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CASE REPORT
Arrhythmias/Electrophysiology

Neglected cause of recurrent syncope: a case report of neurogenic orthostatic hypotension

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Background Syncope commonly results in emergency room and physician visits, leading to hospitalization and invasive investigations. Up to 24% of these presentations may be caused by neurogenic orthostatic hypotension (nOH), which continues to be an under-recognized clinical entity. We review an approach to diagnosing nOH.

Case summary An 85-year-old man with a history of Parkinson's disease was referred for a history of recurrent syncope, which had resulted in extensive cardiac investigation. Collateral history revealed that the events were orthostatic in nature, but with variable time to onset of symptoms. The patient was found to have significant postural drop in blood pressure without compensatory tachycardia. Cardiovascular autonomic function testing was performed, which confirmed significant autonomic nervous system failure, including a marked hypotensive response on tilt-table testing and a lack of vasoconstriction during Valsalva manoeuvre. The patient was diagnosed with nOH and initiated on midodrine with subjective improvement in the frequency of syncope.

Discussion Autonomic nervous system failure, with nOH, is a common cause of recurrent syncope, particularly in older patients. Attention to detail during the medical history, including precipitating factors and the presence of prodromal symptoms prior to syncope, is critical for making the correct diagnosis. Measuring orthostatic vital signs correctly in patients with syncope provides valuable information, is cost-effective, and critical to diagnose nOH.

Keywords Syncope • Neurogenic orthostatic hypotension • Autonomic dysfunction • Case report

Learning points

- Neurogenic orthostatic hypotension (nOH) is a common cause of syncope, which requires an organized approach to history and physical examination to diagnose.
- Measuring orthostatic vital signs correctly in patients with syncope provides valuable information, is cost-effective, and critical to diagnose nOH.

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Introduction

Syncope commonly results in emergency room and doctors visits, leading to hospitalization and invasive investigation costing more than 2 billion dollars annually in the USA.[1] Up to 24% of these presentations may be caused by neurogenic orthostatic hypotension (nOH).[1] The incidence may be even higher in older patients and those with diabetes mellitus or Parkinson's disease (PD). This diagnosis is particularly important to make because syncope is associated with greater morbidity in older patients,[2] and nOH is associated with increased mortality in patients with PD.[3] Accurate diagnosis of nOH may decrease health care resource utilization, reduce unnecessary invasive investigations, and prevent morbidity associated with recurrent syncope.[4] However, accurate diagnosis requires an organized approach which could be applied to all patients with syncope. We review a case of recurrent syncope related to nOH to highlight important aspects of the syncope history and typical findings from cardiovascular autonomic testing.

Timeline

4 months prior	Presented to general practitioner with recurrent syncope, referred to cardiology
3 months prior	Seen by cardiologist, sent for echocardiogram and Holter monitor
2 weeks prior	Echocardiogram and Holter unremarkable, referred for implantable loop recorder
Clinic date	Seen in consultation prior to possible implantable loop recorder. Autonomic testing performed same day and diagnosed with neurogenic orthostatic hypotension. Started on midodrine
3 months later	Seen in follow-up. Patient's family reported decreased frequency of syncopal events

Case presentation

An 85-year old man was referred to the cardiac arrhythmia service for an implantable loop recorder to exclude arrhythmia as a cause of recurrent syncope. The patient had previously been seen in consultation regarding syncope by a general cardiologist, with no definitive diagnosis made. The patient's past medical history included a history of PD with cognitive impairment and labile hypertension. He had no prior history of coronary artery disease or cardiac arrhythmias. His only medication was levodopa/carbidopa.

Previous attempts at characterizing the patient's syncope had been limited by his cognitive impairment. However, a second history was taken in conjunction with the patient's family. Based on the family's recollection, the patient's syncope would only occur while standing. However, the timing between standing and his events were variable, often occurring after several minutes of standing. The presence of symptoms prior to events were unclear, but the family reported they could often tell before he was about to faint based on his appearance. The syncopal events were brief, typically lasting several seconds with rapid return of consciousness. The syncopal events were gradually increasing in frequency, and now occurred several times per day. Previous investigations, including a 24-h Holter monitor and echocardiogram, were unremarkable.

Given this history, there was a high clinical suspicion for nOH. Orthostatic vital signs were assessed, revealing a supine blood pressure of 150/80 mmHg and a heart rate of 70 b.p.m. After standing for 5 min, the patient's heart rate was still 70 b.p.m., but the blood pressure dropped to 90/50 mmHg. Although the patient did not report any symptoms, family members reported that the patient 'looked like he was about to faint'. Cardiovascular autonomic function testing was performed, which confirmed significant autonomic nervous system failure, including a marked hypotensive response on tilt-table testing and a lack of vasoconstriction during Valsalva manoeuvre, which are shown in *Figures 1* and *2*. Overall, the clinical presentation was characteristic of nOH [blood pressure drop of >20/10 mmHg (or >30/15 mmHg with baseline supine hypertension) with only a minimal or absent increase in heart rate].[5]

Although levodopa may be contributing to the patient's hypotension, it was required to manage his PD. Therefore, the patient was given a prescription for midodrine 5 mg PO q4H ×3 (with nominal dosing times of 8 a.m., noon, and 4 p.m.). The patient's family was directed to give midodrine prior to the patient's typical active periods to avoid exacerbating his supine hypertension. Additionally, the family was advised that they should help the patient to a supine position when he appeared similar to the event which was reproduced in clinic. This resulted in a subjective decrease in the frequency of syncope during follow-up.

Discussion

A complete history, physical examination, and 12-lead electrocardiogram are the only investigations for syncope given strong recommendations by guidelines.[6] The history should focus on predisposing situations, prodromal symptoms, physical signs, and recovery time and symptoms.[7] Unfortunately, this is often confounded by the presence of cognitive decline, which certainly played a role in the delayed diagnosis in our patient. Obtaining collateral information may provide incremental value by clarifying critical elements of the history. In the current era of ubiquitous smartphones, a bystander video of the spell can also be very helpful to the physician. Non-neurological causes of orthostatic hypotension should also be evaluated. These include dehydration, blood loss, and predisposing medications.[8] Sheldon *et al.*[9] showed that syncope after prolonged standing or sitting, recurrent headaches, presyncope with stress and fatigue during recovery were strongly associated with vasovagal syncope.

Physical examination also has a central role in evaluating patients with syncope. Intuitively, assessing orthostatic vital signs is critical to identify the postural hypotension characteristic of nOH. Orthostatic vital signs should be measured both after being supine for a few minutes and then for at least 5 min while standing, with frequent recordings of both blood pressure and heart rate.[8] In more frail

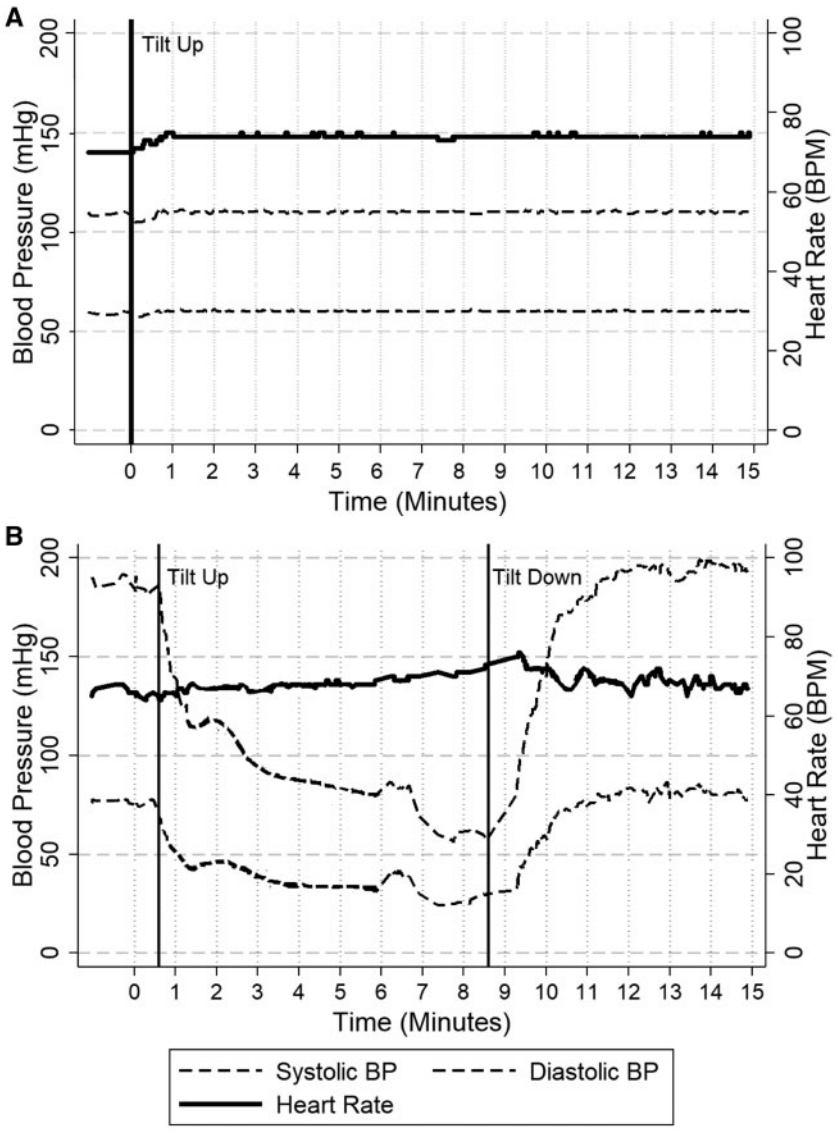

Figure 1 Tilt-table results. (*A*) Normal. (*B*) Patient's response. The patient had supine hypertension with an initial systolic blood pressure of 190 mmHg. Following the head-up-tilt to 80°, there was progressive hypotension without significant heart rate response. The patient's haemodynamics recovered shortly after reversing the tilt.

patients, sit-to-stand assessments of orthostatic vital signs may be more practical, while maintaining reasonable diagnostic accuracy.[10] When a sit-to-stand method is used blood pressure drops of ≥15/7 mmHg should be considered significant.[10] In elderly patients, orthostatic vital signs have a high diagnostic yield with almost no associated increase in health-care costs.[1] In comparison, cardiac enzymes cost an estimated $22 000 and echocardiography $6000 per test impacting diagnosis or treatment.[1] The physical examination may also identify underlying cardiac or neurological disorders which may suggest an alternate aetiology.

Cardiovascular autonomic testing is the gold standard for diagnosing nOH, with the head-up tilt and response to Valsalva manoeuvre being particularly useful clinically. These are sometimes only available at specialized autonomic testing centres. During head-up tilt, there is a decrease in venous return resulting in a drop in cardiac preload, which is sensed through mechanoreceptors in the heart,[11] and sometimes there is also a drop in arterial pressure, which is detected by baroreceptors in the carotid sinuses and aortic arch.[11] These changes trigger a reflex increase in sympathetic tone resulting in increased systemic vascular resistance, as well as compensatory tachycardia.[11] Typical findings of nOH on head-up tilt include rapid and sustained orthostatic hypotension (until the table is brought back to a horizontal position) and a lack of compensatory tachycardia. The Valsalva manoeuvre tests a complex relationship between afferent baroreflex sensing, and autonomic output, including cardiovagal, alpha-adrenergic, and beta-adrenergic receptor activation. The Valsalva manoeuvre is therefore

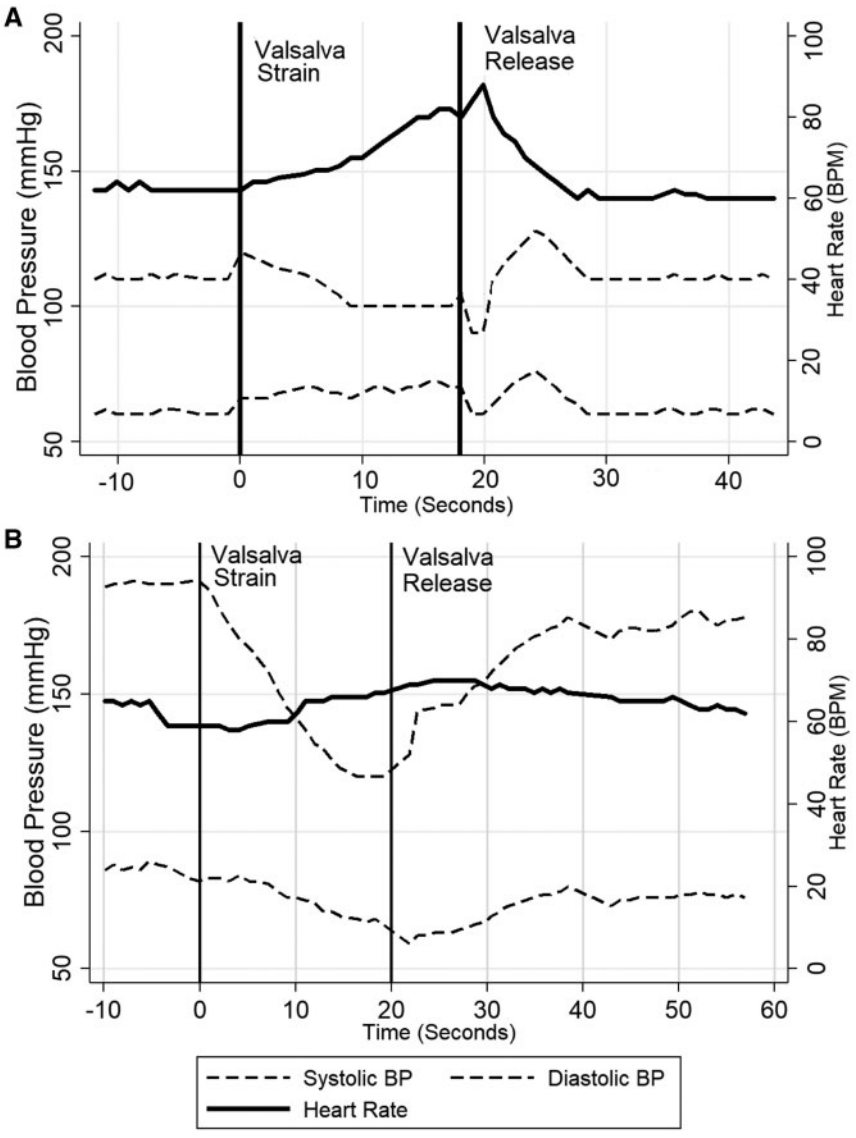

Figure 2 Valsalva results. (*A*) Normal. (*B*) Patient's response. During the strain phase of the Valsalva manoeuvre, there were significant drops in systolic and diastolic blood pressure with no significant change in heart rate.

sensitive for the presence of autonomic failure.[12] Patients with nOH typically display progressive hypotension during Phase II (sustained strain phase) of Valsalva without any recovery, and a slow return to baseline blood pressure during Phase IV (post-release phase), without a blood pressure overshoot.[12] Cold pressor response and response to isometric hand-grip, other methods of sympathetic nervous system activation, can also be assessed if clinical uncertainty remains. Given the discriminative ability of cardiovascular autonomic reflex testing, this may be particularly useful when the diagnosis of nOH is unclear or confounded by alternate aetiologies.

Conclusions

Autonomic nervous system failure, with nOH, is a common cause of recurrent syncope, particularly in older patients. Attention to detail during the medical history, including precipitating factors and the presence of prodromal symptoms prior to syncope, is critical for making the correct diagnosis. Measuring orthostatic vital signs correctly in patients with syncope provides valuable information, is cost-effective, and critical to diagnose nOH.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

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References

1. Mendu ML, McAvay G, Lampert R, Stoehr J, Tinetti ME. Yield of diagnostic tests in evaluating syncopal episodes in older patients. *Arch Int Med* 2009;**169**:1299–1305.
2. Shibao C, Grijalva CG, Raj SR, Biaggioni I, Griffin MR. Orthostatic hypotension-related hospitalizations in the United States. *Am J Med* 2007; **120**:975–980.
3. Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia. *PLoS One* 2012;**7**:e45451.
4. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic hypotension. *J Am Coll Cardiol* 2018;**72**:1294–1309.
5. Gibbons CH, Schmidt P, Biaggioni I, Frazier-Mills C, Freeman R, Isaacson S, Karabin B, Kuritzky L, Lew M, Low P, Mehdirad A, Raj SR, Vernino S, Kaufmann H. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. *J Neurol* 2017;**264**: 1567–1582.
6. Shen W-K, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, Grubb BP, Hamdan MH, Krahn AD, Link MS, Olshansky B, Raj SR, Sandhu RK, Sorajja D, Sun BC, Yancy CW. 2017 ACC/AHA/HRS Guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. *Circulation* 2017;**136**: e60–e122.
7. Sheldon RS, Grubb BP, Olshansky B, Shen W-K, Calkins H, Brignole M, Raj SR, Krahn AD, Morillo CA, Stewart JM, Sutton R, Sandroni P, Friday KJ, Hachul DT, Cohen MI, Lau DH, Mayuga KA, Moak JP, Sandhu RK, Kanjwal K. 2015 Heart Rhythm Society Expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm* 2015;**12**:e41–e63.
8. Nwazue VC, Raj SR. Confounders of vasovagal syncope: orthostatic hypotension. *Cardiol Clin* 2013;**31**:89–100.
9. Sheldon R, Hersi A, Ritchie D, Koshman M-L, Rose S. Syncope and structural heart disease: historical criteria for vasovagal syncope and ventricular tachycardia. *J Cardiovasc Electrophysiol* 2010;**21**:1358–1364.
10. Shaw BH, Garland EM, Black BK, Paranjape SY, Shibao CA, Okamoto LE, Gamboa A, Diedrich A, Plummer WD, Dupont WD, Biaggioni I, Robertson D, Raj SR. Optimal diagnostic thresholds for diagnosis of orthostatic hypotension with a 'sit-to-stand test'. *J Hypertens* 2017;**35**:1019–1025.
11. Grubb BP. Neurocardiogenic syncope and related disorders of orthostatic intolerance. *Circulation* 2005;**111**:2997–3006.
12. Goldstein DS, Sharabi Y. Neurogenic orthostatic hypotension: a pathophysiological approach. *Circ* 2009;**119**:139–146.