
# Unified Multiple System Atrophy Rating Scale (UMSARS)

---

Endorsed by ERN-RND: 25.09.2018

# Introduction to the European Reference Network for Rare Neurological Diseases (ERN-RND):

ERN-RND is a European Reference Network established and approved by the European Union. ERN-RND is a healthcare infrastructure which focuses on rare neurological diseases (RND). The three main pillars of ERN-RND are (i) network of experts and expertise centres, (ii) generation, pooling and dissemination of RND knowledge, and (iii) implementation of e-health to allow the expertise to travel instead of patients and families.

ERN-RND unites 32 of Europe's leading expert centres in 13 Member States and includes highly active patient organizations. Centres are located in Belgium, Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Netherlands, Poland, Slovenia, Spain and the UK.

The following disease groups are covered by ERN-RND:

- Ataxias and Hereditary Spastic Paraplegias
- Atypical Parkinsonism and genetic PD
- Dystonia, Paroxysmal Disorder and Neurodegeneration with Brain Ion Accumulation
- Frontotemporal Dementia
- Huntingtons' Disease and other Choreas
- Leukodystrophies

Specific information about the network, the expert centres and the diseases covered can be found at the networks web site www.ern-rnd.eu.

## Recommendation for clinical use:

**The European Reference Network for Rare Neurological Diseases recommends the use of the Unified Multiple System Atrophy Rating Scale (UMSARS) as best clinical practice for the assessment and rating of Multiple System Atrophy.**

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

Disclaimer:

Clinical practice guidelines, practice advisories, systematic reviews and other guidance published, endorsed or affirmed by ERN-RND are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new information may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgement of the treating provider, as the information does account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ERN-RND provided this information on an "as is" basis, and makes no warranty, expressed or implied, regarding the information. ERN-RND specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ERN-RND assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

# METHODOLOGY

The endorsement process has been performed by the Disease group for Atypical Parkinson of ERN-RND.

## Disease group for Atypical Parkinsonism and genetic PD:

**Disease group coordinators:**

Thomas Gasser[1], Wassilios Meissner[2]

**Disease group members:**

Healthcare professionals:

Alberto Albanese[3]; Norbert Brüggemann[4]; Yaroslau Compta[5]; Malgorazate Dec-Cwiek[6]; Maria Teresa Dotti[7]; Antonio Elia[8]; Antonio Federico[7]; Dusan Flisar[9]; Barbara Garavaglia[8]; Zoltan Grosz[10]; Christine Klein[4], Jiri Klempir[11]; Thomas Klockgether[12]; Thomas Klopstock[13]; Maja Kojovic[9]; Norbert Kovacs[14]; Bernhard Landwehrmeier[15]; Johannes Levin[13]; Gerrit Machetanz[1]; Maria Jose Marti[5]; Anne Pavy-Le Traon[16]; Bart Post[17]; Evžen Růžička[18]; Francesc Valldeoriola[5]; Wim Vandenberghe[19]

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

Patient representatives:
John McFarlane[20]

[1] Universitätsklinikum Tübingen, Germany; [2] CHU de Bordeaux, France; [3] IRCCS Clinical Institute Humanitas – Rozzano, Italy; [4] Universitätsklinikum Schleswig-Holstein, Germany; [5] Hospital Clínic i Provincial de Barcelona y Hospital de Sant Joan de Déu, Spain; [6] University Hospital in Krakow, Poland; [7] AOU Siena, Italy; [8] Foundation IRCCS neurological institute Carlo Besta – Milan, Italy; [9] University Medical Centre Ljubljana, Slovenia; [10] Semmelweis University, Hungary; [11] General University Hospital in Prague, Czech Republic; [12] Universitätsklinikum Bonn, Germany; [13] Klinikum der Universität München, Germany; [14] University of Pécs, Hungary; [15] Universitätsklinikum Ulm, Germany; [16] Centre Hospitalier Universitaire de Toulouse, France; [17] Stichting Katholieke Universiteit, doing business as Radboud University Medical Center Nijmegen, Netherlands; [18] Motol University Hospital, Czech Republic; [19] University Hospitals Leuven, Belgium; [20] European Polio Union

# Endorsement process:

- Mapping of used disease scales by disease group – June 2017– May 2018
- Proposal for endorsement of rating scale by ERN-RND disease group coordinators – 15/05/2018
- Discussion in ERN-RND disease group during annual meeting – 08/06/2018
- Consent on endorsement of disease scale during ERN-RND annual meeting 2018 – 08/06/2018
- Consent on endorsement by whole disease group – 25.09.2018

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

# Annex 1 – UMSA Rating Scale

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

## APPENDIX: UNIFIED MSA RATING SCALE (UMSARS)
### Part I: Historical Review

Rate the average functional situation for the past 2 weeks (unless specified) according to the patient and caregiver interview. Indicate the score that best fits with the patient status. Rate the function independently from the nature of the signs.

| | | |
|---|---|---|
| 1. Speech | | _____ |
| 0 | Not affected. | |
| 1 | Mildly affected. No difficulties being understood. | |
| 2 | Moderately affected. Sometimes (less than half of the time) asked to repeat statements. | |
| 3 | Severely affected. Frequently (more than half of the time) asked to repeat statements. | |
| 4 | Unintelligible most of the time. | |
| 2. Swallowing | | _____ |
| 0 | Normal. | |
| 1 | Mild impairment. Choking less than once a week. | |
| 2 | Moderate impairment. Occasional food aspiration with choking more than once a week. | |
| 3 | Marked impairment. Frequent food aspiration. | |
| 4 | Nasogastric tube or gastrostomy feeding. | |
| 3. Handwriting | | _____ |
| 0 | Normal | |
| 1 | Mildly impaired, all words are legible. | |
| 2 | Moderately impaired, up to half of the words are not legible. | |
| 3 | Markedly impaired, the majority of words are not legible. | |
| 4 | Unable to write. | |
| 4. Cutting food and handling utensils | | _____ |
| 0 | Normal. | |
| 1 | Somewhat slow and/or clumsy, but no help needed. | |
| 2 | Can cut most foods, although clumsy and slow; some help needed. | |
| 3 | Food must be cut by someone, but can still feed slowly. | |
| 4 | Needs to be fed. | |
| 5. Dressing | | _____ |
| 0 | Normal. | |
| 1 | Somewhat slow and/or clumsy, but no help needed. | |
| 2 | Occasional assistance with buttoning, getting arms in sleeves. | |
| 3 | Considerable help required, but can do some things alone. | |
| 4 | Completely helpless. | |
| 6. Hygiene | | _____ |
| 0 | Normal. | |
| 1 | Somewhat slow and/or clumsy, but no help needed. | |
| 2 | Needs help to shower or bathe; or very slow in hygienic care. | |
| 3 | Requires assistance for washing, brushing teeth, combing hair, using the toilet. | |
| 4 | Completely helpless. | |

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

*(Part I, continued)*

| | | |
|---|---|---|
| 7. Walking | | _____ |
| 0 | Normal. | |
| 1 | Mildly impaired. No assistance needed. No walking aid required (except for unrelated disorders). | |
| 2 | Moderately impaired. Assistance and/or walking aid needed occasionally. | |
| 3 | Severely impaired. Assistance and/or walking aid needed frequently. | |
| 4 | Cannot walk at all even with assistance. | |
| 8. Falling (rate the past month) | | _____ |
| 0 | None. | |
| 1 | Rare falling (less than once a month). | |
| 2 | Occasional falling (less than once a week). | |
| 3 | Falls more than once a week. | |
| 4 | Falls at least once a day (if the patient cannot walk at all, rate 4). | |
| 9. Orthostatic symptoms | | _____ |
| 0 | No orthostatic symptoms.* | |
| 1 | Orthostatic symptoms are infrequent and do not restrict activities of daily living. | |
| 2 | Frequent orthostatic symptoms developing at least once a week. Some limitation in activities of daily living. | |
| 3 | Orthostatic symptoms develop on most occasions. Able to stand $>$ 1 min on most occasions. Limitation in most of activities of daily living. | |
| 4 | Symptoms consistently develop on orthostasis. Able to stand $<$ 1 min on most occasions. Syncope/presyncope is common if patient attempts to stand. | |
| | *Syncope, dizziness, visual disturbances or neck pain, relieved on lying flat. | |
| 10. Urinary function* | | _____ |
| 0 | Normal. | |
| 1 | Urgency and/or frequency, no drug treatment required. | |
| 2 | Urgency and/or frequency, drug treatment required. | |
| 3 | Urge incontinence and/or incomplete bladder emptying needing intermittent catheterization. | |
| 4 | Incontinence needing indwelling catheter. | |
| | *Urinary symptoms should not be due to other causes. | |
| 11. Sexual function | | _____ |
| 0 | No problems. | |
| 1 | Minor impairment compared to healthy days. | |
| 2 | Moderate impairment compared to healthy days. | |
| 3 | Severe impairment compared to healthy days. | |
| 4 | No sexual activity possible. | |
| 12. Bowel function | | _____ |
| 0 | No change in pattern of bowel function from previous pattern. | |
| 1 | Occasional constipation but no medication needed. | |
| 2 | Frequent constipation requiring use of laxatives. | |
| 3 | Chronic constipation requiring use of laxatives and enemas. | |
| 4 | Cannot have a spontaneous bowel movement. | |
| **Total score Part I:** | | _____ |

**Part II: Motor Examination Scale**

Always rate the worst affected limb.

| | | |
|---|---|---|
| 1. Facial expression | | _____ |
| 0 | Normal. | |
| 1 | Minimal hypomimia, could be normal ("Poker face"). | |
| 2 | Slight but definitely abnormal diminution of facial expression. | |
| 3 | Moderate hypomimia; lips parted some of the time. | |
| 4 | Masked or fixed facies with severe or complete loss of facial expression, lips parted 0.25 inch or more. | |
| 2. Speech | | _____ |
| | The patient is asked to repeat several times a standard sentence. | |
| 0 | Normal. | |
| 1 | Mildly slow, slurred, and/or dysphonic. No need to repeat statements. | |
| 2 | Moderately slow, slurred, and/or dysphonic. Sometimes asked to repeat statements. | |
| 3 | Severely slow, slurred, and/or dysphonic. Frequently asked to repeat statements. | |
| 4 | Unintelligible. | |

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

(*Part II, continued*)

3. Ocular motor dysfunction _____
   Eye movements are examined by asking the subject to follow slow horizontal finger movements of the examiner, to look laterally at the finger at different positions, and to perform saccades between two fingers, each held at an eccentric posit ion of approximately 30°. The examiner assesses the following abnormal signs: (1) broken-up smooth pursuit, (2) gaze-evoked nystagmus at an eye position of more than 45 degrees, (3) gaze-evoked nystagmus at an eye position of less than 45 degrees, (4) saccadic hypermetria. Sign 3 suggests that there are at least two abnormal ocular motor signs, because Sign 2 is also present.
   0 None.
   1 One abnormal ocular motor sign.
   2 Two abnormal ocular motor signs.
   3 Three abnormal ocular motor signs.
   4 Four abnormal ocular motor signs.
4. Tremor at rest (rate the most affected limb) _____
   0 Absent.
   1 Slight and infrequently present.
   2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
   3 Moderate in amplitude and present most of the time,
   4 Marked in amplitude and present most of the time,
5. Action tremor _____
   Assess postural tremor of outstretched arms (A) and action tremor on finger pointing (B). Rate maximal tremor severity in Task A and/or B (whichever is worse), and rate the most affected limb.
   0 Absent.
   1 Slight tremor of small amplitude (A). No interference with finger pointing (B).
   2 Moderate amplitude (A). Some interference with finger pointing (B).
   3 Marked amplitude (A). Marked interference with finger pointing (B).
   4 Severe amplitude (A). Finger pointing impossible (B).
6. Increased tone (rate the most affected limb) _____
   Judged on passive movement of major joints with patient relaxed in sitting position; ignore cogwheeling.
   0 Absent.
   1 Slight or detectable only when activated by mirror or other movements.
   2 Mild to moderate.
   3 Marked, but full range of motion easily achieved.
   4 Severe, range of motion achieved with difficulty.
7. Rapid alternating movements of hands _____
   Pro-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, each hand separately, rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cereb ellar incoordination. Rate functional performance regardless of underlying motor disorder.
   0 Normal.
   1 Mildly impaired.
   2 Moderately impaired.
   3 Severely impaired.
   4 Can barely perform the task.
8. Finger taps _____
   Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand at least 15 to 20 seconds. Rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cere bellar incoordination. Rate functional performance regardless of underlying motor disorder.
   0 Normal.
   1 Mildly impaired.
   2 Moderately impaired.
   3 Severely impaired.
   4 Can barely perform the task.
9. Leg agility _____
   Patient is sitting and taps heel on ground in rapid succession, picking up entire leg. Amplitude should be approximately 10 cm, rate the worst affected leg. Note that impaired performance on this task can be caused by bradykinesia and/or cer ebellar incoordination. Rate functional performance, regardless of underlying motor disorder.
   0 Normal.
   1 Mildly impaired.
   2 Moderately impaired.
   3 Severely impaired.
   4 Can barely perform the task.
10. Heel-knee-shin test _____
   The patient is requested to raise one leg and place the heel on the knee, and then slide the heel down the anterior tibial surface of the resting leg toward the ankle. On reaching the ankle joint, the leg is again raised in the air to a heig ht of approximately 40 cm and the action is repeated. At least three movements of each limb must be performed for proper assessment. Rate the worst affected limb.
   0 Normal.
   1 Mildly dysmetric and ataxic.
   2 Moderately dysmetric and ataxic.
   3 Severely dysmetric and ataxic.
   4 Can barely perform the task.

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

(*Part II, continued*)

11. Arising from chair _____
Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.
0 Normal.
1 Clumsy, or may need more than one attempt.
2 Pushes self up from arms of seat.
3 Tends to fall back and may have to try more than once but can get up without help.
4 Unable to arise without help.

12. Posture _____
0 Normal.
1 Not quite erect, slightly stooped posture; could be normal for older person.
2 Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 Marked flexion with extreme abnormality of posture.

13. Body sway _____
Rate spontaneous body sway and response to sudden, strong posterior displacement produced by pull on shoulder while patient erect with eyes open and feet slightly apart. Patient has to be warned.
0 Normal.
1Slight body sway and/or retropulsion with unaided recovery.
2 Moderate body sway and/or deficient postural response; might fall if not caught by examiner.
3 Severe body sway. Very unstable. Tends to lose balance spontaneously.
4 Unable to stand without assistance.

14. Gait _____
0 Normal.
1 Mildly impaired.
2 Moderately impaired. Walks with difficulty, but requires little or no assistance.
3 Severely impaired. Requires assistance.
4 Cannot walk at all, even with assistance.

**Total score Part II:** _____

## Part III: Autonomic Examination

Supine blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing. Orthostatic symptoms may include lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, neck and "coat-hanger" ache.

| | | |
|---|---|---|
| Systolic blood pressure | | |
| | Supine | _____ |
| | Standing (2 minutes) | _____ |
| | Unable to record | _____ |
| Diastolic blood pressure | | |
| | Supine | _____ |
| | Standing (2 minutes) | _____ |
| | Unable to record | _____ |
| Heart rate | | |
| | Supine | _____ |
| | Standing (2 minutes) | _____ |
| | Unable to record | _____ |
| Orthostatic symptoms | | |
| | Yes | |
| | No | |

## Part IV: Global Disability Scale

1. Completely independent. Able to do all chores with minimal difficulty or impairment. Essentially normal. Unaware of any difficulty.
2. Not completely independent. Needs help with some chores.
3. More dependent. Help with half of chores. Spends a large part of the day with chores.
4. Very dependent. Now and then does a few chores alone or begins alone. Much help needed.
5. Totally dependent and helpless. Bedridden.

This document was supported by and done in the framework of the European Reference Network for Rare Neurological Diseases (ERN-RND). ERN-RND is one of the 24 European Reference Networks (ERNs) approved by the ERN Board of Member States. The ERNs are co-funded by the European Commission (ERN-RND: 3HP 767231).

# Annex 2 – Original Publication

*Movement Disorders*
Vol. 19, No. 12, 2004, pp. 1391–1402


# Development and Validation of the Unified Multiple System Atrophy Rating Scale (UMSARS)

Gregor K. Wenning, MD, PhD,[1]* François Tison, MD,[2] Klaus Seppi, MD,[1] Cristina Sampaio, MD,[3] Anja Diem, MD,[1] Farid Yekhlef, MD,[2] Imad Ghorayeb, MD,[2] Fabienne Ory, MD,[4] Monique Galitzky, MD,[4] Tommaso Scaravilli, MD,[5] Maria Bozi, MD,[5] Carlo Colosimo, MD,[6] Sid Gilman, MD,[7] Clifford W. Shults, MD,[8] Niall P. Quinn, MD,[5] Olivier Rascol, MD,[4] Werner Poewe, MD,[1] and the Multiple System Atrophy Study Group[†]

[1]*Department of Neurology, University of Innsbruck, Innsbruck, Austria*
[2]*Service de Neurologie, Hopital du Haut-Leveque, Pessac, France*
[3]*Faculdade de Medicine de Lisboa, Hospital Santa Maria, Centro de Neurosciencas, Lisboa, Portugal*
[4]*Toulouse III University, Laboratoire de Pharmacologie, Faculte de Medecine, Toulouse, France*
[5]*University College London, Institute of Neurology, Queen Square, London, United Kingdom*
[6]*Dipartimento di Scienze Neurologiche, Universita' La Sapienza, Rome, Italy*
[7]*Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA*
[8]*Department of Neurosciences, University of California San Diego School of Medicine, La Jolla, California, USA*

**Abstract:** We aimed to develop and validate a novel rating scale for multiple system atrophy (Unified Multiple System Atrophy Rating Scale - UMSARS). The scale comprises the following components: Part I, historical, 12 items; Part II, motor examination, 14 items; Part III, autonomic examination; and Part IV, global disability scale. For validation purposes, 40 MSA patients were assessed in four centers by 4 raters per center (2 senior and 2 junior raters). The raters applied the UMSARS, as well as a range of other scales, including the Unified Parkinson's Disease Rating Scale (UPDRS) and the International Cooperative Ataxia Rating Scale (ICARS). Internal consistency was high for both UMSARS-I (Crohnbach's alpha = 0.84) and UMSARS-II (Crohnbach's alpha = 0.90) sections. The interrater reliability of most of the UMSARS-I and -II items as well as of total UMSARS-I and -II subscores was substantial ($k\ (w) = 0.6–0.8$) to excellent ($k\ (w) > 0.8$). UMSARS-II correlated well with UPDRS-III and ICARS ($r_s > 0.8$). Depending on the degree of the patient's disability, completion of the entire UMSARS took 30 to 45 minutes. Based on our findings, the UMSARS appears to be a multidimensional, reliable, and valid scale for semiquantitative clinical assessments of MSA patients. © 2004 Movement Disorder Society

**Key words:** Unified Multiple System Atrophy Rating Scale; validation; internal consistency; interrater reliability

Multiple system atrophy (MSA) is a degenerative disorder of the central and autonomic nervous systems characterized by abnormal α-synuclein aggregation in oligodendroglia and neurons. Clinically, the cardinal features include autonomic failure, parkinsonism, cerebellar ataxia, and pyramidal signs in any combination. Two major motor presentations can be distinguished clinically. Parkinsonian features predominate in 80% of patients (MSA-P subtype), whereas cerebellar ataxia predominates in the remaining 20% of patients (MSA-C subtype).[1] MSA is a progressive disorder with early disability and shortened life expectancy.[2] Symptomatic treatment strategies are presently limited.[3] Due to advances in our understanding of the etiopathogenesis, several possible targets have been identified for multicenter neuroprotective intervention trials in MSA.[4] However, appropriate trial methodology is lacking. Indeed,

Drs. Wenning and Tison contributed equally to this study.

*Correspondence to: Dr. Gregor K. Wenning, Department of Neurology, University of Innsbruck, A-6020 Innsbruck, Austria.
E-mail: gregor.wenning@uibk.ac.at

[†]See Acknowledgments for a full list of study participants.

Received 16 January 2004; Revised 9 February 2004; Accepted 17 February 2004

**Published online 5 August 2004 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.20255**

**TABLE 1.** *Description of patient series*

| Centre | Bordeaux | Innsbruck | London | Toulouse | Total |
|---|---|---|---|---|---|
| Patients (n) | 11 | 10 | 8 | 11 | 40 |
| Gender (M/F) | 4/7 | 4/6 | 3/5 | 5/6 | 16/24 |
| MSA-P/C | 7/4 | 7/3 | 6/2 | 6/5 | 26/14 |
| MSA-possible/probable | 1/10 | 1/9 | 1/7 | 5/6 | 8/32 |
| Age at onset, yr (mean ± SD) | 59.6 ± 9.1 | 55.9 ± 8.7 | 50.6 ± 6.2 | 60 ± 7.1 | 57 ± 8.5 |
| Disease duration, yr (mean ± SD) | 5.6 ± 2.5 | 4.7 ± 3.8 | 6.3 ± 2.4 | 7.3 ± 6.6 | 6.0 ± 4.2 |
| H&Y stage, median (range) | 5 (3–5) | 4 (2–5) | 4 (3–5) | 3 (2–5) | 4 (2–5) |
| Three-point severity scale | 0 / 2 / 9 | 2 / 2 / 6 | 0 / 4 / 4 | 3 / 5 / 3 | 5 / 13 / 22 |
| Symptomatic orthostatic hypotension | 7 | 6 | 5 | 8 | 26 |
| Urinary incontinence/retention | 9/9 | 9/3 | 8/4 | 4/3 | 30/19 |
| Male erectile dysfunction | 2 | 3 | 3 | 4 | 12 |
| Parkinsonism | 9 | 10 | 7 | 10 | 36 |
| Cerebellar features | 7 | 6 | 6 | 5 | 24 |

MSA-P/C, multiple system atrophy–parkinsonian subtype/cerebellar ataxia subtype; 3-point severity scale: mild/moderate/severe.

clinical rating scales such as the Unified Parkinson's Disease Rating Scale (UPDRS)[5] or the International Cooperative Ataxia Rating Scale (ICARS)[6] focus on either parkinsonism or ataxia alone and, therefore, may not be sufficient to reflect accurately the motor impairment of MSA patients. Future randomized, controlled trials in MSA will be critically dependent on reliable and valid clinical assessment tools to determine the efficacy of a given intervention. The European MSA Study Group (EMSA-SG) was launched in 1999 to promote concerted trial activity in MSA across European countries (online at http://www.emsa-sg.org). In March 2001, EMSA-SG convened a task force with the specific goal of developing and validating a novel Unified MSA Rating Scale (UMSARS). This article introduces the UMSARS, and it gives the methods and results of a multicenter validation study of its use.

## MATERIALS AND METHODS

### Development of UMSARS

UMSARS was developed using established scales as templates, including the Hoehn and Yahr Scale (H&Y), the Schwab and England Scale (SES),[7] the UPDRS, the ICARS, and the Composite Autonomic Symptom Scale (COMPASS).[8] Previous MSA studies showed that cerebellar signs can compromise accurate assessment of parkinsonism by the UPDRS, and conversely, parkinsonism can obscure the evaluation of cerebellar features during assessments with the ICARS.[9,10] The scale construction followed a set of principles defined by the EMSA-SG task force: (1) UMSARS should rate functional impairment independent of underlying motor disorder, which may be cerebellar or parkinsonian or both; (2) UMSARS items should discriminate five grades of functional impairment; (3) Autonomic and urogenital dysfunction should be rated historically, except for recording the blood pressure and heart rate change upon standing; (4) A five-point global disability scale analogous to the H&Y scale should be part of UMSARS to capture the progressive disability of MSA patients.

Based on these principles, the novel UMSARS was designed comprising four parts, including a historical review of disease-related impairments (Part I, 12 items), motor examination (Part II, 14 items), autonomic examination (Part III), and global disability scale (Part IV; see Appendix). A single score using a 0 (no impairment) to 4 (severe impairment) scale was generated for each item. The maximum scores are 48 points for UMSARS-I and 56 points for UMSARS-II. In contrast to the UPDRS, for a given item of the UMSARS-II that involved limb assessment, only the worst limb was rated in the motor examination section.

### Validation of UMSARS

Forty patients with a clinical diagnosis of possible (n = 8) or probable (n = 32) MSA according to the Gilman criteria[1] were recruited in four EMSA-SG centers. The positive predictive value of the Gilman criteria was excellent (>90%) at first neurological visit in a recent validation study.[11] Their clinical characteristics are shown in Table 1. A set of scales and timed tests (see below) was applied to the patients, who were maintained on their regular medication during the assessments.

All patients were evaluated by one senior investigator who traveled to the centers (G.K.W.). Additionally, each center identified one senior and two junior investigators to evaluate the patients in their local center (Local Rater Teams are Bordeaux: F. Tison [senior], I. Ghorayeb

[junior], and F. Yekhlef [junior]; Innsbruck: W. Poewe [senior], K. Seppi [junior], and A. Diem [junior]; London: N. Quinn [senior], M. Bozi [junior], and T. Scaravilli [junior]; Toulouse: O. Rascol [senior], M. Galitzky [junior], and F. Ory [junior]). The scales were distributed to the raters in advance of the rating session. Immediately preceding the rating sessions, the application of UMSARS was demonstrated by G.K.W. to all raters. The patient's basic demographic data, current treatment, and the historical scale sections, including UMSARS-I, UPDRS-I (Mental Dysfunction), UPDRS-II (Activities of Daily Living), and UPDRS-IV (Complications of Therapy) were recorded by the local senior rater. Afterward, the motor examination was performed by the local senior rater and UMSARS-II, UPDRS-III (Motor examination) and ICARS were rated by both junior and senior raters simultaneously. As rigidity cannot be judged by inspection, all raters assessed this item in turn. After completion of the motor assessment, the historical scale sections (as above) were again administered, this time by one of the local junior raters. The global disability scales, including a simple three-point severity scale (mild–moderate–severe, SS-3), H&Y, and SES, were then independently administered by both senior raters. After this evaluation, blood pressure and heart rate responses to standing were determined according to UMSARS-III. In addition, a set of timed tests derived from the CAPSIT-PD protocol[12] was performed.

These tests included the walking test (i.e., walking as fast as possible 7 m back and forth, including turning), recording time and number of steps as well as freezing episodes. Furthermore, two trials of sequential hand movements between two points 30 cm apart were performed recording the mean number of movement cycles within a defined time period of 20 seconds.[12] Finally Gilman's criteria were applied by both senior raters to determine the likelihood of clinical diagnosis.

Each rater used a report form to record the data and, to obtain independent assessments, the examiners were not allowed to exchange opinions during the evaluation. Depending on the degree of the patient's disability, completion of the entire UMSARS took around 30 to 45 minutes.

### Statistical Analysis

The UMSARS items and subscores were used as crude data. All data analyses were conducted using the *SPSS v. 11.0* statistical package and *Microsoft Excel*. Cronbach's alpha[13] was used to assess internal consistency. Interrater reliability for individual items of UMSARS-I and UMSARS-II was determined by center analysis using kappa ($\kappa$) statistics.[14,15] Kappa adjusts the observed agreement for chance occurrence. Weighted $\kappa$ values were calculated using quadratic disagreement weights.[16] For each UMSARS-II item and UMSARS-IV, a weighted group $\kappa$ coefficient was calculated for each center.[17,18] Interrater reliability among senior and junior raters was also determined center by center using $\kappa$ statistics. In addition, the weighted mean of $\kappa$ values was calculated across the four centers, thus yielding an overall $\kappa$ value for each item. Interpretation of $k$ values was based on recommendations by Landis and Koch[19]: 0 to 0.20 slight agreement; 0.21 to 0.40 fair agreement; 0.41 to 0.60 moderate agreement; 0.61 to 0.80 substantial agreement; 0.81 to 1.00 excellent agreement. Interrater reliability of UMSARS-I and -II subscores was determined in each center by intraclass correlation coefficients (ICC) derived using a one-way random effects analysis of variance model.[20] In addition, the weighted mean of ICCs was calculated across the four centers, thus yielding an overall ICC for both UMSARS-I and -II subscores.

Only data obtained by G.K.W. (UMSARS-II) or by the local senior raters (UMSARS-I) were used for subsequent analysis as detailed below. Spearman's rank correlation coefficients (coefficient $r_s$) were calculated to determine the relationship between UMSARS-I and UPDRS-II, SS-3, H&Y, and SES, as well as between UMSARS-II and UPDRS-III, ICARS, SS-3, H&Y, and SES. Correlations between UMSARS-IV and UMSARS-I, UMSARS-II, UPDRS-II, UPDRS-III, ICARS, SS-3, H&Y, and SES were calculated the same way.

The Kruskal–Wallis test with post hoc Mann–Whitney $U$ tests was used to compare UMSARS-I and -II subscores between patients with different disability measured according to the SS-3 (mild vs. moderate vs. severe). Because of the multiple group comparisons, the significance level of the post hoc Mann–Whitney $U$ tests was set at a lower threshold ($P < 0.05/3 = 0.017$).

To determine internal consistency of UMSARS-I and UMSARS-II, a corrected item–total correlation was performed between each item score and the subscore of the remaining items of the corresponding subscale. Spearman's rank correlation coefficients were calculated between Item 9 (orthostatic symptoms) of UMSARS-I and diastolic blood pressure drop (DBPD), systolic blood pressure drop (SBPD), and change of heart rate during autonomic testing.

Following Cohen's classification, the magnitude of a correlation coefficient was categorized as follows: 0.10 to 0.29, low; 0.3 to 0.49, moderate; and 0.5 or higher, large.[21] Limits of statistical significance were given between 0.05 and 0.001. Additionally, a stepwise multiple regression analysis was applied to determine the relation-

**TABLE 2.** *UMSARS I: Interrater reliability*

| Item (N = 40) | Bordeaux, κ (w) (n = 11) | Innsbruck, κ (w) (n = 10) | London, κ (w) (n = 8) | Toulouse, κ (w) (n = 11) | All, κ (wg) (n = 40) |
|---|---|---|---|---|---|
| 1. Speech | 0.59 | 0.90 | 0.50 | 0.78 | 0.70 |
| 2. Swallowing | 0.70 | 0.94 | 0.50 | 0.49 | 0.66 |
| 3. Handwriting | 0.78 | 0.96 | 0.69 | 0.90 | 0.84 |
| 4. Cutting food and handling utensils | 0.90 | 0.73 | 0.85 | 0.46 | 0.73 |
| 5. Dressing | 0.88 | 0.97 | 0.82 | 0.94 | 0.91 |
| 6. Hygiene | 0.94 | 0.88 | 0.82 | 0.74 | 0.85 |
| 7. Walking | 0.84 | 0.87 | 0.50 | 0.84 | 0.78 |
| 8. Falling | 0.47 | 0.51 | 0.73 | 0.95 | 0.66 |
| 9. Orthostatic symptoms | 0.42 | 0.72 | 0.63 | 0.36 | 0.52 |
| 10. Urinary function | 0.52 | 0.60 | 0.69 | 0.79 | 0.65 |
| 11. Sexual function | 0.39 | 0.96 | 1.00 | 0.56 | 0.70 |
| 12. Bowel function | 0.73 | 0.94 | 0.77 | 0.77 | 0.80 |

0–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60 moderate agreement; 0.61– 0.80, substantial agreement; 0.81–1.00, excellent agreement; κ *(w),* weighted kappa; local senior versus local junior rater (2 raters per center); κ *(wg),* weighted mean of kappas over all centers; UMSARS, Unified Multiple System Atrophy Rating Scale.

ship between SS-3 and UMSARS-I as well as UMSARS-II as dependent variables.

## RESULTS

### Reliability

#### Internal Consistency.

As a comprehensive measure of internal consistency, Crohnbach's alpha coefficients of UMSARS-I and UMSARS-II were 0.84 and 0.90, respectively. Additionally, corrected correlations of item versus total subscores were verified for UMSARS-I and UMSARS-II (without inclusion of the score from the analyzed item into the corresponding UMSARS subscore) by Spearman's rank correlation testing. Nine UMSARS-I items correlated highly with the corrected UMSARS-I subscore ($r_s$ 0.5 or higher; $P = 0.001$ or $P < 0.001$): 2, swallowing; 3, handwriting; 4, cutting food and handling utensils; 5, dressing; 6, hygiene; 7, walking; and 12, bowel function. Correlation coefficients of Items: 1, speech; 10, urinary function; and 11, sexual function were moderate ($r_s$ 0.3–0.49; $P < 0.02$). Item 8, falling, showed a low corrected item–total correlation. Only Item 9, orthostatic symptoms, failed to correlate with the corrected UMSARS-I subscore ($r_s = -0.10$; not significant).

Most of the UMSARS-II items showed high correlation coefficients ($r_s = 0.50$ or higher; $P = 0.001$ or $P < 0.001$) with the corrected UMSARS-II subscore: 1, facial expression; 2, speech; 4, tremor at rest; 7, rapid alternating movements; 8, finger tapping; 9, leg agility; 10, heel–shin test; 12, posture; 13, body sway; 11, arising from chair and 14, gait. Item 5, action tremor, and Item 6, increased tone, had a moderate correlation coefficient, and Item 3, ocular motor dysfunction, did not correlate with the corrected total UMSARS-II subscore.

#### Interrater Agreement.

The results of this analysis appear in Tables 2 to 4. Weighted mean kappa values were at least substantial ($k$ *(w)* = 0.6–0.8) or excellent ($k$ *(w)* > 0.8) for all UMSARS-I items, except for Item 9 (orthostatic hypotension; Table 2). UMSARS-I subscores correlated significantly between the junior and senior rater ($r_s$ 0.95; $P < 0.001$). Table 3 summarizes the center by center as well as overall (i.e., all centers) analysis of interrater agreement for the individual UMSARS-II items. The overall analysis showed substantial (κ *(w)* > 0.6) or excellent (κ *(w)* > 0.8) interrater agreement for the majority of UMSARS-II items, including: 1, facial expression; 2, speech; 4, tremor at rest; 5, action tremor; 9, leg agility; 10, heel–shin test; 11, arising from chair; 12, posture; 13, body sway; 14, gait. The remaining items showed moderate interobserver agreement. Generally, interrater agreement for the UMSARS-II items was comparable between senior and junior raters. However, the center by center analysis of single UMSARS-II items revealed κ value discrepancies of >0.4 among senior and junior raters for the following items: 3, ocular motor dysfunction in Bordeaux and London; 4, tremor at rest in London; 6, increased tone in Innsbruck and Toulouse; 7, rapid alternating movements of hands in Innsbruck and Toulouse; 8, finger tapping in Innsbruck, London, and Toulouse; 9, heel–shin test in London. The correlation coefficients of the UMSARS-II subscores between the raters were excellent, ranging between 0.89 and 0.98 ($P < 0.001$).

**TABLE 3.** *UMSARS II: interrater reliability*

| Item (n = 40) | Bordeaux | | | Innsbruck | | | London | | | Toulouse | | | All | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $\kappa^a$ (w) | $\kappa^b$ (w) | $\kappa^c$ (w) | $\kappa^a$ (w) | $\kappa^b$ (w) | $\kappa^c$ (w) | $\kappa^a$ (w) | $\kappa^b$ (w) | $\kappa^c$ (w) | $\kappa^a$ (w) | $\kappa^b$ (w) | $\kappa^c$ (w) | $\kappa^a$ (w) | $\kappa^b$ (w) | $\kappa^c$ (w) |
| 1. Facial expression | 0.66 | 0.52 | 0.71 | 0.63 | 0.81 | 0.75 | 0.55 | 0.60 | 0.61 | 0.58 | 0.60 | 0.56 | 0.61 | 0.63 | 0.66 |
| 2. Speech | 0.76 | 0.95 | 0.74 | 0.85 | 0.83 | 0.84 | 0.80 | 0.77 | 0.83 | 0.71 | 0.64 | 0.83 | 0.78 | 0.80 | 0.80 |
| 3. Ocular motor dysfunction | 0.53 | 0.90 | 0.47 | 0.58 | 0.59 | 0.90 | 0.45 | 0.62 | 0.20 | 0.15 | 0.30 | 0.20 | 0.42 | 0.60 | 0.45 |
| 4. Tremor at rest | 0.59 | 0.55 | 0.65 | 0.89 | 0.57 | 0.89 | 0.63 | 1.00 | 0.17 | 0.83 | 1.00 | 0.62 | 0.70 | 0.77 | 0.60 |
| 5. Action tremor | 0.82 | 0.87 | 0.78 | 0.76 | 0.72 | 0.76 | 0.67 | 0.71 | 0.44 | 0.69 | 0.80 | 0.60 | 0.74 | 0.78 | 0.66 |
| 6. Increased tone | 0.63 | 0.52 | 0.71 | 0.73 | 0.47 | 0.93 | 0.63 | 0.69 | 0.53 | 0.13 | 0.27 | −0.16 | 0.52 | 0.47 | 0.49 |
| 7. Rapid alternating movements of hands | 0.64 | 0.56 | 0.68 | 0.62 | 0.47 | 0.88 | 0.66 | 0.64 | 0.63 | 0.47 | 0.74 | 0.14 | 0.59 | 0.60 | 0.57 |
| 8. Fingertapping | 0.38 | 0.06 | 0.53 | 0.47 | 0.60 | 0.47 | 0.67 | 0.81 | 0.38 | 0.53 | 0.92 | 0.20 | 0.50 | 0.58 | 0.39 |
| 9. Leg agility | 0.68 | 0.85 | 0.56 | 0.52 | 0.56 | 0.51 | 0.35 | 0.39 | 0.14 | 0.81 | 0.86 | 0.84 | 0.61 | 0.69 | 0.54 |
| 10. Heel-Shin Test | 0.72 | 0.88 | 0.58 | 0.94 | 0.92 | 0.93 | 0.59 | 0.88 | 0.45 | 0.91 | 1.00 | 0.82 | 0.80 | 0.92 | 0.71 |
| 11. Arising from chair | 0.92 | 0.89 | 0.88 | 0.94 | 0.93 | 0.97 | 0.97 | 0.96 | 0.96 | 0.91 | 0.89 | 0.93 | 0.93 | 0.91 | 0.94 |
| 12. Posture | 0.69 | 0.84 | 0.57 | 0.86 | 0.83 | 0.93 | 0.71 | 0.69 | 0.60 | 0.89 | 0.80 | 0.91 | 0.79 | 0.80 | 0.76 |
| 13. Body sway | 0.81 | 0.74 | 0.92 | 0.88 | 0.78 | 0.95 | 0.89 | 1.00 | 0.74 | 0.97 | 0.96 | 0.96 | 0.89 | 0.86 | 0.90 |
| 14. Gait | 0.86 | 0.84 | 0.89 | 0.90 | 0.89 | 0.96 | 0.88 | 0.93 | 0.82 | 0.92 | 0.96 | 0.87 | 0.89 | 0.90 | 0.89 |

$\kappa^a$ *(w),* weighted group kappa; $\kappa^b$ *(w),* weighted kappa; interrater agreement between senior raters (2 per centre); $\kappa^c$ *(w),* weighted kappa, inter-rater agreement between junior raters (2 per centre); $\kappa^{a\text{-}c}$ *(wg),* weighted mean of kappas over all centres; 0–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; 0.81–1.00, excellent agreement.

UMSARS, Unified Multiple System Atrophy Rating Scale.

Weighted UMSARS-IV κ values across the four centers were at least substantial for both senior ($\kappa$ *(w)* = 0.76–0.90) and junior raters ($\kappa$ *(w)* = 0.75–0.94). The reliability of the total scores of the UMSARS subscales was 0.88 for UMSARS-I and 0.93 for UMSARS-II as assessed by the ICCs (Table 4).

## Validity

### Criterion-Related Validity.

The distribution of global disease severity according to the SS-3 showed that the majority of MSA patients were either moderately or severely disabled (MSA-P: total, n = 26; mild, n = 4; moderate, n = 5; severe, n = 17; MSA-C: total, n = 14; mild, n = 1; moderate, n = 8; severe, n = 5).

There was a significant difference of UMSARS-I and -II subscores across the SS-3 stages of disability (Kruskal–Wallis $P < 0.001$). Median (ranges) subscores of UMSARS-I and -II for mildly disabled patients were 13 (10–20) and 13 (9–14), for moderately disabled patients were 20 (11–28) and 20 (16–30), and for severely disabled patients were 33 (14–42) and 35 (21–48). Post hoc testing with Mann–Whitney *U* test revealed increased UMSARS-I and -II subscores for severely disabled patients compared to both moderately (for both $P = 0.001$) and mildly (for both $P < 0.001$) disabled patients. Furthermore, the UMSARS-II subscores for moderately disabled patients were significantly increased compared to mildly disabled patients ($P < 0.001$), whereas there was a trend toward a significant increase of UMSARS-I subscores in moderately compared to mildly disabled patients ($P = 0.027$).

Spearman's rank correlation coefficients between the UMSARS-I subscores and SS-3 was 0.68 ($P < 0.001$). A stepwise multiple regression analysis revealed Items 3, handwriting, and 5, dressing, of UMSARS-I to account for 80% of the SS-3 variance.

The UMSARS-II subscore correlated significantly with SS-3 ($r_s = 0.77$; $P < 0.001$). Stepwise multiple regression analysis showed that 62% of the SS-3 variance was explained by UMSARS-II Items 9, finger tapping, and 14, gait.

**TABLE 4.** *Intraclass correlation coefficients for the UMSARS I and II*

| | Bordeaux | Innsbruck | London | Toulouse | All |
|---|---|---|---|---|---|
| UMSARS subscale, ICC (N = 40) | n = 11 | n = 10 | n = 8 | n = 11 | (wm), n = 40 |
| UMSARS I | 0.97 | 0.97 | 0.77 | 0.79 | 0.88 |
| UMSARS II | 0.92 | 0.95 | 0.90 | 0.94 | 0.93 |

ICC, intraclass correlation coefficients; ICC (wm), weighted mean of ICC over all centres; UMSARS, Unified Multiple System Atrophy Rating Scale.

**TABLE 5.** *Timed tests*

| | Spearman rank correlation ($r_s$) | | | |
|---|---|---|---|---|
| | Mean ± SD | Range | UMSARS I | UMSARS II |
| Walking (n = 26)[a] | 25.73 ± 12.63 | 10.10–60.00 | 0.52[c] | 0.42[d] |
| HAM (n = 39)[b] | | | | |
| Right | 25.15 ± 13.21 | 2.50–49.00 | −0.48[c] | −0.53[e] |
| Left | 23.73 ± 12.30 | 3.00–50.00 | −0.54[c] | −0.57[e] |

[a]Seven meters walking back and forth per second, based on data of 26 patients; 14 patients could not perform the test.
[b]Hand-arm movement (HAM): number of movements per 20 seconds, based on data of 39 patients; 1 patient could not perform the test.
[c]$P < 0.01$.
[d]$P < 0.05$.
[e]$P < 0.001$.
UMSARS, Unified Multiple System Atrophy Rating Scale.

UMSARS-IV correlated significantly with other measures of global disability, including SS-3 ($r_s = 0.83$; $P < 0.001$). UMSARS-I and -II subscores also correlated significantly with quantitative timed tests (Table 5).

### Construct Validity.

Table 6 summarizes the results of the construct validity. Discriminant validity was determined through correlations between the subscores of UMSARS-I and -II, and UPDRS-I (mental dysfunction), which assesses cognitive and psychiatric impairment, not usually present in MSA patients (Table 6). Convergent validity was determined by examining correlations between UMSARS subscores and those obtained from UPDRS, ICARS, H&Y, and SES (Table 6). Spearman's coefficients between UMSARS-I and UPDRS-II, H&Y, and SES were $r_s = 0.9$; $r = 0.76$, and $r_s = -0.89$ ($P < 0.001$), respectively, for all patients. Spearman's coefficients between UMSARS-II and UPDRS-III, ICARS, and H&Y showed correlation coefficients of $r_s = 0.93$ (for UPDRS-III and ICARS $P < 0.001$) and $r_s = 0.80$ (for H&Y, $P < 0.001$), respectively, for all patients. UMSARS-IV correlated well with UMSARS-I and -II ($r_s = 0.81$ and $r_s = 0.85$, $P < 0.001$), with UPDRS-II and -III ($r_s = 0.86$ and 0.88, $P < 0.001$), with ICARS ($r_s = 0.72$, $P < 0.001$), as well as H&Y and SES ($r_s = 0.80$ and $r_s = -0.94$, $P < 0.001$; Table 6).

**TABLE 6.** *Construct validity of UMSARS*

| $R_s$ (n = 40) | UMSARS I | UMSARS II | UMSARS IV |
|---|---|---|---|
| UMSARS I | | | 0.81[a] |
| UMSARS II | | | 0.85[a] |
| UPDRS I | −0.21 | −0.17 | −0.12 |
| UPDRS II | 0.90[a] | | 0.86[a] |
| UPDRS III | | 0.93[a] | 0.88[a] |
| ICARS | | 0.93[a] | 0.72[a] |
| H&Y | 0.76 | 0.80 | 0.80 |
| SES | −0.89[a] | | −0.94[a] |

[a]$P < 0.001$.
UMSARS I, Unified MSA Rating Scale, section I: disease-related impairments; II: motor examination, III: autonomic examination, IV: global disability scale; UPDRS I, Unified Parkinson's Disease Rating Scale, section I: mental dysfunction, II: activities of daily living, III: motor examination; ICARS, International Cooperative Ataxia Rating Scale; H&Y, Hoehn and Yahr; SES, Schwab and England Scale.

## Autonomic Examination

Results of cardiovascular autonomic examinations are shown in Table 7. In 13 of 40 patients, an SBPD (>30 mm Hg) was found after 2 minutes of standing, and 11 of 40 patients had a DBPD (>15 mm Hg) or both. Orthostatic symptoms during the autonomic examination were reported by 26 (65%) patients. There was no significant correlation between the magnitude of either SBPD or DBPD and UMSARS-I, -II, or -IV, and no correlation with other measures of global disability. A negative correlation was found between SBPD and Item 9 of UMSARS-I ($r_s = (-0.36$, $P = 0.02$).

**TABLE 7.** *UMSARS-III: Descriptive analysis of autonomic examination*

| N = 40 | Mean ± SD | Range | Median |
|---|---|---|---|
| BPsys–supine[a] | 137.00 ± 29.06 | 90.00–223.00 | 132.50 |
| Bpdia–supine[b] | 81.83 ± 15.84 | 53.00–129.00 | 80.00 |
| HR–supine[c] | 78.15 ± 12.22 | 60–108 | 75.50 |
| BPsys–standing | 112.63 ± 26.61 | 70.00–170.00 | 107.50 |
| Bpdia–standing | 72.21 ± 16.04 | 109.00–32.00 | 70.00 |
| Hr–standing | 79.28 ± 14.80 | 52–108 | 77.00 |
| SBPD | 24.38 ± 26.24 | −19.00–102.00 | 20.00 |
| DBPD | 11.43 ± 18.89 | −18.00–90.00 | 10.00 |
| Difference: Hr supine–standing | −1.13 ± 10.99 | −32–35 | 0.00 |

BPsys, systolic blood pressure; BPdia, diastolic blood pressure; HR, heart rate; SBPD, systolic blood pressure drop on standing; DBPD, diastolic blood pressure drop on standing.

## DISCUSSION

Although many different rating scales are available for PD, the UPDRS is the most thoroughly investigated scale for measuring the severity of parkinsonism and the most commonly used scale for clinical trials. In contrast, there has been a remarkable lack of specific validated instruments to measure functional impairment and disability associated with MSA. Both UPDRS and ICARS have been used to rate severity of parkinsonism and cerebellar ataxia in MSA.[9,10,21–23] However, these scales do not reflect the complex motor impairment of MSA. Indeed, cerebellar ataxia has been shown to contaminate UPDRS ratings in MSA-P and parkinsonism to contaminate ICARS ratings in MSA-C.[9,10]

We here present the first validated rating scale for MSA that may be used in clinical research, including intervention trials. The UMSARS is a multimodal scale containing both impairment and disability sections. One major advantage of UMSARS is that it was developed as a compound scale to capture the multiple aspects of MSA. It assesses both motor and autonomic disability (Part I – historical) and motor impairment (Part II – ME). The historical section was adapted from the UPDRS, and it comprises activities related to motor disability (first eight items) and four novel items related to autonomic dysfunction. The motor examination section of UMSARS was constructed based on modified UPDRS-III items in addition to novel items such as heel–knee–shin ataxia. The construction process was directed by the perceived need to measure functional disability independent of the underlying motor deficits, which may include not only parkinsonism and cerebellar ataxia, but also dystonic, myoclonic, and pyramidal features. In the UMSARS-II section, most of the items (e.g., speech, rapid alternating movements of the hands, finger taps, leg agility) measure the functional impairment of selected complex movements, and only a few items directly refer to specific parkinsonian (tremor at rest) or cerebellar (ocular motor dysfunction, heel–shin test) features. Furthermore, the third part (UMSARS-III) captures the cardinal autonomic feature of MSA, i.e., orthostatic hypotension, and the final part (UMSARS-IV) comprises a global disability scale. In contrast to the UPDRS, cognitive and psychiatric features as well as complications of therapy have not been included in UMSARS because of their limited relevance to MSA-associated disability.[2,24]

The internal consistency of UMSARS was high for both Parts I (Crohnbach's $\alpha = 0.84$) and II (Crohnbach's $\alpha = 0.90$), even though most of the redundancy present in the UPDRS-II subscale[25] was avoided in the UMSARS construction process. The interrater reliability of the UMSARS has also been tested in the present study, and the results show that this scale is reliable. Agreement was consistently substantial or excellent for 11 of 12 UMSARS-I items and for 10 of 14 UMSARS-II items. Although the center by center reliability analysis of UMSARS-II items revealed several discrepancies in $\kappa$ values of senior and junior raters, the interrater agreement was comparable between junior and senior raters in the overall analysis that included data derived from all centers. This finding demonstrates that relatively inexperienced physicians can use the UMSARS reliably, provided they receive clear instructions and brief training, as shown in other validation studies dealing with the UPDRS.[25]

Criterion-related validity of UMSARS demonstrated good correlation coefficients between UMSARS-I, UMARS-II, and SS-3, a three-point global severity scale. Furthermore, patients with severe disability (SS-3 = 3) had significantly higher UMSARS-I and -II subscores than patients with moderate or mild disability (SS-3 = 2 and 1). Of note, UMSARS-II correlated well with UPDRS-III and ICARS, widely used scales to measure parkinsonian and cerebellar motor impairments.

The excellent correlation of UMSARS-II and UPDRS-III was not unexpected, because of the overlap between these motor subscales. However, despite little overlap between UMSARS-II and ICARS, there was an excellent correlation between these scales as well. Therefore, UMSARS-II reflects functional motor impairment that may be parkinsonian, ataxic, or both. UMSARS-I and UMSARS-II subscores also correlated significantly with several timed tests commonly used to quantify the motor disorder in parkinsonian patients, such as the walking test and sequential hand movements. In contrast, there was no significant correlation between orthostatic blood pressure drop and UMSARS-I, II, or -IV. Only Item 9 of UMSARS-I correlated inversely with SBPD. These data suggest that motor and orthostatic dysfunction are dissociated in many MSA patients. Because 65% of the MSA patients complained of symptomatic orthostatic hypotension, inclusion of blood pressure measurements supine and standing into any MSA rating scale appears to be mandatory.

On the basis of our findings, the UMSARS has proven to be a multidimensional, reliable, and valid scale for semiquantitative assessments of MSA patients. Validation of the scale, conducted over a period of approximately 2 years in four different centers across Europe, has met the principal goals that we set during the conception of the scale. Even so, some possible drawbacks should be taken into account. (1) In light of the division between MSA-P and MSA-C phenotypes and categorization into three global divisions (mild, moderate, severe), the sample size is small. Validating UMSARS in the motor variants and across the global disabilities will require a larger cohort of patients that has

already been recruited during an ongoing natural history study by EMSA-SG. (2) As the scale was validated in European Caucasians, its validity and applicability in a different racial or ethnic context have not been examined. In particular, the authors are aware that UMSARS-I is culturally biased, and some items (e.g., 4, cutting food and handling utensils, and 5, dressing) may not apply to some rural and geographically isolated cultures. (3) The sensitivity to change is currently unknown. This aspect of the validation process will be examined during an EMSA-SG natural history study that was launched in December 2002. In the same study, the progression over time of the UMSARS score will be compared with other proposed surrogate laboratory markers for disease progression such as cardiovascular autonomic testing,[26] β-CIT SPECT,[27] $^{123}$IBZM-SPECT,[28,29] and diffusion-weighted magnetic resonance imaging.[30,31]

We are also aware that some key features of MSA are not fully covered by the UMSARS, because of the decision to design a scale that was reasonably simple, short, and user-friendly. Other validated scales, therefore, may be added to evaluate items not covered by the UMSARS that may have an impact on the overall function of MSA subjects, such as bradyphrenia, anhedonia, depression, sleep disorders, fatigue, and quality of life.

**Acknowledgments:** We thank P. Low (Minneapolis, MN) and C. Goetz (Chicago, IL) for providing advice concerning the construction and validation procedure and K. Pfeiffer (Institute of Biostatistics, Innsbruck, Austria) for performing the statistical analysis. We also thank D. Burtscher, F. Geser, H. Granbichler, S. Michlmair, U. Zijerveld, and M. Stampfer-Kountchev (all of Innsbruck, Austria) for their help with the coordination and conduct of the validation study. This study was supported by the 5th framework program of the EC (QLK6-2000-00661). (*continued*)

## APPENDIX: UNIFIED MSA RATING SCALE (UMSARS)

### Part I: Historical Review

Rate the average functional situation for the past 2 weeks (unless specified) according to the patient and caregiver interview. Indicate the score that best fits with the patient status. Rate the function independently from the nature of the signs.

| | | |
|---|---|---|
| 1. Speech | | _____ |
| 0 | Not affected. | |
| 1 | Mildly affected. No difficulties being understood. | |
| 2 | Moderately affected. Sometimes (less than half of the time) asked to repeat statements. | |
| 3 | Severely affected. Frequently (more than half of the time) asked to repeat statements. | |
| 4 | Unintelligible most of the time. | |
| 2. Swallowing | | _____ |
| 0 | Normal. | |
| 1 | Mild impairment. Choking less than once a week. | |
| 2 | Moderate impairment. Occasional food aspiration with choking more than once a week. | |
| 3 | Marked impairment. Frequent food aspiration. | |
| 4 | Nasogastric tube or gastrostomy feeding. | |
| 3. Handwriting | | _____ |
| 0 | Normal | |
| 1 | Mildly impaired, all words are legible. | |
| 2 | Moderately impaired, up to half of the words are not legible. | |
| 3 | Markedly impaired, the majority of words are not legible. | |
| 4 | Unable to write. | |
| 4. Cutting food and handling utensils | | _____ |
| 0 | Normal. | |
| 1 | Somewhat slow and/or clumsy, but no help needed. | |
| 2 | Can cut most foods, although clumsy and slow; some help needed. | |
| 3 | Food must be cut by someone, but can still feed slowly. | |
| 4 | Needs to be fed. | |
| 5. Dressing | | _____ |
| 0 | Normal. | |
| 1 | Somewhat slow and/or clumsy, but no help needed. | |
| 2 | Occasional assistance with buttoning, getting arms in sleeves. | |
| 3 | Considerable help required, but can do some things alone. | |
| 4 | Completely helpless. | |
| 6. Hygiene | | _____ |
| 0 | Normal. | |
| 1 | Somewhat slow and/or clumsy, but no help needed. | |
| 2 | Needs help to shower or bathe; or very slow in hygienic care. | |
| 3 | Requires assistance for washing, brushing teeth, combing hair, using the toilet. | |
| 4 | Completely helpless. | |

(*Part I, continued*)

| | | |
|---|---|---|
| 7. Walking | | _____ |
| 0 | Normal. | |
| 1 | Mildly impaired. No assistance needed. No walking aid required (except for unrelated disorders). | |
| 2 | Moderately impaired. Assistance and/or walking aid needed occasionally. | |
| 3 | Severely impaired. Assistance and/or walking aid needed frequently. | |
| 4 | Cannot walk at all even with assistance. | |
| 8. Falling (rate the past month) | | _____ |
| 0 | None. | |
| 1 | Rare falling (less than once a month). | |
| 2 | Occasional falling (less than once a week). | |
| 3 | Falls more than once a week. | |
| 4 | Falls at least once a day (if the patient cannot walk at all, rate 4). | |
| 9. Orthostatic symptoms | | _____ |
| 0 | No orthostatic symptoms.* | |
| 1 | Orthostatic symptoms are infrequent and do not restrict activities of daily living. | |
| 2 | Frequent orthostatic symptoms developing at least once a week. Some limitation in activities of daily living. | |
| 3 | Orthostatic symptoms develop on most occasions. Able to stand $>$ 1 min on most occasions. Limitation in most of activities of daily living. | |
| 4 | Symptoms consistently develop on orthostasis. Able to stand $<$ 1 min on most occasions. Syncope/presyncope is common if patient attempts to stand. | |
| | *Syncope, dizziness, visual disturbances or neck pain, relieved on lying flat. | |
| 10. Urinary function* | | _____ |
| 0 | Normal. | |
| 1 | Urgency and/or frequency, no drug treatment required. | |
| 2 | Urgency and/or frequency, drug treatment required. | |
| 3 | Urge incontinence and/or incomplete bladder emptying needing intermittent catheterization. | |
| 4 | Incontinence needing indwelling catheter. | |
| | *Urinary symptoms should not be due to other causes. | |
| 11. Sexual function | | _____ |
| 0 | No problems. | |
| 1 | Minor impairment compared to healthy days. | |
| 2 | Moderate impairment compared to healthy days. | |
| 3 | Severe impairment compared to healthy days. | |
| 4 | No sexual activity possible. | |
| 12. Bowel function | | _____ |
| 0 | No change in pattern of bowel function from previous pattern. | |
| 1 | Occasional constipation but no medication needed. | |
| 2 | Frequent constipation requiring use of laxatives. | |
| 3 | Chronic constipation requiring use of laxatives and enemas. | |
| 4 | Cannot have a spontaneous bowel movement. | |
| **Total score Part I:** | | _____ |

**Part II: Motor Examination Scale**

Always rate the worst affected limb.

1. Facial expression _____
   - 0 Normal.
   - 1 Minimal hypomimia, could be normal ("Poker face").
   - 2 Slight but definitely abnormal diminution of facial expression.
   - 3 Moderate hypomimia; lips parted some of the time.
   - 4 Masked or fixed facies with severe or complete loss of facial expression, lips parted 0.25 inch or more.
2. Speech _____

   The patient is asked to repeat several times a standard sentence.
   - 0 Normal.
   - 1 Mildly slow, slurred, and/or dysphonic. No need to repeat statements.
   - 2 Moderately slow, slurred, and/or dysphonic. Sometimes asked to repeat statements.
   - 3 Severely slow, slurred, and/or dysphonic. Frequently asked to repeat statements.
   - 4 Unintelligible.

(*Part II, continued*)

3. Ocular motor dysfunction _____

Eye movements are examined by asking the subject to follow slow horizontal finger movements of the examiner, to look laterally at the finger at different positions, and to perform saccades between two fingers, each held at an eccentric posit ion of approximately 30°. The examiner assesses the following abnormal signs: (1) broken-up smooth pursuit, (2) gaze-evoked nystagmus at an eye position of more than 45 degrees, (3) gaze-evoked nystagmus at an eye position of less than 45 degrees, (4) saccadic hypermetria. Sign 3 suggests that there are at least two abnormal ocular motor signs, because Sign 2 is also present.

0 None.
1 One abnormal ocular motor sign.
2 Two abnormal ocular motor signs.
3 Three abnormal ocular motor signs.
4 Four abnormal ocular motor signs.

4. Tremor at rest (rate the most affected limb) _____

0 Absent.
1 Slight and infrequently present.
2 Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 Moderate in amplitude and present most of the time,
4 Marked in amplitude and present most of the time,

5. Action tremor _____

Assess postural tremor of outstretched arms (A) and action tremor on finger pointing (B). Rate maximal tremor severity in Task A and/or B (whichever is worse), and rate the most affected limb.

0 Absent.
1 Slight tremor of small amplitude (A). No interference with finger pointing (B).
2 Moderate amplitude (A). Some interference with finger pointing (B).
3 Marked amplitude (A). Marked interference with finger pointing (B).
4 Severe amplitude (A). Finger pointing impossible (B).

6. Increased tone (rate the most affected limb) _____

Judged on passive movement of major joints with patient relaxed in sitting position; ignore cogwheeling.

0 Absent.
1 Slight or detectable only when activated by mirror or other movements.
2 Mild to moderate.
3 Marked, but full range of motion easily achieved.
4 Severe, range of motion achieved with difficulty.

7. Rapid alternating movements of hands _____

Pro-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, each hand separately, rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cereb ellar incoordination. Rate functional performance regardless of underlying motor disorder.

0 Normal.
1 Mildly impaired.
2 Moderately impaired.
3 Severely impaired.
4 Can barely perform the task.

8. Finger taps _____

Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand at least 15 to 20 seconds. Rate the worst affected limb. Note that impaired performance on this task can be caused by bradykinesia and/or cere bellar incoordination. Rate functional performance regardless of underlying motor disorder.

0 Normal.
1 Mildly impaired.
2 Moderately impaired.
3 Severely impaired.
4 Can barely perform the task.

9. Leg agility _____

Patient is sitting and taps heel on ground in rapid succession, picking up entire leg. Amplitude should be approximately 10 cm, rate the worst affected leg. Note that impaired performance on this task can be caused by bradykinesia and/or cer ebellar incoordination. Rate functional performance, regardless of underlying motor disorder.

0 Normal.
1 Mildly impaired.
2 Moderately impaired.
3 Severely impaired.
4 Can barely perform the task.

10. Heel-knee-shin test _____

The patient is requested to raise one leg and place the heel on the knee, and then slide the heel down the anterior tibial surface of the resting leg toward the ankle. On reaching the ankle joint, the leg is again raised in the air to a heig ht of approximately 40 cm and the action is repeated. At least three movements of each limb must be performed for proper assessment. Rate the worst affected limb.

0 Normal.
1 Mildly dysmetric and ataxic.
2 Moderately dysmetric and ataxic.
3 Severely dysmetric and ataxic.
4 Can barely perform the task.

(*Part II, continued*)

11. Arising from chair _____
Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.
0 Normal.
1 Clumsy, or may need more than one attempt.
2 Pushes self up from arms of seat.
3 Tends to fall back and may have to try more than once but can get up without help.
4 Unable to arise without help.

12. Posture _____
0 Normal.
1 Not quite erect, slightly stooped posture; could be normal for older person.
2 Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 Marked flexion with extreme abnormality of posture.

13. Body sway _____
Rate spontaneous body sway and response to sudden, strong posterior displacement produced by pull on shoulder while patient erect with eyes open and feet slightly apart. Patient has to be warned.
0 Normal.
1Slight body sway and/or retropulsion with unaided recovery.
2 Moderate body sway and/or deficient postural response; might fall if not caught by examiner.
3 Severe body sway. Very unstable. Tends to lose balance spontaneously.
4 Unable to stand without assistance.

14. Gait _____
0 Normal.
1 Mildly impaired.
2 Moderately impaired. Walks with difficulty, but requires little or no assistance.
3 Severely impaired. Requires assistance.
4 Cannot walk at all, even with assistance.

**Total score Part II:** _____

## Part III: Autonomic Examination

Supine blood pressure and heart rate are measured after 2 minutes of rest and again after 2 minutes of standing. Orthostatic symptoms may include lightheadedness, dizziness, blurred vision, weakness, fatigue, cognitive impairment, nausea, palpitations, tremulousness, headache, neck and "coat-hanger" ache.

| | | |
|---|---|---|
| Systolic blood pressure | | |
| | Supine | _____ |
| | Standing (2 minutes) | _____ |
| | Unable to record | _____ |
| Diastolic blood pressure | | |
| | Supine | _____ |
| | Standing (2 minutes) | _____ |
| | Unable to record | _____ |
| Heart rate | | |
| | Supine | _____ |
| | Standing (2 minutes) | _____ |
| | Unable to record | _____ |
| Orthostatic symptoms | | |
| | Yes | |
| | No | |

## Part IV: Global Disability Scale

1. Completely independent. Able to do all chores with minimal difficulty or impairment. Essentially normal. Unaware of any difficulty.
2. Not completely independent. Needs help with some chores.
3. More dependent. Help with half of chores. Spends a large part of the day with chores.
4. Very dependent. Now and then does a few chores alone or begins alone. Much help needed.
5. Totally dependent and helpless. Bedridden.

**Acknowledgments (*continued*): Members of the European MSA Study Group:** Aarhus, Denmark: Prof. Erik Dupont, Dr. Karen Ostergaard; Barcelona, Spain: Prof. Eduardo Tolosa; Bonn, Germany: Prof. Thomas Klockgether, Dr. Richard Dodel, Dr. Michael Abele; Bordeaux, France: Prof. François Tison, Dr. Imad Ghorayeb, Dr. Farid Yekhlef; Grenoble, France: Prof. Pierre Pollak; Innsbruck, Austria: Prof. Werner Poewe, Prof. Gregor Wenning, Dr. Anja Diem, Dr. Felix Geser, Dr. Klaus Seppi, Dr. Michaela Stampfer; Kiel, Germany: Prof. Günther Deuschl, Dr. Christine Daniels; Lisbon, Portugal: Prof. Cristina Sampaio, Dr. Miguel Coelho; Ljubljana, Slovenia: Prof. Zvezdan Pirtosek; London, United Kingdom: Prof. David J. Brooks, Prof. Clare Fowler, Prof. Andrew Lees, Prof. Christopher J. Mathias, Prof. Niall Quinn, Prof. Tamas Revesz, Dr. Maria Bozi, Dr. Alexander Gerhard, Dr. Janice Holton, Dr. Tomaso Scaravilli, Dr. Anette Schrag, Dr. Nick Wood; Lund, Sweden: Prof. Olle Lindvall, Prof. Håkan Widner, Dr. Martin Grabowski, Dr. Christer F. Nilsson; Marburg, Germany: Prof. Wolfgang Oertel, Dr. Karla Maria Eggert, Dr. Nicole Schimke; Milan, Italy: Prof. Alberto Albanese, Dr. Francesca del Sorbo; Naples, Italy: Prof. Paolo Barone, Dr. Francesco Carella; Petach-Tiqva, Israel: Dr. Ruth Djaldetti; Rome, Italy: Prof. Giuseppe Meco, Prof. Carlo Colosimo; Santander, Spain: Prof. Jose Berciano, Dr. Andres Gonzalez-Mandly; Tel-Aviv, Israel: Prof. Nir Giladi, Dr. Tanya Gurevich; Toulouse, France: Prof. Olivier Rascol, Dr. Monique Galitzky, Dr. Fabienne Ory; Tübingen, Germany: Prof. Thomas Gasser, Dr. Christoph Kamm; Uppsala, Sweden: Prof. Sten-Magnus Aquilonius, Dr. Jonas Bergquist.

## REFERENCES

1. Gilman S, Low P, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. Clin Auton Res 1998;8:359–362.
2. Wenning GK, Ben Shlomo Y, Magalhaes M, et al. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. Brain 1994;117(Pt 4):835–845.
3. Wenning GK, Colosimo C, Geser F, Poewe W. Recent advances in multiple system atrophy. Lancet Neurology 2004;3:93–103.
4. Burn DJ, Jaros E. Multiple system atrophy: cellular and molecular pathology. Mol Pathol 2001;54:419–426.
5. Fahn S, Elton R, members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden C, Calne D, editors. Recent developments in Parkinson's disease. Vol. 2. New York: MacMillan Healthcare Information; 1987. p 153–163.
6. Trouillas P, Takayanagi T, Hallett M, et al. International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. J Neurol Sci 1997;145:205–211.
7. Schwab R, England A. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham F, Donaldson I, editors. Third symposium on Parkinson's disease. Edinburgh: Livingstone; 1969. p 152–175.
8. Suarez GA, Opfer-Gehrking TL, Offord KP, et al. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. Neurology 1999;52:523–528.
9. Tison F, Yekhlef F, Balestre E, et al. Application of the International Cooperative Ataxia Scale rating in multiple system atrophy. Mov Disord 2002;17:1248–1254.
10. Tison F, Yekhlef F, Chrysostome V, et al. Parkinsonism in multiple system atrophy: natural history, severity (UPDRS-III), and disability assessment compared with Parkinson's disease. Mov Disord 2002;17:701–709.
11. Osaki Y, Wenning GK, Daniel SE, et al. Do published criteria improve clinical diagnostic accuracy in multiple system atrophy? Neurology 2002;59:1486–1491.
12. Defer GL, Widner H, Marie RM, et al. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 1999;14:572–584.
13. Armitage P, Colton T. Crohnbach's alpha. Encyclopedia of biostatistics. 2nd ed. New York: John Wiley and Sons; 1998.
14. Cohen J. A coefficient of agreement for internal scales. Educ Psychol Meas 1960;20:37–46.
15. Fleiss J. Statistical models for rates and proportions. 2nd ed. New York: John Wiley and Sons; 1981.
16. Agresti A. Kappa weighted. Categorical data analysis. New York: John Wiley and Sons; 1990.
17. Schouten H. Nominal scale agreement among observers. Psychometrica 1986;51:453–466.
18. de Vet HC, Knipschild PG, Schouten HJ, et al. Interobserver variation in histopathological grading of cervical dysplasia. J Clin Epidemiol 1990;43:1395–1398.
19. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–174.
20. Shrout P, Fleiss J. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420–428.
21. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. New Jersey: Lawrence Erlbaum Associates; 1988.
22. Colosimo C, Merello M, Pontieri F. Amantadine in parkinsonian patients unresponsive to levodopa: a pilot study. J Neurol 1996; 243:422–425.
23. Fetoni V, Genitrini S, Monza D, et al. Variations in axial, proximal and distal motor response to L-dopa in multisystem atrophy and Parkinson's disease. Clin Neuropharmacol 1997; 20:239–244.
24. Hughes A, Colosimo C, Kleedorfer B, et al. The dopaminergic response in multiple system atrophy. J Neurol Neurosurg Psychiatry 1992;55:1009–1013.
25. Martinez-Martin P, Gil-Nagel A, Gracia LM, et al. Unified Parkinson's Disease Rating Scale characteristics and structure. The Cooperative Multicentric Group. Mov Disord 1994;9:76–83.
26. Wenning G, Seppi K, Poewe W, et al. Differential association of orthostatic hypotension with the cerebellar versus parkinsonian presentation of multiple system atrophy. Neurology 2001; 56:444.
27. Pirker W, Djamshidian S, Asenbaum S, et al. Progression of dopaminergic degeneration in Parkinson's disease and atypical parkinsonism: a longitudinal beta-CIT SPECT study. Mov Disord 2002;17:45–53.
28. Brucke T, Wenger S, Asenbaum S, et al. Dopamine D2 receptor imaging and measurement with SPECT. Adv Neurol 1993;60: 494–500.
29. Schulz JB, Klockgether T, Petersen D, et al. Multiple system atrophy: natural history, MRI morphology, and dopamine receptor imaging with 123IBZM-SPECT. J Neurol Neurosurg Psychiatry 1994;57:1047–1056.
30. Schocke MF, Seppi K, Esterhammer R, et al. Diffusion-weighted MRI differentiates the Parkinson variant of multiple system atrophy from PD. Neurology 2002;58:575–580.
31. Seppi K, Schocke MF, Esterhammer R, et al. Diffusion-weighted imaging discriminates progressive supranuclear palsy from PD, but not from the Parkinson variant of multiple system atrophy. Neurology 2003;60:922–927.