Excessive Daytime Sleepiness in Multiple System Atrophy (SLEEMSA Study)

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Background: Sleep disorders are common in multiple system atrophy (MSA), but the prevalence of excessive daytime sleepiness (EDS) is not well known.

Objective: To assess the frequency and associations of EDS in MSA.

Design: Survey of EDS in consecutive patients with MSA and comparison with patients with Parkinson disease (PD) and individuals without known neurologic disease.

Setting: Twelve tertiary referral centers.

Participants: Eighty-six consecutive patients with MSA; 86 patients with PD matched for age, sex, and Hoehn and Yahr stage; and 86 healthy subject individuals matched for age and sex.

Main Outcome Measures: Epworth Sleepiness Scale (ESS), modified ESS, Sudden Onset of Sleep Scale, Tandberg Sleepiness Scale, Pittsburgh Sleep Quality Index, disease severity, dopaminergic treatment amount, and presence of restless legs syndrome.

Results: Mean (SD) ESS scores were comparable in MSA (7.72 [5.05]) and PD (8.23 [4.62]) but were higher than in healthy subjects (4.52 [2.98]) \((P < .001)\). Excessive daytime sleepiness (ESS score >10) was present in 28% of patients with MSA, 29% of patients with PD, and 2% of healthy subjects \((P < .001)\). In MSA, in contrast to PD, the amount of dopaminergic treatment was not correlated with EDS. Disease severity was weakly correlated with EDS in MSA and PD. Restless legs syndrome occurred in 28% of patients with MSA, 14% of patients with PD, and 7% of healthy subjects \((P < .001)\). Multiple regression analysis (with 95% confidence intervals obtained using nonparametric bootstrapping) showed that sleep-disordered breathing and sleep efficiency predicted EDS in MSA and amount of dopaminergic treatment and presence of restless legs syndrome in PD.

Conclusions: More than one-quarter of patients with MSA experience EDS, a frequency similar to that encountered in PD. In these 2 conditions, EDS seems to be associated with different causes.

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patients (36%). Finally, 2 studies have independently reported that hypocretin-1 levels in the cerebrospinal fluid are normal in MSA\(^2\) despite the fact that hypocretin neurons in the brains of patients with MSA are reduced (<70% loss).\(^2\)

Excessive daytime sleepiness is a symptom that may further decrease the quality of life of patients with MSA, and, overall, it seems that the information regarding sleepiness in MSA is insufficient and somewhat contradictory in several areas. The goal of this multicenter study was to assess the prevalence, characteristics, and associations of EDS in a large group of patients with MSA and to compare them with those occurring in patients with PD and healthy subject individuals.

METHODS

This study is a multicenter survey of EDS in consecutive patients with MSA individually matched with patients with PD and healthy subjects without neurologic disorders. The patients and healthy subjects were seen in 12 tertiary care referral centers in Israel and 8 European countries.

INCLUSION CRITERIA

Consecutive patients with MSA diagnosed according to the criteria of the consensus statement on the diagnosis of MSA\(^11\) and seen at the movement disorders clinic of each participating center were included. Patients with PD diagnosed using standard criteria\(^1\) and matched for age, sex, and Hoehn and Yahr (H&Y) stage\(^1\) with each patient with MSA were included. In addition, subjects without relevant neurologic disease and matched for age and sex with each patient with MSA were also evaluated. Caregivers of the patients were excluded. Each participating center had to include at least 6 patients with MSA and, as subjects, the same number of patients with PD and healthy individuals matched according to the previously mentioned requirements.

MOTOR, MOOD, AND COGNITIVE EVALUATION

Disease severity for MSA and PD was evaluated using modified H&Y staging and the Schwab and England (S&E) Activities of Daily Living Scale.\(^14\) In addition, the motor section (Part III) of the Unified Parkinson Disease Rating Scale (UPDRS-III)\(^15\) was used to evaluate motor symptoms in PD, and part II of the Unified Multiple System Atrophy Rating Scale (UMSARS-II) was used to evaluate motor symptoms in MSA.\(^16\) Cognition and mood were evaluated using the Mini-Mental State Examination (MMSE)\(^17\) and the 17-item Hamilton Depression Rating Scale (HAMD-17).\(^18\) Type and amount of dopaminergic treatments, hypnotics, antidepressants, and neuroleptic drugs were recorded in each case. The daily levodopa equivalent dose was calculated according to the formula described by Hobson et al.\(^19\)

EVALUATION OF DAYTIME SLEEPINESS

Sleepiness was assessed using the modified Epworth Sleepiness Scale (M-ESS).\(^19\) which consists of all the questions from the ESS\(^20\) plus 4 additional questions assessing sleepiness in more active situations. When the patient was unable to answer the questionnaire because of cognitive problems, the M-ESS was filled out with the help of the caregiver. To investigate the presence of sleep attacks, we used the Sudden Onset of Sleep (SOS) Scale,\(^20\) which asks about how likely the patient is to fall asleep suddenly or unpredictably while doing the activities described in the M-ESS. Because patients with limited physical mobility cannot perform some of the activities described in these scales, we also assessed sleepiness using the Tandberg Sleepiness Scale\(^21\) (completed with the help of the caregiver). This scale simply asks about the amount of time a patient spends sleeping during the day, and it has been used often to assess sleepiness in PD.

NOCTURNAL SLEEP EVALUATION

Nocturnal sleep was assessed using the Pittsburgh Sleep Quality Inventory (PSQI).\(^22\) This questionnaire collects information regarding sleep duration, habitual sleep efficiency, sleep latency, presence of breathing problems during sleep, nightmares, sleep fragmentation or insomnia, and use of sleeping pills. We analyzed the PSQI global score and the individual values of several items contained in the inventory, such as sleep duration, sleep latency, habitual sleep efficiency, and frequency of bad dreams, visits to the lavatory, and sleep-disordered breathing (questions 5d and 5e regard “difficulties in breathing and snoring”). We also assessed the presence of restless legs syndrome (RLS) using the International Restless Legs Syndrome Study Group diagnostic criteria.\(^23\) Severity of RLS was rated by the patients by answering the following question: “Overall, how would you rate the RLS discomfort in your legs or arms? 4=very severe; 3=severe; 2=moderate; 1=mild; 0=none.” Presence of stridor during sleep and its time of appearance in relation to motor symptoms (before, simultaneously, or after the motor symptoms) was also recorded. Because most patients with MSA have RBD when recorded polysomnographically, self-awareness of RBD symptoms is not high in patients with MSA and PD,\(^1\) and a widely accepted questionnaire for screening of RBD in neurodegenerative disorders is not yet available; we did not investigate the possible presence of this parasomnia in the present study.

STATISTICAL ANALYSIS

We performed a repeated-measures analysis of variance using simple Tukey a posteriori contrast comparisons among the 3 groups. For qualitative measures, \(\chi^2\) and Fisher exact tests were performed when appropriate. Pearson correlations were performed between nocturnal sleep quality measures of the PSQI and the EDS scales with the motor and cognitive characteristics in each different group. Multiple regression analysis was performed to investigate the best possible models explaining EDS in each group. Because some of the variables had nonnormal distributions, \(\beta\) coefficients were validated through nonparametric bootstrapping.\(^24\) We used random resampling with replacement to obtain 10,000 bootstrapped samples. The outcomes measured were M-ESS and Tandberg Sleepiness Scale scores. The variables included in the model were age, levodopa equivalent dose, MMSE score, HAMD-17 score, RLS, UPDRS-III score, UMSAR-III score, sleep duration, habitual sleep efficiency, sleep-disordered breathing, and benzodiazepine use. The percentage of the total variance in the outcomes that was explained by a model was calculated as 100 \(\times R^2\).

RESULTS

We evaluated 86 patients with MSA (73 parkinsonian and 13 cerebellar) (mean [SD] age, 62.9 [7.9] years; age range, 44–82 years); 86 patients with PD matched for age (mean [SD] age, 62.9 [7.9] years; age range, 43–82 years), sex, and H&Y stage (mean [SD], 3.1 [0.9]); and 86 healthy
subjects matched for age (mean [SD] age, 62.5 [7.7] years; age range, 45-78 years) and sex, there being 42 men and 44 women in each group. Mean (SD) duration of disease was significantly shorter in the MSA group (4.4 [2.2] years; range, 1-34 years) than in the PD group (11.7 [7.8] years; range, 1-34 years) (P < .001). Mean (SD) activities of daily living scores as measured using the S&E scale were slightly worse in the MSA group (57.7 [20.5]; range, 10-90) than in the PD group (67.2 [19.6]; range, 20-100) (P < .001). The mean (SD) UMSARS-II score in patients with MSA was 24.4 (8.4) (range, 9-55), and the mean (SD) UPDRS-III score in patients with PD was 26.9 (14.3) (range, 3-74). The mean (SD) MMSE score was similar in MSA (27.6 [2.4]; range, 20-30) and PD (27.8 [2.4]; range, 16-30) but was lower than in healthy subjects (29.0 [1.5]; range, 23-30) (P < .001). The mean (SD) HAMD-17 score was worse in patients with MSA (8.8 [5.3]; range, 1-32; PD: 7.4 [5.0]; range, 0-29) than in healthy subjects (3.3 [4.1]; range, 0-17) (P < .001). Drug treatments received by the 3 study groups are detailed in Table 1.

Table 1. Drug Treatments Received by the Subject Individuals

<table>
<thead>
<tr>
<th>Group</th>
<th>Levodopa (mg)</th>
<th>DA Agonists</th>
<th>Daily Levodopa Equivalent Dose, Mean (SD) [Range], mg</th>
<th>COMT Inhibitors</th>
<th>MAO-Is</th>
<th>Antidepressants</th>
<th>Bz or Bz Agonists</th>
<th>Clonazepam</th>
<th>Neuroleptics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA (n=86)</td>
<td>79</td>
<td>22</td>
<td>572.1 (456.3) [0-17]</td>
<td>9.3</td>
<td>11.6</td>
<td>15.1</td>
<td>29.1b</td>
<td>26.6b</td>
<td>13.9d</td>
</tr>
<tr>
<td>PD (n=86)</td>
<td>86</td>
<td>61a</td>
<td>744.3 (489.4) [0-24]</td>
<td>25.6</td>
<td>15.1</td>
<td>18.6</td>
<td>15.1</td>
<td>14</td>
<td>6.9</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.2</td>
<td>9.3</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Abbreviations: Bz, benzodiazepines (includes clonazepam); COMT, catecol-oxymetiltransferase; DA, dopamine; MAO-I, monoamine oxidase inhibitor; MSA, multiple system atrophy; PD, Parkinson disease.

a Values are percentages of subjects in the group taking the medication except where indicated otherwise.
b P < .03 by x² test, MSA vs PD, and P < .01 by x² test, MSA and PD vs control.
c P < .04 by x² test, MSA vs PD, and P = .006 by x² test, MSA and PD vs control.
d P < .002 by x² test, MSA vs control.
e P < .001 by x² test, MSA vs PD.
f P < .01 by analysis of variance.

Table 2. Excessive Daytime Sleepiness and Nocturnal Sleep Characteristics (PSQI)

<table>
<thead>
<tr>
<th>Group</th>
<th>M-ESS</th>
<th>ESS</th>
<th>ESS &gt;10, %</th>
<th>Tandberg</th>
<th>SOS Scale</th>
<th>PSQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA (n=86)</td>
<td>8.30</td>
<td>6.16</td>
<td>[0-36]</td>
<td>7.22</td>
<td>5.05</td>
<td>[0-24]</td>
</tr>
<tr>
<td>PD (n=86)</td>
<td>8.79</td>
<td>5.45</td>
<td>[0-29]</td>
<td>8.23</td>
<td>4.62</td>
<td>[0-21]</td>
</tr>
<tr>
<td>Healthy subjects (n=86)</td>
<td>4.64</td>
<td>3.14</td>
<td>[0-14]</td>
<td>4.52 (2.98) [0-13]</td>
<td>2c</td>
<td>0.05 (0.21) [4.7] bc</td>
</tr>
</tbody>
</table>

Abbreviations: ESS, Epworth Sleepiness Scale; M-ESS, modified ESS; MSA, multiple system atrophy; PD, Parkinson disease; PSQI, Pittsburgh Sleep Quality Index; SOS, Sudden Onset of Sleep; Tandberg, Tandberg Sleepiness Scale.

a Values are mean (SD) [range] scores except where indicated otherwise. For Tandberg, the values in brackets are the percentage of participants with a score greater than 0.
b P < .001 by analysis of variance.
c P < .001 by x² test.

DAYTIME SLEEPINESS

The M-ESS, the SOS Scale, and the Tandberg Sleepiness Scale showed similar values in MSA and PD but were significantly higher in both patient groups than in healthy subjects (Table 2). Sleepiness in patients with MSA-parkinsonian was not different from that in patients with MSA-cerebellar (P = .4 and P = .8, respectively). More than one-quarter of the patients with PD and MSA had an ESS score higher than 10 (the value generally accepted as EDS) compared with only 2% of healthy subjects (P < .001). In patients with MSA, EDS (measured using any of the sleepiness scales) was not related to severity of disease (measured using the H&Y, S&E, and UMSARS-II scales) or depression (HAM-D-17) (Table 3). In patients with PD, however, EDS, as measured using the Tandberg Sleepiness Scale, was significantly related to severity of disease (as measured using the H&Y, S&E, and UPDRS-III scales); amount of dopaminergic treatment, and cognitive and mood impairment (Table 4). The sleepiness of patients with MSA and PD was similar to that of healthy subjects in that it appeared more often in situations with reduced physical activity. Four items on the M-ESS, however, better discriminated patients with MSA and PD from healthy subjects: “sitting and reading,” “lying down to rest in the afternoon when circumstances permit,” “as a passenger in a car for an hour without a break,” and “sitting and talking to someone” (P = .006 to < .001). In addition, one situation (“sitting and reading”) produced significantly higher scores in patients with PD than in patients...
with MSA (Figure 1). Mean (SD) SOS Scale scores were similar in patients with MSA (4.37 [5.32]) and patients with PD (3.4 [4.0]) and in both groups was higher than in healthy subjects (1.16 [1.85]) (P < .001) (Table 2). Forty-two patients with MSA, 28 with PD, and 14 healthy subjects had an SOS Scale score higher than 3 (P < .001). All SOS Scale scores of 4 or higher were significantly more common in MSA than in PD (P = .03). Three patients with MSA, 5 patients with PD, and 2 healthy subjects reported sudden onset of sleep episodes while driving. However, the situations most likely producing sudden onset of sleep episodes in the 3 groups were watching television, reading, and lying down (Figure 2).

**NOCTURNAL SLEEP CHARACTERISTICS**

The PSQI showed that patients with MSA and PD had poorer sleep quality than did healthy subjects but without differences between the 2 patient groups (Table 5). In 6 of the 7 subcomponents of the PSQI (“subjective sleep quality,” “sleep duration,” “habitual sleep efficiency,” “sleep disturbances,” “use of sleeping medication,” and “daytime dysfunction”), patients with MSA and PD had comparable values, significantly worse than those in healthy subjects (P < .006). Table 6 gives the characteristics of nocturnal sleep in healthy subjects as extracted from the PSQI and indicates that sleep duration or habitual sleep efficiency was higher in the healthy subject group than in both patient groups. Presence of sleep-related breathing disturbance (as extracted from questions 5d and 5e [“presence of loud snoring or breathing difficulties, once or twice a week or more often”]) was significantly more frequent in MSA (54.7%) than in PD (30.2%), and in both diseases more than in the control group (19.8%). Nocturnal stridor occurred in 24% of patients with MSA, with a similar prevalence in the MSA-parkinsonian (19 of 73 [26%]) and MSA-cerebellar (2 of 13 [15%]) subtypes. Stridor appeared before onset of motor symptoms in 6 patients with MSA (29%), simultaneously in 2 (10%), and after onset of motor symptoms in 13 (62%).

Total sleep time (C3 sleep duration) was negatively correlated with the M-ESS score in patients with MSA (r = −.401; P < .001) and PD (r = −.359; P = .001), that is, the longer the sleep duration at night, the lower the sleepiness during the daytime. The SOS Scale score was correlated with sleep duration only in patients with MSA (r = −.374, P < .001). There were no significant correlations between nocturnal sleep measures and EDS in the healthy subjects.

Patients with MSA and frequent breathing respiratory disturbances during sleep had slightly higher mean (SD) M-ESS scores than did those with infrequent breathing disturbances (9.5 [6.8] vs 6.8 [5], P = .04). This difference was not significant in patients with PD (10.5 [5.5] vs 8.1 [3.3], P = .07) or in the healthy subjects (5.2 [3.2] vs 4.7 [4.9], P = .19).
vs 4.5 [3.1], *P = .39). Finally, neither the presence of bad dreams nor the need to visit the lavatory was related to EDS.

RESTLESS LEGS SYNDROME

Restless legs syndrome occurred in 28% of patients with MSA, doubling the frequency encountered in patients with PD (14%) and 4 times more frequent than in the control group (7%) (*P < .001) (Table 7). Restless legs syndrome was reported as moderate to severe in 21 of 23 patients with MSA. Twenty-three of the 73 patients with MSA-parkinsonian (32.0%) and 1 of the 13 patients with MSA-cerebellar (8.0%) had RLS (*P = .07). Restless legs syndrome was unrelated to the amount of dopaminergic treatment in patients with MSA (mean [SD] levodopa dose equivalent of 590 [479] mg in patients with MSA with RLS vs 565 [450] mg in those without RLS; *P = .82). In contrast, patients with PD and RLS had significantly lower mean (SD) levodopa equivalent doses than did those without RLS (552.0 [278] vs 775.5 [510]; *P = .04). This difference in severity was not seen in patients with MSA with and without RLS (mean [SD] UMSARS-II score of 24.1 [5.5] vs 24.4 [9.3], *P = .87). Patients with MSA and RLS had similar mean (SD) M-ESS scores as those without RLS (8.6 [5.9] vs 8.18 [6.3], *P = .76). In contrast, patients with PD with RLS had higher mean (SD) M-ESS scores than did those without RLS (11.8 [8.3] vs 8.3 [4.7], *P = .04).

COMMENT

We show in this multicenter study that EDS occurs in 28% of patients with MSA, with a similar frequency and severity as in PD when patients are matched for disease severity, age, and sex. In both diseases, EDS occurred more often than in a control group matched for age and sex. These results are in contrast to those reported by Ghoo-rayeh et al, who found EDS more often in MSA than in PD. In that study, however, patients were matched for disease duration, resulting in much higher severity in the MSA group than in the PD group. In the present study, EDS in MSA seems to be unrelated to the amount of dopaminergic treatment or the PSQI global score. Subcomponent analysis of the PSQI, however, showed that habitual sleep efficiency and sleep-disordered breathing (ie, presence of snoring or difficulties in breathing during sleep) predicted EDS. In PD, on the other hand, presence of RLS was associated with EDS (measured using the M-ESS or the Tandberg Sleepiness Scale), whereas the amount of dopaminergic treatment predicted EDS only when sleepiness was measured using the Tandberg scale. Although the M-ESS and the Tandberg Sleepiness Scale
An unexpected result of this study was the high prevalence of RLS in patients with PD (matched for age, sex, and H&Y severity), and 7% of the control group fulfilled the criteria for RLS. Few studies assess the prevalence of RLS in MSA and PD. Ghorayeb et al reported RLS in 12.5% of patients with MSA in contrast to 3.2% in those with PD, but this difference was not significant. Wetter et al measured periodic leg movements of sleep in a group of 10 patients with PD, 10 patients with MSA, and 10 healthy subjects who were receiving no dopaminergic treatment and found that the prevalence of periodic leg movements of sleep was higher in PD than in MSA. In that study, however, patients with RLS were excluded. There are only a few studies of the prevalence of RLS in relatively large populations of PD and the International Restless Legs Syndrome Study Group criteria. They have reported prevalences ranging from 20.8% to 24.7%. In none of those studies was a healthy subjects group included. The reasons why RLS appeared more frequently in patients with MSA in the present study are unknown. We cannot exclude that other sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD. We can speculate that the more widespread sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD. We can speculate that the more widespread sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD. We can speculate that the more widespread sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD.

Table 5. PSQI Component Scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjective Sleep Quality</th>
<th>Sleep Latency</th>
<th>Sleep Duration</th>
<th>Habitual Sleep Efficiency</th>
<th>Sleep Disturbances</th>
<th>Use of Sleeping Medication</th>
<th>Daytime Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA (n=86)</td>
<td>1.37 (.85)</td>
<td>0.93 (1.16)</td>
<td>1.26 (1.08)</td>
<td>1.19 (1.19)</td>
<td>1.52 (.61)</td>
<td>0.80 (1.30)</td>
<td>1.35 (1.01)</td>
</tr>
<tr>
<td>PD (n=86)</td>
<td>1.37 (.87)</td>
<td>0.45 (.90)</td>
<td>1.34 (1.01)</td>
<td>1.19 (1.21)</td>
<td>1.36 (.57)</td>
<td>0.72 (1.25)</td>
<td>1.19 (9.4)</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>0.85 (.60)</td>
<td>0.70 (.93)</td>
<td>0.80 (.89)</td>
<td>0.63 (.99)</td>
<td>0.94 (.47)</td>
<td>0.35 (.81)</td>
<td>0.24 (.48)</td>
</tr>
</tbody>
</table>

Abbreviations: MSA, multiple system atrophy; PD, Parkinson disease; PSQI, Pittsburgh Sleep Quality Index.

Table 6. Nocturnal Sleep Characteristics Extracted From the PSQI

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration, h</th>
<th>Habitual Efficiency, %</th>
<th>Latency, min</th>
<th>Breathing Disturbances (Q5d and Q5e)</th>
<th>Bad Dreams or Nightmares (Q5h)</th>
<th>Visit Lavatory (Q5c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA (n=86)</td>
<td>6.38 (1.8)</td>
<td>76.6 (16.8) [27.2-100]</td>
<td>21 (25)</td>
<td>54.7a</td>
<td>40.7</td>
<td>66.3</td>
</tr>
<tr>
<td>PD (n=86)</td>
<td>6.27 (1.58)</td>
<td>78.8 (17.0) [40-100]</td>
<td>18 (26)</td>
<td>30.2</td>
<td>29.1</td>
<td>72.1</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>6.70 (1.26)</td>
<td>86.3 (13.1) [38.4-100]</td>
<td>17 (17)</td>
<td>19.8a</td>
<td>5.8c</td>
<td>40.7c</td>
</tr>
</tbody>
</table>

Abbreviations: MSA, multiple system atrophy; PD, Parkinson disease; PSQI, Pittsburgh Sleep Quality Index; Q, question.

Table 7. Prevalence and Severity of RLS

<table>
<thead>
<tr>
<th>Group</th>
<th>RLS Frequency, No. (%)</th>
<th>Mild</th>
<th>Moderate/Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA total (n=86)</td>
<td>24 (28)a</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>MSA-P (n=73)</td>
<td>23 (32)</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>MSA-C (n=13)</td>
<td>1 (8)b</td>
<td>1</td>
<td>0a</td>
</tr>
<tr>
<td>PD (n=86)</td>
<td>12 (14)d</td>
<td>4</td>
<td>8a</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>6 (7)</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: MSA, multiple system atrophy; MSA-P, MSA-parkinsonian; PD, Parkinson disease; RLS, restless legs syndrome.

of patients with MSA, 14% of patients with PD (matched for age, sex, and H&Y severity), and 7% of the control group fulfilled the criteria for RLS. Few studies assess the prevalence of RLS in MSA and PD. Ghorayeb et al reported RLS in 12.5% of patients with MSA in contrast to 3.2% in those with PD, but this difference was not significant. Wetter et al measured periodic leg movements of sleep in a group of 10 patients with PD, 10 patients with MSA, and 10 healthy subjects who were receiving no dopaminergic treatment and found that the prevalence of periodic leg movements of sleep was higher in PD than in MSA. In that study, however, patients with RLS were excluded. There are only a few studies of the prevalence of RLS in relatively large populations of PD and the International Restless Legs Syndrome Study Group criteria. They have reported prevalences ranging from 20.8% to 24.7%. In none of those studies was a healthy subjects group included. The reasons why RLS appeared more frequently in patients with MSA in the present study are unknown. We cannot exclude that other sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD. We can speculate that the more widespread sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD. We can speculate that the more widespread sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD. We can speculate that the more widespread sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD. We can speculate that the more widespread sensory or pain symptoms may mimic RLS and produce artificially higher rates of the disorder in MSA and in PD.
Table 8. Results of Multiple Linear Regression Models With the Outcome as Excessive Daytime Sleepiness, Measured Using the M-ESS and the Tandberg Sleepiness Scale

<table>
<thead>
<tr>
<th>Group and Outcome</th>
<th>Explanatory Variables</th>
<th>Entire Model R²</th>
<th>P Value</th>
<th>β Coefficients</th>
<th>95% CI</th>
<th>Standardized β Coefficient</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA</td>
<td>None</td>
<td>8.6</td>
<td>.72</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>M-ESS</td>
<td>Sleep duration</td>
<td>23.7</td>
<td>.02</td>
<td>−1.130</td>
<td>−0.205 to −0.002</td>
<td>−0.323</td>
<td>.03</td>
</tr>
<tr>
<td>Sleep-disordered breathing</td>
<td></td>
<td>0.026</td>
<td></td>
<td>0.001 to 0.049</td>
<td></td>
<td>0.213</td>
<td>.04</td>
</tr>
<tr>
<td>PD</td>
<td>Levodopa equivalent dose</td>
<td>33.2</td>
<td>&lt;.001</td>
<td>0.000</td>
<td>0.0000 to 0.0007</td>
<td>0.253</td>
<td>.02</td>
</tr>
<tr>
<td>M-ESS</td>
<td>RLS</td>
<td>28.4</td>
<td>.003</td>
<td>−4.412</td>
<td>−8.949 to −0.774</td>
<td>−0.282</td>
<td>.008</td>
</tr>
<tr>
<td>Sleep duration</td>
<td></td>
<td>−1.216</td>
<td>.01</td>
<td>−0.041</td>
<td>0.142</td>
<td>−0.353</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HAMD-17, 17-item Hamilton Depression Rating Scale; M-ESS, modified Epworth Sleepiness Scale; MSA, multiple system atrophy; NA, not applicable; PD, Parkinson disease; RLS, restless legs syndrome; Tandberg, Tandberg Sleepiness Scale; UPDRS-III, motor section (Part III) of the Unified Parkinson Disease Rating Scale.

*Explanatory variables with P > .07 have been omitted.

In conclusion, we found that EDS in MSA occurs frequently, as in PD, and is associated with decreased sleep duration and sleep-disordered breathing. In PD, EDS was not associated with these sleep disturbances but with the presence of RLS and the amount of dopaminergic treatment.

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REFERENCES


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Announcement

Trial Registration Required. As a member of the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archneurol.com.