



The natural history of multiple system atrophy: a prospective European cohort study

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Summary

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Background Multiple system atrophy (MSA) is a fatal and still poorly understood degenerative movement disorder that is characterised by autonomic failure, cerebellar ataxia, and parkinsonism in various combinations. Here we present the final analysis of a prospective multicentre study by the European MSA Study Group to investigate the natural history of MSA.

Methods Patients with a clinical diagnosis of MSA were recruited and followed up clinically for 2 years. Vital status was ascertained 2 years after study completion. Disease progression was assessed using the unified MSA rating scale (UMSARS), a disease-specific questionnaire that enables the semiquantitative rating of autonomic and motor impairment in patients with MSA. Additional rating methods were applied to grade global disease severity, autonomic symptoms, and quality of life. Survival was calculated using a Kaplan-Meier analysis and predictors were identified in a Cox regression model. Group differences were analysed by parametric tests and non-parametric tests as appropriate. Sample size estimates were calculated using a paired two-group *t* test.

Findings 141 patients with moderately severe disease fulfilled the consensus criteria for MSA. Mean age at symptom onset was 56·2 (SD 8·4) years. Median survival from symptom onset as determined by Kaplan-Meier analysis was 9·8 years (95% CI 8·1–11·4). The parkinsonian variant of MSA (hazard ratio [HR] 2·08, 95% CI 1·09–3·97; *p*=0·026) and incomplete bladder emptying (HR 2·10, 1·02–4·30; *p*=0·044) predicted shorter survival. 24-month progression rates of UMSARS activities of daily living, motor examination, and total scores were 49% (9·4 [SD 5·9]), 74% (12·9 [8·5]), and 57% (21·9 [11·9]), respectively, relative to baseline scores. Autonomic symptom scores progressed throughout the follow-up. Shorter symptom duration at baseline (OR 0·68, 0·5–0·9; *p*=0·006) and absent levodopa response (OR 3·4, 1·1–10·2; *p*=0·03) predicted rapid UMSARS progression. Sample size estimation showed that an interventional trial with 258 patients (129 per group) would be able to detect a 30% effect size in 1-year UMSARS motor examination decline rates at 80% power.

Interpretation Our prospective dataset provides new insights into the evolution of MSA based on a follow-up period that exceeds that of previous studies. It also represents a useful resource for patient counselling and planning of multicentre trials.

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Introduction

Multiple system atrophy (MSA) is a rare but distinctive and fatal α -synucleinopathy characterised by autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal signs in various combinations. These symptoms are the result of overlapping pathologies including striatonigral, olivopontocerebellar, and central autonomic degeneration.^{1,2} Two phenotypes can be distinguished clinically by the predominant motor symptom: the parkinsonian variant (MSA-P) and the cerebellar variant (MSA-C).³ However, autonomic features can predate motor impairment.^{4,5} Premotor MSA is increasingly recognised as a cluster of symptoms including not only progressive autonomic failure, but also sleep disorders such as rapid

eye movement sleep behaviour disorder, central sleep apnoea, and stridor.⁶

With two exceptions that we are aware of,^{7–9} the natural history of MSA has been addressed only in single-centre clinical studies.^{10,11} Additionally, disease progression and prognostic predictors have been investigated in retrospective clinicopathological series.^{4,12–16} These studies found shorter survival in patients with early autonomic failure^{13,15} and a more pronounced functional deterioration in patients with MSA-P than in patients with MSA-C.¹⁵ Rates of functional decline and their determinants were not established using validated disease-specific rating scales.^{4,12–16} Recognising this unmet need, a consortium of dedicated MSA research

groups (European MSA Study Group [EMSA-SG]) established a large patient registry,¹⁷ developed and validated an MSA-specific rating scale (unified MSA rating scale [UMSARS]),¹⁸ and launched a large prospective natural history study with 2 years of follow-up. With this study we aimed to address the following objectives: to determine prospectively clinical predictors of disease progression; to validate the disease-specific UMSARS¹⁸ longitudinally, thereby deriving rates of decline; to facilitate counselling of patients about disease stage (early or advanced disease) and milestones (such as falls or dysphagia); and to promote basic-research driven^{19–22} clinical trial activity^{23,24} within EMSA-SG or other related networks. Preliminary results in 50 patients were previously reported.²⁵ Here we present the final results of the full analysis.

Methods

Study design and patients

15 EMSA-SG centres participated in this prospective natural history study. Recruitment lasted from January, 2003, to July, 2004. Study duration was 2 years with a follow-up every 6 months. Additionally, a vital status survey was done 2 years after the end of the study. Survival and UMSARS decline rates were predefined primary outcome measures. In a post-hoc analysis of UMSARS items, important preterminal clinical milestones as suggested by O'Sullivan and colleagues¹³ were probed. The study was approved by local ethics committees, and written informed consent was obtained from each patient.

All patients were interviewed and examined by board-certified neurologists from the study group who had experience in movement disorders; patients with a clinical diagnosis of MSA as judged by these neurologists were enrolled in the present study. The following features were considered as exclusion criteria: onset under 30 years of age, family history of a movement disorder, secondary cause of parkinsonism (by history or investigation), prominent slowing of vertical saccades, vertical supranuclear palsy (downward or upward gaze palsy), aphasia, alien limb syndrome, parietal dysfunction, generalised areflexia, and any condition which would make the patient, in the opinion of the treating investigator, unsuitable for an MSA natural history study. However, reasons to refrain from recruitment were not recorded systematically. The initial consensus criteria³ were subsequently applied to confine the analysed cohort to patients with MSA. At each study visit the EMSA-SG minimal dataset²⁶ was used to document basic clinical features and diagnostic procedures as well as the current medication. Moreover, validated rating instruments were applied during the follow-up examination by the investigator, patient, or caregiver, as appropriate. Causes of death, MRI findings, and results from post-mortem examinations were not systematically recorded.

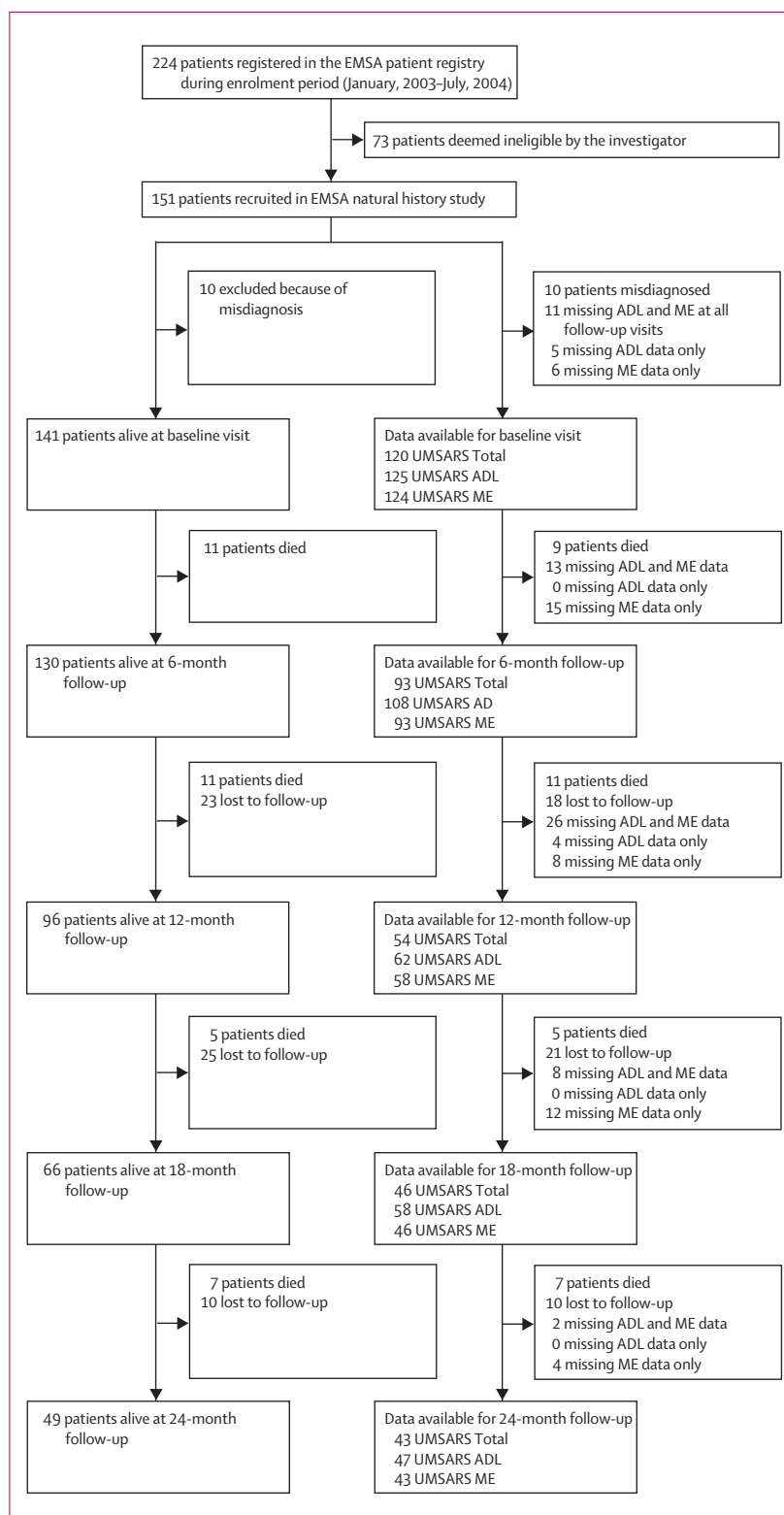


Figure 1: Study flow diagram

Data refer to non-interpolated case numbers. Thus, patients who had incomplete data at one assessment could be included again later. EMSA=European MSA Study Group. ADL=activities of daily living. ME=motor examination. UMSARS=unified MSA rating scale.

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See Online for appendix

Symptom onset was defined as the initial presentation of any motor symptom (ie, parkinsonism or cerebellar ataxia) or selected autonomic features including orthostatic hypotension or neurogenic bladder disturbances (urge incontinence and incomplete bladder emptying). Absent levodopa response was defined as no clinical improvement on chronic treatment as judged by the treating investigator.

Rating scales

Overall disease severity was assessed by the Hoehn and Yahr Parkinson's disease staging scheme (range 1–5, with higher scores indicating greater impairment),²⁷ the Schwab and England activities of daily living scale (range 0–100, with lower scores reflecting greater disease burden),²⁸ and a three-point global disability scale (mild, moderate, severe).¹⁸ We assessed severity of clinical features using a disease specific rating scale (total UMSARS, with scores ranging from 0 to 104; higher scores indicate greater impairment) that includes

autonomic symptoms (questions 9–12 of the UMSARS activities of daily living subscale [range 0–16]) and motor symptoms (questions 1–8 of the UMSARS activities of daily living subscale [range 0–32] and the UMSARS motor examination subscale, range 0–56), as well as their effect on activities of daily life (UMSARS activities of daily living subscale, range 0–48). Probability of clinical milestone events was estimated in a post-hoc analysis of UMSARS items 2 (swallowing) and 8 (falling) of the activities of daily living subscale and items 2 (speech) and

	Overall	MSA-P	MSA-C	p
N (%)	141 (100)	87 (61.7)	54 (38.3)	
Diagnostic certainty				0.351
Possible, n (%)	32 (22.7)	22 (25.3)	10 (18.5)	
Probable, n (%)	109 (77.3)	65 (74.7)	44 (81.5)	
Sex				0.929
Women, n (%)	62 (44)	38 (44)	24 (44)	
Men, n (%)	79 (56)	49 (56)	30 (56)	
Age				
Study entry, years (mean [SD])	62.1 (7.7)	62.6 (8.2)	61.3 (7.1)	0.367
Symptom onset, years (mean [SD])	56.2 (8.4)	56.8 (9.0)	55.4 (7.4)	0.378
Duration of symptoms at entry, years (mean [SD])	5.5 (3.8)	5.1 (3.7)	6.1 (3.9)	0.134
Global disability scale (mean [SD])	2.3 (0.7)	2.3 (0.7)	2.2 (0.7)	0.388
Mild, n (%)	17 (12.1)	9 (10.3)	8 (14.8)	
Moderate, n (%)	60 (42.6)	33 (37.9)	27 (50)	
Severe, n (%)	48 (34.0)	30 (34.5)	18 (33.3)	
Missing values, n (%)	16 (11.3)	15 (17.2)	1 (1.9)	
Schwab and England activities of daily living (mean [SD])	48.9 (22.1)	46.0 (22.2)	52.8 (21.5)	0.088
Hoehn and Yahr (mean [SD])	3.7 (1.0)	3.7 (0.9)	3.8 (1.1)	0.431
Stage 0, n (%)	1 (0.7)	0 (0)	1 (1.9)	
Stage 1, n (%)	2 (1.4)	0 (0)	2 (3.7)	
Stage 2, n (%)	6 (4.3)	6 (6.9)	0 (0)	
Stage 3, n (%)	46 (32.6)	30 (34.5)	16 (29.6)	
Stage 4, n (%)	41 (29.1)	21 (24.1)	20 (37.0)	
Stage 5, n (%)	32 (22.7)	19 (21.8)	13 (24.1)	
Missing values, n (%)	13 (9.2)	11 (12.6)	2 (3.7)	

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	Overall	MSA-P	MSA-C	p
(Continued from previous page)				
Autonomic failure, n (%)	136 (96.5)	84 (96.6)	52 (96.3)	0.936
Urinary incontinence, n (%)	103 (73.0)	66 (75.9)	37 (68.5)	0.241
Orthostatic hypotension, n (%)	80 (56.7)	51 (58.6)	29 (53.7)	0.341
Incomplete bladder emptying, n (%)	72 (51.1)	49 (56.3)	23 (42.6)	0.538
Constipation, n (%)	82 (58.2)	52 (59.8)	30 (55.6)	0.145
Parkinsonism, n (%)	128 (90.8)	87 (100.0)	41 (75.9)	0.0001
Bradykinesia, n (%)	128 (90.8)	87 (100.0)	41 (75.9)	0.0002
Rigidity, n (%)	117 (83.0)	88 (100.0)	30 (55.6)	<0.0001
Postural instability, n (%)	115 (81.6)	75 (86.2)	40 (74.1)	0.607
Postural tremor, n (%)	79 (56.0)	55 (63.2)	24 (44.4)	0.090
Rest tremor, n (%)	50 (35.5)	35 (40.2)	15 (27.8)	0.243
Gait freezing, n (%)	56 (39.7)	45 (51.7)	11 (20.4)	<0.0001
Levodopa treatment				<0.0001
Yes, n (%)	91 (64.5)	71 (81.6)	20 (37.0)	
No, n (%)	44 (31.2)	12 (13.8)	32 (59.3)	
Unknown, n (%)	6 (4.3)	4 (4.6)	2 (3.7)	
Dopamine agonist treatment				0.012
Yes, n (%)	31 (22.0)	24 (27.6)	7 (13.0)	
No, n (%)	91 (64.5)	47 (54.0)	44 (81.5)	
Unknown, n (%)	19 (13.5)	16 (18.4)	3 (5.6)	
Levodopa response				0.086
Beneficial response, n (%)	44 (31.2)	37 (42.5)	7 (13.0)	
Response duration, years (mean [SD])	3.5 (2.7)	3.5 (2.7)	3.3 (2.7)	0.908
Cerebellar symptoms, n (%)	101 (71.6)	47 (54.0)	54 (100.0)	<0.0001
Gait ataxia, n (%)	87 (61.7)	35 (40.2)	52 (96.3)	<0.0001
Limb ataxia, n (%)	79 (56.0)	31 (35.6)	48 (88.9)	<0.0001
Ataxic dysarthria, n (%)	77 (54.6)	29 (33.3)	48 (88.9)	<0.0001
Pyramidal involvement, n (%)	70 (49.6)	39 (44.8)	31 (57.4)	0.146
Babinski sign, n (%)	38 (27.0)	21 (24.1)	17 (31.5)	0.274
Hyper-reflexia, n (%)	58 (41.1)	31 (35.6)	27 (50.0)	0.076
Dystonia, n (%)	43 (30.5)	28 (32.2)	15 (27.8)	0.403

Table 1: Population characteristics at baseline

14 (gait) of the motor examination subscale. Health-related quality of life was assessed by the medical study short form (SF-36)²⁹ and the five-dimensional EuroQoL (EQ-5D).³⁰

Autonomic failure was assessed with the composite autonomic symptom scale (COMPASS)³¹ as well as the COMPASS change scale³¹ in a sub-protocol of the present study that was done in five EMSA-SG sites. The 6-month data for COMPASS decline rates have partly been published elsewhere.³² Here, we present the 24-month follow-up data.

Statistical analysis

Hardcopies of case report forms were returned to the study secretariat to ensure data quality. Any shortcoming was subsequently discussed by investigators through email conversations, telephone calls, and at annual EMSA-SG meetings. Data were entered into an ACCESS Database (Microsoft, Redmond, WA, USA) and analysed with SPSS 19.0 (SPSS, Chicago, IL, USA). Statistical analysis of disease progression was done for all patients for whom data for two UMSARS motor examination and activities of daily life assessments were available. Missing values of the two UMSARS subscales during the follow-up were estimated using linear interpolation of neighbouring measurements. Missing values of baseline and ultimate measurements in patients known to be alive were analogously extrapolated by using two succeeding or preceding measurements. The final rating score was calculated as sum of the two UMSARS subscale measurements per patient.

To validate the interpolation approach we undertook two sensitivity analyses. First, we did a complete-case per-protocol analysis to validate the results received by the linear interpolation procedure, and we compared observed (non-missing) and imputed values at each timepoint with the *t* test. Cases with missing observations, where the missing-at-random assumption came into question, were reviewed manually. Second, we estimated missing values of potential predicting variables for MSA progression using a fully conditional specification³³ multiple imputation procedure assuming that those values were missing at random. The fully conditional specification procedure first substituted missing data of potential predictors by plausible values using an iterative stochastic algorithm, which results in ten multiple complemented replications of the original dataset. These datasets were then separately analysed with a logistic-regression model to obtain the estimates of interest. The estimates from these imputed datasets are then combined (pooled) into one overall estimate and variance, and then compared with the original dataset.

Progression of scores was defined as mean difference between baseline and follow-up values. Annualised slopes of change were presented as comparison of baseline values and the last follow-up examination

available and expressed as score change per year. The following formula was used:

$$\text{Score progression per year} = \frac{(\text{score follow-up} - \text{score baseline})}{(\text{date follow-up in months} - \text{date baseline in months}) * 12}$$

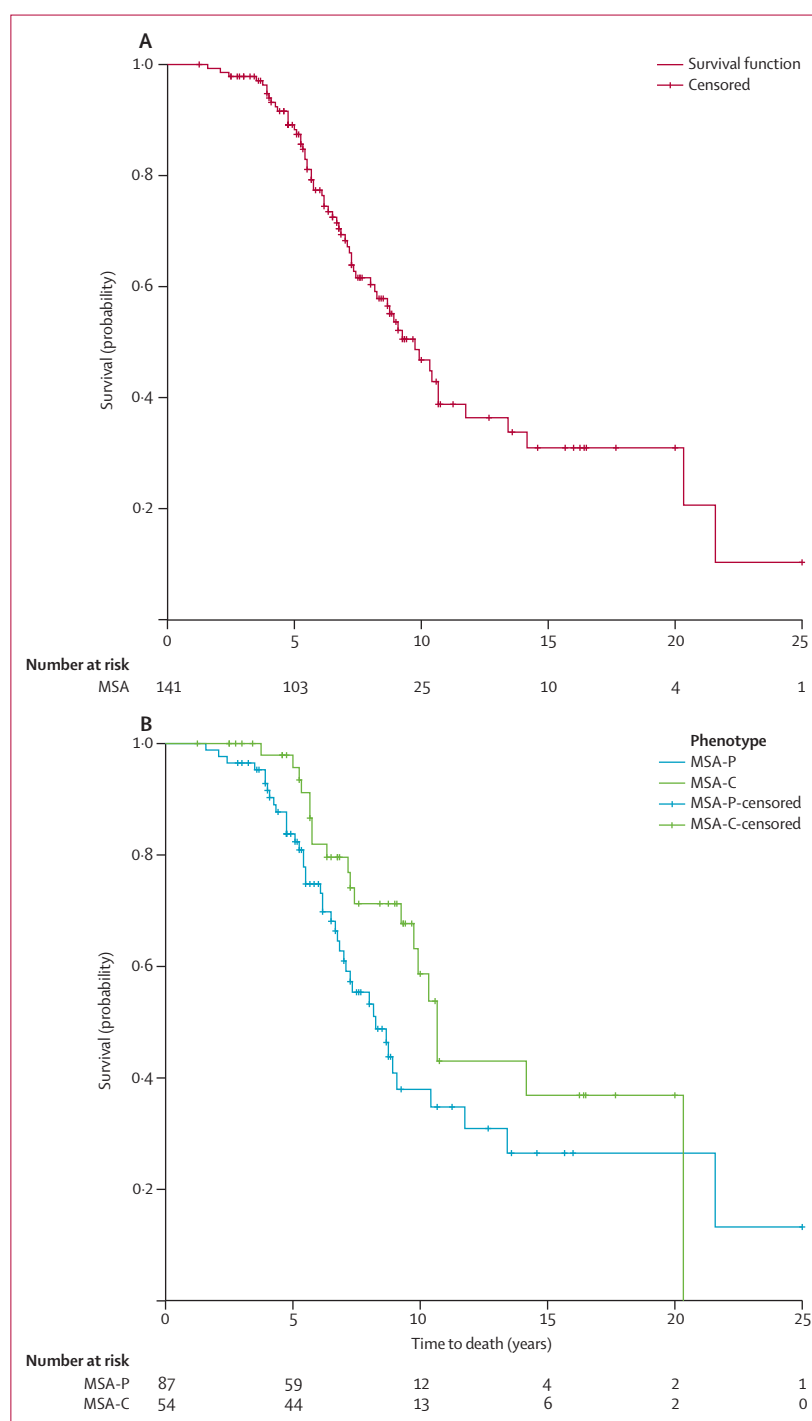


Figure 2: Kaplan-Meier survival plot
Overall survival analysis from symptom onset (A). Survival analysis stratified by phenotype (B).

Gaussian distribution was confirmed by visual analysis of the Q-Q plots and the Kolmogorov–Smirnov test. With respect to the two distinct motor variants, two subgroups were formed. Time effects were analysed by repeated measures ANOVA. Group differences of normally distributed data were analysed by parametric tests (repeated measures ANOVA or Student's *t* test as applicable), non-Gaussian distributed variables by non-parametric tests (Kruskal–Wallis one-way ANOVA by ranks or Mann–Whitney U test as applicable), and distributional differences by the Pearson's χ^2 test for independence. Logistic regression analysis was used to determine predictors of fast or slow motor progression. Consistent with Seppi and colleagues,¹⁰ the cutoff point between fast and slow progression was defined by the median value of annualised progression rates.

Survival from symptom onset was calculated using Kaplan–Meier analysis; covariates were compared with the log-rank test and Cox regression analysis. To reduce the number of censored observations, we surveyed vital status 24 months after study end. Patients lost to follow-up were censored at the last known date alive.

Clinical milestones of preterminal disease that were derived from previous clinicopathological studies¹³ were analysed by retrospective analysis of the UMSARS questionnaires. Each of the four clinical milestones were modelled as binary response variables during different time intervals (symptom onset to baseline visit, during first year of follow-up, and during second year of follow-up) applying a complementary log-log link function to estimate the probability of experiencing one of them.³⁴ Events were defined as progression to the maximum score in the four UMSARS items (feeding by nasogastric tube or gastrostomy because of severe dysphagia, falls at least once a day, unintelligible speech, and the inability to walk).

Sample size estimates were done using two-group *t* test, accepting a two-sided type one error of 5%. The significance level was set at $p < 0.05$.

Role of the funding source

Funds from the European Union supported the development of the study design, study conduct (patient recruitment, study visits), database development, and data collection. The Oesterreichische Nationalbank and

Austrian Science Fund supported data analysis, data interpretation, and drafting of the manuscript. The sponsors had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

151 consecutive eligible patients were initially recruited at the participating centres (figure 1). During the study period, the clinical diagnosis was revised in five cases, and further efforts to retrieve survival information in the post-study survival survey revealed another five misdiagnosed patients. These patients were reclassified during follow-up on the basis of changes in their clinical presentation. 79 (56%) of the remaining 141 patients were men and 62 (44%) were women. Mean age at symptom onset was 56.2 (SD 8.4) years; mean duration of symptoms at baseline was 5.5 (SD 3.8) years (table 1). These findings were not significantly different between MSA-C and MSA-P patients. According to consensus criteria,³ 62% of the patients were classified as having MSA-P and 38% as having MSA-C. 32 patients (23%) fulfilled criteria for possible MSA (possible MSA-P 25%, possible MSA-C 19%) and 109 (77%) for probable MSA (probable MSA-P 75%, probable MSA-C 81%) according to the initial consensus criteria.³ Degree of diagnostic certainty did not differ between MSA-P and MSA-C ($p = 0.351$). There were no sex differences between the two motor presentations ($p = 0.929$).

47 (54%) patients with MSA-P had cerebellar symptoms, and 41 (76%) patients with MSA-C frequently showed parkinsonism. Symptoms of autonomic failure were present in most of the patients studied (136 [96%]). Urinary symptoms (124 patients [88%]) including urinary incontinence (103 [73%]) and incomplete bladder emptying (72 [51%]) combined were more common than orthostatic hypotension (80 [57%]). Irregular postural tremor of the outstretched arms was more common than resting tremor (56% vs 35%). A beneficial response to levodopa was reported in 31% lasting for a mean period of 3.5 years. Some of the patients with a beneficial levodopa response (44 patients, table 1) had motor complications, with

	From symptom onset to baseline visit		During first year of follow-up		During second year of follow-up	
	Number of events/ patients at risk	Estimated probability (95% CI) of an event*	Number of events/ patients at risk	Estimated probability (95% CI) of an event*	Number of events/ patients at risk	Estimated probability (95% CI) of an event*
Falls at least once a day	34/105	23% (13.3–40.0%)†	11/42	21% (10.7–40.2%)†	8/16	45% (20.4–98.4%)‡
Feeding by nasogastric tube or gastrostomy	3/83	3% (0.7–12.9%)†	7/51	13% (4.5–38.0%)§	2/29	6% (1.4–30.0%)¶
Unintelligible speech	12/117	7% (3.2–15.9%)†	11/59	13% (6.0–28.7%)†	5/26	15% (5.3–39.9%)§
Wheelchair dependency	17/123	9% (4.3–18.4%)†	11/59	13% (6.3–28.3%)†	5/25	14% (5.2–37.9%)

*Estimated probabilities of an event fitted by an interval-censored survival model applying a complementary log-log link function. p values are Wald- χ^2 . † $p < 0.0001$. ‡ $p = 0.046$. § $p = 0.0002$. ¶ $p = 0.0005$. || $p = 0.0001$.

Table 2: Estimated probability of clinical milestones

wearing-off fluctuations (ten patients [23%]) and off-dystonia (nine [20%]) being the most common. On-off motor fluctuations (six patients [14%]) and peak-dose dyskinesias (five [11%]) were less frequently present. Further baseline characteristics of the study population are shown in table 1. Dynamics of characteristic motor features throughout the study period are listed in the appendix.

During the study period, including a stand-alone vital status survey 2 years after study end, we recorded 61 deaths in the study population of 141 patients. Neuropathological assessment confirmed the clinical diagnosis in two patients who underwent post-mortem verification. Overall, median survival from symptom onset as determined by Kaplan-Meier analysis was 9.8 years (95% CI 8.1–11.4). Univariable regression analysis adjusted for sex and age at symptom onset identified a diagnosis of MSA-P (hazard ratio [HR] 1.84, 95% CI 1.05–3.25, $p=0.034$), presence of urinary incontinence (2.45, 1.19–5.04, $p=0.015$), presence of incomplete bladder emptying (2.16, 1.08–4.34, $p=0.030$), presence of pyramidal signs (1.60, 0.92–2.79, $p=0.099$), presence of hyper-reflexia (2.62, 0.94–2.81, $p=0.085$), and higher baseline scores for the UMSARS activities of daily living subscale (1.04, 1.01–1.07, $p=0.021$) as predictors of shorter survival at $p<0.1$ (the cutoff criterion). Hyper-reflexia was excluded because of colinearity with pyramidal signs. All parameters with a $p<0.1$ in the univariable regression analysis were entered in a Cox regression model adjusted for age at symptom onset and sex, which identified a diagnosis of MSA-P (HR 2.08, 95% CI 1.09–3.97, $p=0.026$, figure 2) and the presence of incomplete bladder emptying (2.10, 1.02–4.30, $p=0.044$) as the strongest predictors of shorter survival.

An interval-censored survival model was applied to patients with milestone events (complete loss of function) at the beginning or during the study period. The estimated probabilities of clinical milestone events including falls at least once a day, wheelchair dependency, nasogastric tube placement or gastrostomy, and unintelligible speech are shown in table 2.

Progression rates are shown in table 3 and figure 3. First year progression rate for the UMSARS activities of daily living subscale was 32.3% (mean 6.5 points [SD 6.0]) and for the motor examination subscale was 44.9% (8.2 points [7.0]), relative to baseline. In the second year, we recorded attenuated UMSARS decline rates of 11.2% (2.9 points [SD 3.4]) on the activities of daily living subscale and 17.2% (5.0 points [5.4]) on the motor subscale, relative to 12-month scores. The repeated measures ANOVA involving UMSARS measurements at baseline, after 1 year, and at the end of the study yielded a significant time effect ($p<0.0001$) including a second-order term ($p=0.002$) confirming the second year attenuation. Overall 2-year progression rate for UMSARS activities of daily living, motor examination, and total scores were 49.0% (9.4 [SD 5.9]), 74.2% (12.9 [8.5]), and 57.3% (21.9 [11.9]), respectively, relative to baseline. The

sensitivity complete-case per protocol analysis (appendix) confirmed the findings of the linear interpolation analysis. Additionally, we did not find any significant differences between observed (non-missing) and imputed values at each timepoint. In a univariable binary logistic regression analysis, symptom duration at baseline (OR_{1year} [OR for each additional year since symptom onset] 0.81, 95% CI 0.71–0.93, $p=0.003$), the absence of MSA-P (OR 0.51, 0.24–1.08, $p=0.077$), a beneficial levodopa response

	Total	Activities of daily living	Motor examination
Baseline			
N	126	127	129
Score, mean (SD)	51.2 (17)	25.2 (8.8)	25.9 (9)
Score, median	49	25	25
95% CI	48.2–54.2	23.7–26.8	24.3–27.5
6-month follow-up			
N	103	111	105
Score, mean (SD)	59.3 (17.7)	28.4 (8.9)	30.6 (9.5)
Score, median	59	28	29
95% CI	55.8–62.8	26.7–30	28.8–32.5
Score difference, mean (SD)	9.2 (8.9)	3.9 (4.6)	5.3 (5.6)
Score difference, median	8	4	4
95% CI	7.5–11	3–4.8	4.2–6.4
Mean percent change	22%	19.1%	28.2%
12-month follow-up			
N	85	87	87
Score, mean (SD)	64.7 (18.8)	30.9 (9.5)	33.7 (10)
Score, median	64	31	33
95% CI	60.6–68.7	28.9–32.9	31.6–35.8
Score difference, mean (SD)	14.6 (11.8)	6.5 (6)	8.2 (7)
Score difference, median	12.5	5.5	7
95% CI	12.1–17.2	5.2–7.8	6.7–9.7
Mean percent change	36.4%	32.3%	44.9%
18-month follow-up			
N	64	65	64
Score, mean (SD)	69.5 (17.1)	33.3 (8.4)	36.2 (9.9)
Score, median	68.5	32.3	36
95% CI	65.2–73.7	31.3–35.4	33.7–38.6
Score difference, mean (SD)	19.9 (12.2)	8.6 (5.9)	11.4 (7.7)
Score difference, median	17.5	8	10
95% CI	16.9–22.9	7.1–10.1	9.5–13.3
Mean percent change	51.2%	44.3%	63.3%
24-month follow-up			
N	49	49	49
Score, mean (SD)	69.5 (17.1)	33.3 (8.2)	36.6 (11)
Score, median	68	33	37
95% CI	64.6–74.5	31–35.7	33.4–39.7
Score difference, mean (SD)	21.9 (11.9)	9.4 (5.9)	12.9 (8.5)
Score difference, median	20	9	12
95% CI	18.5–25.3	7.7–11.1	10.5–15.3
Mean percent change	57.3%	49%	74.2%

Table 3: UMSARS score decline rates comparing follow-up versus baseline values

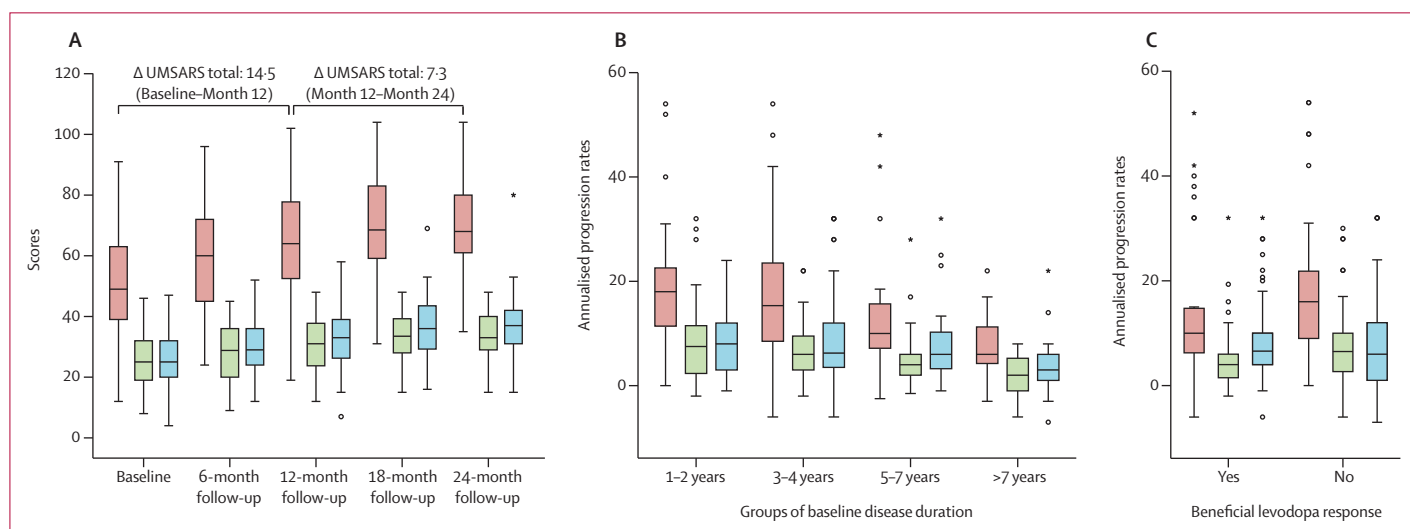


Figure 3: Unified MSA rating scale progression

Box plot of unified MSA rating scale (UMSARS) scores throughout the study period (A). Annualised progression rates stratified by categories of symptom duration (B). Annualised progression rates split by present or absent levodopa response (C). Red=UMSARS total. Green=UMSARS activities of daily living. Blue=UMSARS motor examination.

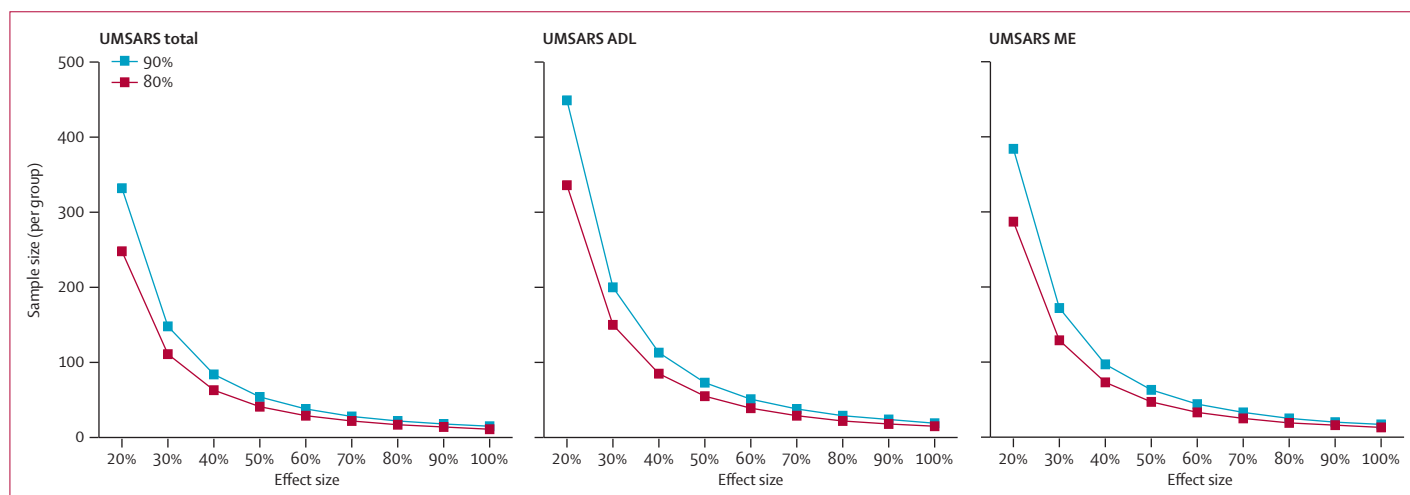


Figure 4: Sample size estimates

Required sample size per group for various effect sizes and different scores. ADL=activities of daily living. ME=motor examination.

(2.52, 1.03–6.18, $p=0.044$), and the presence of sleep disturbances (1.92, 0.91–4.09, $p=0.09$) were found to be associated with slower disease progression (annualised progression rates below the median value) at $p<0.1$.

These parameters were entered in a multivariable binary logistic regression model adjusted for UMSARS baseline score and age at symptom onset, revealing that symptom duration at baseline ($OR_{1\text{ year}} 0.68$, 95% CI 0.52–0.90, $p=0.006$) and an absent levodopa response (3.38, 1.12–10.22, $p=0.03$) were associated with rapid disease progression. Data for quality of life in patients with MSA are shown in the appendix. Subgroup analysis of 24-month follow-up data of the COMPASS change scale showed a continuous increase of self-perceived autonomic symptoms (appendix).

Required sample sizes for interventional trials with 1-year follow-up were estimated based on 12-month UMSARS total, motor examination, and activity decline rates. Estimated sample sizes per group to achieve 80% and 90% power with effect sizes ranging from 20% to 100% are shown in figure 4. For example, an interventional trial with 258 patients (129 per group) would be able to detect a 30% reduction in annual UMSARS motor examination decline rates at 80% power.

Discussion

This multicentre prospective natural history study in a European cohort of MSA patients showed a reduced median survival of 9.8 years and rapid disease progression as determined by the UMSARS rating scale during an

extended 24-month follow-up period. MSA-P and urinary retention were associated with poor survival. Accelerated UMSARS progression was predicted by shorter symptom duration at baseline and an absent levodopa response.

The clinical presentation of the present series corroborates: that MSA is a progressive and fatal disorder; that MSA-P is more common than MSA-C in Europe; that the motor disorder is often mixed, with cerebellar features in MSA-P and parkinsonian features in MSA-C; that MSA-P can mimic Parkinson's disease-like features, including a sustained levodopa response and levodopa-induced motor complications such as fluctuations and peak-dose dyskinesias, which could result in invasive therapies such as fetal mesencephalic grafts³⁵ or deep brain stimulation with short-lived or absent benefit,^{36–41} and that autonomic failure is a characteristic and common feature of both MSA motor subtypes. These observations are consistent with previously published cohorts.^{4,7,15–17,42} However, most of these studies are limited by short follow-up periods and small case numbers.

The amount of progression is below the previously published intermediate analysis in a smaller subset of the present cohort.²⁵ However, the present progression rates exceed previous observations by May and colleagues,⁹ who reported an increase of 17.2% within 12 months of follow-up, by roughly two-fold. This difference could be caused by more rapid decline early in the disease in the EMSA-SG cohort, reflecting a mixed study population of possible and probable cases with more rapid loss of greater baseline function during the first year, whereas the cohort of the North American study⁹ exclusively involved probable (ie, more advanced) MSA cases. This interpretation is further supported by attenuated progression rates in the second year of follow-up of the EMSA-SG cohort. Moreover, the present UMSARS decline rates are similar in magnitude to those for the united Parkinson's disease rating scale reported by Seppi and colleagues,¹⁰ showing an annual increase of 28.3% compared with baseline. A recent publication reported clinical progression using the Parkinson plus scale.⁸ Although direct comparison of the two scales is not possible, the ratio between annual slope of change and baseline score was similar in both studies. In summary, the variation in scale decline rates is likely to reflect both disease-related and scale-related factors. The rapid deterioration as shown by the UMSARS scores in our study was also mirrored by decline rates in both the Hoehn and Yahr scale and the Schwab and England activities of daily living scale. Remarkably, systolic blood pressure drop, as measured by part III of UMSARS, did not change significantly over time (data not shown), possibly as a result of adaptations in antiorthostatic hypotension therapy that were incompletely recorded. By contrast, COMPASS change scale scores that determine subjective impairment resulting from autonomic failure including orthostatic hypotension increased during follow-up in the present study. Mismatch between the

objective presence of orthostatic hypotension and subjective impairment has long been recognised. In general, our COMPASS CSS data confirm previous studies,^{43,44} including a preliminary 6-month follow-up report from the EMSA-SG³² demonstrating that MSA represents a progressive disorder that includes both autonomic and motor domains.

Shorter duration from symptom onset at baseline and an unsatisfactory levodopa response were shown to be the strongest predictors of a rapidly progressive disease course in the present study. These findings suggest that decline is more rapid in patients with greater functional reserve at baseline.^{25,45,46}

In a previous clinicopathological study,¹³ four clinical milestones of advanced MSA were identified. In the current study, we estimated the probability of developing

Panel: Research in context

Systematic review

We searched PubMed with the following search terms [(MSA OR "multiple system atrophy") AND (progression OR survival)] for reports published before Oct 31, 2012. Only peer-reviewed, English language reports were considered. We included natural history studies reporting survival or disease progression as determined by semiquantitative rating scales. In our search we identified 11 observational studies.^{4,7–12,14–16,25}

Interpretation

The natural history of MSA is still poorly understood. Our current knowledge is limited by the study design of published work, which includes retrospective case series with incomplete recordings of clinical features and single-centre studies that are limited by case numbers and only 12-month follow-up. The only multicentre prospective study we found²⁸ used a non-specific Parkinson plus scale that included features poorly reflective of MSA. The present multicentre study is the first natural history study that analyses survival and prognostic predictors in a large homogeneous cohort of European patients with MSA. It further reports semiquantitative decline rates using UMSARS, the only validated disease-specific rating scale available. Our findings suggest that disease progression slows down in the second year of follow-up, which is important to consider when embarking on therapeutic trials. We also provide the first evidence in a prospective European MSA cohort that baseline parkinsonism and neurogenic bladder disturbance are linked to poor survival. Further, a shorter baseline symptom duration and absent levodopa response proved to be independent predictors of faster UMSARS progression. These insights have important implications for patient counselling and planning of drug trials. Finally, our prospective dataset enables sample size calculations for future interventional trials. The reported example shows that MSA trials require large cohorts that can be generated only in a multicentre set-up based on international networks such as EMSA-SG.

these milestones by retrospective analysis of selected UMSARS items and found that the likelihood of falling at least once a day increased with follow-up, particularly during the second year of follow-up. The probability of reaching the other milestones remained similar between years 1 and 2.

Previous studies indicate substantial impairment of health-related quality of life rating scales in early MSA.^{47–50} Thus far, little was known about the progression of these scales over time. As expected, EQ-5D scores were already impaired at baseline. Nonetheless, a further decline in quality of life was observed in three out of five EQ-5D dimensions including mobility, self-care, and usual activities. Comparably, SF-36 items—particularly those requiring preserved motor function—showed progression to more severe impairment (appendix). The continuous clinical deterioration, indicated by the UMSARS motor and activities of daily living scores, supports the findings of May and colleagues,⁹ who state that UMSARS could serve as a favourable and disease-specific outcome measure in interventional trials. The number of patients with MSA we estimate to be needed was substantially lower than those in the reports by May and colleagues⁹ and Payan and colleagues,⁸ highlighting differences of patient cohorts and score variabilities.

Our study has some limitations. The patients were all drawn from highly specialised outpatient clinics lacking the random distribution of prospective population-based study designs. Moreover, restriction of data analysis to patients fulfilling diagnostic criteria resulted in a selection of patients with advanced MSA; thus, mild disease stages might be under-represented in the present study. 2 years of clinical follow-up might also be too short to identify the overall progression and prognosis of MSA. Patients were assembled at a mean (SD) symptom duration of 5.5 (3.8) years, indicating that 16.7% of patients had MSA-related symptoms for over 8 years. These findings suggest that the current study should not be interpreted as an inception-type cohort study. Thus, very early deaths—those happening within a few years of symptom onset, which are likely to be the more severe cases—might be under-represented. Patients were assessed on regular therapy; consequently, treatment effects, although unlikely, cannot be excluded. In the absence of post-mortem verification, misdiagnosis in some of the clinically diagnosed patients might occur. Likewise, MRI findings and causes of death were not predefined outcomes and, thus, were not systematically recorded, restricting conclusions drawn from the latter investigations. Attrition rates were considerable in our study. This was largely caused by death occurring during the study period and the inability of patients to attend study visits, reflecting the major challenge of avoiding dropout in prospective long-term MSA trials. Consequently, progression rates could have been affected by dropout

of patients. Despite these limitations, this academically driven natural history study, involving 15 highly experienced study centres, defines the spectrum of disease courses in European patients with MSA. Our data suggest that both mild and severe forms of MSA exist. Future clinicopathological studies are needed to determine whether the neuropathological lesion distribution, load, and type differ in patients. Our study is also the first that we know of to prospectively apply UMSARS, a carefully validated rating scale, longitudinally over a period of 2 years in a large cohort. The observed clinical decline rates will facilitate planning of future interventional trials in patients with MSA.

Contributors

GKW and WP designed the study. All authors collected data and provided critical revision of manuscript. GKW, FK, KS, MK, GG, and KPP analysed the data. GKW, FK, KS, GG, KPP, and WP interpreted the data. GKW and FK did the literature search. FK was responsible for figures. GKW, FK, and MK drafted the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

KS has been on advisory boards for Novartis, GlaxoSmithKline (GSK), and Lundbeck, had consultancies with AstraZeneca and Teva, and received lecture fees from UCB, GSK, Boehringer Ingelheim, and Lundbeck. SB has been on advisory boards for Novartis, Cephalon, GSK, Lundbeck, Merz, and Allergan. PB has received honoraria from Merck Serono, Boehringer Ingelheim, and Novartis. WO has received honoraria for consultancy and for serving on scientific advisory boards, and travel support from UCB, honoraria for consultancy and lecture fees from Teva, Novartis, GSK, Boehringer Ingelheim, Orion Pharma, and Merck Serono. KME has had consultancies with Orion Pharma, Schwarz Pharma Neuroscience (UCB), Solvay Pharmaceuticals, Valeant Pharmaceuticals International, Desitin, Novartis), has been on advisory boards for Orion Pharma, Schwarz Pharma Neuroscience (UCB), Valeant Pharmaceuticals International, and Novartis, has received honoraria from Orion Pharma, Schwarz Pharma Neuroscience (UCB), Solvay Pharmaceuticals, Valeant Pharmaceuticals International, Desitin, Novartis, Boehringer Ingelheim, GlaxoSmithKline, Abbott, Meda Pharma, and Teva, and received grants from the German Ministry of Health, Pitzer foundation, and Rhon foundation. AA received honoraria from Merz, Ipsen, and TEVA pharmaceuticals. GD has received lecture fees from Orion, Lundbeck, Teva, and Pfizer, has been serving as a consultant for TEVA, has received royalties from Thieme Publishers, is a government employee, and receives funding for his research from the German Research Council, the German Ministry of Education and Health, and Medtronic. RDo is on advisory boards for Solvay, Affiris, GE Healthcare, Lilly, and Baxter, has consultancies with Octapharma, Lilly, Teva/Lundbeck, Pfizer, and Baxter, received grants from UKGM, ZLB Behring, CSL Behring, Behring-Röntgen Stiftung, Michael J Fox Foundation, Rentschler, Deutsche Parkinson Vereinigung, International Parkinson Fond, Faber Stiftung, Movement Disorder Society, Novartis, Hector-Stiftung, Alzheimer Forschung Initiative, DGSM, Lundbeck, Abbott, and Baxter, lecture fees from Boehringer Ingelheim, Novartis, Pfizer, Baxter, GSK, Lundbeck, Merz, Solvay, Eisai, Octapharma, Orion Pharma, UCB, CSL Behring, and Teva Pharma, and prepared manuscripts for Springer Verlag, Westermayer Verlag, Thieme Verlag, and Elsevier. TGA has received speaker's honoraria from Novartis, Merck-Serono, Schwarz Pharma, Boehringer Ingelheim, and Valeant Pharma, and consultancies for Cephalon and Merck-Serono. CK has received speaker's honoraria from Ipsen, UCB, Merz, and GSK, and travel grants from Ipsen and Merz Pharmaceuticals. OR has received scientific grant and consultancy fees from Abbott, Addex, Boehringer Ingelheim, Eisai, GSK, Impax Pharmaceuticals, Lundbeck, Merck Serono, Movement Disorders Society, Novartis, Oxford Biomedica, Schering-Plough, Servier, Teva Neuroscience, UCB, and XenoPort,

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