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Deep vein thrombosis - the review

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Abstract
Deep vein thrombosis impacts between 2.5% and 5% of a population. It mostly affects lower-extremity veins and presents itself as pain, swelling, tenderness, and erythema of an affected region. Thrombus forms when at least one factor from the Virchow's triad is present - vascular damage, venous stasis or hypercoagulability. A range of clinical manifestations is very wide, from asymptomatic to life-threatening course of the disease. Post-thrombotic syndrome is a frequent complication that results in venous hypertension, which leads to tissue edema, subcutaneous fibrosis, and subsequent ulceration. In the diagnostic process, predominantly D-dimer assay and ultrasonographic compression test are performed. Noninvasive treatment relies on anticoagulation therapy which is based on direct oral anticoagulants, parenteral anticoagulants, and vitamin K antagonists. In specific cases, there is an option of invasive treatment, which involves inserting a catheter into a vein with a thrombus. Afterward, a thrombus can be mechanically fragmented and aspired or dissolved with the use of a thrombolytic agent.

Keywords
Deep vein thrombosis; venous thromboembolism; thrombus; anticoagulation; endovascular

Introduction

Thrombosis is a condition in which blood clots within the vascular system, which obstructs the blood flow. The situation in which the thrombus is formed in the venous system is venous thromboembolism (VTE) and its two manifestations are deep vein thrombosis (DVT) and pulmonary embolism (PE). In clinical practice, about two-thirds of VTE events manifest as DVT and one-third as PE. Symptoms of DVT are pain, swelling, tenderness and soreness on pressure. This condition is quite common in the general population which may be the result of many risk factors promoting thrombosis. After DVT, affected veins often recanalize incompletely, which can cause venous valve insufficiency and increased risk of recurrence[1,2]. The basis of treatment for DVT is anticoagulation therapy and endovascular treatment[3].

Epidemiology

Between 2.5% and 5% of the population is affected by DVT. Morbidity increases with age while most patients are over 60 years. There is no difference in DVT incidence among men and women[4]. The mortality rate after 12 months for patients with DVT is between 5-10%[5].
Most DVTs affect the lower-extremity veins, with proximal vessels being commonly affected. Percentage incidences are as follows - common femoral, 20%; femoral, 20%; iliac, 4%; and popliteal, 16%. Distal veins comprise 40% of all cases[6]. Upper limb DVT occurs with a frequency of 4-10% in the general population, but is the complication frequently observed in patients with malignant diseases and central venous catheters inserted[7].

Risk factors

The thrombus formation is triggered by three main contributing factors including vascular damage, venous stasis and hypercoagulability, known as the Virchow's triad. Decreased blood flow in areas such as venous valves and sinuses facilitates this process. Accrued fibrin deposits locally activate clotting factors, leading to thrombus formation and propagation via the coagulation cascade[8].
Despite the fact that there are many risk factors influencing DVT incidence, in between 33% to 50% of events there are no identifiable provoking factors. DVT risk factors will be situations that favor the occurrence of Virchow's triad components. Hypercoagulability can be caused by older age, active neoplasm, antiphospholipid syndrome, estrogen therapy, pregnancy, obesity and systemic, inflammatory diseases. Vascular damage can be an effect of surgery, trauma or central venous catheter, while immobilization can happen during hospitalization, long-haul travels, paresis or paralysis[8]. Also in the case of intravenous drug addiction patients, DVT incidence is especially high[9]. COVID-19 is another major risk factor that emerged in recent years. For at least 70 days after infection, DVT probability is significantly increased[10]. Inherited causes are less common, these are mutations of factor V Leiden or prothrombin gene, protein C or protein S deficiency and antithrombin deficiency. In

addition, there are some anatomical risk factors, such as May-Thurner syndrome and inferior vena cava abnormalities, which both result in slower venous blood flow[1,11].

Clinical Symptoms

In the majority of cases, DVT occurs in deep veins of lower limbs and abdomen, and most often the thrombus dissolves spontaneously, without any symptoms. The range of clinical manifestations of DVT spans from asymptomatic to even life-threatening massive obstruction of the limb's venous outflow[8]. DVT is usually unilateral and suspected in patients presenting acute-onset pain, swelling, erythema, and warmth of the lower extremity[12]. However, symptoms are nonspecific, only approximately 25% of the patients with mentioned signs of DVT, actually do have the disease[13].

In the acute phase, PE is the most serious complication. A clot may detach from its location of origin becoming an embolus. Moving through the venous bloodstream into the right heart and the pulmonary artery tree, it may occlude one or several pulmonary arteries impairing the exchange of oxygen and carbon dioxide in the lung. It then leads to dyspnoea, chest pain, hemoptysis and in severe cases, cardiorespiratory collapse or death[8].

The long-term complication that frequently affects patients after DVT is the post-thrombotic syndrome (PTS). It is caused by the inflammatory response to the acute thrombus, that induces venous obstruction and insufficiency. This results in venous hypertension, which leads to tissue edema, subcutaneous fibrosis and subsequent ulceration. PTS negatively affects the quality of life of patients and becomes a substantial cost to the healthcare system[6,14,15]. Its clinical signs are heaviness, ache, swelling, tingling in the affected limb or skin changes including hyperpigmentation, venous eczema, and venous ulceration[16]. Within two years of DVT occurrence, over 50% of patients develop PTS despite the use of anticoagulation treatment and approximately 5% will develop venous ulceration[1,17].

Phlegmasia cerulea dolens (PCD) is an uncommon but potentially life-threatening complication of acute DVT caused by edema that completely blocks arterial blood flow. It is characterized by marked swelling of the extremities with pain and cyanosis. PCD ultimately causes gangrene, with high amputation and mortality rates[1].

Occasionally there are asymptomatic DVT, due to the existence of alternative routes of blood flow. Collateral veins provide a bypass of the venous return from the acute obstruction and symptoms are relieved in a short period or there are no symptoms. In these cases, patients may remain asymptomatic for many years without treatment[1].

Diagnosis

To ease the diagnostic process and estimate the probability of a given diagnosis, a pre-test probability score is calculated. In the case of DVT, the Wells score is commonly used, which allows classification of a patient with a clinical suspicion into low, intermediate, or high risk (three-level score) or as likely or unlikely (two-level score) for the diagnosis of DVT[18]. There is a wide variety of possible differential diagnoses including chronic venous insufficiency, non-thrombotic vein compression, post-thrombotic syndrome, thrombophlebitis, lymphedema, heart failure and cellulitis[8].

After the initial assessment of the probability of DVT, objective testing is required to confirm or exclude the diagnosis. Diagnostic methods that are being used most often include D-dimer assays and compression ultrasonography (US). D-dimer is the fragment of the fibrin, which is released in the process of blood clothing. Thus it is typically elevated in the presence of DVT. Nevertheless, D-dimer rise is nonspecific and it can be observed in the presence of inflammation, malignancy and other systemic illnesses. In normal conditions, veins are easily compressible under the pressure of the US probe, which can be assessed in a compression US test. However, during acute DVT, the section of the vein with the thrombus is not compressible and obstructed blood flow can be observed with color Doppler mode[12].
Studies showed that to ensure the best results, both methods should be used jointly. Firstly D-dimer assay should be examined because it is a highly sensitive and cost-efficient test. Negative result allows to exclude DVT diagnosis. In case of a positive result, compression US, which is a highly specific diagnostic test, has to be carried out[12]. Although it is also discussed that in case of an easily accessible US examination, it should be performed in first order[2,19].
However, compression US has limited usefulness in diagnosing iliac vein DVT. In such cases, CT venography can be used, which brings additional information about the condition of the iliac vein, which is crucial for the planning of surgical or endovascular treatment[1].

Non-invasive treatment

In the acute phase of DVT, the aim is to prevent thrombus growth and reduce the risk of PE. Anticoagulant therapy significantly decreases the risk of PE and recurrent thrombosis and its early initiation reduces the incidence and severity of PTS[20].
Current guidelines recommend a specific algorithm for anticoagulant therapy. The first step is initial therapy, which takes from 5 to 21 days, during which parenteral anticoagulants or high doses of direct oral anticoagulants (DOAC) are used. The second step is a maintenance phase when the therapeutic dosage is used for at least 3 to 6 months and can be prolonged in individual cases with high thrombus burden[2].
At the end of the maintenance phase, a decision must be made whether to continue or discontinue anticoagulation therapy. When there is confidence that DVT was caused by a reversible risk factor, which no longer affects a patient, then anticoagulant therapy can be discontinued after 3 months and prophylaxis can be introduced in a risk of prothrombotic situation. Therapy can be elongated to 6 months in case of significant obstruction or substantial symptoms during DVT episode. When DVT occurs unprovoked or its causes are uncertain, then anticoagulation therapy should be continued with DOAC at a reduced dosage. High-risk patients, with recurrent DVT or unmodifiable, strong risk factors should continue DOAC in therapeutic dosage with the addition of vitamin K antagonist (VKA) or parenteral anticoagulant for an extended period[2,16,21].
Four DOACs have been approved for the treatment of DVT: rivaroxaban, apixaban, dabigatran, and edoxaban. Compared to VKA, which are the second line of treatment, these agents offer comparable efficacy and improved safety[17].
Another important issue is the prevention and treatment of PTS, which is negatively influencing the quality of life after DVT. The common reason for PTS is insufficient anticoagulation treatment. Compared to VKA, DOAC can be more effective at reducing the

risk. Elastic compression stockings, leg elevation, and moderate exercises are proven strategies for the prevention and management of PTS[15,21].

Invasive treatment

The invasive treatment is also possible in specific circumstances. The widely accepted indications for endovascular thrombus removal for lower extremity DVT include massive proximal acute DVT, i.g. iliofemoral or femoropopliteal thrombosis, with severe symptoms and leg swelling. Cases of massive DVT with PCD require immediate endovascular thrombus removal. On the other hand, there is no evidence to indicate that endovascular thrombus removal could help prevent the propagation of asymptomatic proximal DVT. Additionally, the anticoagulation treatment itself seems to be sufficient enough to reduce the recurrence rate and prevent PE. Also in distal DVT, endovascular techniques are not in use, as a consequence of the low risk of PE[1,22].

There are several endovascular techniques for thrombus removal and recanalization: catheter-directed thrombolysis (CDT), mechanical thrombectomy (MT) with rheolytic, ultrasound, or rotational device, large-bore catheter aspiration, balloon angioplasty, balloon maceration and stent placement[1,17].

Catheter-directed thrombolysis (CDT) refers to the slow administration of a thrombolytic agent by an infusion catheter embedded within the thrombosed vein. Direct infusion of a thrombolytic agent into the thrombus, rather than systemic infusion, can accelerate thrombolysis and lower the dose of a thrombolytic agent. Therefore, systemic thrombolytic therapy is no longer performed in case of DVT[1,23].

Even more advanced techniques are MT, pharmacomechanical catheter-directed thrombolysis (PCDT) and venular stents. MT refers to the use of catheter-based mechanical devices that break a thrombus into small pieces via mechanical energy and then aspires its fragments. In the PCDT method, CDT and MT techniques are combined to release a thrombolytic agent and then perform a thrombectomy. The advantage is reduction in the total volume of the thrombolytic agent required and in the total treatment time[1,24]. Venular stents are placed in specific cases. This is the preferred treatment for iliac vein obstruction or IVC obstruction, especially when the affected vein is almost obliterated because of chronic causes[1,25].

Conclusions

Deep vein thrombosis is a well-examined condition, with established risk factors, diagnostic methods, and treatment algorithms. Despite that, its commonmess and serious complications result in loss of life quality, high recurrence and mortality. Fortunately, with novel oral anticoagulants and endovascular treatment options, therapy becomes more effective and safer for patients. Perhaps, education is the most powerful tool to reduce the number of DVT incidences. It should focus on which situations and states can have a prothrombotic effect and what are the ways to protect from it.

Disclosure

Author's Contribution

Conceptualization - Karol Stępniak; Methodology - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Software - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Check - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Formal analysis - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Investigation - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Resources - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Data curation - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Writing (rough preparation) - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Writing (review and editing) - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Visualization - Karol Stępniak, Wiktor Telega, Kinga Wnuczek, Joanna Wrona, Aleksandra Kaźmierczyk, Jędrzej Kęsik, Daria Madycka, Kacper Michta, Małgorzata Słaboń, Maciej Sobczyk; Supervision - Karol Stępniak; Project administration - Karol Stępniak;

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