Review Article

Pathophysiology of Post-Thrombotic Syndrome: The Effect of Recurrent Venous Thrombosis and Inherited Thrombophilia

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Post-thrombotic syndrome is an important chronic complication of deep vein thrombosis. This syndrome can be debilitating to patients and has a major economic impact on health care services. The pathophysiology of post-thrombotic syndrome is currently incompletely understood. Because therapeutic options for post-thrombotic syndrome are extremely limited and results are often disappointing, recognizing of the pathophysiology and risk factors of this syndrome is essential to prevent the disabling consequences of this disease. The present paper focuses on risk determinants of post-thrombotic syndrome after deep vein thrombosis. The contribution of recurrent venous thrombosis and inherited thrombophilia to the pathogenesis of this syndrome is reviewed and discussed in details.

1. Introduction

Venous thromboembolism (VTE) is currently the third most common disorder in western population following myocardial infarction and stroke [1]. It remains a serious healthcare problem for the community. Pulmonary embolism (PE) is the major early complication of deep venous thrombosis (DVT). With its attendant mortality, PE is the most devastating complication of acute DVT. PE accounts for 200000 deaths each year in the United States (US), and the annual cost of the treatment is measured in billions of dollars [2, 3].

Post-thrombotic syndrome is the most important long-term complication of DVT resulting from venous valvular damage and persistent luminal obstruction. Although less dramatic than PE, post-thrombotic syndrome is responsible for the greater degree of chronic socioeconomic morbidity. As many as 29 to 79% of patients may have long term manifestation of pain, edema, hyperpigmentation, or ulceration after an episode of acute DVT [4–6]. Severe manifestations and ulceration occur in 4% to 6% and 7% to 23%, respectively [7, 8]. The prevalence of venous ulceration is at least 300 per 100000 and approximately 25% are due to DVT [9, 10]. In the United States, skin changes and

ulceration are present in 6 to 7 million and 400,000 to 500,000 people, respectively [11]. Estimates of the overall annual cost of chronic venous insufficiency vary from 720 millions to 1 billion US dollars in western European countries representing 1% to 2% of the total health care budget, to 3 billion US dollars in the US [12, 13]. Appreciation of the factors involved in the development of post-thrombotic syndrome is important in its prevention and management. The purpose of this paper is to determine the factors that contribute to the constitution of this syndrome focusing essentially on the role of venous thrombosis recurrence and inherited thrombophilia.

2. Discussion

Post-thrombotic syndrome (PTS) is observed in 0.5% to 1% of the population with ulcer and in 3% to 5% without ulcer [14]. Pathophysiology of PTS is complex and not entirely understood. This syndrome is more commonly observed in male gender, obese, and elderly patients [15]. The influence of several risk factors on the incidence of PTS is still controversial [16]. The determinants of post-thrombotic manifestations include the rate of recanalization,

the global extend of reflux, the anatomic distribution of reflux and obstruction, the recurrent thrombotic events, and thrombophilia.

Ambulatory venous hypertension may result from either venous reflux or persistence venous obstruction. Although valvular incompetence appears to be clinically more important, severe post-thrombotic sequelae occur in patients having a combination of valvular incompetence and luminal venous obstruction rather than either abnormalities alone [17–19]. Despite its importance, valvular dysfunction is not universal after acute DVT, reflux developing in only 33% to 59% of involved venous segments [20]. Reflux occurs not only in segments involved by thrombus, but also in segments remote from them. Reflux develops and progresses over time not only in venous segment distal to the thrombotic location but also in segments proximal to the site of thrombosis. This mechanism is yet poorly understood [17, 21–23]. A plausible explanation, described by Raju et al., is that perivenous and mural fibrosis may extend beyond the thrombosed segment to involve adjacent segments of preserving valve cusps, but inducing secondary reflux from valve station restriction [24]. Long-term ultrasound follow-up studies of patients treated with anticoagulants have demonstrated that the time to complete recanalization was related to the ultimate development of reflux [25]. Depending upon the venous segment involved, complete recanalization required 2.3 to 7.3 times longer in segments developing reflux than in segments in which valve function was preserved [25].

Proximal DVT, the presence of multiple sites of DVT, and anatomically extensive DVT have been associated with an increased rate of PTS [15, 18, 26–29]. The development of this syndrome is also related to the global extend of reflux and to the anatomic distribution of reflux and obstruction. Involvement of calf veins in the presence of proximal vein thrombosis increases the likelihood of PTS [18]. Reflux in the distal deep venous segments, particularly the popliteal and posterior tibial veins, is most commonly associated with post-thrombotic skin changes [29–31]. With respect to venous obstruction, the severity of post-thrombotic manifestations is most significantly related to persistent popliteal thrombosis [32]. Superficial reflux is also critically important and has been reported in 84% to 94% of patients with chronic skin changes and 60% to 100% of patients with venous ulceration.

Recurrent thrombotic events are common and have a detrimental effect on valvular competence and on the development of PTS [33–35]. Assessment of clinical risk factors for venous thrombosis may provide useful prognostic information for recurrence. Recurrence rate is low in conjunction with a major reversible risk factor (3% the first year and 10% over 5 years), intermediate in minor reversible risk factor (5% in the first year and 15% over 5 years), and relatively high in idiopathic VTE and elderly patients (10% in the first year and 30% over 5 years) [36–39]. Fifty to 70% of idiopathic DVT are due to inherited thrombophilia [40]. The risk of recurrence is higher among patients with permanent risk factors including inherited prothrombotic abnormalities than among patients who have suffered trauma or underwent surgery [32]. Factor V-Leiden, prothrombin G 20210 A

mutation, and MTHFR mutation leading to hyperhomocysteinemia are the most commonly observed prothrombotic genetic abnormalities associated with venous recurrence [41, 42]. Ipsilateral recurrence has been strongly associated with PTS [28, 33, 39, 43]. Re-thrombosis of a partially occluded or recanalized segment further increases the risk of reflux [40]. Reflux has been noted to develop in 36% to 73% of segments with re-thrombosis, a very higher rate, comparing to segments without re-thrombosis [44]. Consistent with these observations, recurrent thrombotic events have been observed in 45% of patients with PTS in comparison to only 17% of asymptomatic subjects [45]. Prandoni et al. reported a six times greater risk of PTS among patients with recurrent thrombosis [7].

Thrombophilia is increasingly recognized as a risk factor for DVT, which in turn is a major risk factor for chronic venous insufficiency. However, available information concerning the relation between thrombophilia and PTS is limited and still controversial. While some authors failed to demonstrate any correlation between thrombophilia and PTS, others suggested a role of inherited thrombophilia and mainly factor V-Leiden mutation in the development of PTS and leg ulcers [46–48]. PTS is commonly reported among patients with proximal DVT. Thrombophilia, detected among 29% of patients with proximal DVT, is considered an independent predictor of persistent residual venous thrombosis which has been recognized as an important factor for recurrent venous thrombosis and PTS [49, 50]. These data suggest that inherited thrombophilia contributes to the constitution of post-thrombotic syndrome.

3. Conclusion

PTS syndrome occurs more frequently when venous thrombosis is extensive or affects proximal veins, popliteal, and calf veins. Superficial veins involvement is also commonly associated with the development of PTS. Recurrence venous thrombosis has been strongly involved in the constitution of PTS. The risk of recurrent venous thrombotic events is higher among patients with idiopathic DVT and with permanent risk factors including inherited prothrombotic abnormalities. Thrombophilia seems to interfere in the development of PTS either directly by prolonging residual venous thrombosis or indirectly by increasing venous thrombotic recurrence rate. Further studies are required to elucidate the pathophysiology of PTS and to confirm the importance of recurrence rate and inherited thrombophilia in the pathogenesis of PTS.

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