LOWER EXTREMITY VEIN THROMBOSIS AND ITS CONSEQUENCES IN STROKE RECOVERY PERIOD

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Post-stroke lower extremity vein thrombosis can be the reason behind complications of embolic nature and death. This study aimed to investigate the influence of provoking factors, frequency and localization of acute thrombosis, post-thrombotic changes in the lower extremity veins during stroke recovery period. The study involved 1315 patients, 885 (67.3%) male and 430 (32.7%) female, ages 18–94 years, mean age 59.23 ± 13.7 years. All participants underwent lower extremity venous duplex scanning in the early and late stages of stroke recovery period. We found no evidence of interconnections between presence of signs of thrombosis and/or its consequences and the pathogenetic variant of stroke the patient had. Acute deep vein thrombosis was diagnosed significantly more often ($p < 0.05$) in the early stage of stroke recovery period. The frequency of acute lower extremity vein thrombosis was 7.8%, post-thrombotic changes — 5.6%. Isolated lesion of the lower leg veins was the most common complication associated with deep veins (49.6%). We have discovered a significant relationship between the side of lower extremity paresis (plegia) of and the side of deep vein thrombosis ($p < 0.001$). No relationship was found between lower extremity superficial and deep vein thrombosis and use of anticoagulants and antiplatelet agents ($p > 0.05$). Excess body weight was associated with damage to the lower extremity proximal veins ($p < 0.05$). Women had lower extremity vein thrombosis significantly more often ($p < 0.05$). Repeated lower extremity venous duplex scanning upon admission to the rehabilitation hospital allowed reducing the risk of venous thromboembolic complications that may develop during the stroke recovery period.

Keywords: stroke, rehabilitation, venous thromboembolic complications, vein thrombosis of lower extremities, stroke recovery period, immobilization.

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ТРОМБОЗ ВЕН НИЖНИХ КОНЕЧНОСТЕЙ И ЕГО ПОСЛЕДСТВИЯ В ВОССТАНОВИТЕЛЬНОМ ПЕРИОДЕ ИНСУЛЬТА

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Тромбоз вен нижних конечностей, развивающийся после перенесенного инсульта, может быть причиной эмболических осложнений и летального исхода. Целью исследования было изучить влияние провоцирующих факторов, частоту и локализацию острого тромбоза и посттромботических изменений вен нижних конечностей в восстановительном периоде инсульта. У 1315 пациентов в раннем и позднем восстановительном периоде инсульта проведено дуплексное сканирование вен нижних конечностей, их которых 885 (67,3%) мужчин и 430 (32,7%) женщин в возрасте 18–94 года, средний возраст 59,23 ± 13,7 года. Показано, что выявление признаков тромбоза и/или его последствий не взаимосвязано с патогенетическим вариантом ишемического инсульта. Достоверно чаще ($p < 0,05$) острый тромбоз глубоких вен отмечен в раннем восстановительном периоде инсульта. Частота острых тромбозов вен нижних конечностей составила 7,8%, посттромботических изменений — 5,6%. Наиболее часто (49,6%) среди поражений глубоких вен наблюдали изолированное поражение вен голени. Обнаружена достоверная взаимосвязь между стороной пареза (плегии) нижней конечности и стороной тромбоза глубоких вен ($p < 0,001$). Взаимосвязи между тромбозом поверхностных и глубоких вен нижних конечностей и приемом антикоагулянтов и дезагрегантов выявлено не было ($p > 0,05$). Избыточная масса тела была ассоциирована с поражением проксимальных отделов вен нижних конечностей ($p < 0,05$). У женщин тромбоз вен нижних конечностей наблюдали достоверно чаще ($p < 0,05$). Результаты повторного дуплексного сканирования вен нижних конечностей при поступлении в реабилитационный стационар позволили снизить риск венозных тромбоэмболических осложнений у пациентов в восстановительном периоде инсульта.

Ключевые слова: инсульт, реабилитация, венозные тромбоэмболические осложнения, тромбоз вен нижних конечностей, восстановительный период, инсульт, иммобилизация

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Embolic complications of venous thrombosis (ECVT) that develop during the acute period of a stroke aggravate the course of the disease and can cause death. Persons with stroke are more likely to develop ECVT among all patients with somatic disease (one of the highest risk groups) [1–4].

The significance of recovery period ECVT is at least comparable to the acute stage ECVT, however, the former were not investigated as thoroughly as the latter, despite the fact that active rehabilitation with undiagnosed thrombosis (primarily deep vein thrombosis, DVT) in the background may be unsafe [5].

Immobilization is one of the main reasons behind slower venous blood flow in stroke survivors. It hinders operation of the lower extremity musculovenous pump system. In such cases, the mobility is restricted due to the severe condition and/or post-stroke paralysis and paresis, causing DVT [2, 6, 7]. It has also been established that the risk of ECVT increases in the first three months after development of the stroke, with immobilization recognized as the main predisposing factor [8, 9]. It should also be taken into account that during the SARS-CoV-2 pandemic, which partially overlapped this study's patient recruitment stage, thrombosis in general becomes a more frequently diagnosed disease (including the lower extremity vein thrombosis [10, 11]), but if the disease was never diagnosed with a PCR test, the fact of infection cannot be established. Currently, there is limited information available regarding the epidemiology, localization and factors influencing the development of thrombosis during the stroke recovery period [12, 13].

Despite the fact that clinical data confirm the relationship between a stroke and development of ECVT, the strength of this relationship and its dependence on time remain to be clarified [8, 14].

Generally, further investigation of the interconnections between historical, constitutional, clinical diagnostic parameters and lower extremity vein thrombosis (and ECVT), as well as its prevalence and peculiarities of localization in stroke survivors, remains an urgent task.

This study aimed to investigate the influence of provoking factors, frequency and localization of acute thrombosis, post-thrombotic changes in the lower extremity veins during the stroke recovery period.

METHODS

The study included data on 1315 patients describing early and late stages of the stroke recovery period. All patients underwent inpatient examination and treatment at the medical rehabilitation departments of the Federal Center of Brain Research and Neurotechnologies of Federal Medical Biological Agency. Eight hundred and eighty five (67.3%) patients were male, four hundred and thirty (32.7%) were female; the ages ranged from 18 to 94 years, the being 59.23 ± 13.7 years. The inclusion criteria were: stroke less than a year ago; 3 point scored on the Rankin scale for neurologic disability; submission of the results of duplex scanning done in other medical establishment, together with a conclusion confirming unimpaired patency of the lower extremity veins, such results and conclusion serving to eliminate the ECVT development risk during active rehabilitation. The patients had been recruited from 2019 to 2021. The exclusion criteria were: no stroke diagnosis in the discharge summary; signs of acute lower extremity vein thrombosis discovered before admission to the rehabilitation departments; over 3 points scored on the Rankin scale for neurologic disability.

During the first days after admission to the medical rehabilitation departments, all patients underwent lower extremity venous duplex scanning. The scanners used for the purpose were Epiq 5 and Epiq 7 (Philips; USA); the broadband multifrequency linear transducer operated at the frequency of 3–12 MHz. The patients were immobilized post-stroke, therefore, all examinations were performed with them in a horizontal position. To detect thrombosis or post-thrombotic changes, the veins (all accessible segments of superficial and deep veins of both lower extremities) were subjected to compression tests every 1–2 cm. When signs of thrombosis and/or post-thrombotic changes were discovered, the factors registered were the side of the lesion and its localization, which could be great/small saphenous veins and their tributaries in case of superficial veins and the following segments in case of deep veins: external iliac vein (EIV) and/or common femoral vein (CFV), popliteal vein (PV) and/or femoral vein (FV), deep veins of the lower leg. Following the detection of signs of acute thrombosis the patients were examined for flotation, and if that was discovered, the length of the floating tip of the thrombus was established.

All participants underwent transthoracic echocardiography (Echo-CG) done with an Epiq 7 scanner (Philips; USA) with a broadband multifrequency sector transducer operating at the frequency of 1–5 MHz.

In addition to the examinations mentioned above, the program included a complex of neuroimaging tests, ultrasound examinations of cerebral vessels and functional diagnostic tests. The results of this complex are not described in this paper.

The data obtained were processed (statistical processing) with the help of SPSS Statistics 26.0 (IBM; USA) and R software 4.0.2 (R Core Team; Austria). The null hypothesis was rejected at the level of significance of $p \leq 0.05$. Frequency and proportion (in percent) were used to describe qualitative and quantitative variables. Pearson's χ^2 test or Fisher's exact test enabled comparison of the frequencies of qualitative dependent variables between categories of independent (grouping) variables. For quantitative dependent variables, the comparison relied on the Mann–Whitney test. A mixed

Table 1. The frequency of occurrence of varieties of ACVA and pathogenetic variants of ischemic stroke (according to the TOAST classification [15]) in the participants of the study

Type of stroke		Frequency, people	Share, %
Hemorrhagic stroke		8	0.6
Ischemic stroke (IS)	atherothrombotic	465	35.4
	cardioembolic	171	13
	lacunar	33	2.5
	cryptogenic	623	47.4
	other established etiology	15	1.1
Total		1315	100

Table 2. Frequency of acute thrombosis and post-thrombotic changes in lower extremity deep and superficial veins

Nature of changes of the lower extremity veins		Frequency, people	Share, %
Acute superficial vein thrombosis	No	1293	98.3
	Yes	22	1.7
Acute deep vein thrombosis	No	1234	93.8
	Yes	81	6.2
Post-thrombotic changes of deep veins	No	1279	97.3
	Yes	36	2.7
Post-thrombotic changes of superficial veins	No	1278	97.2
	Yes	37	2.8
Total number of patients	Total	1315	100

linear model allowed performing a joint analysis of the effect of gender and body mass index (BMI) on the signs of acute deep and superficial vein thrombosis (SVT).

RESULTS

All patients recruited for the study suffered a stroke. In 193 (13.8%) cases it was a second stroke. Depending on the time elapsed from the acute cerebrovascular accident (ACVA), 882 participants (67%) were established to be at the early stage of the stroke recovery period (up to 6 months) and 433 people (33%) were at the late stage thereof (up to 2 years). Table 1 presents characteristics of the types of stroke.

Lower extremity venous duplex scanning revealed echographic signs of deep and superficial vein thrombosis and consequences thereof in 176 (13.4%) patients (Table 2).

We did not discover a significant correlation between pathogenetic variant of IS and the frequency of diagnosed lesion of the lower extremity veins ($p > 0.05$).

The incidence of acute lower extremity deep and superficial vein thrombosis gradually decreased as the number of days passed since the onset of stroke increased (Fig. 1 and 2).

Mann–Whitney test has revealed the stroke onset-dependent differences between groups with and without DVT to be significant ($p < 0.05$) (Fig. 3), while for acute superficial vein thrombosis that was not the case.

Acute and post-thrombotic changes were considered together in the context of analysis of localization of DVT/SVT lesions and investigation of relationships between lesion localization and various factors.

In total, 117 (8.9%) cases of damage to the lower extremity deep veins (acute thrombosis and post-thrombotic changes) were identified.

The most common (49.6%) type of lower extremity deep vein damage were isolated lesions of deep veins of the lower leg (posterior tibial, peroneal, sural veins) (Table 3). There were no cases of damage to the anterior tibial veins registered in our sample.

Seven (6.8%) out of 103 acute thrombosis cases involved a floating thrombus apex, with the length thereof measuring from 7 to 45 mm, the mean being 29 mm.

Chi-squared test allowed identifying a significant relationship between side of the lower extremity paresis (plegia) and side of DVT ($p < 0.001$). No such relationship has been discovered for superficial veins ($p > 0.05$).

Exact T-test allowed identifying significant differences in body weight between groups of patients with distal and proximal deep vein lesions. Individuals with a larger body weight had lesions in the proximal vein segments significantly more often ($p < 0.05$) (Fig. 4).

A total of 59 (4.5%) cases of damage to the main superficial veins (acute thrombosis and post-thrombotic changes) were identified. Table 4 shows the frequency of lesion detection in specific main superficial veins.

Correlation analysis did not reveal significant relationship between SVT/DVT and use of anticoagulants ($rs = 0.045$ at $p = 0.103$; $rs = 0.154$ at $p = 0.113$) and antiplatelet agents ($rs = –0.036$ at $p = 0.195$; $rs = –0.058$ at $p = 0.067$).

Patient groups without echographic signs of damage to the lower extremity veins and with signs of acute thrombosis or post-thrombotic changes in the superficial and deep veins were compared in search for gender-specific dependencies. The chi-squared test revealed that female patients suffer

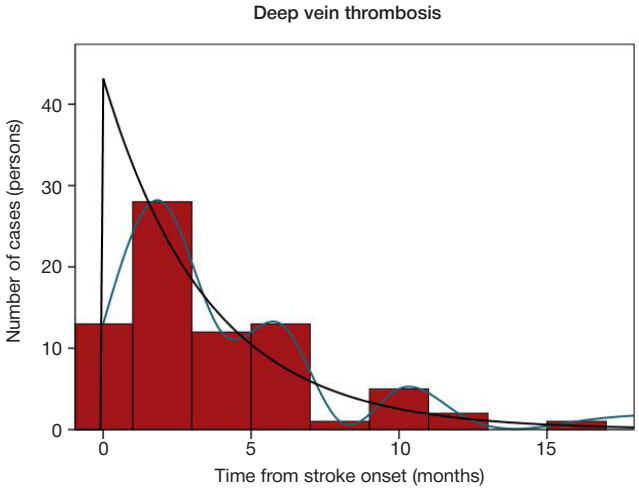

Fig. 1. Time from ACVA to registration of signs of acute deep vein thrombosis

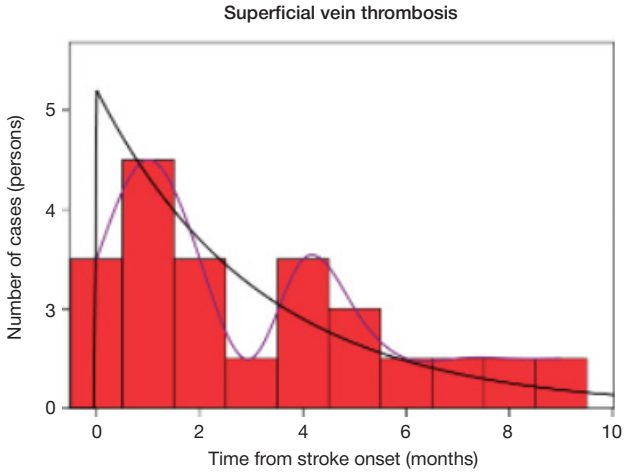

Fig. 2. Time from ACVA to registration of signs of acute superficial vein thrombosis

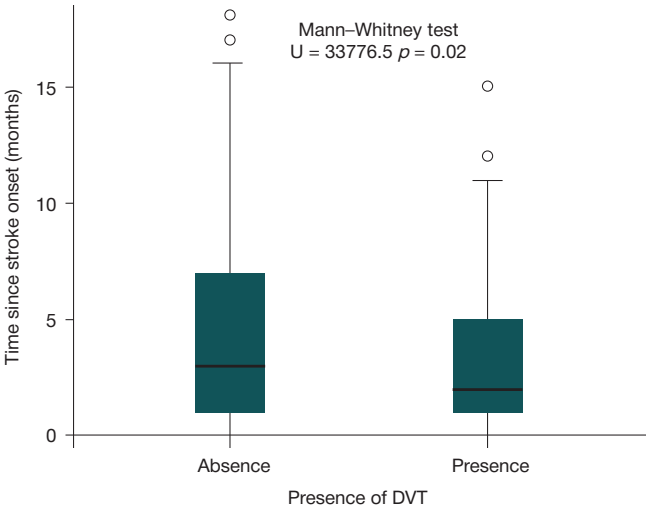

Fig. 3. Manifestations (signs) of DVT depending on time elapsed since the onset of stroke

damage to the lower extremity veins significantly more frequently ($p < 0.05$) (Fig. 5 and 6).

The mean BMI values associated with registered signs of DVT were 25.68 for men and 28.44 for women, those associated with SVT — 27.01 and 29.08, respectively. The differences in BMI of male and female patients not significant ($p > 0.05$). Two-way analysis that factored in gender and BMI with signs of acute SVT/DVT has also revealed no significant differences ($p > 0.05$), however, as a trend ($p = 0.095$), it was established that female patients tend to suffer both SVT and DVT more often as their BMI increases, while for male patients this relationship is inverse.

In the study cohort, echocardiography (and CT) revealed a single DVT case with signs of subclinical pulmonary artery thromboembolia (PATE) that did not result in death.

After registration of signs of acute thrombosis of the lower extremity veins, patients were prescribed anticoagulant therapy or its course was adjusted, the part of the active rehabilitation program associated with movement of lower extremities was limited, intermittent pneumatic compression (if it was done before results of the study have become available) that could contribute to thrombus migration — canceled.

DISCUSSION

The conducted study contains information about an artificial sample of people admitted to the specialized rehabilitation departments for recovery treatment. At the selection stage, the vast majority of patients had to meet a number of requirements (see the study's inclusion criteria). Thus, the studied cohort, despite being large, does not reflect the entire post-stroke population, i.e., it represents such population to a limited extent only.

The presence of SVT/DVT was one of the contraindications for admission. Nevertheless, lower extremity venous duplex scanning done at the Department of Ultrasound and Functional Diagnostics of the Federal Center of Brain Research and Neurotechnologies of the Federal Medical Biological Agency upon admission has revealed a significant number of acute thrombosis manifestation cases, which justifies the need for lower extremity venous ultrasound examination during the stroke recovery period, especially when a patient is admitted for active rehabilitation procedures, which may raise objections due to their economic "inefficiency."

The analysis of cost-effectiveness of routine lower extremity veins ultrasound examination as a thrombosis diagnosing effort [5] upon admission to inpatient rehabilitation has shown that ECVT were established in 6.6% of patients, and for asymptomatic patients that were diagnosed with DVT at ultrasound screening the inpatient rehabilitation period was shorter ($p = 0.045$), PATE incidence smaller ($p < 0.001$) and emergency admissions less frequent ($p = 0.002$) than for those who were diagnosed with thrombosis after the development of clinical symptoms. The authors concluded that routine ultrasound examination of the lower extremity veins upon admission to the inpatient rehabilitation department improves treatment outcomes while having no effect on the cost thereof, which makes such examination a justified measure.

There is no homogeneity in the published data on the frequency of DVT in acute stroke survivors, as well as in the relevant information concerning early and late stages of the stroke recovery period. On average, 12–15% of ACC patients had clinical signs of DVT [2, 16]. There is evidence that less then 10% of acute stroke survivors developed DVT, which had no significant effect on the outcome at the 3 months mark [7]. In another study, DVT was a frequent complication of acute stroke, and hemorrhagic stroke was associated with a higher incidence of damage to the deep veins (DVT was diagnosed in 21.1% of ischemic stroke cases and in 28.5% of hemorrhagic stroke cases) [12] . The frequency of lower extremity DVT in patients with intracerebral hemorrhage was higher than in ischemic stroke survivors, although not significantly [6].

The analysis of results of this study has revealed the incidence of DVT (both acute and chronic) to be at 8.9%, incidence of SVT — at 4.5% (totaling to 13.4%), while the incidence of acute lower extremity vein thrombosis was at 7.8% (103 cases), these value generally being lower that those reported earlier [2, 7, 12, 16] but consistent with data from a study investigating incidence of DVT in patients with acute stroke [7], where 8.7% of ischemic stroke patients also had DVT. Repeated duplex scanning with the aim to detect acute thrombosis of the lower extremity veins may be associated with long-term transportation and forced

Table 3. Localization of lower extremity deep vein lesions

Localization	Frequency, people	Share, %
CFV / IIV / EIV	1	0.8
Combination of CFV/IV/EIV lesions with popliteal and femoral vein lesions	2	1.7
Popliteal and femoral vein	17	14.5
Combination of popliteal and femoral vein lesions and lesions of the deep veins of the lower leg	16	13.7
Isolated lesions of the deep veins of the lower leg (posterior tibial, peroneal and sural veins)	58	49.6
Combination of CFV/IV/EIV lesions and popliteal, femoral vein lesions and lesions of the deep veins of the lower leg	9	7,7
Lesion localization unclear	14	12
Total	117	100

Note: CFV — common femoral vein; IV — iliac veins; IIV — inferior iliac vein; IVC — inferior vena cava.

immobilization of patients at the pre-admission stage. Moreover, the prevalence (and suddenness of occurrence) of venous thrombosis in the inferior vena cava system may be affected by the SARS-CoV-2 pandemic factors [10, 11]. In addition, the possibility of diagnostic errors made at the medical establishments where patients underwent examination for the first time should not be disregarded. All acute thrombosis cases registered in our study were associated with potentially elevated risk of development of PATE, however, after adjustment of the rehabilitation tactics treatment regimens, out of 103 acute thrombosis cases, signs of subclinical PATE (as uncovered with echocardiography and CT) were evident in one case only, with no fatalities.

Patients with longer hospital stays and more severe varieties of stroke are known to be at greater risk of DVT [9, 17]. This is especially important in connection with the peculiarities of our sample, which included patients scoring 3 points on the Rankin scale for neurologic disability, a factor potentially capable of affecting the incidence of lower extremity vein thrombosis.

According to the literature, asymptomatic DVT was found in 11.5% of stroke patients, with 85.9% of thrombi detected in the distal segments of the lower extremity veins [9, 12, 13]. In the vast majority of patients (81%), thrombosis is localized in the lower leg veins, isolated [6]. The data obtained in our study also indicate a relatively higher incidence of isolated lower leg deep vein lesions (49.6%) (combined with lesions in other segments — additional 7.7%) compared with DVT of other localizations (0.8–14.5%).

Ischemic stroke patients develop DVT more often. It typically localizes in the paralyzed leg, however, with prolonged immobilization, there is a risk of bilateral damage [2, 4]. According to some reports, ascending thrombosis and flotation are registered mainly in paretic limbs [6]. Our study has also revealed a significant relationship between the side of lower limb paresis and the side of deep vein thrombosis.

There was no significant relationship discovered between the pathogenetic variant of stroke and the incidence of lower extremity vein damage, which is consistent with previously reported data [6].

As the time elapsed from the onset of stroke increased, the incidence of DVT and SVT in the study cohort decreased, which is probably because of the peculiarities of the sample: there were more individuals at the early stage of stroke recovery period there. This specific feature could also have been affected by the greater immobility of patients in the first weeks and months after stroke before start of the active rehabilitation phase.

According to a number of recent studies, long-term use of direct oral anticoagulants (DOAC) for preventive purposes, compared with combined low molecular weight heparin and an oral vitamin K antagonist, did not cause recurrence of ECVT and decompensated forms of venous insufficiency

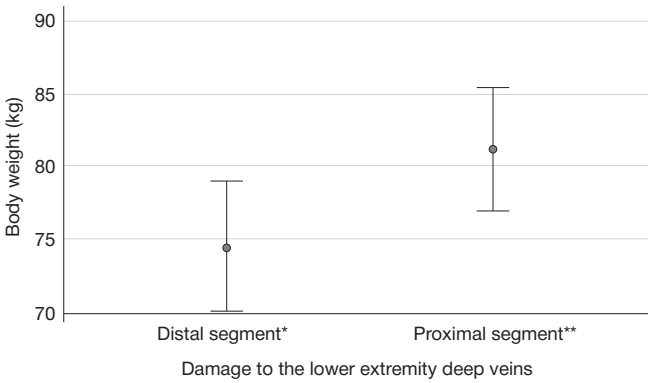

Fig. 4. Body weight of patients depending on the lesion location in proximal and distal segments of the lower extremity deep veins. Distal segment* — lesion of the lower leg deep veins, proximal segment** — lesion of the popliteal, femoral and/or iliac veins with damage (without damage) to the lower leg veins

[18–20]. However, there were described isolated cases of DOAC treatment ineffectiveness, mainly due to the individual differences in concentration of the drug in blood plasma [21]. The results of this study show that there is no relationship between development of lower extremity vein thrombosis and use of anticoagulants and antiplatelet agents. Most likely, this is due to the fact that the majority of study participants have already been taking antiplatelet agents after the stroke as part of the secondary prevention routine, and also received anticoagulants with low molecular weight heparins as part of the standard ischemic stroke therapy, i.e., the patients were in relatively equal conditions or started anticoagulant therapy, including with DOACs, after manifestation of the lower extremity vein thrombosis signs.

The list of established stroke-associated vein thrombosis risk factors includes immobilization, advanced age, obesity, diabetes mellitus, a history of DVT, hereditary coagulopathy [9, 22, 23]. This study has found that patients with a larger body weight were significantly more likely to have proximal segments of the veins affected by the disease. Probably, in such cases, thrombus formation is additionally affected by the factors associated with the increased intra-abdominal pressure conditioned by visceral fat hypertrophy. These factors can lead to compression of the ileofemoral segment with the development of hypertension in the femoral veins and impaired venous blood outflow from the lower extremity [22, 23].

The data in the reports describing incidence of lower extremity vein thrombosis in men and women are conflicting. For example, in 2020 it was shown that, disregarding factors associated with the reproductive function of women, the risk of the first vein thrombosis was twice as high in men than in women [24]. Despite the efforts aimed at studying various factors, the paradox of sex differences as they affect risk of both new and recurrent vein thrombosis remained unexplained.

Table 4. Frequency of acute thrombosis and post-thrombotic changes detection in the main lower extremity superficial veins (various localizations)

Localization	Frequency, people	Share, %
Great saphenous vein (unilateral lesion)	19	32.2
Small saphenous vein (unilateral lesion)	18	30.5
Great saphenous vein (bilateral lesion)	3	5
Small saphenous vein (bilateral lesion)	8	13,6
Great and small saphenous vein	2	3.4
Great saphenous vein (bilateral lesion) and small saphenous vein	1	1.7
Lesion of superficial veins (unspecified localization) combined with damage to deep veins	8	13.6
Total	59	100

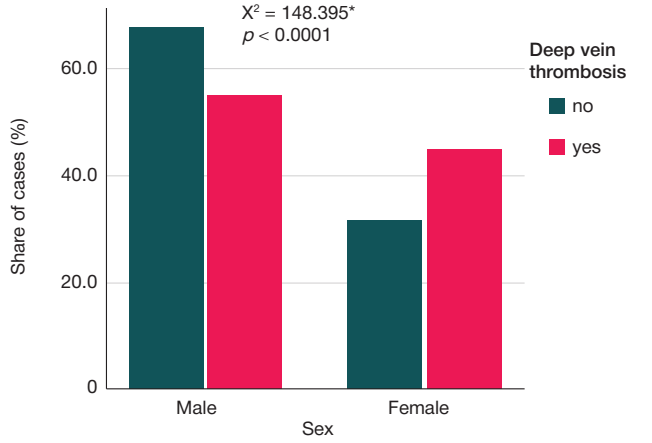

Fig. 5. Frequency of acute DVT depending on gender

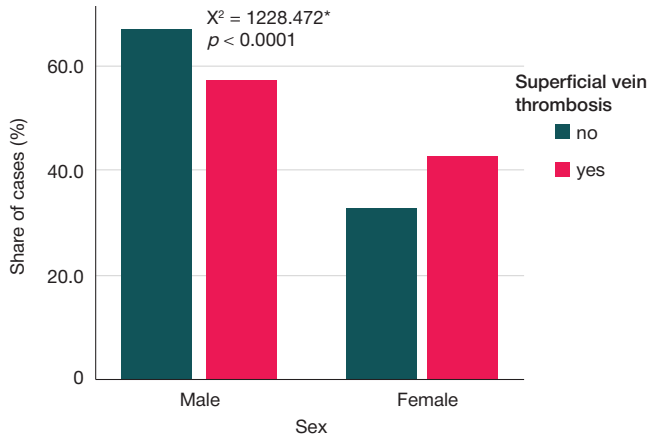

Fig. 6. Frequency of acute SVT depending on gender

There is another study that shows that men run higher risk of first and recurrent vein thrombosis than women [25]. There were suggested several explanations for the sex-associated differences. Body height was the main factor explaining about 20% of the differences in the population-attributable share. The alternative explanations suggested for the said differences hypothesized about presence of X- or Y-linked mutations or a gene mutation with a sex-specific effect [25]. However, in a 2012 study of 323 patients with acute stroke, DVT was significantly more common in women (71.4% versus 49.5%) [7]. According to the results of a 2021 study, female gender and high levels of D-dimer in stroke patients were independent significant factors altering incidence of DVT [26].

In our cohort, women suffered lesion of the lower extremity veins significantly more often, and, given the average age of the patients (59.23 ± 13.7 years), the reproductive system factors can be ignored. One of the probable explanations of this fact is the women's BMI, which, according to the two-way analysis, tended to be higher among those who had signs of the lower extremity vein thrombosis. It can be assumed that increased body weight could play a role in sex-associated distribution. Another probable cause that cannot be ruled is the possible association of higher incidence of thrombosis and increased estrogen levels, especially overweight women, since in such conditions venous tone deteriorates and the circulating blood volume may grow larger [27]. In addition, greater incidence of damage to the lower extremity veins in females may be associated with May-Thurner syndrome (compression of the common iliac vein (usually left) by the common iliac artery). The incidence of this syndrome in the population is up to 20%, and women suffer it more often [28].

CONCLUSIONS

The conducted research allows stating the following. The incidence of acute lower extremity vein thrombosis in the study cohort was 7.8%, post-thrombotic changes — 5.6%. Detection of the signs of thrombosis and (or) its consequences did not correlate with the pathogenetic variant of ischemic stroke, and the incidence of acute thrombosis decreased with the time elapsed from the onset of stroke. Isolated deep vein lesions were more common in lower legs than in other locations. Women have lower extremity vein thrombosis significantly more often. Excess body weight is associated with lesion of the proximal lower extremity veins. Repeated lower extremity venous duplex scanning upon admission to the rehabilitation hospital allowed learning the specifics that altered treatment, prevention and rehabilitation tactics, the alterations, inter alia, aimed at mitigation of the ECVT occurrence risk during the stroke recovery period.

References

1. Gusev EI, Konovalov AN, Skvorcova VI, redaktory. Nevrologiya. Nacional'noe rukovodstvo. Tom 1. M.: GEhOTAR-Media, 2018; 880 s. Russian.
2. Fonyakin AV, Geraskina LA. Faktory riska, diagnostika, lechenie i profilaktika venoznyx trombozov i tromboehmbolij pri ostrom insul'te. Nevrologiya, nejropsixiatriya, psixosomatika. 2013; 5 (4): 4–9. Russian.
3. Konstantinova GD, Zubarev AR, Gradusov EG. Flebologiya. M.: Izd. dom Vidar-M, 2000; 160 s. Russian.
4. Parfenov VA. Venoznye tromboehmbolicheskie oslozhneniya pri ishemicheskom insul'te i ix profilaktika. Nevrologicheskij zhurnal. 2012; 17 (5): 4–9. Russian.
5. Pinto SM, Yassin M, Galang G. Cost-Effectiveness Analysis of Routine Venous Doppler Ultrasound for Diagnosis of Deep Venous Thrombosis at Admission to Inpatient Rehabilitation. Am J Phys Med Rehabil. 2018; 97 (10): 747–53. DOI: 10.1097/PHM.0000000000000961.
6. Kuncevich GI, Maksimova MYu, Popova LA, Ryabinkina YuV, Gnedovskaya EV, Piradov MA. Tromboz ven nizhnix konechnostej v dinamike ostryx narushenij mozgovogo krovoobrashheniya. Angiologiya i sosudistaya xirurgiya. 2012; 18 (2): 77–81. Russian.
7. Bembenek JP, Karlinski M, Kobayashi A, Czlonkowska A. Deep venous thrombosis in acute stroke patients. Clin Appl Thromb Hemost. 2012; 18 (3): 258–64. DOI: 10.1177/1076029611424575. Epub 2011 Nov 8.
8. Rinde LB, Småbrekke B, Mathiesen EB, et al. Ischemic stroke and risk of venous thromboembolism in the general population: the tromsø study. J Am Heart Assoc. 2016; 5 (11): e004311. DOI: 10.1161/JAHA.116.004311
9. Wang Y, Shi Y, Dong Y, Dong Q, Ye T, Fang K. Clinical Risk Factors of Asymptomatic Deep Venous Thrombosis in Patients With Acute Stroke. Clin Appl Thromb Hemost. 2019; 25: 1–7. DOI: 10.1177/1076029619868534. PMID: 31434499.
10. Obi AT, Barnes GD, Napolitano LMб, et al. Venous thrombosis epidemiology, pathophysiology, and anticoagulant therapies and trials in severe acute respiratory syndrome coronavirus 2 infection. J Vasc Surg Venous Lymphat Disord. 2021; 9 (1): 23–35. DOI: 10.1016/j.jvsv.2020.08.030. Epub 2020 Sep 8.
11. Zdanyte M, Rath D, Gawaz M, et al. Venous Thrombosis and SARS-CoV-2. Hamostaseologie. 2021. DOI: 10.1055/a-1661-

0283. Epub ahead of print.
12. Liu XC, Chen XW, Li ZL, Wang SC, Chen C. Anatomical distribution of lower-extremity deep venous thrombosis in patients with acute stroke. J Stroke Cerebrovasc Dis. 2020; 29 (7): 1–5. DOI: 10.1016/j.jstrokecerebrovasdis.2020.104866. Epub 2020 May 11.
13. Valentin ML, Clemens R, Thalhammer C. Duplexsonografie der tiefen Beinvenenthrombose [Duplex ultrasound of deep vein thrombosis of the leg]. Dtsch Med Wochenschr. 2016; 141 (13): 946–9. DOI: 10.1055/s-0042-108930. Epub 2016 Jun 30. German.
14. Kearon C, Salzman EW, Hirsh J. Epidemiology, pathogenesis, and natural history of venous thrombosis. In: George JN, editor. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2001; p. 1153–77.
15. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993; 24 (1): 35–41. DOI: 10.1161/01.str.24.1.35.
16. Kelly J, Rudd A, Lewis RR, et al. Venous thromboembolism after acute ischemic stroke a prospective study using magnetic resonance direct thrombus imaging. Stroke. 2004; 35: 2320–6.
17. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2008; 133: 454–545.
18. Polyancev AA, Frolov DV, Linchenko DV, Shhelokova IV, Litvinova TA, Dyachkova YuA. Rezul'taty lecheniya peroral'nymi antikoagulyantami pacientov s trombozami glubokix ven nizhnix konechnostej. Angiologiya i sosudistaya xirurgiya. 2020; 26 (2): 42–51. DOI: 10.33529/ANGI02020208. Russian.
19. Hekman KE, Chao CL, Morgan CE, Helenowski IB, Eskandari MK. Direct oral anticoagulants decrease treatment failure for acute lower extremity deep venous thrombosis [published online ahead of print, 2021 Sep 26]. Vascular. 2021; OnlineFirst. DOI: 10.1177/17085381211042231.
20. Sharifi M, Freeman W, Bay C, Sharifi M, Schwartz F. Low incidence of post-thrombotic syndrome in patients treated with new oral anticoagulants and percutaneous endovenous intervention for lower extremity deep venous thrombosis. Vasc Med. 2015; 20 (2): 112–6. DOI: 10.1177/1358863X14553882
21. Sharma M, Ramanathan S, Khalighi K. Development of new deep venous thrombosis while on apixaban. Case Rep Cardiol. 2017; 2017: 1–3. DOI: 10.1155/2017/2842935.
22. Shevela AI, Usov SA, Markina VA. Ozhirenie i xronicheskaya venoznaya nedostatochnost': ot faktorov riska k patogenezu. Flebologiya. 2019; 13 (3): 220–6. Russian.
23. Seidel AC, Belczak CEQ, Campos MB, Campos RB, Harada DS. The impact of obesity on venous insufficiency Phlebology. 2015; 30: 475–80.
24. Eichinger S, Kyrle PA. Sex, age and venous thrombosis-Are men and women indeed from different planets? Eur J Intern Med. 2021; 84: 16–17. DOI: 10.1016/j.ejim.2020.12.022.
25. Roach RE, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. J Thromb Haemost. 2014; 12 (10): 1593–600. DOI: 10.1111/jth.12678.
26. Mori T, Yoshioka K, Tanno Y. Frequency of deep vein thrombosis at admission for acute stroke and associated factors: a cross-sectional study. Thromb J. 2021; 19 (1): 62. DOI: 10.1186/s12959-021-00315-5.
27. Hunt BJ. The effect of BMI on haemostasis: Implications for thrombosis in women's health. Thromb Res. 2017; 151 Suppl 1: 53–55. DOI: 10.1016/S0049-3848(17)30068-3.
28. Kiernan TJ, Yan BP, Cubeddu RJ, Rengifo-Moreno P, Gupta V, Inglessis I, et al. May-Thurner syndrome in patients with cryptogenic stroke and patent foramen ovale: an important clinical association. Stroke. 2009; 40 (4): 1502–4. PMID: 19182088. Available from: https://doi.org/10.1161/ STROKEAHA.108.527366.

Литература

1. Гусев Е. И., Коновалов А. Н., Скворцова В. И., редакторы. Неврология. Национальное руководство. Том 1. М.: ГЭОТАР-Медиа, 2018; 880 с.
2. Фонякин А. В., Гераскина Л. А. Факторы риска, диагностика, лечение и профилактика венозных тромбозов и тромбоэмболий при остром инсульте. Неврология, нейропсихиатрия, психосоматика. 2013; 5(4): 4–9.
3. Константинова Г. Д., Зубарев А. Р., Градусов Е. Г. Флебология. М.: Изд. дом Видар-М, 2000; 160 с.
4. Парфенов В. А. Венозные тромбоэмболические осложнения при ишемическом инсульте и их профилактика. Неврологический журнал. 2012; 17 (5): 4–9.
5. Pinto SM, Yassin M, Galang G. Cost-Effectiveness Analysis of Routine Venous Doppler Ultrasound for Diagnosis of Deep Venous Thrombosis at Admission to Inpatient Rehabilitation. Am J Phys Med Rehabil. 2018; 97 (10): 747–53. DOI: 10.1097/PHM.0000000000000961.
6. Кунцевич Г. И., Максимова М. Ю., Попова Л. А., Рябинкина Ю. В., Гнедовская Е. В., Пирадов М. А. Тромбоз вен нижних конечностей в динамике острых нарушений мозгового кровообращения. Ангиология и сосудистая хирургия. 2012; 18 (2): 77–81.
7. Bembenek JP, Karlinski M, Kobayashi A, Czlonkowska A. Deep venous thrombosis in acute stroke patients. Clin Appl Thromb Hemost. 2012; 18 (3): 258–64. DOI: 10.1177/1076029611424575. Epub 2011 Nov 8.
8. Rinde LB, Småbrekke B, Mathiesen EB, et al. Ischemic stroke and risk of venous thromboembolism in the general population: the tromsø study. J Am Heart Assoc. 2016; 5 (11): e004311. DOI: 10.1161/JAHA.116.004311
9. Wang Y, Shi Y, Dong Y, Dong Q, Ye T, Fang K. Clinical Risk Factors of Asymptomatic Deep Venous Thrombosis in Patients With Acute Stroke. Clin Appl Thromb Hemost. 2019; 25: 1–7. DOI: 10.1177/1076029619868534. PMID: 31434499.
10. Obi AT, Barnes GD, Napolitano LMб, et al. Venous thrombosis epidemiology, pathophysiology, and anticoagulant therapies and trials in severe acute respiratory syndrome coronavirus 2 infection. J Vasc Surg Venous Lymphat Disord. 2021; 9 (1): 23–35. DOI: 10.1016/j.jvsv.2020.08.030. Epub 2020 Sep 8.
11. Zdanyte M, Rath D, Gawaz M, et al. Venous Thrombosis and SARS-CoV-2. Hamostaseologie. 2021. DOI: 10.1055/a-1661-0283. Epub ahead of print.
12. Liu XC, Chen XW, Li ZL, Wang SC, Chen C. Anatomical distribution of lower-extremity deep venous thrombosis in patients with acute stroke. J Stroke Cerebrovasc Dis. 2020; 29 (7): 1–5. DOI: 10.1016/j.jstrokecerebrovasdis.2020.104866. Epub 2020 May 11.
13. Valentin ML, Clemens R, Thalhammer C. Duplexsonografie der tiefen Beinvenenthrombose [Duplex ultrasound of deep vein thrombosis of the leg]. Dtsch Med Wochenschr. 2016; 141 (13): 946–9. DOI: 10.1055/s-0042-108930. Epub 2016 Jun 30. German.
14. Kearon C, Salzman EW, Hirsh J. Epidemiology, pathogenesis, and natural history of venous thrombosis. In: George JN, editor. Hemostasis and Thrombosis. Basic Principles and Clinical Practice. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2001; p. 1153–77.
15. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993; 24 (1): 35–41. DOI: 10.1161/01.str.24.1.35.
16. Kelly J, Rudd A, Lewis RR, et al. Venous thromboembolism after acute ischemic stroke a prospective study using magnetic resonance direct thrombus imaging. Stroke. 2004; 35: 2320–6.
17. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest.

2008; 133: 454–545.
18. Полянцев А. А., Фролов Д. В., Линченко Д. В., Щелокова И. В., Литвинова Т. А., Дъячкова Ю. А. Результаты лечения пероральными антикоагулянтами пациентов с тромбозами глубоких вен нижних конечностей. Ангиология и сосудистая хирургия. 2020; 26 (2): 42–51. DOI: 10.33529/ANGI02020208.
19. Hekman KE, Chao CL, Morgan CE, Helenowski IB, Eskandari MK. Direct oral anticoagulants decrease treatment failure for acute lower extremity deep venous thrombosis [published online ahead of print, 2021 Sep 26]. Vascular. 2021; OnlineFirst. DOI: 10.1177/17085381211042231.
20. Sharifi M, Freeman W, Bay C, Sharifi M, Schwartz F. Low incidence of post-thrombotic syndrome in patients treated with new oral anticoagulants and percutaneous endovenous intervention for lower extremity deep venous thrombosis. Vasc Med. 2015; 20 (2): 112–6. DOI: 10.1177/1358863X14553882
21. Sharma M, Ramanathan S, Khalighi K. Development of new deep venous thrombosis while on apixaban. Case Rep Cardiol. 2017; 2017: 1–3. DOI: 10.1155/2017/2842935.
22. Шевела А. И., Усов С. А., Маркина В.А. Ожирение и хроническая венозная недостаточность: от факторов риска к патогенезу. Флебология. 2019; 13 (3): 220–6.
23. Seidel AC, Belczak CEQ, Campos MB, Campos RB, Harada DS. The impact of obesity on venous insufficiency Phlebology. 2015; 30: 475–80.
24. Eichinger S, Kyrle PA. Sex, age and venous thrombosis-Are men and women indeed from different planets? Eur J Intern Med. 2021; 84: 16–17. DOI: 10.1016/j.ejim.2020.12.022.
25. Roach RE, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment. J Thromb Haemost. 2014; 12 (10): 1593–600. DOI: 10.1111/jth.12678.
26. Mori T, Yoshioka K, Tanno Y. Frequency of deep vein thrombosis at admission for acute stroke and associated factors: a cross-sectional study. Thromb J. 2021; 19 (1): 62. DOI: 10.1186/s12959-021-00315-5.
27. Hunt BJ. The effect of BMI on haemostasis: Implications for thrombosis in women's health. Thromb Res. 2017; 151 Suppl 1: 53–55. DOI: 10.1016/S0049-3848(17)30068-3.
28. Kiernan TJ, Yan BP, Cubeddu RJ, Rengifo-Moreno P, Gupta V, Inglessis I, et al. May-Thurner syndrome in patients with cryptogenic stroke and patent foramen ovale: an important clinical association. Stroke. 2009; 40 (4): 1502–4. PMID: 19182088. Available from: https://doi.org/10.1161/ STROKEAHA.108.527366.