Diagnosis and Management of Autonomic Failure in Neurodegenerative Disorders

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Key Words
Neurodegenerative disease · Autonomic nervous system · Cardiovascular reflex tests

Abstract

Background: One of the hallmarks of the α-synucleinopathies is the degeneration of the autonomic nervous system. Summary: This review discusses the diagnosis and management of cardiovascular autonomic failure within the context of the α-synucleinopathies. In addition, it outlines the utility of various laboratory assessments including cardiovascular reflex tests for the differential diagnoses of these disorders, as well as general disease management strategies. Key Messages: Laboratory investigations assessing the autonomic control of the cardiovascular system are useful in the differential diagnosis of α-synucleinopathies, especially in early stages of disease. Clinical Implications: The characterization of the different features of AF in patients with α-synucleinopathies is challenging because it might help to improve the accuracy of the differential diagnosis between these diseases at onset. Further cardiovascular AF has been demonstrated to have a negative prognostic role in α-synucleinopathies, therefore an early detection of cardiovascular dysautonomia allows to positively impact the disease course guiding the appropriate therapy.

Introduction

Progressive central nervous system (CNS) degeneration due to the aggregation and deposition of misfolded proteins characterizes neurodegenerative disorders [1]. Under these conditions, the clinical features are related to the progression of the pathological processes in different areas of the CNS, and some components of the autonomic nervous system (ANS) can be involved. The latter is that part of the nervous system that regulates visceral functions and integrated processes that control vital functions, encompassing any nervous activity that does not reach the level of consciousness [2].

The ANS is composed of the Central Autonomic Network, including several interconnected areas of the CNS that receive and integrate humoral, visceral sensory, and environmental inputs to generate specific autonomic, endocrine, and somatomotor responses, and of an efferent pathway, which comprises the sympathetic and parasympathetic nervous systems. Each efferent pathway is composed of a two-neuron system consisting of pre- and postganglionic neurons, which make synapses with the target organ [3].

The ANS is typically involved in α-synucleinopathies, degenerative disorders characterized by the presence of intracellular inclusions containing α-synuclein, which also affect the CNS (multiple system atrophy [MSA], Par-
kinson’s disease [PD], dementia with Lewy bodies [LBD]), or only the peripheral nervous system (pure autonomic failure [PAF]) [4].

In degenerative disorders, the ANS could be entirely or selectively (either the sympathetic or the parasympathetic component) affected. The autonomic involvement in α-synucleinopathies mainly results in a failure of the sympathetic branch of ANS and only affects the postganglionic component in PAF, mainly the postganglionic component in LBD and PD, and the preganglionic one in MSA.

Sympathetic autonomic failure (AF) is clinically characterized by cardiovascular AF, sexual dysfunction, and neurogenic bladder and bowel. From a clinical perspective, AF is mandatory for a diagnosis of PAF and MSA [5], while symptoms of AF are reported as clinical supportive features of LBD [6, 7]. As cardiovascular AF has been demonstrated to negatively impact the disease course in α-synucleinopathies [8], in this review we will discuss current knowledge on clinical and instrumental diagnosis, and management of cardiovascular AF that presents in the context of these diseases. In addition, we will focus on the utility of the laboratory investigations for assessing the autonomic control of the cardiovascular system (cardiovascular reflex tests) in the differential diagnosis of these disorders, especially in early disease stages.

**Clinical Observation**

The cardinal sign of sympathetic neurocirculatory failure is orthostatic hypotension (OH), which is defined as a sustained reduction in systolic blood pressure (SBP) of at least 20 mm Hg or in diastolic BP (DBP) of at least 10 mm Hg, within three minutes of standing up or head-up tilt to at least 60° on a tilt table (fig. 1) [9]. OH may be asymptomatic or symptomatic. Clinical manifestations of OH are reported in table 1.

In MSA, OH is almost invariably present during the disease course; however, less than 50% of patients experience syncope. OH may occur early in the course of the disease, and in these cases is associated with a shorter survival time [10, 11]. Similarly, recent studies demonstrated

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**Fig. 1.** Cardiovascular responses to standing during head up tilt test in a patient presenting with Parkinson’s disease and orthostatic hypotension and in a normal control. BP = Blood pressure; HR = heart rate; bpm = beats per minute; min = minutes.
that in long-surviving patients, cardiovascular dysautonomia occurred late in the disease course suggesting that late onset of cardiovascular AF in MSA patients may be a favorable prognostic factor [12, 13].

In the diagnosis of PD [6], early and severe autonomic involvement is considered an exclusion criterion. However, it has been observed that OH can occur early in the disease course, even before the hallmark motor phase of PD, and autopsy-proven PD patients misdiagnosed as having PAF or MSA in life have been described [14, 15]. Goldstein reported that, in a cohort of 35 PD patients with OH, 60% had documentation of OH as an early finding (at least one year after the onset of motor symptoms) [14]. Thus, OH has been proposed as a non-motor feature in PD [7], although its prevalence and severity are still controversial. A recent meta-analysis of 25 studies reported a 30% prevalence of OH at any stage of disease in PD with a large statistical heterogeneity between studies. Several individual studies reported in the meta-analysis have shown that OH occurs in older patients and at a later stage of the disease, but this information could not be analyzed because data from individual patients were not reported. Dopaminergic treatment can increase OH risk in PD, but it may occur even in the absence of treatment [16].

In LBD, AF is considered a supportive diagnostic feature. In a series of 29 cases with pathological confirmation, the frequency of OH (defined as SBP lower than 100 mm Hg when standing) including cases without episodes of syncope reached 66%, while syncopal episodes occurred in 28% of patients [17]. Thaisetthawatkul and co-authors compared autonomic dysfunctions in LBD patients with MSA and PD patients. The severity of AF was evaluated through the rating of the frequency and scoring of severity of OH and through the scoring of the Composite Autonomic Severity Score (CASS) [18]. They found that the severity of AF in LBD patients was intermediate between MSA and PD patients, with MSA patients being the most severely affected [17, 19, 20].

PAF is a rare, idiopathic sporadic disorder characterized by severe OH and frequent episodes of syncope, a relatively slow and unchanged heart rate (HR), reduced sweating, erectile dysfunction, and constipation, without symptoms or signs of central neurodegeneration.

Interestingly, patients presenting with PAF, after many years of ‘pure’ autonomic involvement may develop signs of CNS dysfunction (Parkinsonism and/or dementia) suggesting a common pathogenesis between PAF, PD and LBD [21].

In about 50% of patients with OH, supine hypertension (SH), defined as a SBP over 150 mm Hg or DBP over 90 mm Hg, has been reported [7] and similarly seems to be related to the impairment of cardiovascular autonomic control. The association between OH and SH defines the ‘Orthostatic Hypotension-Supine Hypertension’ syndrome. SH can occur at any time during the day when the patient is lying down or even when semi-recumbent, but it is especially prevalent at night during sleep. Since drugs used to reverse OH can worsen SH [22] and nocturnal SH is linked to an increased cardiovascular risk and may contribute to ventricular hypertrophy, renal dysfunction and intracerebral hemorrhage, it is crucial to recognize SH and treat it accordingly.

### Laboratory Assessment

Dysfunction of the autonomic control of the cardiovascular system can be evaluated through noninvasive physiological, biochemical, and pharmacological tests (table 2). These tests should be performed when OH is suspected on the basis of the medical history and the neurological examination (fig. 2). These tests simulate daily activities that induce stress conditions on the autonomic control of the cardiovascular system.

Physiological tests evaluate the integrity of both the effector branches, or selectively of either the sympathetic or the parasympathetic one. The head-up tilt test (HUT) and the valsalva maneuver (VM) assess the functioning of both branches. The heart rate response to deep breathing allows the evaluation of the cardiovagal efferent system and its relationships with breathing. Sustained isometric muscle contraction (sustaining a fixed, isometric handgrip contraction for 3 min at 30% of maximum effort), cold water immersion (immersing a hand in a container of icy water for 1–3 min), and mental stress tests (performing mental arithmetic, e.g., subtracting 7 serially from 100 and the Stroop color word-naming test) are pressure stimuli and markers of the vascular efferent sympathetic system function [23].

### Table 1. Signs and symptoms of orthostatic hypotension

<table>
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<th>Sign/Symptom</th>
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<tr>
<td>Dizziness, weakness, lethargy, fatigue</td>
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<tr>
<td>Visual disturbances: blurred vision, tunnel scotoma, greying out, blacking out</td>
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<tr>
<td>Paracervical and suboccipital ('coat hanger') ache, lower back/buttock ache</td>
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<tr>
<td>Falls and syncope</td>
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<td>Oliguria</td>
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If the medical history is suggestive of OH, cardiovascular responses to standing should be investigated first by the active standing test and, if this is negative, the passive HUT test is recommended [24].

VM is performed by blowing through a mouthpiece connected to a mercury manometer at 40 mm Hg for 15 s. VM consists of four phases. Phase I starts at the beginning of the respiratory strain and is consistent with a transient increase in arterial BP (ABP). Phase IIa is characterized by a fall in ABP due to impaired atrial filling of the heart. The successive phase IIb is triggered by the sympathetic reflex activation due to the fall in ABP and leads to a rise in ABP and an increase in heart rate. At the end of the strain, the sudden decrease in intra-thoracic pressure leads to phase III, where a transient decrease in ABP occurs. This is followed by phase IV, characterized by an overshoot of ABP above baseline, due to the recovery of a normal cardiac output against a still elevated sympathetic tone resulting in an increased total peripheral resistance. A transient bradycardia is the normal response to the ABP overshoot of phase IV (fig. 3) [25].

In patients with chronic primary AF, a particular pattern of pressure responses to the VM has been reported [7, 26]. In these patients, ABP decreases progressively during phase II and does not exceed the baseline value during phase IV. This pattern indicates a sympathetic cardiovascular failure in response to decreased cardiac filling [7].

Recent studies [15, 27–29] have reported that the severity and distribution of the autonomic dysfunction may differentiate PD from MSA. Some of these studies used CASS as a quantitative index measure of overall autonomic dysfunction on standard autonomic testing, including the cardiovascular reflex test. Kimpinsky reported that CASS total scores showed good sensitivity (89%) but a moderate specificity (70%) in discriminating MSA from PD [27]. Lipp et al. reported that autonomic indices (CASS and the thermoregulatory sweat test, TST) were
Fig. 2. Laboratory assessment in the differential diagnosis between PAF and MSA. HUT = Head-up tilt test; VM = valsalva maneuver; OH = orthostatic hypotension; NE = norepinephrine; MIBG = cardiac radionuclide 123-meta-iodo-benzylguanidine imaging; PAF = pure autonomic failure; MSA = multiple system atrophy.

Fig. 3. Valsalva maneuver in a patient with Parkinson’s disease (a) and orthostatic hypotension, compared to a normal control (b). BP = Blood pressure; HR = heart rate; bpm = beats per minute; EP = expiration period; sec = seconds; min = minutes.
significantly more abnormal in MSA than in PD at onset, and that these differences were sustained and became greater at a further evaluation after 12 months. Furthermore, the percentage of sweating at the TST can distinguish between the two diseases [15] but with a minimal overlap between the scores of the different patients.

Unfortunately, these studies were performed on small samples of patients, mainly in advanced stages of the disease, when the maneuvers are problematic to perform, and in patients on medication. Furthermore, none of these studies had pathological confirmation of the disease.

As cardiovascular reflex tests are noninvasive, inexpensive, and reproducible, their accuracy for the differential diagnosis of α-synucleinopathies should be confirmed in a larger prospective autopsy-confirmed study.

The evaluation of epinephrine and norepinephrine (NE) plasma levels provides the measure of adrenal medullary activity and sympathetic neural activity, respectively. Measurement of plasma NE is useful to differentiate PAF from MSA. In PAF, the supine basal concentration of plasma NE is lower compared to MSA in which supine values are within the normal range. In both, however, there is an attenuation or lack of physiological rise in plasma NE during HUT.

PD patients with OH have lower NE supine concentrations than those without OH. Nevertheless, PD patients with OH do not have significantly lower NE supine concentrations compared to healthy people of similar age, and the concentrations are higher than those in patients with PAF [2, 7]. NE concentrations are similar in PD patients with OH and in MSA patients. During HUT, PAF patients, PD patients with OH, and MSA patients with OH have sharp orthostatic increments in plasma NE concentrations, while PD patients without OH have an increase of 60% or more. In LBD, the plasma NE concentration compared to PD patients is lower at rest and the response of plasma NE to HUT is blunted.

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Pharmacological tests can determine the degree of sensitivity of different receptors and the functional integrity of ANS components. A pharmacological challenge with the α-2 adrenoreceptor agonist clonidine causes the stimulation of growth hormone release. It is useful for differentiating PAF patients, who exhibit a rise in growth hormone serum concentrations after clonidine injection, from MSA patients, in whom these concentrations remain stable [2].

Cardiac radionuclide 123-meta-iodo-benzylguanidine (MIBG) imaging assesses cardiac sympathetic innervations. The distribution of cardiac sympathetic nerves and the uptake function at the nerve ending is quantified with the heart to mediastinum (H/M) ratio. MIBG uptake is generally impaired in PAF, LBD, and PD patients with OH and in about one half of PD patients without OH. These abnormalities are not usually present in MSA patients, but impaired myocardial innervations in these patients have been reported [27, 30].

The sensitivity and specificity of MIBG scintigraphy are high (near 90%) with respect to highlighting cardiac denervation. A recent meta-analysis showed that the pooled sensitivity to differentiate PD from other neurodegenerative parkinsonisms by a delayed H/M ratio is 89.7% and the specificity is 82.6% [31]. Treglia and colleagues found a pooled sensitivity and specificity of 89% (95% CI: 86–91%) and 77% (95% CI: 68–84%), respectively, in differential diagnosis between PD and MSA [30]. In another recent study, pooled sensitivity and specificity for differentiating PD and MSA were 90.2% (95% CI: 84.4%, 93.9%) and 81.9% (95% CI: 56.1%, 94.1%), respectively [32].

Several studies have used 6-[18F] fluorodopamine positron emission tomography to evaluate the noradrenergic denervation in cardiac and extracardiac organs. In patients with PAF, PD, and PD with OH, loss of sympathetic innervations was detected in the heart, in the thyroid gland and in the renal cortex.

Finally, as OH in these patients is often linked to SH, 24-h ambulatory BP monitoring may be useful for evaluating SH, especially during the nighttime [22].

Prevention and Management

Unfortunately, there are no targeted treatments for modifying the course of any of these disorders [33]. At present, treatment should be directed toward ameliorating the disease symptoms and resolving OH symptoms in patients with asymptomatic OH, thus improving the patient’s functional status and reducing the risk of falls due to syncope. To achieve a balance between OH and SH, a goal of SBP of 100 mm Hg while standing is recommended, at least in the morning [7].

In patients with asymptomatic OH, a stepwise treatment starting with non-pharmacological measures (table 3) could prevent the need for pharmacological treatment. Non-pharmacological treatment measures are also recommended for patients with symptomatic OH.

Pharmacological treatment is required when lifestyle measures are not effective, in order to increase intravascular volume and pressure. In particular, considering treatment directed toward raising the intravascular volume, 9α-fluorohydrocortisone is the first line drug and the only one recommended with the level of evidence ‘C’
by the European Federation guidelines [24]. Fludrocortisone acetate is a synthetic mineralocorticoid with a long duration of action and is well tolerated by most patients. Treatment is initiated with a 0.1 mg tablet and can be increased until up to 1 mg/day.

In the same categories, erythropoietin corrects the normochromic normocytic anemia that frequently accompanies AF. It is administered subcutaneously or intravenously at doses between 25 and 75 U per kilogram three times a week until the hematocrit level approaches normal. Lower maintenance doses (approximately 25 U per kilogram three times a week) may then be used. Another drug used to expand intravascular volume is the synthetic vasopressin analogue desmopressin acetate (DDAVP) that acts on the V2 receptors in the collecting ducts of the renal tubules and has no V1 receptor constricting potential. DDAVP can be taken as a nasal spray (10–40 μg/day) or orally (100–800 μg/day).

Treatments acting as pressor agents are mainly peripherally-acting α-1 adrenoreceptor agonists. The direct acting α-1 agonist midodrine is the only one recommended by the Food and Drug Administration with a level of evidence ‘A’ for mono- or combined therapy. Patient sensitivity to this agent varies and the dose should be titrated from 2.5 to 10 mg three times a day. The last dose should be administered 4 hours before bedtime because SH is a common adverse effect.

Another pressor agent is the α-2 antagonist yohimbine that increases norepinephrine release from sympathetic nerves by augmenting the central sympathetic outflow and by interfering with inhibitory modulation of pre-synaptic α-2 adrenoreceptors. Yohimbine (5.4 mg/day) is well tolerated in AF patients. Alternatively, pseudoephedrine (30 mg/day), a sympathomimetic amine, can be used. Other pressor agents such as ergotamine alone or in combination with caffeine (1 mg/100 mg/day) and subcutaneous octreotide (25–50 μg/day) can be used.

Pyridostigmine has a different mechanism of action. It inhibits acetylcholinesterase and improves sympathetic ganglion transmission mainly during standing. It can be administered orally, 60 mg per day, to produce significantly increased orthostatic BP without causing SH.

Droxidopa (L-threo-3,4-dihydroxyphenylserine) is an oral prodrug that is converted to norepinephrine through the actions of the enzyme dopa-decarboxylase, which is found centrally and in the periphery. It has been evaluated for efficacy and safety in treating symptomatic neurogenic OH. The optimal dose varies between 200 mg and 2000 mg per day. A careful titration is recommended because patients show different degrees of adrenergic denervation. The pressor effect is observed after 1 h and lasts for 6 h.

In the same way, SH should be treated starting with non-pharmacological measures such as a sweet snack or a glass of wine before bedtime. Water drinking should be avoided within the hour before bedtime in patients with SH.

Supine hypertension, polyuria, and early morning OH can be prevented with the elevation of the bed’s head (20–30 cm) during sleep.

Patients are particularly sensitive to transdermal nitroglycerin, which can be used at doses of 0.1 to 0.2 mg/h applied at bedtime and removed upon arising, and to short acting oral nifedipine (30 mg) or hydralazine (50 to 100 mg), used at bedtime. Unfortunately, none of these antihypertensive drugs prevent nocturia and the nocturnal sodium loss [33], thus leading to worsened OH in the morning.

Table 3. Treatment of OH

<table>
<thead>
<tr>
<th>Non pharmacological treatment</th>
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<tbody>
<tr>
<td>Reduce or discontinue drugs that potentially induce clinical manifestation of OH</td>
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<tr>
<td>Avoid hot environments, carbohydrate-rich meals, alcohol</td>
</tr>
<tr>
<td>Avoid prolonged recumbence during daytime</td>
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<tr>
<td>Take in at least 8 g of NaCl daily</td>
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<tr>
<td>Provide water repletion, 2–2.5 l/day</td>
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<tr>
<td>Move to head-up position slowly</td>
</tr>
<tr>
<td>Sit on the edge of the bed for some minutes after recumbence</td>
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<tr>
<td>Use abdominal binders or compression stockings</td>
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<tr>
<td>Regular practice of isotonic exercises and swimming</td>
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<tr>
<td>At the onset of pre-syncopal symptoms</td>
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<tr>
<td>Activate calf muscle whilst supine</td>
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<tr>
<td>Activate physical counter maneuvers (leg crossing with tension of the thigh, buttock and calf muscle – party position – bending over forward, squatting)</td>
</tr>
<tr>
<td>Provide rapid cool water ingestion</td>
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<tr>
<td>Sleep with elevated bed head (20–30 cm)</td>
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<table>
<thead>
<tr>
<th>Pharmacological treatment</th>
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<tbody>
<tr>
<td>Fludrocortisone acetone 0.1–0.2 mg/day</td>
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<tr>
<td>Erythropoietin 25–75 U per kilogram three times a week</td>
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<tr>
<td>Desmopressin acetate nasal spray (10–40 μg/day) or per os (100–800 μg/day)</td>
</tr>
<tr>
<td>Midodrine 2.5–10 mg t.i.d.</td>
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<tr>
<td>Yohimbine 5.4 mg/day</td>
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<tr>
<td>Pseudoephedrine 30 mg t.i.d.</td>
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<tr>
<td>Pyridostigmine 60 mg/day</td>
</tr>
<tr>
<td>Ergotamine/caffeine 1 mg/100 mg/day</td>
</tr>
<tr>
<td>Octreotide subcutaneous 25–50 mcg/day, half an hour before a meal</td>
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<tr>
<td>Droxidopa 600 mg t.i.d.</td>
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</table>

OH = Orthostatic hypotension; t.i.d. = three times a day.
Future Perspectives

The characterization of the different features of AF in patients with α-synucleinopathies remains a priority because this may help to improve the accuracy of the differential diagnoses between these diseases at onset. Since the prognosis for each of these disorders is completely different, an early diagnosis is crucial [34]. Furthermore, cardiovascular AF has been demonstrated to have a negative prognostic role in α-synucleinopathies [8]; therefore an early detection of cardiovascular dysautonomia will have a positive impact on the disease course by guiding the therapeutic strategy. Finally, an accurate understanding of the pathophysiological basis of AF is needed for the development of new therapies.

References