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Venous thromboembolic disease – potentially life-threatening clinical problem.

Żylna choroba zakrzepowo-zatorowa – potencjalnie groźny dla życia problem kliniczny.

Summary
It is estimated that in Poland deep vein thrombosis affects approx. 60.000 people while pulmonary embolism about 34.000. Both are potentially life-threatening. Nowadays risk factors for venous thromboembolism are well known. Diagnosis of deep vein thrombosis and pulmonary embolism starts with evaluation of patient's clinical condition and likelihood of those diseases. Further diagnostic investigation depends on the size of this probability. Heparins and oral anticoagulant drugs (coumarin derivatives) play main role in treatment of venous thromboembolism.

Key words: deep vein thrombosis, pulmonary embolism, Well's score, D-Dimers, primary prevention, secondary prevention

Streszczenie
Częstość występowania w Polsce żylnej choroby zakrzepowo-zatorowej szacuje się na około 60 tysięcy zachorowań na zakrzepicę żył głębokich oraz około 34 tysiące zachorowań na zatorowość płucną rocznie. Jest to choroba potencjalnie groźna dla życia. Obecnie dobrze znane są czynniki ryzyka, które sprzyjają rozwojowi choroby zakrzepowo-zatorowej. Diagnostyka zakrzepicy żył głębokich i zatorowości płucnej rozpoczyna się od oceny stanu klinicznego pacjenta, oraz oszacowaniu klinicznego prawdopodobieństwa wystąpienia tych chorób. Dalsze postępowanie diagnostyczne jest uzależnione od wielkości tego prawdopodobieństwa. Leczenie żylnej choroby zakrzepowo-zatorowej oparte jest głównie na zastosowaniu heparyn oraz doustnych antykoagulantów (pochodnych kumaryny).

Słowa kluczowe: zakrzepica żył głębokich, zatorowość płucna, skala Wellsa, D-Dimery, profilaktyka pierwotna, profilaktyka wtórna

Introduction

The term of venous thromboembolic disease (VTE) is deep vein thrombosis (DVT) and pulmonary embolism (PE) which stands for its dangerous complication. A few facts about DVT and PE makes these diseases a serious problem and a major challenge for modern medicine. The first is prevalence. It is estimated that in Poland every year DVT affects approx. 60.000 people, PE approx. 34.000. These estimates are based on epidemiological data from the United States and Western European countries (Zawilska et al. 2012; Gutkenecht et al. 2007). The incidence of VTE increases with age. The majority of the cases (approx. 70%) applies to people over 60 years old (Zawilska et al. 2012). In the group of people between 85 and 89 years the incidence of VTE is about 12 times higher in comparison with a group of people under 40 years (Gutknecht et al. 2007).It is associated with a greater number of the risk factors for this disease in the elderly group. Venous thromboembolism, pulmonary embolism in particular, encumbers with high mortality rate. The occurrence of thrombus in the pulmonary vessels causes difficulty in blood flow, which leads to an increase of pressure in the pulmonary vessels and a huge load of the right ventricle. It is estimated that in the United States the mortality rate due to PE is greater than 15% during the first 3 months from diagnosis. The prevalence of this complication is assessed more than 1 case per 1000 population per year. It is said that at least 50.000 deaths per year are caused by PE (Goldhaber et al. 2003). In 2008 the European Society of Cardiology defined the risk of early death due to PE as the probability of death caused by PE during a hospitalization or within 30 days of admission to a hospital. To assess the size of this risk three criteria were proposed: clinical symptoms (occurence of shock or hypotension), symptoms of dysfunction of the right ventricle (enlargement of ventricular, hypokinesia or overload in echocardiography, increase of NT-pro-BNP (N-terminal prohormone of brain natriuretic peptide)), and symptoms of myocardial damage (increased troponin). All patients, who during the course of acute PE appear a shock or hypotension, were qualified to a high risk of early death owing to PE. The risk in this group is more than 15% and these patients represent 5-10% of all patients with acute PE. The patients who present symptoms of the right ventricular dysfunction or symptoms of myocardial damage or both criteria at the same time, were qualified to the intermediate-risk group of early death due to PE amounts to 3-15%. The patients who do not experience any of the above criteria are the low-risk group of less than 1% (Kostrubiec et al. 2010). The mortality which is a result of PE can be reduced owing to apply of DVT prophylaxis and early implemented appropriate treatment.

Another, the most common complication of DVT, is the post-thrombotic syndrome. It develops in 20-50% of the patients with a history of DVT (Khan, 2006). Its main symptoms such as chronic pain, swelling, heaviness, are caused by chronic venous insufficiency. In the serious cases skin ulceration may appear.Because of the high prevalence and significant aggravation in the quality of life and chronic nature, post-thrombotic syndrome is a serious clinical problem.

Risk factors

Venous thrombosis arises from an imbalance between the pro-and antithrombotic processes. Various phenomena and clinical situations as the risk factors for DVT may contribute to this. Their action causes three basic phenomena, which were described in 1856 by Rudolf Virchow: changes in the blood, changes in blood vessel walls and blood flow changes. The most inner layer of the blood vessel wall is the endothelium. The accurate endothelium has a number of mechanisms that inhibits blood clotting, which gives it the antithrombogenical features.These mechanisms include the presence on the surface of endothelial endogenous heparinoids (hepran sulfate and dermatan sulfate) and thrombomodulin – thrombin receptor which takes part in the activation of protein C. The endothelial cells also produce and release a variety of substances such as: tissue plasminogen activator (t-PA), tissue factor pathway inhibitor (TFPI), prostacyclin I_2 (PGI_2) and nitric oxide. Under the influence of inflammation and damaging action of hypoxia, drugs and toxins, endothelial cells loose most of these mechanisms and start to demonstrate some prothrombic potential. In addition to the elimination of antithrombotic properties of endothelium, another phenomen contributing to the development of venous thrombosis is a change in blood fluxion. The driving force of the moving blood in the veins of the lower limbs to the heart are primarily the leg spasms while walking or running. During the muscle contraction the blood is “squeezed” into the heart direction, and during the muscle diastolic the venous valves prevent from a back blood flow. In the situation of prolonged immobility caused by i.e. the nature of the work, long flights, patients undergoing prolonged surgeries, paralysed patients, there is a stagnation of blood in the deep veins of the lower limbs. This stagnation causes hypoxia of endothelial cells which turn into the loss of its anthithrombotic properties. The third element of the Virchow’s triad is change in the blood. The concept of this is a series of apparitions that can be divided into congenital and acquired. The congenital includes, among others: genetically determined deficiency of natural inhibitors of blood coagulation – antithrombin, protein C and protein S, resistance to activated protein C associated with the mutations in the gene encoding factor V (factor V Leiden), the mutation G20210A of the prothrombin gene causing increased concentration of the plasma prothrombin, or genetically determined deficiency of the methylenetetrahydrofolate reductase (MTHFR), resulting in elevated concentration of plasma homocysteine which leads to damage of the endothelial cells. The adverse changes in hemostasis, may have an acquired character, are also favourable to make clots. They are closely related to the age of the patient, his health and the occurrence of various diseases, his lifestyle and physical activity. The most important risk factors for VTE to this group are: patient age, cancer, VTE in an interview, varicose veins of the lower limbs, stroke, septicaemia, severe injuries, major surgery, pregnancy and confinement, use of oral contraception and hormone replacement therapy, hospitalization, prolonged immobilization, obesity, smoking. The approximate incidence of DVT in association with individual risk factors in patients who are not undergoing anticoagulation prophylactic presents Tab.1 (Zawilska et al. 2012).

Tab.1 The approximate incidence of DVT associated with risk factors in patients who are not undergoing thromboprophylaxis.

Risk factors	The approximate incidence of DVT (%)
Hospitalization of a patient who moves on his own	0-10
Small surgery on a patient who moves on his own	0-10
Cancer	5-50
Bedridden patient's hospitalization	10-40
General operation such as gynaecology, urology and neurology	15-40
Ischemic stroke	20-50
Surgery in a patient with cancer	25-60
Hip or knee arthroplasty	40-80
Fracture of the proximal femur	40-80
Severe trauma	40-80
Acute spinal cord injury	60-80
Patients requiring intensive care	10-70

The relation between venous thromboembolism and cancer is very strong and fairly well understood. It was described in 1865 by Armand Trousseau. He observed the cases of travelling phlebitis in patients with cancer. In fact, VTE is one of the most common complications of not only the cancer itself, but also of the treatment: oncological surgery, chemotherapy and radiotherapy. The risk of VTE in patients with cancer is about 4-7 times higher than in the general population (Chojnowski 2012; Wun 2009). It increases further during the treatment and disease progression. It is potentially life-threatening complication and is the second most common cause of the death in this group of patients (Chojnowski et al. 2012; Khorana, 2010). The episode of VTE may be a prodromal symptom of latent cancer (also called latent cancer, lat. carcinoma occultum). According to various reports within two years after appearance of the episode of DVT cancer is diagnosed in 7% up to 20% of patients (Stanisławiak 2008; Wojtukiewicz 1998). Despite the fact that the occurrence of idiopathic DVT increases the likelihood of the presence of tumour, it is not recommended to perform a very detailed diagnostic procedures to detect cancer. These procedures can be limited to basic research in the frequently occurring cancers: chest X-ray, abdominal ultrasound examination, gynaecological examination and mammography, per rectum examination (including prostate in men), and also basic laboratory tests such as hem-occult test (Stanisławiak 2008; Wojtukiewicz 1998). The presence of VTE in patients with cancer significantly worsens the prognosis.

The relation between hormonal contraceptives and an increased risk of VTE is known since the sixties of the twentieth century. It is estimated that taking the second generation preparations is associated with approx. 2-fold increased risk of VTE in comparison to the population of women not taking hormonal contraception. Taking the third generation preparation increases the risk of up to 4-fold (Plu-Bureau 2013; Sandset 2013). It is calculated that the risk of an episode of DVT is the highest in the first five years after the

start of the therapy. If woman is receiving hormonal contraception, and additional risk factors favouring the occurrence of VTE are present (i.e. antiphospholipid syndrome, genetic risk factors, obesity, etc.), the risk of VTE episode is several times higher (Plu-Bureau et al. 2013).

The pregnancy and confinement are mentioned as risk factors for VTE. The risk of deep vein thrombosis in pregnancy is increased 4-5 fold. The largest is in the third trimester and its growth is observed from the first trimester. Further, a huge increase of the DVT risk is observed in the postnatal period. In the first week after birth the risk increases approx. 100 fold over the next five weeks is 60-80 factor of the risk of the pre-pregnancy (Cannegieter et al. 2013). One of the reasons for such a high increase of the risk of thrombotic disease is fact, that during pregnancy, especially before birth blood coagulation process are activated, which is to provide much more efficient inhibition of bleeding caused by the confinement.

Obesity is nowadays a common risk factor. It is associated with decreased physical activity which adversely affects the cardiovascular system. In addition, a number of mechanisms of hemostasis is shifted to the prothrombotic processes primarily through inhibition of the fibrinolytic system in obese people (Szepański 2007). An obesity is not often the sole risk factor but is only co-factor. This obviously increases the overall risk of DVT.

Diagnosis of venous thromboembolism

If VTE is suspected, clinical condition of the patient and the likelihood of tromboembolic complications should always be taken into account. The clinical symptoms or lack of them are not a reliable indicator of presence or absence of disease. It is estimated that approx. 60-70 % of the cases of deep vein thrombosis are asymptomatic (Gutknecht et al. 2007). The clinical symptoms of DVT are very diverse. The most important includes: pain which location and severity does not always match with the location and expansiveness of the disease. In addition, swelling limbs and its warming, redness and tenderness of the skin and knot affection on the course of deep vein are also observed.

In order to assess the clinical probability of DVT and PE can use the Wells score can be used (Tab. 2 and Tab. 3).

Tab. 2 The Wells score to estimate the probability of clinical DVT (Wells et al. 2003)

Clinical symptoms and medical history	**scores**
Active cancer	+1
Current paralysis, weakness, recent lower limb immobilization	+1
Recent immobilization in bed more than 3 days or major surgery within the last 4 weeks	+1
Topical achiness	+1
Entire leg swollen	+1

Swelling in the ankle of affected limb (limb ankle girth higher by at least 3 cm from the healthy ankle)	+1
Pitting oedema	+1
Visible superficial veins of collateral circulation	+1
Equally to or more likely diagnosis other than DVT	-2
Clinical probability of DVT	total
Small probability	=<0
Moderate probability	1-2
Large probability	>=3

Tab.3 The Wells score to estimate the clinical probability of PE (Klok et al. 2008)

Clinical symptoms and medical history	**scores**
Lower extremity oedema and the pain in the course of deep vein	+3
Frequency of heart rate >100/min	+1,5
Immobilization in bed for at least 3 next days or surgery in the past four weeks	+1,5
Documented DVT or PE in the past or in an interview	+1,5
Haemoptysis	+1
Active cancer	+1
Equally or more likely other diagnosis than PE	-3
The clinical probability of PE	total
Small probability	<2
Moderate probability	2-6
Large probability	>6

The Wells Score is used to assess the clinical probability of DVT and takes into account the most common risk factors that elaborates thrombotic disease. Patients can be divided into three groups low, medium and high clinical probability of DVT by means of that score. The assignment of the patient to a particular group defines further diagnostic conduct. It must be carried out very carefully and thoughtful. The concentration of D-Dimer has to be determined in patients with a low clinical probability of DVT. At his work, Wells and his colleagues (Wells et al. 2007) examined whether the result of D–Dimer level below the cut-off value (500ng/ml) can safely rule DVT out. According to the researchers in the group of the patients with a low clinical probability of DVT, the result of D-Dimer level below 500 ng/ml can safely rule thrombosis out and opt out of further diagnostics (ultrasound examination). In this study, a group of the patients with a low clinical probability of DVT (601 patients) were randomly divided into two groups. In 317 patients the concentration of D-Dimer was assessed and in 284 was not, but only ultrasound examinations was performed. Ninety-nine patients had the concentration of D-Dimer greater than 500 ng/ml (positive). DVT was confirmed only in 14 patients and 85 patients had no disease. Two hundred and eighteen patients had

negative D-Dimer result (below 500 ng/ml). Further to the basis of this result and a low clinical probability of DVT, they resigned from the further diagnostics. In this group of patients during the subsequent 3-month follow-up ascertained only 2 cases of VTE. The negative predictive value of D-Dimer (probability of disease when the result is below the cut-off point) determined by the authors was 96,1%.It should be noted that in their work to evaluate D-Dimer concentration a latex agglutination based method of "moderate" sensitivity was used. Despite that, authors obtained a very high negative predictive value. They also expressed the belief that using tests of "high" sensitivity (tests based on immunoassay enzyme reactions), the negative predictive value would be even higher. In the case of the patients with the clinical probability of DVT assessed as medium or high, it is necessary to implement deeper diagnosis, even despite receiving the result of the D-Dimer concentration below 500 ng/ml. Wells score presented in table 3, as well as Geneva Score, may be useful in assessment of the clinical probability of PE. A study comparing the Geneva criteria and Wells criteria in conjunction with the determination of the concentration of D-Dimer exhibited that they are equally useful. Likewise, Wells criteria allow safe exclusion of pulmonary embolism in the patients with estimated probability of pulmonary embolism as low or moderate and the level of D-Dimer below 500 ng/ml (Klok et al. 2008). It has to be noted that the concentration of D-Dimer above 500 ng/ml do not favour the recognition of DVT or PE. In the group of patients with moderate or high probability of VTE or in the patients with low likelihood and values of D-Dimer above 500 ng/ml, the diagnosis should include vivid studies. The ultrasound examination and compression test are the most frequently made. It consists of pushing the vessel by the head of the camera. If the vessel is free of venous thrombosis, it will collapse under embrace. Magnetic resonance is also a valuable examination. It allows you to visualize the veins especially those that are difficult accessible to ultrasound examination. Other vivid examinations, but rarely used are contrast venography and impedance plethysmography.

Treatment and prevention

The treatment of DVT and PE is based on unfractionated heparin (UFH) or low molecular weight heparin (LMWH) at therapeutic dosages. Heparin is not the fibrinolytic medicine, so it does not dissolve a clot. Its purpose is to prevent the accretion of thrombus. Selection of the type of heparin, dose and time of application depends on many factors, notably the severity of the disease, its location, the clinical condition and the coexistence of one or more risk factors of VTE. After the end of heparin therapy it may be necessary to include oral anticoagualnts (coumarin derivatives – acenocoumarol and warfarin) for a certain period or lifelong. The usage of medicines may be difficult for both the patient and the physician. The coumarin derivatives are characterized by a narrow therapeutic index which means that the difference between the very low dose (not causing the desired effect) and too large dose (causing an excessive effect – risk of bleeding) is minor. The use of coumarin derivatives requires laboratory monitoring.

Primary VTE prevention is to prevent the development of the disease. Secondary VTE prevention is to prevent the recurrence of DVT or PE. The methods of prevention can be divided into physical and pharmacological. The physical methods consist of primarily

assisting blood circulation in the veins of the lower limbs. For this purpose the graduated compression stockings or pneumatic compression devices squeezing legs are used. The graduated compression stockings are often used in the patients who are to undergo a surgery, due to the fact that as a consequence of each major surgery is completely or very substantial immobilization of the patient for some period of time. The pharmacological methods rely on using appropriate medication. In the primary prevention the LMWH is used most often. The secondary prevention is based on not only UFH heparin but also on oral anticoagulants. Choosing the right type of prophylaxis and the duration depend on a number of variables. This takes into account the risk of recurrence of VTE. This risk is associated with the occurrence in a patient of generally recognized risk factors for VTE. There are Polish guidelines of the type and duration of prophylaxis and treatment of VTE established by a team of the experts chaired by prof. Zawilska (Zawilska i wsp 2012). These guidelines cover a very wide range of clinical situations and discuss in detail about these proceedings.

Summation

Venous thromboembolism is a major health problem for the general population. It is quite frequently occurring disease potentially life threatening and its diagnosis can be difficult. The complications of VTE under the form of thrombotic syndrome may permanently impair the quality of the patient's life. The diagnosis of VTE, treatment and its complications is very expensive. At the same time this disease can be very effectively prevented. It is necessary to raise awareness of thromboembolic disease, in particular the risk factors and the occurrence of the effective methods of prevention.

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