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Long-term trends in myocardial sympathetic innervation and function in synucleinopathies

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ABSTRACT

Introduction: Parkinson disease (PD), pure autonomic failure (PAF), and multiple system atrophy (MSA) are characterized by intra-cerebral deposition of the protein alpha-synuclein and are termed synucleinopathies. Lewy body synucleinopathies involve decreased cardiac sympathetic innervation and functional abnormalities in residual noradrenergic terminals. This observational, retrospective, cohort study describes long-term trends in indices of cardiac sympathetic innervation and function in synucleinopathies.

Methods: Patients with PD (N = 31), PAF (N = 9), or MSA (N = 9) underwent repeated ^{18}F-dopamine positron emission tomography (median follow-up 3.5 years). Interventricular septal ^{18}F-dopamine-derived radioactivity 8 min after tracer injection (8′ Radioactivity) was used as an index of sympathetic innervation and the slope of mono-exponential decline of radioactivity between 8 and 25 min ($k_{8'\text{-}25'}$) as an index of intraneuronal vesicular storage. Healthy volunteers (HVs) (N = 33) and individuals at high risk of PD (N = 15) were controls.

Results: Upon initial evaluation the groups with PD and orthostatic hypotension (OH), PAF, or PD and no OH had low mean 8′ Radioactivity compared to HVs ($p < 0.0001$, $p = 0.0002$, $p = 0.006$) and had elevated $k_{8'\text{-}25'}$, ($p = 0.0007$, $p = 0.007$, $p = 0.06$). There was no significant difference between MSA and HVs. In PD 8′ Radioactivity decreased by a median of 4% per year and did not decrease in MSA. $k_{8'\text{-}25'}$ values did not change during follow-up in any group.

Conclusions: Neuroimaging evidence of decreased vesicular uptake in cardiac sympathetic nerves is present upon initial evaluation of patients with Lewy body synucleinopathies and may provide a biomarker of catecholaminergic dysfunction early in the disease process.

1. Introduction

Parkinson disease (PD), pure autonomic failure (PAF), and multiple system atrophy (MSA) are neurodegenerative diseases characterized by cytoplasmic deposition of the protein alpha-synuclein in the brain and are termed synucleinopathies. In addition to the well-known nigrostriatal dopamine deficiency that causes the parkinsonian movement disorder, Lewy body synucleinopathies involve drastically decreased myocardial norepinephrine content. Indeed, in Lewy body diseases there is just as much loss of myocardial norepinephrine as there is of putamen dopamine [1,2].

Although one might presume that cardiac norepinephrine depletion in Lewy body diseases directly and solely reflects loss of sympathetic noradrenergic innervation, there is increasing evidence that functional abnormalities in extant nerves contribute to the norepinephrine deficiency. This matter is important, because autonomic involvement seems to occur early in the pathogenetic sequence of synucleinopathies [3,4], and it is reasonable to conceptualize that dysfunction precedes neuronal death. If so, functional cardiac neuroimaging could provide a biomarker of catecholaminergic dysfunction early in the disease process, and a form of disease modification treatment might slow or prevent the progression to motor PD or dementia with Lewy bodies.

In PD neuroimaging indices of cardiac sympathetic innervation decline over years [5–8], but long-term trends in indices of the functional status of myocardial sympathetic nerves have not been reported in PD or other synucleinopathies. Of particular interest is the ability to sequester cytoplasmic catecholamines in vesicles, since this process is energy-dependent and might be particularly sensitive to alterations of

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mitochondrial functions [9,10]. Several in vivo and post-mortem studies have indicated a vesicular storage defect in synucleinopathies, both in the brain and heart [11–14]. Whether this functional abnormality is an early finding, however, has been unknown.

One can assess vesicular storage in myocardial sympathetic nerves indirectly using data from ^{18}F-dopamine (^{18}F-DA) positron emission tomographic (PET) scanning, as described previously [14]. Briefly, decreasing vesicular uptake diverts the fate of cytoplasmic ^{18}F-DA toward metabolism by monoamine oxidase to form ^{18}F-dihydroxyphenylacetic acid (^{18}F-DOPAC), which rapidly exits the nerves (see the concept diagram in the Supplementary Figure), so that tissue ^{18}F-DA-derived radioactivity declines at an increased rate [11]. In contrast with Lewy body diseases, MSA, a non-Lewy body form of alpha-synucleinopathy, generally involves normal myocardial uptake of ^{18}F-DA-derived radioactivity and normal kinetics of loss of the radioactivity [11].

In this study we hypothesized that (1) loss of cardiac sympathetic innervation progresses over time in PD and not in MSA; and (2) neuroimaging evidence of decreased vesicular storage is present upon initial evaluation of patients with Lewy body diseases.

2. Methods

2.1. Subjects

Patients with PD, MSA, and PAF were referred to the Autonomic Medicine Section (formerly Clinical Neurocardiology Section) for evaluation of autonomic function at the Clinical Center of the National Institutes of Health. All the subjects participated in protocols approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke (NINDS) after having given written informed consent.

A diagnosis was assigned to each patient based on the medical and neurological history and the physical and neurological examinations, supported by results of specialized tests described below. The patients then underwent follow-up testing over up to 18 years.

A diagnosis of PD was assigned based on at least 3 of the following 4 clinical criteria: bradykinesia, resting tremor, cogwheel rigidity, and good response of the movement disorder to levodopa treatment. Supportive clinical laboratory findings included central dopaminergic deficiency as indicated by low putamen/occipital cortex ratios of ^{18}FDOPA-derived radioactivity [15] or low cerebrospinal fluid 3,4-dihydroxyphenylacetic acid levels [16]. The PD cohort was stratified in two groups: those with neurogenic orthostatic hypotension (PD + OH) and those without neurogenic orthostatic hypotension (PD No OH).

According to consensus criteria, MSA was also divided into two groups, parkinsonian (MSA-P) and cerebellar (MSA-C). The clinical diagnosis of probable MSA was made based on consensus criteria [17].

A diagnosis of PAF was assigned based on chronic, persistent OH identified as neurogenic by clinical laboratory testing [18], without a known cause (e.g., diabetic autonomic neuropathy, autoimmune autonomic ganglionopathy) and supported by clinical laboratory evidence of sympathetic noradrenergic deficiency [19,20].

In a retrospective, observational, cohort study we analyzed follow-up clinical and laboratory data from 12 patients with PD + OH, 19 with PD No OH, 9 with probable MSA (3 MSA-C and 6 MSA-P), and 9 with PAF. We also analyzed data from 15 subjects included in the PDRisk prospective cohort study of the NINDS. In the PDRisk study, individuals have at least 3 PD risk factors (family history, olfactory dysfunction, dream enactment behavior, orthostatic hypotension) but without sufficient findings to diagnose motor PD. Subjects from the PDRisk study included in the analysis were followed for at least 3 years. A control group (N = 33) consisted of healthy volunteers and patients referred for symptoms of dysautonomia (e.g., orthostatic intolerance) who did not have autonomic dysfunction documented by screening testing. Since there were no differences between these two groups the data were lumped. All subjects in the control group underwent ^{18}F-DA PET scanning once.

Table 1
Subject characteristics.

Group	N	Female N (%)	Age (years) Mean (± SD)	Follow-up (years) Median	Disease duration (years) Median
PD + OH	12	5 (42%)	70.1 (5.5)	3.1	4
PD No OH	19	3 (16%)	60 (10)	3.8	3
MSA	9	3 (33%)	61.4 (6.7)	3.1	3
PAF	9	4 (44%)	65.5 (7.9)	8.6	3
PDRisk	15	13 (87%)	58.2 (8.6)	4.6	N/A
HVs	33	8 (24%)	48.7 (18.0)	N/A	N/A

Abbreviations: PD + OH = Parkinson disease with orthostatic hypotension; PD No OH = Parkinson disease without orthostatic hypotension; MSA = multiple system atrophy; PAF = pure autonomic failure, PDRisk = subjects included in the PDRisk study (multiple PD risk factors), HVs = healthy volunteers. Disease duration = time from symptom onset to initial evaluation (years).

The subjects' characteristics are shown in Table 1.

Seven patients with a diagnosis of synucleinopathy (5 PD, 2 PAF) had normal interventricular septal ^{18}F-DA uptake at baseline and subsequently had decreased radioactivity (radioactivity at 8 min less than 6000 nCi-kg/cc-mCi).

At the time of testing, all the patients were studied off levodopa for at least 72 h.

2.2. Study design

We performed a retrospective analysis of patients diagnosed with a synucleinopathy and subjects from the PDRisk study who underwent ^{18}F-DA PET scanning twice or more at the Clinical Center of the National Institutes of Health. ^{18}F-DA PET scanning was performed only once in the healthy volunteers. All subjects underwent clinical and neurological assessments and routine blood and urine studies as well as ^{18}F-DA PET scanning. The first ^{18}F-DA PET scanning was used as the baseline scan study for each subject.

2.3. Imaging

Subjects underwent cardiac sympathetic neuroimaging by ^{18}F-DA PET scanning as described previously [15]. Briefly, interventricular septal ^{18}F-DA-derived radioactivity was recorded for the 5-min frame with a mid-point about 8 min after initiation of the 3-min infusion of 1 mCi of the tracer. The radioactivity at 8 min (8′ Radioactivity) was used as a measure of neuronal uptake and thereby of innervation. The cutoff value for low 8' Radioactivity concentration was less than 6000 nCi-kg/cc-mCi [21]. Personnel who analyzed the ^{18}F-DA PET scanning data were blinded to the clinical diagnosis.

As a measure of loss of ^{18}F-DA-derived radioactivity during the scanning, the slope of mono-exponential decline in radioactivity ($k_{8'\text{-}25'}$) was calculated from the radioactivity at 8′, 13′, 18′, and 25'. $k_{8'\text{-}25'}$ was used to assess a vesicular storage defect as described previously [14]. ^{18}F-DA radioactivity concentrations were expressed in units of nCi-kg/cc-mCi.

Two different PET scanners were used during the study–GE Advance before February 1, 2016 and Siemens Biograph 128 PET/CT after February 1, 2016. A correction for partial volume effect was applied to account for different spatial resolutions between the two scanners.

2.4. Data analysis and statistics

For baseline (initial) data, analyses of variance (ANOVA) with unequal variances were performed to assess differences in 8′ Radioactivity or $k_{8'\text{-}25'}$, among PD + OH, PD no OH, PAF, MSA, PDRisk, and healthy volunteers. Dunnett's method was applied to adjust for multiple comparisons, with the healthy volunteer group as a control. Age and sex

were considered as covariates, but age was dropped.

For longitudinal data, a random coefficient model (random intercept and slope) was used to examine the change in 8′ Radioactivity over time. The model included group (MSA, PAF, PD + OH, PD no OH, and PDRisk), time and the interaction between group and time. The time variable was the patients' follow-up years. A significant interaction indicated that the 5 groups did not have the same coefficients. For groups with significant coefficients, the average percent change in 8′ Radioactivity per year was estimated based on the coefficient. Bonferroni's method was applied to adjust for multiple comparisons.

SAS version 9.4 was used for the above analyses. Age and sex were considered as covariates. Their effect on the dependent variable (8′ Radioactivity or $k_{8'\text{-}25'}$) was assessed for each subject group separately in both baseline and longitudinal data analysis, the test outcome was then used for model selection. To reduce skewness of the data, square-root transformations based on the Box-Cox procedure were applied for both 8′ Radioactivity and $k_{8'\text{-}25'}$ values.

3. Results

3.1. Longitudinal follow-up of ^{18}F-DA-derived radioactivity

All subjects underwent ^{18}F-DA PET scanning at least twice. Median times to last follow-up were 3.1 years for PD + OH, 3.8 years for PD No OH, 3.1 years for MSA, 8.6 years for PAF, and 4.6 years for PDRisk subjects (Table 1).

Values for initial 8′ Radioactivity varied substantially as a function of subject group (Table 2). The PD + OH, PD No OH, and PAF groups had lower initial mean 8′ Radioactivity than did the HV group ($p < 0.001$, $p = 0.006$ and $p < 0.001$), whereas the MSA and PDRisk groups did not (Fig. 2). There was no effect of age on 8' Radioactivity.

There was a progressive decline in mean 8′ Radioactivity in PD + OH (by 3% per year, $p = 0.018$) and PD No OH (by 4.1% per year, $p = 0.0002$) (Fig. 1). In PAF the decline was less pronounced and not significant (Fig. 1). In contrast, there was a non-significant increase in 8' Radioactivity in the MSA and PDRisk groups (Fig. 1).

3.2. Analysis of $k_{8'\text{-}25'}$ values

Compared to HVs, PD + OH, PD No OH, and PAF patients had higher initial $k_{8'\text{-}25'}$ values ($p < 0.001$, $p = 0.057$, and $p = 0.007$), whereas values in the MSA and PDRisk groups did not differ from the HV group (Fig. 2).

Values for $k_{8'\text{-}25'}$ did not change during follow-up in any of the groups. Mean $k_{8'\text{-}25'}$ remained high in the PD + OH, PD No OH, and PAF groups and remained similar to the HV values in the MSA and PDRisk groups (Fig. 2).

3.3. Subgroup analysis for patients with normal baseline 8' radioactivity

A subgroup of 7 patients (1 PD + OH, 4 PD No OH, and 2 PAF) initially had septal 8' Radioactivity > 6000 nCi-kg/cc-mCi and subsequently < 6000 nCi-kg/cc-mCi.

Table 3 summarizes data from this subgroup, and Fig. 3 depicts an example. In this subgroup the median (Q1-Q3) 8′ Radioactivity averaged 8478 nCi-kg/cc-mCi (7273–8550) and 4161 nCi kg/cc-mCi (3742–4299) at last follow-up (Table 2). There was a trend toward higher median initial $k_{8'\text{-}25'}$ values compared to HVs (0.025 vs. 0.016 min^{-1}, $p = 0.056$; Fig. 4).

4. Discussion

The main new finding in this study is neuroimaging evidence of a functional abnormality, accelerated loss of cytoplasmic catecholamines in myocardial sympathetic nerves, upon initial evaluation of patients with Lewy body forms of synucleinopathy. This abnormality persists without change during follow-up. We interpret these results in terms of a vesicular storage defect occurring relatively early in the disease process. Thus, a population of cardiac noradrenergic neurons seem to be “sick but not dead.”

Both in vivo and post-mortem data support the concept of a vesicular storage defect in sympathetic noradrenergic neurons in Lewy body diseases. A combined neurochemical/neuroimaging study reported increased arterial ^{18}F-DOPAC levels for given amounts of cardiac ^{18}F-DA uptake [11]. Arterial plasma ^{18}F-DOPAC also is increased for a given concentration of 3,4-dihydroxyphenylglycol, the main neuronal metabolite of norepinephrine [22]. As confirmed here, the rate of decline of myocardial ^{18}F-DA-derived radioactivity is increased in Lewy body diseases [14]. Moreover, post-mortem neurochemical data have indicated a shift from vesicular sequestration to oxidative deamination of cytoplasmic catecholamines [13].

Decreased vesicular storage might occur simultaneously with or precede denervation. The findings in a subgroup of 7 patients with initially normal innervation and subsequent loss of innervation fit with the latter view. In this subgroup, at initial evaluation mean $k_{8'\text{-}25'}$ tended to be increased. The small sample size could explain the lack of statistical significance compared to HVs.

Interventricular septal ^{18}F-DA-derived radioactivity 8′ after tracer injection (8' Radioactivity) was found to decline by a median of 4% per year in PD patients. Because of individual variability in the rate of decline, based on the data from the present study we estimate that in a clinical trial of a disease-modifying approach using ^{18}F-DA-derived radioactivity as the outcome measure, to detect a 50% decrease in the loss of cardiac noradrenergic innervation over a 5-year-period would require about 70 patients in each of the experimental treatment and standard treatment groups.

Table 2
Initial and follow-up median (Q1-Q3) values for indices of cardiac sympathetic innervation and function in patient groups with synucleinopathies and in PDRisk subjects.

Group	8′ Radioactivity Initial	8′ Radioactivity Last Follow-up	$k_{8'\text{-}25'}$ Initial	$k_{8'\text{-}25'}$ Last follow-up
PD + OH	3948 (3332–4853)	3092 (2502–3588)	0.039 (0.025–0.051)	0.029 (0.020–0.045)
PD No OH	8092 (4916–8821)	3839 (3460–7097)	0.023 (0.015–0.034)	0.024 (0.021–0.032)
MSA	11096 (9088–12422)	11970 (10366–13115)	0.013 (0.010–0.017)	0.017 (0.012–0.020)
PAF	4574 (4304–6398)	4378 (3673–5319)	0.032 (0.029–0.043)	0.034 (0.028–0.034)
PDRisk	11149 (9261–11806)	12565 (10510–14361)	0.019 (0.017–0.022)	0.018 (0.016–0.023)
Healthy volunteers	9706 (9067–10690)	NA	0.016 (0.012–0.021)	NA
Normal Initial 8′ Radioactivity	8478 (7273–8550)	4161 (3742–4299)	0.025 (0.018–0.032)	0.026 (0.019–0.028)

Abbreviations: PD + OH = Parkinson disease with orthostatic hypotension; PD No OH = Parkinson disease without orthostatic hypotension; MSA = multiple system atrophy; NA = not applicable; PAF = pure autonomic failure; Normal Initial 8′ Radioactivity = patients with normal initial 8′ Radioactivity and decreased 8′ Radioactivity at last follow-up; PDRisk = subjects included in the PDRisk study (multiple PD risk factors); 8′ Radioactivity = ^{18}F-DA-derived radioactivity at 8 min from initiation of tracer injection; $k_{8'\text{-}25'}$ = mono-exponential slope of decline of ^{18}F-DA- derived radioactivity between 8′ and 25′ after initiation of tracer injection. Q1 = first quartile; Q3 = third quartile. The unit of ^{18}F-DA-derived radioactivity was nCi-kg/cc-mCi. The unit of $k_{8'\text{-}25'}$ was min^{-1}.

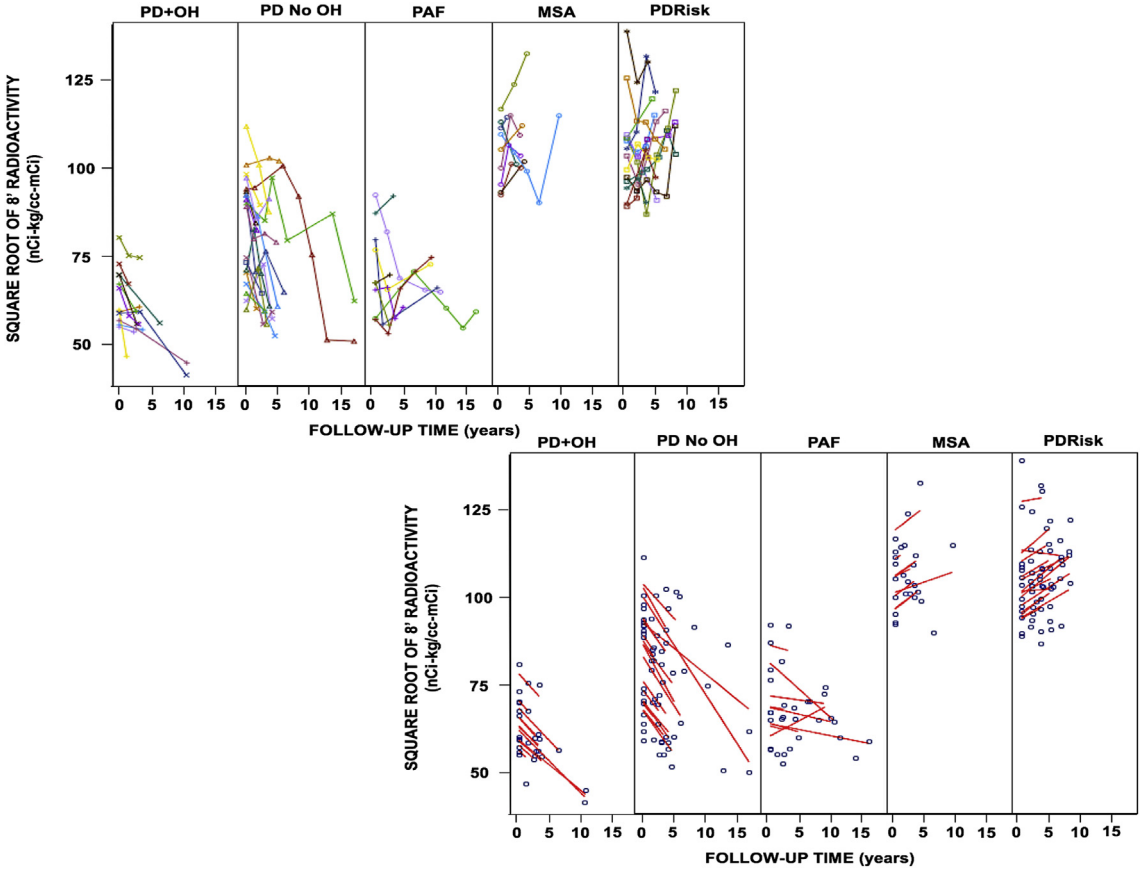

Fig. 1. Individual values for ^{18}F-dopamine- (^{18}F-DA)-derived radioactivity at 8 min after initiation of tracer injection (8′ Radioactivity) as a function of years of follow-up. Square-root transformed data are shown for individuals with Parkinson disease and orthostatic hypotension (PD + OH), PD without orthostatic hypotension (PD No OH), pure autonomic failure (PAF), multiple system atrophy (MSA), and PDRisk study subjects with multiple PD risk factors (PDRisk). Left: individual raw data. Right: modeling of individual changes in 8′ Radioactivity over time based on a random coefficient model. Note consistently decreased 8′ Radioactivity during follow-up in PD No OH.

In MSA there was no evidence for late cardiac sympathetic denervation, and vesicular function in MSA seemed normal initially and unchanged during follow-up. Eight of the 9 MSA had an unexpected increase in ^{18}F-DA-derived radioactivity during follow-up; however, the increase overall in the group was not statistically significant [23]. Since myocardial ^{13}N-ammonia-derived radioactivity, a measure of perfusion, also increased over time in the same MSA patients (data not shown), the increases in ^{18}F-DA-derived radioactivity could have reflected increased myocardial perfusion without an increase in innervation.

Studies using ^{123}I-meta-iodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy have also reported progression of cardiac noradrenergic deficiency in PD [6,24]. In a study by Tsujikawa et al. [6] the "washout" rate of ^{123}I-MIBG-derived radioactivity over 4 h increased by 1.7% per year between initial evaluation and a mean of 3 years of follow-up. The meaning of washout of ^{123}I-MIBG-derived radioactivity is unclear, because vesicular uptake occurs almost immediately after entry of the imaging agent into the neuronal cytoplasm. A vesicular storage defect could result in cytoplasmic ^{123}I-MIBG exiting the neurons by reverse transport across the cell membrane via the cell membrane norepinephrine transporter as the extracellular fluid concentration of ^{123}I-MIBG declines or might reflect increased exocytotic release of vesicular ^{123}I-MIBG due to compensatorily increased traffic to the remaining terminals.

Studies using ^{123}I-MIBG single photon emission tomographic

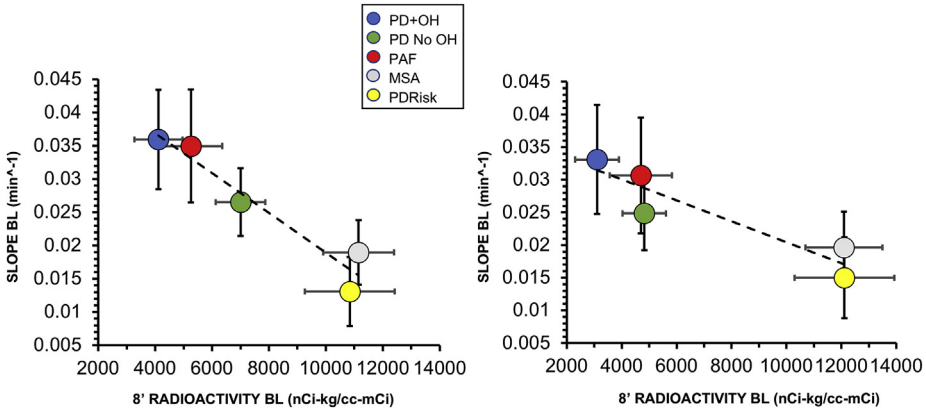

Fig. 2. Backed-transformed mean and 95% confidence interval for the mono-exponential slope of decline of ^{18}F-DA-derived radioactivity between 8 and 25 min after initiation of tracer injection (SLOPE) as a function of 8′ Radioactivity upon initial evaluation (BL, left) and at last follow-up (FU, right). Data are shown for groups with Parkinson disease and orthostatic hypotension (PD + OH), PD without orthostatic hypotension (PD No OH), pure autonomic failure (PAF), multiple system atrophy (MSA), and subjects in the PD Risk study who had multiple PD risk factors (PDRisk). Note decreased 8′ Radioactivity and elevated slopes in the PD + OH, PD No OH, and PAF groups, both upon initial testing and at follow-up.

Table 3
Initial and follow-up mean values for indices of cardiac sympathetic innervation and function in a patient subgroup with normal initial and subsequently decreased ^{18}F-DA-derived radioactivity.

Diagnosis	Time to Last Scan, y	8′ Radioactivity Initial	8′ Radioactivity Last Follow-up	$k_{8'\text{-}25'}$ Initial	$k_{8'\text{-}25'}$ Last follow-up
PD + OH	3.2	6454	5566	0.0191	0.0038
PD No OH	16.8	8092	3839	0.0253	0.0257
PD No OH	5.9	8516	4161	0.0297	0.0321
PD No OH	16.8	8821	2549	0.0147	0.0156
PD No OH	4.9	8478	3646	0.0176	0.0231
PAF	10.1	8585	4220	0.0353	0.0285
PAF	9.6	6398	4378	0.0659	0.0280

Abbreviations: PD + OH = Parkinson disease with orthostatic hypotension; PD No OH = Parkinson disease without orthostatic hypotension; PAF = pure autonomic failure; 8′ Radioactivity = ^{18}F-DA-derived radioactivity at 8 min from initiation of tracer injection; $k_{8'\text{-}25'}$ = mono-exponential slope of decline of ^{18}F-DA- derived radioactivity between 8′ and 25′ after initiation of tracer injection. The unit of ^{18}F-DA-derived radioactivity was nCi-kg/cc-mCi. The unit of $k_{8'\text{-}25'}$ was min^{-1}.

(SPECT) scanning have reported that virtually all individuals with rapid eye movement behavior disorders (RBD) have lower heart/mediastinum ratios of ^{123}I-MIBG -derived radioactivity [25–27], whereas in our study, among the 12 participants in the PDRisk group who reported dream enactment behavior none had septal myocardial ^{18}F-DA-derived radioactivity more than 2 standard deviations below the normal mean. There are three potential explanations for the difference between our results and those based on ^{123}I-MIBG scanning in patients with RBD. First, none of the PDRisk participants had been bothered enough by dream enactment behavior to visit a sleep center. It is possible that some of these participants did not have true RBD. Second, inclusion and exclusion criteria were different between our study and other studies investigating cardiac sympathetic innervation in patients with RBD. In our study, patients who developed PD during follow-up (N = 4) were not included in the analysis, and they all had decreased values for myocardial ^{18}F-DA-derived radioactivity. Third, in our experience,

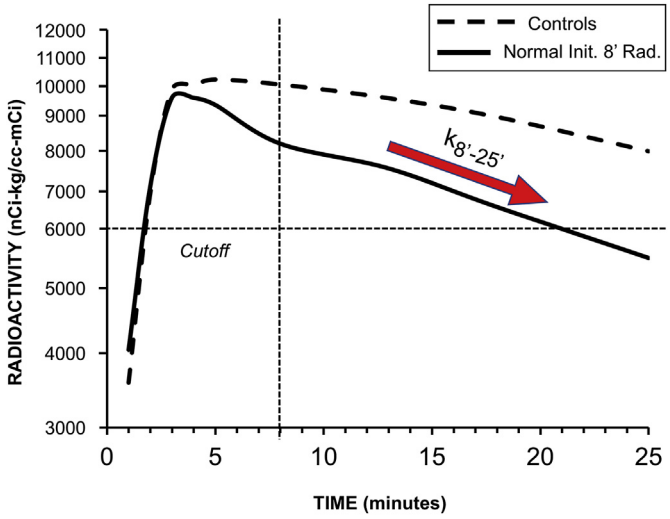

Fig. 4. Curves relating mean interventricular septal ^{18}F-dopamine- (^{18}F-DA)-derived radioactivity as a function of time during scanning in control subjects and in a subgroup of patients with normal initial 8′ Radioactivity and decreased 8′ Radioactivity at last follow-up. In the patient subgroup, upon initial evaluation 8′ Radioactivity is above the cutoff of 6000 nCi-kg/cc-mCi, and there is accelerated loss of ^{18}F-DA-derived radioactivity (red arrow indicates an increased slope of decline in radioactivity). Abbreviations: $k_{8'\text{-}25'}$ = mono-exponential slope of decline of radioactivity between 8 and 25 min. The accelerated loss of radioactivity indicates decreased ability to retain ^{18}F-DA in residual cardiac sympathetic nerves. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

there is an overlap in the distributions of septal 18F-DA-derived radioactivity between controls and patients with PD No OH, such that about 1/2 of patients with PD No OH have ^{18}F-DA-derived radioactivity within 2 standard deviations of the normal mean. Therefore, we would expect ^{18}F-DA-derived radioactivity to be normal in some individuals with pre-motor PD manifesting as RBD.

The clinical significance of the cardiac sympathetic lesion in Lewy

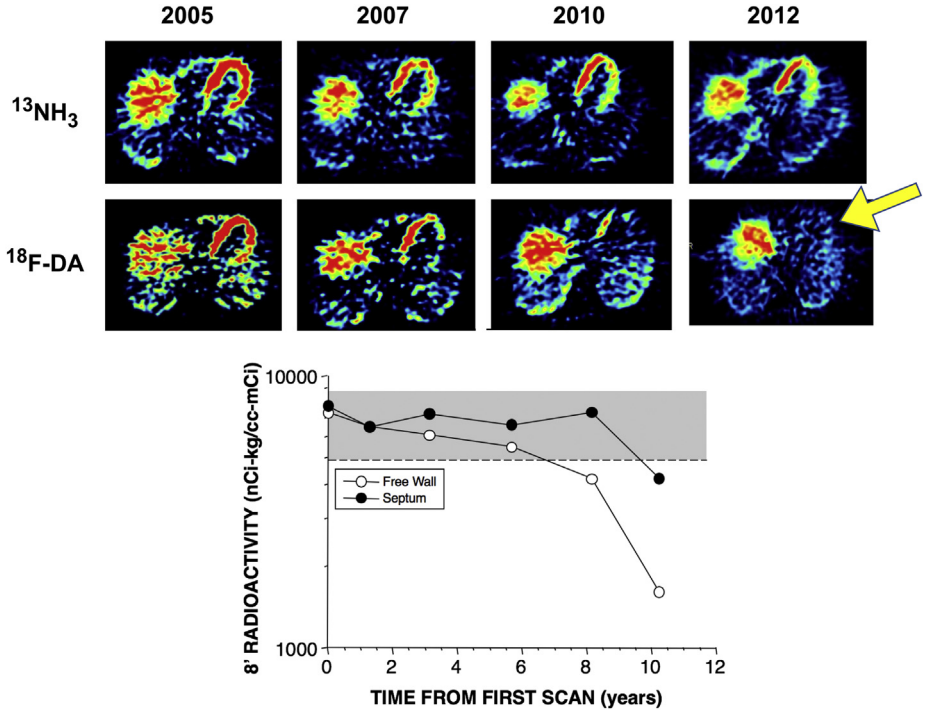

Fig. 3. Positron emission tomographic images showing progressive loss of cardiac sympathetic innervation in a patient with Parkinson disease and no orthostatic hypotension. Myocardial perfusion images using ^{13}N-ammonia ($^{13}NH_3$) scanning are shown in the same patient. There is loss of ^{18}F-dopamine- (^{18}F-DA)-derived radioactivity in the left ventricular free wall preceding loss of radioactivity in the interventricular septum. Yellow arrow indicates no detectable ^{18}F-DA-derived radioactivity in the myocardium with respect to the left ventricular chamber. Myocardial perfusion remains unchanged during follow-up. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

body diseases has not been examined systematically. Cardiac sympathetic innervation is not required for the heart to beat (consider the situation in heart transplantation, where there are no nervous connections to the donor heart). Autonomic failure syndromes are associated with increased atrial ectopy [28], but this applies about equally in MSA, where sympathetic innervation is intact. Neuroimaging evidence of cardiac noradrenergic deficiency does seem be associated with non-specific symptoms such as fatigue, dyspnea on exertion, and cognitive dysfunction [29–31].

The relatively early occurrence of decreased vesicular storage in the course of Lewy body diseases may have implications for concepts about the pathogenesis of synucleinopathies. The autotoxic catecholaldehyde 3,4-dihydroxyphenylacetaldehyde (DOPAL) evokes alpha-synuclein oligomerization [32], and DOPAL-induced alpha-synuclein oligomers interfere with vesicular functions [33]. Since blockade of vesicular uptake shifts the fate of cytoplasmic dopamine toward enzymatic oxidation to form DOPAL [34], interactions between alpha-synuclein and DOPAL might explain the early functional abnormalities that challenge neuronal homeostasis and eventually result in neuronal death.

4.1. Limitations

Because of the retrospective nature of the analysis, there could have been observer or self-selection biases in terms of patients returning for follow-up testing.

In most patients there was no post-mortem neuropathological confirmation of the diagnosis. There is a possibility that some patients without cardiac noradrenergic deficiency by ^{18}F-DA scanning may have been misdiagnosed; however, follow-up evaluations are helpful in distinguishing Lewy body synucleinopathies from MSA. In the present series, 1 patient followed for PD No OH was diagnosed after several years with parkinsonian MSA, based on progressive disability despite levodopa treatment and deep brain stimulation, slurred speech, and development of brainstem and cerebellar atrophy and a positive “hot cross bun” sign on magnetic resonance imaging. Another patient diagnosed initially with PAF also developed parkinsonian MSA. For the purposes of data analysis both these patients were assigned to the MSA group.

Neuroimaging data in isolation cannot identify a vesicular storage defect specifically. Accelerated loss of ^{18}F-DA-derived radioactivity might reflect increased norepinephrine release and decreased reuptake; however, under combining yohimbine to increase norepinephrine release with desipramine to block neuronal reuptake does not appreciably accelerate the loss of ^{3}H–6F-DA in the rat heart [35], and under resting conditions most of tissue catecholamine turnover is from net leakage from vesicles into the cytoplasm, not release with escape from neuronal reuptake [36].

The study did not include a patient cohort with Lewy body dementia, in whom there is often cardiac noradrenergic deficiency [37–39]. This was due to the retrospective analysis of data from protocols that focused on autonomic failure rather than on synucleinopathies. Whether neuroimaging evidence of a vesicular storage defect occurs early in the course of dementia with Lewy bodies remains to be determined.

5. Conclusion

There is a progressive loss of cardiac noradrenergic innervation over years in PD with or without OH and not in MSA. Cardiac noradrenergic neuroimaging may provide an objective biomarker of disease progression that could be useful in future clinical trials testing a disease-modifying experimental therapeutic approach in Lewy body diseases. Decreased vesicular storage seems to be an early functional abnormality in cardiac sympathetic nerves in Lewy body diseases.

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Conflicts of interest

The Corresponding Author affirms that none of the authors has a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.09.014.

References

[1] D.S. Goldstein, Y. Sharabi, The heart of PD: Lewy body diseases as neurocardiologic disorders, Brain Res. 1702 (2019) 74–84.
[2] S.J. Kish, K. Shannak, O. Hornykiewicz, Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications, N. Engl. J. Med. 318 (1988) 876–880.
[3] M.G. Cersosimo, E.E. Benarroch, Autonomic involvement in Parkinson's disease: pathology, pathophysiology, clinical features and possible peripheral biomarkers, J. Neurol. Sci. 313 (1–2) (2012) 57–63.
[4] E. Gelpi, J. Navarro-Otano, E. Tolosa, C. Gaig, Y. Compta, M.J. Rey, M.J. Marti, I. Hernandez, F. Valldeoriola, R. Rene, T. Ribalta, Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders, Mov. Disord. 29 (8) (2014) 1010–1018.
[5] S.T. Li, R. Dendi, C. Holmes, D.S. Goldstein, Progressive loss of cardiac sympathetic innervation in Parkinson's disease, Ann. Neurol. 52 (2) (2002) 220–223.
[6] K. Tsujikawa, Y. Hasegawa, S. Yokoi, K. Yasui, I. Nanbu, T. Yanagi, A. Takahashi, Chronological changes of 123I-MIBG myocardial scintigraphy and clinical features of Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 86 (9) (2015) 945–951.
[7] K.K. Wong, D.M. Raffel, N.I. Bohnen, G. Altinok, S. Gilman, K.A. Frey, 2-Year natural decline of cardiac sympathetic innervation in idiopathic Parkinson disease studied with 11C-Hydroxyephedrine PET, J. Nucl. Med. 58 (2) (2017) 326–331.
[8] D.W. Ryu, J.S. Kim, J.E. Lee, Y.S. Oh, S.W. Yoo, I.R. Yoo, K.S. Lee, Initial versus follow-up sequential myocardial 123I-MIBG scintigraphy to discriminate Parkinson disease from atypical parkinsonian syndromes, Clin. Nucl. Med. 44 (4) (2019 Apr) 282–288.
[9] A.H. Schapira, P. Jenner, Etiology and pathogenesis of Parkinson's disease, Mov. Disord. 26 (6) (2011) 1049–1055.
[10] M. Watabe, T. Nakaki, Mitochondrial complex I inhibitor rotenone inhibits and redistributes vesicular monoamine transporter 2 via nitration in human dopaminergic SH-SY5Y cells, Mol. Pharmacol. 74 (4) (2008) 933–940.
[11] D.S. Goldstein, C. Holmes, I.J. Kopin, Y. Sharabi, Intra-neuronal vesicular uptake of catecholamines is decreased in patients with Lewy body diseases, J. Clin. Investig. 121 (8) (2011) 3320–3330.
[12] C. Pifl, A. Rajput, H. Reither, J. Blesa, C. Cavada, J.A. Obeso, A.H. Rajput, O. Hornykiewicz, Is Parkinson's disease a vesicular dopamine storage disorder? Evidence from a study in isolated synaptic vesicles of human and nonhuman primate striatum, J. Neurosci. 34 (24) (2014) 8210–8218.
[13] D.S. Goldstein, P. Sullivan, C. Holmes, G.W. Miller, Y. Sharabi, I.J. Kopin, A vesicular sequestration to oxidative deamination shift in myocardial sympathetic nerves in Parkinson disease, J. Neurochem. 131 (2014) 219–228.
[14] D.S. Goldstein, C. Holmes, P. Sullivan, D.C. Mash, E. Sidransky, A. Stefani, I.J. Kopin, Y. Sharabi, Deficient vesicular storage: a common theme in catecholaminergic neurodegeneration, Park. Relat. Disord. 21 (9) (2015) 1013–1022.
[15] D.S. Goldstein, C. Holmes, O. Bentho, T. Sato, J. Moak, Y. Sharabi, R. Imrich, S. Conant, B.A. Eldadah, Biomarkers to detect central dopamine deficiency and distinguish Parkinson disease from multiple system atrophy, Park. Relat. Disord. 14 (8) (2008) 600–607.
[16] D.S. Goldstein, C. Holmes, Y. Sharabi, Cerebrospinal fluid biomarkers of central catecholamine deficiency in Parkinson's disease and other synucleinopathies, Brain 135 (Pt 6) (2012) 1900–1913.
[17] S. Gilman, G.K. Wenning, P.A. Low, D.J. Brooks, C.J. Mathias, J.Q. Trojanowski, N.W. Wood, C. Colosimo, A. Durr, C.J. Fowler, H. Kaufmann, T. Klockgether, A. Lees, W. Poewe, N. Quinn, T. Revesz, D. Robertson, P. Sandroni, K. Seppi, M. Vidailhet, Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (9) (2008) 670–676.
[18] D.S. Goldstein, Y. Sharabi, Neurogenic orthostatic hypotension: a pathophysiological approach, Circulation 119 (1) (2009) 139–146.
[19] D.S. Goldstein, C. Holmes, Y. Sharabi, S. Brentzel, G. Eisenhofer, Plasma levels of catechols and metanephrines in neurogenic orthostatic hypotension, Neurology 60 (8) (2003) 1327–1332.
[20] D.S. Goldstein, C. Holmes, R.O. Cannon 3rd, G. Eisenhofer, I.J. Kopin, Sympathetic cardioneuropathy in dysautonomias, N. Engl. J. Med. 336 (10) (1997) 696–702.
[21] D.S. Goldstein, C. Holmes, G.J. Lopez, T. Wu, Y. Sharabi, Cardiac sympathetic

denervation predicts PD in at-risk individuals, Parkinsonism Relat, Disord. 52 (2018) 90–93.
[22] D.S. Goldstein, I.J. Kopin, Y. Sharabi, C. Holmes, Plasma biomarkers of decreased vesicular storage distinguish Parkinson disease with orthostatic hypotension from the parkinsonian form of multiple system atrophy, Clin. Auton. Res. 25 (1) (2015) 61–67.
[23] V. Iodice, A. Lipp, J.E. Ahlskog, P. Sandroni, R.D. Fealey, J.E. Parisi, J.Y. Matsumoto, E.E. Benarroch, K. Kimpinski, W. Singer, T.L. Gehrking, J.A. Gehrking, D.M. Sletten, A.M. Schmeichel, J.H. Bower, S. Gilman, J. Figueroa, P.A. Low, Autopsy confirmed multiple system atrophy cases: mayo experience and role of autonomic function tests, J. Neurol. Neurosurg. Psychiatry 83 (4) (2012) 453–459.
[24] H. Takatsu, H. Nishida, H. Matsuo, S. Watanabe, K. Nagashima, H. Wada, T. Noda, K. Nishigaki, H. Fujiwara, Cardiac sympathetic denervation from the early stage of Parkinson's disease: clinical and experimental studies with radiolabeled MIBG, J. Nucl. Med. 41 (1) (2000) 71–77.
[25] T. Miyamoto, M. Miyamoto, Y. Inoue, Y. Usui, K. Suzuki, K. Hirata, Reduced cardiac 123I-MIBG scintigraphy in idiopathic REM sleep behavior disorder, Neurology 67 (12) (2006) 2236–2238.
[26] K. Knudsen, T.D. Fedorova, A.K. Hansen, M. Sommerauer, M. Otto, K.B. Svendsen, A. Nahimi, M.G. Stokholm, N. Pavese, C.P. Beier, D.J. Brooks, P. Borghammer, In-vivo staging of pathology in REM sleep behaviour disorder: a multimodality imaging case-control study, the Lancet, Neurology 17 (7) (2018) 618–628.
[27] R. Sakakibara, F. Tateno, Y. Aiba, T. Ogata, M. Kishi, H. Terada, T. Inaoka, T. Nakatsuka, K. Matsuoka, MIBG myocardial scintigraphy identifies premotor PD/DLB during a negative DAT scan period: second report, Mov. Disord. Clin. Pract. 6 (1) (2019) 46–50.
[28] D.S. Goldstein, Cardiac ectopy in chronic autonomic failure, Clin. Auton. Res. 20 (2010) 85–92.
[29] T. Nakamura, M. Hirayama, T. Hara, T. Hama, H. Watanabe, G. Sobue, Does cardiovascular autonomic dysfunction contribute to fatigue in Parkinson's disease? Mov. Disord. 26 (10) (2011) 1869–1874.
[30] H. Fujishiro, S. Nakamura, M. Kitazawa, K. Sato, E. Iseki, Early detection of dementia with Lewy bodies in patients with amnestic mild cognitive impairment using 123I-MIBG cardiac scintigraphy, J. Neurol. Sci. 315 (1–2) (2012) 115–119.
[31] J.S. Kim, Y.S. Shim, I.U. Song, J.Y. Yoo, H.T. Kim, Y.I. Kim, K.S. Lee, Cardiac sympathetic denervation and its association with cognitive deficits in Parkinson's disease, Park. Relat. Disord. 15 (9) (2009) 706–708.
[32] W.J. Burke, V.B. Kumar, N. Pandey, W.M. Panneton, Q. Gan, M.W. Franko, M. O'Dell, S.W. Li, Y. Pan, H.D. Chung, J.E. Galvin, Aggregation of alpha-synuclein by DOPAL, the monoamine oxidase metabolite of dopamine, Acta Neuropathol. 115 (2) (2008) 193–203.
[33] N. Plotegher, G. Berti, E. Ferrari, I. Tessari, M. Zanetti, L. Lunelli, E. Greggio, M. Bisaglia, M. Veronesi, S. Girotto, M. Dalla Serra, C. Perego, L. Casella, L. Bubacco, DOPAL derived alpha-synuclein oligomers impair synaptic vesicles physiological function, Sci. Rep. 7 (2017) 40699.
[34] D.S. Goldstein, P. Sullivan, A. Cooney, Y. Jinsmaa, R. Sullivan, D.J. Gross, C. Holmes, I.J. Kopin, Y. Sharabi, Vesicular uptake blockade generates the toxic dopamine metabolite 3,4-dihydroxyphenylacetaldehyde in PC12 cells: relevance to the pathogenesis of Parkinson's disease, J. Neurochem. 123 (6) (2012) 932–943.
[35] P.C. Chang, K. Szemeredi, E. Grossman, I.J. Kopin, D.S. Goldstein, Fate of tritiated 6-fluorodopamine in rats: a false neurotransmitter for positron emission tomographic imaging of sympathetic innervation and function, J. Pharmacol. Exp. Ther. 255 (1990) 809–817.
[36] G. Eisenhofer, I.J. Kopin, D.S. Goldstein, Catecholamine metabolism: a contemporary view with implications for physiology and medicine, Pharmacol. Rev. 56 (3) (2004) 331–349.
[37] S. Orimo, T. Amino, Y. Itoh, A. Takahashi, T. Kojo, T. Uchihara, K. Tsuchiya, F. Mori, K. Wakabayashi, H. Takahashi, Cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia in Lewy body disease, Acta Neuropathol. 109 (6) (2005) 583–588.
[38] M. Suzuki, A. Kurita, M. Hashimoto, N. Fukumitsu, M. Abo, Y. Ito, M. Urashima, K. Inoue, Impaired myocardial 123I-metaiodobenzylguanidine uptake in Lewy body disease: comparison between dementia with Lewy bodies and Parkinson's disease, J. Neurol. Sci. 240 (1–2) (2006) 15–19.
[39] M. Yoshita, J. Taki, K. Yokoyama, M. Noguchi-Shinohara, Y. Matsumoto, K. Nakajima, M. Yamada, Value of 123I-MIBG radioactivity in the differential diagnosis of DLB from AD, Neurology 66 (12) (2006) 1850–1854.