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REVIEW

Orthostatic hypotension in hereditary transthyretin amyloidosis: epidemiology, diagnosis and management

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Abstract

Purpose Neurogenic orthostatic hypotension is a prominent and disabling manifestation of autonomic dysfunction in patients with hereditary transthyretin (TTR) amyloidosis affecting an estimated 40–60% of patients, and reducing their quality of life. We reviewed the epidemiology and pathophysiology of neurogenic orthostatic hypotension in patients with hereditary TTR amyloidosis, summarize non-pharmacologic and pharmacological treatment strategies and discuss the impact of novel disease-modifying treatments such as transthyretin stabilizers (diflunisal, tafamidis) and RNA interference agents (patisiran, inotersen).

Methods Literature review.

Results Orthostatic hypotension in patients with hereditary transthyretin amyloidosis can be a consequence of heart failure due to amyloid cardiomyopathy or volume depletion due to diarrhea or drug effects. When none of these circumstances are apparent, orthostatic hypotension is usually neurogenic, i.e., caused by impaired norepinephrine release from sympathetic postganglionic neurons, because of neuronal amyloid fibril deposition.

Conclusions When recognized, neurogenic orthostatic hypotension can be treated. Discontinuation of potentially aggravating medications, patient education and non-pharmacologic approaches should be applied first. Droxidopa (Northera®), a synthetic norepinephrine precursor, has shown efficacy in controlled trials of neurogenic orthostatic hypotension in patients with hereditary TTR amyloidosis and is now approved in the US and Asia. Although they may be useful to ameliorate autonomic dysfunction in hereditary TTR amyloidosis, the impact of disease-modifying treatments on neurogenic orthostatic hypotension is still uninvestigated.

Keywords Autonomic dysfunction · Autonomic failure · Orthostatic hypotension · Amyloid · Transthyretin · Peripheral neuropathy · Droxidopa

Case vignette

A 44-year-old French-Canadian male presented with a 3-year history of severe diarrhea, unintentional weight loss of 10 kg in the last year and frequent episodes of lightheadedness and feeling about to faint when standing up. Upon further questioning he reported numbness and tingling with occasional shooting pains in his feet at night. He had surgery for left carpal tunnel syndrome at age 35 years. His father had similar symptoms but died at age 52 of lung cancer. Neurologic examination showed normal muscle strength, reduced pin and light touch sensation up to the ankles, very reduced in the calves and reduced in his fingers, bilaterally. Deep tendon reflexes were absent (Achilles and patellar) or reduced (bicipitalis, tricipitalis, brachioradialis). His blood pressure (BP) in the supine position was 139/61 mmHg with a heart rate of 71 bpm. After 3-min of standing, his BP decreased to 89/42 with a heart rate of 74 bpm, and he reported feeling very lightheaded. Plasma norepinephrine levels in the supine position were low (72 pg/ml) and failed to increase significantly on standing (89 pg/ml). Nerve conduction studies were consistent with a moderate axonal sensory neuropathy with no motor involvement. Genetic testing disclosed

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a heterozygous Val71Ala mutation in the *TTR* gene, and a colonic biopsy was positive for amyloid. Treatment with droxidopa (Northera®) 200 mg three times/day resulted in improvement in orthostatic tolerance and increased BP when standing. His diarrhea improved with diphenoxylate and atropine and tincture of opium.

Introduction

Hereditary transthyretin amyloidosis is a rare, autosomal dominant disease caused by mutations in the *TTR* gene encoding transthyretin, a T4-thyroid hormone and retinol transport protein [107]. The liver is the primary source of circulating wild-type tetrameric transthyretin protein. The disease was first reported in Portugal in the 1950s [8] and is estimated to affect ~ 50,000 patients worldwide [107].

More than 150 *TTR* pathogenic mutations have now been identified, with the Val20Met mutation being the most frequent (~ 50% of cases). Mutations in the *TTR* gene destabilize the tetramer structure of transthyretin, turning it into monomers and fibrils that deposit as amyloid predominantly in the peripheral motor, sensory and autonomic nerves, gastrointestinal tract and heart resulting in progressive polyneuropathy and cardiomyopathy [107]. The disease is progressive, with survival of 2–15 years after the onset of neuropathy, but only 2–5 years in patients presenting with cardiomyopathy [23, 74, 86].

Autonomic dysfunction is prominent and disabling in patients with hereditary transthyretin amyloidosis and can be the presenting feature of the disease in ~ 10% of cases before the development of sensory-motor neuropathy or cardiomyopathy [2, 21, 37, 45, 101]. Among the most incapacitating features of autonomic dysfunction is orthostatic hypotension (OH), which is a sustained fall in blood pressure (BP) on standing. The current definition of OH, based on expert consensus [42], is a fall of at least 20 mmHg in systolic BP or 10 mmHg in diastolic BP within 3 min of standing or upright tilt. OH can impair perfusion to organs above the heart, most notably the brain, resulting in symptoms of tissue hypoperfusion, such as dizziness, lightheadedness, feeling about to faint and, sometimes, syncope. These symptoms are disabling, have a profound impact on a patient's quality of life and are associated with worse survival.

This article reviews the current knowledge on the epidemiology, physiopathology and management of OH with emphasis on patients with hereditary transthyretin amyloidosis. We summarize non-pharmacologic and pharmacologic treatment strategies and discuss the impact of novel disease-modifying treatments such as transthyretin stabilizers (diflunisal, tafamidis) and RNA interference agents (patisiran, inotersen) on OH.

Epidemiology of OH in hereditary TTR amyloidosis

Although the first patients reported in 1952 by Corino de Andrade [8] did have gastrointestinal abnormalities and genitourinary disturbances, OH was not specifically mentioned. To our knowledge, the first description of OH in patients with hereditary amyloidosis polyneuropathy was published in 1968 by Araki and colleagues in Japan [9].

The estimated prevalence of OH in patients with hereditary transthyretin amyloidosis is 40–60% [46, 80, 108]. It is frequent, early and severe in patients with the Val30Met mutation and early-onset disease but appears to be less severe in Val30Met cases with late-onset disease [70–72, 74, 108, 138]. OH is also prevalent and severe in patients with some non-Val30Met mutations [12, 15, 20, 24, 25, 27, 49, 53, 57, 60, 69, 73, 78, 79, 95, 96, 113, 115, 119, 136, 137, 142, 145]. For instance, up to 100% of patients with the Ala97Ser mutation have OH, with 71% having frequent syncope, particularly in late stages of the disease [58].

Conversely, OH appears to be infrequent in patients with *TTR* mutations with high prevalence in Scandinavian countries (e.g., Ala45Ser, Tyr69His, Leu111Met) [127], and in patients with the Val122Ile mutation, the most common *TTR* mutation in African Americans [114].

In a recent study involving > 3000 subjects enrolled in the multinational, longitudinal, observational Transthyretin Amyloidosis Outcomes Survey (THAOS), 58.7% had symptomatic OH [46]. Moreover, the severity of the fall in BP when standing appeared to worsen at annual follow-ups, reflecting the progressive nature of autonomic failure. More pronounced orthostatic BP reductions were associated with increasing age, worse polyneuropathy disability (mPND) stage and diarrhea [46].

Pathophysiology of OH in hereditary TTR amyloidosis

OH in patients with hereditary transthyretin amyloidosis who do not have heart failure, volume depletion (frequently caused by diarrhea) or drug effects is usually neurogenic, i.e., caused by impaired norepinephrine release from sympathetic postganglionic neurons, because of neuronal amyloid fibril deposition. This has been documented by neuropathology, neuroimaging and measurements of the plasma concentration of catecholamines.

Autopsy studies in patients with hereditary transthyretin amyloidosis and severe OH showed amyloid-related degeneration of the peripheral autonomic nervous system, namely, anterior and posterior roots of the spinal cord,

sympathetic ganglia, postganglionic sympathetic nerves and the vagus nerve. Neuronal density in the intermediolateral column of the spinal cord was reduced, and there was degeneration of sympathetic postganglionic cholinergic fibers. The brain was consistently unaffected [10, 24, 33, 83, 96, 101, 113, 119, 132, 143].

Studies with ^{123}I-metaiodobenzyiguanidine (MIBG) cardiac neuroimaging showed reduced cardiac sympathetic innervation [34, 56, 97, 134], which can be present before any abnormal echocardiographic sign. Moreover, cardiac sympathetic denervation predicts worse prognosis [3, 31, 55, 120].

Plasma levels of norepinephrine, the main sympathetic neurotransmitter, are severely reduced and fail to increase when standing in patients with hereditary transthyretin amyloidosis. Moreover, administration of norepinephrine elicits noteworthy increases in heart rate and blood pressure, indicating sympathetic denervation supersenstivity [43, 128, 137, 144].

The mechanisms of neurogenic OH in hereditary transthyretin amyloidosis are similar to those of peripheral neurodegenerative synucleinopathies, i.e., Parkinson disease, dementia with Lewy bodies and pure autonomic failure, in which dysfunction of the sympathetic nerves is mediated by accumulation of another misfolded protein, α-synuclein, highlighting the high affinity that both misfolded transthyretin and α-synuclein have for the autonomic nervous system [104].

Approach to the patient with hereditary TTR amyloidosis and neurogenic OH

Neurogenic OH can be symptomatic or asymptomatic. Typical symptoms of neurogenic OH are lightheadedness, dizziness, blurry vision and, when the fall in BP is pronounced, loss of consciousness and postural tone (syncope). Symptoms occur predominantly when standing, less frequently when sitting and always abate when lying down. Patients with nOH may also complain of generalized weakness, fatigue, leg buckling, occipital headache, neck and shoulder ("coat hanger") discomfort, and shortness of breath due to ventilation/perfusion mismatch in the apical lung areas.

Patients with chronic nOH due to neurologic disorders usually tolerate very low BPs with only mild or no symptoms at all but syncope can occur with added orthostatic stressors (e.g., large carbohydrate-rich meals, alcohol intake, very warm weather, dehydration and antihypertensive treatment).

The morning hours tend to be most difficult as symptoms of nOH are aggravated by intravascular volume loss overnight [11]. Meals, particularly carbohydrate-rich, lead to splanchnic vasodilatation and post-prandial hypotension (i.e., fall in blood pressure within 2 h of eating) [118]. Physical inactivity and prolonged bed rest are common in patients with nOH. This leads to cardiovascular deconditioning further worsening the fall in BP and increasing symptoms leading to a vicious cycle.

In addition to nOH, other manifestations of autonomic failure in hereditary transthyretin amyloidosis include erectile dysfunction (ED), particularly in patients with early-onset of the disease (i.e., < 50 years old). The treatment of ED is challenging, as the use of sildenafil and other phosphodiesterase inhibitors may unmask or aggravate nOH. A good strategy is to screen for OH in all male patients with hereditary transthyretin amyloidosis before recommending sildenafil. Ideally, sildenafil should be administered at the office to determine its actual impact on blood pressure. For patients with severe nOH and ED, alternative treatments such as vacuum pumps and intracavernosal and intraurethral devices with or without prostaglandin E1 (PGE1) may be considered instead.

Moderate-severe cardiomyopathy can affect some patients with hereditary transthyretin amyloidosis. Cardiac failure in patients with OH can prevent the heart from pumping efficiently or rapidly enough to compensate for the fall in BP when standing, aggravating the orthostatic fall and potentially resulting in syncope. In these circumstances, treatment of heart failure with diuretics can further aggravate OH. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and beta-blockers have not been well studied in amyloidosis, although they may exacerbate OH. If reducing the preload is imperative, low doses at night are preferable [93].

Diagnosis of neurogenic OH

The diagnosis of OH requires BP readings while supine and upright, either during active standing or during a tilt-table test, to determine the presence of a sustained orthostatic fall of at least 20 mmHg systolic or 10 mmHg diastolic BP. BP and heart rate should be measured after the patient has been supine for at least 5 min and after standing still (or passively tilted) for 1–3 min (Fig. 1).

The changes in heart rate on standing help to determine whether the OH is neurogenic in origin. In patients with nOH, reduced sympathetic innervation causes the heart rate to increase much less than expected considering the magnitude of the BP fall [41, 102]. Therefore, a blunted heart rate increase during hypotension suggests a neurogenic cause. A ratio between the increase in heart rate and fall in systolic BP upon standing or head-up tilt (ΔHR/ΔSBP ratio) < 0.5 bpm/mmHg is diagnostic of nOH [100]. Conversely, a ΔHR/ΔSBP ratio ≥ 0.5 suggests a non-neurogenic cause.

Ascertaining the diagnosis of nOH may require autonomic testing including the BP response to the Valsalva

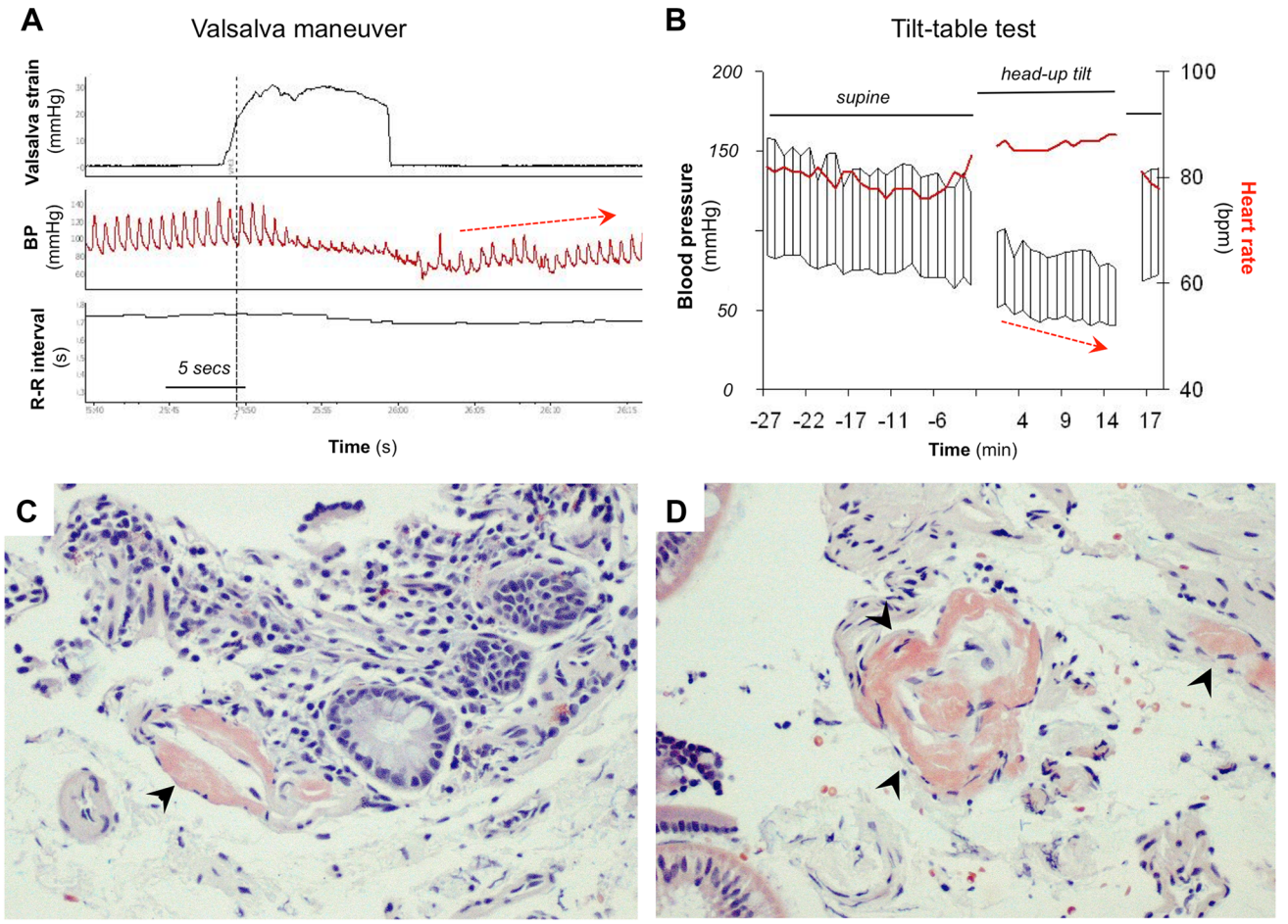

Fig. 1 Cardiovascular autonomic testing and gastrointestinal biopsy in a patient with acquired amyloid polyneuropathy after domino liver transplant. **a**–**d** Representative test results of a 76-year-old female who, as a result of autoimmune liver failure, had a liver transplant at age 55 years. She suffered a liver transplant rejection and required a second liver transplant at age 69. The liver she received was from a donor with hereditary transthyretin amyloidosis (Val71Ala mutation), who had recently died after several years of severe sensory and autonomic neuropathy (i.e., domino liver transplant). Approximately 1 year after receiving the second liver transplant, the patient developed severe diarrhea, exercise intolerance and painful tingling in the feet. Two years after the liver transplant her tingling had worsened significantly and she developed dry mouth and neurogenic bladder. At age 75 she developed severe weight loss (15–20 lb), recurrent orthostatic dizziness and lightheadedness and suffered frequent episodes of loss of consciousness upon standing. She became wheelchair bound at age 76. **a** Cardiovascular autonomic testing showing absent blood pressure overshoot after release of the Valsalva strain (dashed arrow), indicating impaired baroreflex-mediated sympathetic activation. **b** Tilt-table test showing a supine blood pressure of 133/70 mmHg with a heart rate of 79 bpm. After 15 min of head-up tilt, her blood pressure had fallen to 76/40 mmHg and her heart rate was 88 bpm, consistent with severe neurogenic orthostatic hypotension. To confirm that her sensory and autonomic neuropathy was caused by amyloid, she underwent a upper gastrointestinal endoscopy and biopsies from the stomach and duodenum were obtained. **c** and **d** Congo red stain in upper gastrointestinal tissue showing abundant amyloid deposition in the muscularis mucosae (arrows)

maneuver and plasma norepinephrine levels while supine and standing [6, 72, 73]. During the Valsalva maneuver, patients with nOH fail to show the classical BP "overshoot" after release of the strain (phase IV) (Fig. 1). An increase in plasma norepinephrine after 5–10 min of standing below 100% suggests defective baroreflex-mediated sympathetic activation and a diagnosis of nOH.

Ambulatory BP monitoring (ABPM) can help in the diagnosis and management of nOH [99]. Affected patients typically have a reversal of the normal circadian blood pressure pattern with higher BP during the night when the patient is supine in bed than during the day (i.e., non-dipping BP) [5, 22]. Nocturnal supine hypertension causes pressure natriuresis with exaggerated sodium and water loss causing overnight depletion of intravascular volume, worsening OH in the morning. ABPM and a detailed diary of activities are also useful to specifically tailor the use of short-acting pressor agents only at times when OH is severe in patients that may remain seated for long periods of the day or are wheelchair-bound.

Management of neurogenic OH in hereditary TTR amyloidosis

The goal of treatment of nOH in patients with hereditary transthyretin amyloidosis is not to normalize standing BP, but to reduce symptom burden, improve quality of life and reduce the morbidity and mortality associated with nOH. Cardiomyopathy and heart failure are present in many patients. This can complicate the management of nOH, as treatment of heart failure typically involves reducing the cardiac preload with diuretics causing intravascular volume depletion and worsening nOH. Similarly, diarrhea, a manifestation of gastrointestinal involvement in hereditary tranthyretin amyloidosis, causes volume depletion, which aggravates nOH.

Consensus guidelines for the treatment of nOH are available [44, 77]. The steps of nOH management include: (1) correcting aggravating factors, (2) implementing non-pharmacologic measures and (3) drug therapies. When nOH is asymptomatic, treatment may not be required or may be limited to non-pharmacologic measures. When nOH is symptomatic, pharmacologic treatment is usually required.

Correction of aggravating factors

Drugs that reduce intravascular volume (diuretics), induce vasodilatation (sildenafil, nitrates) or block norepinephrine release/activity at the neurovascular junction (α-blockers, centrally acting α_2-agonists, tricyclic antidepressants) worsen nOH and symptoms.

Normocytic and normochromic anemia with low erythropoietin levels is present in ~ 25% of patients with hereditary transthyretin amyloidosis [14]. Anemia can worsen nOH and should be investigated and treated [19]. Correction of anemia with erythropoietin (25–50 units/kg, subcutaneous, 3 times a week) and iron supplements may be beneficial in patients with nOH [14, 106].

Non-pharmacologic treatment and patient education

Patients should be aware of the diuretic effects of caffeine and alcohol and avoid sugary beverages (e.g., bottled juices, sodas) because of the the hypotensive effects of high-glycemic index carbohydrates [118]. Fluid intake should be 2–2.5 l/day. Patients should be encouraged to increase salt intake by adding 1–2 teaspoons of salt to a healthy diet. Other patients prefer using 0.5–1.0 g salt tablets although they can cause abdominal discomfort. In patients with nOH, drinking 0.5 l of water produces a marked increase in BP [88]. This can be used as a rescue measure since the pressor effect is quick (peaks in around 30 min) although short-lived.

Symptomatic nOH can quickly lead to an unwillingness to stand up and avoidance of physical activity. In turn, physical immobility worsens OH, leading to a "vicious cycle" of deconditioning [41]. Physical exercise is therefore a key component of the therapeutic regimen, but because physical activity in the standing position can worsen nOH in patients with hereditary transthyretin amyloidosis [81, 110, 122–124], exercise should be performed in the recumbent or sitting position using a recumbent stationary bicycle or rowing machine. The exception is exercise in a pool as the hydrostatic pressure of water allows upright exercise without hypotension [111]. Patients should be taught specific physical countermaneuvers [140]. Eating results in blood pooling within the splanchnic circulation, and patients can become severely hypotensive within 2 h of eating (i.e., postprandial hypotension), particularly after carbohydrate-rich meals [42, 62, 75, 105]. Eating smaller, more frequent meals and reducing carbohydrates can improve postprandial hypotension. Alcohol is also a vasodilator and should be reserved for the evening, prior to going to bed.

High-waist compression stockings producing at least 15–20 mmHg of pressure can increase BP by augmenting venous return [36]. Patients with painful neuropathy struggle to wear the stockings, which limits their usefulness in everyday life. Elastic abdominal binders are a good alternative [40, 121].

Pharmacologic management

Even after non-pharmacologic methods have been properly implemented, many patients still require pharmacologic treatment to improve symptomatic nOH. Two complementary strategies are commonly used: (1) expanding intravascular volume with fludrocortisone and (2) increasing peripheral vascular resistance with midodrine or droxidopa. Selection of one or the other or both depends on the specific features and needs of each patient as well as the degree of peripheral sympathetic denervation.

Fludrocortisone

Fludrocortisone (9α-fluorocortisol) is a synthetic mineralocorticoid that increases BP by at least two mechanisms: it increases renal sodium and water re-absorption, thus expanding intravascular volume, and also enhances the pressor responsiveness to endogenous catecholamine and pressor drugs [26]. Fludrocortisone is extensively used in patients with nOH [103, 104]. There are no specific controlled studies of fludrocortisone for nOH in patients with hereditary transthyretin amyloidosis although its use has been anecdotally described [20, 89, 109]. Fludrocortisone

exacerbates supine hypertension and target organ damage (left ventricular hypertrophy and renal failure) and may increase the risk of all-cause hospitalization [50]. It should be used with extreme caution—or not at all—in patients with amyloid cardiomyopathy [39]. Additional, frequent adverse events include hypokalemia and ankle edema [26, 98]. To reduce the risk of hypokalemia, patients taking fludrocortisone should be instructed to eat potassium-rich foods or potassium chloride supplements 10–20 mEq/day. Fludrocortisone dosage should not exceed 0.2 mg/day. Higher dosages are rarely more effective but intensify adverse events. Appreciable clinical improvements usually require ~ 7 days of treatment.

Midodrine

Midodrine is an oral α_1-adrenoreceptor agonist that induces vasoconstriction and increases BP [61, 84, 125, 141]. Midodrine is extensively used in patients with nOH [103, 104]. There are no specific controlled studies of midodrine for nOH in patients with hereditary transthyretin amyloidosis although its use has been anecdotally described [82, 89, 109, 112]. Midodrine raises BP in the standing, sitting and supine positions and its pressor effect is noticeable ~ 30–45 min after consumption, reaching a maximum after ~ 1 h, and persists for a total of 2–3 h. Treatment should begin with a 2.5 or 5 mg dose, which can then be increased up to 10 mg to be taken up to three times a day. Supine hypertension is common; hence, patients should not take midodrine < 3–4 h before bedtime. Other adverse events owing to activation of α1-adrenergic receptors are piloerection ("goosebumps"), itching of the scalp and urinary retention. Midodrine has no effect on heart rate as it does not activate β-adrenoreceptors and, given its poor diffusion across the blood-brain barrier, has no CNS adverse effects [91].

Droxidopa (Northera)

Droxidopa (L-threo-3,4-dihydroxyphenyl-serine, L-DOPS) is an oral synthetic amino acid that, once absorbed, is converted to norepinephrine by the enzyme aromatic amino-acid decarboxylase (AAAD) [68]. Early studies in Japan showed that droxidopa increased norepinephrine levels and blood pressure when standing and improved orthostatic tolerance in patients with nOH caused by hereditary transthyretin amyloidosis [7, 129–131]. Consequently, droxidopa was specifically approved in Japan in 1989 for the treatment of nOH in hereditary amyloidosis as well as Parkinson disease and multiple system atrophy. In the US, the Food and Drug Administration (FDA) approved droxidopa in 2014 for the treatment of symptomatic nOH associated with Parkinson disease, multiple system atrophy, pure autonomic failure and non-diabetic autonomic neuropathy, which includes hereditary transthyretin amyloidosis among other causes of autonomic neuropathy [38, 54, 64–66]. Droxidopa is not approved in Europe.

Extensive clinical experience shows that droxidopa is safe and well tolerated [28, 47, 48, 51, 52, 63, 76, 92, 139], even in severely ill patients [90]. Peak plasma concentrations of droxidopa are reached ~ 3 h after oral administration. The dosage used in clinical trials was 100–600 mg three times/day, although clinical experience indicates that the dosage should be tailored to each patient's needs considering the periods of time when he/she is going to be active or inactive [47, 51, 68]. Because the pressor effect of droxidopa varies among patients, a titration procedure supervised by a clinician is highly recommended [103]. ABPM is useful to evaluate the patient's BP profile before and after initiating treatment with droxidopa [67].

Effect of disease-modifying amyloidosis treatment on OH

Liver transplantation

Because the liver produces the vast majority of mutated transthyretin, orthotopic liver transplantation was widely used to stop the production of transthyretin for hereditary transthyretin amyloidosis before the availability of transthyretin stabilizers (diflunisal, tafamidis) and RNA interference agents (patisiran, inotersen). Longitudinal evaluation of patients after transplantation showed that progression of autonomic neuropathy (i.e., cardiac sympathetic denervation) was arrested, resulting in significant improvement in symptoms of nOH [4, 13, 17, 32, 35, 59, 117, 126].

TTR stabilizers

Diflunisal, a nonsteroidal anti-inflammatory drug available in most countries, is effective to stabilize circulating transthyretin tetramers, inhibiting the release of the transthyretin monomer required for amyloid deposition [94, 116]. A 2-year double-blind placebo-controlled trial showed that diflunisal reduced the rate of progression of neurologic impairment and preserved quality of life in patients with hereditary transthyretin amyloidosis [18]. The main outcome measure was the Neuropathy Impairment Score plus seven nerve tests (NIS + 7), which assesses motor and sensory signs, but does not include autonomic items. Secondary outcome measures included the Kumamoto score, a neurologic scale of motor, sensory and autonomic function [135]. However, changes in the autonomic domains were not specifically reported [18]. The effect of diflunisal on autonomic function was specifically evaluated in six patients with late-onset Val20Met variant showing complete abatement of symptoms of nOH,

accompanied by increased cardiac sympathetic innervation [133], suggesting that diflunisal might be useful to specifically slow the progression of autonomic neuropathy.

Tafamidis, a TTR stabilizer, was approved by the European Medicines Agency in 2012 and Japan in 2013 for the treatment of transthyretin amyloid polyneuropathy. The US FDA had not approved tafamidis at the time of publishing this article. The effects of tafamidis on nOH and other autonomic markers were not reported in the clinical trials studying its effects on neuropathy or cardiomyopathy [29, 30, 87]. In a study performed in 29 patients with late-onset Val20Met variant receiving tafamidis, [85], autonomic scores worsened in 6 (21%) with 2 patients developing OH [85]. Overall, the effect of tafamidis on nOH remains unclear.

RNA interference agents

Two phase-3 clinical trials with patisiran and inotersen, newly developed RNA-based antisense therapies approved by the US FDA and the European Medicines Agency in 2018, showed that blocking the production of transthyretin improves the polyneuropathy and quality of life of patients with hereditary transthyretin amyloidosis [1, 16]. Both trials used the modified NIS + 7 (mNIS + 7) as primary outcome measure. In contrast to the NIS + 7, the mNIS + 7 includes BP orthostatic measurements, although this contributes to only 2 out of 304 points of the total score. The patisiran trial reported significant improvements in the BP subcomponent of the mNIS + 7, although this was sparsely reported in a qualitative manner (range: 0–2, where 0 denotes no BP drop, 1 denotes a BP drop $\leq$ 30 mmHg, and 2 denotes a BP drop $\geq$ 30 mmHg) [1]. The inotersen trial did not report any information on BP changes [16]. A specific study on whether RNA interference agents abate the orthostatic drop in BP and improve symptoms of nOH in patients with hereditary transthyretin amyloidosis is warranted.

Conclusion

Orthostatic hypotension is a prominent and disabling manifestation of autonomic dysfunction in patients with hereditary transthyretin (TTR) amyloidosis affecting an estimated 40–60% of patients, reducing quality of life. Orthostatic hypotension in patients with hereditary transthyretin amyloidosis can be a consequence of heart failure due to amyloid cardiomyopathy or volume depletion due to diarrhea or drug effects. When none of these circumstances are apparent, orthostatic hypotension is usually neurogenic, i.e., caused by impaired norepinephrine release from sympathetic postganglionic neurons, because of neuronal amyloid fibril deposition. When recognized, orthostatic hypotension can be treated. Discontinuation of potentially causative/aggravating drugs, patient education and non-pharmacologic approaches are valuable and should be applied first. Droxidopa (Northera®), a synthetic norepinephrine precursor, has shown efficacy in controlled trials of neurogenic orthostatic hypotension in patients with hereditary TTR amyloidosis and is now approved in the US and Asia. Novel disease-modifying treatments such as transthyretin stabilizers (diflunisal, tafamidis) and RNA interference agents (patisiran, inotersen) may have an impact on the natural history of nOH in patients with hereditary TTR amyloidosis, although dedicated studies are yet to be performed.

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Compliance with ethical standards

Conflict of interest Dr. Kaufmann is Editor-in-Chief of Clinical Autonomic Research and has been advisory board member of Lundbeck. Dr. Palma is Managing Editor of Clinical Autonomic Research and has been advisory board member of Lundbeck. Dr. Gonzalez-Duarte was investigator in the tafamidis and patisiran clinical trials and has been advisory board member of Pfizer and Alnylam.

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