

Chronic venous insufficiency symptoms and its potential causes: Are we doing it right?

Síntomas de la insuficiencia venosa crónica y sus posibles causas. ¿Lo estamos haciendo bien?

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Abstract

Background: Chronic venous insufficiency has symptomatology associated with venous hypertension; until now they have never been approached for the purpose of describing a characteristic pattern presentation allowing a clinical differential diagnosis. The largest study addressing this topic is the Vein Restoration Study (VRS) that included 38,750 patients demonstrating discrepancy between signs and symptoms among age groups studied, coupled with the fact that in our own medical practice as a vascular specialist we may face patients with advanced degrees of venous hypertension but completely asymptomatic. Symptoms have been reported as subjective and potentially confoundable with other comorbidities such as neuropathies, as there is a close anatomic relationship between veins and nerves. **Methods:** Electronic literature searches were performed from 1947 to 2021 by the first author using PubMed and the Cochrane Central Register of Controlled Trials. **Results:** We found 1200 articles using those related to venous symptoms noting any of them focused on the pattern presentation with evident discrepancies between signs and symptoms. **Conclusion:** Venous symptoms must be considered subjective, and potentially caused by an underlying and undefined condition or comorbidity. Until now, no author has demonstrated that these are caused directly by venous disease.

Key words: Venous symptoms. Chronic venous insufficiency. Venous hypertension.

Resumen

Introducción: La insuficiencia venosa tiene síntomas relacionados con hipertensión venosa, pero hasta ahora éstos no se han enfocado con el propósito de describir un patrón de presentación característico que permita establecer de forma clínica un diagnóstico diferencial. El estudio más grande Vein Restoration Study (VRS) que incluyó a 38,750 pacientes demostró una discrepancia de los síntomas y signos entre dos grupos etarios estudiados; en la práctica de los autores como especialistas vasculares es posible atender a un paciente con grados avanzados de hipertensión venosa pero asintomáticos. Los síntomas se han notificado como subjetivos y tal vez confundibles con los de otras anomalías comórbidas como las neuropatías, dado que existe una estrecha relación anatómica con los nervios. **Métodos:** Búsqueda electrónica de artículos en relación con síntomas venosos entre los años 1947 y 2021, por investigador principal, a través de PUBMED y Cochrane. **Resultados:** Se encontraron 1200 artículos y se utilizaron aquéllos vinculados con síntomas venosos, sin identificar alguno enfocado en el patrón de presentación esperado y con evidentes discrepancias entre signos y síntomas. **Conclusión:** Los síntomas venosos deben considerarse como subjetivos, y pueden ser causados por una comorbilidad subyacente y no identificada. Hasta ahora ningún autor ha demostrado que estos sean causados de forma directa por la enfermedad venosa.

Palabras clave: Síntomas venosos. Enfermedad venosa crónica. Hipertensión venosa.

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Introduction

A book regarding the description and clinical characterization of the symptoms provoked by chronic venous insufficiency (CVI) was first published in 1964¹. It is no surprise that anatomy and the initial comprehension of venous physiology but above all, its physiopathology was not concentrated by a vascular specialist (vascular surgeon, angiologist, or vascular medicine specialist) because the first workgroup created and identified in the world with medical and no surgical purposes was in 1991² in Europe, emitting first recommendations for the specialty in 1993³. Arnoldi¹, a recognized physician focused on the treatment of diverse orthopedic pathologies, was first in writing a 75 page and 15 chapter's book titled "The venous return from the lower leg in Health and CVI: A Synthesis" based on its own experience and observations on dynamic phlebography, collaboration among with Bauer, Barcroft, Burch, and Sodeman as well of the anatomic studies previously reported by Askar, Cockett, Dodd, Eger, and many other authors; 35 bibliographic references, published in different scientific medical journals.

Arnoldi, based on 307 patients to whom he made phlebography's, characterized five symptoms described in [table 1](#). Arnoldi focused predominantly on bursting diffuse pain but considered all symptoms as subjective. He associated bursting pain mostly to anomalies of the deep venous system, and almost exclusively to extent deep valvular incompetence, either post-thrombotic syndrome (PTS) or as he referred idiopathically. About 17.9% (n = 55) of the cohort studied without symptoms and as high as 42% (n = 21) in Group Ia (only varicosities, normal venous pump, and no thrombosis) and 22% in Group IIa (impaired but functional venous pump with incompetent perforating veins compensating at some point with the superficial system) reporting themselves as asymptomatic, even though by severity, Group II had the higher venous hypertension with 50% of ulcers in IIa and 80% in Group IIb¹.

All the authors as mentioned above have described different surgical techniques, some of them surprising attempts to achieve clinical improvement to patients with severe venous pathology as Bauer's reported technique resecting popliteal vein, treating what we know as PTS, and first-ever lineal venoplasty⁴, forerunner to mayor stripping studies realized by Boyd⁵. All of them had surgical training, and their contributions to our recent experience were a cornerstone. In America, a pioneer in understanding venous function was Seligman in 1956⁶ and its contribution to surgical technique in

1963⁷. Trying to understand physiology, physiopathology, and a way to surgically treat venous disease, all of them described in their studies edema, color ochre discoloration, and sclerosis of the skin (described as induration) with the consequent development of stasis ulcer. The skin's sclerosis was subsequently considered a dermoepidermitis, identifying since 1969 eczema as a characteristic sign in these patients⁸. All of them considered nosologically signs, many of which were described, as well as new strategies for surgical treatment, reported based on experiences in areas as phlebology, allergology, topic dermatotherapy, and dermatosurgery⁹. Never characterized symptoms nor efforts were focused on determining potential comorbidities explaining such symptoms.

Materials and methods

Electronic literature searches were performed from 1947 to 2021 by the first author using PubMed and the Cochrane Central Register of Controlled Trials. The search strategy included "CVI" AND "symptoms" NOT "treatment;" "CVI" AND "symptoms;" "CVI" AND "symptoms pattern presentation," then, we manually search relevant articles missed by electronic searches, language limitation to English and Spanish. After identifying relevant titles, abstracts were revised by the author trying to select those related to venous symptoms and pattern presentation not finding a single one, thereby deciding to revise and concentrate those symptoms in a way allowing us to identify the expected pattern presentation, opening a previously closed subject on to understand venous symptoms better.

Results

There were found 1200 articles. Approximately between 1960 and 1990, all literature reported regarding signs and symptoms is not available online, only historical record; nonetheless, titles focus almost solely on signs provoked by venous stasis, along with different surgical approaches⁸⁻¹⁷. In most recent studies, few of them exclusively concentrate on symptoms, and as shown in [table 2](#)^{1,18-21}, none of them report pattern presentation²²⁻²⁴.

The symptoms that patients with venous hypertension present have varied little over the years ([Table 2](#))^{18,19,25,26}. There are no reports in the literature regarding asymptomatic patients, regardless of the severity of the disease, including chronic ulceration. Some papers report generic symptoms like pain in different degrees. Others

Table 1. Symptoms and signs reported by Arnoldi in its book, 1964¹

Records the subjective symptoms noted on the day of admittance in the various phlebographic groups, together with the number of leg ulcers						
Symptoms	Group Ia (n = 48)	Group Ib (n = 12)	Group IIa (n = 130)	Group IIb (n = 49)	Group III (n = 68)	Total (n = 307)
Without	21 (42%)	3 (25%)	28 (22%)	2 (4%)	1 (1.5%)	55 (17.9%)
Heaviness and tiredness	24 (48%)	8 (67%)	57 (43%)	34 (70%)	37 (54%)	160 (52.1%)
Slight pain	12 (24%)	5 (42%)	43 (33%)	18 (38%)	22 (32%)	100 (32.5%)
Bursting pain	0	1 (8%)	18 (14%)	13 (27%)	31 (46%)	63 (20.5%)
Restless legs and nightly cramps	1 (2%)	3 (25%)	18 (14%)	6 (13%)	13 (29%)	41 (13.3%)
Leg ulcers	7 (14%)	4 (33%)	69 (50%)	50 (81%)	9 (12%)	139 (45.2%)

Table 2. Symptoms of venous hypertension reported by some authors in literature

Prevalence of symptoms							
Author/year			Author/year				
Arnoldi ¹ , 1964 (307)	Symptoms	Total	Marston ¹⁹ , 2010, two sub-analysis		Symptoms	Total	
55	Without	17.9%	National venous screening program ²⁷ (2234)		Pain	77%	
160	Heaviness and tiredness	52.1%			Mild	29%	
100	Slight pain	32.5%			Moderate	19%	
63	Bursting pain	20.5%	The San Diego Study ²⁰ (2211)		Cramps	10-15%	
41	Restless legs and cramps	13.3%			Heaviness	10-15%	
139	Ulcer	45.2%			Swelling	10-15%	
					Pain	<10%	
Duque ¹⁸ , 2005 (100)	Symptoms	Total	Vein Restoration Study ²¹ , 2018 (38,750)		Symptoms	Total	
			A <65a 27,536	B >65a 11,214		A <65a	B >65a
66	Itch	66%	4717	1485	Aching	17.1%	13.2%
44	Pain in itching area	44%	6718	2803	Cramping	24.3%	24.9%
63	Leg fatigue	63%	7348	2736	Fatigue	26.6%	24.3%
62	Leg pain	62%	8315	3005	Heaviness	30.1%	26.7%
48	Muscle aches	48%	2843	1097	Restless legs	10.3%	9.7%
47	Heaviness	47%	16,907	6159	Pain	61.3%	54.9%
53	Cramps	53%	6284	3300	Swelling	22.8%	29.4%
74	Burning sensation	47%	2063	624	Burning	7.4%	5.5%
			1950	542	Itching	7%	4.8%

focus on heaviness, tiredness, pain, and swelling indistinct to edema. Some are more precise at describing

symptoms and signs, establishing a clear difference between swelling and edema but none of them focusing

or even mentioning a symptom pattern presentation and differential diagnosis.

It should be noted from [table 2](#), in the study reported by Duque, itching was the predominantly sign and focus of the study; 66 patients referred itching and 62% had presented it in the past 6 months, 95% mostly during late-afternoon and night, 50% of whom even had sleeping troubles, 40% woke up during the night because of it, and 15% requiring sleep meds to achieve it. About 62% of patients said that itch was in the pretibial region, 45% posterior calf region, and 40% in the thigh with a symmetrical pattern in both legs in 64%. By last, 44% of patients referred pain and 74% burning sensation in the same spot of itching, all of them characteristic neuropathy symptoms, with no correlation between symptoms and severity of the disease, authors concluding according to observations that symptoms despite no correlation with severity, it does with chronic venous disease¹⁸.

In a revision published by Marston¹⁹ from a sub analysis of “National venous screening program” (NVSP)²⁷ and “San Diego Population Study” (SDPS)²⁰, the results contrast regarding pain, reported as high as 77% in NVSP and 10-15% in SDPS; author concluded that although pain is the most predominantly symptom, none of the symptoms referred are specific for the disease, and multiple other diseases may be confused with venous insufficiency. Noting that neither of the two studies described symptoms in the text nor presented frequency, only signs or QoL questionnaires. In “Vein Restoration Study” (VRS)²¹, one of the largest, included prospective and retrospectively 38,750 patients in two main groups, those aged more than 65 years and those aged < 65 years with a significant statistical difference between groups in symptoms and signs. Those aged < 65 years had more frequent pain (61.3% vs. 54.9%), fatigue (26.6% vs. 23.4%), heaviness (30.1% vs. 23.7%), and aching (17.2% vs. 13.2%) $p < 0.0001$ ([Tables 2 and 3](#)), but higher rates of signs in those aged more than 65 years such as swelling (29% vs. 23%), skin changes (12% vs. 6%), hyperpigmentation (8% vs. 4%), edema (55% vs. 43%), and ulcer (5% vs. 2%) $p < 0.0001$ ([Table 3](#)), with no significant difference between cramping (25% vs. 24%) and restless legs (10% vs. 10%). Thus, it is necessary to do further studies explaining why, even though patients aged more than 65 years old presented more signs, they had fewer symptoms with strong statistical significance.

Table 3. Signs and symptoms reported in “Vein Restoration Study”²¹

	2015	2016	Total
Age			
< 65 years	11,252	16,284	27,356
> 65 years	4409	6805	11,214
Gender			
Women	12,204	17,980	30,184
Men	3450	5100	8550
Presenting symptoms	<65 years No. (%)	>65 years No. (%)	p value
Aching	4714 (17)	1485 (13)	< 0.0001
Bleeding	417 (2)	210 (2)	< 0.01
Cramping	6718 (24)	2803 (25)	< 0.21
Fatigue	7348 (27)	2736 (24)	< 0.0001
Heaviness	8315 (30)	3005 (27)	< 0.0001
Pain	16,907 (61)	6159 (55)	< 0.0001
Restless legs	2843 (10)	1097 (10)	< 0.11
Skin changes	1539 (6)	1290 (12)	< 0.0001
Spider veins	4625 (17)	1367 (12)	< 0.0001
Swelling	6284 (23)	3300 (29)	< 0.0001
Thrombosis	1189 (4)	304 (3)	< 0.0001
Ulcer	576 (2)	542 (5)	< 0.0001
Varicosities	1607 (6)	567 (5)	< 0.02
Associated symptoms			
Burning	2063 (7)	624 (6)	< 0.0001
Dermatitis	171 (1)	137 (1)	< 0.0001
Edema or swelling	11,872 (43)	6155 (55)	< 0.0001
Hyperpigmentation	1159 (4)	925 (8)	< 0.0001
Itching	1950 (7)	542 (5)	< 0.0001
Pelvic symptoms	199 (1)	22 (0)	< 0.0001
Skin ulceration	332 (1)	130 (1)	< 0.718
Superficial thrombophlebitis	206 (1)	84 (1)	> 0.99
Tingling	1027 (4)	316 (3)	< 0.0001

Discussion

Today, we understand that venous pathology, either primary or secondary, has important mechanical implications as, in the first place, the unidirectional valve function, which works as cardiac valves, through dynamic gradient pressure. Veins, unlike cardiac valves, are considered capacitance vessels, meaning their distensibility is high. They work along with muscles function in the calf against hydrostatic pressure. Unlike the myocardium, veins are not autonomic. They depend directly proportional to muscular trophic and tropism, physical

activities, and movements in the hip, knee but mostly ankle, even mobility in metatarsophalangeal joints, so any pathologic condition targeting those previously mentioned may provoke muscular venous pump dysfunction, venous stasis, and its consequences.

Signs of venous disease are secondary to venous hypertension and are fully elucidated and include dilation of capacitance vessels until the formation of varix of different degrees, paths, and thickness, the presence of skin discoloration such as blanché atrophy and ochre color and induration now known as dermatoliposclerosis, edema, eczema, and as maximal consequence ulceration, which frequently is chronic and relapsing, mostly in perimalleolar territory, but atypical locations too as calf, toes, or sole. On the contrary, venous symptoms had been transcribed article by article, book by the book based on the observational results in 307 patients, and as the same Arnoldi mentioned, totally subjective. Those symptoms, even nowadays, are subjective in the validated quality of life (QoL) questionnaires, such as SF-36 and Euro-QoL DF and specific for the disease like CIVIQ-2. They are validated on precisely these subjective symptoms (mostly pain). CIVIQ-2 was presented in 1996 and translated into many languages and includes pain in the past weeks (without any specification), physical, social, and psychological repercussions in daily activities. Many authors use these questionnaires based on subjective symptoms as a guide to evaluating surgical, therapeutic compression, and pharmacological outcomes²⁸⁻³⁰.

Returning to previous stipulated conceptions by Arnoldi, where symptoms referred by patients were subjective and by Marston assuming multiple etiologies can produce similar symptoms, open, diverse investigation questions to answer to comprehend symptoms better.

Symptomatic differential diagnosis

EDEMA

First of all, it would be essential to establish a pattern presentation of symptoms associated with venous insufficiency; based on our physiological and physiopathological knowledge, whose we comprehended better than Arnoldi, Bauer, and Barcroft^{31,32}. The venous pump has a 65% ejection fraction approximately, calculated by indirect means (plethysmography), to favor venous return against the column of hydrostatic pressure from ankles to the right atrium, going around 100 mmHg in the erect position and < 30 mmHg after 12 dorsiflexions of ankle's foot³³⁻³⁸. We also know in

Table 4. Etiology of edema of the leg by Dale in 1973¹⁵

General	Lymphatic
Hepatic cirrhosis	Primary lymphedema
Heart failure	Congenital
Nephrosis	Praecox
Hypoproteinemia	Tarda
Allergic disorders	Acquired secondary edema
Idiopathic cyclic edema	Infection
Venous	Filaria
Thrombosis acute	Lymphogranuloma venereum
Chronic post-phlebotic syndrome	Tuberculosis
Extrinsic pressure	Syphilis
Tumor	Tumor
Retroperitoneal fibrosis	Post-radiation
Pressure of overlying iliac artery	Post-operative
Interruption	Toxic
Trauma	Snakebite
Surgical	Insect bite
Arteriovenous fistula	Miscellaneous
	Infectious
	Inflammation after vascular repair

supine position hydrostatic pressure in every point measured turns equal; thus, we assume that venous edema (or symptoms) must never be present at rest while favoring gravitational potential energy, and not only improve but also disappear after some minutes of leg elevation, and above all in early disease stages.

Edema is studied since the eighties and caused by many diseases, initially by Andrew Dale¹⁵ in a text of 66 pages. It laid the foundations for actual etiological classification (Table 4), which required modifications based on physiopathologic mechanisms better defined. Including increased hydrostatic pressure, increased capillary permeability, lymphatic obstruction, hypoalbuminemia, hypercoagulability, refeeding edema (fasting, sodium retaining), and drug induced³⁹, thus modifying Dale's table based on physiopathologic mechanisms to our current knowledge would be as table 5^{40,41}.

This comprehension leads us to affirm that venous edema is caused firstly, by increased hydrostatic pressure in acute illness, plus to the increased capillary permeability in its chronic form, and finally by the potential neurogenic role reported by Napier⁴². In patients with joint movement limitation by any reason, either neurogenic or even without neuropathy secondary to inappropriate muscular contractions, which may be caused by multiple reasons not necessarily neuropathic, rarely studied. However, without considering this last precept, acute venous edema must have a characteristic pattern presentation caused by increased hydrostatic pressure, different from the causes presented in **table 5**.

Given the fact that it is caused mostly by standing postures and less intense during sitting positions⁴³, not abolished by the effects of gravitational potential energy during walking, exerted mechanically (but not exclusively) by venous valves⁴⁴, absent in patients with valvular dysfunction. Therefore, edema must disappear during leg elevation for some minutes and mainly during absolute rest, exacerbated during walking directly proportional to activity, repeating this pattern day after day, never present at mornings in early stages (**Table 6**).

In the context of chronic venous disease, when venous hypertension is constant, and the valve extent damage is vast and involves numerous valves, plus the increased hydrostatic pressure and intrinsic relationship with that column of blood with capillaries, factors are added that contribute to the increase of vascular permeability. Leukocyte trapping (adhesion and migration of macrophage's, T lymphocytes, and mast cells), pro-inflammatory cytokines (select in, ICAM-1, ELAM-1, VCAM-1, VEGF, and TGF-β1), and the role of pressure and shear stress when inverted promoting inflammation and reactive free radical formation had been identified as contributing factors⁴⁵⁻⁴⁷. Under this condition, edema may, accordingly to severity, be present in the morning, less in patients with thin skin trophic changes (or without it) and more in patients with profound skin sclerosis and atrophy blanche, but above all in those with eczema and ulcer; not excluding foot, fingers, or only be present in ankle or shin.

We should avoid confounding edema with venous swelling, which depends directly on venous volume in muscular veins such as soleus and gastrocnemius plexuses in the calf, considered the venous bellows in the leg; when present, there will not be Godette sign during digit pressure because the excess of volume will be in the intravascular compartment but not in the interstitial

Table 5. Etiologic classification of edema of leg by Dale modified by our current concepts^{15,39-42}

Increased hydrostatic pressure	Lymphatic, primary
Hepatic cirrhosis	Primary
Cardiac failure	Congenital
Acute and chronic renal disease	Praecox
Venous insufficiency	Tarda
Arteriovenous fistula	Musculoskeletal
Arterial and venous anomalies	Ruptured Baker's cyst
Arteriovenous malformations	Ruptured medial head of gastrocnemius
May-Thurner syndrome, pelvic congestion	Compartment syndrome, muscular infarct
Acute venous thrombosis	Neurogenic, reflex sympathetic dystrophy
Post-thrombotic syndrome	Lymphatic, secondary
Lymphatic extrinsic compression	Infection sequelae
Tumor	Filaria
Retroperitoneal fibrosis	Lymphogranuloma venereum
	Tuberculosis
Hypoalbuminemia	Syphilis
Protein-losing enteropathy	Post-radiation
Malnutrition	Post-operative
Liver disease, nephrotic syndrome, preeclampsia	Drug induced
Increased capillary permeability	Opioids
Acute and chronic bacterial infections	Antihypertensives (+ channel calcium blockers)
After vascular repair	NSAID
Snakebite	Hormones: corticosteroids, estrogen, testosterone
Insect bite	Pioglitazone, rosiglitazone
Chronic venous edema, mix	Monoamine oxidase inhibitors
Allergic reactions, myxedema	Other
Post-traumatic	Sickle cell crisis
Rheumatic	Idiopathic
Inflammatory myopathy, myositis	Refeeding edema, obesity
Fasciitis	

Table 6. Pattern presentation of edema caused by increased hydrostatic pressure

Disease	Contributing factors	Edema pattern	Increase during walking	Improve during leg elevation	Improve with diuretic	Swelling
Hepatic cirrhosis	Hypoproteinemia Right cardiac failure Portal hypertension Total blood volume Pulmonary hydrostatic pressure	Supine Mild: Absent in mornings Moderate: Mildly present in mornings Severe: During all day	Yes Yes Yes	Yes No No	Yes	
Cardiac failure	Total blood volume Vascular tone Pulmonary hydrostatic pressure	Bimalleolar/All foot Mild: Absent in mornings Moderate: Mildly present in mornings	No Yes	Yes No	Yes Yes	No
Renal insufficiency	Total blood volume	Severe: During all day, including at waking up	Yes	No	No	
Chronic venous disease	Valvular dysfunction Increased local blood volume	Mild: Absent in supine and in morning, it appears hours after walking, it is bimalleolar including anterior foot and toes	Yes / Afternoon	Always		No
Venous malformation	Increased permeability	Moderate: Same characteristics, from middle third leg to the foot including anterior foot and malleolus, usually associated to mild skin changes	Yes / Morning or Late morning	Yes	No	No
Postthrombotic syndrome	Valvular dysfunction Increased local blood volume Return obstruction	Severe: All leg, from calf and down, with swelling, usually associated to severe skin changes, atrophy blanche or eczema	Yes / May be present in morning	Yes, may not improve		Yes
Arteriovenous fistula	Increased arterial flow Vascular tone	Schöbinger: 1 No edema or mild 2 Mild edema or absent, constant	May Yes	Yes No	No	No Yes
Arteriovenous malformations	Increased permeability Increased local blood volume Valvular dysfunction	3 Moderate edema, constant 4 Cardiac failure pattern, constant	Yes Yes	No No		Yes Yes
Arterial malformations	Increased arterial flow Vascular tone Increased local blood volume					
May-Thurner syndrome, pelvic congestion	Return obstruction Valvular dysfunction	Mild: Absent in supine and absent in mornings, few patients	Yes	Yes		No
Acute venous thrombosis	Return obstruction Increased local blood volume	Moderate: May be present in mornings, swelling may be present in mornings too or initiate during walking Severe: Present in mornings with swelling all day	Yes Yes	Mild No	No	Yes Yes

In all cases, to a greater or lesser degree, contribute increased hydrostatic pressure (46) and all of improve with compression; venous etiology tends to improve significantly with compression.

compartment. Nonetheless, they are frequently confused. Along Godette's sign absence, we will observe venous dilation, increased in leg perimetry, and muscular tension, which we most differentiate from muscular contracture.

Pruritus and burning pain

Itching is a symptom present in multiple potential etiologies, since dermatologic as inflammatory, infectious dermatoses, autoimmune, genodermatoses, dermatoses of pregnancy, and cutaneous neoplasms. Systemic diseases are associated with endocrine, metabolic, infectious, hematological and lymphoproliferative diseases, visceral neoplasms, pregnancy and drug-induced pruritus, and even associated with neurologic and psychiatric disorders such as neurogenic (without nerve damage), neuropathic (nerve damage), psychosomatic disorders, mixed, and even idiopathic⁴⁸. All of them are poorly studied and understood, with some authors reporting contradictory results⁴⁹. It is important to note that the paper from the International Forum for the Study of Itch does not mention to venous disease as a cause, although many authors in literature does. We may think that it is included and grouped among inflammatory groups. On the contrary, a complete table for those associated with neurogenic or neuropathic etiology. We must not forget itching is considered as a minimal pain expression.

Trying to associate itching with venous disease, remembering the current role of mast cell degranulation secondary to leukocyte entrapment⁴⁵, may explain why in advance disease with eczema and ulcer patients frequently, although not all of them, refer it. A study by Paul⁵⁰ found a correlation between disease severity and itching of $0.26 p = 0.025$, not strictly linear because itch increased with the skin changes (CEAP 4 and 5) ($n = 33, 44.5\%$), but not necessary with the presence of an ulcer ($n = 5, 6.8\%$). A study by Paul⁴⁹ found a correlation between disease severity and itching of $0.26 p = 0.025$, not strictly linear because itch increased with the skin changes (CEAP 4 and 5) ($n = 33, 44.5\%$), but not necessarily with the presence of an ulcer ($n = 5, 6.8\%$), coupled with the fact that up to 54.7% of patients had an itch in many parts of their bodies, 45.9% of them specifically in legs. Some of them associate itch to a burning sensation in the same spot as Duque described¹⁸ both characteristic symptoms of neuropathies.

Tiredness, heaviness, and pain

These three symptoms are dominant in chronic venous disease symptoms, as proven in VRS²¹. As far as now, there is no author capable of explaining physiopathological mechanisms on those symptoms. We could assume that heaviness and tiredness are associated with increased venous volume, thus as edema present during standing position and exacerbated during walking hours, relieving leg elevation within the 1st min, and never being present at waking up or early in mornings. Because no author concentrates on pattern presentation of these symptoms in venous disease, we must still consider them as subjective. Arnoldi¹ stated that intense (bursting) pain, which was intense enough for some of them to consider amputation, were exclusively present in those with important deep vein damage, associated with the practically constant high pressure in the deep veins of the leg, emphasizing it was never met in patients with simple varicose veins. It is important to remember again that in Arnoldi's study existed an asymptomatic group ($n = 55, 19.7\%$) with no other author or study group considering it as a study variable and the many potential causes explaining leg pain such as musculoskeletal or soft-tissue diseases.

Cramps and restless legs

Cramps and lack of strength are commonly associated with musculoskeletal diseases. There is no physiopathological mechanism explaining the presence of cramps and restless legs in CVI. Thus again, resorting to conjectures, assuming that because of venous congestion (swelling), muscles in calf in an attempt to counteract increased hydrostatic pressure provoke involuntary contractions, nonetheless, those contractions must not be severe or incapacitating or derive in residual muscular contractures, and never be present during night rest. On the other hand, restless legs should not be present during night rest as well considering venous hypertension is absent, thus, until now it is still necessary to make more studies focused in understanding exactly why these patients refer specific types of symptoms.

Conclusion

We may have taken the wrong direction in understanding venous disease symptoms because there is no symptomatic correlation, even though it exists for

signs²¹. New studies are necessary considering the potential role of the anatomic relationship between veins and nerves, described by many authors in other medical areas, trying to rule out causality, but never casualty⁵¹⁻⁵⁵. Comorbid pathologies to consider are peripheral neuropathy (26-54%)⁵⁶⁻⁵⁷ and underdiagnosed low back pain associated with radiculopathy^{58,59}, as herniation incidence has been reported similar between low back pain and radiculopathy⁶⁰⁻⁶², with a higher prevalence in younger patients^{59,63}.

There may be other contributing factors to consider such as leg shortness⁶⁴, history of trauma, and even microtraumas associated with daily life activities, against we know spinal hygiene. We must not forget that nerves are known as “the great simulators of the body” because they can simulate when damaged syndromes^{65,66} or minor symptoms such as itching or cough⁶⁷.

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