Postthrombotic Syndrome: Long-Term Sequela of Deep Venous Thrombosis

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ABSTRACT

Postthrombotic syndrome is a common long-term complication of proximal lower extremity deep venous thrombosis, which not only significantly affects the quality of life of patients but also imposes a substantial financial burden on our healthcare system. Due to limited awareness and inability of physicians to recognize and treat this condition early, its prevalence is steadily increasing. In this article, we review the pathophysiology, the risk factors involved, diagnostic workup, and the various management options available to treat this condition.

Key Indexing Terms: Postthrombotic syndrome; Deep venous thrombosis; Catheter-directed thrombolysis. **[Am J Med Sci 2018;356(2):152–158.]**

INTRODUCTION

Venous thromboembolism (VTE) is the clotting of blood in the venous system and includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Hospitalization and other risk factors including immobility, obesity, advanced age and surgery are major risk factors for DVT, which affects 1-2 per 1,000 people in the general population. An estimated average of 348,558 hospitalizations with DVT occur each year in the United States.[1,2] The cost of VTE treatment is considerable; the estimated annual health plan payments for services related to VTE treatment in the United States is an average of $15,123 for a VTE event from 2008-2011.[3]

EPIDEMIOLOGY

Although an understandable focus of therapy in deep venous thrombosis is the prevention of recurrent thrombus or the development of pulmonary embolism, the long-term sequelae are seldom emphasized. Postthrombotic syndrome (PTS) is the most common long-term complication of DVT and can occur in 50% or more of patients after an episode of DVT.[4-6] It usually becomes established within the first 2 years of DVT,[5,6] but can present within a year up to several years later. PTS is a constellation of symptoms and signs that develop after DVT as a result of venous hypertension in the affected limb. The clinical presentation varies in severity, ranging from mild lower extremity swelling to chronic leg pain, venous claudication and leg ulcers.[4] In addition, PTS is a chronic condition where symptoms of leg pain and swelling wax and wane, and a diagnosis of PTS should only be made once the acute phase of DVT completely resolves, which can range between 3 and 6 months.[4]

PATHOPHYSIOLOGY

Normally, the venous flow is determined by the venous pump, which is defined as the pumping effect of leg muscles on venous flow and by the venous valves which are bicuspid structures that direct blood flow in a unidirectional fashion from distal to proximal veins and from the superficial to the deep venous system.[7] PTS occurs due to a combination of mechanisms including venous outflow obstruction, destruction of the venous valvular apparatus, development of venous reflux, calf muscle pump dysfunction, and reduced wall shear stress, which triggers an inflammatory process within the involved vein.[8] These mechanisms result in elevated venous pressures in the affected limb particularly in an upright position, and can worsen venous reflux resulting in a vicious cycle of events.

The exact pathogenesis of PTS is not completely understood. The limited ability to quantify the venous obstruction and venous valvular reflux has resulted in conflicting literature on whether PTS development is mainly a consequence of outflow obstruction, valvular incompetence, or both.[4] After an episode of acute proximal DVT, patients with venous obstruction persisting for the first 3-6 months were reported to be at increased risk for developing PTS.[9-11] However, other studies have disputed the importance of persistent venous obstruction and suggested that the presence of venous reflux was more likely to contribute to the development of PTS.[12-14] Calf muscle pump dysfunction may also be involved in the late onset of PTS because it

takes more than 2 years post-DVT for the damage to involve muscle tissues.[15]

Ultimately, the end result of persistent venous obstruction and worsening valvular reflux results in the development of ambulatory venous hypertension. In such a situation, the ambulatory venous pressures can reach up to 60-90 mm Hg, which subsequently promotes venous distention and further valve incompetence. Incompetent valves leads to sluggish proximal blood flow. As a result, the superficial and deep veins become more distended and the venous hypertension worsens, which further damages the valves. When the superficial veins become maximally distended, only a small volume of refluxed blood through the incompetent valves is required to produce a large increase in pressure which leads to third spacing[16] and tissue edema.

After acute DVT, the evolution of the thrombus is a dynamic process.[17] Neutrophil and monocyte chemoattractants, such as pro-inflammatory proangiogenic interleukin-8, are released and stimulate the release of vascular endothelial growth factor and basic fibro-blast growth factor, which then regulates the formation of neo-vascular channels within the thrombus.[18] However, the resultant recanalization is usually incomplete, resulting in residual ambulatory venous hypertension.[19] It has been shown that even after the use of anticoagulation, residual venous thrombosis persists in many patients,[20] which is capable of initiating the anatomical, and histologic changes associated with chronic venous insufficiency and then the development of PTS.[21-23]

Low wall shear stress stimulates the adhesion of leukocytes to the capillary endothelium and trans-endothelial migration resulting in perivascular leukocyte stasis and inflammation. The inflammation increases capillary permeability resulting in capillary leakage[24,25] and lower extremity edema. The exact mechanism by which low wall shear stress stimulates these inflammatory events is not well understood.[26]

Pain is a major symptom of PTS and is stimulated by pro-inflammatory mediators, which activate the nociceptors located within the venous walls.[27] Moreover, as leukocytes adhere to the vein walls, they become activated and release inflammatory cytokines which contribute to further valvular damage.[18,28] This promotes worsening of the cycle of reflux and elevated venous pressure.

RISK FACTORS AND BIOMARKERS

Several studies investigated the risk factors lead to the development of PTS (Table). They include clinical, radiological and inflammatory biomarkers that predict progression to PTS in DVT patients. Both obesity (body mass index $\geq$ 30) and contralateral limb ectasia increases the risk of having PTS 2-fold.[29,30] A subtheraputic INR for more than 20% of the time during the first 3 months of warfarin therapy was significantly associated with increased risk of developing PTS.[31] Sex, ethnicity and combination of DVT and PE versus DVT alone did not alter the risk of PTS.[4,32]

Proximal DVT (iliac, femoral and popliteal vein) is a strong predictor for developing PTS. This is likely related to the involvement of the profunda femoral vein in proximal thrombosis, which impairs the development of collateral channels and worsens the underlying pathophysiological mechanisms described earlier. Moreover, involvement of the common femoral vein impairs drainage from the lower extremity resulting in severe DVT symptoms and PTS. On long-term follow up, patients with proximal DVTs were found to have greater residual vein thrombosis (75.9% versus 16.1%; $P < 0.001$) and deep venous reflux compared to patients with distal DVTs (30.8% versus 1.8%; $P < 0.001$).[33] In addition, the thrombus recanalization rate was found to be much lower for ilio-femoral DVT compared to distal DVT.[34]

Radiological risk factors for developing PTS based on ultrasound include the following: "extensive clot load on presentation, clot regression at 6 months not exceeding 50%, venous filling index exceeding 2.5 mL/s, and abnormal outflow rate measured by a 2 second maximum outflow volume (<60% of the volume depleted after 2 seconds). Patients with 3 or more of the above mentioned ultrasound findings had a significant risk of developing PTS with a sensitivity of 100%, specificity of 83% and positive predictive value of 67%."[35] Moreover, residual thrombus and deep venous reflux increased the risk for PTS. Johnson et al[34] reported that on 6 months follow-up ultrasound of patients with DVT, 65% of cases were found to have both obstruction and venous reflux and were 3.5 times more likely to develop PTS compared to patients without obstruction and reflux.

Underlying hypercoagulable states may contribute to the development of PTS, as shown by a recent prospective study that revealed an independent association between F VIII activity and PTS with an odds ratio of 2.83 (95% CI: 1.09-7.42, $P = 0.034$).[33] Studies have also suggested a strong relationship between inflammation and thrombosis. For example, Shbaklo et al[36] observed increased levels of intracellular adhesion molecules-1 (ICAM) and interleukin 6 (IL-6) in patients who develop PTS and a recent systemic review similarly showed significant correlations between ICAM and PTS.[37] In addition, several studies have also shown an association between c-reactive protein (CRP), IL 6, IL 8, IL 10 and ICAM and the development of PTS, however, the results have not been consistent. Although inflammatory biomarkers associated with PTS are currently under investigation, PTS is still a clinical diagnosis and the value of measuring these markers is still not clear and is not currently used in routine clinical practice.

CLINICAL PRESENTATION AND DIAGNOSIS

Patients who develop PTS commonly report pain and swelling of the affected limb, especially after prolonged standing or walking, which eventually improves