Symptoms in Dilating Venous Disease

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Abstract: Lower extremity venous diseases or insufficiency include clinically deteriorating conditions with morphological and functional alterations of the venous system, including venous hypertension, vascular wall structural abnormality, and venous valvar incompetency in association with an inflammatory process. In fact, the same pathophysiological processes are the main underlying mechanisms of other venous insufficiencies in different vascular territories such as Peripheral Varicose Vein (PVV), varicocele, Pelvic Varicosities or Congestion Syndrome (PCS) and Hemorrhoidal Disease (HD). Regarding the anatomical continuity of lower extremity venous system, urogenital system (pampiniform plexus in male and broad ligament and ovarian veins in female) and anorectal venous system, it is reasonable to expect common symptoms such as pain, burning sensation, pruritus, swelling, which arise directly from the involved tissue itself. High coexistence rate of PVV, varicocele/PCS and HD between each other underlines not only the same vascular wall abnormality as an underlying etiology but also the existence of common symptoms originating from the involved tissue in dilating venous disease. Accordingly, it might be reasonable to query the common symptoms of venous dilating disease in other venous vascular regions in patients with complaints of any particular venous territory.

Keywords: Dilating venous disease, chronic venous disorders, peripheral varicose vein, hemorrhoidal disease, varicocele, pelvic varicocities, pelvic congestion syndrome.

1. INTRODUCTION

Chronic Venous Disorders (CVDs) have been assigned to lower extremity vein pathologies accounting great medical and socioeconomic burdens worldwide. It has prevalence as high as 70% in women and 50% in men [1]. Venous vascular diseases have gained an increasing interest in terms of Dilating Venous Disease (DVeD) in the last decade. CVD traditionally represents the clinical situation of a general venous insufficiency of lower extremities that span a wide spectrum of clinical signs from silent telangiectatic Varicose Veins (VVs) to venous ulceration and symptoms from restlessness to intractable leg pain. Lower extremity venous diseases or insufficiency include clinically deteriorating conditions with morphological and functional alterations of the venous system including venous hypertension, vascular wall structural abnormality, and venous valvar incompetency in association with an inflammatory process [2, 3]. In fact, the same pathophysiological processes are the main underlying mechanisms of other venous insufficiencies in different vascular territories such as varicocele, Pelvic Varicosities or Congestion Syndrome (PCS) and Hemorrhoidal Disease (HD) [4]. All these clinical entities have been supposed to be a local manifestation of systemic vascular wall abnormality depending on the vascular territory and so-called DVeD [5-7]. Clinical features of all venous insufficiency diseases are connected to each other, because they have a common pathophysiological mechanism(s), mediated by the inflammatory responses of the venous wall, in which the crucial events of hemodynamic alterations pave the way for a self-sustained vicious cycle of subsequent inflammatory and proteolytic cascades [3, 4, 8, 9].

Peripheral Varicose Vein (PVV) is the most commonly evaluated one among the other DVeD in terms of mortality, morbidity and socioeconomic and cosmetic burden. On the other hand, PCS, varicocele, and HD have also their own clinical circumstances depending on the VV territory. Accordingly, symptoms of these venous dilatations may manifest itself with different clinical course, signs and symptoms (Table 1 and Fig. 1). In this review, we have essentially sought to summarize symptoms of DVeD, mainly focusing on the common ones with a brief glance on diagnostic approaches, treatment modalities and prognosis.

2. PERIPHERAL VARICOSE VEIN

Description of venous leg symptoms and their association with clinical or Doppler ultrasonographic presence of VV or CVD is still a challenging issue in phlebology. Venous symptoms might exist in all clinical, etiological, anatomical

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Table 1. Common symptoms in dilating venous disease.

| -                                | Peripheral Varicose Vein | Varicocele | Pelvic Varicosities | Hemorrhoid |
|----------------------------------|--------------------------|------------|---------------------|------------|
| Pain (aching, throbbing)         | + [19, 26]               | + [19]     | + [42, 43]          | + [58]     |
| Swelling (edema)                 | + [30, 26]               | + [72]     | + [43]              | + [57, 58] |
| Burning (heat)                   | + [18, 26]               | + [72]     | + [43]              | + [58]     |
| Pruritis (itching)               | + [23, 26]               | + [73]     | + [43]              | + [56, 58] |

Note: [1] Refers to related references.

Fig. (1). Illustration of common symptoms in different venous territories. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

and pathological (CEAP) classifications from C0 to C6 [10]. Moreover, the Edinburgh Vein Study has not shown a significant association between “venous” leg symptoms and VVs and concluded that most of these symptoms probably have a non-venous cause. Interestingly, little attention has been paid to venous leg symptoms so far. Leg symptoms are not diagnostic of venous disease but deserve to be assessed and treated appropriately [11]. Diagnostic inefficiency of venous leg symptoms might have been the result of inadequate literature and widespread use of duplex scanning for decision making irrespective of symptoms [12]. Additionally, a high co-existence rate of co-morbid diseases, such as peripheral artery disease, diabetes mellitus, arthritis, and obesity, is another possible pitfall making the assessment of lower limb symptoms more complex. Likewise, diabetes mellitus, which has never been questioned or assessed in the studies assessing the diagnostic value of venous leg symptoms, is likely to play a role as an underlying cause in the pathogenesis of aching legs, burning sensation, swelling, or itching [13]. Moreover, neither population based, nor symptom oriented studies have never included patients’ medication in their analysis. Drugs, such as calcium antagonists, diuretics, painkillers and oral anti-diabetics may affect the manifestation of venous leg symptoms [11].

The common symptoms of PVV or CVD have been included by both CEAP classification and venous symptoms scoring studies in the literature [10]. Although the diagnostic value remains to be elucidated, the most common symptoms of PVV include pain, burning sensation, night cramps, swelling, throbbing, heaviness, restless legs, pruritis and tightness. Less commonly, tenderness and ecchymosis have been considered to be symptoms of PVV [6, 14-16]. Pain may be localized along the course of a VV (phlebalgia), but it is usually felt in the lower limbs, mainly at the calf level. Although most of these symptoms are very common in the general
The symptoms of venous disorders such as swelling, burning, pruritis, and pain have been mediated through biochemical and molecular steps in which inflammatory response of venous wall results in increased permeability and cytokines release into circulatory system [2, 3]. Pain, being one of the most common venous leg symptoms, is the result of an increase in venous pressure that is transmitted to the microcirculation, resulting in the activation of subendothelial and perivascular nerve endings known as nociceptors. Localized release of proinflammatory mediators such as bradykinin, prostaglandins E2 and D2, platelet-activating factor, and leukotriene B4 [19-21] due to mechanisms triggered by capillary stasis and local hypoxia seems to play a decisive role in the activation of venous and perivenous nociceptors and may account for the occurrence of pain [22]. Likewise, primary afferent C fibers are supposed to play a role in the sensation of heat, cold and itching through the dorsal horn of the spinal cord to the brain [23]. Afferent C fibers are also capable of stimulating the circulatory and immune responses through the release of neuropeptides such as substance P and calcitonin gene-related peptide [24]. Mast cells, which have also been implicated in the pathophysiology of VV, can interact directly with the sensory terminals in afferent C fibers through the release of algogenic and pruritogenic mediators [25].

2.1. Diagnosis

After a detailed physical examination including lower extremities and abdomen, Duplex ultrasound (DUS) is recommended as the primary imaging tool in suspected CVD. Besides, phlebography, plethysmography, computed venography, and magnetic resonance venography examinations constitute alternative diagnostic tests [26]. Due to its good reproducibility, portable, non-invasive and inexpensive nature, DUS is at the forefront of imaging and diagnosing CVD [27]. Retrograde flow lasting more than 0.5 seconds in the superficial venous system, the deep femoral vein, and the calf veins; more than 1 second in the common femoral vein, the femoral vein, and the popliteal vein; and more than 0.35 seconds in the perforating veins is defined as a cut-off value to define venous insufficiency [26]. However, it should be noted that using DUS imaging may not be a suitable tool to identify patients with real venous symptoms [28]. In addition, reflux in small superficial veins solely is usually not considered for treatment due to the thought that the clinical severity of CVD is associated with the reflux in the large truncal veins [29]. Besides, there may not be an association between the truncal varicose vein diameter and patients' symptoms and clinical status [30]. A recent study demonstrated that severity of CVD is associated with the reflux in small diameter veins compared to reflux in truncal veins. There was a strong relationship between the reflux in small veins and symptoms such as edema, cellulitis, itching, ulceration, and hyperpigmentation. On the other hand, only pain was associated with the reflux in great diameter veins [31]. In this context, it is reasonable to suggest that symptom evaluation and a detailed clinical evaluation of DVeD are important as imaging varicose veins and documentation of the reflux in CVD patients [32].

2.2. Treatment

Treatment options for VVs include non-invasive modalities such as elastic stockings, intermittent pneumatic compression, leg massage, laser therapy and self-care techniques including exercise, weight loss, leg elevation, and wearing wide clothes. In addition, venotonic drugs such as sulodexide and Micronized Purified Flavonoid Fraction (MPFF) are widely used in the symptomatic treatment of CVD. Venoactive drugs have provided symptomatic improvement in up to two-thirds of the patients with CVD [33]. On the other hand, sclerotherapy, phlebectomy, and various catheter-assisted and surgical procedures include invasive treatment approaches for the treatment of CVD [26]. With appropriate treatment, the vast majority of patients have a good prognosis. Death may occur due to rupture of varicose veins causing significant bleeding [34]. However, the main cause of mortality associated with CVD is entirely venous thromboembolism, which is associated with approximately 5 times increased incidence in varicose vein patients [35].

3. PELVIC VARICOSITIES AND PELVIC CONGESTION SYNDROME

PCS is a specific entity also known as pelvic varicocele, which comprises the pathologic dilatation of broad ligament, ovarian plexus veins and incompetent ovarian veins [36]. The real prevalence of PCS is unclear, but up to 50% of patients with no apparent causes of pelvic pain have pelvic venous insufficiency or ovarian vein dilatation. It has been reported that pelvic varices occur in 10% of the general female population [36-38]. Pelvic varices have been shown to be associated with vulvar, perineal, and lower limb varices [36, 39, 40]. Moreover higher rates of venous insufficiency have been reported in lower extremity veins namely, common femoral, superficial femoral, the deep femoral vein in patients with pelvic veins >5 mm in diameter by Gultasli et al. [41]. Beyond the symptoms of superficial VV in the vulvar and inguinal area such as pain, pruritis, swelling and pain of the pelvic region, particularly ovarian is the most frequent reason for outpatient gynecologic visits and most devastating symptom of PCS.

VVVs of the pelvis have been shown to manifest itself with chronic pelvic pain in 31% of patients, coital or postcoital pain in 45% of patients, hypogastric discomfort in 60% of patients, menstrual disorders in 13%, and urinary symptoms in 9.9% of patients [42]. Symptoms of venous stasis such as aching swelling, edema and pruritis have also been reported in patients with VVs in the pelvic region [43]. In pregnant women, symptoms associated with vulvar varicosities have been more pronounced and characterized by the combination of vulvar, perineal, and inguinal varicosities with symptoms
of hormone-induced phlebopathy (swelling, heaviness, fatigue, presence of telangiectasia, reticular veins). Varicose disease of the lower extremities has been shown in the vast majority of patients with vulvar varicosities [42].

3.1. Diagnosis

Physical examination often reveals vulvar varicosities accompanying pain on cervical motion. In addition, hemorrhoids and VVs of the perineum, buttocks or lower extremities may be observed, whereas their presence is not required for the diagnosis. Pelvic ultrasonography is the first-line investigation tool due to its non-invasive and radiation sparing nature, cost and reproducibility. It provides information about the diameter of veins, and antegrade and retrograde flow. Computed tomography and magnetic resonance imaging are alternative non-invasive imaging modalities. Venography and laparoscopic examinations constitute invasive imaging tools. Among these, venography is considered the gold standard for the diagnosis of PCS.

3.2. Treatment

Treatment options include medical, surgical and endovascular interventions. Non-steroidal anti-inflammatory drugs, ovarian suppression, medroxyprogesterone acetate, gonadotrophin-releasing hormone agonists, and venotonic drugs are medical treatment options. Cognitive behavioral therapy has also been shown to be beneficial when combined with surgical and endovascular treatment procedures [44–46]. Surgical hysterectomy with or without oophorectomy, ovarian vein ligation, hormonal treatment and endovascular embolization have shown symptomatic significance in more than two-thirds of the patients with PCS [47, 48].

4. HEMORRHOIDS

Hemorrhoids or HD is one of the most common diseases of the anorectal region, which has an important socioeconomic health burden. Self-reported incidence of hemorrhoids has been reported to be 10 million per year in the USA, which corresponds to 4.4% of the general population [49]. The exact incidence of hemorrhoids is unknown, and estimates vary [49–52]. Prevalence studies suggest a rate of around 40% [53]. Pregnancy is associated with an increased risk for hemorrhoids and there is a slightly increased prevalence in women compared with men. Hemorrhoids become more common with age in both genders, with a peak incidence between the ages of 45 and 65 years [54]. Both structural changes in anal channel and venous system play a role in the pathogenesis of hemorrhoids. Hemorrhoidal veins are typically characterized by dilated, thin-walled vessels within the submucosal arteriovenous plexus [55]. Typical complaints associated with HD include pain, bleeding, pruritis, burning, and swelling [56]. Patients that have symptomatic internal hemorrhoids may complain of itching, bleeding, pain, burning, prolapse, mucus discharge, moisture, swelling or difficulty with perianal hygiene [57]. Patients may describe a sensation of fullness, an urge to defecate, or a sensation of incomplete defecation with internally prolapsing internal hemorrhoids [58].

Epidemiologically higher rates of hemorrhoid and PVVs have been documented in patients with HD by Aslan et al. [59], who reported an increased prevalence of PVVs in patients with varicocele. Likewise, Holdstocks et al. reported the coexistence of hemorrhoids and internal iliac vein reflux linked with PVV in their study [39]. These three venous territories, namely PVV, pelvic vein and hemorrhoidal veins, are closely related to each other through a volume or pressure continuity or direct connections [60]. In this regard, it is reasonable to expect that refluxing pelvic veins might be of significance in the pathophysiology of the hemorrhoids [60]. Additionally, the association of hemorrhoids with other venous continuity has been reported in literature recently. Kilciler et al. [61] reported 25% coexistence of hemorrhoids with varicocele in patients with chronic constipation. Besides, Godeberge et al. demonstrated the coexistence of HD and CVD in their study population, highlighting the significance of examining for CVD among patients with HD. CVD presence and severity have also been shown to be associated with HD grade in this study [62].

4.1. Diagnosis

The diagnosis of HD depends on a detailed clinical history, digital rectal examination and anoscopy. In general, hemorrhoids are classified into three groups according to their location: external, internal, and mixed type. External hemorrhoids are located distal to the dentate line and covered by skin, while internal hemorrhoids are covered by anal mucosa and located above the dentate line. Mixed type hemorrhoids are a combination of internal and external types. Additionally, internal hemorrhoids are classified according to their appearance and severity of prolapse: grade 1, if the anal cushions bleed but do not prolapse; grade 2, if the anal cushions prolapse through the anus while straining and reduce spontaneously; grade 3, if the prolapsed anal cushions require manual reduction; and grade 4, if the prolapsed cushions stay out constantly without reduction. Grade 1 and 2 HD are defined as “low-grade”, while grade 3 and 4 HD are considered as “high-grade” [63]. Low-grade hemorrhoids are easily managed with conservative treatment strategies such as medication and lifestyle changes.

4.2. Treatment

Medication includes topical treatments such as lubricants, local anesthetic agents, corticosteroids, antibiotics, and anti-inflammatory agents; and orally taken venotonic drugs. On the other hand, lifestyle modifications include fluid consumption, fiber intake, and reduced fat consumption, avoiding straining and regular exercise. Office-based and surgical procedures decided by choice of surgeon and patients can effectively treat hemorrhoids refractory to medical therapies. Rubber band ligation, sclerotherapy and infrared coagulation are also operative procedures preferred in the treatment of HD. Acutely thrombosed hemorrhoids, incarcerated internal hemorrhoids, and strangulated hemorrhoids are considered as “complicated” hemorrhoids and usually require surgical interventions. The outcome of the disease is usually good after an appropriate treatment [58, 63].

5. VARICOCELE

Varicocele, a disease of pampiniform plexus, affects approximately 15% of the world's male population and is usually asymptomatic and diagnosed incidentally [64, 65].
Pathogenesis of varicocele involves structural changes in the venous vascular wall and venous valve in association with increased venous pressure [66-68]. Varicocele has been supposed to be not only a disease of pampiniform plexus but also a local manifestation of systemic vascular wall abnormality including arterial territory. Increased prevalence of varicocele has been reported in patients with coronary artery ectasia compared to those with coronary artery disease [69]. Likewise, Kilic et al. [70] also reported that varicocele is associated with an increased prevalence of PVVs. Another recent study published by Oztekin and colleagues has demonstrated that flow-mediated dilatation of brachial artery is significantly lower in high grade symptomatic varicocele patients suggesting endothelial dysfunction might have a role in the pathophysiology of varicocele [71]. The authors of this study have recommended that symptomatic varicocele patients should be evaluated regularly for cardiovascular pathologies. Sakamoto and Ogawa [72] demonstrated that men with bilateral varicoceles have increased mean diameter, and peak retrograde and antegrade flow velocity of the prostatic venous plexus. While most patients with varicocele remain asymptomatic, the most common clinical symptoms include male factor infertility and chronic scrotal pain [65]. Symptomatic varicoceles are typically described as a dull, aching, or throbbing pain in the testicle, scrotum, or groin; rarely, varicocele-induced pain can be acute, sharp or stabbing. A varicocele may also be described as a scrotal heaviness that worsens with exercise, activity, or after standing for prolonged periods of time. Proposed mechanisms include compression of nearby neural fibers by the dilated veins, increased scrotal temperature, oxidative stress to the testicular parenchyma, and tissue ischemia secondary to venous stasis [65, 73]. Although data is controversial, varicocele has also been implicated as a cause of angiokeratoma of scrotum or groin due to increased venous pressure [74, 75]. Patients with angiokeratoma may complain of itching, soreness and bleeding [74-78]. In recently published Vein-Turkey study, we have demonstrated for the first time that varicocele patients have more frequent venous leg symptoms compared to patients without varicocele and severity of symptoms correlates with the degree of the varicocele. In detail, patients with varicocele have higher rates of pain, burning, swelling, and pruritis on their lower extremities compared to those without varicocele [79].

5.1. Diagnosis

Varicocele is usually diagnosed during the evaluation of infertility and physical examination constitutes the most important diagnostic test. The grading system, which was developed by Dubin and Amelar based on the clinical features during the examination, is widely used for the evaluation of varicocele: grade 1, if the varicocele is palpable only during Valsalva maneuver; grade 2, if easily palpable but not visible; and grade 3, if easily visible. In addition, grade 0 (subclinical), if varicocele detected by Doppler ultrasonography is nonpalpable [80, 81]. In addition to physical examination, a varicocele can be detected with high-resolution color-flow Doppler ultrasonography, which will show dilatation of the vessels of the pampiniform plexus. It is a non-invasive, economic imaging modality with high sensitivity and can be used in the outpatients’ room.

5.2. Treatment

The management of varicocele includes conservative strategies such as scrotal elevation, non-steroidal anti-inflammatory drugs, and limited physical activity, which are not effective in most of the patients. Asymptomatic varicoceles do not require treatment unless asymptomatic. Surgical procedures are indicated for patients with resistance to conservative treatments or persistence of symptoms despite a reasonable period of observation and inability to perform the limited activity. Varicocelectomy is accepted as a standard surgical approach for symptomatic varicoceles [80]. Treatment of varicocele may improve semen parameters and fertility rates in the majority of patients [82].

6. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Having a new insight into the symptoms of DVeD would certainly improve our understanding of the pathophysiology of venous disease. Detailed clinical history with questioning the common or presenting symptoms of other vascular territories plays a pivotal role not to overlook the presence of DVeD and is the cornerstone of the diagnosis. Afterwards, selected patients should be considered for further examination and tests such as ultrasonographic imaging depending on the suspected vascular region. Although it is not practical to suggest routine and complete cardiovascular evaluation in the light of the current scientific evidence, it should be kept in mind that data from recent studies point out a generalized vascular wall pathology including both venous and arterial territories in these patients. For instance, the coexistence of hemorrhoid and PVVs [59], hemorrhoid and varicocele [61], varicocele and coronary ectasia [69], varicocele and PVV [70] has been demonstrated in previous studies. Nevertheless, all of these studies aimed to investigate an epidemiological and pathophysiological relationship instead of symptoms of patients. In this context, future research on DVeD should focus on not only the pathophysiological but also the symptomatologic association of venous diseases.

High coexistence of venous diseases raises the question that whether these patients are underdiagnosed in the clinics, due to the lack of a recommendation about routine and complete cardiovascular evaluation. Besides, the lack of multidisciplinary approaches is likely another reason for possible underdiagnosis. In addition, it is not possible to suppose the exact number of underdiagnosed venous pathologies. We believe that future researches will shed light on our knowledge about this issue. Diagnostic techniques including the most commonly used duplex ultrasonography, plethysmography, venous pressure measurement, phlebography, computed tomography venography, magnetic resonance venography have all been well described in Clinical Practice Guidelines of European Society of Vascular Surgery as recommendations [26]. In order to have a prompt diagnosis and guide the therapy, clinicians should evaluate the patients systematically regarding the symptoms and physical examination and suspect DVeDs.

Venotonic drugs are widely used in the symptomatic treatment of venous diseases and the effects of these agents on DVeDs should also be investigated in future studies. However, previous clinical and animal model studies give
important clues about this issue. Arman and colleagues have observed favorable effects of MPFF therapy on the regression of testicular damage secondary to varicocele in male Wistar rats [83]. Kılç et al. [84] found improved varicocele-associated pain with MPFF therapy in a small patient group. Beneficial effects of MPFF therapy have also been shown on pelvic pain of women with laparoscopically diagnosed PCS [46]. Pharmacologic enhancement of venous tonus and improvement in venous dysfunction and stasis have been thought to be underlying mechanisms of pain in PCS [46]. In contrast to PCS and varicocele, venotonic treatment has been a well-established treatment modality in patients with HD. A meta-analysis of randomized trials of venotonic agents has shown a significant reduction in pain by 65%, itching by 35% and the risk of bleeding by 67% [85]. Regarding the pharmacologic effects of flavonoids on microcirculation permeability, inflammation and venous tonus [57], it is reasonable to expect observing beneficial effects in other territories of DVeD. However, more studies, especially randomized placebo-controlled trials, are warranted to assess the possible use of flavonoids on all aspects of DVeD.

The concomitant venous disease of the lower extremities, pelvic including iliac, ovarian, testicular vein and perianal veins would put forward insights into the pathophysiology and therapeutic approaches as well. Given the fact that venous diseases, VVs or venous reflux originate from the vascular pathology of the vascular wall, studies should also focus on the genetic or inherent basis of the dilating vascular disease. Individual assessments of patients in different clinics such as cardiology, urology, gynecology, or gastroenterology would be gathered in a systematic manner in selected patients complaining of signs and symptoms of DVeD.

CONCLUSION

Symptoms of DVeDs have been known for decades in any vascular territory. However, their systematic descriptions are so scarce in the literature. Frequently one or more heading symptoms or cosmetic concerns are the main requirements for medical attention. In everyday clinical practice, clinicians are faced with the multifaceted presentation of DVeD. The assessment of venous symptoms in the presence of other comorbid diseases such as arthrosis, diabetes mellitus, osteoporosis remains as one of the major clinical issues. On the one hand, extensive varicosities may be entirely asymptomatic; on the other hand, relatively small varicosities can cause significant symptoms. Determining which lower limb symptoms are caused by VVs remains a matter of individual clinical judgment [86]. It is rather difficult to assess venous symptoms in individuals without clinically visible VVs. In this regard, description of the normal vein or VV might be a diagnostic challenge in the clinical evaluation of venous leg symptoms [87, 88].

Regarding the anatomical continuity of lower extremity venous system, urogenital system (pampiniform plexus in male and broad ligament and ovarian veins in female) and anorectal venous system, it is reasonable to expect common symptoms such as pain, burning sensation, pruritus, swelling, which arise directly from the involved tissue itself. High coexistence rates of PVV, varicocele/PCS and HD between each other underline not only the same vascular wall abnormality as an underlying etiology but also existence of common symptoms originating from the involved tissue in DVeD. On the other hand, each diseased venous vascular territory manifests itself with clinically different predominating symptoms such as infertility in patients with varicocele, chronic pelvic pain in patients with PCS, and bleeding in those with hemorrhoids. It might be reasonable to query the common symptoms of venous dilating disease in other venous vascular regions in patients with complaints of any particular venous territory.

AUTHORS’ CONTRIBUTION

All the authors have substantial contributions to concept and design, or acquisition of data, analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

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