

Pure Autonomic Failure-A Localized Alpha Synucleinopathy with a Potential for Conversion to More Extensive Alpha Synucleinopathies

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Abstract

Pure autonomic failure (PAF) is an alpha synucleinopathy with predominant involvement of the autonomic ganglia and peripheral nerves. The hallmark clinical feature is orthostatic hypotension. However, genitourinary, sudomotor, and cardiac involvement is also common. Many patients also develop supine hypertension. Almost a quarter of patients can phenoconvert or evolve into Parkinson's disease, multiple system atrophy, and Lewy body dementia in the future. Early severe bladder involvement, higher supine noradrenaline level, early motor involvement, and dream enactment behavior increase the risk of phenoconversion. The diagnosis is confirmed via autonomic function testing and serum noradrenaline measurement. The treatment is mainly supportive. The non-pharmacological treatment includes adequate fluid, dietary salt, compression stockings, and abdominal binders. The drug therapies to improve blood pressure include midodrine, fludrocortisone, pyridostigmine, and droxidopa. The diagnostic criteria need to be updated to incorporate the recent understandings. The treatment of orthostatic hypotension and supine hypertension is mainly based on case series and anecdotal reports. Randomized control trials are needed to ascertain the best treatment strategies for PAF.

Keywords: Alpha synucleinopathy, autonomic, failure, hypotension, orthostatic, phenoconversion

INTRODUCTION

Pure autonomic failure (PAF) is a rare variant of alpha synucleinopathy characterized by the deposition of alpha-synuclein predominantly in autonomic ganglia and peripheral nerves.^[1-5] The involvement of autonomic ganglia results in deficient norepinephrine synthesis and release from the nerve terminals. The consensus diagnostic criteria of 1996 stated that PAF is an idiopathic sporadic disorder characterized by orthostatic hypotension, usually with evidence of more widespread failure. The hallmark clinical feature of PAF is orthostatic hypotension (OH) though genitourinary, cardiovascular, and sudomotor involvements are also common.^[1-5] OH is defined as the drop of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within three minutes of standing or within three minutes of the 60-degree head-up tilt test.^[6] As it was first reported by Bradbury and Eggleston in 1925, it was previously known as Bradbury-Eggleston disease.^[7] Later, Shy and Drager and then Thomas and Schirger also described a large cohort of patients with neurogenic orthostatic hypotension and genitourinary symptoms.^[8,9] A recent study revealed that a quarter of all PAF patients can phenoconvert to more extensive alpha synucleinopathy like Parkinson's disease (PD), multiple system atrophy (MSA), or Lewy body dementia (LBD).^[10,11]

PATHOPHYSIOLOGY [FIGURE 1]

PAF is characterized by the deposition of neuronal cytoplasmic inclusion bodies (Lewy bodies) in various peripheral structures

like autonomic ganglia, nerves, epicardial fat, adrenal gland, and urinary bladder.^[12-15] However, the central structures can also be involved.^[1,14] These Lewy bodies mainly affect the sympathetic ganglia and sympathetic nerves, though cholinergic nerves can also be affected.^[1] This results in a post-ganglionic autonomic dysfunction with a loss of predominantly noradrenergic nerve fibers.

The central or preganglionic structures involved in PAF are locus coeruleus, substantia nigra, and sacral spinal cord though they show no neuronal loss.^[14,15] This might explain why central signs of neurodegeneration like parkinsonism are absent in most PAF patients unless they phenoconvert to PD, LBD, or MSA.

The dysfunction of sympathetic ganglia reduces the production of catecholamines, including noradrenaline.^[16] The serum

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Submitted: 17-Dec-2021 **Revised:** 22-Mar-2022 **Accepted:** 04-Apr-2022

Published: 24-Jun-2022

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DOI: 10.4103/aian.aian_1078_21

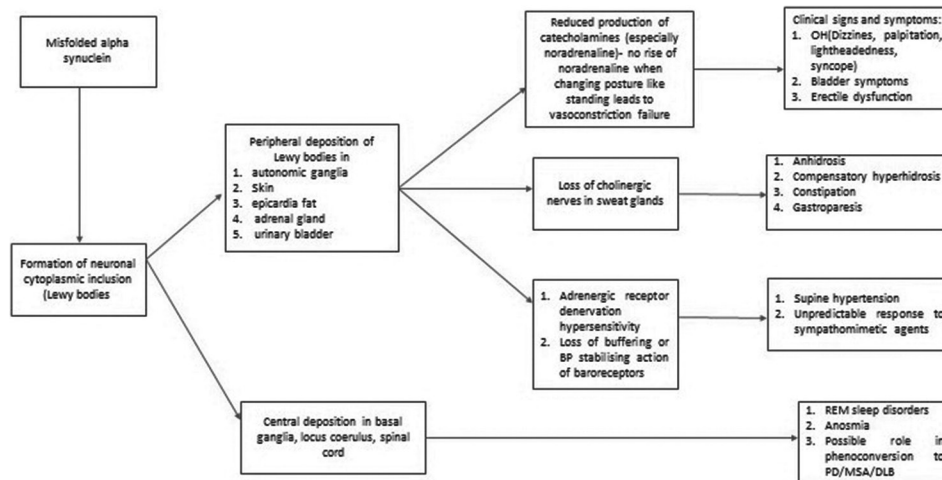


Figure 1: Flowchart that describes the pathophysiology of pure autonomic failure^[1-5]

noradrenaline level is low when someone is supine and fails to increase while standing.^[1,2] This results in postural blood pressure drop and orthostatic symptoms [Figure 1]. The loss of adrenergic nerves in the skin results in poor vasoconstriction and venous pooling of blood. The loss of cholinergic nerves leads to sweat gland denervation and anhidrosis. Cardiac sympathetic innervation is affected in Lewy body deposition diseases like PAF. Cardiac denervation is rare at the early stages of MSA, a close differential diagnosis of PAF.^[1,7]

Receptor hypersensitivity also plays an important role in the pathophysiology of PAF.^[1,2] The pressor agents with direct peripheral sympathetic stimulant action trigger an exaggerated response because of the receptor hypersensitivity.

CLINICAL SYMPTOMS AND SIGNS

Orthostatic hypotension

Peripheral cardiac and vasomotor denervation contributes to the OH in PAF. Normally, 300–1000 ml of blood pools into the lower extremities and splanchnic vessels when someone stands up.^[18] The normal compensatory rise in the heart rate and cardiac contractility on standing is impaired in PAF due to inadequate availability of the catecholamine and the malfunctioning of the baroreceptors. The baroreceptors of the carotid and aortic arch that regulate blood pressure is severely impaired.^[2] The common clinical features of OH are lightheadedness, palpitation, anxiety, dizziness, syncope, blurred vision, fatigue, coat-hanger type of shoulder and neck pain, and cognitive symptoms. The blood pressure (BP) may drop between 50–70 mmHg within 30 minutes of a meal, especially after a large carbohydrate-rich meal.^[19] OH is also more common in the morning, probably due to the additional factor of nocturnal diuresis.

Supine hypertension

Supine hypertension (SH) is defined as the systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg after a minimum of five minutes of rest in the supine position.

Biaggioni *et al.*^[20] reported that supine BP could go up to 228/140 mmHg in some PAF patients. SH is very common in PAF and often remains unrecognized in general practice. SH can be more detrimental than OH as many with OH can develop ischemic heart diseases, cerebral small vessel disease, and nephropathy. The exact cause of SH is not clear though poor buffering action of the baroreceptors and the hypersensitivity of the adrenergic receptors seem to play an important role.^[21]

Genitourinary dysfunction

A natural history study reported that bladder dysfunction could be seen in 50% of patients and erectile dysfunction in 65% of patients within five years of the onset of symptoms.^[22] The common symptoms reported are urgency, frequency, incontinence, and urinary retention. Most long-standing PAF patients developed bladder symptoms. However, severe bladder dysfunction at the early stages of PAF is uncommon and should alert the clinician about the possible phenoconversion to MSA.

Sudomotor dysfunction

Hypohidrosis (reduced sweating) and compensatory hyperhidrosis are both common in PAF. Exercise intolerance can develop due to poor sweating.

Gastrointestinal symptoms

Constipation is common in PAF, like any other Lewy body disorder. Yamanaka *et al.*^[23] reported pseudo-obstruction in a patient with PAF. Many PAF patients developed various degrees of gastroparesis, bloating, nausea, and early satiety though they rarely had acute abdomen. PAF patients with troublesome gastrointestinal symptoms should be referred to neuro-gastroenterology for investigation and management.

Ophthalmological symptoms

Dryness of eyes and visual blurring had been reported in PAF though most patients do not experience major eye symptoms.

Anosmia

Though olfactory testing can reveal anosmia in 80% of PAF patients, they rarely complain of anosmia in our clinical

practice.^[22] One study previously observed that the prevalence of hyposmia was less in PAF when compared to PD.^[24]

REM sleep disorders

RBD (Rapid eye movement sleep behavior disorder) is observed in 63–72% of patients.^[22,25] The presence of RBD provides clinical evidence of central involvement in PAF.^[25]

Neurological symptoms

Some patients would demonstrate mild generalized bradykinesia, hypomimia, abnormal gait, and mild cognitive impairment.^[1] However, obvious bradykinesia, rest tremor, or rigidity would indicate a phenoconversion to PD or LBD.^[10]

Differential diagnosis [Tables 1 and 2]

The differential diagnoses of PAF include other alpha synucleinopathies (PD, MSA, LBD), drugs (antihypertensive therapy), systemic diseases (diabetes, amyloidosis, adrenal failure, Sjogren's syndrome), paraneoplastic and autoimmune diseases (autoimmune ganglionopathy), and genetic causes (familial dysautonomia). The table provides the list of differentials for PAF. The common differentials are idiopathic or drug-induced OH, alpha synucleinopathies (especially MSA) diabetes, and autoimmune causes. Table 2 describes the difference between MSA and PAF.

INVESTIGATIONS [TABLE 3]

A standard autonomic testing protocol for the diagnosis of PAF. Includes ambulatory 24 hours blood pressure, tilt table test, Valsalva test, handgrip exercise test, heart rate variation with respiration, serum catecholamines, and sweat test. In selected cases, a liquid meal challenge test and a post-exercise autonomic function test can also be performed. Serum catecholamines during supine and standing posture can also be helpful. Low baseline catecholamine levels with no significant increase during the tilt also favours the post-ganglionic involvement like in PAF.^[1,2,4,5,11] The drugs that can interfere with autonomic function (antihypertensives, anticholinergics, antihistaminics, and opioids) should be stopped for four to five half-lives (if possible) before any autonomic testing.

The ratio of change of HR/the change of SBP lower than 0.5 bpm/mmHg during the tilt test was proposed to be diagnostic of neurogenic OH.^[26] Recently, orthostatic intolerance ratio (ratio of systolic blood pressure drop during the tilt table test divided by the duration of tilt tolerated in minutes) is found it to be a sensitive marker for autonomic testing during the head-up tilt test.^[27]

A 24-hour BP monitoring can be very helpful to measure the response to therapy, identify the triggers for OH (if any), and detect early supine hypertension. Most patients are instructed to complete a diary of their daily activities during the 24 hours BP monitoring to assess the BP fluctuation during various activities like eating, lying supine or exercise.

The thermoregulatory sweat test (TST) evaluates sudomotor function from the thalamus to sweat glands as a response

Table 1: Differential diagnoses of pure autonomic failure

1. Neurodegenerative
Alpha synucleinopathies
Parkinson disease
multiple system atrophy
Lewy body dementia
2. Autonomic neuropathies
Guillain Barre syndrome
Chronic Inflammatory demyelinating polyneuropathy
Autoimmune ganglionopathy
3. Systemic and metabolic diseases
Diabetes Mellitus
Amyloidosis
Sjogren's syndrome
Systemic lupus erythematosus
4. Drug/toxin
Antihypertensives
Anticholinergic
Older antihistaminic
Neuroleptic
Amiodarone
Anticancer chemotherapy
Toxins (alcohol, heavy metals)
5. Paraneoplastic
(Anti Hu antibody, Lambert Eaton myasthenic syndrome, Collapsin response mediator protein 5 (CRMP-5) autoantibody)
6. Endocrine
Pheochromocytoma
Adrenal failure
Allgrove syndrome (genetic disease also)
7. Infectious
HIV, Herpes virus, Syphilis, Lyme's disease, Chagas disease
8. Hereditary/genetic
Familial dysautonomia
Hereditary sensory autonomic neuropathy
Dopamine B hydroxylase deficiency
9. Miscellaneous
Autonomic dysreflexia (after high spinal cord injury)
Baroreflex failure (post radiotherapy, cervical spine surgery)

to raised body temperature. On the other hand, both the quantitative sudomotor axon reflex test (QSART) and DST evaluate post-ganglionic sudomotor function by stimulating the peripheral autonomic axons and sweat glands using acetylcholine analog iontophoresis. Combining TST and QSART/DST shows reduced sweat production and helps localize sudomotor dysfunction to post-ganglionic autonomic nerves in PAF.^[1,4,11] DST is more patient-friendly and less time-consuming though DST needs further standardization.

Skin biopsy showing deposition of alpha-synuclein is evident in patients with PAF and at a higher burden compared to other alpha-synucleinopathies with more central involvement like multiple system atrophy.^[28] However, the authors do not recommend skin biopsy for the diagnosis of PAF.

The cardiac meta-iodobenzylguanidine (MIBG) and Dopamine transporter (DaT) scan can help in the diagnosis. Cardiac

Table 2: A comparison of pathophysiology, clinical features, and investigation outcome between multiple system atrophy (MSA) and pure autonomic failure (PAF)

Features	MSA	PAF
Pathophysiology	deposition of alpha-synuclein in the central nervous system until the late stages when peripheral nervous system involvement occurs	deposition of alpha-synuclein predominantly in peripheral structures like autonomic ganglia, nerves, epicardial fat, adrenal gland, and urinary bladder; rarely central structures involved
Clinical features		
Orthostatic hypotension	can be severe at the beginning	mild to moderate at the beginning
diurnal or nocturnal inspiratory laryngeal stridor	common	uncommon
Bladder dysfunction	can be severe at the early stages	rarely severe at early stages
Motor symptoms	Parkinsonism can be seen early in MSA-P and later in MSA-C	mild bradykinesia can be seen, but florid parkinsonism uncommon
Prognosis	usually rapidly progressive	slowly progressive though phenoconversion to PD/DLB/MSA reported in up to 25% of cases
Investigation:		
Head-up tilt test	normal baseline noradrenaline with the adequate rise of catecholamines on standing	low baseline noradrenaline levels with no significant increase in tilt due to post-ganglionic involvement
Magnetic resonance imaging (MRI) of the brain	can show profound orthostatic hypotension at the outset	mild to moderate orthostatic hypotension at the outset
Clonidine-induced growth hormone stimulation test (detect the integrity of the central autonomic pathway)	can show hot cross bun sign in the pons, putaminal slit sign, disproportionate cerebellar atrophy	unremarkable
Dopamine Transporter scan (DaT)	abnormal	normal
Metaiodobenzylguanidine scan (MIBG)	abnormal	normal (unless it evolves into MSA/PD/LBD without motor features)
Thermoregulatory sweat test (detection of preganglionic sweat disorder)	normal (can be abnormal at late stages)	abnormal
Quantitative sudomotor axon reflex test (QSART) (detection of postganglionic sweat disorder)	abnormal	normal
	normal	abnormal

Table 3: Investigations and their outcome in pure autonomic failure

Autonomic function test		Preganglionic function assessment	Imaging/Histology	Other investigations:
Cardiovascular function	Sudomotor function			
Cardiovascular failure (reduced respiratory sinus arrhythmia)	Quantitative sudomotor axon reflex test (QSART)-reduced sweating suggestive of post-ganglionic pathology	TST reduced sweating	Cardiac MIBG -reduced sympathetic uptake	Urodynamic study and urinary sphincter electromyogram
Cardio-sympathetic failure (heart rate and blood pressure response to Valsalva manoeuvre)		Growth hormone response to clonidine stimulation (preserved)	Skin biopsy shows alpha-synuclein deposition	Some patients may have small bladder capacity, detrusor hyperreflexia, low bladder compliance, detrusor-sphincter dyssynergia, denervation supersensitivity
Head-up tilt test (tilt table test)- drop of Systolic BP>20 mmHg and Diastolic BP>10 mmHg within 3 minutes of tilt			Ultrasound kidney can show signs of hypertensive nephropathy- similarly, echocardiogram can show left ventricular hypertrophy	Cerebrospinal fluid: (research use so far)
24 hours blood pressure-fluctuating BP (significant postural drop >20/10 mmHg and supine hypertension (>140/90 mmHg after 5 minutes of rest)			DaT scan usually shows normal traced uptake	Neurofilament was found to be high in some PAF patients who phenoconverted to MSA later
Catecholamine levels are usually low, with no significant rise in standing	Dynamic sweat test (DST)- reduced sweating suggestive of post-ganglionic pathology			Alpha synuclein oligomer found in the CSF of all PAF patients

MIBG usually shows evidence of cardiac post-ganglionic sympathetic denervation in PAF.^[29] MIBG is helpful to distinguish PAF from MSA at early stages though it is expensive and not widely available even in the UK. DaT scan generally shows normal tracer uptake through PAF patients with no signs of degenerative parkinsonism had been found to have abnormal DaT scans.^[30] Repeating the DaT imaging

is generally not helpful (at least within 24 months of a normal scan) unless there are florid clinical signs of parkinsonism in patients. Moreover, the high cost of the DaT scan is also a major obstacle for a repeat scan outside specialist centers.

The urodynamic studies and sphincter electromyography can reveal small bladder capacity, detrusor hyperreflexia,

detrusor-external sphincter dyssynergia, and denervation supersensitivity in PAF patients.^[31]

Recently, PAF patients with high cerebrospinal fluid neurofilament levels were found to have had a higher risk of evolving into MSA in the future.^[32] However, lumbar punctures for the diagnosis of PAF is generally recommended outside the research settings.

TREATMENT

No disease-modifying therapy is available for PAF. A combined approach of non-pharmacological measures and drugs works the best.

Non-pharmacological measures to improve OH: [Supplementary Table 1]

We routinely recommend patients to drink at least 2-liter water daily with a rapid bolus of 500 ml of water before standing up. Such a bolus worked within five minutes of ingestion and was reported to increase BP by as much as 40 mmHg.^[2,20]

We also recommend 1–2 tsp of salt (2.3–4.6 gm) salt. The urinary sodium excretion of more than 170 mEq within 24 hours can be used as a marker of adequate salt intake.^[1] Small meals are recommended to avoid postprandial hypotension.^[1,2,33]

Physical counter maneuvers (isometric exercises like heel stretching, leg crossing) before standing can reduce venous pooling of blood in the lower extremities and help elevate the blood pressure. Simple leg crossing alone can increase the BP by 20 mmHg.^[33] Compression stockings and abdominal binders can also be very helpful to prevent OH. Abdominal binders exert 30–40 mmHg pressure on the splanchnic circulation, which may contain up to 25% of total blood volume at rest.^[34] The authors noticed that abdominal binders were more effective than compression stockings though some would need both. However, they work the best during the early stages of the disease.

Lifting the head of the bed by a few inches at night can reduce the risk of SH, nocturnal pressure diuresis, and subsequent early morning OH. The SH should not lie flat on the bed especially during the daytime as that would worsen SH. We have put our non-pharmacological recommendations in Table 3.

Pharmacotherapy [Supplementary Table 2]

The drug therapy mainly includes agents to elevate BP (fludrocortisone, midodrine, droxidopa, pyridostigmine, etc.) and antihypertensives to lower BP. The common antihypertensives used to treat SH are nitroglycerine, nifedipine, losartan, captopril, and clonidine. The management of RBD, constipation, nocturnal diuresis, genitourinary symptoms, speech, swallowing, and other co-morbidities, especially anemia, renal, and cardiac diseases, also constitute an important part of the management.

Fludrocortisone, a mineralocorticoid, is one of the most common drugs used to raise BP in OH. It is a volume expander

as it stimulates renal sodium retention.^[1-4,18,34-36] A small study found that Fludrocortisone, along with head tilt, can improve standing time from three minutes to ten minutes. However, we found it to be more effective in the early stages. It works best when someone is not dehydrated. Fludrocortisone, a longer-acting drug, is not a great option for PAF patients with a mixture of OH and SH though shorter-acting drugs like midodrine works better in such cases. Moreover, fludrocortisone can promote water retention, which can be detrimental for patients with congestive heart failure.

Midodrine, a peripheral selective alpha-1-agonist, is a Food and drug administration (FDA) approved drug to treat OH. Midodrine directly elevates systolic BP by direct vasoconstriction.^[1-4,18,34-36] It is advisable not to take midodrine after 6 PM. We routinely enquire about scalp itchiness, hypertension, and bladder symptoms after midodrine, as midodrine can trigger or worsen those symptoms.

Droxidopa is a prodrug that is converted to norepinephrine in the body. The conversion happens in the sympathetic post-ganglionic terminal and kidney.^[36] It gets both central and peripheral action. Like midodrine, it should be taken 3–4 hours before bedtime to reduce the risk of supine hypertension. Droxidopa is not widely available in the UK.

Synucleinopathies with low plasma norepinephrine levels (like PAF) respond better to droxidopa and midodrine. Patients with normal or high norepinephrine levels (usually multiple system atrophy) may respond better to norepinephrine reuptake inhibitors. However, this observation was not replicated in the recently concluded amprelosetine (norepinephrine reuptake inhibitors) phase 3 trial. Amprelosetine failed to raise BP significantly when compared to placebo in MSA patients.^[37]

Pyridostigmine, an acetylcholinesterase inhibitor, got a modest effect on BP elevation (mainly diastolic BP) and posed little risk of supine hypertension.^[38] The authors noticed that this drug is particularly suitable for PAF patients with anhidrosis and constipation as pyridostigmine promotes the secretion of various body fluids through cholinergic stimulation.

Octreotide, a somatostatin analog, reduces the secretion of the vasodilatory intestinal polypeptide. This drug is quite effective in reducing postprandial hypotension (PPH) when used alone or with midodrine.^[39] Acarbose, an alpha-glucosidase inhibitor, can also reduce the risk of postprandial hypotension.^[36] Octreotide is helpful in the management of PPH and refractory cases of OH. However, acarbose is rarely used.

Desmopressin, a synthetic vasopressin analog, can reduce nocturnal polyuria, which is a major cause of early morning OH. One study found that 2–4 mcg of intramuscular desmopressin can elevate the early morning sitting BP by an average of 15 mmHg.^[40] We also found desmopressin helpful in selected cases of OH though we prescribe it only after discussion with our uro-neurology team.

Pharmacotherapy for supine hypertension (SH)

Nifedipine, captopril, transdermal nitroglycerine, losartan, hydralazine, and clonidine had all been tried to control supine hypertension.^[1,2,36] Though there is a lack of head-to-head studies on the efficacy of antihypertensives on SH, we noticed good results with losartan, clonidine, and nifedipine. The coexistence of OH and hypertension often makes the management of PAF challenging.

PROGNOSIS

Though PAF got a slowly progressive course, a recent retrospective study reported that almost 24% of PAF patients could evolve into MSA, PD, or LBD.^[10,11] However, no other study revealed such a high rate of phenoconversion. A preganglionic pattern of anhidrosis, higher baseline supine noradrenaline level, and early severe bladder involvement enhances the risk of phenoconversion to MSA. Raised cerebrospinal fluid neurofilament level in PAF patients was also reported to be a risk factor for transformation into MSA. Subtle motor signs, dream enactment behavior, and constipation increase the risk of PD/LBD in the future. Phenoconversion to MSA occurs earlier (usually within three years) than to PD or LBD (average eight years).^[10] We also noticed that phenoconversion to MSA happens much quicker than to PD or LBD.

OUR VIEWPOINT ON THE FUTURE OF PAF

The diagnostic criteria of PAF need to be upgraded to incorporate our current understanding of pathophysiology, clinical features, and newer diagnostic modalities like MIBG, Dopamine transporter scan, skin biopsy, and sweat tests. The recent discovery of risk factors for the phenoconversion of PAF to PD, MSA, and LBD should encourage the exploration of more reliable biomarkers before the phenoconversion as such biomarkers may play an important role in the diagnosis of PD, MSA, or DLB. The recent discovery of cerebrospinal fluid neurofilament as a potential biomarker for PAF is encouraging though it needs further studies. Clonidine-induced growth hormone stimulation, a marker of the integrity of the central autonomic pathway, is preserved in PAF but not in MSA.^[41] The role of the Clonidine growth hormone stimulation test (CGHST) needs to be explored further as it can be helpful to distinguish PAF from early MSA. However, CGHST needs intravenous infusion, which makes the test less attractive. We need to design oral CGHST to gain acceptability. Recently, cerebral blood flow to the grey matter was found to be higher in PAF when compared to the control population.^[42] However, its significance in the pathophysiology of PAF is not yet clear. Similarly, the role of genetic factors in PAF needs to be studied in detail. In addition to a reliable and effective biomarker, more effective treatments are needed to tackle OH and SH. There are not enough randomized control clinical trials to ascertain the best treatment strategy for OH and SH. Currently recommended drugs for the management of OH and

SH are mainly based on case series and open-labeled studies. Unfortunately, Amprelosetine, a norepinephrine transporter blocker, failed to raise BP in OH during the phase 3 study in MSA and PAF patients. This trial raised questions about our understanding of the pathophysiology of OH in PAF. A posthoc or subsection analysis of amprelosetine trial data might help us understand its effect on various age and ethnic groups of PAF patients. Similarly, there is no effective therapy to address hypohidrosis, a very common clinical symptom in PAF. The management of PAF needs to be holistic with active input from physiotherapy, occupational therapy, neuropharmacist, neurologists, gastroenterologist, uro-neurologist, cardiologists etc., though organizing such multidisciplinary management can be challenging in resource-limited settings. However, PAF is a rare disease, so trials need to be multidisciplinary involving both autonomic and movement disorders specialists, multicentric, and multiethnic.

Author's contribution

1. Study concept and design, acquisition of data, analysis and interpretation of data, study supervision, critical revision of the manuscript for intellectual content, analysis, and interpretation of data
2. Critical revision of the manuscript, analysis, and interpretation of data.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Non-pharmacological approach to the management of orthostatic hypotension

1. Maintain adequate hydration (2-3 liter daily)
2. Adequate salt intake (1-2 tsp daily) is important. A urinary 24 hours sodium excretion or more than 170 mEqL is an indicator of adequate salt replacement.
3. Water bolus (500 ml) before standing up as it can boost BP by more than 40 mmHg within 5 minutes.
4. Practise physical counter manoeuvres before standing (leg crossing, heel lifting, fist-clenching)
5. Avoid a heavy meal (especially carbohydrate-rich meal) to reduce the risk of postprandial hypotension.
6. Avoid hot showers and prolonged standing in hot weather
7. Lift the head of the bed by (6-8 inches) at night to reduce the risk of supine hypertension
8. A light snack at night can reduce the risk of nocturnal supine hypertension
9. Abdominal binder and/or compression stocking (waist or thigh-high compression) can reduce the risk of postural BP drop.
10. Daily exercise can improve the strength of lower limb muscles and core muscles.

Supplementary Table 2: The pharmacological management of pure autonomic failure (PAF)

Drug	Mechanism of action	Dose	Side effects	Special consideration
Fludrocortisone	Mineralocorticoid that stimulates Na retention	100 mcg–400 mcg/day	Supine hypertension, edema, dyselectrolytemia	Can worsen congestive heart failure due to fluid retention
Midodrine	Alpha adrenergic receptor agonist-triggers vasoconstriction	2.5 mg–10 mg TDS	Supine hypertension, urinary retention, scalp itchiness, peripheral vascular disease	Avoid lying flat for 3-4 hours after the dose to reduce supine hypertension
Pyridostigmine	Acetylcholine esterase inhibitor improves sympathetic tone on standing	15 mg–90 mg TDS-QDS	Hypersalivation, abdominal cramps, diarrhea, hyperhidrosis	Better for OH with supine hypertension with constipation and anhidrosis-modest efficacy
Droxidopa	Prodrug of norepinephrine-promotes vasoconstriction	100–600 mg TDS	Supine hypertension, headache, fatigue	Avoid lying flat for 3-4 hours after the dose to reduce supine hypertension
Octreotide	Stimulates somatostatin receptor	100–200 mcg TDS	Diarrhea, alopecia, cholestasis, hyperglycemia	Needs caution in diabetic patients Mainly used for postprandial hypotension
Acarbose	Alpha glucosidase inhibitor	25–100 mg TDS	Diarrhea, gastrointestinal symptoms	Mainly effective in postprandial hypotension
Desmopressin	Vasopressin analogue- reduces the nocturnal urinary frequency and improves early morning hypotension	5 mcg intranasal (also available subcutaneously)	Fluid overload, hyponatremia, hypertension,	Used only for nocturia-needs caution in cardiovascular and renal disease as hypervolemia can worsen these conditions