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The role of autonomic testing in the differentiation of Parkinson's disease from multiple system atrophy

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Abstract

Differentiation of idiopathic Parkinson's disease (PD) from multiple system atrophy (MSA) can be difficult. Methods devised to help distinguish the two disorders include standardized autonomic testing and cardiac imaging with iodine-123 meta-iodobenzylguanidine myocardial scintigraphy. MSA patients had more severe adrenergic and overall autonomic dysfunction when compared to control and PD patients. Area of anhidrosis on thermoregulatory sweat testing was greater in MSA (67.4 ± 12.42 , $p < 0.001$) versus PD patients (area of anhidrosis, 1.7 ± 2.96). Postganglionic cardiac sympathetic innervation (iodine-123 meta-iodobenzylguanidine) expressed as heart to mediastinal ratio was significantly lower in Parkinson's disease patients (1.4 ± 0.40 , $p = 0.025$) compared to controls (2.0 ± 0.29), but not in multiple system atrophy (2.0 ± 0.76). These findings indicate that autonomic dysfunction is generalized and predominantly preganglionic in multiple system atrophy, and postganglionic in Parkinson's disease. In our hands the Thermoregulatory Sweat Test provides the best distinction between MSA and PD. However further confirmatory studies using larger patient numbers are required. Currently a combination of clinical judgment and autonomic testing are recommended to help differentiate MSA and PD.

Keywords

multiple system atrophy; Parkinson's disease; ¹²³I MIBG myocardial scintigraphy; autonomic reflex screen

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Introduction

Differentiation between idiopathic Parkinson's disease (PD) and multiple system atrophy (MSA) can be difficult. Accurate, early diagnosis of both MSA and PD has important clinical consequences, as the prognosis is dismal in MSA, with death from onset averaging 7 years [1]. However, one in five patients with the incorrect diagnosis of PD has a pathological diagnosis of MSA [2]. Additionally 38–47% of PD patients may develop orthostatic hypotension (OH), approximately half being symptomatic [3]. The occurrence of OH does not, therefore, signify the diagnosis of MSA in patients with the extrapyramidal features of PD.

As a result multiple diagnostic tests have been devised to help with the differentiation of these disorders. Standard autonomic testing may distinguish MSA from PD [4]. Thermoregulatory sweat testing (TST) shows a significant increase in total body anhidrosis in MSA patients compared to PD [4, 5]. The reduction in postganglionic sympathetic cardiac innervation in PD measured by iodine-123 meta-iodobenzylguanidine (^{123}I MIBG) myocardial scintigraphy has been proposed as a method to distinguish this disease from MSA [6–12]. However, several investigators have reported significant reduction in ^{123}I MIBG uptake in MSA patients [13–16]. However, specific tests of autonomic function are not part of the current diagnostic criteria for MSA [17, 18]. Here we set out to build on previous work, by combining MIBG with detailed autonomic testing to compare prospectively all major techniques with respect to autonomic function in PD and MSA.

Methods

Patients

Patients were enrolled prospectively based on the following criteria for PD, MSA and control groups (see below). Healthy controls were of either male or female gender, age range between 40 to 80 years of age, had no autonomic related symptoms, and normal autonomic reflex screen. Exclusion criteria included pregnant or lactating females, any chronic illness potentially involving the central or autonomic nervous system, concomitant medications that could interfere with testing of autonomic function, history of structural brain disease or brain surgery, or known allergy to iodine.

Patients with PD were defined based on previously modified criteria [19]. Inclusion criteria included the presence of all 3 cardinal features of PD (resting tremor, bradykinesia, and rigidity), asymmetrical onset, and a favorable response to levodopa therapy. Exclusion criteria included those listed for controls in addition to the presence of drug-induced parkinsonism or regular neuroleptic medication use six months prior to enrollment.

Patients with MSA were defined based on prior consensus criteria [17]. To be included in the MSA group, patients had to meet both inclusion criteria including OH (fall in SBP ≥ 30 mmHg) or urinary incontinence and Parkinsonism responding poorly to levodopa or cerebellar ataxia. Exclusion criteria were the same as those listed for normal controls.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients gave written and informed consent prior to enrollment. The study was approved by the Mayo Clinic (Rochester, MN) Institutional Review Board.

Autonomic Reflex Screen

Quantitative sudomotor axon reflex test (QSART) was performed as per standard protocols to assess postganglionic sympathetic sudomotor axon integrity [20]. Cardiovascular function

was measured using heart rate (HR) response to deep breathing and Valsalva ratio. The control values were based on 157 healthy subjects aged 10 to 83 years [21]. Cardiovascular adrenergic function was evaluated by the blood pressure (BP) and heart rate response to the Valsalva maneuver and head-up tilt [22]. Serum catecholamine levels were drawn prior to and at 5 minutes HUT. The severity and distribution of autonomic failure seen on the autonomic reflex screen was quantified by the CASS score, 0 indicating no dysfunction and 10 indicating maximum autonomic impairment [23]. The CASS score is further divided into three sub-scores: sudomotor, cardiovagal, and adrenergic; normalized for confounding effects of age and gender [21].

Thermoregulatory Sweat Test (TST)

The TST assesses the pattern of sweat loss and provides a quantitative evaluation of percent of anterior body surface anhidrosis. Results were expressed as the percentage of body-surface area that did not sweat 100 percent indicates complete anhidrosis [4].

¹²³I- meta-iodobenzylguanidine (MIBG) Myocardial scintigraphy

This method depends on identifying the noradrenaline containing nerve terminals among the myocardial cells in the heart using ¹²³I-MIBG. Studies were performed per standard protocols [6]. MIBG data was expressed as heart to mediastinal (H:M) ratios at 15 minutes and 4 hours. Sestamibi scans were performed 24 hours prior to MIBG scans to ensure the absence of cardiac ischemic disease.

Statistical Analysis

Summary statistics are presented as the mean $\pm$ standard deviation (SD). Non-parametric data requiring multiple group comparisons was analyzed using the Kruskal–Wallis one-way analysis of variance with a post hoc analysis using a Dunn's comparison to determine differences between individual groups. Non-parametric data requiring comparison between two groups (in this case only applying to data derived from the TST results; Fig. 1) were analyzed using the Mann-Whitney U test. Receiver operated characteristic (ROC) curve analysis was used to analyze the area under the curve (AUC) for MIBG data (H/M ratios), CASS total scores, and TST results (% anhidrosis) for the differential diagnosis of PD versus MSA. Sensitivity, specificity, and likelihood ratios (LR) were derived from ROC analysis. Correlation analysis of non-parametric data was performed using the spearman rho (r) test. A p-value of < 0.05 was considered significant.

Results

Patient groups

A total of 29 subjects were enrolled in the study (control n=10, PD n=10, and MSA n=9). The mean age and range for all groups were comparable in control, PD, and MSA groups with a mean age of 62.5 years (range 42–75), 65.3 years (range 47–80), and 68.1 years (range 57–80), respectively. There was a modest increase in the male to female ratio in the PD group (4:1) based on availability of research subjects. The male to female ratios were distributed equally for both the control (1:1) and MSA (5:4) groups.

Autonomic Testing

CASS total scores and, and adrenergic sub-domains were determined for each group (controls n=10, PD n=10, MSA n=9). Adrenergic and overall autonomic dysfunction was significantly greater in MSA patients when compared to control and PD groups (Fig. 1). CASS sudomotor and cardiovagal sub-scores did not differ between groups. CASS total scores showed good sensitivity (89 %) but a moderate specificity (70 %) with AUC of 0.772

in discriminating MSA from PD (Table 1). Total body anhidrosis (% area) on TST was significantly greater in MSA (n=9) when compared to the PD (n=8) group (Fig. 1), with no overlap in the values being observed. Of note was that 7/9 MSA patients had TST% >30%, while all PD patients had TST% <10%.

I^{123} MIBG myocardial scintigraphy data for controls (n=10), PD (n=10), and MSA (n=9) patients at 4 hours are shown in Figure 1. There was a significantly lower I^{123} MIBG uptake as exhibited by reduced heart to mediastinal (H/M) ratios in PD patients versus controls at both 15 minutes and 4 hours. Most PD patients (7/10) had lower ratios at both time-points. The majority (6/9) of MSA patients had normal ratios at both time-points, although in 3/9, the ratios were below control values. Overall, I^{123} MIBG uptake at both time points was lower for PD compared to MSA patients, but this did not reach statistical significance. There were no significant differences in the H/M ratios when comparing the MSA group to controls. At 15 minutes and 4 hours, the AUCs of the ROC curves were 0.767 and 0.717, respectively (Table 1).

Norepinephrine levels did not significantly differ between groups (control, supine 243.2 ± 130.4 pg/mL, standing 377.2 ± 128.9 pg/mL; PD, supine 268.7 ± 219.0 pg/mL; MSA supine 220.6 ± 87.6 , standing 294.0 ± 125.1 pg/mL) with the exception of the difference in norepinephrine levels associated with postural change (standing-supine) between PD (245.5 ± 180.5 pg/mL, n=10) and MSA patients (73.5 ± 64.6 pg/mL, n=8; $p < 0.034$).

Relationships among tests of autonomic function

PD patients with orthostatic hypotension (PD-OH; CASS adrenergic score of 4) versus PD patients without orthostatic hypotension (CASS adrenergic scores of 3 or less) did not significantly differ in their H/M ratios at either 15 minutes (PD, 1.503 ± 0.412 ; PD-OH, 1.227 ± 0.110 ; $p = 0.517$) or 4 hours (PD, 1.543 ± 0.413 ; PD-OH, 1.103 ± 0.091 ; $p = 0.067$). However, there was a trend toward reduced cardiac uptake of I^{123} MIBG particularly at the later time point (4 hours). However, it is difficult to draw further conclusions based on this data given the low number of patients in the PD group with orthostatic hypotension (n=3) versus the PD groups without orthostatic hypotension (n=7).

There was no correlation between CASS total score and I^{123} MIBG myocardial scintigraphy for controls (H/M ratio at 15 minutes, $r = 0.039$, $p = 0.918$; H/M ratio at 4 hours, $r = 0.234$, $p = 0.514$), PD patients (H/M ratio at 15 minutes, $r = -0.137$, $p = 0.707$; H/M ratio at 4 hours, $r = -0.376$, $p = 0.279$), or MSA patients (H/M ratio at 15 minutes, $r = 0.220$, $p = 0.581$; H/M ratio at 4 hours, $r = 0.110$, $p = 0.776$). Additionally, CASS total scores did not correlate with TST results (% anhidrosis) for either PD ($r = -0.289$, $p = 0.501$) or MSA groups ($r = -0.083$, $p = 0.843$).

Discussion

I^{123} MIBG myocardial scintigraphy has been advocated for distinguishing MSA from PD. In our series, I^{123} MIBG values of most PD cases were indeed separated from MSA and control values; however, there was substantial overlap, and mean values were not significantly different. Thus, I^{123} MIBG values from several PD cases were similar to those of control subjects and conversely, values from several MSA cases were similar to those of PD. The CASS scores from the autonomic reflex screen separated MSA from PD (and each group from normals); however, there continued to be overlap. What separated MSA from PD best was the thermoregulatory sweat test, where the overlap was minimal. Plasma catecholamine assessment was not helpful in this study. These results attest to the value of formal autonomic testing to differentiate MSA from PD. However, no single test has sufficient sensitivity or specificity by itself.

Our results are in keeping with previous data showing more widespread anhidrosis on TST among MSA patients, and that this degree of anhidrosis distinguishes this disorder from PD (Fig. 1) [4, 5]. Similarly overall autonomic dysfunction, as indicated by the CASS score, was more severe and widespread in the MSA group versus the PD group supporting similar data from previous studies (Fig. 3) [4]. These findings continue to support our previous assertions that the severity and distribution (pre ganglionic) of autonomic dysfunction in MSA patients are useful clinical additions in distinguishing this disorder from PD [4].

Adrenergic and overall autonomic dysfunction, as represented by their respective CASS scores, showed a significant difference when comparing groups. Previous studies have proposed that specific autonomic tests including Valsalva maneuver, HUT, QSART, or heart rate variability to deep breathing, alone or in combination, can not distinguish between MSA and PD [15, 24–26]. The CASS total score is a representative quantitative measure of overall autonomic dysfunction on standard autonomic testing [23]. As a result, it may be a more useful index of autonomic dysfunction when trying to discriminate between MSA and PD. Similarly, the CASS adrenergic score is a composite measure of autonomic dysfunction seen on both HUT (with respect to the presence or absence of OH) and the sympathetic adrenergic components of Valsalva maneuver (late phase II and phase IV) which in combination appear to better distinguish MSA from PD, when compared to each individual measure alone.

Our findings showed that I^{123} MIBG myocardial scintigraphy did significantly differ in PD patients versus controls but did not differentiate PD from MSA in contrast to prior studies [6, 9, 12]. We did see a trend toward decreased MIBG uptake (exhibited by lower H/M ratios) during myocardial scintigraphy in the PD versus MSA group, but potentially our study did not have sufficient statistical power due to recent isotope shortages affecting recruitment [27]. Additionally, more recent studies have indicated that parkinsonism-predominant forms of MSA cannot consistently be distinguished from PD based on I^{123} MIBG myocardial scintigraphy [13–15]. We did not distinguish between the various forms of MSA in our prospective study. However, our definition of MSA, based on prior diagnostic criteria, arguably favored those patients with autonomic dysfunction [17]. Prior studies have reported that autonomic testing including the TST and I^{123} MIBG myocardial scintigraphy are less able to discriminate between PD and MSA patients (parkinsonian and cerebellar types) at earlier time points in the disease course [13–15]. At later time points when autonomic dysfunction becomes more severe, we would hypothesize that this would be less of a concern.

Our findings support prior studies that ^{123}I MIBG myocardial scintigraphy may be somewhat useful in the clinical diagnosis of PD by showing reduced MIBG uptake in cardiac post ganglionic sympathetic nerve fibers. However, it was interesting that 3/9 MSA patients had H/M ratios below the mean for the control group. Several studies have shown alpha-synuclein immunoreactivity in sympathetic ganglia in MSA patients [28, 29]. In a cohort of 26 MSA patients 42.3% of subjects revealed involvement of sympathetic ganglia [29]. Furthermore this post ganglionic sympathetic denervation has been correlated to reduced cardiac uptake of MIBG in MSA patients [30]. This post sympathetic denervation seen with MIBG myocardial scintigraphy in a subset of MSA patients likely reduced the effectiveness of the procedure to differentiate MSA from PD as seen in our patients. We did not find a clear trend toward post ganglionic dysfunction on the remainder of the autonomic testing in these three MSA patients but the number of patients was insufficient to derive any specific conclusions.

Our data shows that standardized clinical autonomic dysfunction can discriminate MSA from PD based on increased severity and distribution of autonomic dysfunction seen in

MSA. Furthermore, this autonomic dysfunction is primarily preganglionic in MSA but postganglionic in PD patients. A limitation is that our conclusion is based on a small dataset and sensitivity/specificity may change with larger N's. The present study support our recent experience from that prospective autopsy-confirmed study, in that distinguishing MSA from PD can be optimized by fulfilling consensus criteria [17], supplemented by autonomic tests. Among the tests, the most useful in our hands are the TST% combined with the autonomic reflex screen (to generate the CASS score). When MIBG is available, it further aids in the differentiation. Plasma catecholamines do not seem to help in differentiation. Until larger confirmatory studies are available a combination of clinical judgment aided by autonomic testing is recommended to distinguish MSA from PD.

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Figure 1. Comparison of specific autonomic tests in the differentiation of control, PD and MSA patients

CASS scores for all three groups (control n=10; PD n=10; MSA n=9) are broken down into adrenergic (A), and CASS total (B) scores. MSA patients exhibited significantly higher adrenergic and overall autonomic dysfunction compared to controls and PD patients as shown by their respective CASS scores (Kruskal–Wallis one-way analysis of variance, * $p < 0.001$ for both CASS adrenergic and CASS total scores). There was a significant increase in % anhidrosis on TST in MSA (n=9) versus PD (n=8) patients (C; Mann-Whitney U test, * $p < 0.001$). Heart to mediastinal (H/M) ratios for I^{123} MIBG uptake at 4 hours (D) are shown for control (n=10), PD (n=10) and MSA (n=9) groups. Cardiac uptake of I^{123} MIBG was significantly reduced as indicated by lower H/M ratios for PD patients versus controls (Kruskal–Wallis one-way analysis of variance, * $p = 0.025$). There were no significant differences in I^{123} MIBG uptake when comparing MSA to PD or control groups. Data are expressed as scatter plots with each individual symbol representing a single patient and the horizontal line representing the mean of the corresponding group.

Table 1

Sensitivity, specificity and area under the curve for MIBG H/M ratio and CASS total score for the diagnosis of PD and MSA.

	<u>MIBG H/M ratio</u>		CASS total score	TST results (% anhidrosis)
	15 minutes	4 hours		
Sensitivity (%)	70	100.0	88.9	100
Specificity (%)	77.8	55.6	70.0	100
AUC	0.767	0.717	0.772	1.0
LR	3.15	2.25	2.96	8.0
Cut off value	<1.380	<2.135	>4.50	>9.0
p value	0.050	0.465	0.046	0.001

AUC, area under the curve; CASS, composite autonomic severity score; H/M ratio, heart to mediastinal ratio; LR, likelihood ratio; MIBG, ¹²³I-meta-iodobenzylguanidine; MSA, multiple systems atrophy; PD, Parkinson's disease; TST, thermoregulatory sweat test