MAYO CLINIC

REVIEW

Pure Autonomic Failure

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Abstract

Pure autonomic failure (PAF) is a neurodegenerative disorder of the autonomic nervous system clinically characterized by orthostatic hypotension. The disorder has also been known as Bradbury-Eggleston syndrome, named for the authors of the 1925 seminal description. Patients typically present in midlife or later with orthostatic hypotension or syncope. Autonomic failure may also manifest as genitourinary, bowel, and thermoregulatory dysfunction. With widespread involvement, patients may present to a variety of different specialties and require multidisciplinary treatment approaches. Pathologically, PAF is characterized by predominantly peripheral deposition of α-synuclein. However, patients with PAF may progress into other synucleinopathies with central nervous system involvement.

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Pure autonomic failure (PAF) is a neurodegenerative disorder of the autonomic nervous system characterized by orthostatic hypotension. Previously known as Bradbury-Eggleston syndrome from the seminal description in 1925, PAF typically presents in midlife to late in life with symptoms of orthostatic hypotension or syncope.[1] Although neurogenic orthostatic hypotension is a requisite for diagnosis of PAF, autonomic dysfunction may be widespread, leading to genitourinary, bowel, thermoregulatory, and systemic manifestations of disease, such as anemia, that require multidisciplinary treatment approaches. Pathophysiologically, PAF is an α-synucleinopathy characterized by predominantly peripheral deposition of α-synuclein in autonomic ganglia and nerves. Patients with PAF, by definition, have no evidence of central nervous system (CNS) dysfunction other than rapid eye movement sleep behavior disorder (RBD).[2] However, there is increasing awareness that patients with PAF may progress to other synucleinopathies characterized by CNS involvement, such as multiple system atrophy (MSA), Parkinson disease (PD), or dementia with Lewy bodies (DLB).[3,4]

HISTORICAL BACKGROUND

Bradbury and Eggleston[1] described 3 patients in 1925 with severe orthostatic hypotension. The detailed clinical depictions are of 3 men with gradually progressive autonomic syndromes highlighted by syncope. The authors' physiologic examinations highlighted important features of the disorder: absence of heart rate response to orthostatic hypotension, anhidrosis, mild systemic features, and subtle neurologic signs. Bradbury and Eggleston[1] differentiated the syndrome from endocrine causes and also found that the syndrome was not due to excessive activity of the vagus nerve: "There was no evidence in any of the cases that the slowed heart rate might have been due to increased vagus activity," and they delineated the blood pressure (BP) drops from "[o]rdinary syncopal attacks." The authors correctly postulated that the main dysfunction was in "[d]iminution of normal sympathetic tone" based on experiments with atropine and also found that administration of epinephrine led to "powerful sympathetic stimulant action," which has later been found to be due to denervation supersensitivity.[5] In addition to delineating the features of the disorder, Bradbury and Eggleston[1] made multiple attempts to "cure … or to control their disorders" to no avail.

After the 1925 publication, the terms *Bradbury-Eggleston syndrome* and *idiopathic orthostatic hypotension* were used to describe patients with the phenotype of PAF. In 1960,

For Limelight, see page 1915

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ARTICLE HIGHLIGHTS

- Neurogenic orthostatic hypotension is the hallmark of pure autonomic failure; however, autonomic dysfunction may be widespread, leading to genitourinary, bowel, thermoregulatory, and systemic manifestations of disease.
- Pure autonomic failure is an α-synucleinopathy characterized by predominantly peripheral deposition of α-synuclein in autonomic ganglia and nerves.
- Pure autonomic failure may progress into other synucleinopathies characterized by central nervous system involvement, such as multiple system atrophy, Parkinson disease, or dementia with Lewy bodies.

Shy and Drager[6] referenced the Bradbury and Eggleston report in relation to their clinicopathologic study. Shy and Drager described 2 patients who initially developed autonomic failure. This was followed by motor involvement, and CNS degeneration was found on autopsy of one of the patients. The authors concluded that "a primary 'degenerative' nervous system disorder may be one etiological factor in orthostatic hypotension" and that it represented a "recognizable syndrome," which was later called *Shy-Drager syndrome*, now known as *multiple system atrophy*.[6-8]

Further physiologic studies led by Bannister and colleagues[9] included a cohort of 4 patients, all with an initial syndrome of autonomic failure, with 2 later developing evidence of CNS dysfunction, similar to Shy and Drager's patients.[6,9] Bannister et al[9] used negative pressure to the lower extremities to elucidate the mechanisms behind the orthostatic hypotension and also studied sweating function: "there was evidence … [that b]aroregulator involvement was more extensive than thermoregulatory involvement." Bannister and colleagues[9] also elucidated the selective degeneration of sympathetic fibers with preservation of vasodilator response in the syndrome now known as *PAF*.

Although multiple publications in the mid-20th century highlighted the interest in understanding the neurologic relationship to orthostatic hypotension, Thomas and Schirger, a neurologist and an internist, were interested in the clinical features defining the disorder. Thomas and Schirger[10] reported on a cohort of 30 patients who presented with orthostatic hypotension attributed to neurologic dysfunction. They summarized the syndrome as a slowly progressive disorder presenting with "either postural dizziness or bowel and bladder dysfunction" with later development of additional autonomic manifestations. Thomas and Schirger[10] focused on the later development of "widespread somatic nervous involvement" with the goal of determining how neurologic symptom manifestation influenced course and prognosis. Of the 30 patients in the cohort, the authors reported that 23 (77%) with initial idiopathic orthostatic hypotension evolved into a neurodegenerative syndrome. This has implications today as recent advances in PAF have highlighted features that predict conversion to other neurologic disorders.[3,4] We now know that the disorders that patients with PAF most frequently develop fall under the neuropathologic category of α-synucleinopathies.

NEUROPATHOLOGIC FEATURES

The synucleinopathies are a collection of neurodegenerative disorders in which the anatomical location of α-synuclein deposition and the pattern of neuronal degeneration leads to distinct neurologic phenotypes.[11,12] The neuropathologic hallmark of PAF is accumulation of misfolded α-synuclein in the form of neuronal cytoplasmic inclusions termed *Lewy bodies*. Of the synucleinopathies, PAF, PD, and DLB are due to Lewy body deposition in various peripheral and central structures. In contrast, MSA is due to α-synuclein deposition in glial cells termed *glial cytoplasmic inclusions*.[13] Recent evidence suggests the prionlike spread of α-synuclein in a cell-to-cell manner in transgenic mouse models with lysates from patients with MSA,[14] although it is unclear whether Lewy bodies from patients with PAF would show similar features of prionlike spread.

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The characteristic pattern of Lewy body involvement in PAF is of predominant peripheral inclusions; however, central structures may also manifest pathology.[15,16] Loss of sympathetic nerves has been found by immunofluorescence studies demonstrating noradrenergic nerve fiber loss in PAF.[17,18] The sympathetic ganglia and peripheral autonomic nerves show α-synuclein deposition, leading to a primarily postganglionic pattern of autonomic denervation.[19-21] Although Lewy bodies are found in visceral nerves such as those in epicardial fat, the adrenal gland, and the urinary bladder, the pathologic α-synuclein deposition may be distant from the autonomic ganglia.[15] Central structures may also be involved in PAF, with Lewy bodies found in areas affected in other synucleinopathies, such as the substantia nigra, locus coeruleus, and thoracolumbar and sacral spinal cord. In contrast, patients with central α-synuclein deposition often do not have accompanying neuronal loss, which may explain the absence of central neurologic findings such as parkinsonism in patients with PAF.[15] In PAF, Lewy bodies and neurites have also been found in sympathetic nerves from skin biopsy samples.[22,23] The presence of α-synuclein deposition in peripheral nerves may be helpful in differentiating patients with PAF from those with MSA, who may have preserved autonomic innervation of the skin; however, these findings may be difficult to replicate.[24,25] Although α-synuclein is an important marker for PAF, the role of α-synuclein as either a diagnostic marker or a postmortem finding needs further study. A recent case of PAF was reported that underwent autopsy with no evidence of peripheral or central α-synuclein deposition, raising the question of whether the presence of α-synuclein is necessary for postmortem confirmation of the diagnosis of PAF.[12,26]

PATHOPHYSIOLOGY

With most α-synuclein deposition in PAF confined to the ganglia and peripheral autonomic nerves, the prominent phenotype is of postganglionic (efferent) autonomic failure. Dysfunction or loss of peripheral sympathetic nerves leads to impaired production of catecholamines, including norepinephrine. Plasma concentrations of norepinephrine are low when patients are lying supine, and they do not increase, or only marginally increase, on standing. There is evidence of impaired catecholamine biosynthesis in PAF with low levels of plasma 3,4-$_L$-dihydroxyphenylalanine and 3,4-dihydroxyphenylacetic acid.[27,28] Plasma dihydroxyphenylglycol levels are especially low in PAF related to reduced turnover of norepinephrine stores in sympathetic nerves.[28,29] In cerebrospinal fluid, the level of dihydroxyphenylglycol, an index of brain noradrenergic neurons, is much more reduced than the level of 3,4-dihydroxyphenylacetic acid, an index of dopaminergic central neurons.[30]

Postganglionic denervation is also evident, with immunofluorescence demonstrating loss of noradrenergic and cholinergic autonomic nerves in skin biopsies of patients with PAF.[24] The loss of these fibers underlies deficits in vasoconstriction, which contributes to venous pooling and orthostatic hypotension as well as sweat gland denervation, leading to anhidrosis.

In addition to peripheral denervation, receptor hypersensitivity is a feature of PAF as pressor agents with direct peripheral action on sympathetic receptors produce exaggerated BP responses. This has been reported with agents acting directly on α-adrenergic receptors (norepinephrine, phenylephrine, midodrine)[5,31,32] and β-adrenergic receptors.[33] Use of clonidine-induced increases in serum growth hormone levels can also determine central vs peripheral etiology of autonomic failure. In PAF, the central brainstem reflex is preserved, leading to increases in growth hormone levels in response to clonidine administration.[34,35] Release of vasopressin from the pituitary gland in response to hypotension is also preserved in patients with PAF, consistent with intact afferent baroreceptor pathways.[36]

Cardiac sympathetic innervation is affected in PAF, similar to other Lewy body disorders.[37-39] Low myocardial

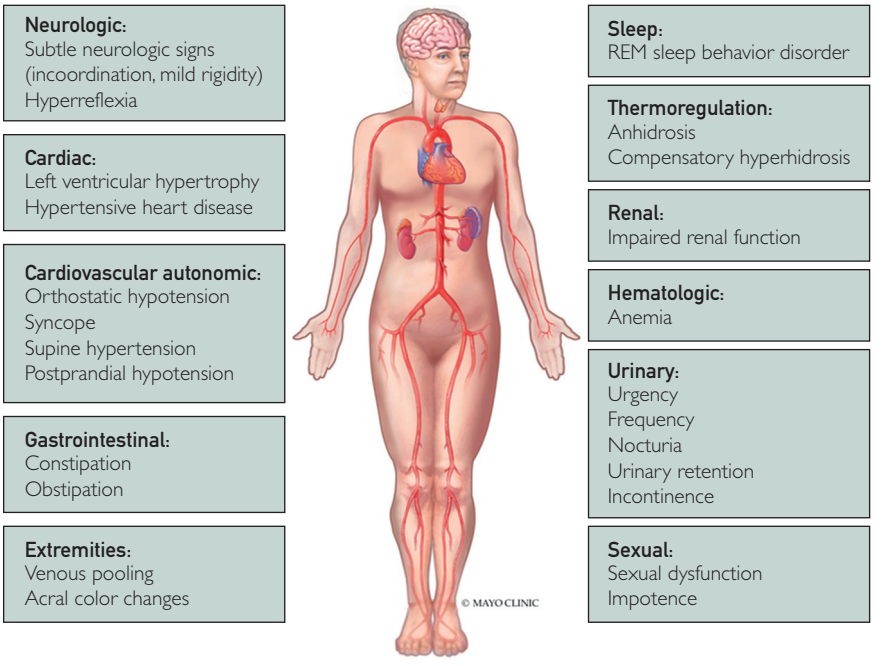

FIGURE 1. Multiple organ involvement in pure autonomic failure. Autonomic manifestations in pure autonomic failure influence a variety of different organ systems, which underscores the variety of clinical areas where patients may initially seek consultation and require coordination of care during their disease. REM = rapid eye movement.

concentrations of markers related to sympathetic innervation are evident on single-photon emission computed tomography or positron emission tomography.[40,41] Evidence of peripheral denervation can usually be used to differentiate the Lewy body disorders from MSA, which has predominantly central involvement and preservation of cardiac innervation.[42,43]

Although the hallmark of PAF is sympathetic denervation, parasympathetic function is also impaired in PAF. Clinically, this is evident on autonomic testing showing impaired cardiovagal function and impaired heart rate variability.[3,4]

ETIOLOGY

Pure autonomic failure is a rare, sporadic disorder that is more common in men, with no known genetic or environmental cause. Although no genetic forms of PAF have been described, genetic causes of parkinsonism are known to cause autonomic dysfunction, with asymptomatic carriers of some *SNCA* mutations having evidence of autonomic involvement with abnormal cardiac innervation on imaging studies.[44] Therefore, patients presenting with autonomic failure akin to PAF but with a family history of parkinsonian disorders should be closely monitored for the development of motor symptoms.

CLINICAL FEATURES

As in the 3 patients described by Bradbury and Eggleston,[1] orthostatic hypotension with a tendency for syncope is the hallmark of PAF. Subsequent studies have found that genitourinary or bowel dysfunction may precede or accompany orthostatic hypotension.[10] With the absence of characteristic neurologic symptoms and signs, many patients with PAF initially present to primary care providers or specialists within cardiology, endocrinology, gastroenterology, or urology (Figure 1). The diagnosis of PAF should be considered in patients presenting with subacute to chronic orthostatic

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hypotension in the absence of significant parkinsonism, dementia, neuropathy, or medical conditions such as valvular heart disease, congestive heart failure, or chronic kidney disease.

Orthostatic Hypotension

Orthostatic hypotension is defined as the sustained reduction in systolic BP of at least 20 mm Hg or diastolic BP of 10 mm Hg within 3 minutes of standing or 60° head-up tilt.[45] When supine hypertension is present, defined as a systolic BP greater than or equal to 140 mm Hg or diastolic BP greater than or equal to 90 mm Hg, then a systolic BP reduction greater than 30 mm Hg is deemed more appropriate to meet the orthostatic hypotension criteria.[45,46]

Mechanistically, orthostatic hypotension is related to venous pooling. On standing, 300 to 1000 mL of blood pools in the lower extremities and splanchnic vascular beds, which leads to a reduction in venous return to the heart and reduced filling pressure. Cardiac output and stroke volume are reduced, which, in healthy individuals, leads to an increase in sympathetic outflow through the baroreflex with resultant increase in vascular tone, cardiac contractility, and heart rate. Inadequate sympathetic response to standing in PAF is due to predominantly peripheral cardiac and vasomotor denervation contributing to orthostatic hypotension. In addition to the fall in BP in PAF, a blunted rise in heart rate is evident in Lewy body disorders such as PAF.[47]

Orthostatic hypotension may be symptomatic or asymptomatic. With a reduction in mean arterial pressure, cerebral blood flow drops. Because PAF is a slowly progressive disorder, often with insidious onset, there may be a shift in the cerebral autoregulatory curve, which leads to a proportion of patients tolerating a substantial drop in BP without symptoms.[34] When decreased cerebral blood flow symptoms are present, lightheadedness is commonly reported. Dizziness, blurred or loss of vision, weakness, fatigue, and cognitive symptoms such as inattention may be noted by the patient. Occipitocervical distribution (coat-hanger) pain may also indicate hypoperfusion of the neck muscles.[48] Autonomic hyperactivity symptoms such as palpitations, tremulousness, anxiety, and nausea may be present and suggest only partial autonomic failure.[49] Severe and sustained orthostatic hypotension will lead to syncope. Often, once patients are able to recognize specific triggers and take corrective measures, the frequency of syncope lessens.

Worsening of orthostatic hypotension may occur with prolonged standing and accentuation of venous pooling with a shift of plasma from the circulation to the tissues.[50] Triggers such as high ambient heat, hot showers or baths, lead to a rise in core temperature and subsequent vasodilation of skin vessels that accentuates orthostatic hypotension. Physical activity that is sufficient to cause vasodilation to muscles often worsens symptoms, and patients often note worsening of symptoms with activity such as climbing stairs. Postprandial hypotension is commonly seen in patients with PAF due to increased splanchnic blood flow, but it paradoxically may improve with worsening severity of the disease as the splanchnic-mesenteric bed loses the capability to vasodilate postprandially later in disease.[51] The vasodilatory effects of alcohol may also exacerbate orthostatic hypotension. Patients often report worsening of orthostatic symptoms in the morning, which is potentiated by nocturnal diuresis and augmented in patients with supine hypertension.[52]

Supine Hypertension

Although, by definition, all patients with PAF have orthostatic hypotension, approximately half of patients with PAF have concomitant supine hypertension.[53] The mechanism behind supine hypertension, in the absence of pressor medications, may be impaired baroreflex function with inadequate buffering of BP, sensitivity of adrenergic receptors, and mineralocorticoid receptor activation.[54] Patients with PAF may record systolic BPs greater than 200 mm Hg. Patients may be asymptomatic or complain of headache or a vague sense of discomfort. Long-term sequelae of supine

hypertension include end organ damage, including left ventricular hypertrophy[55] and renal impairment.[56] The cerebral white matter may also show evidence of end organ damage, with a radiographic increase in T2-weighted lesions noted in patients with PAF and supine hypertension.[57]

Genitourinary Dysfunction

Genitourinary dysfunction may be the initial or presenting symptom in a proportion of patients with PAF. Of 100 patients in a prospective natural history study of PAF, 50% had bladder disturbances and 65% of men reported erectile dysfunction at a median of 5 years after disease onset.[3] Bladder symptoms in PAF may range from urgency and frequency to more severe dysfunction with urinary retention and incontinence. Severe bladder dysfunction is more commonly seen in patients with MSA than in those with PAF and other Lewy body disorders and should, therefore, raise the concern for conversion to MSA.[3,4] In addition, patients with PAF tend to develop urinary dysfunction later in the course of disease compared with patients with MSA.[58] Urodynamic studies most commonly show detrusor hyperreflexia; however, results may be variable, with some patients demonstrating normal bladder function and other patients showing evidence of underactive bladder on urologic testing.[58]

Gastrointestinal Features

Constipation is reported in more than half of the patients with PAF[3] and is frequently an early symptom of the disease.[58] Constipation may be severe, with one case of intestinal pseudo-obstruction reported as the initial feature of PAF.[59]

Thermoregulation

Abnormal sweating is reported in approximately half of all patients with PAF and may be noted by patients as a reduction in sweating or excessive sweating, the latter due to compensatory hyperhidrosis.[3,9] The pattern of sweat loss on autonomic testing is frequently postganglionic, fitting with the pathologic features of disease, and findings of preganglionic sweat loss, although not absolute, may indicate a higher likelihood of conversion to MSA.[4]

Anosmia

Although patients with PAF rarely note subjective lack of smell, more than 80% have deficits on objective olfactory testing.[3] This is in keeping with the other Lewy body disorders, which demonstrate impaired odor identification and may separate them from MSA, which tends to have preserved olfaction.[39,60]

Rapid Eye Movement Sleep Behavior Disorder

The prevalence of RBD in PAF is 72%, with one-third of patients having a history of harm to themselves or their bed partner during sleep.[3] The history of dream enactment behavior from patients may precede the development of autonomic symptoms or become evident after diagnosis. Often, RBD is associated with synucleinopathies with pathologic evidence of α-synuclein affecting pontomedullary brainstem nuclei.[61,62] Therefore, although PAF is considered a predominantly peripheral disorder, the high prevalence of RBD is further evidence of central involvement.

Neurologic Symptoms

As in one of the original Bradbury and Eggleston cases, subtle signs of neurologic dysfunction may be present in patients with PAF. Bradbury and Eggleston's third case had hyperreflexia and Babinski signs on examination.[1] Patients with PAF may demonstrate subtle signs that do not meet the clinical diagnostic criteria of PD, MSA, or DLB. These signs may include mild, generalized bradykinesia with hypomimia or reduced blink rate. Gait may be subtly abnormal, with slowing and reduced arm swing.[3,4] However, care should be taken to ensure that the patient is not markedly hypotensive when performing the examination. Although not absolute, the presence of subtle motor signs may indicate later conversion to MSA, PD, or DLB.[4]

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Cognitive function may be subtly affected in PAF, with the most frequent impairment found in deficits of speed, attention, and executive functioning. These cognitive changes may not be related to white matter changes seen on imaging in patients with supine hypertension.[63] They may, in part, relate to episodes of hypotension, but a patient with PAF showing signs of cognitive dysfunction should be closely monitored for evidence of progression to DLB.

Systemic Involvement

Mild anemia is noted in approximately half of all patients with PAF and median hemoglobin levels of 13.1 g/dL (to convert to g/L, multiply by 10) and hematocrit values of 39% in a prospective study.[3] End organ damage due to supine hypertension and wide fluctuations in BP also influences renal function, with proteinuria noted in one-quarter of patients with PAF.[3,56] However, when present, proteinuria tends to be mild. Left ventricular hypertrophy is also considered end organ damage from supine hypertension and extreme BP variability and should be evaluated by echocardiography. Patients with autonomic failure may also develop hypertensive heart disease and increased arterial stiffness.[64] Patients with PAF may have also undergone pacemaker placement, which may precede diagnosis of PAF and is often seen when the presenting complaint is syncope, although pacemaker placement is not indicated for syncope in the setting of orthostatic hypotension.[65]

DIAGNOSIS

The diagnosis of PAF is based on the consensus statement issued by the American Autonomic Society and the American Academy of Neurology in 1996.[2] The criteria state that PAF is an idiopathic sporadic disorder characterized by orthostatic hypotension usually with evidence of more widespread failure.[2] Although the criteria require that no other neurologic features are present, it references that some PAF may evolve into other disorders.[2] Careful clinical history and physical examination with a thorough neurologic examination should be performed to differentiate PAF from other disorders that may present with orthostatic hypotension (Table 1).

Whereas bedside testing of orthostatic BPs may lead to the diagnosis of orthostatic hypotension, autonomic function testing can be crucial in delineating whether the presence of orthostatic hypotension is due to a neurologic cause. The autonomic reflex screen is able to characterize the autonomic defect while defining the severity and distribution through the analysis of postganglionic sudomotor, cardiovagal, and adrenergic function.[66] Patients with PAF often have a reduction in quantitative sudomotor axon reflex test (QSART) volumes with impaired cardiovagal function on heart rate to deep breathing and Valsalva maneuver. Adrenergic failure is determined by analyzing the phases of beat-to-beat BP response to the Valsalva maneuver. The

TABLE 1. Differential Diagnosis of Pure Autonomic Failure

Nonneurogenic orthostatic hypotension
• Medication induced
• Hypovolemia
• Venous pooling
• Cardiac disease
• Endocrine disease
Syncope
Synucleinopathies
• Multiple system atrophy
• Parkinson disease, autonomic failure
• Dementia with Lewy bodies
Autonomic neuropathies
• Diabetes
• Amyloidosis
• Autoimmune mediated (autoimmune autonomic ganglionopathy, Sjögren syndrome, lupus, rheumatoid arthritis, paraneoplastic mediated)
• Inherited sensory and autonomic neuropathies
• Toxin-induced (chemotherapy agents, amiodarone, heavy metals, alcohol)
• Infectious (human immunodeficiency virus, Chagas disease, Hanson disease, diphtheria)
Inherited disorders
• Dopamine β-hydroxylase deficiency

head-up tilt test is able to determine whether supine hypertension is present and the presence and severity of orthostatic hypotension. The severity of autonomic dysfunction can then be graded using a composite autonomic severity score, with higher scores indicating more severe autonomic failure.[67] The thermoregulatory sweat test can be used in conjunction with the QSART to assess the severity and distribution of sudomotor deficits. The thermoregulatory sweat test assesses the thermoregulatory system from the hypothalamus to the eccrine sweat glands, with defects anywhere along this pathway leading to areas of anhidrosis. Therefore, an area of anhidrosis on the thermoregulatory sweat test with normal postganglionic sudomotor function on the QSART suggests a preganglionic or central, rather than peripheral, lesion. The presence of central sweat loss in a patient with the PAF phenotype is concerning for progression to MSA.[4]

Imaging studies in patients with PAF include cardiac functional imaging with ^{123}I-metaiodobenylguanidine myocardial single-photon emission computed tomography and 6-[^{18}F]fluorodopamine positron emission tomography, which characteristically demonstrate decreased cardiac sympathetic innervation similar to patients with PD and in contrast to patients with MSA, which typically show normal cardiac innervation.[40,68,69] Brain magnetic resonance imaging may be useful to rule out evidence of CNS pathology because brain imaging in PAF should be normal, or in cases of supine hypertension may show white matter lesions.[57]

Laboratory data supporting the diagnosis of PAF include low supine norepinephrine levels with minimal to no increase on standing. The combination of autonomic function testing, functional imaging, and orthostatic catecholamines may be useful for differentiating PAF from other synucleinopathies.[70] Evaluation of skin biopsy for α-synuclein needs to be validated and may be useful in the future for diagnosis of PAF but is currently not in clinical practice.

PROGNOSIS

Patients with PAF may have a slowly progressive course for decades. Although the data should be evaluated cautiously due to low numbers, median survival in PAF has been reported to be 12.5 years (range, 5.1-15.9 years).[71] However, a subset of patients evolves into a synucleinopathy with significant CNS involvement. In a prospective study of 100 patients with PAF, 34% of patients met the clinical criteria for a synucleinopathy, including PD, DLB, or MSA, within 4 years of follow-up.[3] Another 30% had evidence of central involvement, such as RBD, impaired olfaction, or subtle neurologic signs. Patients retaining the PAF phenotype tended to be slightly younger at onset of orthostatic hypotension, with median disease duration of 6 years and a very low plasma norepinephrine level.[3]

Patients with PAF who phenoconvert to MSA often have evidence of predominantly central dysfunction on testing. Factors suggesting central involvement include supine norepinephrine levels greater than 100 pg/mL (to convert to pmol/L, multiply by 5.911), a preganglionic pattern of anhidrosis, subtle motor signs, and preserved olfaction on objective testing.[3,4] Clinical features may also help distinguish patients with PAF who have a higher likelihood of converting to MSA. Higher severity of autonomic symptoms of constipation and urinary dysfunction early in disease predict conversion to MSA.[3,4,58] In contrast to MSA, patients with PAF do not develop respiratory symptoms of stridor, and sleep apnea is uncommon.[3,58] The concept of phenoconversion from PAF to MSA is challenging because, by definition, PAF is a peripheral Lewy body disorder and MSA is characterized by central involvement of glial cytoplasmic inclusions. Patients meeting the criteria for PAF with features suggestive of central involvement should be closely monitored for the development of motor signs consistent with the diagnosis of MSA.

Conversion to MSA from the PAF phenotype tends to occur earlier than to PD or DLB. The median time to conversion to

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TABLE 2. Orthostatic Hypotension Treatment Recommendations

Nonpharmacologic Measures	Pharmacologic Measures
Increase fluid intake • Goal of 2 L/d (approximately 64 oz) • Cold water bolus (rapidly taking 16 oz of ice cold water) 3 times per day	Midodrine • Typical dosing is 2.5-15 mg 1-3 times per day • Adverse effects: sHTN, scalp itching, piloerection, urinary retention
Increase salt intake • Goal of an additional 1-2 teaspoons (2.3-4.6 g) to diet • 24-h urinary sodium excretion goal of 170 mEq	Droxidopa • Typical dosing is 100-600 mg 3 times per day • Adverse effects: sHTN, headache, dizziness, nausea, fatigue
Improve physical conditioning • Lower body and core strength training to reduce venous pooling	Fludrocortisone • Typically dosed at 0.1-0.2 mg/d; little benefit >0.3 mg/d • Adverse effects: sHTN, hypokalemia, edema, renal fibrosis
Elevate head of bed • Use of wedge or blocks under headboard legs to elevate head 4-6 in	Pyridostigmine • Typically dosed at 30-60 mg 1-3 times per day • Adverse effects: sialorrhea, diarrhea, abdominal cramps, sweating
Compression garments • Waist or thigh-high compression garments of 30-40 mm Hg	

sHTN = supine hypertension.

MSA from PAF is 2.4 years from onset of orthostatic hypotension compared with almost 4 years for PD and 9.5 years for DLB.[3,4] Patients converting to PD or DLB also tend to show less severe autonomic failure on autonomic testing, a preserved increase of norepinephrine level on standing, and less severe constipation and urinary symptoms. Subtle signs of parkinsonism are often noted on early examinations in this patient group.[3,4]

Although conversion to a different synucleinopathy is of concern, this occurs in few patients, and it is important for clinicians to establish the diagnosis of PAF. Patients with PAF who retain their PAF phenotype may have some improvement in symptoms with nonpharmacologic and pharmacologic treatment of orthostatic hypotension and maintain control of activities of daily living. Other patients, however, may be restricted in mobility because of orthostatic hypotension. In addition, rapid or severe fluctuations in BP may lead to end organ damage, and sudden death is also reported in patients with PAF.[15,26] Patient education, tailored therapy, and monitoring for end organ damage are crucial in the long-term care of patients with PAF.

THERAPEUTIC PRINCIPLES

Although there is currently no cure for PAF, patients may improve clinically with nonpharmacologic and pharmacologic measures aimed at controlling BP fluctuations. The goal of treatment is to reduce syncope and offer measures to improve symptomatic management rather than normalization of standing BP.[72] The first step involves discontinuing or modifying offending medications. Nonpharmacologic and pharmacologic measures to treat orthostatic hypotension are shown in Table 2.

Patient education regarding triggers of orthostatic hypotension and lifestyle modifications, such as transitioning position gradually and avoiding hot environments, are crucial. Nonpharmacologic measures are aimed at increasing plasma volume through intake of fluid and salt. Elevating the head of the bed is also recommended to reduce supine hypertension, which can also improve nocturnal pressure diuresis, reducing nocturia and problematic early-morning orthostatic hypotension.[73]

Pharmacologic measures to treat orthostatic hypotension target various mechanisms and should be used with nonpharmacologic approaches. Midodrine

is Food and Drug Administration approved to treat orthostatic hypotension, and droxidopa is approved to treat neurogenic orthostatic hypotension. Midodrine is an α_1-adrenoreceptor agonist that leads to peripheral vasoconstriction. Droxidopa is a pro-drug that is converted to norepinephrine in central and peripheral tissues. Patients should be counseled to stay upright for at least 4 to 5 hours after taking midodrine or droxidopa due to risk of supine hypertension. Fludrocortisone increases renal sodium and water reabsorption to expand intravascular blood volume and should be used with caution in patients with congestive heart failure. Pyridostigmine is an acetylcholinesterase inhibitor that potentiates neurotransmission through the peripheral cholinergic ganglia and contributes to a modest improvement in orthostatic hypotension.[74]

Supine hypertension may be treated with transdermal agents such as nitroglycerin or clonidine when recumbent or with oral agents with short duration of action such as clonidine, nifedipine, losartan, hydralazine, sildenafil, or nebivolol.[75,76] Octreotide and acarbose may be used to treat postprandial hypotension.[77]

In addition to monitoring and managing BP, treatment of other autonomic and systemic features can improve quality of life. Erythropoietin has been used to treat anemia and may improve standing BP.[78,79] Bladder symptoms may respond to anticholinergics or α-blockers; however, care must be used to avoid worsening of orthostatic hypotension. Severe cases of urinary retention or incontinence may require catheterization. Constipation treatment includes dietary measures such as fiber supplements and increasing water intake. Pyridostigmine is often prescribed for orthostatic hypotension and may help constipation; other pharmacologic treatments include stimulants, osmotic laxatives, stool softeners, or enemas and suppositories. To limit injury potential, RBD should be treated with melatonin or clonazepam.[80] In this multisystem disorder, coordination of a multispecialty team is important for optimization of therapies.

CONCLUSION AND FUTURE DIRECTIONS

As Bradbury and Eggleston described nearly 100 years ago, PAF is a slowly progressive neurodegenerative disorder of the autonomic nervous system. The disorder is predominantly peripheral in origin and due to α-synuclein deposition, classifying PAF as a synucleinopathy. Although patients with PAF may retain their purely autonomic phenotype for many years, some patients progress to more sinister synucleinopathies, such as MSA, PD, or DLB. Recent studies have highlighted clinical, autonomic, and laboratory features that may predict which patients are at a greater risk for developing CNS dysfunction. Future directions will likely hone these predictive measures and seek to find biomarkers that may predict stable PAF vs conversion. Following these advances, disease-modifying agents may then be able to target susceptible patients to prevent CNS degeneration. With the heightened awareness of conversion to other synucleinopathies and further insight into features that define these diseases, the autonomic field may also want to update the consensus criteria for PAF from 1996 to reflect the increased understanding of this rare disorder.

Abbreviations and Acronyms: **BP** = blood pressure; **CNS** = central nervous system; **DLB** = dementia with Lewy bodies; **MSA** = multiple system atrophy; **PAF** = pure autonomic failure; **PD** = Parkinson disease; **QSART** = quantitative sudomotor axon reflex test; **RBD** = rapid eye movement sleep behavior disorder; **REM** = rapid eye movement

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