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CASE SERIES
Other

May-Thurner syndrome in patients with postural orthostatic tachycardia syndrome and Ehlers-Danlos syndrome: a case series

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Background Postural orthostatic tachycardia syndrome (POTS), Ehlers-Danlos syndrome (EDS), and May-Thurner syndrome (MTS) are three syndromes that are often misdiagnosed or underdiagnosed. The true prevalence of these syndromes may be higher than currently reported. The following case series is the first to report a three-way association between POTS, EDS, and MTS.

Case summary We describe three patients with concomitant POTS, EDS, and MTS. Although abdominopelvic vasculature evaluation can be difficult via conventional imaging techniques, we present the use of novel dynamic contrast-enhanced magnetic resonance angiography with Differential Subsampling with Cartesian Ordering (DISCO) and four-dimensional flow magnetic resonance imaging to aid vasculature evaluation and the diagnosis of MTS. Two patients underwent left common iliac vein stenting to treat MTS, experiencing significant improvement in their POTS symptoms and quality of life.

Discussion Ehlers-Danlos syndrome, POTS, and MTS may interact synergistically to exacerbate symptoms. Patients with EDS should be evaluated for possible POTS and pelvic venous complications. Left common iliac vein stenting for MTS can mitigate POTS symptoms by decreasing lower extremity venous pooling and should be considered in this patient population. Further research is needed to understand the exact mechanism and intricacies of this syndrome triad.

Keywords Case series • Dysautonomia • Postural orthostatic tachycardia syndrome • Ehlers-Danlos syndrome • May-Thurner syndrome • 4D flow MRI • Pelvic congestion syndrome

ESC Curriculum 7.4 Percutaneous cardiovascular post-procedure • 5.2 Transient loss of consciousness • 5.1 Palpitations • 2.1 Imaging modalities

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Learning points

- Patients with Ehlers-Danlos syndrome (EDS) often have postural orthostatic tachycardia syndrome (POTS). Patients with EDS and POTS presenting with pelvic pain and leg swelling should be evaluated for May-Thurner Syndrome.
- Dynamic contrast-enhanced magnetic resonance angiography with Differential Subsampling with Cartesian Ordering and four-dimensional flow magnetic resonance imaging are more accurate than conventional imaging techniques when evaluating pelvic vasculature.
- Left common iliac vein stenting should be considered in this patient population as it can significantly relieve POTS symptoms and improve quality of life.

Introduction

Postural orthostatic tachycardia syndrome (POTS) is a complex, often misunderstood form of orthostatic intolerance that disproportionately affects women.[1] It is classically defined as having chronic orthostatic intolerance and a ≥30 beats/min (BPM) increase in heart rate (HR) upon standing without orthostatic hypotension.[1] Symptoms can include lightheadedness, palpitations, near-syncope, venous pooling, mental clouding, and dyspnoea, often resulting in poor quality of life.[1] Postural orthostatic tachycardia syndrome is thought to be comprised of five subtypes: hyperadrenergic, hypovolemic, neuropathic, immune-related, and joint hypermobility-related, which is linked to Ehlers-Danlos syndrome (EDS).[2]

Postural orthostatic tachycardia syndrome is found in 15–41% of patients with EDS.[3] Ehlers-Danlos syndrome is an autosomal dominant, heterogenous group of connective tissue disorders characterized by connective tissue fragility, joint hypermobility, and skin hyperextensibility.[3] Although genetic testing is available for several EDS subtypes (i.e. classical EDS, dermatosparactic EDS), the genetic basis for hypermobile EDS is still unknown.[4] Thus, hypermobile EDS is diagnosed based on a physical evaluation to confirm the clinical features of hypermobile EDS, evaluating for family history of hypermobile EDS, and a positive score on the Beighton test, which measures joint hypermobility using a nine-point scale (a score of 5≤ is positive for hypermobile EDS).[2,3,5] The Beighton test assesses joint mobility of the spine and both elbows, knees, thumbs, and pinky fingers.[4]

Ehlers-Danlos syndrome can be associated with pelvic congestion and venous compression disorders, such as Nutcracker syndrome—compression of the left renal vein by the superior mesenteric artery (SMA).[6] Another venous compression disorder is May-Thurner syndrome (MTS)—when the right common iliac artery (RCIA) compresses the left common iliac vein (LCIV). Symptoms include pelvic congestion syndrome in women, leg swelling and pain, oedema, skin discolouration, and venous claudication. Interestingly, POTS patients often report these symptoms. Current first-line diagnostic tools (e.g. ultrasound) are often insufficient to evaluate abdominopelvic vasculature.[7] To aid the diagnosis of MTS, we utilized dynamic contrast-enhanced magnetic resonance angiography (MRA) with Differential Subsampling with Cartesian Ordering (DISCO) and four-dimensional flow magnetic resonance imaging.[7] The indication for an LCIV stent is stenosis >50–70% with associated symptoms such as pelvic pain and lower extremity swelling.[8]

We present a unique case series on a convergence of POTS, EDS, and MTS. Given these syndromes are often misdiagnosed or underdiagnosed, the true prevalence of this association is currently unknown. With this case series, we aim to not only bring greater visibility to the POTS, EDS, and MTS community, but also provide the medical field with advancements in knowledge and treatment of this syndrome triad. Moreover, this is the first case series on patients with concomitant POTS, EDS, and MTS.

Timeline

Case number	Time point	Event
1	2017 (symptom onset)	Patient experiences palpitations, difficulty concentrating and standing for long periods of time, and dizziness upon standing.
	May 2019 (presentation and clinical assessment)	*Presentation* Patient reports palpitations, difficulty concentrating due to mental clouding, dizziness upon standing, left leg swelling, and pelvic pain independent of menstruation. *Clinical assessment* 60 BPM supine HR, 118/60 mm Hg supine blood pressure (BP); 101 BPM standing HR, 109/70 mm Hg standing BP
	September 2019 (investigations)	MRA/MRV found severe compression of the left renal vein by the superior mesenteric artery (SMA), severe compression of the left common iliac vein (LCIV) by the right common iliac artery (RCIA).
	December 2019 (intervention)	Percutaneous transluminal LCIV angioplasty and stenting were performed.
	March 2020 (follow-up)	Patient reported complete resolution of symptoms. She

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Case number	Time point	Event
		also no longer reported concentration difficulties and she had improved activity levels.
2	March 2019 (presentation and clinical assessment)	*Presentation* Patient reports chronic abdominal pain, severe concentration difficulties, weakness, lightheadedness, palpitations, and lower abdominal bloating that worsened during menses. *Clinical assessment* Scored 8 out of 9 on the Beighton test. Performed tilt table test: 65 BPM supine HR, 104/72 mm Hg supine BP, 104 BPM standing HR, and 116/84 mm Hg standing BP.
	August 2019 (investigations)	MRA/MRV found occlusion of the left renal vein as it passes under the SMA, severe stenosis of the LCIV as it passes under the RCIA, and severe dilation of the left ovarian vein and right ovarian vein with retrograde flow in the left ovarian vein and antegrade flow in the right ovarian vein.
	October 2019 (intervention)	LCIV was stented.
	February 2020 (intervention)	Left gonadal vein embolization was performed.
	March 2021 (follow-up)	Patient reported significant improvement in POTS symptoms, decreased abdominal bloating, and no longer experienced difficulties performing activities while upright and left leg pain, swelling, and claudication.
3	October 2018 (presentation and clinical assessment)	*Presentation* Patient reported orthostatic dizziness, palpitations, sweating, face flushing, anxiety, and difficulty speaking due to mental clouding upon standing. She also noted pelvic pain radiating down her legs. Symptoms would worsen during menses. *Clinical assessment* Tilt table test: 66 BPM supine HR, 113/76 mm Hg supine BP, 105 BPM standing HR, and 120/83 mm Hg standing BP. Norepinephrine levels assessed: supine (685 pg/mL) and standing (1386 pg/mL).
	October 2019 (investigations)	MRA/MRV showed moderate–severe compression of the LCIV by the RCIA with asymmetric iliac venous return, mildly dilated pelvic venous collaterals, and moderate compression of the left renal vein under the SMA.
	Present day (follow-up)	Currently considering intervention for MTS

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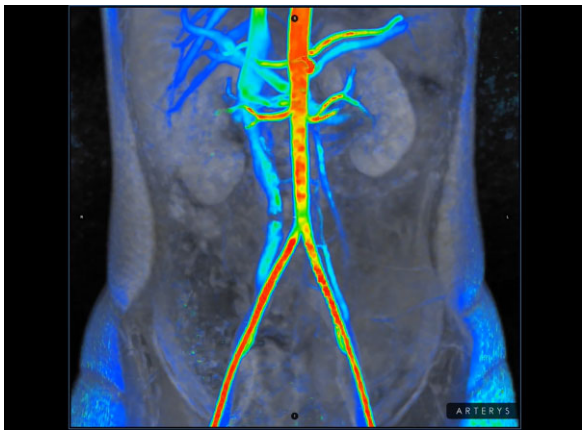
Patient 1

A 16-year-old female with hypermobile EDS and POTS presented for evaluation of palpitations, concentration difficulties due to mental clouding, difficulty staying upright and performing activities while standing, and dizziness while standing up. Her symptoms began 2 years ago and would worsen during menstruation or infection. She also reported left leg swelling and pelvic pain independent of menstruation that began 3 years ago. The initial evaluation confirmed POTS [60 BPM supine HR, 118/60 mm Hg supine blood pressure (BP); 101 BPM standing HR, 109/70 mm Hg standing BP]. The physical evaluation found her lower extremities to be warm to touch and pink, but no signs of varicosities. Mild left lower extremity oedema was also noted. Joint laxity consistent with hypermobile EDS was also found. She was diagnosed with hypermobile EDS by a medical geneticist 8 months ago and her mother and maternal grandmother also have hypermobile EDS.

She was initially prescribed 10 mg propranolol twice daily but changed to 0.1 mg of fludrocortisone once daily and compression socks due to her fatigue and anxiety worsening while on propranolol. Despite this change, her POTS symptoms did not sufficiently improve. Although a pelvic ultrasound was normal, chronic pelvic pain radiating down her left leg persisted. This was further evaluated with MRA/magnetic resonance venography (MRV) evaluation.

Novel imaging techniques such as four-dimensional flow magnetic resonance imaging were used to evaluate for MTS (*Video 1*) and found severe LCIV compression (0.01 L/min blood flow) with dilated

lumbar collaterals. Magnetic resonance angiography/magnetic resonance venography also showed severe compression of the LCIV by the RCIA (*Figure 1A and B*) and of the left renal vein by the SMA, indicating MTS and Nutcracker syndrome. Consistent with POTS, she exhibited severe lower extremity orthostatic venous blood pooling. Seven months after initial presentation, she underwent a percutaneous transluminal LCIV angioplasty and stenting with a 16 mm × 80 mm Venovo self-expanding stent post-dilated with a 10 mm × 60 mm balloon. Post-procedure venogram indicated successful stenting (*Video 2*). No stent was placed in the left renal vein since the ovarian vein was not dilated and given her age, less intervention to alleviate symptoms was prioritized. Three months post-stenting, she reported complete resolution of symptoms and no longer needed fludrocortisone. Also, her concentration difficulties were completely resolved, and her endurance and activity levels improved.



Video 1 Four-dimensional flow. Severe stenosis of the left common iliac vein with extensive lumbar collateral venous filling. Left iliac venous flow is re-routed through lumbar collaterals in a pattern similar to the contrast venogram shown in *Figure 1A*.

Patient 2

A 24-year-old female with POTS and hypermobile EDS presented with chronic abdominal pain, weakness, severe concentration difficulties, lightheadedness, and palpitations. She noted significant pelvic pain, left leg swelling, and lower abdominal bloating that would worsen during menses. During the physical examination, left lower extremity swelling, skin hyperextensibility, and joint hypermobility were observed, and she scored an 8 out of 9 on the Beighton test, confirming EDS. Additionally, the patient reported her mother also had hypermobile EDS. A tilt table test confirmed POTS: 65 BPM supine HR, 104/72 mm Hg supine BP, 104 BPM standing HR, and 116/84 mm Hg standing BP. She had been taking midodrine for 1.5 years prior and experienced mild improvement but stopped due to her recent pregnancy.

Since she was breast-feeding, conservative lifestyle changes were suggested, including staying hydrated and increasing exercise and salt intake. Given her left leg swelling and pelvic pain, a diagnostic venogram was performed and showed marked left gonadal vein reflux and narrowing of the LCIV. Differential Subsampling with Cartesian Ordering and four-dimensional flow imaging showed (i)

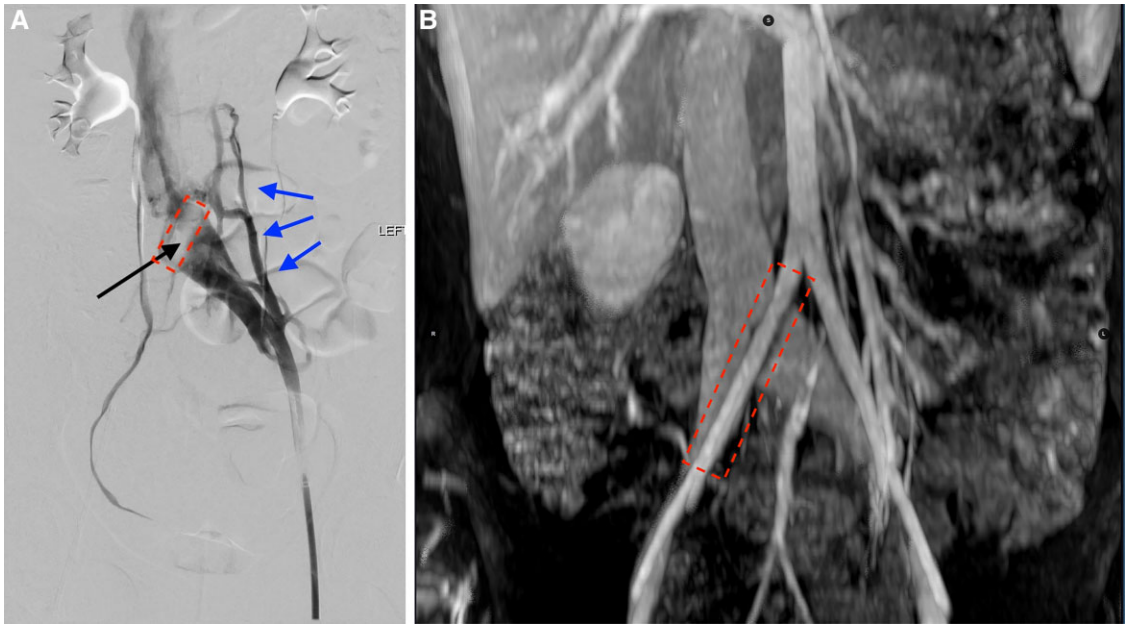
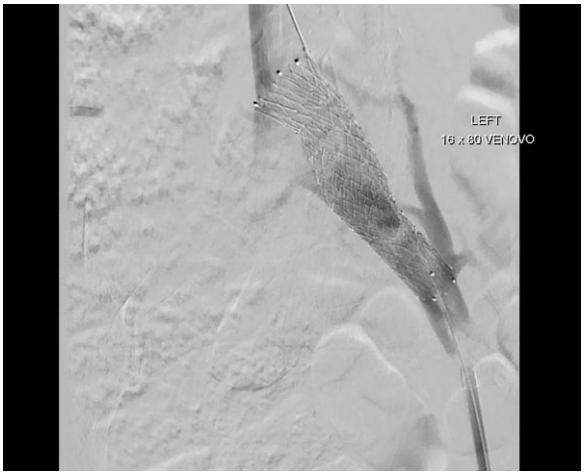


Figure 1 (*A*) Left common iliac vein antegrade venogram, (*B*) abdominopelvic vasculature–coronal view. (*A* and *B*) Severe stenosis of the left common iliac vein (arrow pointing into dashed box in *A*) with lumbar collateral venous filling (three blue arrows pointing leftward along lumbar collaterals in *A*). The left common iliac vein is compressed by the right common iliac artery (dashed box).



Video 2 Left common iliac vein antegrade venogram: post-stent placement. Venogram following a percutaneous transluminal left common iliac vein angioplasty and stenting with a 16 mm × 80 mm Venovo self-expanding stent post-dilated with a 10 mm × 60 mm balloon. Venogram shows free flow of contrast through the left common iliac vein and minimal collateral filling. Patient reported complete resolution of POTS symptoms.

occlusion of the left renal vein as it passes under the SMA, indicating Nutcracker physiology, (ii) retrograde flow in the left ovarian vein pathognomonic of pelvic congestion syndrome, and (iii) severe stenosis of the LCIV by the RCIA, indicating MTS (*Videos 3 and 4*). These findings are consistent with severe venous insufficiency, which is a common feature of POTS.

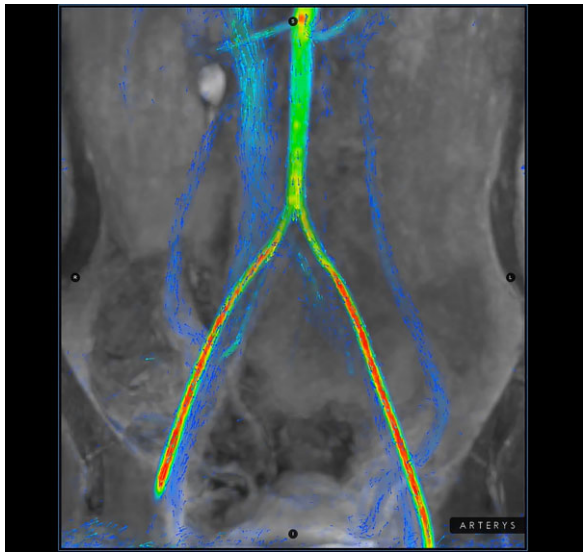
Seven months after initial presentation, the LCIV was stented using an 18 mm × 10 cm Venovo stent to address MTS (*Video 5*). This resolved her left leg pain, swelling, and claudication. She continued to experience abdominal pain and bloating—symptoms of pelvic congestion—prompting left gonadal vein embolization 4 months later. No stent was placed in the left renal vein since there was sufficient flow through the vein without evidence of lumbar collaterals.

One year after embolization, she exhibited marked improvement in LCIV diameter and decreased internal iliac venous filling. She reported significant improvement in POTS symptoms, decreased abdominal bloating, and her difficulties of remaining upright and left leg pain had dissipated. Since she had residual and occasional presyncopal episodes, she continued to take 2.5 mg of midodrine 3× daily.

Patient 3

A 41-year-old woman with hypermobile EDS and mast cell activation disorder was seen for dizziness, palpitations, face flushing, sweating, faintness, feelings of anxiety, and difficulty speaking due to mental clouding upon standing. She also noted pelvic pain radiating down her legs and that her symptoms worsen during menses. She has an extensive family history of hypermobile EDS on her maternal side, and she was diagnosed with hypermobile EDS following evaluation by a medical geneticist and a positive score on the Beighton test 3 years ago. A tilt table test confirmed her POTS: 66 BPM supine

Video 3 Differential Subsampling with Cartesian Ordering dynamic contrast-enhanced angiography. Differential Subsampling with Cartesian Ordering shows brisk retrograde flow in the left ovarian vein, filling pelvic venous collaterals, bypassing the iliac veins, and ascending the contralateral right ovarian vein.



Video 4 Four-dimensional flow. Retrograde flow in the left ovarian vein measures 290 mL/min to fill pelvic venous collaterals, which then return via the contralateral iliac vein, inferior vena cava, and the right ovarian vein.

HR, 113/76 mm Hg supine BP, 105 BPM standing HR, and 120/83 mm Hg standing BP. Hyperextensibility at her fingers, wrists, elbows, and toes was also noted during the initial evaluation. Given her symptoms of flushing, anxiety, and faintness upon assuming an upright position, supine (685 pg/mL) and standing (1386 pg/mL) norepinephrine levels were assessed and suggested hyperadrenergic POTS. Although an initial abdominal ultrasound was normal, an

Video 5 Left iliac venogram: post-stent. An 18 mm × 10 cm Venovo venous stent was placed in the left common iliac vein. Following stenting, the diameter of the vein in the region of the right common iliac artery crossing is 20 mm × 13 mm. Stent is widely patent and there is marked improvement in left common iliac vein diameter and filling. There was also a decrease in the filling of the internal iliac veins.

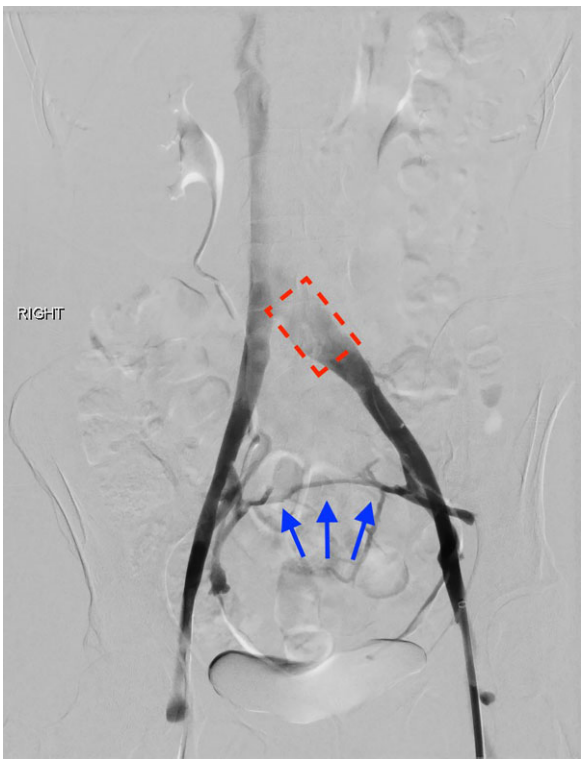


Figure 2 Left common iliac vein antegrade venogram. Moderate–severe compression of the left common iliac vein by the right common iliac artery (dashed box). Extensive pelvic venous collateral filling is present (arrows).

MRA/MRV was performed given her persistent pelvic pain. Magnetic resonance angiography/magnetic resonance venography showed moderate–severe compression of the LCIV by the RCIA with asymmetric iliac venous return, indicating MTS (*Figure 2*). Mildly dilated pelvic venous collaterals were also present. She initially tried 25 mg of atenolol daily but did not experience improvement. She then tried 5 mg of ivabradine twice daily but stopped after 6 months due to financial cost and minimal benefit. Currently, she is considering intervention for MTS.

Discussion

We report the first case series on concomitant POTS, EDS, and MTS. These cases illustrate the importance of assessing for possible MTS or Nutcracker syndrome in EDS patients presenting with POTS and pelvic or lower extremity symptoms. Chronic pelvic pain or discomfort, left leg swelling, or venous pooling should prompt evaluation for venous compression syndromes. Although abdominal and pelvic ultrasound are first-line diagnostic tools to evaluate for MTS, Nutcracker syndrome, and pelvic congestion syndrome, these syndromes can be challenging to diagnose given it requires both evaluation of venous anatomy and physiologic evaluation of blood flow in the abdominopelvic veins. This was evident in two of our patients, whose ultrasound results were normal, yet their pelvic congestion symptoms persisted. Following the use of dynamic contrast-enhanced MRA with DISCO and four-dimensional flow magnetic resonance imaging, MTS and Nutcracker syndrome were successfully diagnosed. We therefore highlight the importance of using these more accurate imaging techniques when evaluating abdominopelvic vasculature.

Following successful LCIV stenting, two patients' POTS symptoms and quality of life significantly improved, paralleling Knuttinen *et al.*'s[9] finding that LCIV stenting significantly alleviated dysautonomia symptoms in patients with POTS and MTS. Their study, however, did not characterize the presence of EDS. Dysautonomia and orthostatic intolerance are well-documented in hypermobile EDS. Gazit *et al.*'s[2] study on dysautonomia in patients with hypermobile EDS found reduced vasomotor tone, and ß-1 and α-1 adrenoreceptor hyperresponsiveness during orthostatic testing. Furthermore, EDS may

predispose patients to abnormal venous distention during orthostatic stress, leading to the venous pooling found in POTS.[10] Moreover, EDS-related hypermobility and viscera fragility may contribute to pelvic congestion and venous compression (e.g. MTS, Nutcracker syndrome) risk.[6,11]

We postulate EDS-related connective tissue abnormalities and the resulting increased risk for vein stenosis may interact synergistically to produce more severe haemodynamic and autonomic POTS symptoms. Furthermore, MTS may exacerbate the common POTS symptoms of hypovolemia and lower extremity venous pooling by decreasing venous return.[9] Coupling reduced venous return with the resulting changes in blood flow when standing up, patients with POTS experience decreased venous return, leading to sympathetic hyperactivation, orthostatic intolerance, baroreceptor inactivation, and tachycardia.[9] Left common iliac vein stenting can mitigate these symptoms by decreasing lower extremity venous pooling and subsequently improve downstream sympathetic nervous system hyperactivation.[6]

Conclusions

We present the first report on a three-way association of EDS, POTS, and MTS. Patients with EDS should be evaluated for POTS and pelvic venous complications. Moreover, we highlight DISCO and four-dimensional flow's utility in evaluating pelvic vasculature. Left common iliac vein stenting can relieve POTS symptoms in this patient population.

Lead author biography

Cameron K. Ormiston is a recent graduate of University of California, San Diego with a Bachelor of Science in Global Health. He has worked as a research assistant in Dr Pam Taub's clinical cardiology lab for over 3 years, researching novel pharmacological, behavioral, and technological therapies for postural orthostatic tachycardia syndrome and cardiometabolic disease. Cameron currently works as a research trainee at the National Institute on Minority Health and Health Disparities, studying immigrant and racial/ethnic minority health. Cameron will be applying to medical school in Spring 2022.

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 authors confirm that written consent for submission and publication of this case series including images and associated text has been obtained from all three patients in line with COPE guidance.

Conflict of interest: P.R.T. is a consultant for Amgen, Esperion, Boehringer Ingelheim, Medtronic, Novartis, Novo Nordisk, and Sanofi, and is a shareholder in Epirium Bio. A.H. receives research grant support from GE Healthcare and Bayer AG, unrelated to the presented work, and is a co-founder and shareholder of Arterys, Inc. All other authors have no conflicts of interest to disclose.

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References

1. Taub PR, Zadourian A, Lo HC, Ormiston CK, Golshan S, Hsu JC. Randomized trial of ivabradine in patients with hyperadrenergic postural orthostatic tachycardia syndrome. *J Am Coll Cardiol* 2021;**77**:861–871.
2. Gazit Y, Nahir AM, Grahame R, Jacob G. Dysautonomia in the joint hypermobility syndrome. *Am J Med* 2003;**115**:33–40.
3. Miglis MG, Schultz B, Muppidi S. Postural tachycardia in hypermobile Ehlers-Danlos syndrome: a distinct subtype? *Auton Neurosci* 2017;**208**:146–149.
4. Sobey G. Ehlers-Danlos syndrome: how to diagnose and when to perform genetic tests. *Arch Dis Child* 2015;**100**:57–61.
5. The Ehlers-Danlos Support UK. Hypermobile EDS and hypermobility spectrum disorders. The Ehlers-Danlos Support UK. https://www.ehlers-danlos.org/what-is-eds/information-on-eds/hypermobile-eds-and-hypermobility-spectrum-disorders/ (27 December 2021).
6. Amato ACM, da Silva AEC, Bernal IM, Bernal IM, de Oliveira JC, Di Paschoal Almeida Ribeiro M, Schinzari PS, dos Santos RV. Combined nutcracker and Ehlers-Danlos syndromes: a case report. *EJVES Vasc Forum* 2020;**47**:12–17.
7. Malone CD, Banerjee A, Alley MT, Vasanawala SS, Roberts AC, Hsiao A. Pelvic blood flow predicts fibroid volume and embolic required for uterine fibroid embolization: a pilot study with 4D flow MR angiography. *Am J Roentgenol* 2018;**210**:189–200.
8. Birn J, Vedantham S. May-Thurner syndrome and other obstructive iliac vein lesions: meaning, myth, and mystery. *Vasc Med* 2015;**20**:74–83.
9. Knuttinen M-G, Zurcher KS, Khurana N, Patel I, Foxx-Orenstein A, Harris LA, Lawrence A, Aguilar F, Sichlau M, Smith BH, Smith SJ. Imaging findings of pelvic venous insufficiency in patients with postural orthostatic tachycardia syndrome. *Phlebology* 2021;**36**:32–37.
10. Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* 1999;**135**:494–499.
11. Lum YW, Brooke BS, Arnaoutakis GJ, Williams TK, Black JH. Endovascular procedures in patients with Ehlers-Danlos syndrome: a review of clinical outcomes and iatrogenic complications. *Ann Vasc Surg* 2012;**26**:25–33.