The final protocol and the informed consent form were reviewed by properly constituted Investigational Review Boards, in accordance with laws and regulation of the participating countries, and ethical approval was granted. Written, informed consent was obtained from each patient or legal guardian before subjecting the patient to any study-related procedures.

TABLE 1. *Abbreviated Unified Multiple System Atrophy Rating Scale (modified from Wenning et al., 2004[12])*

Part I: Historical review
1. Speech
2. Swallowing
3. Handwriting
4. Cutting food and handling utensils
5. Dressing
6. Hygiene
7. Walking
8. Falling (the past month is rated)
9. Orthostatic symptoms
10. Urinary function
11. Sexual function
12. Bowel function
Part II: Motor Examination Scale
1. Facial expression
2. Speech
3. Ocular motor dysfunction
4. Tremor at rest
5. Action tremor
6. Increased tone
7. Rapid alternating movements of hands
8. Finger taps
9. Leg agility
10. Heel-knee-shin test
11. Arising from chair
12. Posture
13. Body sway
14. Gait
Part III: Autonomic examination
Systolic/diastolic blood pressure and heart rate are measured after 2 minutes of rest in supine position and again after 2 minutes of standing
Part IV: Global Disability Scale
Stage 1 (completely independent) to 5 (totally dependent and helpless; bedridden)

Statistical Analysis

Data Processing.

Hardcopy-based data were entered in a central ACCESS database hold at the Innsbruck site and analyzed using SPSS 12.0 for Windows (SPSS, Inc., USA).

Patient Characteristics.

The "average" or "spread" of data on patient characteristics were estimated by calculating the median and the interquartile range (for ordinal grouped data) and the mean, median, and standard deviation (SD, for continuous data), respectively (Table 2). Normally distributed

TABLE 2. *Baseline patient characteristics*

Characteristic	Value
Male:female ratio	1:0.9
Age at onset (yr) mean, median, SD	55.8, 55.0, 8.4
Age at baseline (yr) mean, median, SD	61.1, 60.0, 7.9
Disease duration at baseline (yr) mean, median, SD	5.3, 4.0, 3.5
Delay between baseline and follow up (months) mean, median, SD	12.3, 12.3, 1.0
HY stage (median, interquartile range)[a]	3.5, 2.7 to 4.4
SE ADL (median, interquartile range)[a]	56.0, 37.7 to 71.4
SS3 (median, interquartile range)[a]	2.2, 1.5 to 2.8
Dysautonomia (%)	96.0
Parkinsonian signs (%)	100
Cerebellar dysfunction (%)	78.0
Pyramidal signs (%)	54.0

[a]Calculated from grouped data.

HY, Hoehn and Yahr Parkinson's disease staging; SE ADL, Schwab and England Activities of Daily Living; SS3, Severity Scale 3.

data were analyzed using parametric and non-Gaussian distributed variables using nonparametric tests. In fact, group differences (according to motor subtype, diagnostic category, and sex) were analyzed using the Student's *t* test and Mann–Whitney *U* test, respectively. The χ^2 test (or Fisher's exact test if the expected frequency was < 5 in one cell of the contingency table) was used to estimate the proportions of individuals with the presence of cardinal diagnostic features. The significance level was set at $P < 0.05$.

UMSARS Progression and Sensitivity to Change.

Disease progression was defined as the difference in points between the follow-up and baseline scores of the UMSARS, HY, SE ADL, and SS3 scales. The change between baseline and follow-up was calculated in relation (percentage) to the baseline value of the respective scores. Progression was analyzed by comparing the scores of baseline versus follow-up using the Wilcoxon signed-rank test. Because of multiple group comparisons (i.e., six), the significance level was set at a threshold of $P < 0.05/6 = 0.008$. For the correlation analysis between the change in UMSARS scores and change in measures of global disease severity, the Spearman's rank correlation coefficients were calculated. The correlation coefficients were interpreted as follows: < 0.30 as low, 0.30 to 0.60 as moderate, 0.60 to 0.90 as moderately high, and $>$ 0.9 as high correlation.

Effects of Baseline Factors on UMSARS Progression.

Tests for differences in the change between baseline and follow-up evaluation of the UMSARS I and UMSARS II scores according to categorical baseline factors (gender, motor subtype, diagnostic category, and the presence or absence of cardinal diagnostic features) were made using the Mann–Whitney *U* test. Furthermore, to identify features present at baseline associated with a rapid disease progression, Spearman rank's correlation coefficients were calculated between (1) change of UMSARS I or UMSARS II scores and (2) the following baseline parameters: age, disease duration, the respective UMSARS I or UMSARS II scores as well as HY, SE ADL, and SS3 scores.

RESULTS

Patient Characteristics

We examined 50 patients with MSA at eight EMSA SG sites: 58% of patients showed a predominance of parkinsonian signs (MSA-P), and 42% of them showed a predominance of cerebellar dysfunction (MSA-C); 16% percent fulfilled criteria for possible and 84% for probable MSA. The baseline patient characteristics are shown in Table 2. The mean delay between first and follow-up evaluation was 12.3 months (SD: 1.0).

UMSARS Progression and Sensitivity to Change

All of the scales indicated worsening of impairment or function at follow-up compared to baseline evaluation (Table 3). The mean difference of UMSARS I scores between baseline and follow-up was 6.7 points (95% confidence interval [CI], 5.1 to 8.3; Fig. 1), corresponding to a 35.6% (95% CI, 23.6 to 47.5) increase relative to baseline. The mean difference of UMSARS II between baseline and follow-up was 9.6 points (95% CI, 7.5 to 11.7; Fig. 2), corresponding to a 57.3% (95% CI, 33.9 to 80.7) increase relative to baseline. The mean difference of UMSARS IV between baseline and follow-up was 0.8 points (95% CI, 0.5 to 1.0; Fig. 3), corresponding to a 33.3% (95% CI, 22.1 to 44.6) increase relative to baseline. Relative increases of UMSARS I, UMSARS II, and

TABLE 3. *Baseline and follow-up scores*

Parameter	Item(s)	Max. score	Baseline, mean (median, SD)[a]	Follow-up, mean (median, SD)[a]	Difference follow-up to baseline, mean (median, 95% CI)[a]	Difference follow-up to baseline (%), mean (median, 95%CI)[a,b]	P[c]
UMSARS I	1–12	48	23.4 (22.2, 8.4)	30.2 (28.3, 9.4)	6.7 (6.3, 5.1 to 8.3)	35.6 (27.1, 23.6 to 47.5)	<0.0001
UMSARS II	13–26	56	23.8 (23.0, 8.5)	33.4 (33.5, 9.0)	9.6 (7.8, 7.5 to 11.7)	57.3 (33.3, 33.9 to 80.7)	<0.0001
UMSARS IV		5	2.9 (2.9, 1.1)	3.7 (3.8, 1.0)	0.8 (0.7, 0.5 to 1.0)	33.3 (25.0, 22.1 to 44.6)	<0.0001
HY		5	3.5 (3.5, 1.1)	4.0 (4.2, 1.0)	0.5 (0.5, 0.4 to 0.7)	20.9 (16.4, 8.2 to 33.7)	<0.0001
SE ADL		100	54.4 (56.0, 21.5)	40.2 (38.8, 21.6)	−14.2 (−11.9, −18.8 to −9.6)	−27.1 (−23.4, −35.6 to −18.6)	<0.0001
SS3		3	2.1 (2.2, 0.7)	2.4 (2.5, 0.6)	0.3 (0.3, 0.1 to 0.5)	22.3 (18.3, 11.3 to 33.4)	0.001

[a]Calculated from grouped data.
[b]Relative to baseline score.
[c]Baseline vs. follow-up examination, Wilcoxon signed-rank test.
UMSARS, Unified Multiple System Atrophy Rating Scale; HY, Hoehn and Yahr Parkinson's disease staging; SE ADL, Schwab and England Activities of Daily Living; SS3, Severity Scale 3.

UMSARS IV correlated significantly with relative increases of global measures of disability as shown in Table 4.

Predictors of UMSARS Progression

There were no differences in the progression of activities of daily living (ADL) as assessed by the UMSARS I scores between motor subtypes, diagnostic categories, and gender. Patients without pyramidal signs showed a significantly greater worsening of UMSARS I (mean, 51.8%; median, 32.5%; 95% CI, 28.4% to 75.2%) compared to patients with pyramidal signs (mean, 21.8%; median, 22.7%; 95% CI, 13.6% to 30.0%; $P = 0.040$). Baseline parameters that were found to correlate significantly with the deterioration of UMSARS I include disease duration ($r = -0.535$; $P < 0.0001$) and the UMSARS I ($r = -0.444$; $P = 0.001$) scores.

Rates of decline of UMSARS II scores did not differ between motor subtypes, diagnostic categories, and gender (Table 5). Patients with cerebellar features present at baseline showed a significantly greater increase of UMSARS II scores compared to patients without cerebellar features (Table 5). Conversely, patients without any pyramidal signs present at baseline showed a higher progression of UMSARS II scores compared to patients with pyramidal signs (Table 5). Baseline parameters that were found to correlate significantly with motor progression as assessed by the UMSARS II include disease duration ($r = -0.334$; $P = 0.018$), the UMSARS II ($r =$

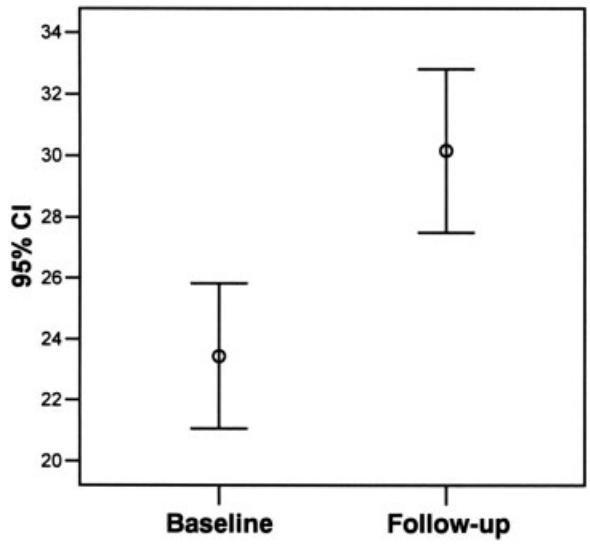

FIG. 1. Error bars showing narrow confidence intervals with no overlap of the Unified Multiple System Atrophy Rating Scale (UMSARS) I scores both at baseline and 12-month follow-up visit ($P < 0.0001$). CI, confidence interval.

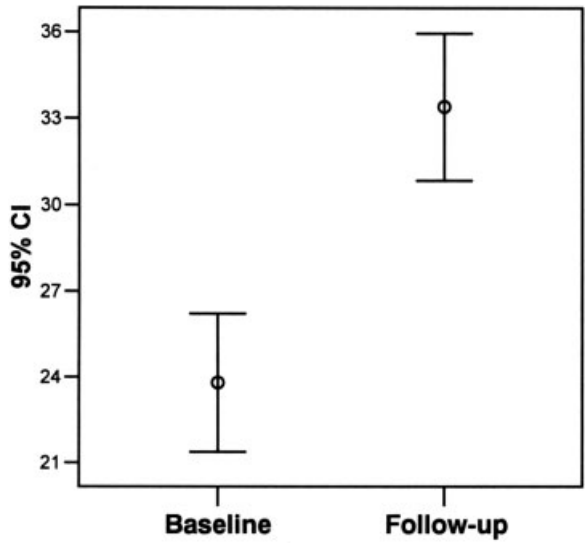

FIG. 2. Error bars showing narrow confidence intervals with no overlap of the Unified Multiple System Atrophy Rating Scale (UMSARS) II scores both at baseline and 12-month follow-up visit ($P < 0.0001$). CI, confidence interval.

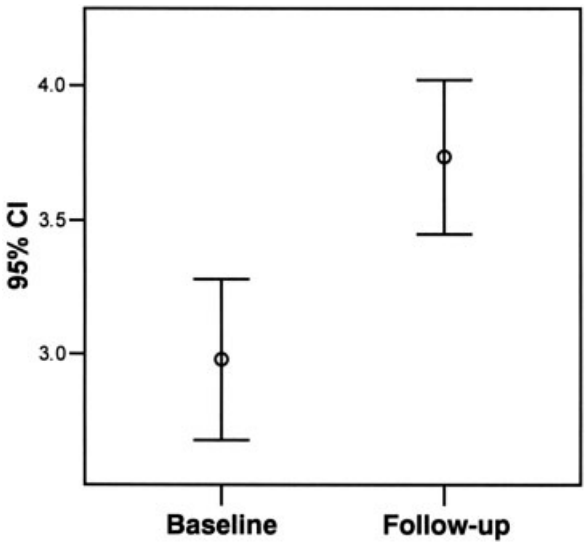

FIG. 3. Error bars showing narrow confidence intervals with no overlap of the Unified Multiple System Atrophy Rating Scale (UMSARS) IV scores both at baseline and 12-month follow-up visit ($P < 0.0001$). CI, confidence interval.

-0.574; $P < 0.0001$) as well as SS3 scores ($r = -0.324$; $P = 0.022$).

DISCUSSION

In contrast to PD, where UPDRS progression rates in treated and untreated patients have been well defined in several prospective clinical trials, there are only few data on the progression of disability in MSA.[7,9,10] The present study was planned to fill this gap by providing data on progression of disability in MSA using a variety of measures. One of the principal goals also was to investigate the sensitivity to change over time of the UMSARS—a novel scale that was generated to measure severity and progression of functional impairment in MSA.[12]

To address these issues, we prospectively followed up a cohort of 50 patients with MSA recruited into an ongoing natural history study by the EMSA SG; 84% were diagnosed as probable and 16% as possible MSA, according to the Consensus Criteria of Gilman and colleagues.[13] More than half (58%) of our study population showed the parkinsonian variant of the disease, and in the remaining patients (42%), the motor disorder was dominated by cerebellar dysfunction. This slight predominance of the parkinsonian variant compared to the cerebellar subtype in Europe is consistent with previous reports.[2,3,14] In contrast, a cerebellar presentation of MSA appears to be more common than the parkinsonian variant in Japan compared to Western countries.[8] Cardinal diagnostic features are given in Table 1. At baseline visit, after a median disease duration of 4.0 years, the median HY stage was 3.5, the median SE ADL was 56.0, and the median SS3 was 2.2. This further corroborates the notion that, compared to PD, MSA patients are more advanced in their disease within a short time period.

The short observation period of 12.3 months was sufficient to demonstrate a significant mean increase of UMSARS I of 6.7 points (median, 6.3; Table 3). This finding corresponded to a mean increase of 35.6% in relation to baseline score. Progression as measured by the UMSARS I correlated moderately with global disease progression as measured by the HY staging, SE ADL, and SS3 staging, suggesting that the UMSARS is a useful instrument to capture changes in motor and autonomic functional status. We observed a moderate inverse association between (1) disease duration as well as UMSARS I scores at baseline and (2) change in UMSARS I, suggesting that functional deterioration is more rapid in early disease stages (when there is still low impairment in activities of daily living) rather than at later time points in the course of the disease.

Within the short follow-up period of this study, there was a significant mean increase of the UMSARS II by 9.6 points (median, 7.8; Table 3). This finding corresponded to a mean increase of 57.3% in relation to baseline score. Fast progression of UMSARS II scores was associated with mild baseline disability according to UMSARS II and SS3 as well as with short disease duration. Similarly, a nonlinear progression of motor

TABLE 4. *Correlation analysis between change in UMSARS I, UMSARS II, and UMSARS IV and change in measures of global disease severity between baseline and follow-up examination relative to baseline scores*

	Change HY		Change SE ADL		Change SS3	
	r[a]	*P*	r[a]	*P*	r[a]	*P*
Change UMSARS I	0.440	<0.01	−0.420	<0.01	0.334	<0.05
Change UMSARS II	0.485	<0.001	−0.400	<0.01	0.444	<0.001
Change UMSARS IV	0.476	<0.001	−0.410	<0.01	0.527	<0.001

[a]Spearman's rank correlation coefficients.

UMSARS, Unified Multiple System Atrophy Rating Scale; HY, Hoehn and Yahr Parkinson's disease staging; SE ADL, Schwab and England Activities of Daily Living; SS3, Severity Scale 3.

TABLE 5. *Baseline factors and change of UMSARS II in 50 MSA patients*

Baseline factor	Mean UMSARS II change between baseline and follow-up evaluation (median; 95% CI)[a]	P[b]
Motor subtype		n.s.
MSA-P (n = 29)	48.7 (28.6; 31.6 to 65.7)	
MSA-C (n = 21)	69.2 (40.7; 16.3 to 122.1)	
Diagnostic category		n.s.
Possible MSA (n = 8)	40.9 (19.1; −3.9 to 85.8)	
Probable MSA (n = 42)	60.4 (38.4; 33.3 to 87.5)	
Gender		n.s.
Male (n = 26)	71.6 (47.4; 29.0 to 114.1)	
Female (n = 24)	41.8 (29.5; 23.5 to 60.1)	
Cerebellar signs		0.020
Present (n = 39)	67.6 (47.4; 38.4 to 96.8)	
Absent (n = 11)	20.8 (17.1; 7.3 to 34.3)	
Corticospinal tract signs		0.007
Present (n = 27)	32.0 (25.0; 19.2 to 44.8)	
Absent (n = 23)	86.9 (56.5; 39.3 to 134.6)	

Medians are calculated from grouped data.
[a]Relative to baseline score.
[b]Mann–Whitney *U*-test.
n.s., not significant; UMSARS, Unified Multiple System Atrophy Rating Scale; MSA, multiple system atrophy; MSA-P, multiple system atrophy, parkinsonian type; MSA-C, multiple system atrophy, cerebellar type; CI, confidence interval.

decline has been reported in PD with a faster progression early in the disease when disability is still mild.[15–18] However, an extended follow-up period is required to further substantiate nonlinear progression rates in MSA. Annual UMSARS progression rates of close to 60% as shown in our study would represent approximately an at least threefold or even greater increase compared to published annual UPDRS Motor score decline rates in PD.[15,17,19–23] Our progression data are consistent with a previous retrospective clinicopathological study on 81 patients with Parkinsonism showing faster rates of HY progression in MSA (and other atypical parkinsonian disorders, APD) compared to PD. However, the progression to each HY stage was unhelpful in distinguishing the APDs from each other.[7] We observed an average increase of the HY stage of 0.5 points during this short time period. Progression as measured by the UMSARS II correlated significantly with progression as measured by the HY staging, SE ADL, and SS3, suggesting that UMSARS II is able to capture deterioration of motor disability sensitively. The annual progression rate of the motor disorder in our study is even faster than that reported in a recent prospective study by Seppi and Colleagues on MSA-P patients using the UPDRS III, which showed an average increase by 10.8 points, corresponding to an annual increase of 28.6% in relation to baseline score.[10] Natural history studies focusing on the cerebellar presentation of MSA have also shown fast motor progression, suggesting that the natural history of MSA-C and MSA-P is comparable.[8,9] In fact, in a retrospective study comparing disease progression in different types of degenerative ataxia, including 67 patients with MSA (MSA-P, 35.8%; MSA-C, 64.2%) and 399 patients with hereditary ataxias, disease progression was fastest in MSA; intermediate in Friedreich's ataxia, autosomal dominant cerebellar ataxia type I, and autosomal dominant cerebellar ataxia type III; and slowest in early onset cerebellar ataxia.[9] In MSA patients, the median latency to loss of independent gait was 3 years, to confinement to wheelchair 6 years, and to death 9 years. Although our data and the above-mentioned studies by Müller and associates[7] or Klockgether and coworkers[9] are derived from differing study designs, these sets of data clearly show that there is rapid progression of disability in patients with MSA. The same holds true for a large study on 230 Japanese patients[8] (MSA-P, 32.6%; MSA-C, 67.4%), showing that median intervals from onset to aid-requiring walking, confinement to a wheelchair, a bedridden state, and death were 3, 5, 8, and 9 years, respectively.

Within the short follow-up period of this study, there was a significant mean increase of the UMSARS IV by 0.8 points (median: 0.7) corresponding to a mean increase of 33.3% relative to the baseline score (Table 3). A significant correlation between (1) the deterioration in the global disability scale UMSARS IV, and (2) the increase in HY staging, SE ADL, and SS3 staging was present, suggesting that the UMSARS IV is a sensitive scale for measuring global disease severity.

In the large study conducted in Japan, MSA-P patients had a more rapid functional deterioration than MSA-C patients but showed similar survival.[8] In contrast, no differences in the progression rates between the motor subtypes in the UMSARS I, UMSARS II, and UMSARS IV scores were present in our study cohort. Consistent with our data, gender was not associated with faster worsening of motor disability in the Japanese study by Watanabe and colleagues[8] and the more recent smaller European study on MSA-P patients by Seppi and associates.[10] However, we observed that patients with any cerebellar symptoms present at baseline showed a significantly greater increase of the UMSARS II (by 67.6% in relation to baseline score) compared with patients without (by 20.8%). Conversely, patients with pyramidal signs at baseline showed a slower progression of UMSARS II (by 32.0%) compared to patients without pyramidal signs (by 86.9% relative to baseline scores). Lack of pyramidal signs was also associated with faster worsening of UMSARS I (51.8 vs. 21.8%). Taken together, these findings suggest that progression in MSA is not uniform but depends on the presence or absence of distinct core features. However, in the study on the progression of MSA using the UPDRS, motor progression was unrelated to the presence of additional cerebellar symptoms and pyramidal signs at baseline.[10] This difference may be partly due to the fact that the UPDRS III captures parkinsonian motor impairment only. Although the UPDRS has hitherto been the instrument used to measure motor disability in MSA,[24–27] it does not accurately reflect the complex motor presentation of MSA with a combined cerebellar and parkinsonian motor impairment occurring in most patients.[28]

We evaluated patients on regular therapy, and it might be argued that the assessment of the parkinsonian syndrome may be affected by alterations of the symptomatic therapy. However, less than half of patients were treated with levodopa, and there were no significant changes in standard L-dopa dose between baseline and follow-up examination (data not shown).

Our observational or exploratory study has some limitations. First, the patients in our study were all drawn from specialty clinics and were considered to have MSA based on clinical criteria over a relatively short period of observation. It is possible that a community-based sample of MSA patients might have shown different rates of disease progression. Because patients coming to clinical attention represent a nonrandom fraction of those affected with MSA, it is important to replicate our findings in population-based studies. On the other hand, our sample is well suited for estimates of progression in patients likely to be enrolled in outpatient clinical trials at specialty clinics. Second, patients with milder disease may have been underrepresented in our study, because they did not meet the formal stringent diagnostic criteria. This finding may create additional bias, as patients with advanced MSA progress less rapidly to each motor disability milestone and to death according to the study by Watanabe and coworkers.[8] Furthermore, misdiagnosis in some of the clinically diagnosed patients cannot be excluded in the absence of postmortem verification.[29]

Despite these limitations, this report is the first study to demonstrate a rapid deterioration of the motor disorder, impairment in activities of daily living, and global disability in MSA using the UMSARS. This observational study further corroborates—irrespective of motor subtypes, diagnostic category and gender—the rapidly progressive nature of MSA, in particular in patients with early disease and mild disability at baseline. The presence of cerebellar signs seems to be associated with a faster worsening of UMSARS II, and the lack of pyramidal signs with a faster worsening of UMSARS I, and UMSARS II. Furthermore, the correlation of (1) progression as measured by scales of global disease severity including HY staging, SE ADL, and SS3 with (2) deterioration in the UMSARS I, UMSARS II, and UMSARS IV suggests that the UMSARS is a useful and sensitive tool to determine functional deterioration over time in MSA. These data, enabling sample size calculations, will facilitate the planning and implementation of future neuroprotective interventional trials.

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APPENDIX

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