Original Article

Phlebology

Nonpelvic comorbid symptoms of 45 patients with pain of pelvic venous origin, before and after treatment

Phlebology
2024, Vol. 0(0) 1–14

DOI: 10.1177/02683555241273109
journals.sagepub.com/home/phl
Sage

Steven J Smith[1], B Holly Smith[2,3], Michael J Sichlau[1], Brenda Chen[4], Dacre Knight[5] and Peter C Rowe[6]

Abstract

Objective: To report the prevalence and severity of nonpelvic symptoms for patients with venous-origin chronic pelvic pain (VO-CPP) and to describe outcomes after pelvic vein stenting and embolization.
Methods: We retrospectively reviewed outcomes of 45 women with VO-CPP who underwent treatment with iliac vein stenting and/or embolization. Patients completed symptom-severity questionnaires before and after treatment that assessed for pelvic pain, and multiple other symptoms, including brain fog, anxiety, depression, musculoskeletal pain, fatigue, migraines and more.
Results: Patient age ranged from 18 to 65 years. The prevalence of common symptoms was as follows: migraines, 69%; brain fog, 76%; anxiety attacks, 58%; excess sweating, 64%; hip pain, 73%; diarrhea, 62%; constipation, 76%; and abdominal bloating, 82%. After treatment, most symptom scores improved by more than 50%; exceptions were excessive sweating (41% improvement) and bloating (47% improvement). Prevalence of individual symptoms that bundle into POTS ranged from 29% to 76%, where symptom improvement ranged from 23% to 59% after treatment. Overlapping individual symptoms characteristic of fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) were present in 64% to 82% of patients and all improved by 49% to 63% after treatment.
Conclusions: Pelvic venous flow abnormality is linked causally to a spectrum of interrelated symptoms, of which many can be bundled into named syndromes of unknown cause. With catheter- based treatment of pelvic venous pooling, nonpelvic symptom and syndrome scores improved.

Keywords

Chronic fatigue, ehlers-danlos syndrome, migraine headaches, pelvic congestion syndrome, postural orthostatic tachycardia syndrome syndrome

Introduction

Venous-origin chronic pelvic pain (VO-CPP) has been associated with 4 comorbid syndromes (orthostatic intolerance; dysuria or interstitial cystitis; and irritable bowel syndrome [IBS]) with standardized surveys.[1] However, many patients with VO-CPP also report additional symptoms beyond these syndromes. A previous online survey of patients with VO-CPP[2] identified abnormally common coexisting symptoms including: chronic fatigue (72%), dizzyness (63%,) IBS type symptoms (61%), dysuria (41%), brain fog (33%), excessive sweating (31%), temporomandibular joint (TMJ) pain (31%), and joint hypermobility (18%). The named syndromes of irritable bowel syndrome (29%), fibromyalgia (13%), migraines (49%), postural tachycardia syndrome (POTS), chronic fatigue syndrome (ME/CFS), and Ehlers-Danlos syndrome (EDS) were formally diagnosed in the respondents abnormally

[1]Vascular and Interventional Professionals, Hinsdale, IL, USA
[2]Center for the Advanced Study of Human Paleobiology, George Washington University, Washington, DC, USA
[3]Museum of Anthropological Archaeology, University of Michigan, Ann Arbor, MI, USA
[4]College of Osteopathic Medicine, Touro University California, Vallejo, CA, USA
[5]Division of General Internal Medicine, Mayo Clinic, Jacksonville, FL, USA
[6]Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

Corresponding author:
Dacre Knight, Division of General Internal Medicine, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA.
Email: Knight.Dacre@mayo.edu

frequently. Previous studies have linked VO-CPP to hip pain,[3,4] myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS),[5–7] migraine headaches, and chronic fatigue.[2,7–9] Orthostatic intolerance has been linked to migraine headaches, ME/CFS, brain fog, fibromyalgia, and anxiety.[1,10–15] Interstitial cystitis is frequently diagnosed concurrently with fibromyalgia and other dysautonomias,[16–18] and patients with IBS have symptoms overlapping with those of fibromyalgia, orthostatic intolerance, hypermobile EDS, and CPP.[6,19–22] EDS has been linked to all these conditions, as well as to TMJ and other joint pain and migraines.[1,23–31]

Here, symptom prevalence and treatment effects, as measured by reported scores, were reviewed for 21 individual nonpelvic symptoms. These 21 were selected for analysis because each has its own *International Classification of Diseases,* Tenth Revision (ICD-10) code (Table S1). Because these symptoms are recognized as individual concerns or conditions, they merit individual attention. Symptoms analyzed include migraines, hip pain, fatigue, excessive sweating, anxiety attacks, brain fog, TMJ pain, muscle pain, prolonged recovery after exercise and more. Many of these symptoms are components of recognized "syndromes of unknown cause," such as POTS (heart palpitations, anxiety attacks, brain fog, excessive sweating, dizziness, heat intolerance, and skin sensitivity),[32–35] CFS (fatigue, weakness, prolonged recovery after exercise, brain fog),[13,36–38] and fibromyalgia (head and neck discomfort, brain fog, and muscle or joint pain in the arm, shoulder, or neck).[14,15,28,39] Other included symptoms, such as migraines, low back pain, or hip pain, are frequently comorbid with other conditions.[40–42]

The purpose of examining individual symptoms is a vital one because the treatments administered to patients depend on how their problems are detected and possibly bundled by the diagnostician into a syndrome. A patient seeking care for a nonspecific symptom such as dizzyness or severe fatigue is unlikely to be screened for pelvic venous flow abnormality as a possible cause.

In this study of 45 patients with VO-CPP, we examined the effects of stenting and/or embolizing pelvic veins in the light of a developing hypothesis of an "orthostatic flow syndrome," in which pelvic vein dysfunction contributes to symptoms manifesting in various organ systems by sequestering blood below the waist during upright posture. This vein dysfunction causes local pelvic pain, may release vasoactive substances and may also diminish blood return above the waist, triggering compensatory physiology.[14,34,43–48]

Materials and methods

We conducted a retrospective, observational review of patients with VO-CPP. The cohort described here is the same as that reported in a prior retrospective study, in which several syndromes were surveyed.[1] Patients were referred to an interventional radiology clinic (VIRChicago, Hinsdale, Illinois) and presented from June 13, 2018, through September 1, 2021, for evaluation and treatment of VO-CPP. The AMITA Health Institutional Review Board approved this study (protocol 2020-0114-02), with certain precautions for data handling. No patient was treated differently if their health records were included in this analysis. The reporting of this study is in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[49]

Symptom questionnaire

An extensive questionnaire about symptoms was derived from the literature of linked syndromes and our prior survey of members of an online support group for pelvic congestion syndrome (PCS).[2] We developed the current questionnaire as a clinical tool to help identify problems that patients sometimes did not volunteer, for various reasons.[50]

The 65-question survey was incorporated into the electronic health record as a clinical tool (Supplement). A nurse or medical assistant administered the survey at the patient's initial clinical visit and at follow-up visits (after treatment). Fifty questions from the Orthostatic Hypotension Questionnaire (OHQ), International Pelvic Pain Society, Pelvic Pain and Urgency/Frequency symptom scale and modified Rome III survey were discussed in the previous report.[1] Fifteen of the 65 questions asked patients to rate the perceived severity of other (miscellaneous) symptoms that were not addressed in the previously validated questionnaires.

Exact instructions for questions varied but included phrases such as "rate your level of pain," "how distressed are you by," or "how much are you bothered by," as appropriate. Patients indicated their answers on a scale of 0 to 10.

Patient sample

All patients had clinical and imaging findings indicating a venous origin for CPP.[1] Patients were asked to return for follow-up office appointments at intervals of 3, 6, and 12 months after completion of treatment. Of the 52 patients who completed pretreatment questionnaires and received treatment, 7 did not complete follow-up (3 because of COVID-19 restrictions; 4 were lost to follow-up). Forty-four patients returned for 1 or more follow-up visits after 2 to 8 months and 1 patient returned after 11.3 months. The median time to the first follow-up visit was 4 months.

The 45 women who were included in the final cohort ranged in age from 18 to 65 years (mean, 38.7 years). Parity

ranged from 0 through 5 births (median, 2 births). The 7 patients who did not complete a follow-up questionnaire had virtually the same age range (18-62 years) as that of the overall group.

Treatment

Treatment was described previously.[1] Briefly, patients underwent interventional stent placement and/or embolization of pelvic veins. The treatments targeted only pelvic venous blood flow, and the goal was to treat all pelvic venous abnormalities until patients were asymptomatic, if possible.[51,52] The average number of procedures was 1.4. The type of treatment was limited by various factors, such as insurance coverage and intravenous contrast limits. Of the 45 patients in the cohort, 17 had iliac stents only, 5 had gonadal and/or iliac vein embolization only and 23 had stent placement plus embolization.

Statistical analysis

Forty-five patients had 1 follow-up visit, 16 had 2 visits and very few had 3 visits, making a stronger case for comparing before-versus after-treatment scores, rather than tracking longitudinal posttreatment change. To avoid discarding data, when both 3- and 6-months follow-up visits occurred, scores for the 2 visits were averaged. If only 1 posttreatment response was available, then that was used. Averaging follow-up scores had additional advantages, creating a response variable with more levels (e.g., "0, 0.5, 1.0, 1.5, 2.0" rather than "0, 1, 2") and a response variance that generally declined.

All data were in the form of pain or distress scores ranging from 0 through 10. Because the survey questions were wide ranging, no single symptom was present for every patient. The analysis discarded data from patients who never experienced a given symptom before or after treatment (i.e., scoring 0 and 0). Paired *t*-tests investigated treatment effects for those who ever reported a symptom score of 1 through 10. One patient (aged 60 years, parity of 0) always scored all 21 symptoms as 0, although she had other symptoms specific to VO-CPP. Data from this patient were retained only to provide the correct denominator for symptom prevalence, although they do not appear in any paired test.

The distributions of severity scores often were skewed or kurtotic, but the paired *t*-test assumed only that the *difference* in scores was normally distributed. Kolmogorov-Smirnov tests rejected the hypotheses (at $p < .05$) of normal distributions for difference in scores (before minus after) for depression and fatigue. As a conservative measure, calculations for these possibly nonnormal variables were repeated with the nonparametric Wilcoxon signed-rank test, which tests the null hypothesis that the medians are unchanged (when underlying distributions are at least symmetric) or that the distributions are unchanged (if distributions are asymmetric). We calculated treatment effects as percent change, using the difference in mean values, although the change in medians was sometimes even larger; *p* values less than 0.05 were considered statistically significant. Data were maintained with Excel spreadsheet software (Microsoft Corporation) and analyzed with SPSS software, version 29 (IBM Corporation).

Data availability statement

Data cannot be publicly posted due to protocol, but individually submitted inquiries will be considered by the authors.

Results

On average, pain and distress scores decreased for all 21 non-pelvic symptoms after interventions aimed at improving pelvic venous blood flow. Eighteen symptoms (86%) were significantly improved after treatment. Results are organized into tables that correspond to common comorbid conditions or stand-alone concerns.

Table 1 shows results for 8 symptoms often associated with POTS, ordered by prevalence. "Brain fog/trouble concentrating" was the most commonly reported POTS symptom ($n = 34$ [76%]). Before treatment, patients had a mean brain fog score of 6.53; after treatment, the score decreased to 2.69 (59% decrease) (Figure 1). The severity of anxiety attacks decreased from 5.81 to 2.37 (59% decrease) (Figure 2). Skin sensitivity and heat intolerance were the least common symptoms.

We tracked 6 symptoms associated with fibromyalgia and ME/CFS, and all improved significantly (Table 2). Muscle or joint pain (in the arm, shoulder, and neck) improved by 50%, head or neck discomfort improved by 60%, and weakness improved by 63%. We had few data points for the question pertaining to prolonged recovery from exercise. That symptom was added to the questionnaire late in the study, and only 11 patients had the opportunity to respond.

The survey included 3 questions about symptoms associated with IBS. All 3 symptoms improved significantly (Table 3), with diarrhea showing the greatest improvement (70%).

The survey included questions about hip pain, migraine headache, and depression (Table 4), as well as TMJ pain, that were common in this patient population and also possibly linked to POTS, fibromyalgia, ME/CFS, or IBS. Thirty-three patients (73%) indicated having hip pain; of these, 11 patients had pretreatment pain scores ranging from 8 to 10 (Figure 3). Not all patients had less hip pain after treatment, but most reported scores that improved by 2 to 8 points. Thirty-one patients (69%) reported at least some

Table 1. Severity of symptoms associated with postural orthostatic tachycardia syndrome and dysautonomia, before and after treatment of chronic pelvic pain of venous origin (N = 45).

		Score, mean[a]		Paired difference (before minus after)		
Symptom	No. of affected patients (%)[a]	Before	After	Mean (SEM)	Decrease in symptom score, %[c]	P value[d]
Brain fog[e]	34 (76)	6.53	2.69	3.84 (0.54)	59	<.001
Dizziness	33 (73)	5.52	2.69	2.79 (0.59)	50	<.001
Excessive sweating	29 (64)	4.38	2.60	1.78 (0.65)	41	.01
Vision problem	28 (62)	5.04	3.73	1.30 (0.65)	26	.05
Irregular heartbeat	28 (62)	4.86	2.63	2.23 (0.58)	46	<.001
Anxiety attacks	26 (58)	5.81	2.37	3.44 (0.58)	59	<.001
Heat intolerance	17 (38)	5.47	3.56	1.91 (0.90)	35	.049
Skin sensitivity	13 (29)	5.77	4.44	1.33 (1.03)	23	.22

[a]Number of patients with a symptom severity score greater than 0 at any time (before or after treatment).
[b]Possible scores ranged from 0 to 10.
[c]Calculated as follows: % Decrease = [(mean "Paired Difference")/(mean "Before" score)]*100.
[d]Paired t- test to determine whether the difference in scores was significantly different from 0.
[e]Brain fog also is associated with fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome.

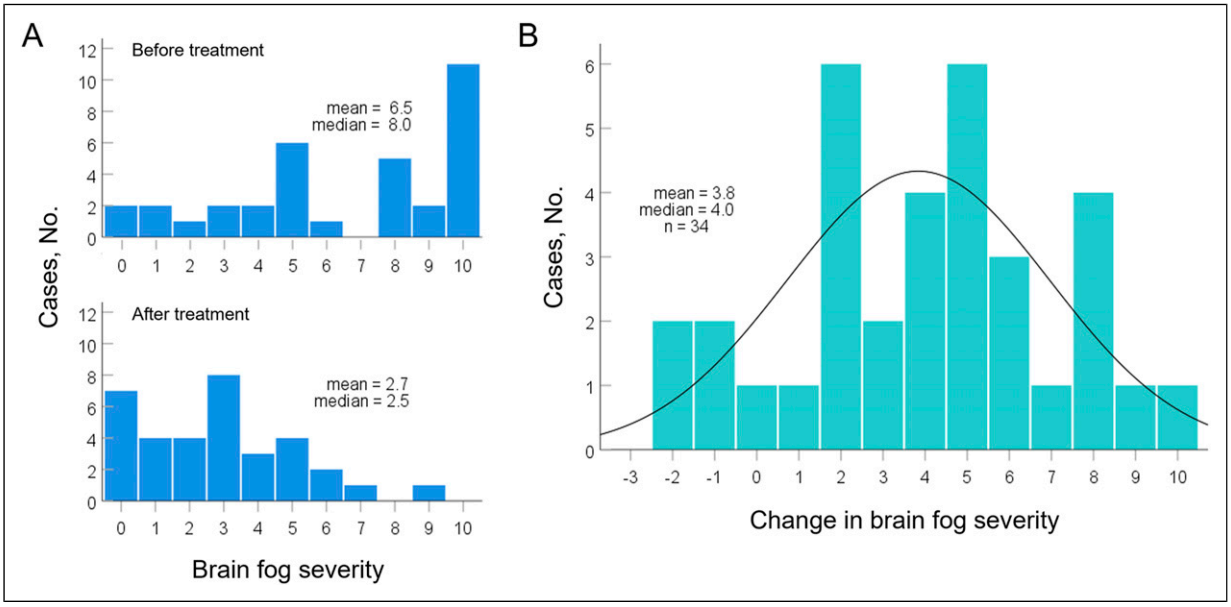

Figure 1. Brain Fog Severity Scores. In the cohort, 34 patients reported nonzero scores (0-10 scale). (a), Comparison of scores before and after treatment. (b), distribution of paired differences. Four patients reported worsening brain fog, One patient had unchanged brain fog, and 29 reported improvement. The curved line indicates best fit to a normal distribution.

migraine pain (mean score at consultation, 6.90), and 25 patients had severe migraines (pain score, ≥6) (Figure 4). Migraine pain improved by 54% overall and only 6 patients (19%) continued to have severe pain. Depression affected 25 patients (56%). It was only moderately severe at baseline and decreased to a low level after treatment. TMJ pain did not change significantly.

Discussion

The 45 patients in this cohort all had some degree of pelvic pain, and treatment was aimed solely at improving pelvic venous blood flow.[1] However, the high symptom burden and the widespread improvement after pelvic venous treatment suggest a more systemic effect.

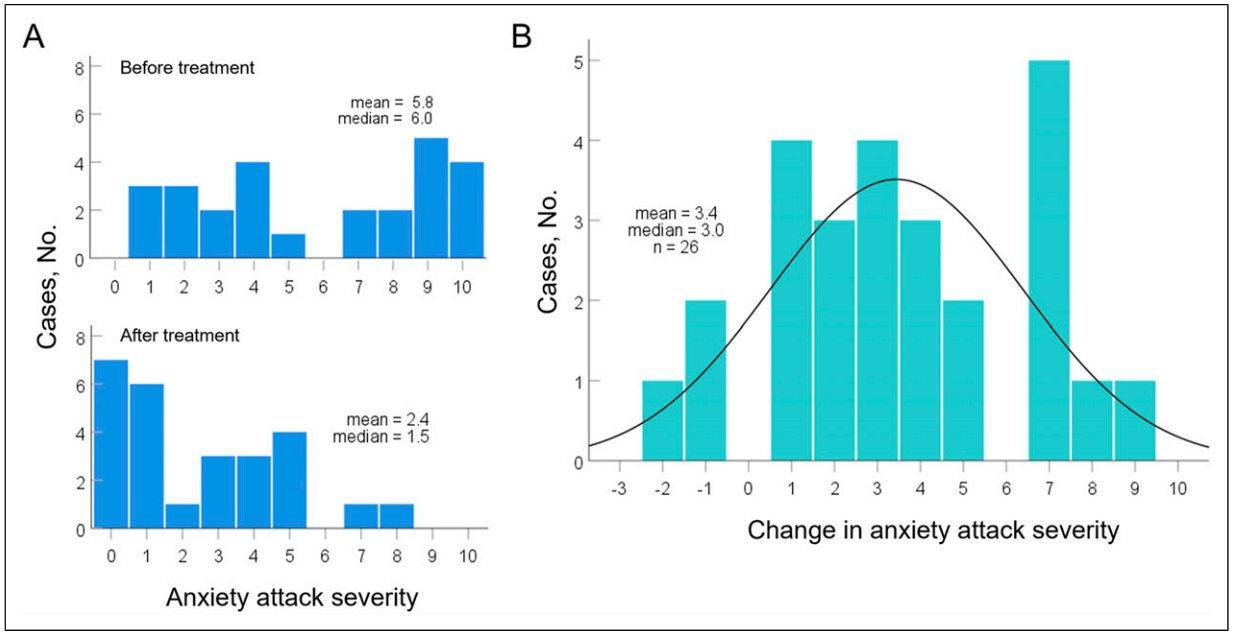

Figure 2. Anxiety Attack Severity Scores. In the cohort, 26 patients reported nonzero scores (0-10 scale). (a), Comparison of scores before and after treatment. (b), distribution of paired differences. Three patients reported worsening distress, and 23 reported improvement. The curved line indicates best fit to a normal distribution.

Table 2. Severity of symptoms associated with fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome, before and after treatment of chronic pelvic pain of venous origin (N = 45).

Symptom	No. of affected patients, %[a]	Score, mean[b]		Paired difference (before minus after)		
		Before	After	Mean (SEM)	Decrease in symptom score, %[c]	P value[d]
Fatigue[e]	37 (82)	7.30	3.45	3.85 (0.43)	53	<.001
Muscle or joint pain (arm, shoulder, neck)	36 (80)	5.81	2.93	2.88 (0.62)	50	<.001
Low back pain	36 (80)	6.86	3.49	3.37 (0.54)	49	<.001
Weakness	35 (78)	5.84	2.14	3.70 (0.46)	63	<.001
Head or neck discomfort	33 (73)	5.94	2.38	3.56 (0.56)	60	<.001
Prolonged recovery from exercise[f]	7/11 (64)	7.21	3.21	4.00 (0.98)	55	.007

[a]Number of patients with a symptom severity score greater than 0 at any time (before or after treatment).
[b]Possible scores ranged from 0 to 10.
[c]Calculated as follows: % Decrease = [(mean "Paired Difference")/(mean "Before" score)]*100.
[d]Paired t- test to determine whether the difference in scores was significantly different from 0.
[e]Brain fog is also a symptom of these conditions. Data for brain fog are shown in Table 1.
[f]Late addition to questionnaire (responses available for only 11 patients).

Symptoms associated with POTS

The interventional radiology clinic did not perform tilt table tests, and POTS requires specific pulse changes and other criteria for formal diagnosis. Pulse data were not tracked regularly because some patients were being treated with β-blockers. Nevertheless, many classic symptoms of POTS occurred in the group and 6 of 8 POTS symptoms improved significantly with treatment, several by more than 50% (Table 1). From these data, we posit that some POTS symptoms may be linked to reduced pelvic blood flow. This mechanism is further supported by an imaging review by Knuttinen et al,[53] who showed that iliac vein stenosis was 30% more common for patients with POTS than for control patients. POTS symptoms also were abnormally common in a survey of members of a PCS support group (63% vs 1% in

Table 3. Severity of symptoms associated with irritable bowel syndrome, before and after treatment of chronic pelvic pain of venous origin (N = 45).

		Score, mean[b]		Paired difference (before minus after)		
Symptom	No. of affected patients, %[a]	Before	After	Mean (SEM)	Decrease in symptom score, %[c]	P value[d]
Abdominal bloating	37 (82)	6.41	3.39	3.01 (0.69)	47	<.001
Constipation	34 (76)	5.15	2.53	2.62 (0.69)	51	<.001
Diarrhea	28 (62)	4.79	1.43	3.36 (0.70)	70	<.001

[a]Number of patients with a symptom severity score greater than 0 at any time (before or after treatment).
[b]Possible scores ranged from 0 to 10.
[c]Calculated as follows: % Decrease = [(mean "Paired Difference")/(mean "Before" score)]*100.
[d]Paired *t*- test to determine whether the difference in scores was significantly different from 0.

Table 4. Severity of miscellaneous symptoms, before and after treatment of chronic pelvic pain of venous origin (N = 45).

		Score, mean[b]		Paired difference (before minus after)		
Symptom	No. Of affected patients, %[a]	Before	After	Mean (SEM)	Decrease in symptom score, %[c]	P value[d]
Hip pain	33 (73)	5.91	2.60	3.31 (0.72)	56	<.001
Migraine	31 (69)	6.90	3.21	3.69 (0.46)	53	<.001
Depression[e]	25 (56)	4.68	2.44	2.24 (0.52)	48	<.001

[a]Number of patients with a symptom severity score greater than 0 at any time (before or after treatment).
[b]Possible scores ranged from 0 to 10.
[c]Calculated as follows: % Decrease = [(mean "Paired Difference")/(mean "Before" score)]*100.
[d]Paired *t*- test to determine whether the difference in scores was significantly different from 0.
[e]Differences were not normally distributed; substituting a Wilcoxon signed-rank test returned $p < .001$, with medians decreasing by 50% (from 4 to 2).

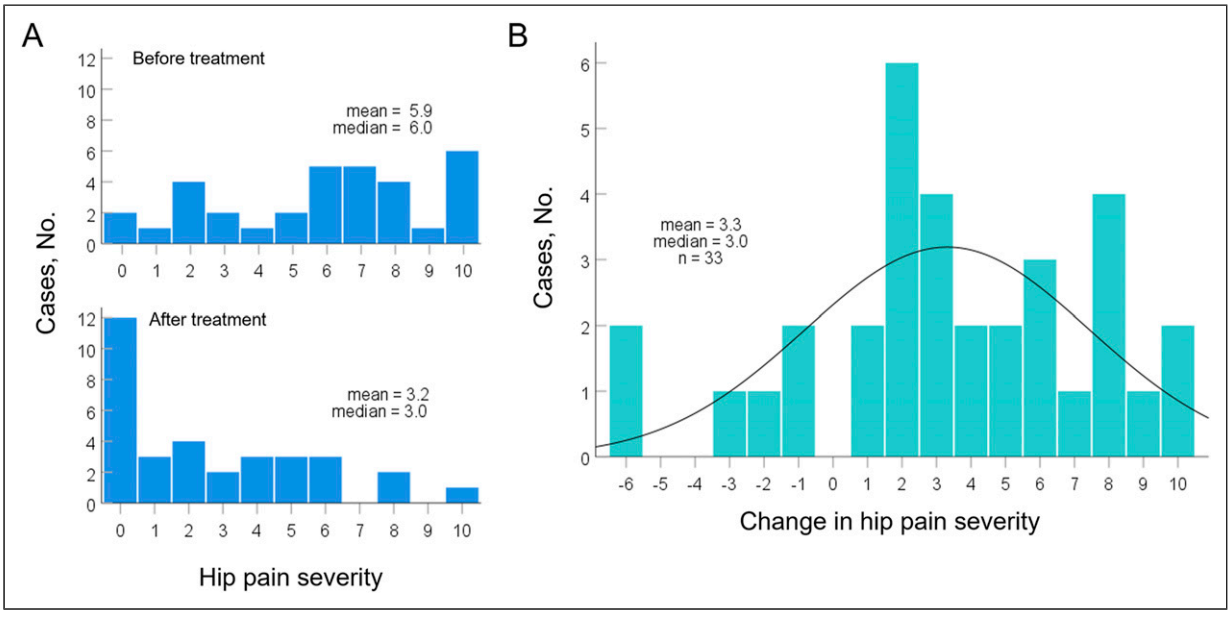

Figure 3. Hip Pain Severity Scores. In the cohort, 33 patients reported nonzero scores (0-10 scale). (a), Comparison of scores before and after treatment. (b), distribution of paired differences. Six patients reported worsening pain, and 27 reported improvement (several by as much as 10 points). The curved line indicates best fit to a normal distribution.

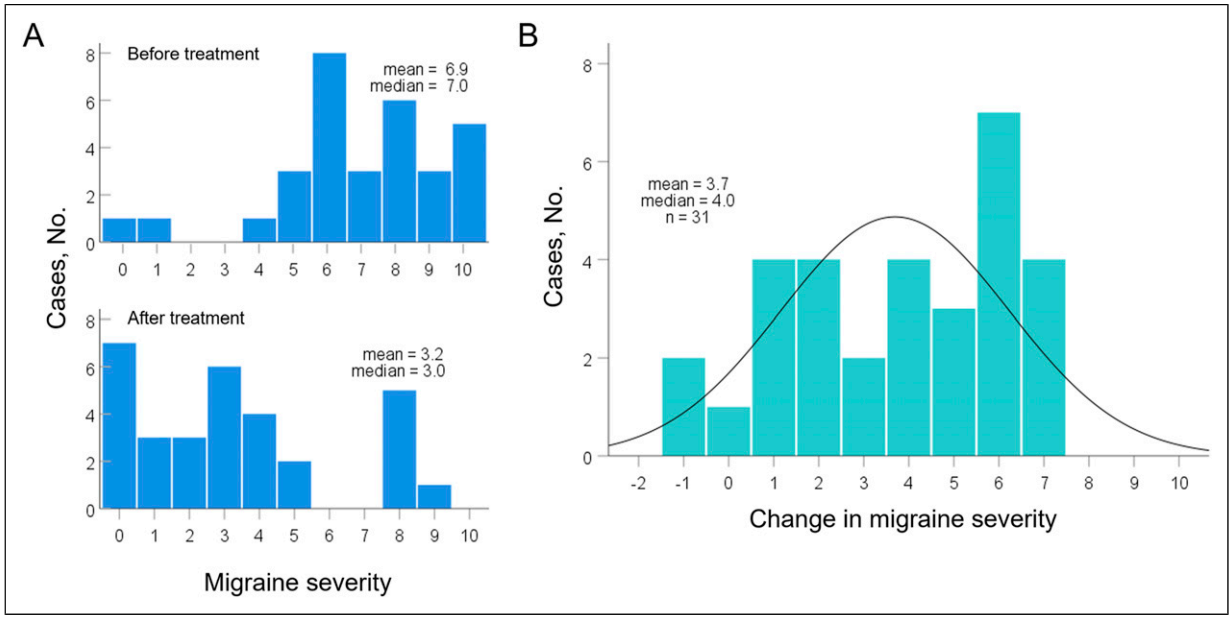

Figure 4. Migraine Pain Severity Scores. In the cohort, 31 patients reported nonzero scores (0-10 scale). (a), Comparison of scores, before and after treatment. (b), distribution of paired differences. Two patients reported worsening pain, 1 had unchanged pain, and 28 reported improvement. The curved line indicates best fit to a normal distribution.

the general population).[2] Prospective evaluation of patients with confirmed POTS is needed to directly evaluate a putative benefit of normalizing pelvic blood flow.

Brain fog, which is associated with dysautonomia and orthostatic intolerance, can be severe for patients with ME/CFS, POTS and fibromyalgia.[1,10,14,54,55] It has recently been linked to post–COVID-19 condition.[30,56,57]

Van Campen et al[15,38] noted that in tilt table testing, patients with ME/CFS, POTS, or orthostatic hypotension had a 28% decrease in cerebral blood flow with upright posture. Pelvic flow is a new link suggesting that patients with brain fog may benefit from pelvic vein evaluation. For several patients, disabling brain fog (scores of 8-10) decreased sharply or vanished (Figure 1). With the elimination of such severe disability, some patients from the current cohort were able to resume driving or to enroll in college. The brain fog of fibromyalgia also is typically evaluated without consideration of blood flow (central causes have been suspected instead).[58,59]

Symptoms associated with fibromyalgia

Patients with pelvic venous pain commonly reported symptoms that were consistent with fibromyalgia (Table 2). However, without specific evaluations, it is not possible to say how many patients in the current cohort had fibromyalgia. Many patients had HSD or EDS, which is associated with muscle and joint pain and with fibromyalgia.[28,60,61] Determining whether musculoskeletal pain is due to EDS or HSD versus fibromyalgia is difficult because the conditions share widespread pain symptoms. Fairweather et al[28] described a cohort of patients at an EDS clinic and reported that 70% had fibromyalgia.

In the current cohort, the relationship between musculoskeletal pain symptoms and VO-CPP was strong, and the posttreatment improvement was remarkable. One symptom, low back pain, is a nonspecific symptom commonly associated with pelvic venous pain[40] and it improved by 49% with venous treatment.

Fibromyalgia pain is a form of orthostatic intolerance, as determined by tilt table evaluations.[14,47,62] Fibromyalgia is frequently diagnosed concurrently with other dysautonomias, as well as IBS, interstitial cystitis, and myofascial pain syndrome.[20] In this group of patients with VO-CPP, fibromyalgia symptoms were common, but improved blood return appeared to alleviate many symptoms. A physiologic pathway may exist that explains musculoskeletal pain changes through sympathetic nervous system modulation. Zamuner et al[47] reported that greater sympathetic activity can cause more severe fibromyalgic pain. Moreover, increasing flow into the inferior vena cava directly reduces sympathetic activity in humans.[43]

Symptoms associated with ME/CFS

ME/CFS is characterized by orthostatic intolerance, brain fog, fatigue and weakness. In addition, prolonged recovery from exercise is relevant for diagnosing ME/CFS.[46] Many symptoms that are associated with ME/CFS were common among these patients with VO-CPP[1] and all associated symptoms included in the questionnaire improved significantly, including weakness (by 63%) and fatigue (by 53%)

(Table 2). Although we were able to collect only a few data points for prolonged recovery (n = 7) because of its late addition to the questionnaire, the patients who did answer reported marked improvement (55%). ME/CFS has been associated with low blood pressure, poor blood flow in the brain, and hypermobility (HSD and EDS)—and now, perhaps also with pelvic vein insufficiency.[10,15,38]

Symptoms associated with IBS

IBS is poorly understood in terms of causality and is often associated with nausea, bloating, constipation, diarrhea, weight loss, and dyspepsia. Many patients with IBS diagnoses have overlapping diagnoses of fibromyalgia, POTS, HSD, ME/CFS, anxiety, EDS, and CPP.[6,19–22,41,63]

Three questions about IBS symptoms were included separately because the Rome III scale (used in a previous analysis[1]) was a poor tool for directly querying patients. However, when patients were asked about these 3 symptoms in the current questionnaire, most indicated that they had gastrointestinal tract issues (Table 3), similar to surveyed members of an online PCS support group.[2] After treatment, abdominal bloating improved by 47%, constipation by 51%, and diarrhea by 70%.

Hip pain and migraine headaches

Case reports have linked VO-CPP treatment with improvement in hip pain.[3,4] This group overall showed an improvement of 2 to 8 points in pain score (Figure 3). EDS is associated with joint pain.[60,64] Thus, patients with EDS or HSD might be expected to have hip pain that would not necessarily improve with vein treatment. Three patients still had pain scores of 8 or higher and a few had worse pain postprocedure (probably from phlebitis from sclerotherapy, an adverse effect). At least 1 patient in the group had previous exploratory hip surgery (with negative findings), and indeed, pelvic veins are not in the differential diagnosis for hip pain.[65] Nevertheless, considering that 56% of the total group of patients with VO-CPP had a diagnosis of EDS/HSD, the observed improvement in hip pain (averaging 56%) might indicate that varicose veins in the low pelvis are causing referred pain in the hip area. Of note, an imaging study from Turkey showed that 32% of patients imaged for sacroiliitis had signs of pelvic venous congestion.[66]

Migraines are a huge cause of morbidity worldwide, with many millions of individuals affected.[67] We posit that a subset of these patients may have *orthostatic migraines*. Headaches can be associated with POTS and dysautonomia[8,11,68,69] and with EDS.[9,31]

EDS is associated with other separate causes of headache, including Chiari formation, CSF leaks, and craniocervical instability (due to ligamentous laxity),[70] which should not be affected by pelvic vein repair. However, migraines have been linked to venous insufficiency in the legs and with nutcracker syndrome, both of which are associated with pelvic venous insufficiency.[9,71] Dramatic improvements in migraine symptoms have not previously been attributed to pelvic vein repair. In the current cohort, migraine pain improved by 54% overall after treatment of pelvic veins. Remarkably, restoration of pelvic venous blood flow reduced the number of patients with severe migraine pain from 25 to 7 (Figure 4). For some patients, the reduction in pain enabled them to go to school or work. We believe that this improvement in severe migraine pain after resolution of pelvic venous blood flow abnormalities has considerable clinical significance. Even if such migraines accounted for only a small percentage of the total estimated 1 billion migraineurs, pursuit of a new link is worthwhile.

One possible explanation is the link between painful pelvic veins and calcitonin gene-related peptide (CGRP) and substance p because those peptide mediators also cause migraines. They are powerful vasodilators and drugs blocking those mediators stop migraines. Does improving pelvic venous blood flow decrease concentration of CGRP and substance p, thereby affecting migraines?[48,72]

Orthostatic intolerance and ME/CFS

Previously, we reported a high incidence of orthostatic intolerance in this cohort, as measured by the validated OHQ, and described a 49% improvement after pelvic vein intervention.[1] We had compared severity of orthostatic intolerance among these patients with venous CPP with the severity reported by Ruzieh et al[73] of patients with severe POTS who received weekly intravenous saline infusions, a mainstay treatment for POTS. In that study, the overall improvement in orthostatic symptoms (47%) was similar.

One of the improved symptoms in our cohort was fatigue. As early as 1949, Taylor[7,74] noted low blood pressure and chronic "invalid-like fatigue" as common findings among patients with pelvic congestion fibrosis syndrome. Severe fatigue was one of the most frequent extrapelvic concerns (72%) in a recent online survey of patients with PCS, with 10% reporting a formal diagnosis of severe chronic fatigue.[2] Furthermore, patients with ME/CFS have increased odds of having CPP.[5] In terms of treatment, one report indicated that compression stockings improved cardiac output and cerebral blood flow for patients with ME/CFS, as measured by tilt table testing, further strengthening the link between lower-body blood pooling, low blood return and ME/CFS.[15,46] Improved pelvic blood flow may directly augment blood flow to the brain, or it may improve fatigue through other pathophysiologic mechanisms.

Other theories about ME/CFS implicate viral infection (e.g., Epstein-Barr, COVID-19), mitochondrial dysfunction, or central nervous system–mediated processes.[36,75–79]

Are anxiety and depression causative?

The anxiety that is commonly associated with POTS and dysautonomia is not thought to be psychologically based[35]; rather, it is likely a physiologic response to a compensatory adrenergic increase and to sympathetic overdrive stimulation (i.e., the "fight or flight" effect). In the present group, a majority of patients (n = 26 [58%]) reported having anxiety attacks. For these patients, the severity of anxiety attacks improved by 59% with treatment (Figure 2), and many patients with crippling anxiety attacks reported much improvement. The severity of excessive sweating (hyperhidrosis), which showed a 41% improvement after treatment, may share this physiologic mechanism.

Although anxiety is strongly associated with POTS, it is also an independent problem. Certainly, for patients with constant or frequent pain, relief from pain is expected to decrease anxiety. Many studies, however, connect anxiety to multiple syndromes of unknown cause and even EDS, with some researchers implying that syndromes could also be an effect of anxiety (or hypervigilance, catastrophizing, and functional illness) because they are unaware of the vascular effects.[19,24,63,80–84] A straightforward circulatory disorder triggering anxiety-type symptoms, if confirmed, would provide hope for these patients with multiple syndromes and disabling anxiety attacks.

Depression was a concern for 25 patients (56%), but only moderately severe depression was reported at baseline, and depression decreased by 48% after treatment. Thus, depression perhaps is only a reaction to illness. Physical symptoms of ME/CFS do not improve with treatment of depression[85] and no treatment for depression was offered in this study.

Anxiety and depression are commonly associated with chronic illness. More research is needed, such as physiologic testing to identify factors that are causing anxiety.

Other symptoms

Twenty-four patients (53%) reported jaw pain, which did not improve significantly with treatment. Although a strong or specific relationship between TMJ pain and the VO-CPP group was not observed in the current study, jaw pain can be a symptom of EDS.[25,86] Skin rashes from mast cell activation may occur with the rest of the symptoms; our questionnaire had only 1 item about skin sensitivity, and the responses showed no significant change.[87,88]

Venous flow abnormalities as a novel causative mechanism for syndromes of unknown cause

Abnormal vein function is associated with poor upright blood return in dysautonomia. Our observations suggest that abnormal pelvic blood flow is connected to many of the conditions evaluated in this study. Still, VO-CPP syndrome and its hallmark stagnant blood circulation have not been considered to have a potentially central or contributing role to other interrelated flow-deficit conditions.

Patients with seemingly disparate, multisystemic concerns are often not well evaluated in our allopathic health care system.[50] Anecdotally, we noted that several patients in this group had been seen in the emergency department 50 to 100 times or had more than 60 doctors' numbers in their contacts (suggesting a long history of severe illness). As a group, they had interacted with health care systems hundreds of times before VO-CPP was diagnosed. One had VO-CPP undiagnosed for 20 years, despite receiving treatment at a tertiary medical center. The literature shows that these conditions may be treatment resistant or thought to be psychosomatic.

Findings of the current study support a developing model of an "orthostatic flow syndrome", in which pelvic vein dysfunction acts to sequester blood below the waist during upright posture. This stagnant flow causes local pelvic pain but may also diminish blood flow above the waist. The present data suggest that abnormal pelvic vein blood flow is a possible mechanism underlying numerous conditions of unknown cause. Risk factors are unclear for pelvic venous damage that causes stagnant flow, varices, obstruction, and orthostatic pain, but the high prevalence of HSD and EDS in this group (56%)[1] may explain the dilation and fragility of pelvic veins that has long been observed by interventional radiologists (in addition to pregnancy effects[89]). However, venous pooling in the pelvis may be just one of a number of conditions (e.g., immunologic disorders, Sjögren syndrome, viral illness, central sensitization) that contribute to orthostatic intolerance and dysautonomia.[33,90–92] A separate study of young patients with comorbidities of POTS showed that POTS did not directly cause the cluster of comorbid conditions[93]; rather, POTS was itself a comorbid condition of something else.

Limitations. This study focused on the venous hemodynamics that we observed in this patient group. To assume that structural abnormalities of pelvic veins by themselves are causative of a wider spectrum of symptoms oversimplifies the larger question of causation because genetic, molecular, and neurobiologic factors (CGRP, substance p, histamine) have not been considered. Patients with EDS have alterations in collagen, and the known collagenous makeup of the extracellular matrix of vein walls could render these patients more susceptible to venous compression or engorgement.[7,29,94]

The questionnaire did not ask about symptoms of nausea (strongly associated with EDS and HSD), weight loss, or weight gain, and these stand as omissions.[18,95,96] The retrospective study design precluded having a control group, so treatment effect consists of the entire patient experience.

Patients and staff were not blinded to results because the questionnaires were used as clinical tools.

Conclusion

This review of 45 patients with VO-CPP supports the following conclusions:

1. Nonpelvic symptoms are strongly associated with this patient group, most notably migraines (69%), brain fog (76%), anxiety attacks (58%), excessive sweating (64%), hip pain (73%), diarrhea (62%), constipation (76%), and abdominal bloating (82%).
2. Nonpelvic symptoms that bundle into syndromes are strongly associated with this patient group, including POTS (29%-76%) and overlapping symptoms that are characteristic of fibromyalgia and ME/CFS (64%-82%).
3. 18 nonpelvic symptoms significantly improved with treatment. TMJ pain and skin sensitivity did not show significant improvement.
4. Not all patients showed improvement, and we believe that good clinical follow-up and subsequent referrals or consultations are vital for those patients.

The reported findings suggest that pelvic venous pooling is associated with a wider syndrome. On the basis of the present hypothesis of an orthostatic flow syndrome, many straightforward tests of pathophysiology can be designed to fill gaps in the proposed theory. Establishing widely available interventional procedures as safe and effective treatments for these conditions could be life changing for many patients.

Acknowledgements

The Scientific Publications staff at Mayo Clinic provided editorial consultation, proofreading, and administrative and clerical support.

Author contributions

Design of study and authors: Steven J. Smith, MD, Michael J. Sichlau, MD; Authors and editing: Dacre Knight, MD, Peter C. Rowe, MD; Statistical analysis: B. Holly Smith, PhD; Data collection and organization: Brenda Chen, BA.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical statement

Ethical approval

The AMITA Health Institutional Review Board approved this study (protocol 2020-0114-02).

Guarantor

Dacre Knight, MD, is the guarantor of this report.

ORCID iDs

Steven J Smith https://orcid.org/0000-0002-3369-4534
B Holly Smith https://orcid.org/0000-0001-5126-5445
Dacre Knight https://orcid.org/0000-0001-6206-0680
Peter C Rowe https://orcid.org/0000-0002-3586-2677

Supplemental Material

Supplemental material for this article is available online.

References

1. Smith SJ, Sichlau MJ, Smith BH, et al. Improvement in chronic pelvic pain, orthostatic intolerance and interstitial cystitis symptoms after treatment of pelvic vein insufficiency. *Phlebology* 2024; 39: 202–213. DOI: 10.1177/02683555231219737.
2. Smith SJ, Sichlau M, Sewall LE, et al. An online survey of pelvic congestion support group members regarding comorbid symptoms and syndromes. *Phlebology* 2022; 37(8): 596–601. DOI: 10.1177/02683555221112567.
3. Dos Santos SJ and Whiteley MS. Pelvic congestion syndrome masquerading as osteoarthritis of the hip. *SAGE Open Med Case Rep* 2016; 4: 2050313X16683630. DOI: 10.1177/2050313X16683630.
4. Shelkey J, Huang C, Karpa K, et al. Case report: pelvic congestion syndrome as an unusual etiology for chronic hip pain in 2 active, middle-age women. *Sport Health* 2014; 6(2): 145–148. DOI: 10.1177/1941738113481940.
5. Aaron LA, Herrell R, Ashton S, et al. Comorbid clinical conditions in chronic fatigue: a co-twin control study. *J Gen Intern Med* 2001; 16(1): 24–31. DOI: 10.1111/j.1525-1497.2001.03419.x.
6. Aaron LA and Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med* 2001; 134(9 Pt 2): 868–881. DOI: 10.7326/0003-4819-134-9_part_2-200105011-00011.
7. Taylor HC. Vascular congestion and hyperemia; their effect on function and structure in the female reproductive organs; the clinical aspects of the congestion-fibrosis syndrome. *Am J Obstet Gynecol* 1949; 57(4): 637–653. DOI: 10.1016/0002-9378(49)90704-8.
8. Seo JG and Park SP. Significance of fatigue in patients with migraine. *J Clin Neurosci* 2018; 50: 69–73. DOI: 10.1016/j.jocn.2018.01.032.

9. Stubberud A, Cheema S, Tronvik E, et al. Nutcracker syndrome mimicking new daily persistent headache: a case report. *Cephalalgia* 2020; 40(9): 1008–1011. DOI: 10.1177/0333102420918554.
10. Ross AJ, Medow MS, Rowe PC, et al. What is brain fog? An evaluation of the symptom in postural tachycardia syndrome. *Clin Auton Res* 2013; 23(6): 305–311. DOI: 10.1007/s10286-013-0212-z.
11. Mack KJ, Johnson JN and Rowe PC. Orthostatic intolerance and the headache patient. *Semin Pediatr Neurol* 2010; 17(2): 109–116. DOI: 10.1016/j.spen.2010.04.006.
12. Roma M, Marden CL, De Wandele I, et al. Postural tachycardia syndrome and other forms of orthostatic intolerance in Ehlers-Danlos syndrome. *Auton Neurosci* 2018; 215: 89–96. DOI: 10.1016/j.autneu.2018.02.006.
13. Hakim A, De Wandele I, O'Callaghan C, et al. Chronic fatigue in Ehlers-Danlos syndrome-Hypermobile type. *Am J Med Genet C Semin Med Genet* 2017; 175(1): 175–180. DOI: 10.1002/ajmg.c.31542.
14. Bou-Holaigah I, Calkins H, Flynn JA, et al. Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. *Clin Exp Rheumatol* 1997; 15(3): 239–246.
15. van Campen C, Rowe PC, Verheugt FWA, et al. Orthostatic stress testing in myalgic encephalomyelitis/chronic fatigue syndrome patients with or without concomitant fibromyalgia: effects on pressure pain thresholds and temporal summation. *Clin Exp Rheumatol* 2021; 10(3): 39–47. DOI: 10.55563/clinexprheumatol/1qj9zu.
16. Chelimsky G, Simpson P, McCabe N, collaborative, et al. Autonomic testing in women with chronic pelvic pain. *J Urol* 2016; 196(2): 429–434. DOI: 10.1016/j.juro.2016.03.142.
17. Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. *Pediatr Res* 2000; 48(2): 218–226. DOI: 10.1203/00006450-200008000-00016.
18. Ulas UH, Chelimsky TC, Chelimsky G, et al. Comorbid health conditions in women with syncope. *Clin Auton Res* 2010; 20(4): 223–227. DOI: 10.1007/s10286-010-0070-x.
19. Riedl A, Schmidtmann M, Stengel A, et al. Somatic comorbidities of irritable bowel syndrome: a systematic analysis. *J Psychosom Res* 2008; 64(6): 573–582. DOI: 10.1016/j.jpsychores.2008.02.021.
20. Aaron LA, Burke MM and Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med* 2000; 160(2): 221–227. DOI: 10.1001/archinte.160.2.221.
21. Mazur M, Furgala A, Jablonski K, et al. Autonomic nervous system activity in constipation-predominant irritable bowel syndrome patients. *Med Sci Mon Int Med J Exp Clin Res* 2012; 18(8): 493–499. DOI: 10.12659/msm.883269.
22. Whitehead WE, Palsson O and Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002; 122(4): 1140–1156. DOI: 10.1053/gast.2002.32392.
23. Aubry-Rozier B, Schwitzguebel A, Valerio F, et al. Are patients with hypermobile Ehlers-Danlos syndrome or hypermobility spectrum disorder so different? *Rheumatol Int* 2021; 41(10): 1785–1794. DOI: 10.1007/s00296-021-04968-3.
24. Castori M, Celletti C and Camerota F. Ehlers-Danlos syndrome hypermobility type: a possible unifying concept for various functional somatic syndromes. *Rheumatol Int* 2013; 33(3): 819–821. DOI: 10.1007/s00296-011-2275-2.
25. Dahan H, Shir Y, Velly A, et al. Specific and number of comorbidities are associated with increased levels of temporomandibular pain intensity and duration. *J Headache Pain* 2015; 16: 528. DOI: 10.1186/s10194-015-0528-2.
26. De Wandele I, Calders P, Peersman W, et al. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: a comparative study with two other EDS types, fibromyalgia, and healthy controls. *Semin Arthritis Rheum* 2014; 44(3): 353–361. DOI: 10.1016/j.semarthrit.2014.05.013.
27. De Wandele I, Rombaut L, Leybaert L, et al. Dysautonomia and its underlying mechanisms in the hypermobility type of Ehlers-Danlos syndrome. *Semin Arthritis Rheum* 2014; 44(1): 93–100. DOI: 10.1016/j.semarthrit.2013.12.006.
28. Fairweather D, Bruno KA, Darakjian AA, et al. High overlap in patients diagnosed with hypermobile Ehlers-Danlos syndrome or hypermobile spectrum disorders with fibromyalgia and 40 self-reported symptoms and comorbidities. *Front Med* 2023; 10: 1096180. DOI: 10.3389/fmed.2023.1096180.
29. Glayzer JE, McFarlin BL, Castori M, et al. High rate of dyspareunia and probable vulvodynia in Ehlers-Danlos syndromes and hypermobility spectrum disorders: an online survey. *Am J Med Genet C Semin Med Genet* 2021; 187(4): 599–608. DOI: 10.1002/ajmg.c.31939.
30. Pollack B, von Saltza E, McCorkell L, et al. Female reproductive health impacts of Long COVID and associated illnesses including ME/CFS, POTS, and connective tissue disorders: a literature review. *Front Rehabil Sci* 2023; 4: 1122673. DOI: 10.3389/fresc.2023.1122673.
31. Puledda F, Vigano A, Celletti C, et al. A study of migraine characteristics in joint hypermobility syndrome a.k.a. Ehlers-Danlos syndrome, hypermobility type. *Neurol Sci* 2015; 36(8): 1417–1424. DOI: 10.1007/s10072-015-2173-6.
32. Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. *J Intern Med* 2019; 285(4): 352–366. DOI: 10.1111/joim.12852.
33. Johansson M, Stahlberg M, Runold M, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep* 2021; 3(4): 573–580. DOI: 10.1016/j.jaccas.2021.01.009.

34. Mizumaki K. Postural orthostatic tachycardia syndrome (POTS). *Journal of Arrhythmia* 2011; 27(4): 289–306. DOI: 10.1016/S1880-4276(11)80031-1.
35. Wagner C, Isenmann S, Ringendahl H, et al. Anxiety in patients with postural tachycardia syndrome (POTS). *Fortschr Neurol Psychiatr* 2012; 80(8): 458–462. DOI: 10.1055/s-0031-1299106.
36. Clayton EW. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: an IOM report on redefining an illness. *JAMA* 2015; 313(11): 1101–1112. DOI: 10.1001/jama.2015.1346.
37. De Wandele I, Rombaut L, De Backer T, et al. Orthostatic intolerance and fatigue in the hypermobility type of Ehlers-Danlos Syndrome. *Rheumatology* 2016; 55(8): 1412–1420. DOI: 10.1093/rheumatology/kew032.
38. van Campen C, Verheugt FWA, Rowe PC, et al. Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: a quantitative, controlled study using Doppler echography. *Clin Neurophysiol Pract* 2020; 5: 50–58. DOI: 10.1016/j.cnp.2020.01.003.
39. Arnold LM, Clauw DJ and McCarberg BH, FibroCollaborative. Improving the recognition and diagnosis of fibromyalgia. *Mayo Clin Proc* 2011; 86(5): 457–464. DOI: 10.4065/mcp.2010.0738.
40. Beard RW, Reginald PW and Wadsworth J. Clinical features of women with chronic lower abdominal pain and pelvic congestion. *Br J Obstet Gynaecol* 1988; 95(2): 153–161. DOI: 10.1111/j.1471-0528.1988.tb06845.x.
41. Ritelli M, Venturini M, Cinquina V, et al. Multisystemic manifestations in a cohort of 75 classical Ehlers-Danlos syndrome patients: natural history and nosological perspectives. *Orphanet J Rare Dis* 2020; 15(1): 197. DOI: 10.1186/s13023-020-01470-0.
42. Thwaites PA, Gibson PR and Burgell RE. Hypermobile Ehlers-Danlos syndrome and disorders of the gastrointestinal tract: what the gastroenterologist needs to know. *J Gastroenterol Hepatol* 2022; 37(9): 1693–1709. DOI: 10.1111/jgh.15927.
43. Cui J, Gao Z, Blaha C, et al. Distension of central great vein decreases sympathetic outflow in humans. *Am J Physiol Heart Circ Physiol* 2013; 305(3): 378–385. DOI: 10.1152/ajpheart.00019.2013.
44. Stewart JM and Montgomery LD. Regional blood volume and peripheral blood flow in postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2004; 287(3): 1319–1327. DOI: 10.1152/ajpheart.00086.2004.
45. Stewart JM, Taneja I and Medow MS. Reduced central blood volume and cardiac output and increased vascular resistance during static handgrip exercise in postural tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2007; 293(3): 1908–1917. DOI: 10.1152/ajpheart.00439.2007.
46. van Campen CLMC, Rowe PC and Visser FC. Compression stockings improve cardiac output and cerebral blood flow during tilt testing in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) patients: a randomized crossover trial. *Medicina* 2021; 58(1): 51. DOI: 10.3390/medicina58010051.
47. Zamuner AR, Barbic F, Dipaola F, et al. Relationship between sympathetic activity and pain intensity in fibromyalgia. *Clin Exp Rheumatol* 2015; 33(1 Suppl 88): 53–57.
48. Gavrilov SG, Vasilieva GY, Vasiliev IM, et al. Calcitonin gene-related peptide and substance P as predictors of venous pelvic pain. *Acta Naturae* 2019; 11(4): 88–92. DOI: 10.32607/20758251-2019-11-4-88-92.
49. von Elm E, Altman DG, Egger M, STROBE Initiative, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; 61(4): 344–349. DOI: 10.1016/j.jclinepi.2007.11.008.
50. O'Rourke M. *The invisible kingdom: reimagining chronic illness*. New York, NY: Riverhead Books, 2022, p. 324.
51. Kim HS, Malhotra AD, Rowe PC, et al. Embolotherapy for pelvic congestion syndrome: long-term results. *J Vasc Intervent Radiol* 2006; 17(2 Pt 1): 289–297. DOI: 10.1097/01.RVI.0000194870.11980.F8.
52. O'Sullivan G and Smith S. Deep venous stenting in females. *CVIR Endovasc* 2023; 6(1): 14. DOI: 10.1186/s42155-023-00354-1.
53. Knuttinen MG, Zurcher KS, Khurana N, et al. Imaging findings of pelvic venous insufficiency in patients with postural orthostatic tachycardia syndrome. *Phlebology* 2020; 36(1): 268355520947610. DOI: 10.1177/0268355520947610.
54. Ibraheem W, McKenzie S, Wilcox-Omubo V, et al. Pathophysiology and clinical implications of cognitive dysfunction in fibromyalgia. *Cureus* 2021; 13(10): e19123. DOI: 10.7759/cureus.19123.
55. van Campen C, Rowe PC, Verheugt FWA, et al. Cognitive function declines following orthostatic stress in adults with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). *Front Neurosci* 2020; 14: 688. DOI: 10.3389/fnins.2020.00688.
56. Al-Aly Z and Topol E. Solving the puzzle of long covid. *Science* 2024; 383(6685): 830–832. DOI: 10.1126/science.adl0867.
57. Kwan AC, Ebinger JE, Wei J, et al. Apparent risks of postural orthostatic tachycardia syndrome diagnoses after COVID-19 vaccination and SARS-cov-2 infection. *Nat Cardiovasc Res* 2022; 1(12): 1187–1194. DOI: 10.1038/s44161-022-00177-8.
58. Clauw DJ. Fibromyalgia: an overview. *Am J Med* 2009; 122(12 Suppl): S3–S13. DOI: 10.1016/j.amjmed.2009.09.006.
59. Williams DA and Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *J Pain* 2009; 10(8): 777–791. DOI: 10.1016/j.jpain.2009.06.001.
60. Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J*

Med Genet C Semin Med Genet 2017; 175(1): 8–26. DOI: 10.1002/ajmg.c.31552.
61. Tinkle BT, Bird HA, Grahame R, et al. The lack of clinical distinction between the hypermobility type of Ehlers-Danlos syndrome and the joint hypermobility syndrome (a.k.a. hypermobility syndrome). *Am J Med Genet* 2009; 149A(11): 2368–2370. DOI: 10.1002/ajmg.a.33070.
62. Martinez-Lavin M. Biology and therapy of fibromyalgia. Stress, the stress response system, and fibromyalgia. *Arthritis Res Ther* 2007; 9(4): 216. DOI: 10.1186/ar2146.
63. Bulbena A, Gago J, Pailhez G, et al. Joint hypermobility syndrome is a risk factor trait for anxiety disorders: a 15-year follow-up cohort study. *Gen Hosp Psychiatr* 2011; 33(4): 363–370. DOI: 10.1016/j.genhosppsych.2011.03.004.
64. Castori M and Colombi M. Generalized joint hypermobility, joint hypermobility syndrome and Ehlers-Danlos syndrome, hypermobility type. *Am J Med Genet C Semin Med Genet* 2015; 169C(1): 1–5. DOI: 10.1002/ajmg.c.31432.
65. Tibor LM and Sekiya JK. Differential diagnosis of pain around the hip joint. *Arthroscopy* 2008; 24(12): 1407–1421. DOI: 10.1016/j.arthro.2008.06.019.
66. Peker A, Camkerten GT, Balci A, et al. Increased prevalence of pelvic venous congestion sign on sacroiliac MRI in women with clinically suspected sacroiliitis. *North Clin Istanb* 2020; 7(6): 551–556. DOI: 10.14744/nci.2020.48030.
67. Burch R, Rizzoli P and Loder E. The prevalence and impact of migraine and severe headache in the United States: figures and trends from government health studies. *Headache* 2018; 58(4): 496–505. DOI: 10.1111/head.13281.
68. Gazerani P and Cairns BE. Dysautonomia in the pathogenesis of migraine. *Expert Rev Neurother* 2018; 18(2): 153–165. DOI: 10.1080/14737175.2018.1414601.
69. Piovesan EJ, Sobreira CF, Scola RH, et al. Episodic migraine associated with postural orthostatic tachycardia syndrome and vasovagal syncope: migraine triggers neuromediated syncope. *Arq Neuropsiquiatr* 2008; 66(1): 77–79. DOI: 10.1590/s0004-282x2008000100018.
70. Lohkamp LN, Marathe N and Fehlings MG. Craniocervical instability in ehlers-danlos syndrome-A systematic review of diagnostic and surgical treatment criteria. *Global Spine J* 2022; 12(8): 1862–1871. DOI: 10.1177/21925682211068520.
71. Cuglan B, Onalan A, Ozturk S, et al. Venous leg symptoms in patients with migraine: a potential clue on the pathophysiology of migraine (Vein-Migraine study). *Eur Heart J* 2021; 42(Supplement_1). DOI: 10.1093/eurheartj/ehab724.1980.
72. Ashina M, Hansen JM, Do TP, et al. Migraine and the trigeminovascular system-40 years and counting. *Lancet Neurol* 2019; 18(8): 795–804. DOI: 10.1016/S1474-4422(19)30185-1.
73. Ruzieh M, Baugh A, Dasa O, et al. Effects of intermittent intravenous saline infusions in patients with medication-refractory postural tachycardia syndrome. *J Intervent Card Electrophysiol* 2017; 48(3): 255–260. DOI: 10.1007/s10840-017-0225-y.
74. Taylor HC. Vascular congestion and hyperemia; their effect on structure and function in the female reproductive system. *Am J Obstet Gynecol* 1949; 57(2): 211–230. DOI: 10.1016/0002-9378(49)90422-6.
75. DeLuca J, Johnson SK, Ellis SP, et al. Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. *J Neurol Neurosurg Psychiatry* 1997; 62(2): 151–155. DOI: 10.1136/jnnp.62.2.151.
76. Kanjwal K, Karabin B, Kanjwal Y, et al. Autonomic dysfunction presenting as orthostatic intolerance in patients suffering from mitochondrial cytopathy. *Clin Cardiol* 2010; 33(10): 626–629. DOI: 10.1002/clc.20805.
77. Novak P. Post COVID-19 syndrome associated with orthostatic cerebral hypoperfusion syndrome, small fiber neuropathy and benefit of immunotherapy: a case report. *eNeurologicalSci* 2020; 21: 100276. DOI: 10.1016/j.ensci.2020.100276.
78. Okamoto LE, Raj SR, Peltier A, et al. Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes. *Clin Sci* 2012; 122(4): 183–192. DOI: 10.1042/CS20110200.
79. Wang L, Wang FS and Gershwin ME. Human autoimmune diseases: a comprehensive update. *J Intern Med* 2015; 278(4): 369–395. DOI: 10.1111/joim.12395.
80. Carbone F, Fikree A, Aziz Q, et al. Joint hypermobility syndrome in patients with functional dyspepsia. *Clin Transl Gastroenterol* 2020; 11(11): e00220. DOI: 10.14309/ctg.0000000000000220.
81. Castelnuovo-Tedesco P and Krout BM. Psychosomatic aspects of chronic pelvic pain. *Psychiatr Med* 1970; 1(2): 109–126. DOI: 10.2190/ru4y-6r90-2khe-j35l.
82. Lewis I, Pairman J, Spickett G, et al. Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. *J Intern Med* 2013; 273(5): 501–510. DOI: 10.1111/joim.12022.
83. Nee J, Kilaru S, Kelley J, et al. Prevalence of functional gi diseases and pelvic floor symptoms in marfan syndrome and ehlers-danlos syndrome: a national cohort study. *J Clin Gastroenterol* 2019; 53(9): 653–659. DOI: 10.1097/MCG.0000000000001173.
84. Tai FWD, Palsson OS, Lam CY, et al. Functional gastrointestinal disorders are increased in joint hypermobility-related disorders with concomitant postural orthostatic tachycardia syndrome. *Neuro Gastroenterol Motil* 2020; 32(12): e13975. DOI: 10.1111/nmo.13975.
85. Morriss RK, Ahmed M, Wearden AJ, et al. The role of depression in pain, psychophysiological syndromes and medically unexplained symptoms associated with chronic fatigue syndrome. *J Affect Disord* 1999; 55(2-3): 143–148. DOI: 10.1016/s0165-0327(98)00218-3.
86. Mitakides J and Tinkle BT. Oral and mandibular manifestations in the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet* 2017; 175(1): 220–225. DOI: 10.1002/ajmg.c.31541.

87. Smolinska S, Winiarska E, Globinska A, et al. Histamine: a mediator of intestinal disorders-A review. *Metabolites* 2022; 12(10): 895. DOI: 10.3390/metabo12100895.
88. Theoharides TC, Twahir A and Kempuraj D. Mast cells in the autonomic nervous system and potential role in disorders with dysautonomia and neuroinflammation. *Ann Allergy Asthma Immunol* 2024; 132(4): 440–454. DOI: 10.1016/j.anai.2023.10.032.
89. Hodgkinson CP. Physiology of the ovarian veins during pregnancy. *Obstet Gynecol* 1953; 1(1): 26–37.
90. Basantsova NY, Starshinova AA, Dori A, et al. Small-fiber neuropathy definition, diagnosis, and treatment. *Neurol Sci* 2019; 40(7): 1343–1350. DOI: 10.1007/s10072-019-03871-x.
91. Castro RA, Vernetti PM, Biaggioni I, et al. Long-Term outcomes of hyperadrenergic orthostatic hypotension. *Res Sq* 2023; 3. DOI: 10.21203/rs.3.rs-3318273/v1.
92. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. *Brain* 2005; 128(Pt 11): 2518–2534. DOI: 10.1093/brain/awh605.
93. Chelimsky G, Kovacic K, Nugent M, et al. Comorbid conditions do not differ in children and young adults with functional disorders with or without postural tachycardia syndrome. *J Pediatr* 2015; 167(1): 120–124. DOI: 10.1016/j.jpeds.2015.03.039.
94. Laszlo J and Gyory G. Pathogenesis of pelvic pain. *Am J Obstet Gynecol* 1963; 85(2): 141–148.
95. Baeza-Velasco C, Van den Bossche T, Grossin D, et al. Difficulty eating and significant weight loss in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Eat Weight Disord* 2016; 21(2): 175–183. DOI: 10.1007/s40519-015-0232-x.
96. Nguyen L, Wilson LA, Miriel L, NIDDK Gastroparesis Clinical Research Consortium GpCRC, et al. Autonomic function in gastroparesis and chronic unexplained nausea and vomiting: relationship with etiology, gastric emptying, and symptom severity. *Neuro Gastroenterol Motil* 2020; 32(8): e13810. DOI: 10.1111/nmo.13810.

Appendix

Abbreviations

CGRP	Calcitonin gene-related peptide
CPP	Chronic pelvic pain
EDS	Ehlers-Danlos syndrome
HSD	Hypermobility spectrum disorder
IBS	Irritable bowel syndrome
ICD-10	*International Classification of Diseases,* Tenth Revision
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
OHQ	Orthostatic Hypotension Questionnaire
PCS	Pelvic congestion syndrome
POTS	Postural orthostatic tachycardia syndrome
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TMJ	Temporomandibular joint
VO-CPP	Venous-origin chronic pelvic pain