CLINICAL AND EPIDEMIOLOGICAL PROFILE OF OUTPATIENT VENOUS THROMBOEMBOLIC COMPLICATIONS

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UDC 616.14-005.6/.7-036.22

Key words: *venous thromboembolism, pulmonary embolism, deep vein thrombosis, epidemiology.*

FOR REFERENCES. V.Ya. Khryshchanovich, S.S. Kalinin, I.P. Klimchuk, N.A. Rogovoy. CLinical and epidemiological profile of outpatient venous thromboembolic complications. *Neotlozhnaya kardiologiya i kardiovaskulyarnye riski* [Emergency cardiology and cardiovascular risks], 2020, vol. 4, no. 1, pp. 873–876.

Aim. To determine the demographic and clinical structure of venous thromboembolic (VTE) complications in the population of a large industrial center.

Methods. Prospective clinical observational cohort study is based on the results of management of 753 patients with VTE complications in Minsk city in the period from 2013 to 2018. VTE complications were diagnosed in accordance with the current recommendations of the American College of Chest Physicians (ACCP). Compression ultrasonography (USG) and duplex scanning were used to visualize lower limb veins in all 753 patients. The following USG parameters were studied: diameter of the target vein, its compressibility, state of the lumen and surrounding tissues, deep vein valves, localization of thrombotic masses, presence of the free-floating part of the thrombus, its length and thickness of the base. In 97 patients with high clinical probability of pulmonary embolism (PE) computed tomography angiography was performed.

Results. Examination of 753 patients with VTE complications revealed high prevalence (90%) of proximal deep vein thrombosis, which was complicated by embolous thrombus flotation (37%), PE (10%) and acute venous insufficiency in 2% of cases. The ratio of male/female with VTE complications was 1.1:1, which was not a significant difference. More than a half (53%) of VTE complications occurred in patients of working-age.

Conclusion. VTE complications are a very common pathology, and high probability of life-threatening complications such as PE and acute venous insufficiency puts VTE complications on a par with other urgent surgical diseases.

Introduction

The findings of major epidemiological studies concerning both clinically significant and asymptomatic cases of venous thromboembolic (VTE) complications allow us to classify this pathology as prevailing, socially significant and life-threatening [1, 2, 3]. Despite significant achievements of the health care system in many areas, pulmonary embolism (PE) ranks third among the causes of sudden death after myocardial infarction and stroke, and, in terms of mortality, surpasses road traffic injuries, breast and prostate cancer, and acquired immunodeficiency syndrome combined [1, 4, 5]. According to the results of large population studies, the incidence of VTE complications does not tend to decrease and amounts to ~70-113 cases per 100,000 population a year, exponentially increasing after 40 years without significant gender differences [1, 5]. While at the age of 25-35 years ~ 30 cases of VTE complications are recorded per 100,000 of the population a year, in the 70+ age group the incidence is already ~ 300-500 cases [1, 2, 6].

According to statistical data, cavailiofemoral localization of deep vein thrombosis (DVT) is observed in 70-80% of cases [1, 2, 3, 6], thrombus flotation occurring in 8-15% of patients [1, 2, 7] and mortality from massive pulmonary embolism reaching 11-23% [1, 4, 8]. The most embolus-threatening zone is the inferior vena cava (IVC) system, which accounts for over 90% of PE [1, 4, 5]. Another relatively infrequent, but no less serious complication of acute DVT is acute venous insufficiency or phlegmasia of the lower extremities, the incidence of which, according to various authors, reaches 1.7–8.2% [1, 6, 7].

A large number of publications are devoted to the treatment of VTE complications; however, the rational choice between the conservative and surgical treatment options is still a matter of considerable debate. The current diverse approaches to the management of patients with VTE complications sometimes put the doctor in charge in a difficult position, and the choice of treatment method is often based on personal preferences, rather than on an objective assessment of immediate and long-term results. At the same time, epidemiological studies related to the study of the structure of outpatient VTE complications, as well as the range of therapeutic measures used, have not been conducted in our country before [1].

Aim of the study

To determine the demographic and clinical structure of venous thromboembolic (VTE) complications in the population of a large industrial center.

Methods

A prospective clinical observational cohort study is based on the results of the management of 753 patients with VTE complications who, in the period from 2013 to 2018, were directed for urgent hospitalization to Minsk from the outpatient settings. Of these, 327 patients were admitted to the 4th Minsk Clinical Hospital, Department of Vascular and Purulent Surgery. 426 patients received treatment in ten other city hospitals and three Republican Scientific and Practical Centers (Table 1) [1].

Diagnosis of VTE complications was carried out in accordance with the latest recommendations of the American College of Thoracic Physicians (ACCP) [8, 9]. Ultrasound (US) examinations using high-resolution scanners Mindray M7 (Shenzhen Mindray Bio-Medical Electronics Co. Ltd, China), Samsung Medison SonoAce R7 (Samsung Medison Co. Ltd, DPRK) were used as a method for visualizing the veins of the lower extremities in all 753 patients. The scanners were used in various modes: B, M, Anatomical M (Free Xros M, Free Xros CM, Color M-mode Color M), C (color doppler, energy doppler), D (PW, CW, Power and DirPower energy and directional doppler), special visualization (Smart 3D, 4D, iScape panoramic, TDI fabric doppler, automatic calculation of the thickness of the intima-media complex (IMT). To perform compression sonography and duplex angioscanning, a linear sensor with a frequency of 5-10 MHz and a convex sensor with a frequency of 2.5-5 MHz were used [1]. During an ultrasound examination, the following parameters were studied: diameter of the target vein, target vein compressibility (compression by the sensor until the blood flow stops), specific location, state of the lumen and surrounding tissues, preservation of the valve apparatus, localization and prevalence of thrombotic masses, wall changes, the presence of the movable part of the thrombus, thrombus length and thickness of its stalk [1].

Table 1.
Distribution of patients with venous thromboembolic complications according to the place of hospitalization

Hospital	Number of patients, n (%)
4th City Clinical Hospital	327 (43.4)
1st City Clinical Hospital	21 (2.8)
2nd City Clinical Hospital	117 (15.5)
3rd City Clinical Hospital	33 (4.4)
5th City Clinical Hospital	25 (3.3)
6th City Clinical Hospital	55 (7.3)
9th City Clinical Hospital	55 (7.3)
10th City Clinical Hospital	16 (2.2)
11th City Clinical Hospital	5 (0.7)
Minsk City Emergency Hospital	30 (4)
Minsk City Clinical Oncologic Dispensary	9 (1.2)
Republican Research and Clinical Center of Neurology and Neurosurgery	33 (4.4)
Republican Scientific and Practical Center of Traumatology and Orthopedics	26 (3.5)
Republican Scientific and Practical Center of Mother and Child	1 (0.1)

Ultrasonographic signs of occlusive DVT included the presence of a hyperechoic heterogeneous structure in the lumen of the vein, increased blood flow and expansion of the saphenous veins (collateral blood flow), complete filling of the vessel lumen with thrombotic masses, the absence of movement of the vessel walls on compression by the sensor, an increase in the diameter of the vein, and the absence of blood flow through the vessel in Doppler or color mode, the presence of low-amplitude monophasic blood flow unsynchronized with the act of breathing more distal than the thrombosis zone [1]. Incomplete closure of the vessel walls on compression by the sensor, presence of the vessel lumen between the thrombotic masses and the venous wall, and the presence of monophasic low velocity blood flow unsynchronized with the act of breathing were confirmation of non-occlusive thrombosis [1].

Ultrasonic criteria for floating thrombosis were an echogenic structure located in the lumen of the vein with the presence of free space, oscillatory movements of the thrombus top, the absence of contact of the walls of the vein on compression by the sensor, the presence of free space when performing breathing tests, the circumflex type of blood flow on color coding, the presence of spontaneous blood flow on spectral Doppler sonography. In this case, a thrombus was considered embolus-threatening, the length of the floating part of which was 30 mm or more, and / or the width of the "stalk" of the movable section was ≥2 times less than its length [1].

CT angiopulmonography (General Electric, USA) was performed after an intravenous bolus injection of 100 ml of Omnipaque® (Takeda, Japan), Tomohexol (Farmak, Ukraine) in 97 cases aimed at visualization of the proximal border of the thrombus located in the iliac veins and IVC, as well as at proper diagnosing in patients with a high clinical probability of pulmonary embolism [1].

Statistical analysis of the data obtained was carried out on a personal computer using Statistica 10.0 (StatSoft Inc., USA, license No.AXXR012E839529FA) [1].

Results

The results of the study showed that among patients with VTE complications, males were slightly prevailing, while the male / female ratio was 1.1: 1 (Fig. 1) [1]. In more than a half (53%) of cases, patients of working age prevailed, while in 47% of cases phlebothrombosis was revealed in elderly and senile patients. In young patients (under 45), VTE complications occurred in 179 (24%) cases (Fig. 2) [1].

In 75 (10%) cases distal DVT localization was revealed: in the tibial segment – in 30 (4%) patients, in the tibioperoneal segment – in 45 (6%) (Fig. 3) [1]. Proximal phlebothrombosis was diagnosed in 678 (90%) patients, while in 452 (60%) cases the thrombotic process was localized in

the femoropopliteal segment and in 226 (30%) in the ileofemoral segment [1].

On the first day from the time of admission to hospital embolus-threatening flotation of the thrombus head was detected in 279 (37%) cases, and in 15 (2%) acute venous insufficiency (phlegmasia) was revealed (Fig. 4) [1].

Non-fatal pulmonary embolism was diagnosed on admission in 74 patients, which accounted for 10% of all cases of VTE complications (Fig. 5) [1]. It should be noted that out of 753 patients who underwent inpatient treatment for DVT, there were no cases of development of hospital pulmonary embolism nor its relapse [1].

The choice of treatment method depended directly on the revealed anatomical and clinical features of venous thrombosis: localization, length, duration, degree of the vein lumen occlusion and compensation of blood circulation in the limb [1]. An active therapeutic approach in combination with one or another variant of anticoagulant therapy (vitamin K antagonists [AVK] or new oral anticoagulants [NOAC]), was aimed primarily at arresting DVT complications and / or preventing pulmonary embolism [1]. As a result, invasive interventions were used in 303 (40%) cases, while isolated anticoagulant therapy was prescribed to 450 (60%) patients (Fig. 6) [1]. It should be noted that in more than 40% of cases of conservative treatment of VTE complications, direct oral anticoagulants, rivaroxaban or dabigatran etexilate, were used [1].

Discussion

The obtained data largely confirm the results of previous epidemiological studies [1, 3, 7, 11]. However, M. Silverstein et al. [12] indicated a higher prevalence of DVT and PE in the elderly and senile patients, viz. 180-800 cases per 100,000 population, with some male prevalence. Moreover, the incidence of DVT in patients under 60 years of age did not have significant sex differences and amounted to 50-100 cases per 100,000 population. Other authors [1, 7, 13] noted a higher incidence of VTE complications in women of reproductive age (16-45 years) compared with their male counterparts, while, after 45 years, gender differences were directly opposite, which is generally consistent with personal observations [1].

R. White [11], J. Heit et al. [14] explain similar demographic statistics by the influence of the existing risk factors for venous thrombosis characteristic of certain age periods of life. For young women, these risks include pregnancy and the postpartum period, hormone replacement therapy, and oral contraceptive therapy. The risk factors for elderly patients are acute and chronic diseases of internal organs (myocardial infarction, stroke, coronary heart disease, chronic heart failure, diabetes mellitus, etc.), cancer pathology and antitumor therapy, long-term immobilization (paralysis, paresis), overweight [1, 11, 14].

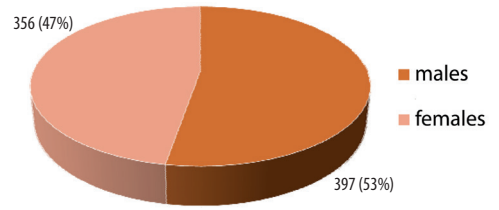

Figure 1. Distribution of patients with venous thromboembolic complications according to sex

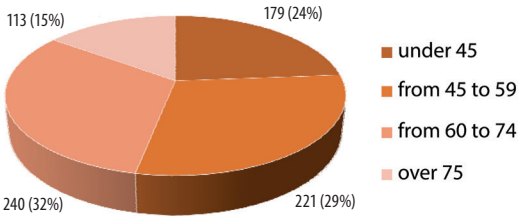

Figure 2. Distribution of patients with venous thromboembolic complications according to age

At the same time, according to J. Heit et al. [14], in at least 25–40% of cases in the European and African populations and in 19% of cases in the Asia-Pacific region, the causes of VTE complications remain unclear [1]. In this regard, J. Heit et al. [14], F. Spencer et al. [15] believe that congenital thrombophilia (primarily mutations of F5rs6025 gene [V Leiden factor] and F2rs1799963 gene [prothrombin 20210G > A]) or May-Thurner syndrome should be presumed in young

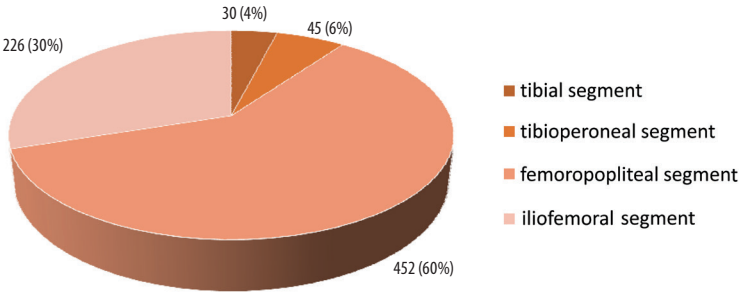

Figure 3. Sites of deep vein thrombosis

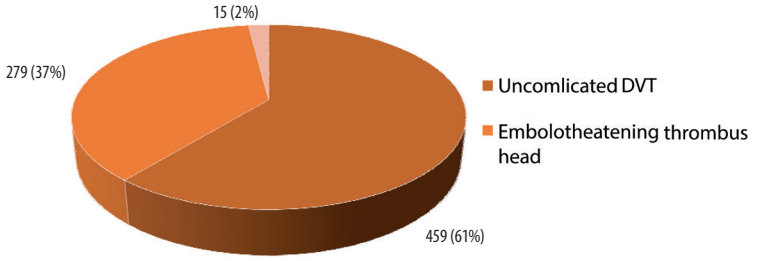

Figure 4. Structure of venous thromboembolic complications

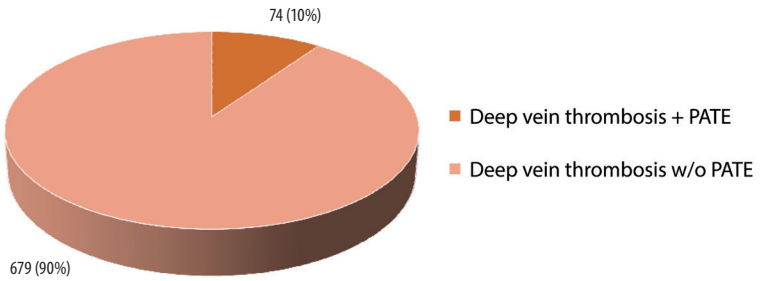

Figure 5. Ratio of out-of-hospital pulmonary embolism (PATE) in the structure of venous thromboembolic complications

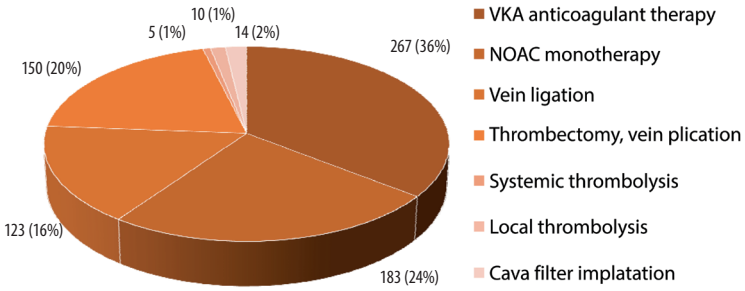

Figure 6. Treatment options for venous thromboembolic complications

patients with unprovoked DVT, and cancer-associated thrombosis should be suggested in elderly patients (first of all, gastric cancer, pancreatic cancer, lung cancer, ovarian cancer, colon cancer, brain tumor, hematologic malignancies, metastatic lesions) [1].

Of course, the localization of the thrombotic process determines not only the clinical picture of the disease, but also the probability of PE development, the course of the acute and post-thrombotic periods, and the prognosis for the patient's life and ability to work [1, 16, 17]. According to the results of our own observations, the thrombotic process most often (in 90% of cases) involved the proximal segments of deep veins, which generally corresponds to the data of large population studies [1, 3, 11, 12]. However, J. Heit et al. [14] provide information on the higher incidence of distal DVT, viz. up to 40%, while thrombosis of the popliteal, femoral and iliac segments is detected in 16%, 40% and 4% of cases, respectively [1].

The data obtained regarding the prevalence of ileofemoral DVT are consistent with reports of other authors [1, 3, 7]. Thrombosis of this localization occurs in 30-45% of cases, while the predominance of patients of working age emphasizes not only the medical, but social significance of the problem. It was found out that the immediate outcome of the ileo-femoral DVT was pulmonary embolism and phlegmasia of the affected limb in 10% and 2% of cases, respectively. In addition, P. Prandoni et al. [18], S. Kahn et al. [19] indicated a high (23-60%) probability of developing post-thrombotic disease after suffering proximal DVT, while the statistics were largely dependent on the chosen treatment method [1].

Conclusion

Venous thromboembolism syndrome is a very common pathology, including among people of working age, and therefore is an urgent medical and social problem [1]. The high probability of developing life-threatening complications, such as pulmonary embolism and severe forms of acute venous insufficiency, ranks venous thromboembolism together with other urgent surgical diseases [1]. An equally important public health problem is post-thrombotic disease, the manifestations of which are very diverse ranging from minor symptoms and signs of chronic venous insufficiency to the emergence of long-term non-healing trophic ulcers [1]. That is why an extremely important task of modern medicine and surgery in particular is the development of effective and pathogenetically substantiated methods of treatment of acute deep vein thrombosis and reliable prevention of its complications [1].

Source of Financing
The work was carried out in accordance with the Research Plan of Belarusian State Medical University. The authors did not receive financial support from manufacturers of medical devices.
Conflict of Interest
The authors declare no conflict of interest.

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Поступила 03.02.2020