JACC: CASE REPORTS VOL. 3, NO. 8, 2021

CASE REPORT

ADVANCED

CLINICAL CASE

Dysautonomia Causing Severe Orthostatic Hypotension

An Important, Early Finding in Neurodegenerative Disorders

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ABSTRACT

Orthostatic hypotension is common and dangerous; it has neurogenic and nonneurogenic causes. We present the case of a 40-year-old man with severe neurogenic hypotension, caused by young-onset multiple system atrophy. In patients presenting with neurogenic orthostatic hypotension, underlying neurodegenerative diseases should always be considered. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1156–60) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION AND PHYSICAL EXAMINATION

A 40-year-old man was referred to the Barts Blood Pressure Clinic in February 2018 with variable blood pressure (BP) complicated by postural BP drops of up to 60/40 mm Hg with associated symptoms of presyncope and dizziness but no syncope/falls/injuries as a result. On detailed questioning, he reported numerous autonomic symptoms since 2012: orthostatic intolerance, erectile dysfunction, thermodysregulatory symptoms, cold hands and feet, anhidrosis, early satiety, constipation, and poor urinary stream. On initial examination, the lying BP was 182/111 mm Hg, and heart rate (HR) was 99 beats/min; on immediate standing, the BP dropped to 137/88 mm Hg, and the HR was 113 beats/min; and after 3 min of standing, BP was 122/79 mm Hg, and HR was 114 beats/min. The remainder of the cardiovascular examination findings were normal. Neurological examination findings were also normal.

LEARNING OBJECTIVES

- To recognize that OH is likely to present to cardiologists and is common, even in middle-age patients, and causes significant problems, contributing to increased mortality and morbidity.
- To understand that OH can be caused by neurodegenerative disorders and can be one of the initial presenting features.
- To appreciate that early detection of neurodegeneration is critical to allow patient access to specialized services and appropriate support.

MEDICAL HISTORY

Please refer to **Figure 1** (timeline).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 23, 2020; revised manuscript received March 2, 2021, accepted March 10, 2021.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.03.006

DIFFERENTIAL DIAGNOSIS

This patient presented with low-normal seated BP and recumbent hypertension associated with orthostatic hypotension and symptoms of autonomic dysfunction. At this the point, the differential diagnoses included causes of nonneurogenic orthostatic hypotension (OH) and neurogenic orthostatic hypotension (nOH) and allied causes of autonomic dysfunction (Table 1).

INVESTIGATIONS

The 24-h ambulatory blood pressure monitoring demonstrated a daytime mean of 122/81 mm Hg, with preserved nocturnal dipping to a mean of 105/74 mm Hg a numerous episodes of spontaneous daytime hypotension to a nadir of 86/66 mm Hg. Metabolic and endocrine causes of OH were excluded. Autonomic nervous system studies confirmed profound nOH, with a postural BP drop of 40/30 mm Hg without an increase in heart rate and findings indicative of pandysautonomia with both severe sympathetic and parasympathetic failure, consistent with an underlying neurodegenerative process (Figure 2).

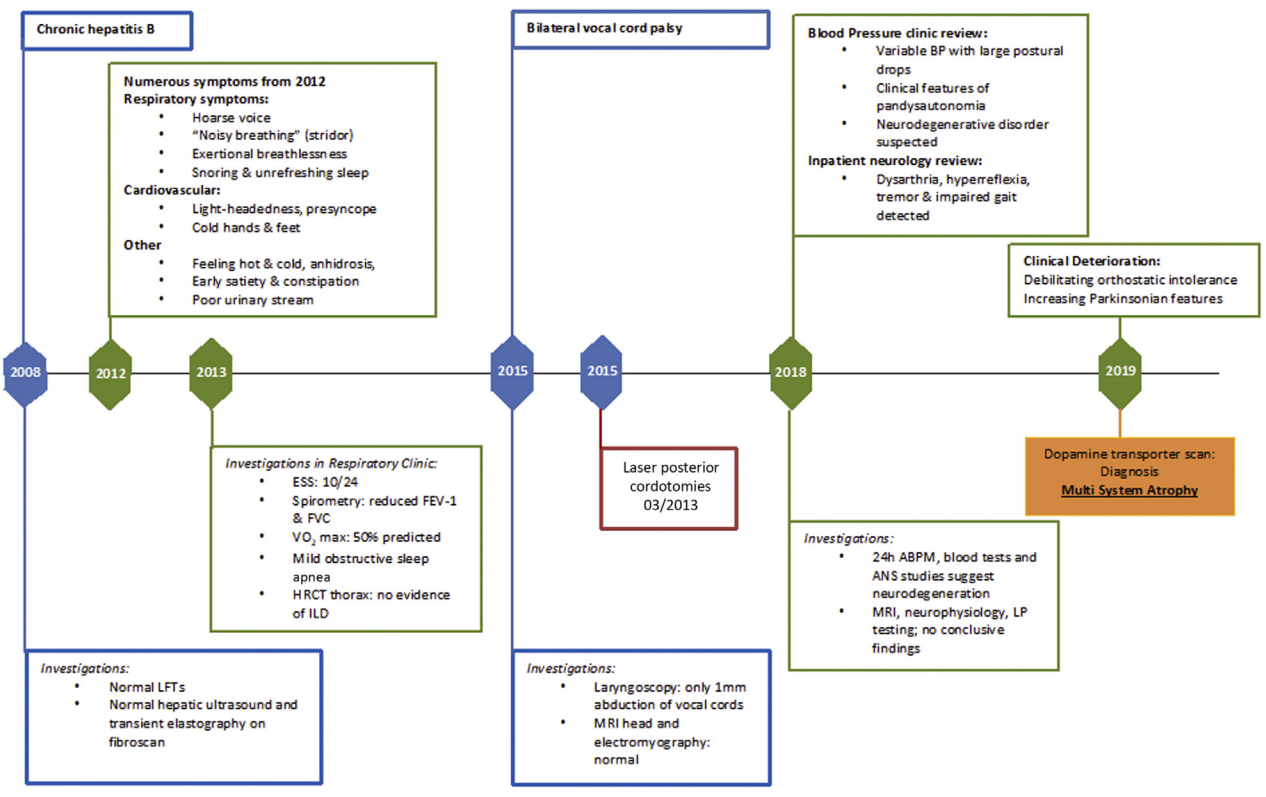
CLINICAL COURSE AND MANAGEMENT

At this stage, outpatient neurology review was arranged to consider a neurodegenerative cause (August 2018). Examination showed dysphonia and dysarthria, mildly unsteady gait, generalized hyperreflexia, and bilateral postural upper limb tremor, but there was no parkinsonism. Repeat magnetic resonance imaging of the brain and whole spine, neurophysiology (nerve conduction studies and electromyography), cerebrospinal fluid examination, and assessment for amyloidosis provided no diagnostic findings.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure
HR = heart rate
nOH = neurogenic orthostatic hypotension
MSA = multiple system atrophy
OH = orthostatic hypotension

FIGURE 1 Timeline of Clinical Course



ABPM = ambulatory blood pressure; ANS = autonomic nervous system; BP = blood pressure; ESS = Epworth Sleepiness Scale; FEV-1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRCT = high resolution computed tomography; ILD = interstitial lung disease; LFT = liver function test; LP = lumbar puncture; MRI = magnetic resonance imaging; V_{O_2} max = maximal oxygen uptake.

TABLE 1 Neurogenic and Other Causes of Orthostatic Hypotension and Causes of Autonomic Dysfunction

Causes of orthostatic hypotension
Neurogenic
Multisystem atrophy
Parkinson disease
Dementia with Lewy bodies
Pure autonomic failure
Dopamine beta-hydroxylase deficiency
Spinal cord damage or disease
Peripheral neuropathies (e.g., Guillain-Barré syndrome, diabetes mellitus, hereditary neuropathies)
Nonneurogenic
Hypovolemia (e.g., due to vomiting, diarrhea, blood loss, or reduced oral intake)
Heart failure
Venous pooling
Alcohol
Advancing age
Medications
Idiopathic
Cortisol deficiency
Causes of autonomic dysfunction
Toxins
Structural brain abnormality
Neurodegenerative disorder
Autoimmune disorder
Vasculitis
Amyloidosis
Sarcoidosis

By February 2019, the patient's gait had slowed considerably, and he exhibited reduced left arm swing on walking, left-sided extrapyramidal rigidity with cog wheeling, slightly stooped posture, and some bradykinesia suggestive of early parkinsonism. There was also unsteadiness on tandem gait, pyramidal signs (hyper-reflexia), and subtle dystonic posturing of fingers.

The clinical constellation of the marked dysautonomia (including an orthostatic BP drop of >30/15 mm Hg within 3 minutes of standing), parkinsonism, and cerebellar signs (dysarthria and gait unsteadiness), together with respiratory and ear, nose, and throat features (increased snoring, sleep apnea, stridor, and dysphonia from bilateral vocal cord palsy) and pyramidal signs (hyper-reflexia) fulfill the consensus criteria for probable multisystem atrophy (MSA). A dopamine transporter scan demonstrated loss of pre-synaptic dopaminergic terminals throughout the striata bilaterally, also confirming a neurodegenerative cause. The patient was diagnosed with young-onset MSA, for which management remains largely supportive. Treatment has included compression hosiery for postural hypotension (which offered minimal improvement) and volume expansion therapy with fludrocortisone has been commenced.

DISCUSSION

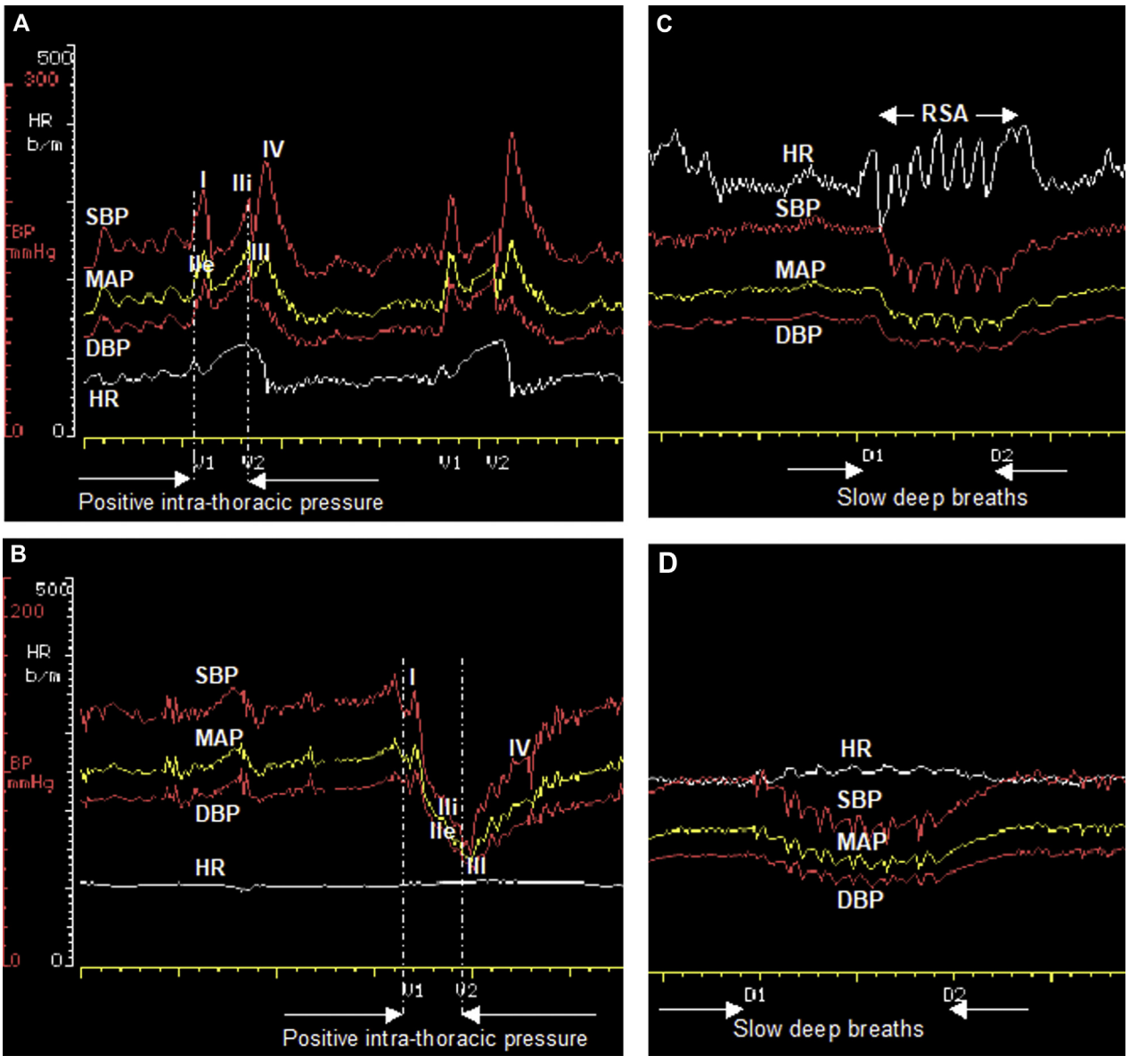
This patient was referred to the BP clinic because of severe OH but had a protracted illness over several years (**Figure 1**), and by the time of our first encounter, we also noted numerous clinical findings in keeping with pandysautonomia. Clinical consensus defines OH as a reduction of >20 mm Hg systolic or >10 mm Hg diastolic BP within 3 min of standing (1). Possible causes of OH (**Table 1**) include dehydration, blood loss, and antihypertensive medication use and are referred to as non-neurogenic OH. There is an important distinction between this and nOH, which is due to primary failure of vasoconstriction, an important feature of autonomic nervous system dysfunction that can commonly occur in Parkinson disease, MSA, and diabetes (2). Importantly, we excluded causes of non-neurogenic OH, and moreover, our patient demonstrated a recumbent to 3-minute standing ΔHR/Δsystolic BP ratio of 0.25 (<0.5 is diagnostic for nOH), and this is a validated bedside test with excellent sensitivity and specificity for a diagnosis of nOH (3).

Orthostatic hypotension is relatively uncommon in young people. Indeed, OH is far more prevalent in the elderly; this is due to a combination of natural physiological decline with advancing age and the increased prevalence of neurodegenerative diseases, which cause OH, in older people (4). However, OH can present in adults of all ages, and nOH is now recognized as a proven biomarker of central nervous system α-synucleinopathies responsible for disorders such as pure autonomic failure, Parkinson disease, and MSA (5,6).

OH can present with a myriad of posture-dependent symptoms ranging from light-headedness, vertigo, and syncope to headache and visual problems. Patients with OH are at greatly increased risk of recurrent falls, with resultant high burden and enormous costs to health care services due to consequences such as fractures and head injury (7). In addition, OH increases all-cause mortality (compared to patients without OH) even after adjustment for comorbidities, and a meta-analysis of 13 studies found OH to increase all-cause mortality by 1.5 times (8,9). The mortality risk is further increased in patients with neurodegenerative diseases, particularly in patients with MSA (1).

Currently, recommendations for non-pharmacological measures to treat nOH include

FIGURE 2 **Autonomic Function Testing of Cardiovascular Regulation**



(A) BP response during Valsalva maneuver (V_1 to V_2) in a healthy patient. **(B)** Vasoconstrictor failure during Valsalva maneuver (V_1 to V_2) in our patient showing progressive BP decline during phase II and failure to exceed the baseline value during phase IV. This pattern indicates a failure of sympathetically mediated vasoconstriction in response to decreased cardiac filling. **(C)** Respiratory sinus arrhythmia during slow deep breathing in a healthy individual. Heart rate increase/decrease with inspiration/expiration is modulated by changes in parasympathetic nervous system activity. **(D)** Loss of respiratory sinus arrhythmia in our patient due to parasympathetic dysautonomia. DBP = diastolic blood pressure; HR = heart rate; MAP = mean arterial pressure; RSA = respiratory sinus arrhythmia; SBP = systolic blood pressure.

physical countermaneuvers, compression hosiery, and increased salt and water ingestion (2). Following this, pharmacological agents such as fludrocortisone or midodrine have shown benefit, and newer pressor agents such as droxidopa and atomoxetine also appear promising (2). Unfortunately, the prognosis of nOH is far worse than that of non-neurogenic OH because of its underlying causes (10). Early identification of patients with neurogenic OH is desirable so that available support can be implemented, and this

will also enable disease-modifying medications to be commenced once available.

FOLLOW-UP

This patient is receiving regular follow-up appointments with the cardiology clinic as well as with neurology, speech therapy, and otorhinolaryngology specialists.

CONCLUSIONS

OH is a common, important, and dangerous problem. This case highlights the importance of clinicians being vigilant for possible symptoms and signs of neurodegenerative disorders in patients with nOH so that supportive management can be commenced as soon as possible for such conditions.

ACKNOWLEDGMENT

The authors thank the patient for kindly consenting to his case being written up for educational purposes.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Lobo has received honoraria from Medtronic, St Jude Medical, CVRx, and Kona Medical; and has served as a consultant to ROX Medical, ReCor Medical, Ablative Solutions, Vascular Dynamics, and Tarilian Laser Technologies. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS dysautonomia, neurodegeneration, orthostatic hypotension