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Different phenoconversion pathways in pure autonomic failure with vs. without Lewy bodies

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Abstract

Pure autonomic failure (PAF) is a rare disease in which chronic neurogenic orthostatic hypotension (nOH) dominates the clinical picture. Longitudinal studies have reported that PAF can phenoconvert to a central synucleinopathy with motor or cognitive involvement—i.e., to Parkinson disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA). These studies have classified patients clinically as having PAF based on nOH without an identified secondary cause or clinical evidence of motor or cognitive impairment due to central neurodegeneration. This approach lumps together two nOH syndromes that are pathologically and neurochemically distinct. One is characterized by intraneuronal cytoplasmic alpha-synuclein aggregates (i.e., Lewy bodies) and degeneration of postganglionic sympathetic neurons, as in PD and DLB; the other is not, as in MSA. Clinical and post-mortem data show that the form of PAF that involves sympathetic intra-neuronal synucleinopathy and noradrenergic deficiency can phenoconvert to PD or DLB—but not to MSA. Conversely, PAF without these features leaves open the possibility of premotor MSA.

Keywords

pure autonomic failure; orthostatic hypotension; multiple system atrophy; Parkinson disease; alpha-synuclein; norepinephrine; sympathetic nervous system

Introduction

Pure autonomic failure (PAF) is a rare disease characterized by chronic neurogenic orthostatic hypotension (nOH). Retrospective [14] and prospective [42] longitudinal studies

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have reported that PAF can phenoconvert to a central nervous system synucleinopathy with motor or cognitive involvement—i.e., to Parkinson disease (PD), dementia with Lewy bodies (DLB), or multiple system atrophy (MSA).

PAF is defined clinically by nOH without an identified secondary cause or clinical evidence of motor or cognitive impairment attributable to central nervous system neurodegeneration [39]. Review of the literature shows that what historically has been called PAF or idiopathic orthostatic hypotension should be conceptualized in terms of two pathologically and neurochemically separate entities, one a Lewy body disease, as in PD, and the other not a Lewy body disease, as in MSA. Both PAF phenotypes involve a sympathetic preganglionic lesion, but only Lewy body PAF, PD, and DLB entail a postganglionic noradrenergic lesion.

Historical perspective and review of autopsy studies

The several designations that have been used for nOH syndromes, including PAF, have been confusing. It is worthwhile to review the history of the area and the published autopsy data.

After the initial case reports of “postural hypotension” by Bradbury and Eggleston [11], descriptions appeared of patients with “asympathicotonic orthostatic hypotension” [50] or “idiopathic orthostatic hypotension” [5, 75]. Post-mortem analyses of idiopathic orthostatic hypotension patients (now referred to as PAF) revealed Lewy bodies in sympathetic ganglia [77], as in PD (Table 1).

In the early 1970s, Sir Roger Bannister proposed that idiopathic orthostatic hypotension can occur in two forms, one with brainstem abnormalities resembling those in PD and the other with multiple sites of central neuropathology, as in what was then called the Shy-Drager syndrome [67]. Graham and Oppenheimer introduced the term MSA [29], which includes central autonomic failure but not necessarily OH [6, 62], as some patients in the original description only had decreased sweating and bladder abnormalities.

In the first edition of his textbook, *Autonomic Failure,* Bannister used the abbreviation, PAF, to denote “progressive autonomic failure” [2], which he viewed as including the Lewy body disease PD and the non-Lewy body disease MSA. He wrote, “It is an important fact that Lewy bodies, some of which may contain catecholamine degeneration products, are also found in the brains of patients with progressive autonomic failure without Parkinson’s disease but rarely in patients with multiple system atrophy.”

Bannister noted in the second edition of his textbook that idiopathic orthostatic hypotension can be “pure” in the sense of lacking clinical evidence of motor or cognitive deficits indicating central nervous system neurodegeneration. Now he used the abbreviation PAF to stand for pure autonomic failure. In contrast with what he wrote in the first edition, in the second he wrote, “It must be recognized that at an early stage an accurate prognosis of autonomic failure cannot be given. It may remain as pure autonomic failure for many years, relatively static, or in time it may also come to be associated either with Parkinson’s disease or MSA…” [3].

Subsequent autopsy studies of PAF cases continued to report Lewy bodies in sympathetic ganglia [30, 76]. Thus, a consistent feature of the PAF cases that have come to autopsy has been Lewy body pathology in the brainstem, sympathetic nervous system, or both (Table 1). In contrast, MSA patients rarely have been found to have brainstem or sympathetic nervous system Lewy bodies [43, 51, 52], whether or not OH has been an early clinical manifestation (Tables 2 and 3). The patient with Lewy bodies in sympathetic neurons and in the brainstem reported by Thapedi et al. [74] as having the Shy-Drager syndrome likely had PD rather than MSA, as suggested by lack of cerebellar or brainstem atrophy on neuropathology (Table 2). The first complete autopsy of a patient with PAF showed Lewy bodies in sympathetic ganglia and in sympathetic nerves close to innervated organs [30].

Postganglionic sympathetic noradrenergic neurons are affected in Lewy body PAF but mostly spared in MSA.

A difference between the two types of PAF is the pathological involvement of sympathetic postganglionic noradrenergic neurons in the Lewy body type and not in the non-Lewy body type (Table 4). In 1976, Black and Petito reported evidence that what they referred to as idiopathic orthostatic hypotension, and today would be diagnosed as PAF, involved a postganglionic sympathetic noradrenergic lesion [8]. In sympathetic ganglion tissue harvested at autopsy the patients had severely decreased activity of the enzyme dopamine-beta-hydroxylase (DBH), which catalyzes the conversion of dopamine to norepinephrine. Bannister noted decreased catecholamine fluorescence surrounding blood vessels or decreased numbers of vesicles in sympathetic nerves in PAF patients [3]. In 1977 Ziegler, Lake, and Kopin differentiated idiopathic orthostatic hypotension (now PAF) from MSA (called Shy-Drager syndrome at the time) in vivo by low plasma levels of the sympathetic neurotransmitter norepinephrine in PAF but not in MSA [79]. The subsequent finding of blunted plasma norepinephrine responses to the indirectly acting sympathomimetic amine tyramine in patients with PAF but not in those with MSA supported the view that the occurrence of a sympathetic postganglionic lesion distinguishes the two conditions [57].

It should be noted that some patients with Lewy body PAF have normal plasma norepinephrine levels. This can give the impression of functionally intact sympathetic noradrenergic nerves; however, these patients have diminished clearance of norepinephrine from the plasma, due to substantially attenuated neuronal uptake of circulating norepinephrine [56]. The decrease in clearance can result in a normal plasma norepinephrine level despite a decreased rate of entry of norepinephrine into the systemic circulation. Assaying plasma levels of norepinephrine and of its main neuronal metabolite 3,4-dihydroxyphenylglycol (DHPG) simultaneously helps avoid confusion in this regard. A decrease in levels of both catechols fits with postganglionic sympathetic noradrenergic deficiency [25].

The sympathetic noradrenergic lesion in the Lewy body form of PAF is especially prominent in the heart, as revealed by studies using the cardiac sympathetic neuroimaging agents ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) [37] or ^{18}F-dopamine [27], measurement of the rate of appearance of norepinephrine in coronary sinus plasma [47], and post-mortem

neurochemistry (Table 4). In contrast, most (but not all) patients with MSA have normal cardiac sympathetic neuroimaging [24], normal cardiac norepinephrine spillover [35], and normal post-mortem myocardial neurochemistry [27]. For separating PD from the parkinsonian form of MSA when both have nOH, ^{18}F-dopamine PET is remarkably sensitive and specific [44] but currently has only very limited availability.

Analysis of alpha-synuclein in patients with nOH

In 1997 Lewy bodies in sporadic PD were found to contain the protein alpha-synuclein [72]. Soon afterward, glial cytoplasmic inclusions, a histopathologic feature of MSA [54], were reported to contain alpha-synuclein as well [78]. As one would expect from PAF being an alpha-synucleinopathy, alpha-synuclein deposition was also described in sympathetic ganglion tissue and distal axons from PAF patients [30, 40].

Immunofluorescence microscopic methods enable one to visualize alpha-synuclein in sympathetic noradrenergic nerves in skin biopsies from living patients [15]. Alpha-synuclein deposition in sympathetic noradrenergically innervated skin constituents (arrector pili muscles, blood vessels, and sweat glands) has been reported in PAF but not in most patients with MSA [17, 33]. It should be noted that eccrine sweat glands receive both cholinergic and catecholaminergic sympathetic innervation [53, 61]. In MSA patients with a long disease duration there can be mild postganglionic involvement [16] or involvement of other than sympathetic noradrenergic fibers [17]. Lewy body forms of nOH entail both increased colocalization of alpha-synuclein with immunoreactive TH in skin biopsies and low myocardial ^{18}F-dopamine-derived radioactivity [33].

Real-Time Quaking-Induced Conversion (RT-QuIC) assays may separate Lewy body synucleinopathies from MSA when patients are in the PAF stage. In this method, cerebrospinal fluid samples are assayed for alpha-synuclein seeding activity using wild-type recombinant alpha-synuclein as a substrate. The results of a recent study indicate that DLB, PD, and Lewy body PAF are identified with high sensitivity, whereas most MSA patients have no increase in alpha-synuclein seeding activity [60].

Protein misfolding cyclic amplification (PMCA), a similar but not identical technique to RT-QuIC, shows different alpha-synuclein seeding activity in PD/DLB compared to MSA [65, 70]. A recent study by the same group showed different alpha-synuclein seeding activity using PMCA in PAF patients who eventually phenoconverted to MSA from those who phenoconverted to PD/DLB [71].

Applications of laboratory tools such as cardiac sympathetic neuroimaging, skin biopsy analyses, body fluid biomarkers, and genetic testing have revealed multiple distinct abnormalities that fall under the umbrella of PAF. Table 5 lists some of these disorders.

How should one classify patients who have nOH, no clinical signs of cognitive or motor deficits attributable to central neurodegeneration, intact noradrenergic innervation by cardiac sympathetic neuroimaging, and no evidence of increased alpha-synuclein deposition in sympathetic noradrenergic nerves? As indicated in Table 5, among several conditions that can include this clinical laboratory pattern, one is premotor MSA. Based on the cases listed

in Tables 2 and 3, patients with autopsy-proven MSA can present initially with nOH and no clinical symptoms or signs of motor or cognitive impairment. As yet there is no clinical laboratory test that can positively diagnose premotor MSA, although as noted above the recent findings from cross-sectional studies related to neurofilament light chain and PMCA kinetics are promising in this regard.

Clinical and autonomic findings

Several studies have reported that, compared to patients who phenoconvert to PD or DLB, patients with PAF who phenoconvert to MSA are younger at disease onset and have early, severe urinary symptoms [42, 69]. The urinary symptoms include urge incontinence and urinary retention with a post-void residual volume greater than 100 mL. While rapid eye movement sleep behavior disorder (RBD) can be present in both MSA and Lewy body synucleinopathies, episodic nocturnal inspiratory stridor should raise suspicion of MSA [73]. Loss of sense of smell (anosmia) favors evolution to a Lewy body disease, as olfactory function is normal or only mild to moderately decreased in MSA [38]. PAF with neuroimaging evidence of cardiac noradrenergic deficiency is associated with olfactory dysfunction [26] and both features are predictive of phenoconversion to PD or DLB [42]. Without stratification in terms of the occurrence of sympathetic noradrenergic deficiency and increased intra-neuronal alpha-synuclein deposition, studies have disagreed about whether pre-motor MSA differs from PAF [20, 68].

Reports about cardiovascular autonomic reflexes have noted relative preservation of chronotropic function in patients with MSA compared to PD [22, 49], and this can be seen before phenoconversion in the PAF stage; however, there is substantial overlap in distributions of the values. Therefore, physiological cardiovascular testing, even under controlled laboratory conditions, has limited utility in identifying PAF patients at risk of developing MSA vs. PD or DLB.

Recently, Borghammer and colleagues have proposed a “body-first” vs. “brain-first” bi-directional sequence of alpha-synucleinopathy [31], the body-first aspect corresponding roughly to Braak’s staging schema [10]. Both concepts have aroused intense interest but also controversy and debate. Lewy body PAF may constitute the prototype of “body-first” synucleinopathy [9].

Conclusion

PAF has two phenotypes, a Lewy body form and a non-Lewy body form. Lewy body PAF involves cardiac noradrenergic deficiency and increased deposition of alpha-synuclein in sympathetic noradrenergic nerves and may phenoconvert to PD or DLB, but it does not phenoconvert to MSA. Non-Lewy body PAF can phenoconvert to MSA. Combining biomarkers of sympathetic cardiac innervation with intra-neuronal alpha-synuclein deposition in skin biopsies may improve the predictive value of clinical laboratory testing in patients with PAF as defined clinically. A collaborative prospective natural history study [42] is testing this hypothesis.

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Table 1:

Autopsy findings in postural hypotension / idiopathic orthostatic hypotension (IOH) / pure autonomic failure (PAF)

First Author (Year) [Cit. No.]	No.	Brainstem Lewy bodies	SNS Lewy bodies	Note
Bradbury (1926) [12]	1	No comment	No comment	Brain & SNS not included
Gordon (1957) [28]	1	No comment	No comment	Brain & SNS normal
Fichefet (1965) [19]	1	1	1	(Article in French)
Johnson (1966) [36]	Case 1	1	Eosinophilic bodies as in PD	No SNS cell loss. IL column cell loss
Martin (1968) [46]	Case 4	0	0	Stridor. No PD or MSA
Vanderhaeghen (1970) [77]	Case 1 Case 2	1 1	1 1	(Same as Fichefet[19]) IOH with Lewy bodies
Roessmann (1971) [59]	Case 1 Case 2	1 0	1 0	No PD or MSA (Same as Martin [46] Case 4)
Bannister (1972) [6]	Case 3	1	0	OH+PD+Lewy bodies
Schober (1975) [63]	Case 2	1	1	OH then dementia, visual hallucinations, then mild PD
Black (1976) [8]	Case A Case B Case C	1 No comment 1	No comment No comment 1	IOH IOH+Parkinsonism IOH
Petito (1978) [55]	Patient 1 Patient 3	1 1	No comment Hyaline bodies	Pathology as in MSA Cognitive dysfunction
van Ingelghem (1994) [76]	1	0	1	No PD or MSA
Hague (1997) [30]	1	1	1	No PD or MSA
Arai (2000) [1] Kaufmann [40]	1	1	1	No PD or MSA No PD or MSA
Kaufmann (2004) [41]	Case 1 Case 2	1 1	1 1	Evolved to PD+OH Evolved to DLB
Isonaka (2017) [32]	1	0	0	No PD or MSA
Isonaka (2018) [34]	1 2	1 1	1 1	PAF+DLB+PD PAF+DLB+PD

Abbreviations: Cit. No.=citation number; DLB=dementia with Lewy bodies; IL=intermediolateral column; IOH=idiopathic orthostatic hypotension: MSA=multiple system atrophy; OH=orthostatic hypotension; PD=Parkinson disease; SNS=sympathetic nervous system.

Table 2:

Autopsy findings in Shy-Drager syndrome (SDS) / Olivopontocerebellar atrophy (OPCA) / multiple system atrophy (MSA), in which orthostatic hypotension was the initial clinical manifestation.

First Author (Year) [Cit. No.]	No.	Brainstem Lewy bodies	SNS Lewy bodies	Note
Johnson (1966) [36]	Case 2	0	0	OH first. Late bradykinesia, cerebellar signs. OPCA. IL column cell loss
Schwarz (1967) [64]	Case 2 Case 3	No comment No comment	No comment No comment	OH first. SDS. OPCA OH first. SDS
Nick (1967) [48]	1	0	0	OH first. SDS
Thapedi (1971) [74]	1	1	Hyaline eosinophilic bodies	OH first. SDS. Parkinsonism. No comment on CBL/Brainstem atrophy
Bannister (1972) [6]	Case 2	0	0	OH first. MSA
Evans (1972) [18]	1	0	No comment	OH first. OPCA, no typical LBs
Schober (1975) [63]	Case 1	0	0	OH first. Putamen shrinkage. MSA.
Petito (1978) [55]	Patient 4	No comment	No comment	OH first. Pathology as in MSA

Abbreviations: CBL=cerebellar; Cit. No.= citation number; IL=intermediolateral column; MSA=multiple system atrophy; OH=orthostatic hypotension; OPCA=olivopontocerebellar atrophy; SDS=Shy-Drager syndrome; SNS=sympathetic nervous system.

Table 3:

Autopsy findings in Shy-Drager syndrome (SDS) / olivopontocerebellar atrophy (OPCA) / multiple system atrophy (MSA), in which orthostatic hypotension was not the initial clinical manifestation.

First Author (Year) [Cit. No.]	No.	Brainstem Lewy bodies	SNS Lewy bodies	Note
Shy (1960) [67]	Case 2	0	0	H&E done, no comment on Lewy bodies
Schwarz (1967) [64]	Case 1	No comment	No comment	SDS
Bannister (1972) [6]	Case 1 Case 4	0 0	0 Unavailable	OPCA MSA
Petito (1978) [55]	Patient 2	0	No comment	Pathology as in MSA
Isonaka (2018) [34]	3	0	0	MSA

Abbreviations: Cit. No.=citation number; H&E=hematoxylin & eosin staining; MSA=multiple system atrophy; OPCA=olivopontocerebellar atrophy; SDS=Shy-Drager syndrome; SNS=sympathetic nervous system.

Table 4:

Tissue neurochemical or histopathologic assessments of sympathetic noradrenergic innervation in postural hypotension / idiopathic orthostatic hypotension / pure autonomic failure

First Author (Year) [Cit. No.]	No.	Variables	Findings	Note
Black (1976) [8]	Case 3	TH, DBH activities	Normal TH, decreased DBH	
Petito (1978) [55]	Case 4	TH, DBH activities	Normal TH, decreased DBH	Overlaps with Black [8]
Bannister (1988) [4]	1 2	Catechol. fluor. EM	Reduced fluor. Reduced vesicles	Catecholamine fluorescence in arteriolar walls Nerve near blood vessel
Donadio (2010) [16]	9	PGP 9.5 or DBH	Decreased adrenergic scores in 9/9	Immunofluorescence in skin biopsies
Goldstein (2019) [27]	1 2	Myo. NE Myo. NE	Decreased myo. NE Decreased myo. NE	
Isonaka (2017) [32]	1	Myo. NE SNS TH	Decreased myo. NE Decreased SNS TH	No Lewy bodies

Abbreviations: Cit. No.=citation number; DBH=dopamine-beta-hydroxylase; EM=electronic microscopy; myo. NE=myocardial norepinephrine; PGP 9.5=protein gene product 9.5; TH=tyrosine hydroxylase; SNS=sympathetic nervous system.

Table 5:

Neurogenic orthostatic hypotension syndromes that fit clinical criteria for pure autonomic failure.

Condition [Citation No.]	Syndromic Features
Lewy body nOH [33]	SNS intra-neuronal AS deposition, cardiac SNS lesion
Premotor MSA [6, 18, 36, 55, 63]	Intact cardiac SNS, normal olfaction, normal plasma catechols, CNS signs at follow-up
DBH Deficiency [7, 58]	Very low NE & DHPG, high DA, DOPAC, normal sweating
AAG [21]	Anti-nAChR, low NE, sicca syndrome, intact cardiac SNS, anhidrosis
Hyperadrenergic nOH [45]	High upright NE
PAF without Lewy bodies [32]	Cardiac SNS lesion, no SNS intra-neuronal AS deposition
AAD [23]	Very low NE, DHPG, autoimmunity, cardiac SNS lesion
MSA with SNS Lesion [13]	Low NE, cardiac SNS lesion
CYB561 mutation [66]	Low NE, normal sweating, genotyping

Abbreviations: AAD=autoimmunity-associated autonomic failure with sympathetic denervation; AAG=autoimmune autonomic ganglionopathy; Anti-nAChR=antibodies to the nicotinic acetylcholine receptor; AS=alpha-synuclein; CNS=central nervous system; DA=plasma dopamine; DBH=dopamine-beta-hydroxylase; DHPG=plasma 3,4-dihydroxyphenylglycol; DOPAC=plasma 3,4-dihydroxyphenylacetic acid; MSA=multiple system atrophy; NE=plasma norepinephrine; nOH=neurogenic orthostatic hypotension; PAF=pure autonomic failure; SNS=sympathetic nervous system.