Autonomic nervous system testing may not distinguish multiple system atrophy from Parkinson's disease

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Studies of autonomic function comparing patients with Parkinson's disease and multiple system atrophy (MSA) have reported differences between the two diseases in cardiovascular,^{1–3} urinary,^{4–6} anorectal,⁷ and skin temperature and sweating regulatory functions.^{1–3, 8–9} These studies segregated patients with parkinsonism according to clinical diagnostic criteria, either published^{10–16} or devised ad hoc,^{4–6} into clinically probable MSA or Parkinson's disease depending on the presence of overt dysautonomia. This process virtually ensured that patients diagnosed with MSA would have more autonomic dysfunction by laboratory testing than those diagnosed with Parkinson's disease. Thus these studies completed a circular argument: parkinsonian patients with symptoms and signs of dysautonomia are designated as having MSA, then subsequent formal autonomic studies show greater dysfunction in MSA patients than in those with Parkinson's disease. Pathological studies, however, demonstrate that Parkinson's disease can cause profound global dysfunction of the autonomic nervous system, identical to that considered characteristic of MSA.^{17–24} Thus segregation into Parkinson's disease or MSA diagnostic categories on the basis of clinical dysautonomia appears unfounded. No study has assessed whether the two diseases manifest real differences in the type or degree of autonomic dysfunction if they are diagnosed by means other than symptomatically overt dysautonomia. Such an analysis is clinically relevant, as differentiating the two diseases is difficult when parkinsonism and autonomic dysfunction are both prominent.

We divided patients into Parkinson's disease and MSA groups according to clinical criteria that did not include autonomic dysfunction. We then analysed their formal autonomic studies to determine differences between Parkinson's disease and MSA. We hoped to determine whether laboratory evalua-

Background: Formal laboratory testing of autonomic function is reported to distinguish between patients with Parkinson's disease and those with multiple system atrophy (MSA), but such studies segregate patients according to clinical criteria that select those with autonomic dysfunction for the MSA category.

Objective: To characterise the profiles of autonomic disturbances in patients in whom the diagnosis of Parkinson's disease or MSA used criteria other than autonomic dysfunction.

Methods: 47 patients with parkinsonism and autonomic symptoms who had undergone autonomic laboratory testing were identified and their case records reviewed for non-autonomic features. They were classified clinically into three diagnostic groups: Parkinson's disease (19), MSA (14), and uncertain (14). The performance of the patients with Parkinson's disease was compared with that of the MSA patients on five autonomic tests: RR variation on deep breathing, heart rate changes with the Valsalva manoeuvre, tilt table testing, the sudomotor axon reflex test, and thermoregulatory sweat testing.

Results: None of the tests distinguished one group from the other with any statistical significance, alone or in combination. Parkinson's disease and MSA patients showed similar patterns of autonomic dysfunction on formal testing of cardiac sympathetic and parasympathetic, vasomotor, and central and peripheral sudomotor functions.

Conclusions: This study supports the clinical observation that Parkinson's disease is often indistinguishable from MSA when it involves the autonomic nervous system. The clinical combination of parkinsonism and dysautonomia is as likely to be caused by Parkinson's disease as by MSA. Current clinical criteria for Parkinson's disease and MSA that direct patients with dysautonomia into the MSA group may be inappropriate.

tion of autonomic function truly helps in distinguishing Parkinson's disease from MSA in individual patients with parkinsonism.

METHODS

Patient selection

We searched the University Hospitals of Cleveland autonomic laboratory database for patients referred with a diagnosis or clinical information containing the key words "parkinsonism," "Parkinson's disease," and "multiple system atrophy." All patients had undergone laboratory testing because of symptoms suggestive of dysautonomia. The entire clinical record of each patient, compiled by a movement disorders specialist (DER), was reviewed for the occurrence of the clinical features listed in table 1. After the review of their records, the patients were classified into Parkinson's disease or MSA groups according to non-autonomic features shown to be indicative of, or inconsistent with, each disease by clinicopathological correlation studies. Table 1 lists under the heading "Criteria for diagnosis of Parkinson's disease" various clinical features found to be characteristic of Parkinson's disease and unusual in MSA, and under "Criteria for diagnosis of MSA," various clinical findings associated with MSA rather than Parkinson's disease. Patients who did not meet criteria for either diagnosis, or met criteria for both, were placed in an "uncertain" category.

Autonomic testing

Autonomic testing was conducted according to standard clinical methods.³⁹ Patients were contacted beforehand and instructed to discontinue, if relevant, fludrocortisone or midodrine (ProAmatine) five days before their laboratory evaluations, and withhold antiparkinsonian drug treatment on the

Table 1 Clinical diagnostic criteria

Criteria for diagnosis of Parkinson's disease	Criteria for diagnosis of multiple system atrophy
<i>Patients must have a history, or show three or more, of the following clinical features, including at least two of those marked by an asterisk</i>	<i>Patients must have a history, or show two or more, of the following clinical features</i>
Rest tremor* ²⁵⁻²⁷	Dysarthria ³⁵
Asymmetrical onset* ^{26 28-30}	Dysphagia ³¹
Preserved postural stability* ^{31 32}	Facial/cervical dystonia ^{25 35-37}
Typical levodopa responsiveness* ²⁶	Action myoclonus ³⁵
Typical dyskinesias* ^{25 28}	Stridor/vocal cord palsy ^{25 35 38}
Dementia* ^{25 28 31}	Hand contractures ²⁵
Cognitive fluctuations ³⁴	Corticospinal tract signs ^{25 35}
Psychosis ^{22 30 31}	Gait ataxia ³⁵
	Limb ataxia ³⁵
	Nystagmus ³⁵
<i>Exclusion criterion: ataxia of limb or gait</i>	<i>Exclusion criterion: dementia³¹</i>

day of testing. All patients underwent four tests, three of cardiovascular autonomic function (cardiac response to deep breathing, cardiovascular response to the Valsalva manoeuvre, and cardiovascular response to upright tilt) and one of sudomotor function (the axon reflex sweating test). Some patients underwent an additional test of sudomotor function, the thermoregulatory sweat test, if diagnostic questions remained and physical fitness permitted.

All tests of cardiovascular function used electrocardiographic recording and continuous beat to beat blood pressure monitoring with a photoplethysmograph. In addition, the last two studies also employed an intermittent automated blood pressure measurement every 60 seconds.

The deep breathing response was done in the supine position with the patient breathing slowly, evenly, and deeply at six breaths a minute for one minute. Recordings were repeated once. The best five (of 12) responses were averaged to yield the final result.

The response to the Valsalva manoeuvre was assessed twice, using 15 seconds of intrathoracic pressure against a mercury manometer at 40 mm Hg. Lesser pressures were accepted and the norms reduced accordingly by 20% per 10 mm Hg. The Valsalva ratio was calculated by dividing the heart rate in phase II by the heart rate in phase IV.

Tilt table testing was done at 90° from horizontal for 10 to 20 minutes, after 20 minutes in the supine position.

The axon reflex test used 10% acetylcholine iontophoresed in five sites (dorsum of both feet, lateral calf, dorsum of the hand, and forearm) using 2 mA direct current for five minutes. Sweat output was recorded for this time and for an additional five minutes using a thermal conductivity based device.

The thermoregulatory sweat test employed an environment of 50% humidity and 50°C (skin at 40°C) for 30 minutes, or when core temperature had increased by more than 1.5°C. Sweat output was quantitated as for the axon reflex test, and an alizarin-red-S based marker for sweat was used to quantitate the geographical pattern of anhidrosis.

Statistical analysis

The review of the patients' clinical records and patient group assignments were completed independently of and before the statistical analysis of laboratory results. Autonomic test results were judged normal or abnormal by comparison with normal value ranges for comparable demographic categories. Data were compared across the two patient groups using a two tailed Student *t* test with expected probability (*p*) value for significance corrected to 0.1 by the Bonferroni method.

RESULTS

We reviewed 47 patients' records. Fourteen patients were given an uncertain diagnosis owing to insufficient clinical data to qualify for either Parkinson's disease or MSA (*n* = 11), sufficient features to warrant a diagnosis of Parkinson's disease in the presence of gait ataxia (*n* = 2), or mixed features of Parkinson's disease and MSA (three Parkinson's disease features and four MSA features) (*n* = 1). Fourteen patients were diagnosed with MSA, with a mean (SD) age of 66 (6.0) years and disease duration of 5.7 (3.8) years. Nineteen patients with Parkinson's disease had a mean age of 69 (9.9) years and a disease duration of 5.8 (4.0) years.

Abnormal results on individual tests occurred in a majority of patients in each group (table 2). Only one patient (who had Parkinson's disease) had no classic autonomic abnormalities (that is, normal deep breathing and Valsalva manoeuvre, no orthostatic hypotension or tachycardia on tilt, and a normal axon reflex test). However, upright tilt increased his blood pressure by 50/26 mm Hg, and thermoregulatory sweat testing was not done. Whenever the thermoregulatory sweat test was undertaken, it was abnormal in all tested patients from both

Table 2 Autonomic test results

Test	MSA	PD	<i>t</i> Test
<i>Deep breathing</i>			
Patients with abnormal results	11/13 (84.6%)	13/19 (68.4%)	NS
Average heart rate variation below expected*	4.18 beats/min	4.15 beats/min	
<i>Valsalva manoeuvre</i>			
Patients with abnormal results	5/8 (62.5%)	14/18 (77.8%)	NS
Average Valsalva ratio below expected*	0.135	0.131	
<i>Tilt table testing</i>			
Patients with abnormal results	10/13 (76.9%)	16/18 (88.8%)	NS
Average decrease of systolic blood pressure*	47 mm Hg	55 mm Hg	
<i>Sudomotor axon reflex</i>			
Patients with abnormal results	10/14 (71.4%)	15/19 (78.9%)	NS
Average % of sites with low or absent sweating*	70.7%	62.5%	
<i>Thermoregulatory sweat test</i>	8/8 (100%)	8/8 (100%)	NS

*Among patients with abnormal results.
MSA, multiple system atrophy; PD, Parkinson's disease.

Figure 1 Thermoregulatory sweat patterns in five typical subjects (three with multiple system atrophy (MSA); two with Parkinson's disease (PD)). The patterns were similar in the two groups, and most commonly showed a "central" distribution of anhidrosis involving the thoracic and proximal limb regions disproportionately more than the distal acral areas.

groups. Figure 1 shows typical findings. One patient in each group had a classic myelopathic pattern, at the mid-thoracic level. We found an abnormal axon reflex sweat test in the same proportion of patients in both groups.

No individual test distinguished the two groups of patients, either by the frequency or by the magnitude of abnormal results (table 2). Pairing the two tests showing the greatest disparity between the two groups (the trend toward an abnormal response to deep breathing with a normal response to the Valsalva manoeuvre in the MSA group, table 2) did not prove statistically significant in distinguishing the two groups.

Of note in the MSA group, there appeared to be a discrepancy between vital sign changes on tilt table testing and symptoms suggestive of hypotension, some patients being more symptomatic than expected and others less. None of the four MSA patients with a systolic blood pressure fall of ≥ 50 mm Hg had symptoms of hypotension, whereas five of the seven whose systolic pressure fell by ≤ 30 mm Hg experienced such symptoms. In comparison, in the Parkinson's disease

group, three of 10 patients with a blood pressure fall of ≥ 50 mm Hg had no symptoms, while three of the four patients with a blood pressure fall of ≤ 30 mm Hg had orthostatic symptoms. In summary, nine of 11 MSA patients had symptoms that did not correlate with expectations based on vital sign changes, compared with six of 14 Parkinson's disease patients. The difference constituted only a trend towards statistical significance ($p = 0.05$).

Some patients were unable to complete one or more segments of the test battery. Inability to perform the Valsalva manoeuvre occurred more often in the MSA group ($p < 0.01$).

DISCUSSION

We sought to study autonomic function in Parkinson's disease and MSA patients after attempted elimination of selection bias based upon the degree of symptomatic dysautonomia. We studied a group of parkinsonian patients with dysautonomia and segregated them according to those clinical features (other than autonomic dysfunction) that had previously been

shown in clinicopathological studies to be more characteristic of either Parkinson's disease or MSA (table 1). We were unable to find any distinguishing characteristics in the profiles of their deficits on the autonomic test battery employed (table 2). Our results indicate that formal testing of autonomic function cannot distinguish between patients with Parkinson's disease and MSA who have autonomic symptoms when the presence of such symptoms is not included in the diagnostic criteria. We cannot exclude the possibility that this finding resulted from an inadequate sample size. However, our results support anecdotal observations that the pattern of autonomic dysfunction in Parkinson's disease mimics that of MSA, and that autonomic studies cannot distinguish the two.¹⁵

We do not know how widespread is the arbitrary designation of the combination of parkinsonism and dysautonomia as MSA in clinical practice. However, two reports on autonomic function in Parkinson's disease and MSA where diagnosis was based on postmortem confirmation are instructive. In one, a majority of the patients with Parkinson's disease and clinical dysautonomia was misdiagnosed as having MSA.²⁴ In the other, none of 10 MSA patients (from a cohort of 33 patients) who were clinically misdiagnosed as Parkinson's disease had autonomic problems at disease onset, while 46% of the correctly diagnosed MSA patients did.⁴⁰ Interestingly, in the latter study a retrospective review found that 76% of 135 patients with Parkinson's disease had some degree of autonomic dysfunction during life, despite the observation by the investigators that the case records of patients correctly diagnosed premortem with MSA showed more diligent searches for autonomic symptoms than those of Parkinson's disease patients. This figure is comparable to the 74% frequency of autonomic dysfunction in 203 pathologically proven cases of MSA in Wenning *et al*'s review.²⁵

Our results cannot be used as epidemiological data describing the frequency of autonomic disturbances in Parkinson's disease or MSA, as all the patients were selected for laboratory study on the basis of autonomic symptoms. As the prevalence of Parkinson's disease appears to be many times that of MSA,¹⁴⁻⁴¹ the relatively equal proportions of our two patient groups support the notion that autonomic disturbances are indeed more common in MSA than in Parkinson's disease.²⁶ Thus an absence of dysautonomia in a patient with parkinsonism suggests the diagnosis of Parkinson's disease. However, our study also indicates that, in an individual patient, the combination of parkinsonism and dysautonomia is at least as likely to result from Parkinson's disease as MSA.

Current clinical diagnostic criteria allow for considerable overlap between Parkinson's disease and MSA. One consequence is that many MSA patients appear indistinguishable from those with Parkinson's disease, even up to death.¹⁴⁻⁴¹ Correspondingly, patients with Parkinson's disease may present a clinical picture identical to that of MSA.¹⁷⁻²⁴ Confusion arises chiefly because both diseases can lead to a combination of parkinsonism and dysautonomia. A means of distinguishing between the two conditions other than by existing clinical criteria is needed, as segregation of patients according to the presence or absence of dysautonomia appears to be inadequate and inappropriate.

Finally, some of our laboratory observations warrant further comment. The universal abnormality of thermoregulatory sweat test in both patient groups suggests that this test may be the most sensitive one for autonomic involvement in both Parkinson's disease and MSA, but the number of patients tested was small. The patterns of anhidrosis were similar in the two groups (fig 1), ranging from the expected "central pattern" which was most common, to segmental, and myelopathic, shown by one patient in each group. This wide spectrum of anhidrotic patterns implies that initial involvement and progression of autonomic system cellular loss varies considerably. The comparable abnormality of axon reflex testing suggests ganglionic or postganglionic involvement in the

majority of patients in both groups. Rajput and Rozdilsky attributed dysautonomia in Parkinson's disease to neuronal loss and Lewy body formation in sympathetic ganglia,⁴² while Bannister and Oppenheimer correlated dysautonomia in MSA with degeneration of the intermediolateral cell column of the spinal cord.⁴³ However, our results are consistent with reports of impaired postganglionic sympathetic function demonstrated by impaired sweat axon reflexes in MSA patients.³⁹⁻⁴⁴ The seemingly paradoxical relation between symptoms and signs that we found on tilt table testing, particularly striking in the MSA group, deserves further exploration in the future. Other investigators have noted a lack of symptoms in MSA patients with orthostatic hypotension.⁴⁵ MSA patients may be quite symptomatic early in their disease course, but may lose the ability to develop orthostatic symptoms when vasomotor failure is advanced.

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