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RESEARCH ARTICLE

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Orthostatic hypotension as an early finding in Parkinson's disease

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Abstract Patients with Parkinson's disease (PD) commonly have clinically significant orthostatic hypotension (OH). In such patients PD + OH might be confused with multiple system atrophy (MSA), in which OH is a frequent finding, or with pure autonomic failure (PAF), if OH preceded clinical manifestations of the movement disorder. This study addressed whether OH can occur as an early finding in PD + OH. Historical data were analyzed from 35 patients with PD + OH evaluated at the NIH. OH was considered early if the patient had OH before, concurrent with, or starting within 1 year after onset of a symptomatic movement disorder. MSA was excluded by myocardial 6-[^{18}F]fluorodopamine-derived radioactivity more than 2 standard deviations below the normal mean. Among the 35 PD + OH patients, 21 (60 %) had documentation of OH as an early finding. In 4 such patients, OH had preceded parkinsonism, and in 4 others, OH had dominated the early clinical picture, even after cessation of levodopa treatment for the movement disorder. In PD, OH can occur early in the disease, occasionally preceding or overshadowing the movement disorder.

Key words autonomic · sympathetic · Parkinson's disease · fluorodopamine · multiple system atrophy

Introduction

In Parkinson's disease (PD), orthostatic hypotension (OH) can pose a major management problem [10, 27, 81]. Studies have varied widely in reported frequencies of OH in PD (Table 1). In 5 relatively large studies involving more than 80 patients each, the frequency of OH ranged from 30 to 58 % [2, 16, 45, 52, 80]. A substantial minority of PD patients therefore have OH.

In parkinsonian patients, OH has been thought to be a side effect of levodopa treatment [33] or to develop late in the disease course or only in more severe cases [49, 92]. Among parkinsonian patients in whom OH is an early or dominant finding, with respect to the movement disorder, the alternative diagnosis of multiple system atrophy (MSA) is usually favored [22, 53, 79], because MSA is well known to feature early OH as part of a constellation of findings reflecting autonomic failure. Nevertheless, case reports have noted early OH in autopsy-proven PD diagnosed during life as MSA [7, 73]. Conversely, according to Magalhaes et al. one-third of patients with pathologically proven MSA die misdiagnosed with PD [52]. Other case reports have noted that when OH is the initial manifestation of disease, PD + OH can be attributed to pure autonomic failure (PAF, previously called idiopathic orthostatic hypotension, asympathicotonic hypotension, or Bradbury-Eggleston syndrome) [42].

The notion that OH can be an early finding in PD and even precede the movement disorder is by no means new. More than a half century ago, Nylin and Levander [59] reported such a case, a patient with OH who developed orthostatic intolerance at the age of 67. Eight years later he was diagnosed with OH from "asympathicotonic

Table 1 Reported criteria and frequencies of orthostatic hypotension in Parkinson disease

First author [Ref. No.]	Prevalence (%)	N	Notes
Allcock [2]	**47**	**89**	**Community-based cohort 20 mm Hg dec. BPs or to < 90 Indep. of PD duration Indep. of PD severity Higher prevalence if older**
Awerbuch [5]	10	20	Untreated early PD 20 mm Hg dec. BPs
Bellon [6]	65	46	> 30 mm Hg dec. BPs
Bhattacharya [9]	49	49	20 mm Hg dec. BPs and 10 mm Hg dec. BPd All on levodopa
Bonuccelli [11]	14	51	*de novo* untreated PD 20 mm Hg dec. BPs
Briebach [16]	**40**	**250**	**20 mm Hg dec. BPs**
Hillen [32]	58	36	PD patients > 65 y old. 15 mm Hg dec. BPs
Holmberg [34]	60	47	Dec. in MAP > 2 SD fr. normal Higher prevalence if older Higher prevalence if longer duration
Hubble [35]	100	27	All had episodes of OH All on selegiline, none on levodopa 20 mm Hg dec. BPs at 1′
Korchounov [45]	**30**	**148**	**20 mm Hg dec. BPs or 10 mm Hg dec. BPd, and < 15 bpm HR increment at 2′**
Krygowska-Wajs [46]	36 4	20 15	Early Advanced
Kujawa [47]	14	29	> 25 mm Hg dec. BPs or > 10 mm Hg dec. BPd
Kuroiwa [48]	25	16	> 2 SD dec. BPs fr. normal
Loew [51]	20	10	20 mm Hg dec. BPs
Magalhaes [52]	**30**	**135**	**Pathology-proven PD**
Micieli [54]	54	13	25 mm Hg dec. BPs and 10 mm Hg dec. BPd Untreated
Papapetropoulos [65]	10	52	At disease presentation
Rajput [69]	50	6	Autopsy study
Sandyk [74]	31	37	Untreated Related to PD severity
Senard [80]	**58**	**91**	**≥20 mm Hg dec. BPs All on levodopa Indep. of disease duration Related to PD severity**
Thaisetthawatkul [88]	5	20	≥30 mm Hg dec. BPs
Tranchant [90]	53	19	> 20 mm Hg dec. BPs
Turkka [91]	Unreported	52	Indep. of disease duration
Wenning [96]	78	11	Autopsy study
AVERAGE	41		
SUM		1237	

In constructing the listing of studies, PubMed was searched for the intersection between "orthostatic hypotension" and "parkinson", then the culled Abstracts were reviewed to identify peer-reviewed journal articles that reported original clinical data, and then the articles were examined to determine if they quantified the frequency of OH. All the resulting literature is depicted. The 5 largest studies are shown in boldface

orthostatism" [12] and over the course of the next year a resting unilateral tremor, masked face, and "cogwheel" rigidity, findings recognized by the authors as typical of PD. Of 3 post-mortem case reports about PD + OH patients, where the timing of onset of OH with respect to the movement disorder was reported, in all 3 OH had developed first [42, 77, 94].

Previous studies do not seem to have assessed the frequency of OH as an early finding in PD + OH. Carrying out such an analysis would require evidence that the pa-

tients did not have MSA. Diagnosing MSA differentially from PD + OH can be very difficult clinically. Autopsy studies have revealed a disappointingly high frequency of erroneous diagnosis, even by well experienced academicians [50, 52].

In an effort to exclude patients with MSA from the analysis, the present study took a novel tack based on results of cardiac sympathetic neuroimaging. Remarkably consistent and by now abundant literature, summarized in Table 3, shows that cardiac sympathetic neuroimaging distinguishes PD from MSA, with cardiac sympathetic denervation in the former but not the latter. Three autopsy studies of patients who during life had undergone cardiac sympathetic neuroimaging and had postmortem histopathologic assessments of tyrosine hydroxylase (TH) immunoreactivity reported that all patients with neuroimaging evidence of cardiac sympathetic denervation had pathologic confirmation of PD and markedly reduced or absent TH in epicardial nerves, whereas all patients with evidence of intact innervation had pathologic confirmation of MSA and normal TH [3, 62, 64].

In the present study, medical history data were reviewed from patients with PD + OH evaluated at the NIH, to determine the frequency with which OH was an initial or early finding. For the reasons explained above, neuroimaging evidence of cardiac sympathetic denervation was used to exclude MSA.

Materials and methods

The study protocol was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke. Each subject gave informed, written consent.

Of more than 200 adult patients referred for autonomic function testing, 35 had PD + OH, identified by satisfying all of the following criteria.

(1) Bradykinesia coupled with resting "pill-roll" tremor (N = 19), "cogwheel" rigidity (N = 27), or improvement in movement by levodopa (N = 23). Of the 35 patients, 22 had at least 3 of these findings, and 15 had all 4. Five patients had never been treated with levodopa. Two patients had rigidity without the rigidity type specified.

(2) OH, defined by a fall in systolic blood pressure of at least 20 mm Hg and a fall in diastolic pressure of at least 5 mm Hg between the supine position (after 15 minutes of rest) and 5 minutes of upright posture. As noted in Table 1, despite a consensus statement on the definition of OH as an orthostatic fall in systolic blood pressure of at least 20 mm Hg and fall in diastolic pressure of at least 10 mm Hg [41], criteria actually used in PD research have varied, the most common criterion being an orthostatic decrease in systolic blood pressure of at least 20 mm Hg.

(3) Interventricular septal myocardial 6-[^{18}F]fluorodopamine-derived radioactivity more than 2 standard deviations below the normal mean [23, 26].

6-[^{18}F]Fluorodopamine, synthesized as described previously [23], was infused i. v. at a constant rate for 3 minutes. Tomographic images (35 contiguous transaxial slices 4.25 mm apart) were acquired for up to 30 minutes. For the scanning interval between 5 and 10 minutes after initiation of 6-[^{18}F]fluorodopamine, the average radioactivity concentration in two circular regions of interest in the interventricular septum was normalized for the administered dose of radioactive drug per unit body mass of the subject [23].

For each patient, the medical history in the patient's NIH medical record and referral documents were analyzed retrospectively, with attention to the timing of onset of OH with respect to that of the movement disorder. Onset of OH was considered "early," if OH, or symptoms later determined to be the result of OH, started before, concurrent with, or within 1 year after the onset of symptoms of a movement disorder.

Results

Among the 35 patients with PD + OH, there were 22 men and 13 women, 32 Caucasians and 3 black, with mean age 71 ± 2 years (age range 44–84 years). Mean age at onset of the movement disorder was 60 ± 2 years. The patients were studied a mean of 11 ± 2 years after onset of the movement disorder (range 0–38 years, median 9 years).

Twenty-one (60 %) of the 35 PD + OH patients had an early onset of OH. In 4 (13 %), OH had developed before symptoms of a movement disorder. In 4 others, the patients had no symptoms of a movement disorder at the time of evaluation but nevertheless had sufficient clinical signs to diagnose PD. Since in these patients, treatment with levodopa or other dopaminergic drugs had not yet been initiated, in at least 8 of the 21 patients with early OH (at least 23 % of PD + OH patients overall), early OH could not be ascribed to treatment.

Of the 4 patients in whom symptomatic OH had become manifest within a year of symptoms of a movement disorder, 3 had a referral diagnosis of MSA. Subsequent development of a resting tremor, clear and reproducible improvement in movement during levodopa treatment, relatively slow progression, and neuroimaging evidence of cardiac sympathetic denervation led to a change in the diagnosis to PD + OH. Of the 4 patients in whom OH had dominated the clinical picture, without symptoms of a movement disorder at the time, all 4 had a referral diagnosis of PAF.

Of the remaining 13 patients with PD + OH and a history of early onset of OH, 6 were on levodopa at the time of evaluation, so that OH from levodopa treatment could not be excluded. In 7 patients, OH persisted despite discontinuation of levodopa, but the medical records did not specify whether the patients had been on levodopa at the time of early onset of OH.

Discussion

In the current analysis of medical historical data from patients with PD + OH who were evaluated at the NIH, OH had developed early in the disease course in 60 %. Previous studies have not assessed the timing of onset of OH with respect to the movement disorder in a group of patients with PD + OH.

As indicated in Table 2, several clinicopathological reports have described patients with autopsy proven PD in whom OH had dominated the clinical picture. A few such reports included sufficient medical historical information to determine the timing of onset of OH with respect to that of the movement disorder [20, 21, 42, 94]. In all such patients, OH had developed before the onset of parkinsonism, and the patients all carried a diagnosis of PAF during life. Analogously, in the present series, 4 patients with PD + OH had a referral diagnosis of PAF and had never been diagnosed with or treated for a parkinsonian movement disorder.

In attempting to estimate the frequency of OH as an early finding in PD, the main scientific stumbling block has been the lack of a "gold standard," short of post-mortem pathologic findings, for differential diagnosis of PD vs. MSA. To deal with this issue the present study used a unique approach–cardiac sympathetic neuroimaging. The finding of markedly decreased 6-[^{18}F]fluorodopamine-derived radioactivity throughout the left ventricular myocardium, which indicated loss of post-ganglionic sympathetic noradrenergic nerves, was taken to exclude MSA, because numerous neurochemical [26, 28, 44, 66, 67], neuroimaging (Table 3), and pharmacologic [68, 81] studies, as well as 3 recent post-mortem pathological studies [3, 62, 64], have agreed on

Table 2 Post-mortem findings in primary chronic autonomic failure or Parkinson disease (PD)

First author [Ref. No.]	Diagnosis	N	SN LB?	SNS LB?
Benarroch [7]	PD + OH	3	Yes	Not reported
Kato [40]	PD + OH	3	Yes	Not reported
Kaufmann (Case 1) [42]	PD + OH	1	Yes	Yes
Orimo [62]	PD + OH	3	Yes	Yes
Schober (Case 2) [77]	PD + OH	1	Yes	Yes
Vanderhaeghen (Case 1) [94]	PD + OH	1	Yes	Yes
Saito [73]	PD + OH	1	Yes	?**
Arai [4]	PAF	1	Yes	Yes
Evans [20]	PAF	1	No	No
Hague [30]	PAF	1	Yes	Yes
Johnson (Case 1) [39]	PAF	1	Yes	No
Miura [55]	PAF	1	Yes	?**
Orimo [62]	PAF	1	Yes	Not reported
Roessman [71]	PAF	1	Yes	Yes
Terao [87]	PAF	1	Yes	Yes
Van Ingelghem [93]	PAF	1	No	Yes
Benarroch [7]	MSA	6	No	Not reported
Graham [29]	MSA	1	No	No
Johnson (Case 2) [39]	MSA	1	No	No
Kato [40]	MSA	7	No (implied)	Not reported
Kluyskens (Case 5) [43]	MSA	1	No	Not reported
Nick [57]	MSA	1	No	No
Nishie [58]	MSA	8	No*	No*
Orimo [62]	MSA	3	No	No
Schober (Case 1) [77]	MSA	1	No	No*
Schwarz [78]	MSA	1	No	No
Shy (Case 2) [82]	MSA	1	No	No
Thapedi [89]	MSA	1	No	No*
Iwanaga [36]	PD	11		Yes (9/11)
Jager [18]	PD	6		Yes (5/6)
Rajput [69]	PD	6		Yes (5/6)
Takeda [85]	PD	1		Yes
Wakabayashi [95]	PD	10		Yes (9/10)

PAF pure autonomic failure (previously called idiopathic orthostatic hypotension); *MSA* multiple system atrophy (previously called Shy-Drager syndrome); *PD + OH* Parkinson disease with orthostatic hypotension; *SN LB* substantia nigra Lewy bodies; *SNS LB* sympathetic nervous system Lewy bodies
* eosinophilic neuronal inclusions; ** Japanese article with English abstract

Table 3 Cardiac sympathetic neuroimaging findings in Parkinson disease (PD) or multiple system atrophy (MSA)

First author [Ref. No.]	Year	Im. Agent	Den.?	Notes
PD				
Goldstein [24]	1997	18F-6F-DA	Yes	
Satoh [76]	1997	123I-MIBG	Yes	
Yoshita [98]	1997	123I-MIBG	Yes	
Braune [14]	1998	123I-MIBG	Yes	
Iwasa [37]	1998	123I-MIBG	Yes	
Yoshita [97]	1998	123I-MIBG	Yes	Indep. PD sever./OH
Braune [15]	1999	123I-MIBG	Yes	Even early, indep. of dur./sever. AF/PD
Orimo [63]	1999	123I-MIBG	Yes	
Satoh [75]	1999	123I-MIBG	Yes	
Druschky [19]	2000	123I-MIBG	Yes	Early disease
Goldstein [26]	2000	18F-6F-DA	Yes	
Ohmura [60]	2000	123I-MIBG	Yes	
Reinhart [70]	2000	123I-MIBG	Yes	Early p onset of auton dysfunct
Takatsu [84]	2000	123I-MIBG	Yes	Early PD, even w/o OH
Takatsu [83]	2000	123I-MIBG	Yes	
Taki [86]	2000	123I-MIBG	Yes	
Braune [13]	2001	123I-MIBG	Yes	
Orimo [64]	2001	123I-MIBG	Yes	Pathologic confirmation
Goldstein [25]	2002	18F-6F-DA	Yes	Worse if OH
Orimo [62]	2002	123I-MIBG	Yes	Pathologic confirmation
Akincioglu [1]	2003	123I-MIBG	Yes	Indep. of PD severity
Berding [8]	2003	11C-HED	Yes	
Courbon [17]	2003	123I-MIBG	Yes	
Hamada [31]	2003	123I-MIBG	Yes	Related to onset age, PD severity
Jimenez-Hoyuelaa [38]	2003	123I-MIBG	Yes	Indep. of PD dur./sever./Tx
Saiki [72]	2004	123I-MIBG	Yes	Related to onset age, PD severity
Nagayama [56]	2005	123I-MIBG	Yes	
MSA				
Goldstein [24]	1997	18F-6F-DA	No	
Braune [15]	1999	123I-MIBG	No	Even early, indep. of dur./sever. AF/PD
Druschky [19]	2000	123I-MIBG	No	Early disease
Goldstein [26]	2000	18F-6F-DA	No	
Reinhart [70]	2000	123I-MIBG	No	Early after onset of auton. dysfunct.
Takatsu [84]	2000	123I-MIBG	No	
Braune [13]	2001	123I-MIBG	No	
Orimo [64]	2001	123I-MIBG	No	Pathologic confirmation
Goldstein [25]	2002	18F-6F-DA	No	
Orimo [62]	2002	123I-MIBG	No	Pathologic confirmation
Berding [8]	2003	11C-HED	No	
Courbon [17]	2003	123I-MIBG	No	
Saiki [72]	2004	123I-MIBG	No	
Nagayama [56]	2005	123I-MIBG	No	

18F-6F-DA 6-[^{18}F]fluorodopamine; *123I-MIBG* ^{123}I-metaiodobenzylguanidine; *11C-HED* ^{11}C-hydroxyephedrine; *AF* autonomic failure; *auton. dysfunct.* autonomic dysfunction; *den.* cardiac sympathetic denervation; *dur.* duration; *ind.* independent; *OH* orthostatic hypotension; *sever.* severity; *Tx* treatment

the absence of a post-ganglionic sympathetic noradrenergic lesion in MSA.

In the relatively large studies of Allcock et al. [2], Senard et al. [80], and Turkka et al. [91], frequencies of OH in PD were independent of duration of the movement disorder, implying that a proportion of patients with PD had OH at about the time of onset of the movement disorder. Krygowska-Wajs et al. [46] reported a 36 % prevalence of OH in patients with early PD. Studies of de novo PD [5, 11, 65] could have missed patients with prominent OH and mild parkinsonism, because such patients might not have sought consultation by a movement disorders specialist.

The post-mortem pathological studies summarized in Table 2 show that most patients with PD have Lewy bodies in sympathetic ganglia, and most patients with

PAF have Lewy bodies in the substantia nigra. The overlapping pathological findings suggest that PAF and PD may lie along a spectrum of Lewy body diseases. In contrast, MSA does not involve Lewy body pathology either in the substantia nigra or sympathetic ganglia. Relative localization of pathology to peripheral norepinephrine-producing cells in PD + OH and PAF and to central glial cells in MSA might help explain cardiac sympathetic denervation in PD + OH and PAF but not in MSA; however, the basis for such cellular localization remains unknown.

A recent neuropathological study has demonstrated that in PD, cardiac sympathetic denervation precedes neuronal loss in the sympathetic ganglia [61]. Because of substantial sympathetic noradrenergic innervation of the heart and arterioles, a pathogenic mechanism involving neuronal uptake and intraneuronal oxidative metabolism of catecholamines might explain cardiac sympathetic denervation and OH as early findings in at least some patients with PD.

Study limitations

Application of the cardiac sympathetic neuroimaging approach for excluding MSA led to a surprisingly high frequency of OH as an early finding in PD. A potential limitation of the analysis of case histories is that it involved only patients referred to the NIH for evaluation by our group. Such a population of referred patients might not reflect the general population of patients with parkinsonian symptoms and OH. Quantitative estimation of the frequency of OH as an early finding in PD overall would require a community-based, prospective study about the timing of onset of OH with respect to the movement disorder.

Orthostatic vital signs had not been recorded when some of the patients had first been evaluated for a movement disorder, despite the complaint of orthostatic intolerance. This necessitated categorization of OH as "early" if the patient had had orthostatic intolerance that was shown subsequently to result from OH. Hopefully, increased recognition of the possibility of OH as an early finding in PD will lead to a greater frequency of formal measurement of orthostatic vital signs as part of the initial evaluation of patients with new onset of parkinsonism.

In the US, relatively few centers routinely perform sympathetic neuroimaging, and the scheme used in the present study depended on evidence of cardiac sympathetic denervation for inclusion in the PD + OH group.

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