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The role of clinical and genealogical study in the examination of patients with chronic venous insufficiency

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Objective — to demonstrate the role of heredity in the development of varicose veins using a clinical-genealogical study, analyze family cases of varicose veins of the lower extremities, determine the type of disease inheritance in the examined patients, and assess the possible outcomes of genetic inheritance for their descendants.

Materials and methods. The study involved 64 patients, mostly women — 52 (81.3 %), with different clinical classes of varicose veins. The clinical-genealogical method of pedigree analysis was used to establish the type of inheritance. We determined the nature of the disease trait (hereditary or non-hereditary) and the type of inheritance (autosomal dominant, autosomal recessive, or gender-linked).

Results. Among the 64 examined patients, 28 (43.8 %) had familial cases of varicose veins. In our clinical-genealogical study of the pedigrees of patients with chronic venous insufficiency, we found an autosomal dominant inheritance of this pathology, not linked to gender. Direct inheritance across generations was observed.

Conclusions. The analysis of the pedigrees of patients with varicose veins of the lower extremities and other manifestations of chronic venous insufficiency revealed the familial nature of disease inheritance, characterized by an autosomal dominant inheritance type and a high degree of gene expression. In these families, children are more likely to show signs of the disease. A hereditary predisposition to certain forms of varicose veins has also been noted. Consequently, in individuals with reticular varicose veins, the main veins of the lower extremities exhibited no alterations with age, whereas reticular varicose veins simply increased in prevalence.

Keywords
varicose disease, chronic venous insufficiency, reticular varicose veins, clinical and genealogical study.

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Functional disorders of the veins of the lower extremities that cause swelling, skin changes, or venous ulcers are clinically known as chronic venous insufficiency (CVI).

The most common manifestation of CVI is varicose veins, or varicose vein disease of the lower extremities (VDLE). In Western countries, approximately one-third of the adult population suffers from varicose veins [11].

Despite its significant prevalence, the etiology of varicose veins remains incompletely understood.

Throughout the history of the study of VDLE, the importance of heredity has always been pointed out. In questionnaires of patients with varicose veins, it was found that at least 25 % of patients had close relatives who suffered or are suffering from one of the forms of this disease [5]. This is probably due to the inheritance of a certain connective tissue defect, which is confirmed by the frequent combination of varicose veins and hemorrhoids, hernia of the anterior abdominal wall, and flat feet. Unfortunately, cases of hereditary predisposition to varicose veins are not always easy to detect, since not only a tendency to general weakness of connective tissue can be inherited, but also isolated weakness of the vein walls or even individual venous valves [1—3].

Population studies conducted in the last century in France showed that a history of varicose veins in

a first-degree relative is the most important risk factor for both men and women. Patients with varicose veins were 21.5 times more likely to report a positive family history [4]. A similar study conducted in Japan found that almost half of patients with varicose veins had a family history, compared to only 14 percent of patients without the condition [6]. Although no gene has been identified as specific for the development of varicose veins, there is evidence in the literature of other gene mutations associated with the formation of varicose veins [9, 10, 13]. For example, *FOXC2* mutations, which are commonly found in patients with lymphedema-distichiasis. In a study of patients with a *FOXC2* mutation, all 18 had large saphenous vein reflux on duplex ultrasound compared with only one case of reflux in 12 patients without the mutation [10]. However, understanding the role of genetic factors in the development of VDLE is a complex task and requires further study.

The role of heredity in the development of varicose veins can also be proven using a fairly simple and long-known clinical-genealogical study method. The clinical-genealogical method is the main approach for studying human genetics. This method became widespread and popular in the 20th century and made it possible to understand the genetic nature of many diseases. This method identifies familial cases of the disease in patients with CVI, determines the type of disease inheritance in the examined patients, and assesses the prognosis of inheritance for descendants [5, 7, 12].

Objective — to demonstrate the role of heredity in the development of varicose veins using a clinical-genealogical study, analyze family cases of varicose veins of the lower extremities, determine the type of disease inheritance in the examined patients, and assess the possible outcomes of genetic inheritance for their descendants.

Materials and methods

The study involved 64 patients, mostly women — 52 (81.3 %), with different classes of varicose veins according to the CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification: C0-C1 were 27 (42.2 %) patients, C2-C3 — 21 (32.8 %) patients, C4-C6—16 (25 %) patients. The inclusion criteria were the presence of reticular varicose veins (C0–C6 varicose veins classes according to the CEAP classification), the presence of a family history of at least 3 generations, and the patient's consent to participate in the study. The exclusion criteria included the patient's disagreement and the absence of family history data.

During the family history collection process, 28 (43.8 %) patients had first-degree relatives with VDLE of any class according to CEAR. To establish the type of inheritance in the identified cases, we applied the clinical-genealogical method of pedigree analysis.

This method can clearly identify the presence or absence of similar diseases in the family. The genealogical method is a pedigree-based approach used when a hereditary pathology is suspected [8].

Currently, the method allows us to solve a number of important issues, in particular:

- to establish if a specific symptom or disease is unique to a family or if there are several cases of this pathology;
- identify individuals suspected of having this disease and develop a plan for their examination to clarify the diagnosis;
- determine the type of inheritance and find out which line, maternal or paternal, the disease is transmitted through;
- identify individuals who need medical and genetic counseling, determine the clinical prognosis for the proband and his sick relatives, taking into account the characteristics of the disease and its genetic characteristics;
- develop a treatment and prevention algorithm taking into account individual and family characteristics of the disease;
- predict the likelihood of hereditary pathology in subsequent generations depending on the type of inheritance.

The pedigree analysis reveals:

1. Nature of the trait or disease (hereditary or non-hereditary).

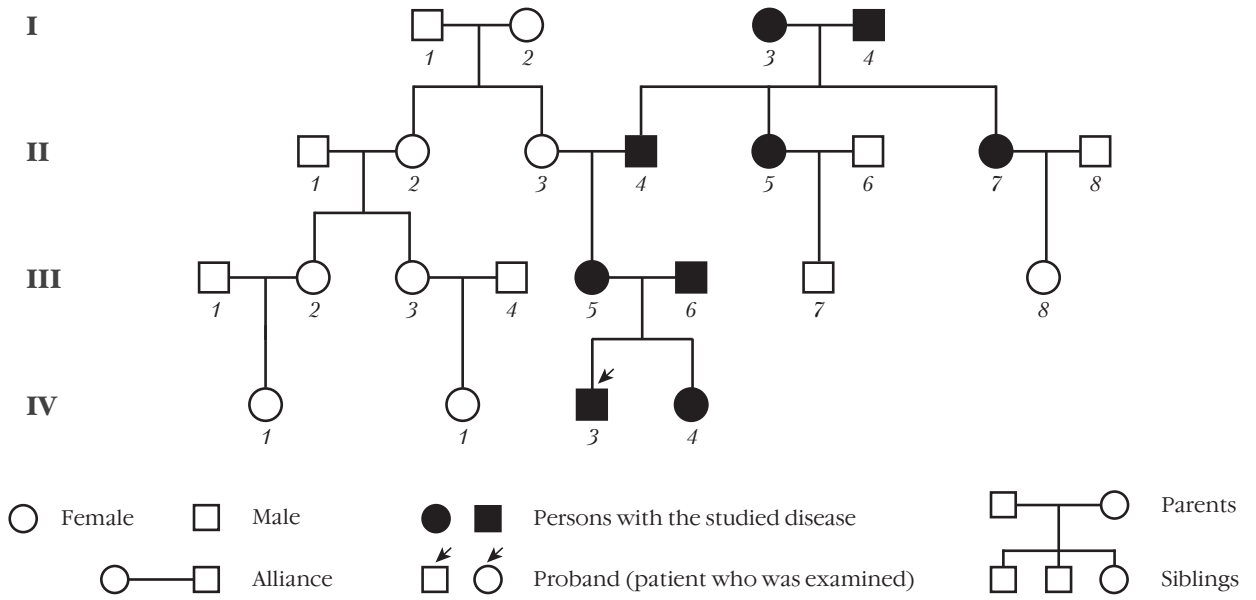
2. Type of inheritance: autosomal dominant, autosomal recessive, gender-linked.

For the autosomal dominant type of inheritance, it is typical that one of the parents of each patient is sick; the probability of the disease occurring in the offspring is 50 % and depends on the degree of manifestation of this gene in generations [8, 12].

Only in families where both parents carry the genes in a heterozygous state can we identify recessive genes in pedigrees with an autosomal recessive type of inheritance. Children with the autosomal recessive type inherit the disease in 25 % of cases with full expression of the gene.

When linked to the gender (X chromosome), the mother is a carrier of the gene, and half of her sons inherit the disease [8].

In the clinical examination of patients with VDLE, duplex mapping of the venous system was used to establish the type of CVI and the clinical class of the disease.



Roman numerals denote generations, and Arabic numerals denote the number and numbering of individuals in each generation of a family.

Figure 1. **The pedigree of family P. with autosomal dominant inheritance, case history No. 18252**

Results and discussion

Among the 64 examined patients, 28 (43.8 %) were found to have a familial nature of the disease, which is a fairly high indicator. Our clinical-genealogical study of the pedigrees of patients with CVI revealed the inheritance of this pathology according to the autosomal dominant type. There is direct inheritance across generations. The tendency to develop varicose veins is passed down from generation to generation without any gaps. The following pedigrees serve as an example (Fig. 1, 2).

The P. family pedigree (see Fig. 1) is unique to our study because we collected data from all four generations of this family. This pedigree clearly demonstrates the inheritance of the disease according to the autosomal dominant type. Proband IV (3), his mother and father III (5, 6), grandfather II (4), great-grandmother and great-grandfather I (3, 4) — had CVI. Thus, the proband inherited this pathological gene in accordance with the autosomal dominant type of inheritance, exhibiting a high degree of manifestation.

The analysis of the M. family pedigree, revealed that the disease (propensity to develop various forms of CVI) is passed down in this family in an autosomal dominant type (see Fig. 2). The gene manifests itself in three generations (I (2,4), II (2,4,5), III (2,3,4)). With a high degree of manifestation. Thus, in the examined proband III (3), her sister and brother have different manifestations of CVI, the mother also has a severe form of CVI of both lower extremities with repeated surgical interventions due to relapses, the proband's father has VDLE on the right lower extremity, and both grandmothers had different manifestations of CVI. A high degree of gene expression is noted in this family.

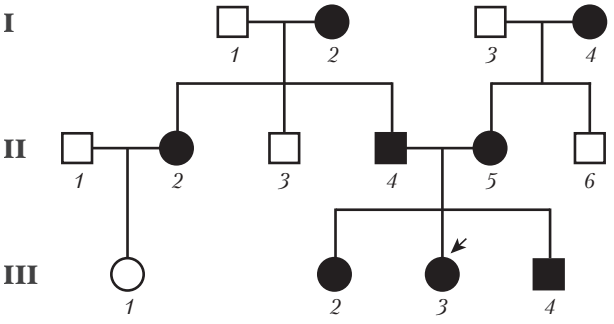


Figure 2. **The pedigree of family M. with an autosomal dominant type of inheritance, case history No. 846**

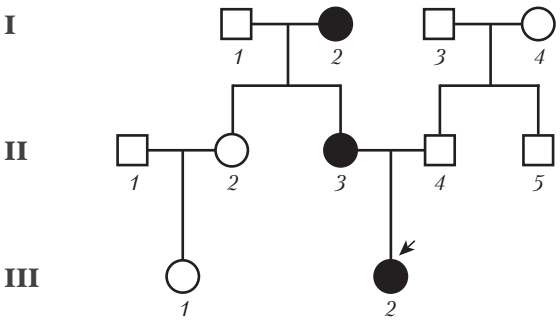


Figure 3. **The pedigree of family K. with autosomal dominant type of inheritance of reticular varicose veins, case history No. 1636**

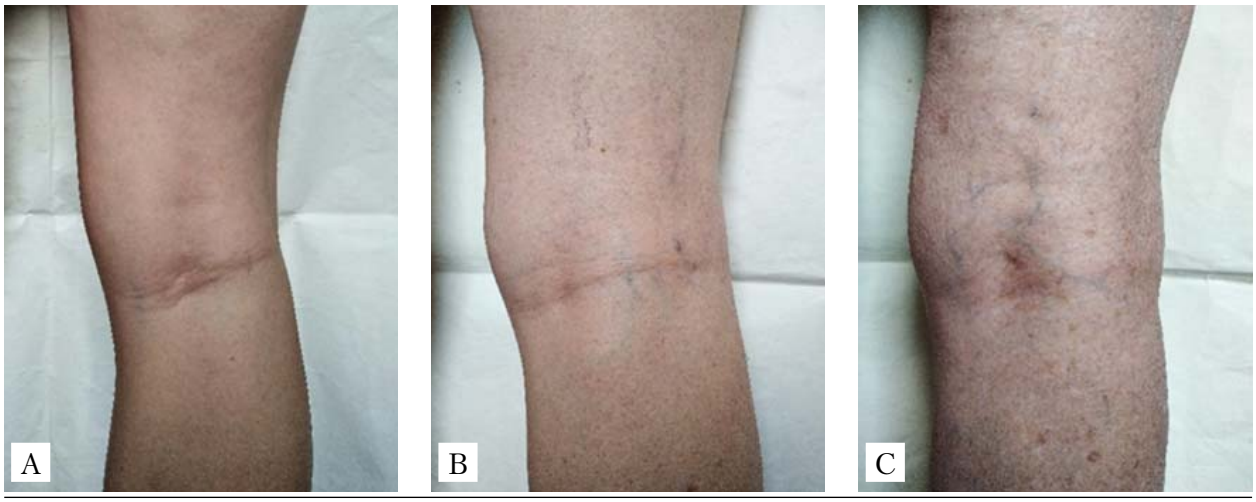


Figure 4. **Manifestations of reticular varicose veins and telangiectasias in three generations of family K.: A — proband, 28 years old; B — proband's mother, 59 years old; C — proband's grandmother, 81 years old**

In the examined families, there is a high risk of having children with varicose veins or other manifestations of CVI.

Also, when analyzing the obtained data, we drew attention to the fact that certain classes of varicose veins have a separate family inheritance pattern. Thus, three patients with reticular varicose veins (class C1 according to the CEAR classification) have direct relatives (mother and grandmother) who also suffer from them. An example of such a pedigree can be found in the case history No. 1636 of family K. (Fig. 3). In this family, reticular varicose veins become more common over the years, but other manifestations of CVI do not develop, and the disease does not progress according to the CEAR classification classes (Fig. 4).

These three families with distinct manifestations of reticular varicose veins underwent duplex mapping of the lower extremity veins, which revealed no changes in the main veins, their diameter, or any reflux. This shows that reticular varicosities follow a separate family pattern of inheritance and are inherited independently of other forms of VDLE. Furthermore, reticular varicose veins were exclusively observed in women in these families, indicating that the gene responsible for the development of this type of varicose vein may also be associated with gender.

There is also a familial pattern in the anatomical structure of the venous system. We identified 6 (9.4 %) probands among the examined patients, exhibiting strong branching of the superficial venous network and pronounced varicose changes in the tributaries across all three generations of their families. We detected varicose changes in the lateral femoral vein in two family cases (3.1 %). Upon collecting patient histories, we discovered that 9 (14.1 %) patients had a family history of other diseases associated with connective tissue weakness, such as hernias and hemorrhoids, in addition to varicose veins.

Conclusions

The pedigree analysis of 64 patients with CVI revealed that 28 (43.8 %) patients had first-degree relatives with VDLE of any class according to CEAR, which indicates the familial nature of disease inheritance, characterized by an autosomal dominant inheritance type and a high degree of gene expression. In the examined families, there is a high risk of having children with varicose veins or other manifestations of CVI. A hereditary predisposition to certain forms of VDLE has also been noted. Consequently, in patients with reticular varicose veins, the main veins of the lower extremities exhibited no alterations with age, whereas reticular varicose veins simply increased in prevalence.

Declaration of interests

The authors have no conflicts of interest to declare.

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Ethics approval and written informed consents statements

The assessment and usage of all clinical data was approved and permitted before the study by the ethics committee of Bogomolets National Medical University. The study protocol conformed to the ethical guidelines of the «World Medical Association (WMA) Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects» adopted by the 18th WMA General Assembly, Helsinki,

Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008. Written informed consent was obtained from all individual participants included in the study.

Authors contributions

I. V. Kolosovych: work concept and design, critical review; K.O. Korolova: work concept and design, data collection and analysis, writing the manuscript; Z.V. Korolova: work concept and design, critical review.

References

1. Ahmed WU, Kleeman S, Ng M, Wang W, Auton A; 23andMe Research Team; Lee R, Handa A, Zondervan KT, Wiberg A, Furniss D. Genome-wide association analysis and replication in 810,625 individuals with varicose veins. Nat Commun. 2022 Jun 2;13(1):3065. doi: 10.1038/s41467-022-30765-y. PMID: 35654884; PMCID: PMC9163161.
2. Antani MR, Dattilo JB. Varicose Veins. 2023 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29262112.
3. Aslam MR, Muhammad Asif H, Ahmad K, et al. Global impact and contributing factors in varicose vein disease development. SAGE Open Med. 2022 Aug 25;10:20503121221118992. doi: 10.1177/20503121221118992. PMID: 36051783; PMCID: PMC9425889.
4. Carpentier PH, Maricq HR, Biro C, Ponçot-Makinen CO, Franco A. Prevalence, risk factors, and clinical patterns of chronic venous disorders of lower limbs: a population-based study in France. J Vasc Surg. 2004;40:650-9.
5. Fukaya E, Flores AM, Lindholm D, Gustafsson S, Zanetti D, Ingelsson E, Leeper NJ. Clinical and genetic determinants of varicose veins. Circulation. 2018 Dec 18;138(25):2869-80. doi: 10.1161/CIRCULATIONAHA.118.035584. PMID: 30566020; PMCID: PMC6400474.
6. Hirai M, Naiki K, Nakayama R. Prevalence and risk factors of varicose veins in Japanese women. Angiology. 1990;41:228-232.
7. Ho TV, Chowdhury N, Kandl C, Hoover C, Robinson A, Hoover L. Genealogical databases as a tool for extending follow-up in clinical reviews. Int Forum Allergy Rhinol. 2016 Aug;6(8):880-2. doi: 10.1002/alr.21744. Epub 2016 Mar 25. PMID: 27013063.
8. Korolova K, Teplyi V. A genetic study of patients with chronic venous insufficiency based on clinical and genealogical method. Med Sci of Ukr. [Internet]. 2018Jun.21;14(1-2):59-3. https://doi.org/10.32345/2664-4738.1-2.2018.09.
9. MacColl E, Khalil RA. Matrix metalloproteinases as regulators of vein structure and function: implications in chronic venous disease. J Pharmacol Exp Ther. 2015;355(3):410-28. https://doi.org/10.1124/jpet.115.227330.
10. Mao C, Ma Z, Jia Y, et al. Nidogen-2 maintains the contractile phenotype of vascular smooth muscle cells and prevents neointima formation via bridging Jagged1-Notch3 signaling. Circulation. 2021 Oct 12;144(15):1244-61. doi: 10.1161/CIRCULATIONAHA.120.053361. Epub 2021 Jul 28. PMID: 34315224.
11. Rabe E, Berboth G, Pannier F. Epidemiologie der chronischen Venenkrankheiten [Epidemiology of chronic venous diseases]. Wien Med Wochenschr. 2016 Jun;166(9-10):260-3. German. doi: 10.1007/s10354-016-0465-y. Epub 2016 Jun 8. PMID: 27277219.
12. Serra R, Buffone G, de Franciscis A, et al. A genetic study of chronic venous insufficiency. Ann Vasc Surg. 2012 Jul; 26(5):636-42. https://doi.org/10.1016/j.avsg.2011.11.036.
13. Suda T, Katagiri A, Fujii H. Klippel-Trenaunay syndrome. Intern Med. 2023 May 1;62(9):1377-8. doi: 10.2169/internalmedicine.0251-22. Epub 2022 Sep 28. PMID: 36171122; PMCID: PMC10208789.

Роль клініко-генеалогічного методу в обстеженні хворих на хронічну венозну недостатність

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Мета — використовуючи клініко-генеалогічний метод обстеження, продемонструвати роль спадковості у розвитку варикозної хвороби, проаналізувати сімейні випадки варикозної хвороби нижніх кінцівок, визначити тип успадкування захворювання в обстежених пацієнтів і прогноз успадкування для нащадків.

Матеріали та методи. У дослідження було залучено 64 хворих, переважно жінок (52 (81,3 %)), з різними клінічними класами варикозної хвороби. Для встановлення типу успадкування застосовували клініко-генеалогічний метод дослідження родоводів. Визначали характер хвороби (спадкова чи неспадкова), тип успадкування (автосомно-домінантний, автосомно-рецесивний, зчеплений зі статтю).

Результати. З 64 обстежених пацієнтів у 28 (43,8 %) виявлено сімейний характер варикозної хвороби. У нашому дослідженні родоводів хворих на хронічну венозну недостатність за допомогою клініко-генеалогічного методу виявлено успадкування цієї патології за автосомно-домінантним типом. Зафіксовано пряме спадкування за поколіннями.

Висновки. Аналіз родоводів хворих на хронічну венозну недостатність виявив сімейний характер успадкування хвороби, автосомно-домінантний тип успадкування із високим ступенем вияву гена. У цих родинах існує високий ризик народження дітей, які матимуть хронічну венозну недостатність. Відзначено спадкову схильність до певних форм варикозу. У пацієнтів із ретикулярним варикозом із віком не відбувалися зміни в магістральних венах нижніх кінцівках, а ретикулярний варикоз набував більшого поширення.

Ключові слова: варикозна хвороба, хронічна венозна недостатність, ретикулярний варикоз, клініко-генеалогічний метод обстеження.

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