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Prospective Differentiation of Multiple System Atrophy from Parkinson's Disease, with and without Autonomic Failure

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Abstract

Objective—The severity, distribution, and pattern of autonomic failure appear to be different in multiple system atrophy (MSA) compared with Parkinson's disease (PD), but reports have been retrospective reviews and have tended to exclude PD with autonomic failure (PD_AF). We report preliminary results of a prospective ongoing study of MSA and PD, with a large subset of PD_AF (25%) to evaluate autonomic indices that distinguish MSA from PD.

Methods—We used Consensus criteria, detailed autonomic studies (composite autonomic symptom score (COMPASS), composite autonomic severity score (CASS), thermoregulatory sweat test percent anhidrosis (TST%), plasma catecholamines, and functional scales (Unified MSA rating scale (UMSARS) I–IV, Hoehn-Yahr grading) on a prospective, repeated, and ongoing basis.

Results—We report the results of a study based on 52 patients with MSA (61.1±7.8 years; BMI 27.2±4.6; Hoehn-Yahr grade, 3.2±0.9; UMSARS_1 21.5±7.4; UMSARS_2, 22.7±9.0) and 29 patients with PD, including PD_AF (66.0±8.1 years; BMI 26.6±.5.5; Hoehn-Yahr grade, 2.2±0.8; UMSARS_1 10.4±6.1; UMSARS_2, 13.0±5.9). Autonomic indices were highly significantly more abnormal in MSA than PD ($P<0.001$) for each of: CASS (5.9±1.9 vs. 3.3±2.3), COMPASS (54.4 ±21.8 vs. 24.7±20.5), TST% (57.4±35.2 vs. 9.9±17.7). These differences were sustained and greater at 1 year follow-up indicating a greater rate of progression of dysautonomia in MSA than PD.

Interpretation—The severity, distribution, and pattern of autonomic deficits at entry will distinguish MSA from PD and MSA from PD_AF. These differences continue and increase with 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/postganglionic while MSA is preganglionic.

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Introduction

Multiple system atrophy (MSA) is a sporadic multi-system progressive disorder characterized by autonomic failure, with orthostatic hypotension (OH), neurogenic bladder/erectile dysfunction, cerebellar ataxia, corticospinal dysfunction, plus parkinsonism that may be poorly levodopa-responsive.[1, 2] A major clinical dilemma for the clinician is whether a patient with parkinsonism has Parkinson's disease (PD) or MSA, since the prognosis of MSA is much worse. Autonomic involvement is common in Parkinson's disease but is more variable in severity than MSA.[3–5] Mild OH is relatively commonly in PD and occasionally severe OH can occur.[6, 7] In the Mayo retrospective studies, we reported that, when quantitative methods were used, the severity and distribution of autonomic deficits appeared to distinguish MSA from PD.[4, 5] In contrast to MSA, which is predominantly a preganglionic disorder, autonomic pathology in PD is primarily postganglionic,[9] a fact that could be exploited in autonomic function tests. Indeed postganglionic adrenergic neuropathy forms the basis of neuroimaging studies of the postganglionic axons of the heart with [^{123}I]MIBG or other postganglionic adrenergic markers suitable for PET scanning, where uptake is markedly reduced or absent in PD and usually normal in MSA.[10–14]

The studies above and Consensus criteria[1] and its update[2] have resulted in significant advances. However, these approaches have been retrospective; lacking is a comprehensive prospective evaluation of autonomic function. As part of an NIH-funded program project on MSA, we undertook a prospective study of MSA and PD patients who underwent full neurological, and autonomic evaluation, using standardized instrument to evaluate symptom (autonomic symptom profile (ASP), motor including autonomic activities of daily living (UMSARS), and deficits (composite autonomic severity score (CASS); percentage anhidrosis on thermoregulatory sweat test (TST%). The composite autonomic symptoms score (COMPASS) provides a score of autonomic symptoms with appropriate weighting.[22, 23] 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 hypothesis is that, for those 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 MSA from PD and is predictive of the rate of progression of MSA. The relevant indices are changes in CASS, TST%, and COMPASS (COMPASS_change). We defined mild autonomic failure as autonomic deficits of TST% <40% of 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.

Since autonomic failure is part of the criteria for the diagnosis of MSA,[1, 2] 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, 6/29 PD patient had Parkinson's disease with autonomic failure (PD_AF), defined as PD patients with symptomatic and severe OH that either preceded or dominated symptomatology. Patients with PD_AF were indistinguishable from MSA in OH and indeed often had more severe OH than MSA.

Methods

Patients

Parkinson's disease—We utilized criteria modified from Hughes et al.[24] that defines clinically definite PD. Patients were required to have the presence of 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 parkinsonism due to drugs

(including neuroleptics, α-methyldopa, reserpine, metoclopramide), other causes of parkinsonism, dementia, history of stroke, history of brain surgery for Parkinson's disease, and history of structural brain disease.

Multiple system atrophy—We use the criteria of Gilman et al.[1, 2] The diagnosis of probable MSA requires (1) the presence of OH (fall in systolic BP ≥ 30 mm Hg) or urinary incontinence (persistent involuntary partial or total bladder emptying, accompanied by erectile dysfunction (in men) or both; (2) poorly levodopa responsive parkinsonism or cerebellar ataxia.

Tests and Instruments

Patients stopped medications that could interfere with autonomic function for 5 half lives of the drugs prior to autonomic testing.

Thermoregulatory sweat test (TST) is a modification of Guttmann's[25] quinizarin sweat test. Unclothed subjects lie supine and exposed body surface is covered with an indicator powder mixture[26, 27] With warming to 38°C, sweating is recognized by indicator color change. 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 of anhidrosis and the percentage of anhidrosis (TST%).

The Unified Multiple System Atrophy Rating Scale (UMSARS) is a validated, disease-specific scale representing the diverse signs and symptoms in MSA.[28] It can assess rates of progression and is sensitive to change over time.[29] It has an Activities of Daily Living score (UMSARS_1, 12 questions) that evaluates motor including autonomic activities and the Motor Examination score (UMSARS_2, 14 questions). Poorer health is signified by higher scores on the UMSARS scales.

Composite autonomic Symptom Score (COMPASS) is the score derived from the ASP, which is a self-report instrument of 169 questions designed to provide an index of autonomic symptom severity.[30] It yields one total score reflecting overall severity of autonomic symptoms and eleven weighted subscale scores that assess severity of symptoms within the following domains: orthostatic intolerance, syncope, sexual failure (males only), bladder dysfunction, diarrhea, constipation, upper gastrointestinal (GI) symptoms, secretomotor dysfunction, sleep dysfunction, vasomotor symptoms, and pupillomotor symptoms. ASP scores correlates with objective indices of autonomic function,[30] and we have generated norms for the profile based on a sample of 245 healthy controls who completed the instrument.[23] COMPASS_change 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.[31, 32]

Composite Autonomic Severity Score (CASS) is the score of autonomic deficits derived of postganglionic sudomotor, adrenergic, and cardiovagal function.[33, 34] Results are compared to a normative database of 557 normal subjects.[35] A 10-point score (CASS) is generated that corrects for the confounding effects of age and gender.[36] It has three subscales: adrenergic (range = 0–4), sudomotor (range = 0–3), and cardiovagal (range = 0–3). Generally, a total CASS score ≤ 3 indicates no or mild autonomic failure, scores from 4–6 indicate moderate autonomic failure, and scores from 7–10 indicate severe autonomic failure.

Statistical analysis—Summary statistics were presented as means and standard deviations (SD). Comparisons of initial evaluation and month twelve measures were based on Wilcoxon signed rank sum/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 on age, gender and BMI (Table 1). PD patients were slightly older. Mean age was 61.1±7.8 years in MSA and 66.0±8.1 years in PD (P=0.011). Duration of disease was estimated to be 7.2±2.9 years in MSA and 10.1±5.1 years in PD. Breakdown by type of MSA was as follows: MSA-P = 32, MSA-C = 20.

Autonomic Symptoms and Functional Status

COMPASS (Table 2) for MSA was significantly greater (P<0.001) than that of PD. Six of eleven domains were significantly more affected in MSA. Three of the domains related to BP control (syncope, orthostatic intolerance, vasomotor). The other three were domains focused on symptoms of disturbed secretomotor, bladder, and sleep function. These six domains, designated COMPASS_Select, were markedly different between MSA and PD and comprise the domains selected for focus in subsequent analysis. For COMPASS_Select domains, MSA at 47.7±19.7 was significantly higher than PD, at 19.4±16.0 (P<0.001), being 245% that of PD.

UMSARS_1 (Table 1), evaluates functional status and was significantly greater (P<0.001) at 21.5±7.4 in MSA than PD (10.4±6.1). UMSARS_2 (Table 1) evaluates neurologic deficits, was also significantly different (P<0.001). The greater impairment in functional status was also reflected in Hoehn-Yahr (P<0.001) and UMSARS_4 (P<0.001) grading in MSA than PD.

Autonomic Function Tests

CASS was significantly greater (P<0.001) in MSA (5.9±1.9) than PD (3.3±2.3) (Table 1; Figure 1), indicating more severe and widespread autonomic failure in MSA than PD. The TST% demonstrated more diffuse anhidrosis in MSA than PD (Table 1; Figure 1; P<0.001) with little overlap. Anhidrosis in MSA affected entire regions while that in PD and PD_AF tended to be distal, typical of a length-dependent “neuropathic” pattern. When the QSART component of CASS was separately considered, postganglionic sudomotor involvement was not severe (MSA: N=52, 1.75±1.27; PD: N=28, 0.79±1.17, P=0.001). OH was common in PD and almost invariable in MSA (Figure 1). Supine norepinephrine (NE) and its orthostatic increment was not significantly different between MSA and PD (NS).

Figure 2 illustrates typical TST patterns in MSA, PD and PD_AF. MSA (top left) shows regional and progressive anhidrosis not seen in PD or PD_AF. PD patients have a normal pattern or distal anhidrosis (top right) typical of postganglionic length-dependent denervation. PD_AF is associated with either normal TST (bottom left) or a pattern indicative of ganglionic and/or distal denervation (bottom right). Hence while clinical autonomic failure of PD_AF was indistinguishable from MSA, the distribution of anhidrosis was dramatically different.

When MSA is compared with the subset of PD_AF patients alone (N=6), PD_AF has a peripheral pattern of anhidrosis and a significantly lower TST% than MSA (MSA 27.1±34.9 vs. PD 10.9±7.4; P=0.01). The other tests (UMSARS_1, COMPASS_Select, CASS) were not significantly different between MSA and PD_AF.

Correlations

Figure 3 shows the following correlations: Autonomic deficits (CASS) correlate very well with autonomic symptoms (COMPASS) (Rho = 0.67) and with COMPASS_Select (Rho = 0.68). Functional status evaluated by UMSARS_1 correlated well with both COMPASS_Select (Rho=0.60) and CASS (Rho=0.53), suggesting that autonomic failure might be responsible for a significant part of functional deficits (Figure 2).

Progression of Autonomic and Functional Status

This 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 (Tables 1 and 3). The change in autonomic symptoms, (COMPASS_Change) was almost three-fold greater in MSA than PD (Table 3; Figure 4). COMPASS_Change at 56.9±45.9 was significantly greater (P=0.008) in MSA than PD (22.1±32.8). When domains were confined to the five selected (COMPASS_Change_Select), variance was less and the change in autonomic symptoms in MSA at 49.8±37.8 was significantly greater (P=0.007) than in PD (17.7±26.5) (Figure 4).

For the same patients, changes in UMSARS_1 and 2 continue to be more than 2 times greater in MSA than PD and progress at a greater rate in MSA (Table 1; Figure 4). Progression is well-exemplified in Figure 2, showing progressive anhidrosis in MSA, not seen in PD.

Discussion

The main findings of this prospective study to date are that functional status (UMSARS_1) and especially certain select autonomic symptom domains (COMPASS_Select) and deficits (CASS; TST%) will distinguish PD from MSA. Additionally, a repeat study in 12 months will further differentiate the two conditions, since MSA is characterized by a much more rapid progression of dysautonomia and functional status. This two-step approach of systematic evaluation at entry and at one year enhances the ability of the clinician to diagnose MSA with greater sensitivity and specificity.

While autonomic failure has long been recognized as being an integral component of MSA, much of the focus has been confined to presence of OH and neurogenic bladder. This study confirms both the observation that OH is almost invariably present in MSA[4, 5, 15] but that OH is also relatively common in PD,[6, 7] being present in 41.7% (baseline) and 29.4% (1-year). The frequency of OH in PD should not be surprising, since OH is relatively common in PD subjects of this age group[37, 38] and there is, additionally, postganglionic adrenergic denervation in PD.[9, 37, 38] This study emphasizes the cautionary point that the presence of OH as the sole autonomic manifestation in PD is not a strong red flag for MSA.

The selection of autonomic function tests was done with two goals in mind. We selected tests that we hypothesized, based on preliminary data and autonomic pathophysiology, should discriminate between MSA and PD. Second, we chose tests that were currently available at clinical autonomic laboratories, that are well-validated and reproducible, with a coefficient of variability <20%. MSA differs from PD in the involvement of hypothalamic regions responsible for thermoregulation,[39, 40] in addition to involvement of preganglionic neurons, [41] so that the distribution of anhidrosis should be more diffuse. The finding in this study that diffuse anhidrosis is usually present in MSA confirms our earlier findings[4, 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[5, 9] and serves as a reliable diagnostic test to differentiate PD_AF from MSA. The QSART values in MSA are significantly higher than that of PD, indicating that the denervated postganglionic axon undergoes some secondary changes. Of note is that the values are typically <2 indicating that there are areas of anhidrosis on TST that maintain a sweat response to QSART, supporting 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_AF patients where autonomic failure dominates the clinical phenotype is problematic to the clinician since they could closely mimic MSA. When MSA is compared with PD_AF subset alone, COMPASS_Select, UMSARS, and CASS 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_AF and central-preganglionic in MSA) and %-anhidrosis are significantly different in MSA. Additionally by combining QSART and TST, intact QSART in anhidrotic areas is typical of MSA and confirms a preganglionic site of the lesion.

Plasma norepinephrine measured in both the supine and standing positions has been reported to differentiate a preganglionic from postganglionic disorder.[42, 43] Supine norepinephrine is reduced in widespread postganglionic disorder such as PAF and normal in a preganglionic disorder of MSA.[42, 43] In contrast, the latter condition is associated with a failure of norepinephrine to approximately double, because of widespread preganglionic failure disorder.[42, 43] The poor discriminatory value of norepinephrine or its intracellular metabolite, DHPG, 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.[23, 30] The domains that are significantly different between MSA and PD are those on BP control (syncope, orthostatic intolerance, vasomotor) and dysfunctional secretomotor, bladder, and sleep. The high correlation of COMPASS_select with CASS supports the notion that these autonomic symptoms are due to autonomic failure in MSA (and PD). Its high correlation with UMSARS 1 and 2 emphasize that autonomic dysfunction affect activities of daily living and that autonomic dysfunction parallels neurologic deficits. The high discriminatory value of COMPASS_Change over 12 months emphasize that change in autonomic function over time is greater, being almost 3-fold that of PD.

One potential limitation of the study is the reduced number of patients at follow-up compared to the number recruited. We have therefore not been able to test part 2 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 inability to return for autonomic evaluation are death and incapacity. We minimized the problem by the use of UMSARS 1 and COMPASS_Change, 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 since 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,[1] one 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 have 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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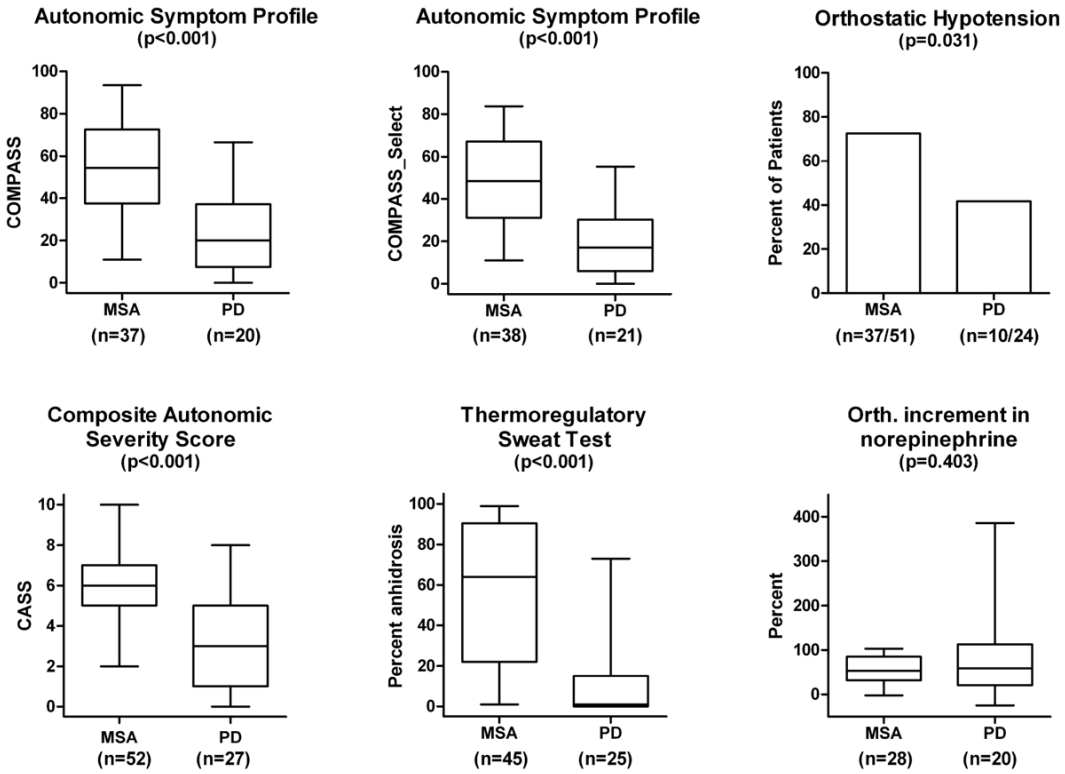

Figure 1.

Results at baseline. Autonomic symptoms (COMPASS and COMPASS_Select) based on the Autonomic Symptom Profiles, deficits (composite autonomic scoring scale, thermoregulatory sweat test) are significantly greater in MSA than PD (P<0.001). Orthostatic hypotension is common in both but more so in MSA (P=0.031) while orthostatic increment in plasma norepinephrine was not significantly different.

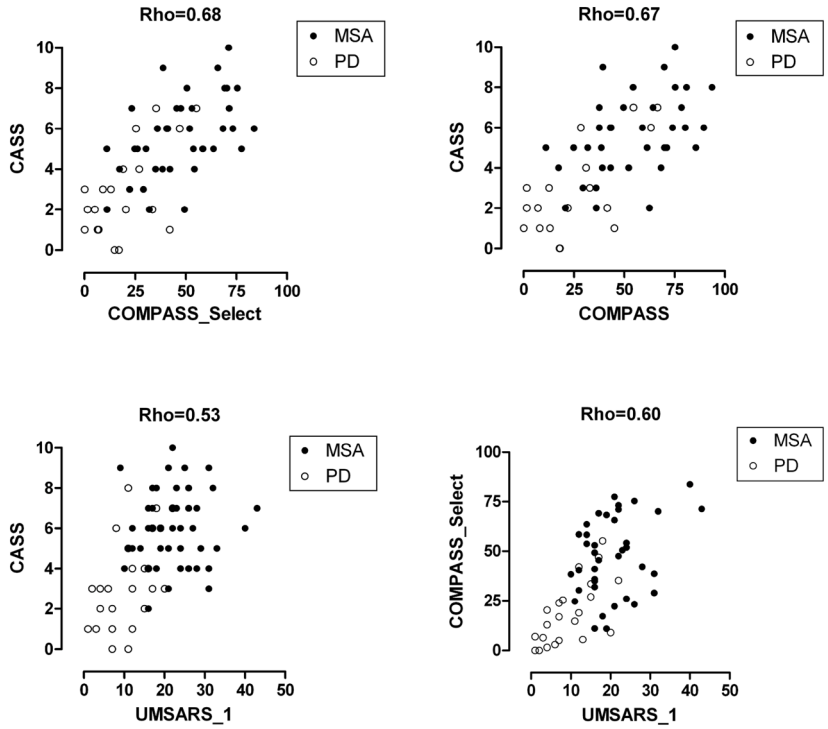

Figure 2.

Representative thermoregulatory sweat test (TST) findings in Multiple System Atrophy (MSA, left upper panel), Parkinson's Disease (PD, right upper panel) and PD_AF (lower two panels). The regional (lower extremities) preganglionic sweat loss (TST abnormal, QSART normal) 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 feet and toes in 2004 and progression only to fingers over 4 years (right upper). PD_AF may have a normal TST (left-lower) or may show a more extensive sudomotor deficit (right-lower) that on further testing with QSART reveals a predominantly ganglionic (large truncal segmental sweat loss with reduced QSART) or a postganglionic, length-dependant deficit (feet, fingers). (Sweating in purple shading)

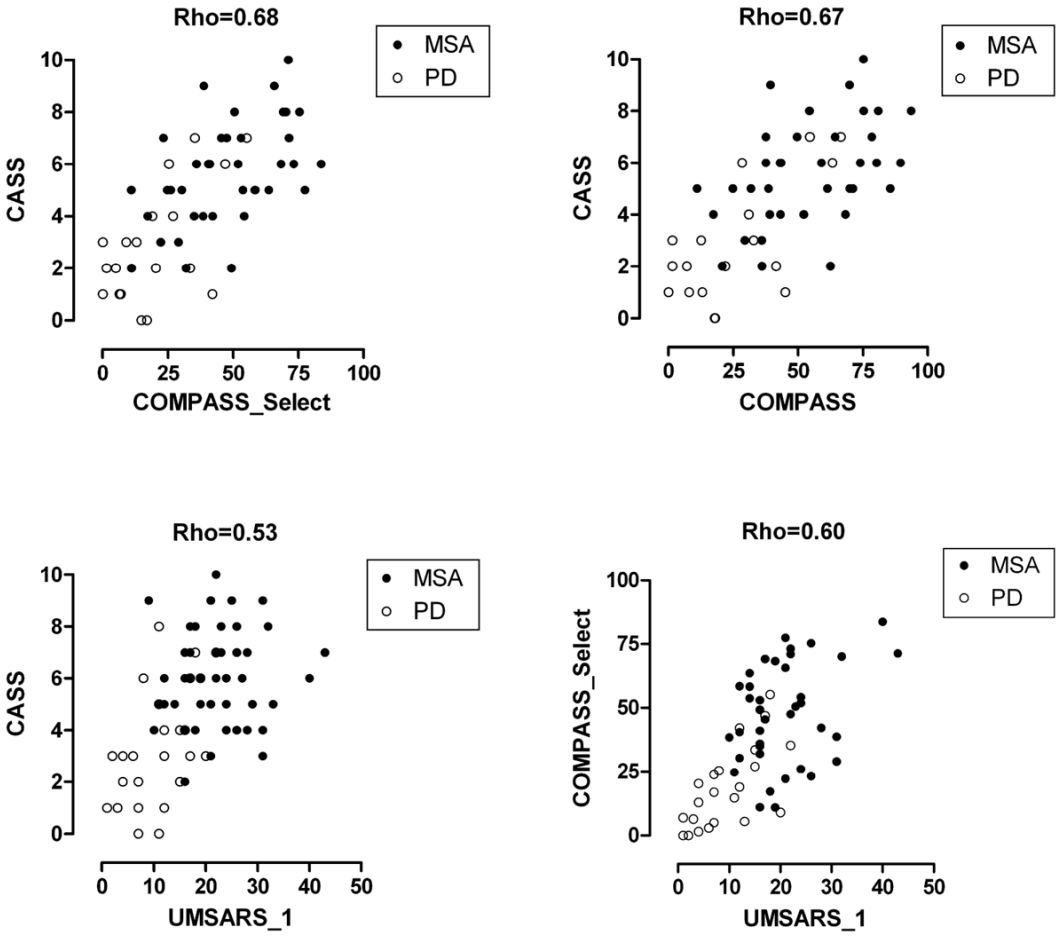

Figure 3.
Regression of autonomic deficits (CASS) with autonomic symptoms (COMPASS_Select, COMPASS) and functional status (UMSARS) and of autonomic symptoms (COMPASS_Select) with functional status (UMSARS_1).

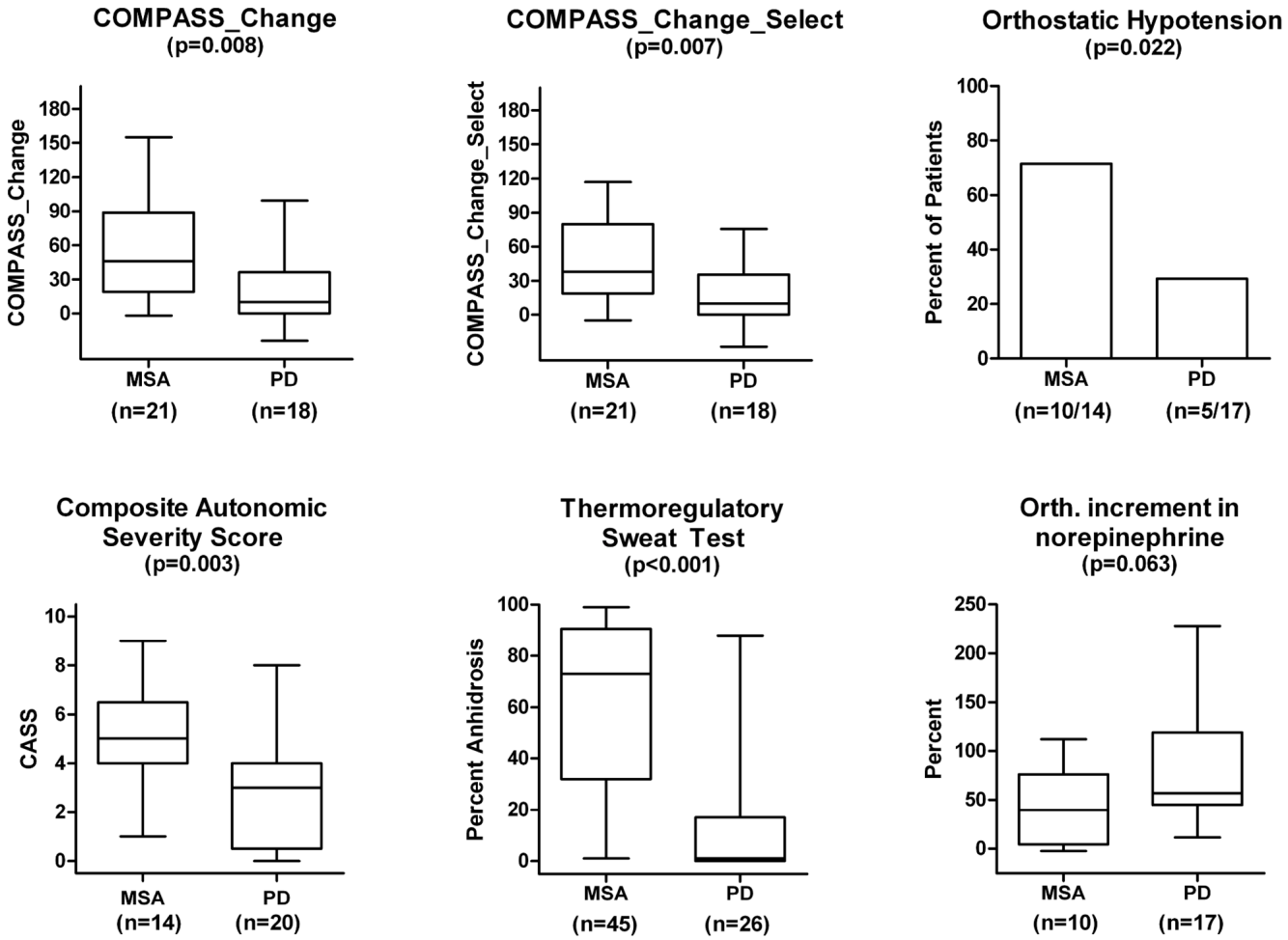

Figure 4.

Results at 1 year of follow up or last available autonomic data.

COMPASS_Change and COMPASS_Change_Select based on a modified Autonomic Symptom Profile, percent of patients with orthostatic hypotension, CASS, TST%, and orthostatic increment in plasma norepinephrine expressed as a percent.

Table 1

Summary demographics, autonomic and functional scores at baseline and after one year follow-up.

Variable	Dx	baseline			year 1		
		N	mean (SD)	P-Value*	N	mean (SD)	P-Value*
Gender	MSA PD	male: 26 female: 26 male: 17 female: 12			male: 12 female: 13 male: 11 female: 9		
Age	MSA PD	52 29	61.1 (7.8) 66.0 (8.1)	0.011	25 20	64.0 (7.7) 68.2 (7.4)	0.062
BMI	MSA PD	46 29	27.2 (4.6) 26.6 (5.5)	0.687	15 18	27.1 (6.4) 27.0 (5.8)	0.691
CASS	MSA PD	52 27	5.9 (1.9) 3.3 (2.3)	<0.001	14 20	5.1 (1.9) 2.9 (2.3)	0.003
TST%	MSA PD	45 25	57.4 (35.2) 9.9 (17.7)	<0.001	45 26	59.0 (34.6) 14.2 (26.2)	<0.001
UMSARS_1	MSA PD	52 29	21.5 (7.4) 10.4 (6.1)	<0.001	25 20	28.7 (10.7) 11.4 (5.4)	<0.001
UMSARS_2	MSA PD	52 29	22.7 (9.0) 13.0 (5.9)	<0.001	14 20	24.3 (6.6) 11.5 (6.8)	<0.001
Hoehn-Yahr	MSA PD	52 29	3.1 (1.0) 2.2 (0.8)	<0.001	22 20	3.4 (1.0) 2.1 (0.7)	<0.001

*Based on Wilcoxon sign rank sum test

Table 2

Autonomic symptom scores for patients with MSA and PD at baseline.

Autonomic Symptom Profile Domains	DX	N	Mean	SD	P-Value*
Orthostatic Intolerance	MSA PD	47 23	22.02 9.89	11.83 10.07	<0.001
Upper Gastrointestinal Symptoms	MSA PD	47 24	0.89 0.63	1.43 1.29	0.416
Bladder Dysfunction	MSA PD	49 25	10.73 4.16	5.58 3.31	<0.001
Syncope	MSA PD	49 25	1.39 0.00	2.09 0.00	0.001
Vasomotor Symptoms	MSA PD	48 25	3.10 1.34	3.04 2.22	0.012
Diarrhea	MSA PD	49 25	1.63 1.76	3.64 3.07	0.621
Constipation	MSA PD	49 25	3.09 2.28	2.81 2.57	0.179
Pupillomotor Symptoms	MSA PD	49 25	1.62 1.30	1.40 0.95	0.518
Sleep Dysfunction	MSA PD	44 23	4.33 1.92	3.34 2.33	0.003
Secretomotor Dysfunction	MSA PD	44 24	5.83 2.94	4.28 3.26	0.004
Sexual Failure (men only)	MSA PD	25 15	11.80 8.30	3.91 7.19	0.054
COMPASS (w/o Sexual Failure)	MSA PD	37 20	54.40 24.72	21.81 20.44	<0.001
COMPASS_Select (6 domains)	MSA PD	38 21	47.66 19.43	19.74 15.97	<0.001

*Based on Wilcoxon sign rank sum test.

Table 3

COMPASS_Change Scores for patients with MSA and PD at 1-year follow-up.

COMPASS_Change Domains	DX	N	Mean	Std. Dev.	P-Value*
Orthostatic Intolerance	MSA PD	21 18	29.52 10.50	19.14 19.16	0.003
Upper Gastrointestinal Symptoms	MSA PD	21 18	1.52 0.22	1.99 2.46	0.038
Bladder Dysfunction	MSA PD	21 18	8.81 2.50	13.68 5.22	0.133
Vasomotor Symptoms	MSA PD	21 18	2.14 −0.56	2.54 2.36	0.001
Diarrhea	MSA PD	21 18	0.95 0.28	4.64 1.18	0.674
Constipation	MSA PD	21 18	1.43 1.11	4.78 2.74	0.575
Pupillomotor Symptoms	MSA PD	21 18	2.29 1.67	2.78 2.40	0.415
Sleep Dysfunction	MSA PD	21 18	2.50 0.28	8.25 3.31	0.216
Secretomotor Dysfunction	MSA PD	21 18	6.81 5.00	8.45 5.99	0.760
Sexual Failure (men only)	MSA PD	11 10	1.82 2.00	3.37 3.50	0.918
COMPASS_Change (max score 200)	MSA PD	21 18	56.93 22.11	45.92 32.79	<0.001
COMPASS_Change_Select (5 domains)	MSA PD	21 18	49.79 17.72	37.84 26.45	<0.001

*Based on Wilcoxon sign rank sum test.