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COMMENTARY

Management of Neurogenic Orthostatic Hypotension in Neurodegenerative Disorders: A Collaboration Between Cardiology and Neurology

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ABSTRACT

Treatment of patients with α-synucleinopathies (e.g., Parkinson disease, multiple system atrophy, diffuse Lewy body disease) may require clinicians to manage both neurologic and cardiovascular issues due to autonomic dysfunction. In addition to the underlying neurodegenerative condition, patients often experience blood pressure dysregulation, such as neurogenic orthostatic hypotension (nOH) and/or supine hypertension. This commentary details the collaborative care between a cardiologist and neurologist to effectively manage medically complex patients with nOH by illustrating the case of a 76-year-old man with a history of multiple system atrophy who experienced recurrent syncope when standing or sitting and falls with loss of consciousness. The patient could walk only a few steps before experiencing a substantial drop in systolic blood pressure (100 mmHg). He also had features of profound parkinsonism (e.g., tremor, facial masking) that required treatment with levodopa, but orthostatic symptoms related to the blood pressure drop needed improvement first. The neurologist and cardiologist collaborated to diagnose nOH and initiate droxidopa treatment, which led to resolution of syncope, control of orthostatic symptoms, and improvement of orthostatic blood pressure. Considerations in the collaborative care of patients with nOH are outlined, including screening protocols, treatment goals and options, mitigation of supine hypertension risk (a condition that frequently coexists with nOH), and management of other comorbidities. In conclusion, collaboration between neurologists and cardiologists is an efficient method to improve outcomes for patients with nOH because this care model allows specialist providers to leverage their areas of expertise to manage the wide spectrum of clinical features associated with nOH. Further, communication and cooperation of the patient care team can lead to reduced patient morbidity, optimal relief of nOH symptoms, improvements in activities of daily living and quality of life, and decreased caregiver burden.

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PLAIN LANGUAGE SUMMARY

People with nervous system disorders such as Parkinson disease, multiple system atrophy, or diffuse Lewy body dementia often experience neurogenic orthostatic hypotension (nOH). nOH occurs when blood pressure becomes too low when a person stands up after lying down or sitting, which can cause weakness, loss of consciousness, and falls. Other common symptoms of nOH include lightheadedness, fainting/feeling faint, trouble thinking clearly, pain in the neck and shoulders ("coat hanger" pain), and feeling tired. People with nOH are at risk of incurring injuries from a fall. A neurologist or cardiologist can identify if a person has nOH by asking about symptoms and measuring the person's blood pressure when lying down and after standing. They may also ask the patient to keep a diary of blood pressure measurements taken at home. When a patient's neurologist and cardiologist work together as a team, they can ensure that nOH is treated safely and effectively, and patients may find their nOH symptoms are better managed. nOH can be treated with lifestyle changes such as drinking more water, eating more salty food, or gentle exercises. If needed, healthcare providers can prescribe medications to treat nOH.

Keywords: Autonomic failure; Blood pressure; Cardiovascular; Collaborative care; Comorbidities; Droxidopa; Parkinsonism; Multiple system atrophy; Supine hypertension

Key Summary Points

Patients with α-synucleinopathies (e.g., multiple system atrophy, Parkinson disease, diffuse Lewy body dementia) often present with both neurologic and cardiovascular issues resulting from the autonomic dysfunction, including neurogenic orthostatic hypotension (nOH).

The benefits of management of nOH by collaboration between a neurologist and a cardiologist are illustrated in a case study of a patient with multiple system atrophy and recurrent syncope due to nOH.

By working together, the neurologist and cardiologist were able to resolve the patient's syncope and stabilize orthostatic blood pressure by treatment with droxidopa, which then allowed the patient's parkinsonism symptoms to be treated with dopaminergic medications that have hypotensive effects.

Collaboration between neurologists and cardiologists allows these specialists to leverage their areas of expertise, optimize efficiency, and improve clinical outcomes for patients with nOH.

DIGITAL FEATURES

This article is published with digital features, including a video abstract and plain language summary, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14958714.

INTRODUCTION

Neurogenic orthostatic hypotension (nOH) is a drop of systolic blood pressure (BP) by ≥ 20 mmHg or diastolic BP by ≥ 10 mmHg

on standing that often occurs in neurodegenerative diseases associated with α-synuclein accumulation, such as Parkinson disease (PD), multiple system atrophy, and pure autonomic failure [1–3]. Patients with nOH may experience lightheadedness, presyncope, syncope, falls, cognitive difficulties, neck pain (i.e., "coat hanger" pain), fatigue, or weakness [2, 3]. nOH may increase the risk of falls and fall-related injuries, leading to increased healthcare costs and negatively affecting activities of daily living and quality of life [4, 5]. In a recent survey, 87% of patients and 95% of caregivers stated that nOH negatively impacted patients' daily activities, with more than half of the patients reporting that nOH symptoms negatively affected their quality of life [5].

Despite the burdensome effects of nOH symptoms, patients with cardiovascular autonomic failure may be undertreated because of the coexistence of supine hypertension (SH), which has been shown to occur in up to 70% of patients [6]. Because of neurologic and cardiovascular involvement, a patient's initial contact with a medical specialist may be with either a neurologist or a cardiologist. However, the specialist being consulted may be challenged to comprehensively treat such patients because certain aspects may extend beyond their individual areas of expertise or comfort. A collaboration between specialties is critical for effective management of medically complex patients with nOH who need to have both neurologic and cardiovascular issues addressed. For these patients, a collaborative effort between neurologists and cardiologists should enable better management of the underlying neurodegenerative condition, BP dysregulation related to autonomic dysfunction (e.g., nOH, SH), and other cardiovascular comorbidities by leveraging each specialist's individual area of expertise to navigate complicated treatment decisions. To the best of our knowledge, there have been no reports that describe this type of multidisciplinary approach for comprehensive care of patients with nOH.

Here we describe the elements needed for successful collaboration between neurologists and cardiologists in the management of nOH in patients with autonomic dysfunction. A case study of a patient with multiple system atrophy and severe symptomatic nOH illustrates how a neurologist and a cardiologist effectively interacted in the evaluation, diagnosis, and management of this patient.

A COLLABORATIVE MANAGEMENT APPROACH TO TREATING nOH

A 76-year-old man under the care of a general neurologist for the treatment of multiple system atrophy (> 4-year history) was referred to a cardiologist because of recurrent syncope. Ten episodes of falling with loss of consciousness were reported in the past year. Syncope occurred when the patient was standing or sitting, but not in the supine position. The patient could walk for only a few seconds before his systolic BP dropped by 100 mmHg. He had not previously received a formal diagnosis of nOH. Increased salt intake and fludrocortisone (0.1 mg twice per day) did not improve these symptoms. Concomitant daily medications included lisinopril (10 mg), aspirin (81 mg), ranitidine (150 mg), and oral clonazepam (0.1 mg at night). The initial cardiovascular examination was unremarkable, and testing revealed a normal electrocardiogram and echocardiogram. A previous stress test showed no ischemia. During the examination, the patient had a supine BP of 116/82 mmHg, but a standing BP was not obtained because the patient could not stand for testing. A diagnosis of nOH was supported by patient-obtained data showing a > 60-mmHg BP drop on standing without a heart rate change. A neurologist (i.e., a movement disorder specialist) was consulted because the patient displayed features of profound parkinsonism (e.g., tremor and facial masking) that required treatment (Fig. 1). However, orthostatic symptoms were the chief complaint that needed to be stabilized before treating his parkinsonism. Specifically, the patient's motor symptoms could not be treated with levodopa (L-DOPA) until the orthostatic symptoms (i.e., BP) were stabilized because of the hypotensive effects of L-DOPA. The specialists collaboratively decided to initiate droxidopa for symptomatic nOH. Droxidopa was

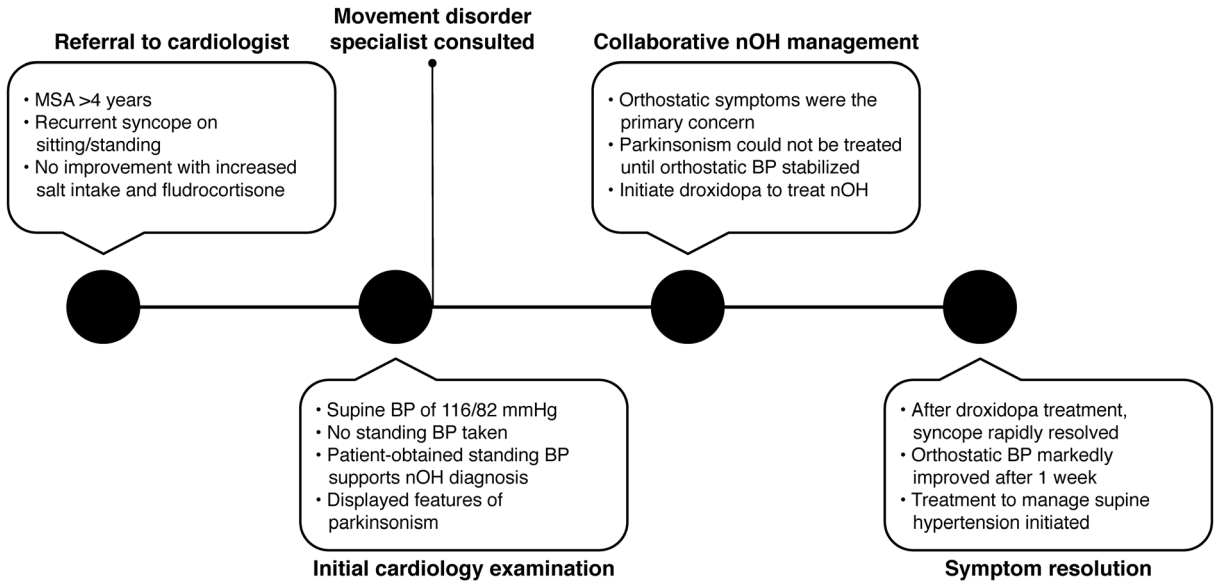

Fig. 1 Case decision timeline in the collaborative management of nOH in a patient with autonomic dysfunction. *BP* blood pressure, *MSA* multiple system atrophy, *nOH* neurogenic orthostatic hypotension

started at a 100-mg dose 3 times per day, which was titrated every 2 days to optimal symptom control with a daily dose of 900 mg. Syncope rapidly resolved after treatment initiation, and orthostatic BP markedly improved at 1 week. To manage nocturnal SH and avoid worsening of nOH symptoms in the morning, the patient was switched from lisinopril to the shorter-acting antihypertensive captopril (12.5 mg at bedtime). The patient returned to the cardiologist 1 week after initiation of treatment to assess orthostatic BP and tolerability. Upon evaluation, the patient was able to stand with a < 20-mmHg drop in systolic BP. He has experienced no syncope since starting droxidopa.

KEY CLINICAL LESSONS AND MANAGEMENT CONSIDERATIONS FOR THE TREATMENT OF PATIENTS WITH nOH

Healthcare providers (HCPs) commonly seen by patients with nOH include general neurologists, movement disorder specialists, and cardiologists [5]. Patient presentation may differ depending on the HCP's specialty, which may hinder the diagnosis of nOH. In a neurology setting, patients with parkinsonian syndromes (particularly those characterized as synucleinopathies) are at high risk of developing nOH but may not typically present with symptoms of presyncope or syncope [7]. Furthermore, common nonspecific symptoms, such as fatigue, weakness, exertional intolerance, or sedation, may be overlooked, and orthostatic testing in patients with PD is not a routine practice. The confluence of these factors may often cause diagnosis of nOH to be missed until the patient experiences a poor clinical outcome (e.g., a fall or syncope). Thus, neurologists should regularly perform orthostatic BP screening in patients with parkinsonian syndromes; we recommend a similar schedule to that for cognitive examinations (i.e., twice per year; Table 1). Implementation of this screening protocol could ensure that a diagnosis of nOH is not overlooked and appropriate treatment is initiated before potentially devastating consequences occur, such as falls, syncopal events, or emergency department visits.

In a cardiology setting, patients may present with symptoms of dizziness, syncope, and falls, all symptoms thought to be related to arrhythmias or other cardiac dysfunction; consequently, diagnosis of nOH could be missed.

Table 1 Key clinical points and recommendations for collaborative management of nOH in patients with autonomic dysfunction

Key practice points	Recommendations
Patients with nOH may benefit from a collaboration between a neurologist and a cardiologist	Collaboration between a neurologist and a cardiologist to manage patients with autonomic dysfunction and nOH should be a coordinated effort
	Collaborative management of patients with nOH should allow the neurologist and cardiologist to leverage their areas of expertise
Orthostatic testing should be routine in patients with PD	Neurologists should perform orthostatic BP screening in patients with PD twice per year
Cardiologists should consider and evaluate possible noncardiac causes of syncope in certain patient populations	Cardiologists should evaluate patients with PD or similar disorders for nOH

BP blood pressure, *nOH* neurogenic orthostatic hypotension, *PD* Parkinson disease

When patients have comorbid PD or other neurodegenerative disorders, they should be evaluated for nOH by taking orthostatic vital signs (Table 1). If nOH is suspected but in-office orthostatic BP does not confirm the diagnosis of nOH, a formal tilt-table study or home BP monitoring should be considered [8].

The lack or delay of nOH diagnosis often leads to poor outcomes. A recent survey of patients and caregivers indicated that most patients with long-term nOH symptoms did not have a formal diagnosis of nOH [5]. Many patients did not mention their nOH symptoms to their HCPs unless the symptoms were severe, or they may have minimized or underreported symptoms because they were embarrassed or felt uncomfortable discussing their symptoms with their HCPs, making a diagnosis of nOH difficult [5]. In this same survey, of those patients with a formal diagnosis of nOH or orthostatic hypotension (OH), 43% reported seeing ≥ 3 HCPs before receiving a formal diagnosis, while 70% of those with a formal diagnosis of nOH believed that management of symptoms improved after being diagnosed [5]. Thus, better approaches to evaluating and diagnosing patients with nOH and coordinated efforts between the different specialties that routinely encounter these patients in their clinical practice are needed. In this case, not only was the patient's mobility significantly impaired because of the symptoms of nOH, the ability to treat his motor symptoms was limited because of the profound nOH and the hypotensive effects of L-DOPA. Therefore, it was necessary to stabilize his BP before treating his parkinsonism. The collaborative approach led to a rapid improvement in BP, thereby allowing for treatment of his parkinsonism.

TREATMENT OPTIONS FOR PATIENTS WITH nOH

Treatment goals for patients with nOH should be to alleviate symptoms and improve patient independence and quality of life; BP normalization should not be expected [3]. Initial approaches to treating symptoms of nOH typically include a medication review and discontinuation of medications that may exacerbate nOH and nonpharmacologic measures, such as increased salt and fluid intake, compression garments, sleeping in a head-up position, and gentle exercise performed supine or seated [3]. Patients with nOH should be encouraged to implement a recumbent exercise regimen even if they are unable to stand because improvement in the lower extremity musculature is a key (and often overlooked) component of

management. If these approaches do not work, pharmacologic treatments such as droxidopa, midodrine, or fludrocortisone are the next option.

We found that our patient experienced improved orthostatic BP and resolution of syncope after initiation of droxidopa treatment. Droxidopa, a norepinephrine prodrug, has been approved for the treatment of nOH in Japan since 1989 and in the USA since 2014 [9]. The US Food and Drug Administration approved droxidopa for the treatment of orthostatic dizziness in patients with symptomatic nOH [10] based on data from short-term clinical trials that showed droxidopa reduced patient-reported symptoms of dizziness and lightheadedness [11–13].

Midodrine is an α_1-adrenergic agonist prodrug approved for the treatment of symptomatic OH based on its ability to increase standing systolic BP [14]. In clinical trials, midodrine increased standing BP and was associated with some improvements in orthostatic symptoms [15, 16], but clinical benefit (e.g., improved ability to perform activities of daily living) has not been adequately proven [14]. Fludrocortisone is often used off-label for the treatment of OH/nOH because it increases fluid volume, although there is limited formal evidence to support its efficacy [3]. However, for the patient described in this case, midodrine in combination with fludrocortisone did not provide adequate symptom relief and was poorly tolerated because of substantially elevated supine BP (i.e., supine hypertension). Thus, the lack of tolerability of midodrine because of supine hypertension was the reason that midodrine was discontinued and droxidopa treatment was initiated.

Patients with nOH are at risk for SH because the underlying autonomic dysfunction causes loss of BP regulatory mechanisms, but pharmacologic treatments for nOH may also increase the risk of SH [17]. Clinicians can mitigate SH risks by initially considering the safety profile associated with individual medications and monitoring BP during titration and treatment periods. In a Bayesian meta-analysis and mixed treatment comparison, an increased risk of SH was associated with midodrine but not droxidopa [18]. Our approach to monitoring BP during treatment with droxidopa involves supine BP measurements at home (after 5 min of rest in a head-up tilt position) every 48 h during titration or when increasing dose. Measurements should be taken twice per week during early treatment at the maintenance dose and once per week after a stable dose has been reached. After a week of titration, additional in-office BP checks may be considered to evaluate tolerance and the development of SH. Severe SH (i.e., supine BP $\geq$ 180/100 mmHg) may require pharmacologic intervention with short-acting antihypertensive agents at bedtime (e.g., captopril, hydralazine, losartan, nitroglycerin patch) [3]. SH can be readily managed by either the neurologist or the collaborating cardiologist.

In addition to SH, neurologists can safely manage patients with other cardiovascular comorbidities, such as those who have a diagnosis of coronary artery disease with no stent or with a stent implanted in the distant past ($\geq$ 10 years) with no issues after implantation. Although the extent of management is dependent on the comfort level of the neurologist, the threshold for cardiology consultation should be low in these patients. Collaboration between the neurologist and cardiologist is warranted for patients with substantial cardiovascular morbidities (e.g., congestive heart failure, recent cardiac event or procedure [myocardial infarction or cardiac valve procedure in the past 2 years]) or who present with an unusual symptom profile, such as those occurring when patients are seated. Often these patients require continued management of their hypertension to reduce vascular risk. If the patient is receiving antihypertensive medications, the collaboration with the prescribing clinician (usually the primary care physician or cardiologist) to discuss dose modification (e.g., tapering, discontinuation) is advisable [3].

In conclusion, patients will benefit when neurologists and cardiologists collaborate to provide their expertise in managing PD and BP regulation in patients with nOH due to autonomic failure. When a patient's care team communicates and works together effectively, optimal relief of nOH symptoms can be

achieved. Although collaborative management may pose some minor challenges (e.g., time required to contact other physicians, time to write referrals), the overall value of a cooperative approach, including the reduction in patient morbidity and mortality, greatly outweighs any inconvenience. Further, the rapid integration of technology, such as electronic medical records and telemedicine, into clinical care may serve to facilitate efficiency and convenience in implementing a multidisciplinary approach for patient care, foster better collaboration between specialists, and lead to better patient outcomes. Based on our experience, we find that patients can efficiently achieve optimal relief of nOH symptoms when neurologists and cardiologists collaborate and leverage their areas of expertise.

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Compliance with Ethics Guidelines. Institutional review board approval was not required for this single-patient case study. The patient consent for publication of the case described in our manuscript was obtained verbally. A letter describing the process used to obtain patient consent has been provided to the journal. All patient information has been anonymized.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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