THE ROLE OF HEREDITY IN CHRONIC VENOUS DISEASE

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Summary

Due to the increased frequency among the population and the serious consequences upon the individual and upon the society, the chronic venous disease represents a field of high medical interest, being one of the pathologies with the greatest impact on patient decreasing the quality of life, comparable to diabetes mellitus, heart failure and oncological diseases. Together with the determinant and causative factors of chronic venous disease (varicose veins, deep vein thrombosis, congenital venous dysplasia, deep vein compression syndrome), an important role in the onset and progression of the disease is due to favoring factors (risk factors): heredity, constitutional factors (female sex, obesity, static foot anomalies), occupational factors (lack of physical exercises, orthostatic). The frequent association of several favoring factors in the same patient increases the risk of worsening the disease.

Key words: *chronic venous disease, varicose veins, favoring factors, risk factors, inheritance.*

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Introduction

Considered by René Leriche "a disruption of the vasomotricity, secondary itself to a venous thrombosis", "a decompensation syndrome in the circulatory pathology of the lower limbs, comparable with heart failure (HF) in the pathology of the heart" by P. Brînzeu, defined by Nicolaides as "the decompensation stage of the venous circulation in the lower limbs with symptoms and clinical signs produced by the venous hypertension as a result of the structural and functional venous abnormalities", chronic venous disease (CVD) is considered today a chronic, progressive, inflammatory disease with a complex pathogenesis, which affects the entire venous system of the lower limbs, or just a specific anatomic territory. [1], [2]

The increased prevalence, the magnitude of the clinical manifestations, the severe complications as well as the medical practice and socioeconomic issues raised by them, places CVD among the complex multidisciplinary pathologies. The severe impact on the quality and style of life of CVD patients transform this disease into a public health issue comparable to cancer, diabetes mellitus, HF or etilism. [3], [4], [5], [6] The quality of life (QoL) in patients with CVD is progressively affected from class C1 to C5-C6 CEAP (Clinical, Etiological, Anatomical and

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Pathophysiological) classification comparable to other chronic severe conditions.

Identifying and assessing the impact that risk factors have on CVD progression has been and remains a concern for the medical world, representing „the key for effective prevention and management of the disease" [3], [4], [7], [9] and evidence of the importance of multi-disciplinarity when assessing it. [10], [11]

Heredity

The role of genetic inheritance in CVD was reported in 1851 by Virchow and in 1868 Gay. They created the pedigree chart of two families with varicose veins (VVs) of the lower limbs. Later on Botkin, Secenov, Pavlov, Timiriazev [10], [12] defined the heredity as "a product of the external environment over the previous generations", considering that "the general neurotrophic factors that lead to a loss of connective and elastic tissue are the ones that are inherited". They also insisted on the fact that "only the terrain or heredity is not enough to produce VVs, unless active factors intervene to increase venous pressure". In 1958 Wiedmann A. [11], [13] discusses the "great hereditary predilection" in the occurrence of venous insufficiency.

The analysis of the family predisposition in CVD represented the field of study of many authors. The family succession was appreciated in 1949 by Anning at 89.9%, by Ottleyla at 72%, by Kashimura at 66% [11], [13], while Tănase V describes a history of VVs in 68% of patients. Generally, the hereditary factor is found in over 50% of patients with unilateral VVs and nearly 100% in patients with bilateral VVs. [1] In SEPIA (Epidemiological Study on Prevalence of Chronic Venous Insufficiency in Ambulatory, in Romania), heredity was considered in 58% of cases. [12] However there are studies in which the family history of VVs was reported in only 3.5% to 12-25% of cases. [13], [15]

The way heredity intervenes in venous insufficiency represented another important study objective for the medical world. During 1950-1980 the researchers believed that the inherited factors were "the quality of a connective tissue that causes agenesis or valvular and parietal insufficiency", "the existence of supernumerary glomus or abnormalities of the development and functioning of arteriovenous anastomoses", "congenital dysplasia", "meiopragia of vascular walls", congenital malformations. Nierman considers the varicose complex being secondary to certain chromosomal changes and Muresanu discussed in 1967 about "a particularity of microcirculation response". In the same period it was discussed the role of heredity in phlebitis (75%) and the concept of "constitutional tipus embolicus". [11], [13] Current studies confirmed the role of genetic factors in increasing the risk of deep vein thrombosis and venous insufficiency but the genes involved have not yet been identified. [14-16]

At first the way of transmitting genetic risk factors to descendants was also a controversial subject. The idea of the heredity "exerted in poligenic dominance" was sustained by Broussais, Virchow, Quenue, Delbet, Ottley, Touraine, Curtius and Wetz, while Troisier, Le Bayan, and Huriez proposed the concept of genetic inheritance "in simple or sexuat recessivity". [11], [13] The transmission of VVs from affected parent to the descendants is predominantly dominant with variable penetration (85%), with a net predominance in favour of female sex. [17], [18] In an individual the probability of developing VVs is 85-90% if both parents suffer from this disease and up to 20-22% if the family history is negative. [7], [9], [18-21] When a single parent has VVs the risk of developing the disease is 60-62% for female descendants and 25% for male descendants.

The development of technology and medical sciences allowed a deeper analysis regarding the role of the genetic factor in CVD, highlighting not only the role of matrix metalloproteinases (MMPs) in the physiopathology of the disease, but also their importance as risk factors of CVD. The excessive pathophysiological activity of MMPs in the tissues, which is induced by high venous pressure (HVP), is controlled by their endogenous tissue inhibitors of metalloproteinases (TIMP). Increased levels of MMPs due to an imbalance between the activity of MMPs and TIMP lead to pathological changes of the venous wall and subsequently to CVD. [21], [22] As the imbalance between MMPs and TIMP expressions can be genetically modulated [22],

[23] their genetic polymorphism is considered to be an important predisposing factor of this imbalance [23], [24], and its study can help to better identify patients at high risk of developing CVD. [18] Analyzing the relationship between the polymorphisms of MMP-2 (rs243864), MMP-9 (3918242), MMP-12 (rs7123600) and TIMP-2 (rs8176329) and CVD risk in a case-control study published in 2017, V. Slonková et al. [19] reported that certain MMPs alleles are more common among CVD patients and that their presence could represent an unfavorable prognostic factor.

It has been showed that patients with Klippel-Trenaunay syndrome, Parke-Weber syndrome, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, FOXC2 gene mutation, desmulin dysregulation and Ehlers-Danlos syndrome often develop VVs and CVD. [24], [25], [26]

Recent studies have reported that patients with genetic changes as: severe congenital neutropenia type 4, hemochromatosis C282Y gene mutation, certain Factor XIII V43L gene, collagen type I, α2 (COLIA2) gene may have risk impact in developing venous ulcer.

Conclusions

Heredity has a great importance in triggering and evolving CVD. The correct and complete evaluation of heredity through complete assessment (anamnesis, clinical and genetic examination) is a mandatory stage and it is a method of identifying people at risk of developing CVD. It requires multidisciplinary collaboration and patient's compliance.

Thus, the application of a prevention plan for CVD, individualized to each case, is an essential objective in reducing the risk of developing the disease or, when it has occurred: slowing down the progression, complications and relapses.

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Conflict of interest
NONE DECLARED

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