

Reflex Vasovagal Syncope in Ehlers-Danlos Syndrome

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Abstract

Ehlers–Danlos syndrome (EDS) is frequently associated with autonomic dysfunction, including postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension (OH). Overlapping phenotypes such as orthostatic hypotension–tachycardia syndrome (OHTS) may complicate diagnosis and management. We report two patients with EDS presenting with recurrent presyncope and palpitations. Diagnoses were confirmed with table tilt test. Pharmacological management was tailored for POTS and OHTS, low-dose beta-blockers improved POTS, whereas beta-blockers alone worsened OHTS, requiring adjunctive fludrocortisone. These cases highlight the heterogeneous autonomic phenotypes associated with EDS and underscore the diagnostic value of tilt-table testing. Accurate differentiation between POTS and mixed orthostatic syndromes is essential, as management strategies differ and inappropriate therapy may exacerbate symptoms.

Learning Objective

Recognize and suspect autonomic dysfunction in patients with Ehlers–Danlos syndrome (EDS). Common manifestations include orthostatic hypotension, with variants such as postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension–tachycardia syndrome (OHTS). These conditions may present with similar symptoms, including syncope, presyncope, and palpitations. Diagnosis is confirmed by head-up tilt-table testing. Management strategies differ for POTS and OHTS; therefore, accurate differentiation is essential to guide appropriate therapy.

Introduction

Ehlers-Danlos syndrome (EDS) is a collection of hereditary and heterogeneous connective tissue disorders with a prevalence of about 1 in 5000 people(1). Around 40% of EDS patients have autonomic dysregulation, with postural orthostatic tachycardia syndrome (POTS) and orthostatic hypotension (OH) being the most prevalent conditions associated(2). Some patients do exhibit overlapping features of tachycardia and hypotension on standing, referred to as orthostatic hypotension tachycardia syndrome (OHTS)(2). Patients often present with overlapping symptoms of palpitations and lightheadedness in these different diseases. Making an accurate and early diagnosis is crucial, as management strategies differ. Here we present a case series of 2 patients with EDS – one with classic POTS and the other with OHTS requiring individualized treatment approaches.

Case Presentation

Case 1

A 29-year-old woman with a known history of EDS presented with recurrent episodes of near-syncope and palpitations for two weeks. She reported a long-standing history of intermittent palpitations. Laboratory studies were overall unremarkable. Hemoglobin was 13.8 g/dL, with an MCV of 90 fL and an MCH of 29.4 pg, all within normal limits. Iron panel results were also normal, with a TIBC of 268, serum

iron of 74, and an iron saturation of 28%. Vitamin B12 was normal at 799. Thyroid studies showed a suppressed TSH of 0.164 with a normal free T4 of 0.96, total T3 of 105, and reverse T3 of 13.5, consistent with a euthyroid state. Morning cortisol (7.6) and ACTH (14.3) were within expected physiological ranges.

Initial 12-lead electrocardiograms (EKGs) and ambulatory heart rhythm monitoring using a loop recorder demonstrated a normal sinus rhythm. A stress echocardiogram was also normal. The patient was started on metoprolol succinate 50 mg twice daily; however, she developed worsening near-syncope, prompting discontinuation of beta-blocker therapy. She was subsequently referred for head-up tilt-table testing, which revealed sinus tachycardia with a heart-rate increase of greater than 30 beats per minute (bpm), significant hypotension, and reproducibility of symptoms—findings consistent with OHTS.

Treatment with fludrocortisone was initiated, followed by reintroduction of metoprolol succinate at a reduced dose of 25 mg daily after five days. She was also advised on non-pharmacologic measures, including increased oral fluid intake and the use of mid-thigh compression stockings. At her six-week follow-up visit, the patient reported marked improvement in presyncopal episodes and palpitations.

Case 2

A 43-year-old woman with a history of EDS presented with one month of recurrent near-syncope and palpitations. Laboratory studies were unremarkable overall. Hemoglobin was 13.7 g/dL and hematocrit was 40.8%, both within normal limits. Vitamin B12 was 238 with a normal methylmalonic acid level of 108, indicating adequate B12 status. Thyroid studies showed a TSH of 3.48 and a free T4 of 1.17, consistent with a euthyroid state. Thyroglobulin antibody was 1.6 and TPO antibody was elevated at 249, suggestive of underlying autoimmune thyroiditis. Initial evaluation showed sinus tachycardia on EKG while an ambulatory heart rhythm monitoring using a loop recorder demonstrated a normal sinus rhythm with few episodes of sinus tachycardia ranging from 110s to 140s, and stress echocardiogram was within normal limits. The patient was started on metoprolol succinate 50 mg daily; however, her symptoms persisted. A subsequent head-up tilt-table test demonstrated sinus tachycardia with a heart-rate increase of more than 30 bpm, without associated hypotension or symptom reproduction, consistent with POTS.

Therapy was adjusted to metoprolol succinate 25 mg daily, and she was counselled to maintain high fluid intake and gradual position changes. On follow-up, the patient reported notable symptomatic improvement and reduction in palpitations.

Discussion

Our case report highlights two patients with EDS who presented with recurrent presyncope and palpitations and were ultimately diagnosed with orthostatic intolerance syndromes—one with classic POTS and the other with OHTS. Both patients underwent comprehensive cardiac evaluation, including ECGs, electrophysiologic studies, and echocardiography, which were unrevealing. Definitive diagnoses

were established only after head-up tilt-table testing. The clinical improvement in POTS with beta blockers and non-pharmacologic measures, meanwhile, fludrocortisone along with low-dose beta blockers in OHTS. This illustrates the importance of recognizing and appropriately managing autonomic dysfunction in patients with EDS, as orthostatic syndromes are frequently underdiagnosed and may present with near-syncope, palpitations, or syncope, with management strategies differing between these two syndromes. Despite this, many EDS patients experience diagnostic delays or misattribution of symptoms to anxiety or deconditioning(3).

POTS is defined by a ≥ 30 bpm rise in heart rate without hypotension, while mixed patterns such as OHTS reflect excessive venous pooling and impaired autonomic compensation leading to tachycardia and/or hypotension(4). The pathophysiologic link is multifactorial and includes vascular connective tissue laxity, excessive venous pooling, and impaired autonomic compensation leading to tachycardia, hypotension, or both(5, 6). This venous pooling reduces effective circulating volume and triggers exaggerated autonomic responses (catecholamine surge and tachycardia) as the body attempts to maintain cerebral perfusion(7). Indeed, Rowe *et al.* first described an association between EDS and orthostatic intolerance in 1999, reporting a series of 12 young EDS patients with chronic fatigue in whom head-up tilt testing unmasked POTS as the cause of their symptoms(8). Since then, numerous studies have confirmed a high prevalence of POTS and related autonomic disorders in hypermobile EDS(6).

Management of orthostatic intolerance in EDS requires individualized, multimodal therapy, and current literature supports a combination of non-pharmacologic and pharmacologic strategies. First-line conservative measures—including liberal salt and fluid intake, compression garments, and gradual positional changes—are supported across multiple observational studies and expert reviews(5, 6, 9). Therapy is tailored to the predominant phenotype: fludrocortisone for hypovolemia, midodrine or droxidopa for hypotension-dominant orthostatic intolerance, and beta-blockers or ivabradine for tachycardia-predominant POTS(6, 10). Rowe and colleagues, as well as subsequent studies, have demonstrated symptomatic improvement in EDS-associated POTS with beta-blockers and mineralocorticoid therapy, though responses vary due to underlying connective tissue laxity and autonomic dysregulation(5, 6). Accurate differentiation between POTS, OH, and mixed OHTS presentations is essential, as inappropriate therapy—such as high-dose beta-blockers in hypotension-predominant patients—may worsen symptoms, as exemplified in our first case.

In conclusion, these two cases highlight the strong association between EDS and orthostatic intolerance, the diagnostic value of tilt-table testing, and the need for tailored therapeutic strategies. Early recognition is critical, as autonomic symptoms in EDS are frequently overlooked or mischaracterized. Our findings emphasize that clinicians should maintain a high index of suspicion for POTS, OH, and mixed orthostatic syndromes in patients with connective-tissue disorders. Timely diagnosis and individualized treatment can substantially improve quality of life and functional status in this unique patient population.

Abbreviations

EDS
Ehlers- Danlos Syndrome
EKG
Electrocardiogram
OH
Orthostatic Hypotension
OHTS
Orthostatic Hypotension Tachycardia Syndrome
POTS
Postural Orthostatic Tachycardia Syndrome

Declarations

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None

Conflict of Interest

None

Consent

Written informed consent was obtained from the patient

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