Prospective Differentiation of Multiple System Atrophy From Parkinson Disease, With and Without Autonomic Failure

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Objective: To report preliminary results of a prospective ongoing study of multiple system atrophy (MSA) and Parkinson disease (PD), with a large subset of patients with PD with autonomic failure (25%), to evaluate autonomic indices that distinguish MSA from PD.

Methods: We used consensus criteria, detailed autonomic studies (Composite Autonomic Symptom Scale, Composite Autonomic Scoring Scale, thermoregulatory sweat test, and plasma catecholamines), and functional scales (Unified MSA Rating Scale [UMSARS] I-IV and Hoehn-Yahr grading) on a prospective, repeated, and ongoing basis.

Results: We report the results of a study on 52 patients with MSA (mean [SD], age, 61.1 [7.8] years; body mass index, 26.6 [5.5]; Hoehn-Yahr grade, 2.2 [0.8]; UMSARS I score, 10.4 [6.1]; and UMSARS II score, 13.0 [5.9]). Autonomic indices were highly significantly more abnormal in MSA than PD (P < .001) for the Composite Autonomic Scoring Scale (5.9 [1.9] vs 3.3 [2.3], respectively), Composite Autonomic Symptom Scale (54.4 [21.8] vs 24.7 [20.5], respectively), and thermoregulatory sweat test (percentage anhidrosis, 57.4% [35.2%] vs 9.9% [17.7%], respectively). These differences were sustained and greater at 1-year follow-up, indicating a greater rate of progression of dysautonomia in MSA than PD.

Conclusions: The severity, distribution, and pattern of autonomic deficits at study entry will distinguish MSA from PD, and MSA from PD with autonomic failure. These differences continue and are increased at follow-up. Our ongoing conclusion is that autonomic function tests can separate MSA from PD. Autonomic indices support the notion that the primary lesion in PD is ganglionic and postganglionic, while MSA is preganglionic.

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MULTIPLE SYSTEM ATROPHY (MSA) is a sporadic multisystem progressive disorder characterized by autonomic failure, with orthostatic hypotension (OH), neurogenic bladder and erectile dysfunction, cerebellar ataxia, corticospinal dysfunction, and parkinsonism that may be poorly responsive to levodopa.1,2 A major clinical dilemma is whether a patient with parkinsonism has Parkinson disease (PD) or MSA, as the prognosis of MSA is much worse. Autonomic involvement is common in PD but is more variable in severity than MSA.3,4 Mild OH is relatively common in PD and occasionally severe OH can occur.6,7 In retrospective studies from the Mayo Clinic, we reported that, when quantitative methods were used, the severity and distribution of autonomic deficits appear to distinguish MSA from PD.8-10 In contrast to MSA, which is predominantly a preganglionic disorder, autonomic pathology in PD is primarily postganglionic,8 which can be explored in autonomic function tests. Postganglionic adrenergic neuropathy forms the basis of neuroimaging studies of the postganglionic axons of the heart with iodine-123 meta-iodobenzylguanidine or other postganglionic adrenergic markers suitable for positron-emission tomography, whereas uptake is markedly reduced or absent in PD and usually normal in MSA.9,10

These studies and consensus criteria1 and their update2 have resulted in significant advances in the diagnosis of MSA. However, these approaches have been retrospective; lacking is a comprehensive prospective evaluation of autonomic function. As part of a National Institutes of Health–funded...
program project on MSA, we undertook a prospective study of patients with MSA and patients with PD who underwent full neurological and autonomic evaluation. We used standardized instruments to evaluate symptoms (Autonomic Symptom Profile), motor symptoms, including autonomic activities of daily living (Unified MSA Rating Scale [UMSARS]), and deficits (Composite Autonomic Scoring Scale [CASS] and percentage anhidrosis on the thermoregulatory sweat test [TST]). The Composite Autonomic Symptom Scale (COMPASS) provides a score of autonomic symptoms with appropriate weighting. We had 2 hypotheses. The first is that the severity, distribution, and pattern of autonomic failure at entry into the study will separate MSA from PD. The second is that, for MSA patients with mild autonomic failure, the increase in autonomic deficit documented at the first return visit (at the end of 1 year) will differentiate these patients from those with PD and will predict the rate of progression of MSA. The relevant indices are changes in CASS, TST percentage, and COMPASS score. We defined mild autonomic failure as autonomic deficits of TST (40%) and CASS (<=4). Presumably, the more severe and rapid progression of autonomic failure reflects the more widespread and intense distribution of neuronal loss and glial cytoplasmic inclusions.

Because autonomic failure is part of the criteria for the diagnosis of MSA, we have gone to pains to match the severity of clinical autonomic failure between MSA and PD. We included PD patients with florid autonomic failure, as long as they fulfilled criteria for PD. Specifically, 6 of 29 patients with PD also had autonomic failure. Patients with PD and autonomic failure were indistinguishable from those with MSA in OH, who often had more severe OH than MSA.

**METHODS**

**PATIENTS**

Parkinson Disease

We used criteria modified from those by Hughes et al, which clinically define definite PD. Patients were required to have 3 of the 3 cardinal features of PD (resting tremor, bradykinesia, and rigidity). We included PD patients with autonomic failure, defined as PD patients with severe and symptomatic OH that either preceded motor symptoms or comprised a dominant complaint. We excluded those with parkinsonism due to drugs (including neuroleptic drugs, a-methyl-dopa, reserpine, and metoclopramide) and other causes, dementia, and history of stroke, brain surgery for PD, and structural brain disease.

Multiple System Atrophy

We used the criteria from Gilman et al to identify patients with MSA. The diagnosis of probable MSA requires (1) the presence of OH (fall in systolic blood pressure of >= 30 mm Hg) and/or urinary incontinence (persistent involuntary partial or total bladder emptying accompanied by erectile dysfunction in men); and (2) parkinsonism or cerebellar ataxia that is poorly responsive to levodopa.

**TESTS AND INSTRUMENTS**

Patients stopped taking medications that could interfere with autonomic function for 5 half-lives of the drugs prior to autonomic testing. The TST is a modification of Guttmann’s quinizarin sweat test. An unclothed subject lies supine and his or her exposed body surface is covered with an indicator powder mixture. The body is warmed to 38°C; sweat is recognized by a change in color in the indicator. The sweat distribution is documented by digital photography. The digital images are processed by a pixel counter to derive an accumulative value for the area and percentage of anhidrosis.

The UMSARS is a validated, disease-specific scale that represents the diverse signs and symptoms of MSA. It can assess rates of progression and is sensitive to change over time. It has an activities of daily living score (UMSARS I, 12 questions) that evaluates motor (including autonomic) activities and the motor examination score (UMSARS II, 14 questions). Poorer health is signified by higher scores on the UMSARS.

The COMPASS is a test derived from the Autonomic Symptom Profile, which is a self-report instrument of 169 questions designed to provide an index of autonomic symptom severity. It yields 1 total score that reflects the overall severity of autonomic symptoms and 11 weighted subscale scores that assess severity of symptoms within the following domains: orthostatic intolerance, syncope, sexual failure (men only), bladder dysfunction, diarrhea, constipation, upper gastrointestinal symptoms, secretomotor dysfunction, sleep dysfunction, vasomotor symptoms, and pupillomotor symptoms. Autonomic Symptom Profile scores correlate with objective indices of autonomic function, and we have generated norms for the profile based on a sample of 245 healthy controls who completed the instrument. The change in COMPASS is a derivative of COMPASS and evaluates the change in symptoms over time on selected domains of symptoms. The focus is on 7 selected domains. We have made the instruments available to selected research centers.

The CASS is the measure of autonomic deficits derived from postganglionic sudomotor, adrenergic, and cardiovagal function. Results are compared with those in a database of 557 normal subjects. A 10-point score, which corrects for the confounding effects of age and sex, is generated. It has 3 subscales: adrenergic (range, 0-4), sudomotor (range, 0-3), and cardiovagal (range, 0-3). Generally, a total CASS score of 3 or less indicates no or mild autonomic failure; scores from 4 to 6 indicate moderate autonomic failure; and scores from 7 to 10 indicate severe autonomic failure.

**STATISTICAL ANALYSIS**

Summary statistics are presented as mean (standard deviation [SD]). Comparisons of initial evaluations and measures at month 12 were based on Wilcoxon signed rank sum or Mann-Whitney U tests. Spearman estimates of correlation were determined. P values were not adjusted for multiple comparisons.

**RESULTS**

**COMPARISON OF MSA WITH PD AT INITIAL EVALUATION**

Patients were compared for age, sex, and body mass index (calculated as weight in kilograms divided by height in meters squared) (Table 1). Patients with PD were slightly older. Mean age was 61.1 [7.8] years in patients with MSA and 66.0 [8.1] years in patients with PD (P = .01). Duration of disease was estimated to be 7.2 [2.9] years in patients with MSA and 10.1 [3.1] years in patients with PD. There were 32 patients with parkinsonian type MSA and 20 with cerebellar type MSA.
Autonomic Symptoms and Functional Status

The COMPASS score (Table 2) in patients with MSA was significantly greater \( (P < .001) \) than that of PD. Six of 11 domains were significantly more affected in MSA. Three of the domains related to blood pressure control (syncope, orthostatic intolerance, and vasomotor symptoms). The other 3 were domains focused on symptoms of disturbed secretomotor, bladder, and sleep function. These 6 domains, designated COMPASS select, were markedly different between MSA and PD and comprise the domains selected for focus in the subsequent analysis. For COMPASS select domains, scores in patients with MSA (47.7 [21.7]) were significantly higher than those in patients with PD (19.4 [16.0]) \( (P < .001) \).

Scores on UMSARS I, which evaluates functional status, were significantly greater \( (P < .001) \) in patients with MSA (21.5 [7.4]) and PD (10.4 [6.1]).

Table 1. Demographics and Autonomic and Functional Scores at Baseline and Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th></th>
<th>P Value</th>
<th></th>
<th>Follow-up at 1 Year</th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td></td>
<td>Patients With MSA</td>
<td>Patients With PD</td>
<td></td>
<td>Patients With MSA</td>
<td>Patients With PD</td>
</tr>
<tr>
<td>Sex, No.</td>
<td>M 26</td>
<td>F 12 17</td>
<td>.01</td>
<td>M 12</td>
<td>F 11</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Age, y (^b)</td>
<td>61.1 (7.8)</td>
<td>66.0 (8.1)</td>
<td>.01</td>
<td>64.0 (7.7)</td>
<td>68.2 (7.4)</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>BMI (^c)</td>
<td>27.2 (4.6)</td>
<td>26.6 (5.5)</td>
<td>.69</td>
<td>27.1 (6.4)</td>
<td>27.0 (5.8)</td>
<td>.69</td>
<td></td>
</tr>
<tr>
<td>CASS score (^d)</td>
<td>5.9 (1.9)</td>
<td>3.3 (2.3)</td>
<td>&lt;.001</td>
<td>5.1 (1.9)</td>
<td>2.9 (2.3)</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>TST result, % (^e)</td>
<td>57.4 (25.2)</td>
<td>9.9 (17.7)</td>
<td>&lt;.001</td>
<td>59.0 (34.6)</td>
<td>14.2 (26.2)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>UMSARS I score (^b)</td>
<td>21.5 (7.4)</td>
<td>10.4 (6.1)</td>
<td>&lt;.001</td>
<td>28.7 (10.7)</td>
<td>11.4 (5.4)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>UMSARS II score (^e)</td>
<td>22.7 (9.0)</td>
<td>13.0 (5.9)</td>
<td>&lt;.001</td>
<td>24.3 (6.6)</td>
<td>11.5 (6.8)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Hoehn-Yahr score (^g)</td>
<td>3.1 (1.0)</td>
<td>2.2 (0.8)</td>
<td>&lt;.001</td>
<td>3.4 (1.0)</td>
<td>2.1 (0.7)</td>
<td>&lt;.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CASS, Composite Autonomic Scoring Scale; MSA, multiple system atrophy; PD, Parkinson disease; TST, thermoregulatory sweat test; UMSARS, Unified Multiple System Atrophy Rating Scale.

Table 2. Autonomic Symptom Scores in Patients With MSA and PD at Baseline

<table>
<thead>
<tr>
<th>Autonomic Symptom Profile Domain</th>
<th>Patients With MSA</th>
<th>Patients With PD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic intolerance (^b)</td>
<td>22.02 (11.83)</td>
<td>9.89 (10.07)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Upper gastrointestinal symptoms (^c)</td>
<td>0.89 (1.43)</td>
<td>0.63 (1.29)</td>
<td>.42</td>
</tr>
<tr>
<td>Bladder dysfunction (^d)</td>
<td>10.73 (5.8)</td>
<td>4.16 (3.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Syncope (^d)</td>
<td>1.39 (2.09)</td>
<td>0.00 (0.00)</td>
<td>.001</td>
</tr>
<tr>
<td>Vasomotor symptoms (^e)</td>
<td>3.10 (3.04)</td>
<td>1.34 (2.22)</td>
<td>.01</td>
</tr>
<tr>
<td>Diarrhea (^d)</td>
<td>1.63 (3.64)</td>
<td>1.76 (3.07)</td>
<td>.62</td>
</tr>
<tr>
<td>Constipation (^d)</td>
<td>3.09 (2.81)</td>
<td>2.28 (2.57)</td>
<td>.18</td>
</tr>
<tr>
<td>Pudendal motor symptoms (^d)</td>
<td>1.62 (1.40)</td>
<td>1.30 (0.95)</td>
<td>.52</td>
</tr>
<tr>
<td>Sleep dysfunction (^f)</td>
<td>4.33 (3.34)</td>
<td>1.92 (2.33)</td>
<td>.003</td>
</tr>
<tr>
<td>Secretomotor dysfunction (^g)</td>
<td>5.83 (4.28)</td>
<td>2.94 (3.26)</td>
<td>.004</td>
</tr>
<tr>
<td>Sexual failure, men only (^h)</td>
<td>11.80 (3.91)</td>
<td>8.30 (7.19)</td>
<td>.05</td>
</tr>
<tr>
<td>COMPASS, without sexual failure (^i)</td>
<td>54.40 (21.81)</td>
<td>24.72 (20.44)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>COMPASS select, 6 domains (^j)</td>
<td>47.66 (19.74)</td>
<td>19.43 (15.97)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: COMPASS, Composite Autonomic Symptom Scale; MSA, multiple system atrophy; PD, Parkinson disease.

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with MSA than those with PD (10.4 [6.1]). The UMSARS II (Table 1) evaluates neurologic deficits; scores were also significantly different between MSA and PD ($P < .001$). The greater impairment in functional status in patients with MSA compared with those with PD was also reflected in Hoehn-Yahr ($P < .001$) and UMSARS IV ($P < .001$) grading.

**AUTONOMIC FUNCTION TESTS**

The CASS scores were significantly greater ($P < .001$) in MSA (5.9 [1.9]) than in PD (3.3 [2.3]) (Table 1 and Figure 1), indicating more severe and widespread autonomic failure in the former. The TST revealed more diffuse anhidrosis in MSA than PD ($P < .001$) with little overlap (Table 1 and Figure 1). Anhidrosis in MSA affected entire regions while that in PD and PD with autonomic failure tended to be distal, which is typical of a length-dependent neuropathic pattern. When the quantitative sudomotor axon reflex test component of the CASS was separately considered, postganglionic sudomotor involvement was not severe (52 patients with MSA, 1.75 [1.27]; 28 patients with PD, 0.79 [1.17]; $P = .001$). Orthostatic hypotension was common in both but more so in MSA ($P = .03$), while orthostatic increment in plasma norepinephrine was not significantly different.

**Figure 1.** Results of baseline autonomic function tests. Autonomic symptoms (Composite Autonomic Symptom Scale [COMPASS] and COMPASS select) based on the Autonomic Symptom Profile and deficits (Composite Autonomic Scoring Scale [CASS] and thermoregulatory sweat test) are significantly greater in multiple system atrophy (MSA) than Parkinson disease (PD) ($P < .001$). Orthostatic hypotension is common in both but more so in MSA ($P = .03$), while orthostatic increment in plasma norepinephrine was not significantly different.

**Figure 2** illustrates typical TST patterns in MSA, PD, and PD with autonomic failure. Patients with MSA (Figure 2A) shows regional and progressive anhidrosis not seen in PD or PD with autonomic failure. Patients with PD have a normal pattern or distal anhidrosis (Figure 2B) typical of postganglionic length-dependent denervation. Parkinson disease with autonomic failure is associated with either normal TST percentage (Figure 2C) or a pattern indicative of ganglionic and/or distal denervation (Figure 2D). Hence, while clinical autonomic failure in PD was indistinguishable from MSA, the distribution of anhidrosis was dramatically different.

When MSA is compared with the subset PD with autonomic failure ($n=6$), the latter has a peripheral pattern of anhidrosis and a significantly lower TST percentage (MSA, 27.1% [34.9%] vs PD 10.9% [7.4%]; $P = .01$). Results of the other tests (UMSARS I, COMPASS select, and CASS) were not significantly different between MSA and PD with autonomic failure.

**CORRELATIONS**

**Figure 3** shows the following correlations: autonomic deficits (CASS) correlate very well with autonomic symptoms (COMPASS) ($p=0.67$) and with COMPASS select ($p=0.68$) scores. Functional status evaluated by UMSARS I correlated well with both COMPASS select ($p=0.60$) and CASS ($p=0.53$) scores, suggesting that autonomic failure might be responsible for a significant part of functional deficits (Figure 2).
PROGRESSION OF AUTONOMIC
AND FUNCTIONAL STATUS

Autonomic and functional status progression is based on a preliminary analysis of 25 patients with MSA and 20 patients with PD who had completed follow-up evaluation at 12 months (Table 1 and Table 3). The change in autonomic symptoms (change in COMPASS), was almost 3-fold greater in MSA than PD (Table 3 and Figure 4). The change in COMPASS score was significantly greater (P = .008) in MSA (56.9 [45.9]) than PD (22.1 [32.8]). When only the 5 selected domains were used (change in COMPASS select), variance was less and the change in autonomic symptoms in MSA (49.8 [37.8]) was significantly greater (P = .007) than in PD (17.7 [26.5]) (Figure 4).

For the same patients, changes in UMSARS I and II scores continue to be more than 2 times greater in MSA than PD, progressing at a greater rate in MSA (Table 1 and Figure 4). Progression is well-exemplified in Figure 2, showing progressive anhidrosis in MSA that is not seen in PD.

COMMENT

The main findings of this prospective study to date are that functional status (UMSARS I) and especially certain select autonomic symptom domains (COMPASS select) and deficits (CASS and TST percentage) will distinguish PD from MSA. Distal sudomotor impairment with minimal progression is typical of PD. Note anhidrosis of distal digits in 2004 and progression only to fingers during 4 years (B). A patient with PD with autonomic failure may have a normal TST (C) or may show a more extensive sudomotor deficit (D), which on further testing reveals a predominantly ganglionic (large truncal segmental sweat loss with reduced QSART values) or a postganglionic, length-dependent deficit (feet and fingers). Sweating is shown in purple.

Figure 2. Representative thermoregulatory sweat test (TST) findings in multiple system atrophy (MSA) (A), Parkinson disease (PD) (B), and PD with autonomic failure (C and D). The regional (lower extremities) preganglionic sweat loss (abnormal TST response and a normal quantitative sudomotor axon reflex test [QSART] response) in 2002 with subsequent progression to global anhidrosis in 2005 is nearly pathognomonic of MSA. Distal sudomotor impairment with minimal progression is typical of PD. Note anhidrosis of distal digits in 2004 and progression only to fingers during 4 years (B). A patient with PD with autonomic failure may have a normal TST (C) or may show a more extensive sudomotor deficit (D), which on further testing reveals a predominantly ganglionic (large truncal segmental sweat loss with reduced QSART values) or a postganglionic, length-dependent deficit (feet and fingers). Sweating is shown in purple.
ings\(^1,^5\) that there is more widespread anhidrosis in MSA than PD. The distribution of anhidrosis in PD supports the notion that the lesion is postganglionic in PD irrespective of severity of autonomic failure\(^1,^8\) and serves as a reliable diagnostic test to differentiate PD with autonomic failure from MSA. The quantitative sudomotor axon reflex test results in MSA are significantly higher than those in PD, indicating that the denervated postganglionic axon undergoes some secondary changes. The values are typically less than 2, indicating that there are areas of anhidrosis revealed by TST that maintain a sweat response to quantitative sudomotor axon reflex test, supporting the presence of a preganglionic lesion in MSA. The reason for a lower score in PD reflects the much more restricted or absent area of anhidrosis in PD.

The subset of PD patients with autonomic failure in whom autonomic failure dominates the clinical phenotype is problematic to the clinician, as these patients may closely mimic those with MSA. When MSA is compared with the PD with autonomic failure subset, COMPASS select, UMSARS, and CASS scores are not significantly different, reflecting the influence of autonomic failure on these scores. On the other hand, the pattern of anhidrosis (peripheral or ganglionic in PD with autonomic failure and central-preganglionic in MSA) and anhidrosis percentage are significantly different in MSA. By combining quantitative sudomotor

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**Figure 3.** Regression of autonomic deficits (Composite Autonomic Scoring Scale [CASS]) with autonomic symptoms (Composite Autonomic Symptom Scale [COMPASS] select and COMPASS) and functional status (Unified Multiple System Atrophy [MSA] Rating Scale [UMSARS]) and of autonomic symptoms (COMPASS select) with functional status (UMSARS I). PD indicates Parkinson disease.
axon reflex test and TST, we found that intact quantitative sudomotor axon reflex test in anhidrotic areas is typical of MSA and confirms a preganglionic site of the lesion.

Plasma norepinephrine measured in both supine and standing positions has been reported to differentiate a preganglionic from a postganglionic disorder.\(^{34,35}\) Supine norepinephrine is reduced in widespread postganglionic disorders, such as paroxysmal atrial fibrillation, and normal in a preganglionic disorder like MSA.\(^{34,35}\) In contrast, the latter condition is associated with a failure of norepinephrine to approximately

| Table 3. COMPASS Change Scores in Patients With MSA and PD at 1-Year Follow-up |
|---------------------------------|-------------------|-------------------|
| **COMPASS Change Domain**       | **Patients With MSA** | **Patients With PD** |
| Orthostatic intolerance\(^b\)   | 29.52 (19.14)       | 10.50 (19.16)     |
| Upper gastrointestinal symptoms\(^b\) | 1.52 (1.99)       | 0.22 (2.46)       |
| Bladder dysfunction\(^b\)       | 8.81 (13.68)       | 2.50 (5.22)       |
| Vasomotor symptoms\(^b\)       | 2.14 (2.54)        | -0.56 (2.36)      |
| Diarrhea\(^b\)                  | 0.95 (4.64)        | 0.28 (1.18)       |
| Constipation\(^b\)              | 1.43 (4.78)        | 1.11 (2.74)       |
| Pupillomotor symptoms\(^b\)    | 2.29 (2.78)        | 1.67 (2.40)       |
| Sleep dysfunction\(^b\)        | 2.50 (8.25)        | 0.28 (3.31)       |
| Secretomotor dysfunction\(^b\) | 6.81 (8.45)        | 5.00 (5.99)       |
| Sexual failure, men only\(^c\)  | 1.82 (3.37)        | 2.00 (3.50)       |
| COMPASS change\(^b,d\)         | 56.93 (45.92)      | 22.11 (32.79)     |
| COMPASS change select\(^b,e\)  | 49.79 (37.84)      | 17.72 (26.45)     |

Abbreviations: COMPASS, Composite Autonomic Symptom Scale; MSA, multiple system atrophy; PD, Parkinson disease.

\(^a\) Based on Wilcoxon sign rank sum test.
\(^b\) Twenty-one patients with MSA and 18 with PD.
\(^c\) Eleven patients with MSA and 10 with PD.
\(^d\) Maximum score, 200.
\(^e\) Five domains.

Figure 4. Results at 1-year follow-up or last available autonomic data in patients with multiple system atrophy (MSA) or Parkinson disease (PD). Composite Autonomic Symptom Scale (COMPASS) change and COMPASS select change are based on a modified Autonomic Symptom Profile. CASS indicates Composite Autonomic Scoring Scale.

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double, because of widespread preganglionic failure disorder.\textsuperscript{34,35} The poor discriminatory value of norepinephrine or its intracellular metabolite, dihydroxyphenylglycol, indicates that PD is not characterized by sufficiently widespread postganglionic adrenergic failure to be regularly detectable by this test. This test does not have sufficient sensitivity for routine use to discriminate between MSA and PD.

The Autonomic Symptom Profile provides a comprehensive evaluation of autonomic symptoms and has been validated.\textsuperscript{14,15} The domains that are significantly different between MSA and PD are those on blood pressure control (syncope, orthostatic intolerance, and vasomotor symptoms) and dysfunctional secretomotor, bladder, and sleep. The high correlation of COMPASS select score with CASS score supports the notion that these autonomic symptoms are due to autonomic failure in MSA (and PD). Its high correlation with UMSARS I and II scores emphasizes that autonomic dysfunction affects activities of daily living and that autonomic dysfunction parallels neurologic deficits. The high discriminatory value of change in COMPASS scores throughout 12 months emphasizes that change in autonomic function over time is greater, almost 3-fold, than PD.

One potential limitation of our study is the reduced number of patients at follow-up compared with the number recruited. We have therefore not been able to test the second part of our hypothesis, that the rate of change of autonomic failure in those with initially mild autonomic deficits will distinguish MSA from PD. The main reasons for the inability to return for autonomic evaluation are death and incapacity. We minimized this problem by the use of UMSARS I and change in COMPASS score, which allows for an evaluation of autonomic symptoms and activities of daily living by telephone interview. The results at 1 year likely reflect an underestimate of deterioration in MSA, because the most common reason for inability to return was incapacity or death. The median time to death from entry in the study, according to Kaplan-Meier estimate of survival, was 2.1 years (not shown). Although we use consensus criteria,\textsuperscript{1} 1 limitation is that the diagnosis of MSA is still an assumption. Five patients have died since starting the study. In all cases, patients who underwent brain autopsy studies had pathologically confirmed MSA, suggesting that the consensus criteria are relatively robust. Another limitation of the study is the relatively advanced stage of the disease when MSA diagnosis is made. This limitation reflects the strict set of criteria. We plan to explore the predictive value of our evaluative approach in cases of possible MSA within 4 years of onset.

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