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Health-Related Quality of Life in Multiple System Atrophy

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Abstract: Although multiple system atrophy (MSA) is a neurodegenerative disorder leading to progressive disability and decreased life expectancy, little is known about patients' own evaluation of their illness and factors associated with poor health-related quality of life (Hr-QoL). We, therefore, assessed Hr-QoL and its determinants in MSA. The following scales were applied to 115 patients in the European MSA-Study Group (EMSA-SG) Natural History Study: Medical Outcome Study Short Form (SF-36), EQ-5D, Beck Depression Inventory (BDI), Mini-Mental state examination (MMSE), Unified MSA Rating Scale (UMSARS), Hoehn & Yahr (H&Y) Parkinson's disease staging scale, Composite Autonomic Symptom Scale (COMPASS), and Parkinson's Disease Sleep Scale (PDSS). Forty-six percent of patients had moderate to severe depression (BDI $\geq$ 17); Hr-QoL scores on the SF-36 and EQ-5D were significantly impaired. Pain, the only domain with similar scores in MSA and published PD patients, was reported more frequently in patients with MSA-P (predominantly parkinsonian motor subtype) than MSA-C (predominantly cerebellar motor subtype; 76% vs. 50%; $P = 0.005$). Hr-QoL scores correlated most strongly with UMSARS motor, COMPASS, and BDI scores but not with MMSE scores, age at onset, or disease duration. The COMPASS and UMSARS activities of daily living scores were moderate-to-strong predictors for the SF-36 physical summary score and the BDI and UMSARS motor scores for the SF-36 mental summary score. This report is the first study to show that Hr-QoL is significantly impaired in MSA. Although not all possible factors related to impaired Hr-QoL in MSA could be assessed, autonomic dysfunction, motor impairment, and depression were most closely associated with poor Hr-QoL, and therapeutic management, therefore, should concentrate upon these aspects of the disease. © 2006 Movement Disorder Society

Key words: health-related quality of life; multiple system atrophy; depression; autonomic dysfunction

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Multiple system atrophy (MSA) is a sporadic, chronic, progressive neurodegenerative disorder with shortened life expectancy and without a known cure. Clinically, it is characterized by various combinations of parkinsonian, autonomic, cerebellar, and pyramidal signs,[1] which lead to marked disability and handicap. Although clinical assessments with physician-rated measures can assess disease severity, the impact of the disorder on patients' lives cannot be fully evaluated using these scales. Health-related quality of life (Hr-QoL) scales are used increasingly as measures of health status, concentrating on the patients' own perceptions and experiences of their disease. To date, only one study has assessed the subjective health status in patients with MSA.[2] Moreover, with the exception of this recent study, only few studies with small numbers of patients have assessed the occurrence of depression in MSA.[2–4] Here we report the results of a large, multicenter and multinational survey of the European MSA-Study Group (EMSA-SG) on Hr-QoL and assess its correlates in patients with MSA.

PATIENTS AND METHODS

Study Design

This cross-sectional analysis is based on the baseline visit of the prospective EMSA-SG Natural History Study.[5]

Patients

A cohort of European Caucasian MSA patients was enrolled in the study. Inclusion criteria were a parkinsonian or cerebellar syndrome associated with autonomic failure fulfilling the consensus criteria for possible or probable MSA.[6] The following features were considered as exclusion criteria: onset under 30 years of age, family history of a similar disorder, secondary cause (by history or investigation), prominent slowing of vertical saccades, vertical supranuclear palsy (down/upward gaze palsy), aphasia, alien limb syndrome, parietal dysfunction, and generalized areflexia. This study was conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and amendments laid down by the 29th (Tokyo, 1975), the 35th (Venice, 1983), and the 41st (Hong-Kong, 1989) World Medical Assemblies; the European Guidelines for Good Clinical Practice (ISBN 92-825-9563-3); and the contract signed by the EMSA-SG and the European Union (QLK6-CT-2000-00661). The final protocol and the informed consent form were reviewed by properly constituted Investigational Review Boards in accordance with laws and regulation of the participating countries, and ethical approval was granted. Written informed consent was obtained from each patient before subjecting the patient to any study-related procedures. Patients were recruited based on a chart review with an invitation to attend the clinic. In addition, consecutive patients attending outpatient clinics were included.

Clinical Assessments/Questionnaires

Patients were assessed clinically using a range of scales comprising both interviewer-administered rating scales and self-administered questionnaires. The clinical rating scales included the Unified MSA Rating Scale (UMSARS),[1] the Hoehn & Yahr (H&Y) Parkinson's disease staging scale[7] (scales developed to assess disease severity in MSA and parkinsonian disorders), and the Mini-Mental-State Examination (MMSE).[8] The self-administered scales included the Beck Depression Inventory (BDI),[9] which has been used widely to assess depression in patients with parkinsonian disorders, and 2 generic Hr-QoL instruments: the Medical Outcome Study Short Form (SF-36)[10] and the EQ-5D.[11] These scales were chosen for use in this multinational study because they are available in multiple languages, are used widely, and have been validated in patients with PD.[12–14] For the BDI, a cutoff score of 17 was used to identify moderate to severe depression. The SF-36 has 8 subscores and 2 summary scores, i.e., the physical and mental summary score. The EQ-5D has five subscores, from which an index score can be calculated, and a visual analogue scale (VAS) of general health. As this study was undertaken in multiple countries, for many of whom no country-specific algorithms are available, we used the standard algorithm for the United Kingdom. To assess the impact of other potentially important aspects of MSA for Hr-QoL in MSA, a subgroup of patients were also asked to complete the Composite Autonomic Symptom Scale (COMPASS)[15] ($n = 33$) and the Parkinson's Disease Sleep Scale (PDSS)[16] ($n = 19$). If the patients could not complete the questionnaires, caregivers were permitted to help with completion, provided the patient's answer was recorded.

A comparison of Hr-QoL and depression scores was performed between patients with MSA in this study and patients with Parkinson's disease (PD) in a previous study with similar disease duration.[17] In addition, the data were compared to data reported in patients with PD in the literature.[13,14]

Statistical Analysis

All data were entered in a central ACCESS database and analyzed using SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL). The subscores, summary scores and indices of the SF-36 and EQ-5D were calculated according

to the respective scoring algorithms. Data were analyzed for normality of distribution. Normally distributed data were analyzed using parametric and non-Gaussian distributed variables using nonparametric tests. Group differences were analyzed using the Student's *t* tests or Mann–Whitney *U* test. The Chi-squared test was used to estimate the proportions. The degree of correlation between variables was analyzed with Spearman's rank correlations. Correlations above 0.6 were considered strong, between 0.3 and 0.6 moderate, and below 0.3 as weak or negligible. This strategy was considered a more appropriate measure of association than *P* values as not all patients completed the COMPASS and the PDSS, and the strength of a correlation is measured more appropriately by the size of the correlation coefficient than by the *P* value, which depends on the sample size.[18] For all correlations, the level of significance is given. The significance level for all other comparisons was set at $P < 0.05$. A forward stepwise regression analysis was performed to determine the factors that best accounted for the variance in Hr-QoL scores using variables that were significant in the bivariate analysis. The results were confirmed by repeating the analyses using backward regression analysis.

RESULTS

Patient Characteristics

This analysis is based on a cohort of 115 MSA patients at 14 EMSA-SG sites, including Innsbruck (n = 20), London (n = 11), Naples (n = 11), Milan (n = 10), Aarhus (n = 9), Barcelona (n = 8), Lund (n = 8), Tel-Aviv (n = 8), Kiel (n = 7), Lisbon (n = 7), Bonn (n = 6), Marburg (n = 4), Petach-Tiqva (n = 4), and Rome (n = 2). Ninety-eight patients (85%) completed the SF-36. The remaining 17 patients (15%) either declined, were not able to answer the questions, or were not invited to complete the SF-36 at the beginning of the study. Their UMSARS activities of daily living (ADL) scores of these patients were significantly worse than those of participants (median, 27.0; interquartile range, 21.0–39.0 vs. median 23.0; interquartile range, 17.0–29.0; $P = 0.039$), but the motor and global disability scores did not differ. Mean age of onset was 57.3 years (SD 8.7), and the median disease duration was 4.3 years (interquartile range, 2.9–6.2).

There were 26 patients (22.6%) categorized as possible MSA and 89 (77.4%) as probable MSA[6]; 72 (62.6%) were diagnosed as MSA-P (predominantly parkinsonian motor subtype) and 43 (37.4%) as MSA-C (predominantly cerebellar motor subtype).

Depression

Moderate to severe depression, defined through a BDI score of 17 points or higher, was common (46.3%), with no significant differences between motor subtypes, diagnostic categories (possible vs. probable),[6] and sexes. The mean BDI score was 16.5 (SD 9.1). This value was higher than in patients with PD after a similar disease duration[19,20] (12.0, SD 10.5,[21] $P < 0.0001$). On the EQ-5D, 60% of patients indicated having moderate and 11% having severe depression or anxiety.

Health-Related Quality of Life

Hr-QoL scores on the EQ-5D and SF-36 are shown in Table 1. The areas of greatest impairment were those of physical functioning, physical role limitations, vitality, and general health on the SF-36; and of usual activities, self-care, and mobility on the EQ-5D. The areas of bodily pain and mental and social health were reported as less impaired. Compared with patients with PD after similar disease duration (median, 5.0; interquartile range, 3.0–8.6 years, not significant), patients with MSA had worse Hr-QoL scores in all domains of SF-36 and EQ-5D, except for the domain of pain on both scales, which was similarly common in both disease groups (Table 1).

There was no difference in Hr-QoL scores between sexes, and Hr-QoL scores did not correlate significantly with age or age at onset. Patients with probable MSA did not differ from patients with possible MSA in their EQ-5D scores but had worse physical functioning subscores (20.3 vs. 32.6, $P = 0.04$), worse bodily pain subscores (58.2 vs. 72.3 $P = 0.05$), and worse physical summary scores on the SF-36 (27.8 vs. 35.5; $P < 0.05$). Patients with MSA-P had significantly worse scores in the domain of pain on both scales and the EQ-5D index score compared with patients with MSA-C, but there was no difference between the motor subtypes on any of the other subscales (Table 2). On the EQ-5D, 66% of patients reported moderate or severe pain. It was found in 76% patients with MSA-P and 50% of patients with MSA-C ($P = 0.005$).

Disease Factors Associated with Worse Hr-QoL Scores

The UMSARS motor, ADL, and global disability scores and the H&Y scale correlated negatively and strongly with the EQ-5D index score ($r = -0.72$, $r = -0.64$, $r = -0.69$, and $r = -0.61$, respectively) and moderately with the EQ-5D VAS ($r = -0.49$, $r = -0.43$, $r = -0.48$, $r = -0.38$, respectively) and the SF-36 physical summary scale ($r = -0.50$, $r = -0.50$, $r = -0.49$, $r = -0.30$, respectively), but only the UM-

TABLE 1. *Comparison between health-related quality of life scores in patients with multiple system atrophy and Parkinson's disease*

	MSA	PD*	PD**	PD***	P^1
EQ-5D domains					
Mobility[a]	2.1 (0.4)			1.8 (0.6)	<0.0001
Self-care[a]	2.2 (0.7)			1.5 (0.6)	<0.0001
Usual activities[a]	2.3 (0.5)			1.9 (0.7)	<0.0001
Pain/discomfort[a]	1.7 (0.6)			1.8 (0.7)	n.s.
Anxiety/depression[a]	1.8 (0.6)			1.6 (0.6)	<0.0001
EQ index	0.3 (0.3)			0.5 (0.4)	<0.0001
EQ-5D Health state	44.5 (20.9)			64 (22.8)	<0.0001
SF-36 domains					
Physical functioning	23.2 (26.2)	49.3 (30.8)	55.4 (2.1)	62.9 (24)	<0.0001
Physical role limitations	21.7 (33.5)	32.4 (39.9)	49.7 (3.1)	62.9 (24)	<0.0001
Bodily pain	61.8 (31.1)	63.1 (29.4)	64.6 (2.0)	61.4 (32.8)	n.s.
General health perception	38.3 (19.7)	51.9 (21.9)	52.9 (1.5)	48.5 (19.5)	<0.0001
Vitality	35.9 (23.0)	43.0 (22.5)	48.2 (1.6)	50.0 (18.7)	<0.0001
Social functioning	50.0 (32.6)	63.1 (31.0)	73.0 (1.9)	65.0 (25.6)	<0.0001
Emotional role limitations	49.6 (46.4)	52.8 (44.6)	70.6 (3)	79.0 (52.5)	<0.0001
General mental health	55.2 (23.3)	65.3 (20.9)	73.1 (1.2)	62.0 (23.1)	0.006
SF-36 physical summary score	29.7 (18.5)	-	38.2 (0.7)	35.9 (11.5)	0.003
SF-36 mental summary score	47.8 (22.1)	-	50.0 (0.7)	47.0 (10.7)	n.s.

Values are expressed as mean (SD) unless indicated otherwise.
*Data from Fitzpatrick et al.[14]
**Data from Rubenstein et al.[13]
***Data from Schrag et al.[17] (age group, 55-64 years).
[1]Compared to Schrag et al.[17]
[a]Higher scores indicate greater impairment; for all other data in this table, higher scores indicate better health. MSA, multiple system atrophy; PD, Parkinson's disease; SF-36, Medical Outcome Study Short Form; n.s., not significant.

SARS motor part and ADL part correlated weakly with the SF-36 mental subscale (r = −0.30 and −0.30, respectively; Table 3). Among other scales, the BDI had a strong correlation with the SF-36 mental subscale (r = −0.68) and moderate correlations with the EQ-5D index (r = −0.45) and the SF-36 physical subscale (r = −0.36); the COMPASS scale correlated moderately with all Hr-QoL measures (r = −0.42 to −0.54); the PDSS correlated moderately with the SF-36 mental subscale (r = 0.44); the MMSE and disease duration only had negligible correlations with Hr-QoL measures.

TABLE 2. *Comparison of health-related quality of life parameters between patients with different subtypes of multiple system atrophy*

	MSA-P	MSA-C	*P*
EQ-5D domains			
Mobility	2.1 (0.4)	2.1 (0.4)	n.s.
Self-care	2.3 (0.7)	2.1 (0.7)	n.s.
Usual activities	2.4 (0.6)	2.3 (0.5)	n.s.
Pain/discomfort	1.8 (0.6)	1.6 (0.6)	0.01
Anxiety/depression	1.9 (0.6)	1.7 (0.6)	n.s.
EQ index	0.3 (0.4)	0.4 (0.3)	0.04
EQ-5D Health state	46.4 (20.3)	41.2 (21.8)	n.s.
SF-36 domains			
Physical functioning	26.4 (26.9)	17.4 (24.2)	n.s.
Physical role limitations	21.9 (35.3)	21.2 (30.4)	n.s.
Bodily pain	55.5 (29.9)	74.0 (30.0)	0.006
General health perception	37.4 (20.3)	40.1 (18.6)	n.s.
Vitality	33.3 (21.6)	40.9 (25.1)	n.s.
Social functioning	50.1 (32.6)	49.7 (33.1)	n.s.
Emotional role limitations	48.0 (47.7)	52.7 (44.5)	n.s.
General mental health	53.9 (24.8)	57.6 (20.3)	n.s.
SF-36 physical summary score	30.3 (20.0)	28.5 (15.7)	n.s.
SF-36 mental summary score	46.0 (22.8)	51.0 (20.9)	n.s.

Values are expressed as mean (SD) unless indicated otherwise.
MSA-P, multiple system atrophy, parkinsonian subtype; MSA-C, multiple system atrophy, cerebellar subtype; SF-36, Medical Outcome Study Short Form; n.s., not significant.

In a forward stepping multiple linear regression analysis of data from patients who completed all variables except the PDSS, 47% of the variance of the SF-36 physical summary scores could be explained by UMSARS ADL and COMPASS scores, but no other features contributed further to the prediction of SF-36 physical scores (Table 4). Fifty-five percent of the variance of the SF-36 mental summary scores could be predicted by the BDI and UMSARS motor scores. The UMSARS motor score and the BDI also predicted 51% of the variance of the EQ-5D index scores; COMPASS and UMSARS motor score predicted 45% of the EQ-5D visual analogue scores. Repetition of the analysis using backward multiple regression analysis confirmed that the greatest prediction of the variance of the SF-36 physical summary score was achieved by using UMSARS ADL and COMPASS scores, of the SF-36 mental subscore by the UMSARS motor and BDI scores, of the EQ-5D index scores

TABLE 3. *Correlations between health-related quality of life scores and clinical variables*

	Disease duration	Hoehn and Yahr stage	UMSARS motor score	UMSARS ADL score	UMSARS IV (GDS)	Beck Depression Inventory score	MMSE score	COMPASS score*	PDSS score**
EQ-5D SI	−0.28[b]	−0.61[d]	−0.72[d]	−0.64[d]	−0.69[d]	−0.45[d]	0.27[b]	−0.42[a]	0.28
EQ-5D VAS	−0.19[a]	−0.38[d]	−0.49[d]	−0.43[d]	−0.48[d]	−0.28[b]	0.14	−0.54[c]	0.19
SF-36 physical summary score	−0.18	−0.3[b]	−0.50[d]	−0.5[d]	−0.49[d]	−0.36[c]	0.15	−0.45[a]	0.23
SF-36 mental summary score	−0.06	−0.21[a]	−0.30[b]	−0.3[b]	−0.24[a]	−0.68[d]	0.17	−0.43[a]	0.44

*Significance levels lower as only measured in a subgroup of 33 patients.
**Significance levels lower as only measured in a subgroup of 19 patients.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
[d]$P < 0.0001$.
SI, summary index; VAS, visual analogue score; UMSARS, Unified Multiple System Rating Scale; ADL, activities of daily living; GDS, Global Disability Score; MMSE, Mini-Mental State Examination; COMPASS, Composite Autonomic Symptom Scale; PDSS, Parkinson's Disease Sleep Scale; SF-36, Medical Outcome Study Short Form.

by the UMSARS motor and BDI scores, and of the EQ-5D visual analogue scores by the COMPASS and UMSARS motor scores.

DISCUSSION

This study demonstrates that Hr-QoL scores, as assessed by two generic Hr-QoL measures, are significantly impaired in patients with MSA and appeared worse than previously reported in cohorts of patients with PD after similar disease duration. The worst affected areas were those related to physical functioning and activities of daily living, whereas mental dysfunction and pain were less impaired. Cognitive dysfunction is relatively uncommon in MSA, and frank dementia is one of the exclusion criteria for the clinical diagnosis of MSA.[6] Cognitive impairment, therefore, is unlikely to have a major impact on patients' Hr-QoL. On the other hand, pain and sensory discomfort occurred in a portion of patients (66% reported moderate or severe pain on the EQ-5D) but did not exceed the rates reported by patients with PD. Pain is a recognized manifestation of Parkinsonism. This result is supported by the finding that pain scores were significantly higher in patients with the parkinsonian than in those with the cerebellar presentation of MSA. The EQ-5D index score was also significantly worse in MSA-P than MSA-C, suggesting that, overall, the parkinsonian syndrome contributes more to disease burden than cerebellar ataxia. Patients with possible MSA differed only in the degree of physical dysfunction from those with probable MSA, reflecting the milder degree of impairment in early cases where there still is some diagnostic uncertainty.

Hr-QoL scores deteriorated significantly with increasing stages of illness as evaluated by H&Y and UMSARS scores. This finding reflects the deterioration of Hr-QoL with progression of the disease. However, there was no correlation between disease duration and Hr-QoL scores,

TABLE 4. *Multiple regression analyses for prediction of health-related quality of life scores in multiple system atrophy*

	Adjusted R^2	Standardized regression coefficient	R^2 change	*P*
SF-36 physical score predictors[a]	0.47			
UMSARS ADL score		−0.47	0.33	0.009
COMPASS score		−0.45	0.19	0.02
SF-36 mental subscore predictors[b]	0.55			
Beck Depression Inventory score		−0.64	0.51	0.001
UMSARS motor score		−0.29	0.08	0.05
EQ-5D index score predictors[c]	0.51			
UMSARS motor score		−0.51	0.38	0.001
Beck Depression Inventory score		−0.42	0.17	0.007
EQ-5D visual analogue score of general health predictors[d]	0.45			
COMPASS score		−0.46	0.35	0.002
UMSARS motor score		−0.4	0.15	0.02

SF-36, Medical Outcome Study Short Form; UMSARS, Unified Multiple System Rating Scale; ADL, activitites of daily living; COMPASS, Composite Autonomic Symptom Scale.

indicating that Hr-QoL is affected relatively independently of disease duration. Among the factors associated with worse Hr-QoL, autonomic dysfunction was most consistently associated with worse Hr-QoL scores, as assessed on both generic Hr-QoL measures. In a multiple regression analysis, it was a better predictor for the SF-36 physical subscore and the EQ-5D VAS of overall health than the motor part of the UMSARS, indicating that in addition to motor impairment, autonomic function is an important contributor to poor Hr-QoL in MSA. This finding is consistent with that reported in the only previous study on Hr-QoL in patients with MSA in a different, North American, sample, in which autonomic dysfunction was also an important factor associated with worse SF-36 and life satisfaction scores.[2] In contrast to the previous study, which did not assess motor impairment, in our study, patients were assessed using the recently validated disease-specific rating scale for MSA (i.e., the UMSARS) and the H&Y staging.

BDI scores indicated the presence of moderate or severe depression in almost half of all patients with a mean BDI score of 16.5. This score is slightly higher than previously reported depression scores in MSA of 13 to 14.[3,4] This rate of depression is similar to that reported recently in a large North American study,[2] which found that 39% of patients had a mean BDI score of 17 or above, and was worse than that reported in PD. However, as the data were drawn from different studies, further matched studies need to be conducted to compare the degree and pattern of depression between MSA and PD. It is also known that the prevalence of depression using a clinical diagnosis of depression in parkinsonian syndromes is lower than using a cutoff score on the BDI.[22] This is likely to be at least partly due to the considerable overlap of physical symptoms in depression and Parkinsonism. This overlap would be even greater in the physically more affected patients with MSA. These results, therefore, should be interpreted with caution, and we suggest that the rate of clinically diagnosed depression is lower than the rate found using the BDI in this study. Nevertheless, at least moderate depression or anxiety was also reported by more than 70% of patients with MSA on the EQ-5D. As expected, depression scores correlated with the mental subscore of the SF-36 but, unlike in patients with PD, were not the main predictor for Hr-QoL scores in MSA. This finding suggests that whereas depression occurs in MSA and is a contributor to poor Hr-QoL, particularly the mental domain, it is not universally the most important factor associated with poor Hr-QoL in parkinsonian syndromes. Therefore, other factors play a greater role for Hr-QoL in MSA. Cognitive impairment does not appear to be related to poor Hr-QoL in MSA, which is consistent with the clinical finding that clinically relevant cognitive decline in MSA is uncommon. Sleep disturbance, as assessed on the PDSS, is related to worse mental functioning on the SF-36, which is consistent with findings in previous studies on sleep and Hr-QoL.[23] However, the correlation with other measures of Hr-QoL was weak, suggesting that despite the known disturbances of sleep in MSA,[24] compared to other aspects of this disorder, sleep disturbance contributes less to overall impairment of Hr-QoL. However, as only 19 patients in this study completed the PDSS, further studies into the role of sleep disturbances, including rapid eye movement sleep behavior disorder and sleep disordered breathing, on Hr-QoL are warranted. Age and sex did not correlate with Hr-QoL scores, a finding similar to the previous study.[2]

This study has limitations, most importantly due to its cross-sectional nature, which prevents analysis of causality. Thus, longitudinal studies are needed to determine which prospective factors lead to a deterioration of Hr-QoL. Second, although we were able to use the disease-specific clinical rating scale for MSA, the UMSARS, only generic measures were used to assess Hr-QoL. Thus, the results must be interpreted with caution, as these scales may have limited validity in patients with MSA. Third, depression was not assessed using a clinical evaluation of depression according to *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, or other clinical criteria but by the self-assessment rating scale the BDI. The validity of this scale in MSA has not been established against a clinical diagnosis of depression in MSA. Finally, we compared the results in patients with MSA from tertiary referral centers to those in patients with PD in a different community-based sample. Whereas the rates of depression and Hr-QoL in the PD study were similar to those reported in other clinical samples of patients with PD, such a comparison should be interpreted with caution and future studies should be conducted with matched controls.

In conclusion, the greater impact of MSA than PD patients was reflected in the worse scores on the generic Hr-QoL measures in this study. Only pain did not occur more frequently in MSA but was more common in MSA-P than in MSA-C. Depression scores are commonly increased, but depression does not appear to be the main contributor to poor Hr-QoL in MSA. Autonomic dysfunction and motor impairment are most closely associated with poor Hr-QoL in MSA, and management of MSA, therefore, should concentrate upon these aspects. Demographic features, disease duration, and cognition have little impact on Hr-QoL, as measured on generic instruments. Sleep dysfunction is moderately related to the mental domain of Hr-QoL scores only. However, given the small number of

patients assessed for sleep disturbances and limited number of assessed potentially influential factors for impaired Hr-QoL in MSA, including sexual dysfunction or urinary problems, future studies should explore the additional contribution of these factors on Hr-QoL in MSA.

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APPENDIX

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REFERENCES

1. 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.
2. Benrud-Larson LM, Sandroni P, Schrag A, Low PA. Depressive symptoms and life satisfaction in patients with multiple system atrophy. Mov Disord 2005;20:951–957.
3. Pilo L, Ring H, Quinn N, Trimble M. Depression in multiple system atrophy and in idiopathic Parkinson's disease: a pilot comparative study. Biol Psychiatry 1996;39:803–807.
4. Gill CE, Khurana RK, Hibler RJ. Occurrence of depressive symptoms in Shy-Drager syndrome. Clin Auton Res 1999;9:1–4.
5. 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.
6. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. J Auton Nerv Syst 1998;74: 189–192.
7. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427–442.
8. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
9. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571.
10. McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993;31:247–263.
11. EuroQol–a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199–208.
12. Schrag A, Selai C, Jahanshahi M, Quinn NP. The EQ-5D - a generic quality of life measure - is a useful instrument to measure quality of life in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2000;69:67–73.
13. Rubenstein LM, Voelker MD, Chrischilles EA, Glenn DC, Wallace RB, Rodnitzky RL. The usefulness of the Functional Status Questionnaire and Medical Outcomes Study Short Form in Parkinson's disease research. Qual Life Res 1998;7:279–290.
14. Fitzpatrick R, Peto V, Jenkinson C, Greenhall R, Hyman N. Health-related quality of life in Parkinson's disease: a study of outpatient clinic attenders. Mov Disord 1997;12:916–922.
15. Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. Neurology 1999;52:523–528.
16. Chaudhuri KR, Pal S, DiMarco A, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73:629–635.
17. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. Mov Disord 2000;15:1112–1118.
18. Persaud R. Correlation, regression, and repeated data. BMJ 1994; 308:1510.
19. Leentjens AF, Verhey FR, Luijckx GJ, Troost J. The validity of the Beck Depression Inventory as a screening and diagnostic instrument for depression in patients with Parkinson's disease. Mov Disord 2000;15:1221–1224.
20. Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. Mov Disord 2001;16: 507–510.
21. Schrag A, Jahanshahi M, Quinn NP. What contributes to depression in Parkinson's disease? Psychol Med 2001;31:65–73.
22. Tandberg E, Larsen JP, Aarsland D, Cummings JL. The occurrence of depression in Parkinson's disease. A community-based study. Arch Neurol 1996;53:175–179.
23. Reimer MA, Flemons WW. Quality of life in sleep disorders. Sleep Med Rev 2003;7:335–349.
24. Vetrugno R, Provini F, Cortelli P, et al. Sleep disorders in multiple system atrophy: a correlative video-polysomnographic study. Sleep Med 2004;5:21–30.