

Presentation, Diagnosis, and Management of Multiple System Atrophy in Europe: Final Analysis of the European Multiple System Atrophy Registry

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Abstract: Multiple system atrophy (MSA) is a Parkinson's Disease (PD)-like α -synucleinopathy clinically characterized by dysautonomia, parkinsonism, cerebellar ataxia, and pyramidal signs in any combination. We aimed to determine whether the clinical presentation of MSA as well as diagnostic and therapeutic strategies differ across Europe and Israel. In 19 European MSA Study Group centres all consecutive patients with a clinical diagnosis of MSA were recruited from 2001 to 2005. A standardized minimal data set was obtained from all patients. Four-hundred thirty-seven MSA patients from 19 centres in 10 countries were included. Mean age at onset was 57.8 years; mean disease duration at inclusion was 5.8 years. According to the consensus criteria 68% were classified as parkinsonian type (MSA-P) and 32% as cerebellar type (MSA-C) (probable MSA: 72%, possible MSA: 28%). Symptomatic dysautonomia was present in

almost all patients, and urinary dysfunction (83%) more common than symptomatic orthostatic hypotension (75%). Cerebellar ataxia was present in 64%, and parkinsonism in 87%, of all cases. No significant differences in the clinical presentation were observed between the participating countries. In contrast, diagnostic work up and therapeutic strategies were heterogeneous. Less than a third of patients with documented orthostatic hypotension or neurogenic bladder disturbance were receiving treatment. This largest clinical series of MSA patients reported so far shows that the disease presents uniformly across Europe. The observed differences in diagnostic and therapeutic management including lack of therapy for dysautonomia emphasize the need for future guidelines in these areas. © 2010 Movement Disorder Society

Key words: multiple system atrophy; natural history; EMSA-SG

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by α -synuclein positive glial cytoplasmic inclusions and selective neurodegeneration in multiple brain areas including substantia nigra, striatum, cerebellum, pontine nuclei, and spinal cord.

Clinical features include dysautonomia, parkinsonism, cerebellar ataxia, and pyramidal signs in any combination. Two clinical variants can be distinguished, dominated by either parkinsonism (MSA-P) or cerebellar ataxia (MSA-C).¹

Prevalence rates range from 1.9 to 4.4/100,000^{2,3} and the incidence has been estimated as 3/100,000 per year.⁴ The disease is sporadic and there is no clear association with any epidemiological factor. Currently, the most plausible causation is a combination of genetic predisposition and exposure to environmental toxins.⁵

Data on the natural history of MSA are available from multiple clinical series: the largest European series comprises around 200^{6,7} and the largest Japanese series 230 patients.⁸ These studies confirmed the predominance of MSA-P in Europe and of MSA-C in Japan. Up to now it has been unclear whether regional differences exist between European countries since most data on the natural history of MSA are obtained from single countries. In addition, many studies have originated from a single reference centre, thus potentially introducing selection bias.

As MSA is a relatively rare disease multicentre studies are needed to recruit sufficient numbers of patients to reach appropriate statistical power. The European MSA Study Group (EMSA-SG) was founded in 1999 as a network for collaborative research on MSA. One major aim of establishing the EMSA registry was to

compare disease presentation and patterns of diagnostic work up as well as therapeutic strategies in a large number of MSA patients across Europe.⁹

PATIENTS AND METHODS

In 19 participating EMSA-SG centres across 10 countries all consecutive patients with a diagnosis of clinical MSA were recruited from 2001 to 2005. Patients were included by movement disorder specialists. Inclusion and exclusion criteria from the consensus conference were used.¹

Minimal Data Set

A standardized case report form, the minimal data set (MDS) was allotted to all patients. The MDS was developed by EMSA-SG based on literature review and expert opinion and comprises basic demographic data, motor features, dysautonomia, neuropsychiatric symptoms, drug treatment, and ancillary investigations performed.^{9,10} Information has been recorded at time of inclusion, no follow-up data are available.

Medical records were examined to corroborate the presence or absence of features, to complete information on drug treatment, and to determine ancillary investigations performed.

Data Collection

To comply with European and national data protection regulations patients were coded with a five digit number providing information only on the centre (first two digits). The hard copy-based MDS were completed on site and sent to the coordinating centre in Innsbruck. Data were entered into a password-protected

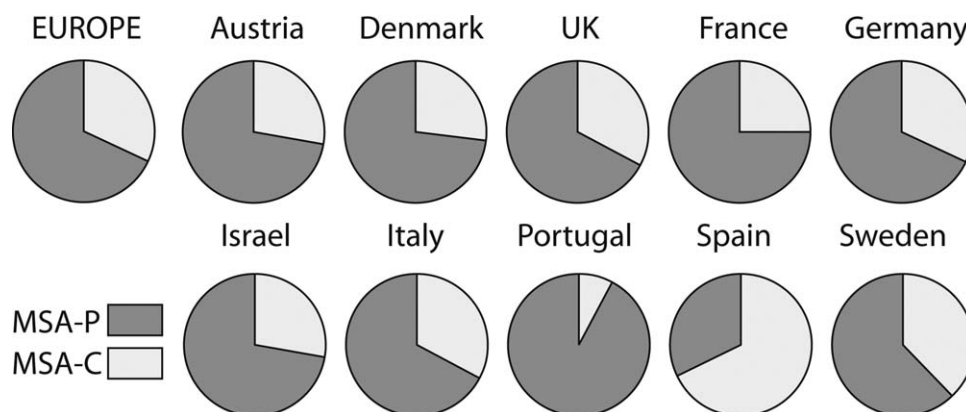


FIG. 1. Clinical phenotype distribution.

ACCESS database and patient codes were stored separately from patient data.

Data Analysis

Statistical analysis was performed using SPSS 14.0 (SPSS Inc). All data are presented as mean $\pm$ standard deviation or median (interquartile range). For the calculation of overall European mean values cases were weighted for the actual number of patients per country. Data obtained from single countries were compared to the overall European means. Frequencies of symptoms were compared using χ^2 or Fisher's exact test. Group comparisons were performed using *t* test or Mann-Whitney-U tests, depending on data distribution and sample size. All tests were two sided, and significance level was set at $P = 0.05$. Due to the explorative character of the analysis no post hoc correction was applied.

RESULTS

Patient Characteristics

A total of 437 patients were recruited from 10 countries (Austria, Denmark, UK, France, Germany, Italy, Israel, Portugal, Spain, and Sweden). Mean age at disease onset was 57.8 years, disease duration at entry 5.8 years with no significant differences between motor subtypes and genders. Onset of either motor symptoms or of dysautonomia was allowed to define disease onset. Genders were equally distributed. When applying the 1998 Consensus criteria,¹ 68.2% were classified as MSA-P and 31.8% as MSA-C (Fig. 1). In 72% a diagnosis of probable MSA was made, 28% were classi-

fied as possible MSA. Patient characteristics for single countries are given in Tables 1 and 2.

Dysautonomia

Symptomatic dysautonomia was present in 99% of patients, urinary symptoms (83%) being more frequent than orthostatic dysregulation (75%). Urge incontinence was the most frequent urinary feature (73%); incomplete bladder emptying was documented less commonly (48%). In 37% incontinence and incomplete bladder emptying were both present. Erectile dysfunction was reported in 84% of male patients. Whereas incomplete bladder emptying was more common in male patients ($P = 0.02$), incontinence was more frequent in female patients ($P = 0.001$) and in MSA-C compared to MSA-P ($P = 0.04$). In 59% of patients an orthostatic blood pressure drop of at least 20 mm Hg systolic or 10 mm Hg diastolic (20/10) was documented, in 46% a drop of 30/15 mm Hg or more. Orthostatic complaints were recorded in 59% of all patients, and 19% experienced orthostatic syncope. Orthostatic symptoms were more frequent in MSA-P ($P = 0.04$). Of those patients who had a documented blood pressure drop of 30/15 mm Hg or more, only 68% suffered from orthostatic symptoms and 27% experienced syncope. Conversely, only 67% of patients with a history of syncope had a documented blood pressure drop of at least 30/15 mm Hg (71% for 20/10 mm Hg). One-third of patients complained of chronic constipation. Despite dysautonomia being ubiquitous only 36% received pharmacological treatment. Orthostatic symptoms were treated in 27%, urinary dysfunction in 19%, and erectile dysfunction in 2.5% of affected patients. For the pharmacological treatment of

TABLE 1. Patient characteristics

	<i>n</i>	Age at onset (years)	Disease duration (years)	Gender		Diagnosis			
				Male (%)	Female (%)	Poss MSA-P (%)	Prob MSA-P (%)	Poss MSA-C (%)	Prob MSA-C (%)
Europe	437	57.8	5.8	52.5	47.5	19	49	9	23
Austria	58	57.4	6.0	50	50	7	65	13	15
Denmark	15	58.9	5.6	33	67	20	53	20	7
UK	61	53.8	5.5	49	51	21	46	2	31
France	73	60.3	6.2	45	55	11	64	10	15
Germany	44	57.4	4.3	56	44	18	50	0	32
Israel	85	57.7	6.6	53	47	20	52	9	19
Italy	40	58.5	4.7	45	55	22	45	13	20
Portugal	13	58.8	5.9	77	23	46	46	0	8
Spain	35	56.7	5.6	57	43	0	32	3	66
Sweden	13	58.8	7.9	60	40	23	39	23	15

poss. = possible, prob. = probable.

orthostatic hypotension mainly midodrine (69%), fludrocortisone (25%), and dihydroergotamine (11%) were employed. Drug treatment of urinary dysfunction consisted mainly of tolterodine (52%) and oxybutynin (45%).

Parkinsonism

Parkinsonism was observed in 87% of all cases, since 61% of patients with MSA-C also fulfilled the UK Parkinson's Disease Brain Bank criteria for parkinsonism.¹¹ Bradykinesia was accompanied by rigidity (93%), postural instability (89%), postural (54%) and rest (33%) tremor, and freezing of gait (38%). At time of inclusion 82% of patients with parkinsonism received antiparkinsonian therapy. The most commonly used drug was levodopa (L-dopa) (73% of treated patients); dopamine agonists were given in 29%, MAO-B inhibitors in 12% and COMT inhibitors in 8%. Amantadine was administered in 39%. Mean

L-dopa total daily dose was 631 ± 402 mg, and mean L-dopa equivalent dose¹² of dopamine agonists 184 ± 121 . Total L-dopa equivalent dose given was 642 ± 432 . In 37% a beneficial L-dopa response was recorded by the treating physician lasting for a median time of 3 years (interquartile range: 2–5). Dyskinesias were reported in 7% of patients receiving dopaminergic therapy, wearing off in 4.1% and on-off fluctuations in 3.5; off dystonia was recorded in 10%. However, data on motor complications of dopaminergic therapy were recorded in only one-third of patients.

Cerebellar Signs

Ataxia was present in 64% of cases since cerebellar signs were observed also in 47% of MSA-P patients. The most frequent cerebellar signs were gait ataxia (86%) and limb ataxia (78%), followed by ataxic dysarthria (69%). Sustained gaze-evoked nystagmus was observed in 35% of ataxic patients.

TABLE 2. Clinical presentation of MSA in Europe

	Dysautonomia (%)	Parkinsonism (%)	L-Dopa Response (duration*)	Ataxia (%)	Babinski (%)	Hyper-reflexia
Europe	78	87	38% (3)	63	28	43
Austria	67	95	32% (3)	92	38	38
Denmark	87	100	40% (3.5)	53	27	33
UK	87	85	27% (3)	84	48	56
France	86	90	18% (3)	71	30	59
Germany	80	86	26% (4)	71	14	25
Israel	78	86	55% (3)	56	59	37
Italy	88	100	45% (2)	58	33	73
Portugal	46	100	45% (2)	39	15	62
Spain	74	49		71	14	34
Sweden	87	80	67% (5.5)	40	7	13

Dysautonomia was defined as either orthostatic hypotension (blood pressure drop of more than 20 mm Hg systolic or 10 mm Hg diastolic) or urinary failure (incontinence or incomplete bladder emptying). Beneficial L-dopa response was defined as clinically meaningful.

*Median response duration is given in years.

Pyramidal Signs

An abnormal plantar reflex was found in 28% of patients, and generalized hyper-reflexia in 43%. The latter was more common in MSA-C (54%) than MSA-P (38%, $P = 0.002$).

Neuropsychiatric Features and Sleep Disturbance

Information on neuropsychiatric features and sleep disturbances were extracted from medical records in a subset of 199 patients.

Depression was reported in 41%, psychotic symptoms in 6%, mainly hallucinations (5.5%). Delusions were rare (2%). In 4.5% dementia was reported. There were no significant differences between genders. Psychosis was more frequent in MSA-P than in MSA-C ($P = 0.02$). Insomnia was reported in 19% and excessive daytime sleepiness in 17%. Almost 10% of patients complained about restless legs.

Ancillary Investigations

To supplement the clinical diagnosis of MSA ancillary diagnostic tests were performed in 80% of patients.

Overall, formal autonomic testing was done in 38% of patients. While cardiovascular function tests were performed in 32% of patients, urodynamics (14%), and respiratory (9%) and sudomotor function tests (8%) were only conducted in a minority of patients. Sphincter electromyogram (EMG) was performed in 13% of cases. Anal sphincter EMG (performed in 11% of patients) was abnormal in 43% of examined cases, urethral sphincter EMG (performed in 4% of patients) was abnormal in 56% of examined cases.

Magnetic resonance imaging (MRI) (71%) was the preferred neuroimaging modality, 69% of scans being performed on a 1.5T scanner. Single photon emission tomography (SPECT), using dopamine receptor and dopamine transporter ligands, was performed in 19% of patients. Positron emission tomography (PET) was rarely utilized (<5%), mostly in research protocols. We have no information on the results of these investigations.

Disease Presentation Across Europe

Clinical Presentation

This study population was homogenous with only a few exceptions. These probably reflect differences between centres rather than true country-to-country differences. The high proportion of MSA-C patients in Spain, for example, is due to the expertise in ataxias of

one of the two participating centres from this country. Clinical presentation of patients was comparable across all countries, parkinsonian and cerebellar symptoms were present in similar proportions with only minor exceptions. In Spain ($P < 0.001$) and Italy ($P = 0.006$) fewer patients reported orthostatic symptoms compared to all European patients, syncope was also less frequently reported in these two countries.

Ancillary Investigations

The use of ancillary investigations and treatment protocols was more variable. Whereas in Europe MRI was used as standard imaging tool the centres from Israel relied more frequently ($P < 0.001$) on CT scans; MRI was less often employed than in Europe ($P < 0.001$). Since SPECT and PET imaging depend on the availability of a (major in case of PET) nuclear medicine centre there were obvious differences in its use.

Cardiovascular function was frequently assessed in the centres from Austria, Israel, and Italy ($P = 0.002$), urodynamic investigations were more frequently performed in Austria ($P < 0.001$), less frequently in the centres from Germany ($P = 0.025$).

Treatment

Treatment of parkinsonism was largely based on L-dopa. The total daily dose given (631 ± 402 mg) was similar in all countries. Dopamine agonists also were given to a similar extent across Europe. MAO-B inhibitors were not administered in Germany and Sweden, and rarely used in France ($P = 0.02$) and the UK ($P = 0.008$). In Portugal the proportion of patients receiving MAO-B inhibitors was high (46%, $P = 0.002$). COMT-inhibitors were rarely used. (see Table 3).

DISCUSSION

Currently available data on the clinical presentation of MSA are largely based on small cohorts from single centres. EMSA-SG has entered 437 MSA patients in 19 centres from 10 countries into the EMSA registry using a standardized minimal data set.

Being a cross-sectional study disease duration at inclusion was 5.9 years. This is rather late, considering that disease progression is rapid in MSA. Mean age at onset was 58 years, in France 2 years later and in the UK 4 years earlier. This could have been influenced by the fact that dysautonomia was allowed as an alternative to motor symptoms to define disease onset. It is

TABLE 3. Anti-parkinson medication

	L-dopa (%)	Daily dose mean $\pm$ SD (mg)	DA (%)	DA daily L-dopa equivalent mean $\pm$ SD (mg)	MAO-B inhibitors (%)	COMT- inhibitors (%)
Europe	73	631 $\pm$ 402	29	184 $\pm$ 121	11	8
Austria	78	661 $\pm$ 355	22	250 $\pm$ 195	9	7
Denmark	73	677 $\pm$ 538	27	117 $\pm$ 29	7	7
UK	54	533 $\pm$ 422	35	215 $\pm$ 116	2	8
France	73	579 $\pm$ 388	29	199 $\pm$ 119	5	8
Germany	68	644 $\pm$ 345	18	230 $\pm$ 104	0	8
Israel	67	532 $\pm$ 344	26	145 $\pm$ 97	18	11
Italy	75	589 $\pm$ 242	23	133 $\pm$ 104	5	3
Portugal	77	813 $\pm$ 555	46	239 $\pm$ 177	46	15
Spain	71	721 $\pm$ 312	47	164 $\pm$ 120	18	12
Sweden	100	510 $\pm$ 366	20	67	0	0

Percentage of patients with clinical parkinsonism receiving treatment. Daily Dopa dose and Dopa equivalent¹² is given in mg.
DA = dopamine agonists.

known that erectile dysfunction and incontinence can precede MSA by many years.^{12,13}

According to the consensus criteria¹ 72% of patients were classified as probable MSA, 28% as possible MSA. Together with the rather long disease duration at inclusion in the registry this indicates that clinicians are rather cautious in making the devastating diagnosis of MSA and tend to want to be reasonably certain before conveying it to the patient.

The most frequent disease feature was dysautonomia, present in almost all patients when including also orthostatic intolerance without significant blood pressure drop. Orthostatic hypotension with a drop of more than 30/15 mm Hg was documented in half of patients; however, 70% fulfilled the less stringent criteria of the American Autonomic Society (i.e., 20/10 mm Hg).¹⁴ In keeping with previous studies^{15,16} there was no clear relationship between the blood pressure drop and the occurrence of orthostatic symptoms including syncope. Only 27% of patients with orthostatic symptoms (with or without significant blood pressure drop) received pharmacological treatment at time of inclusion. Unfortunately, information on nonpharmacological measures was not included in the MDS. Urinary incontinence was more common in female patients. Since anatomically women are more at risk for urinary incontinence¹⁷ this difference is probably not disease-related. Similarly, the predominance of incomplete bladder emptying in men is likely to reflect the impact of gender-specific non-neurogenic factors like prostatic hyperplasia.¹⁸ Although erectile dysfunction, known to severely impair quality of life,¹⁹ was present in a vast majority only a small proportion received pharmacological treatment despite effective agents being available.²⁰ It is unclear whether there is no demand, or whether these problems need more medical attention.

Parkinsonism, particularly bradykinesia and rigidity, postural instability and freezing, were present not only in MSA-P patients but also in the majority of MSA-C patients, underpinning the multisystem character of this disease. Rest tremor, which is common in Parkinson's disease,¹¹ was only found in one-third (presence of classical pill rolling rest tremor was not specifically recorded), whereas postural tremor was seen in half of all patients. Postural stability was massively impaired, and freezing of gait was observed in the majority of patients still ambulant.

There was some support for the use of dopaminergic therapy with a documented beneficial response in one-third of patients, lasting for ~3 years. Beside therapeutic benefit also complications usually associated with dopaminergic drugs such as motor fluctuations and dyskinesias were observed in our patients. These complications define a subgroup of MSA-P patients with a PD like presentation that clearly often leads to misdiagnosis.^{21,22}

L-dopa was the mainstay of dopaminergic therapy and dopamine agonists were used less frequently. MAO-B and COMT Inhibitors were employed even more rarely except in Portugal. Amantadine was prescribed in 32% of patients with parkinsonism although the only controlled study of amantadine in MSA was negative and only anecdotal reports exist on its efficacy.^{23,24} The absence of level 1 evidence for antiparkinsonian treatment strategies in MSA highlights the importance of consensus therapeutic guidelines.

Cerebellar ataxia dominated the motor disorder of MSA-C patients, but it was also present in nearly half of MSA-P patients. Consistent with previous smaller series MSA appears to present as a mixed motor disorder in the majority of patients with variable combinations of parkinsonism and ataxia.^{8,24} The Unified MSA

Rating Scale (UMSARS) was therefore developed as a functional scale not attempting to discriminate parkinsonian and cerebellar deficits.²⁵

Data on sleep function, though available in fewer than half of patients, indicate that sleep is severely compromised in MSA, with excessive daytime sleepiness (EDS) as a consequence. Unfortunately, the frequency of REM sleep behaviour disorder (RBD) was not assessed in the MDS. In a smaller study with 57 MSA patients RBD was present in approximately half of the patients²⁶ and may eventually occur in over 90% of all MSA patients.²⁷ Associated with sleep disturbances are also dystonic vocal cord contractions resulting in nocturnal stridor and apnea.²⁸

Depression, affecting more than 40% of patients, impairs quality of life in MSA.^{29,30} Other neuropsychiatric features appeared to be uncommon in contrast to PD. The psychosis rate was similar to the general population,³¹ and much lower than in PD.³² A recent clinical study suggested that the absence of hallucinations in parkinsonian patients points towards MSA rather than PD and related Lewy body disorders.³³

The diagnosis of MSA can be difficult even for movement disorder specialists. PD, cerebellar ataxias, fragile X-associated tremor/ataxia syndrome (FXTAS), other atypical parkinsonian disorders, but also vascular parkinsonism have to be considered in the differential diagnosis.³⁴ A number of ancillary investigations have been proven to be helpful in the diagnostic process. Others, with more limited diagnostic value, can nevertheless assist in making therapeutic decisions. CT and MRI were widely used in the diagnostic workup of patients with suspected MSA across most European countries. Differences observed may also reflect differences in health care access rather than medical decisions. Brain SPECT and PET utilization showed high variability depending on availability of a specialized nuclear imaging centre and funding to perform the investigations routinely.

In the EMSA registry we have included 437 patients from 19 centres from 10 countries using standardized data acquisition methods. The clinical presentation appeared to be relatively uniform across Europe with only a few differences. In contrast to the clinical homogeneity, diagnostic work-up and therapeutic management were inconsistent across the sites.

Some limitations have to be acknowledged. The diagnosis of patients was based on clinical expert opinion without histopathological confirmation. Therefore it cannot be excluded that the diagnosis has to be revised in some cases. On the other hand, long disease duration and the high proportion of probable MSA cases

indicate that relatively few uncertain cases were included into the registry. Although data were weighted for the number of patients per country, the fact that only national reference centres have contributed is likely to have resulted in selection bias towards more severe cases. The typical European MSA patient might still look different as we probably recruited MSA patients likely to be enrolled in clinical studies. National or regional MSA registries as currently underway in Aquitaine³⁵ will be required to complement the emerging European perspective presented here. Our current analysis is based on cross-sectional data only, and not including follow up data that were obtained in a subgroup of patients from this registry who were enrolled in the EMSA natural history study.^{9,10}

We conclude that presentation of MSA across centres and countries in Europe is uniform and therefore multicentre studies are feasible and valid. In addition, due to the considerable differences in the diagnosis and treatment we emphasize the need for standardized guidelines in these areas.

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REFERENCES

- Gilman S, Low P, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. *American Autonomic Society and American Academy of Neurology. Clin Auton Res* 1998;8:359–362.
- Chrysostome V, Tison F, Yekhlief F, Sourgen C, Baldi I, Dartigues JF. Epidemiology of multiple system atrophy: a prevalence and pilot risk factor study in Aquitaine, France. *Neuroepidemiology* 2004;23:201–208.
- Schrag A, Ben Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet* 1999;354:1771–1775.
- Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence of progressive supranuclear palsy and multiple system atrophy in Olmsted County, Minnesota, 1976 to 1990. *Neurology* 1997;49:1284–1288.
- Hanna PA, Jankovic J, Kirkpatrick JB. Multiple system atrophy: the putative causative role of environmental toxins. *Arch Neurol* 1999;56:90–94.
- Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord* 1997;12:133–147.
- Wullner U, Schmitz-Hubsch T, Abele M, Antony G, Bauer P, Eggert K. Features of probable multiple system atrophy patients identified among 4770 patients with parkinsonism enrolled in the multicentre registry of the German competence network on Parkinson's disease. *J Neural Transm* 2007;114:1161–1165.
- Watanabe H, Saito Y, Terao S, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. *Brain* 2002;125 (Part 5):1070–1083.
- Geser F, Seppi K, Stampfer-Kountchev M, et al. The European multiple system atrophy-study group (EMSA-SG). *J Neural Transm* 2005;112:1677–1686.
- Geser F, Wenning GK, Seppi K, et al. Progression of multiple system atrophy (MSA): a prospective natural history study by the European MSA study group (EMSA SG). *Mov Disord* 2006;21:179–186.
- Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:745–752.
- Ito T, Sakakibara R, Yasuda K, et al. Incomplete emptying and urinary retention in multiple-system atrophy: when does it occur and how do we manage it? *Mov Disord* 2006;21:816–823.
- Sakakibara R, Hattori T, Uchiyama T, Yamanishi T. Videourodynamic and sphincter motor unit potential analyses in Parkinson's disease and multiple system atrophy. *J Neurol Neurosurg Psychiatry* 2001;71:600–606.
- The Consensus Committee of the American Autonomic Society and the American Academy of N. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology* 1996;46:1470.
- Low PA, Opfer-Gehrking TL, McPhee BR, et al. Prospective evaluation of clinical characteristics of orthostatic hypotension. *Mayo Clin Proc* 1995;70:617–622.
- Mathias CJ, Mallipeddi R, Bleasdale-Barr K. Symptoms associated with orthostatic hypotension in pure autonomic failure and multiple system atrophy. *J Neurol* 1999;246:893–898.
- Romanzi LJ. Urinary incontinence in women and men. *J Gen Specif Med* 2001;4:14–20.
- Lemack GE, Dewey RB, Jr, Roehrborn CG, O'Suilleabhain PE, Zimmern PE. Questionnaire-based assessment of bladder dysfunction in patients with mild to moderate Parkinson's disease. *Urology* 2000;56:250–254.
- Köllensperger M, Stampfer-Kountchev M, Seppi K, et al. Progression of dysautonomia in multiple system atrophy: a prospective study of self-perceived impairment. *Eur J Neurol* 2007;14:66–72.
- Zesiewicz TA, Helal M, Hauser RA. Sildenafil citrate (Viagra) for the treatment of erectile dysfunction in men with Parkinson's disease. *Mov Disord* 2000;15:305–308.
- Hughes AJ, Colosimo C, Kleedorfer B, Daniel SE, Lees AJ. The dopaminergic response in multiple system atrophy. *J Neurol Neurosurg Psychiatry* 1992;55:1009–1013.
- Hughes AJ, Daniel SE, Ben Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* 2002;125 (Part 4):861–870.
- Wenning GK. Placebo-controlled trial of amantadine in multiple-system atrophy. *Clin Neuropharmacol* 2005;28:225–227.
- Wenning GK, Ben Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy. An analysis of 100 cases. *Brain* 1994;117 (Part 4):835–845.
- Wenning GK, Tison F, Seppi K, et al. Development and validation of the Unified Multiple System Atrophy Rating Scale (UMSARS). *Mov Disord* 2004;19:1391–1402.

26. Ghorayeb I, Yekhlief F, Chrysostome V, Balestre E, Bioulac B, Tison F. Sleep disorders and their determinants in multiple system atrophy. *J Neurol Neurosurg Psychiatry* 2002;72:798–800.
27. Iranzo A. Sleep and breathing in multiple system atrophy. *Curr Treat Opt Neurol* 2007;9:347–353.
28. Vetruigno R, Liguori R, Cortelli P, et al. Sleep-related stridor due to dystonic vocal cord motion and neurogenic tachypnea/tachycardia in multiple system atrophy. *Mov Disord* 2007;22:673–678.
29. Schrag A, personal communication.
30. Schrag A, Selai C, Mathias C, et al. Measuring health-related quality of life in MSA: the MSA-QoL. *Mov Disord* 2007;22:2332–2338.
31. Perala J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 2007;64(1):19–28.
32. Poewe W. Psychosis in Parkinson's disease. *Mov Disord* 2003;18 (Suppl 6):S80–S87.
33. Williams DR, Warren JD, Lees AJ. Using the presence of visual hallucinations to differentiate Parkinson's disease from atypical parkinsonism. *J Neurol Neurosurg Psychiatry* 2008;79: 652–655.
34. Poewe W, Wenning G. The differential diagnosis of Parkinson's disease. *Eur J Neurol* 2002;9 (Suppl 3):23–30.
35. Krim E, Yekhlief F, Chrysostome V, Ghorayeb I, Tison F. [Multiple system atrophy: prognostic factors in the "MSA-Aquitaine" cohort.]. *Rev Neurol (Paris)* 2007;163:54–65.