Venous Thrombosis at Unusual Sites and the Role of Thrombophilia

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ABSTRACT

Thrombophilia includes multiple inherited and acquired risk factors that determine a shift in the balance of procoagulant and anticoagulant factors promoting hypercoagulability, which is associated with an increased risk of venous thromboembolism (VTE). VTE is characterized by more common clinical manifestations, such as deep vein thrombosis of the lower limbs or pulmonary embolism, and less common clinical manifestations affecting cerebral, splanchnic, upper limbs, and retinal veins. The role of inherited thrombophilia in the pathogenesis of VTE at unusual sites is better established in cerebral vein thrombosis, but its role is less clear in splanchnic, upper limbs, and retinal vein thrombosis, in which acquired risk factors such as malignancy, central venous catheters, or systemic diseases also are frequently involved. The complex interactions between different inherited and acquired thrombophilic risk factors and their relationship with endothelium may be considered the pathophysiologic key of underlying phenotypic manifestations of thrombosis. The understanding of these mechanisms might facilitate diagnosis with appropriate investigations and improve therapeutic decision making.

KEYWORDS: Thrombophilia, thrombosis of the upper extremities, retinal vein occlusion, cerebral vein thrombosis, splanchnic vein thrombosis

Venous thromboembolism (VTE) is a multifactorial disease in which multiple inherited and acquired risk factors act synergistically determining different thrombotic manifestations. Although thrombosis can potentially involve any section of the venous system, common manifestations of VTE are deep vein thrombosis (DVT) of the lower limbs and pulmonary embolism. Uncommon manifestations of VTE affect atypical sites, such as cerebral sinus, splanchnic, upper limbs, and retinal veins. Different thrombotic manifestations can result from different inherited and acquired thrombophilic states. For example, the antiphospholipid syndrome is associated with placenta thrombosis,[1] myeloproliferative disorders are associated with abdominal vein thrombosis,[2] and the prothrombin mutation G20210A (PTM) increases the risk of lower limb thrombosis, portal vein thrombosis (PVT) and cerebral vein thrombosis (CVT).[3,4] In the complex pathophysiology of different phenotypic manifestations of thrombosis, even the endothelium might play a critical role by acquiring in response to different signals procoagulant and anticoagulant properties that could be expressed differently throughout the vascular tree.[5] In recent years, it became clear that congenital and acquired

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Thrombophilia in Clinical Practice; Guest Editors, Saskia Middeldorp, M.D., Ph.D., and Marcel Levi, M.D., Ph.D.

Semin Thromb Hemost 2007;33:582–587.
DOI 10.1055/s-2007-985754. ISSN 0094-6176.

thrombophilia through complex interactions with the vessel wall may induce alterations in the hemostatic balance that predispose to thrombosis at unusual sites. However, despite reasonable evidence that different risk factors could lead to specific clinical manifestations of VTE, most of these observations were derived from small studies because of the relative rarity of thrombotic events at unusual sites.

This review article focuses on the role of thrombophilia in the pathogenesis of unusual sites of VTE. The interactions among different risk factors and the strength of their associations in this field are also discussed.

THROMBOSIS OF THE UPPER EXTREMITIES

The incidence of upper extremities deep vein thrombosis (UEDVT) is ~10% of the total incidence of venous thrombosis.[6] UEDVT can be classified into different categories according to its etiology: idiopathic, including Paget-Schroetter syndrome or effort syndrome; and secondary, in which a trigger or underlying disorder such as indwelling intravenous catheters or neoplasms can be identified. The clinical importance of UEDVT has increased in recent years mainly due to the increasing use of central venous catheters (CVCs), which are an important risk factor. Until a decade ago, the prevalence was low, with an estimated range from 1% to 4%.[7] Idiopathic UEDVT accounts for ~10 to 30% of all cases,[8,9] and strenuous muscular effort is detected in one fourth of primary cases.[10] The Paget-Schroetter syndrome or effort syndrome is a pinching of the axillary–subclavian vein at the thoracic outlet by muscular and osteo-tendinous structures induced by abduction and extension of the arm determining a mechanical obstruction. The compression of the axillary–subclavian vein is physiologic but it may be aggravated by anatomical abnormalities or by repetitive compression, given that it usually happens during sports or occupational activities, leading to endothelial damage and inflammation[11] and to the development of venous thrombosis. This form of UEDVT is frequently reported in athletes,[12] and patients usually are apparently healthy young males.[13,14]

The prevalence of inherited thrombophilia in patients with primary UEDVT ranges from 10% to 20%.[9,10,13–15] Martinelli et al[10] showed after multivariate analysis a 5- to 6-fold increased risk for factor V Leiden mutation (FVL) and PTM, respectively, and a 5-fold increased risk for natural inhibitors (antithrombin, protein C, and protein S deficiency) considered together, whereas there was no association with hyperhomocysteinemia. Blom et al[9] found a 3-fold increased risk for the combination of FVL and PTM. In line with these studies, two small studies with 51 and 31 consecutive patients, respectively, also found a high prevalence of thrombophilic defects in UEDVT patients.[13,14] For patients with a history of strenuous muscular effort the association with thrombophilia is less clear, but this could be due to the small size of the studies.[10,13,14] The presence of antiphospholipid antibodies in patients with primary UEDVT varies from 8 to 31%,[10,13–15] but it is approximately 8% in two studies with a larger series of patients.[10,15] Another important risk factor for apparently idiopathic UEDVT is an occult malignancy, which can be diagnosed in about one fourth of cases within 1 year of follow-up.[16]

Secondary cases of UEDVT are more common than primary cases and are more frequent in older and hospitalized patients.[6,8,14,17] The most important risk factors are the presence of CVC (accounting for up to 70% of secondary cases),[6,8,9,17,18] and cancer (diagnosed in up to 61% of cases).[8,9,17–19] The presence of FVL and PTM mutations seems to increase the risk of CVC-related thrombosis, with an odds ratio (OR) of 2.7 (95% confidence interval [CI], 1.9 to 3.8).[20] Different studies showed a synergistic effect in increasing the risk of UEDVT between oral contraceptives (OCs) and thrombophilia of up to 9-fold (95% CI, 2.8 to 30.2).[9,10,15] A recent review reported an important link between UEDVT and pregnancies achieved with the use of assisted reproductive techniques in which the higher incidence of thrombosis involving the internal jugular vein (81%) has not yet been understood.[21] Inherited thrombophilia was detected in 41% of these women, but the limitation is that these data are derived mainly from case reports.[21]

The decision to carry out routine testing for inherited thrombophilia among patients with an episode of either primary or secondary UEDVT is controversial for at least two reasons: (1) the increased risk of recurrence determined by thrombophilia is not well known and it seems to be modest[10]; and (2) clinical implications of thrombophilia such as prophylactic or optimal duration of anticoagulation are unknown. Considering the possible synergistic effects between genetic thrombophilia and environmental risk factors, such as OCs, young patients with unexplained or hormone-related DVT could be advised about screening for thrombophilia.

RETINAL VEIN OCCLUSION

Retinal vein occlusion (RVO) is a paradigm of complexity of VTE that results from multiple and synergistic risk factors, including local factors and systemic diseases, that determine the thrombogenic conditions of the Virchow's triad, such as stasis, vessel wall damage, and hypercoagulability. RVO is the most common vascular disease of the eye and is the main cause of visual loss after diabetes. The incidence rate of RVO is ~0.5 per 1,000 persons older than 40 years and increases significantly

with age,[22] with more than 50% of patients older than 65 years.[23] RVO can be classified accordingly to the site of occlusion into branch RVO, hemicentral RVO, and central retinal vein occlusion (CRVO). CRVO affects the venous flow of the entire retina, determining a more severe clinical picture. Local risk factors of RVO include open-angle glaucoma, ocular hypertension (which affects up to 43% of patients), and local inflammation.[24] An anatomical factor involved in the pathophysiology of RVO is the course of the vessels through the lamina cribrosa, which can degenerate with aging, causing a mechanical obstruction leading to endothelial damage. Systemic diseases associated with a higher incidence of RVO are hypertension, diabetes, dyslipidemia, increased blood viscosity, and cardiovascular diseases.[25–29] The potential role of thrombophilia in the development of RVO is still unclear, with conflicting results in the literature; however, it seems to be marginal. A recent meta-analysis[30] assessed the prevalence of thrombophilia among patients with RVO. The included studies often were retrospective, with a limited number of patients. FVL was evaluated in 14 case-control studies and had an overall OR for RVO of 1.5 (95% CI, 1.0 to 3.2).[30] In most studies the incidence of FVL was not significantly higher in patients with RVO. The role of PTM in RVO also seemed marginal (OR, 1.6; 95% CI, 0.8 to 1.6).[30] In five studies, none of the patients and in one study none of the controls were carriers of PTM.[30] Deficiencies of natural inhibitors were scarce and not associated significantly with RVO.[30] Hyperhomocysteinemia had an overall OR of 8.9 (95% CI, 5.7 to 13.7), derived from 11 studies that included a total of 527 cases and 955 controls.[30] Thermolabile variant of methylenetetrahydrofolate reductase (MTHFR) was not associated with RVO (overall OR, 1.2; 95% CI, 0.9 to 1.6).[30] The overall OR for combined anticardiolipin immunoglobulin (Ig) M and IgG from seven case-control studies was 3.9 (95% CI, 2.3 to 6.7), whereas the role of lupus anticoagulant was unclear.[30] Table 1 reports the main results found in Janssen meta-analysis.[30]

A study of 234 consecutive patients with RVO confirmed that the frequency of FVL was similar between cases and controls, with a slight increased prevalence in the subgroup of patients younger than 60 years.[31] In the same study, the prevalence of PTM was not significantly different between cases and controls.[31] In line with the aforementioned meta-analysis, a large cross-sectional study confirmed the association between high plasma homocysteine levels and RVO in patients younger than 70 years, with an OR of 3.76 (95% CI, 1.06 to 13.40).[32] In contrast, two recent case-control studies failed to demonstrate an association between increased levels of homocysteine and RVO.[33,34]

In conclusion, the role of thrombophilia in RVO is unclear and therefore routine testing for the presence of genetic thrombophilia is probably not advisable. Increased plasma levels of homocysteine may be an important risk factor, but this may reflect systemic inflammation, which is associated with cardiovascular risk factors. Atherosclerotic risk factors, such as hypertension and diabetes, play an important role in the development of RVO, and recently, RVO has been associated with a more than 2-fold increased risk of cardiovascular mortality.[35]

CEREBRAL VEIN THROMBOSIS

CVT is a rather uncommon disease. However, thanks to the general availability of noninvasive techniques, in the last few years CVT is diagnosed more frequently, and less clinically severe cases of CVT are detected. In previous studies, the majority of CVTs were found to be secondary to local or systemic infections, and more than 30% of cases of CVT were considered idiopathic.[36,37] However, more recent studies reported other risk factors, such as thrombophilia or the use of OCs to be associated with CVT.[38,39]

The prevalence of thrombophilic abnormalities in patients with CVT has been evaluated only in small studies and the results are often conflicting or not conclusive. Our group recently has published a systematic review and a meta-analysis of the studies that analyzed the association between CVT and the most frequent thrombophilic conditions.[4] A total of 17 studies were included in the analysis. We found a strong association between both FVL and the PTM, and CVT. In detail, 13 studies including 469 cases and 3023 controls evaluated the role of FVL and nine studies including 360 cases and 2688 controls evaluated the role of PTM in patients with CVT. FVL was associated with

Table 1 Summary of the Results of the Meta-Analysis on Association between Thrombophilia and RVO[30]

Thrombophilic Abnormality	OR (95% CI)	No. of Included Studies	No. of Cases	No. of Controls
Factor V Leiden	1.5 (1.0–2.2)	14	792	1418
G20210A mutation of prothrombin	1.6 (0.8–3.2)	12	700	1334
Hyperhomocysteinemia	8.9 (5.7–13.7)	11	527	955
MTHFR	1.2 (0.9–1.6)	10	581	1080
Anticardiolipin antibodies	3.9 (2.3–6.7)	7	412	508

RVO, retinal vein occlusion; OR, odds ratio; CI, confidence interval; MTHFR, thermolabile variant of methylenetetrahydrofolate reductase.

CVT, with an OR of 3.38 (95% CI, 2.27 to 5.05); PTM was associated with CVT, with an OR of 9.27 (95% CI, 5.85 to 14.67). We also found an equally strong association between CVT and hyperhomocysteinemia (OR, 4.07; 95% CI, 2.54 to 6.52), although only four studies were actually retrieved.

Data on antiphospholipid antibodies syndrome and on deficiencies of antithrombin, protein C, and protein S were inadequate to allow any conclusions. Two studies analyzed the role of deficiencies of antithrombin, protein C, and protein S as risk factors for CVT.[40,41] The combined OR of the two studies was 2.69 for antithrombin (95% CI, 0.66 to 10.96), 11.10 for protein C (95% CI, 1.87 to 66.05), and 12.49 for protein S (95% CI, 1.45 to 107.29; $p = 0.03$).[40,41] Because of the low number of eligible patients, the confidence intervals are very wide. Only one study considered antiphospholipid syndrome[40] and one study included anticardiolipin antibodies alone.[42] In the first study,[40] the prevalence of antiphospholipid antibodies was higher in CVT patients (nine of 121) compared with controls (zero of 242). In the second study,[42] the authors found a significantly higher incidence of positive anticardiolipin antibodies in CVT patients (seven of 31) in comparison with controls (one of 31; OR, 8.75; 95% CI, 1.01 to 75.64). Table 2 summarizes the results of the aforementioned meta-analysis.[4]

The risk of CVT in women of reproductive age taking OCs and with concomitant thrombophilic conditions was evaluated in two studies.[40,43] Martinelli et al[40] found an OR of 19.5 (95% CI, 5.7 to 67.3) in the presence of hyperhomocysteinemia, an OR of 30.0 (95% CI, 3.4 to 263.0) in the presence of FVL mutation, and an OR of 79.3 (95% CI, 10.0 to 629.4) in the presence of PTM as compared with control women without any thrombophilic condition. A similar result was observed in a study performed by Gadelha et al,[43] in which a multivariate analysis proved the independent association between CVT, PTM, and the use of OCs.

The role of other thrombophilic abnormalities was investigated in CVT patients in recent studies. Bugnicourt et al[44] found significantly higher levels of factor VIII and von Willebrand factor in 16 CVT patients in comparison with controls. Conversely, Lichy et al found no significant association between CVT and a single nucleotide polymorphism of the thrombin activatable fibrinolysis inhibitor, and between CVT and the protein Z gene mutation (intron F G79A), which is linked with low protein Z levels.[45]

In conclusion, CVT appears to be strongly associated with the FVL mutation, with the PTM G20210A, and with hyperhomocysteinemia. The role of the other thrombophilic abnormalities in the pathogenesis of CVT remains to be clarified.

SPLANCHNIC VEIN THROMBOSIS

Splanchnic vein thrombosis (SVT) is an uncommon but potentially life-threatening disease. Mesenteric vein thrombosis (MVT), PVT, and Budd-Chiari syndrome (BCS) are three autonomous diseases, but the involvement of two or more different abdominal vein segments is common.

Because symptoms are nonspecific, diagnosis of SVT is difficult and its true incidence is likely underestimated. However, advances in imaging techniques, especially Doppler ultrasonography and computed tomography, have facilitated its early diagnosis. Acquired causes of SVT vary according to the site of thrombosis. For MVT, the most common causes are cancer, intra-abdominal inflammatory conditions (pancreatitis, abscess, inflammatory bowel disease, diverticulitis), postoperative state, liver cirrhosis, and portal hypertension.[46] For PVT, the most common causes are included liver cirrhosis, hepatocellular carcinoma, and myeloproliferative disorders.[47]

Only few studies have examined the role of thrombophilia in patients with SVT. Janssen et al performed a case-control study in which they investigated the prevalence of FVL, PTM, and of inherited deficiencies of protein C, protein S, and antithrombin in 43 patients with BCS, in 92 patients with PVT, and in 474 population-based controls.[48] Among the BCS patients, FVL (OR, 11.3; 95% CI, 4.8 to 26.5) and

Table 2 Summary of the Results of the Meta-Analysis on Association between Thrombophilia and CVT[4]

Thrombophilic Abnormality	OR (95% CI)	No. of Included Studies	No. of Cases	No. of Controls
Factor V Leiden	3.38 (1.27–5.05)	13	469	3023
G20210A mutation of prothrombin	9.27 (5.85–14.67)	9	360	2688
Hyperhomocysteinemia	4.07 (2.54–6.52)	4	222	472
Protein C	11.10 (1.87- 66.05)	2	147	362
Protein S	12.49 (1.45–107.29)	2	147	362
Antithrombin	2.69 (0.66–10.96)	2	172	362
Antiphospholipid antibodies syndrome	40.96 (2.36–709.87)	1	121	242
Anticardiolipin antibodies	8.75 (1.01–75.64)	1	31	31

CVT, cerebral vein thrombosis; OR, odds ratio; CI, confidence interval.

inherited deficiency of protein C (OR, 6.8; 95% CI, 1.9 to 24.4) were more prevalent than in controls, whereas the prevalence of PTM was not different in comparison to controls and no patient had an inherited deficiency of protein S or antithrombin. Similarly, among the PVT patients, FVL (OR, 2.7; 95% CI, 1.1 to 6.9) and inherited deficiency of protein C (OR, 4.6; 95% CI, 1.5 to 14.1) were again more prevalent than in controls, whereas the prevalence of PTM and of inherited deficiency of protein S or antithrombin was not different in comparison to controls. The use of OCs was an important acquired risk factor for both BCS and PVT, given that 12 of 20 BCS women (60%) and 12 of 25 PVT women (48%) between 15 and 49 years had been using OCs at the time of diagnosis in comparison to 65 of 169 controls (38%). In another recent study, Primignani et al[3] evaluated the prevalence of FVL, PTM, hyperhomocysteinemia, and deficiency of protein C, protein S, and antithrombin in 65 patients with extrahepatic portal vein obstruction and in 700 healthy controls. They found an association among PTM (OR, 8.1; 95% CI, 3.8 to 17.5), deficiency of protein C, protein S, or antithrombin taken together (OR, 4.5; 95% CI, 1.1 to 18.0), and portal vein obstruction, whereas the prevalence of hyperhomocysteinemia was not different in comparison to controls. In contrast to the study conducted by Janssen,[48] the prevalence of FVL was not different between cases and controls, and the use of OCs was not associated with an increased risk of portal vein obstruction, given that OCs were used in a similar proportion of patients and controls (26% and 28%, respectively). Recently, Amitrano et al[49] evaluated the prevalence of common thrombophilic abnormalities in 12 patients with MVT and in 431 healthy controls. FVL (OR, 6.2; 95% CI, 1.6 to 24.5), PTM (OR, 6.9; 95% CI, 1.7 to 27.3), and MTHFR TT677 genotype (OR, 4.5; 95% CI, 1.4 to 14.4) were associated with an increased risk of MVT, whereas anticardiolipin antibodies, lupus anticoagulant, and deficiency of protein C, protein S, and antithrombin were not.

In conclusion, the results of these studies seem to suggest a potential role of thrombophilic abnormalities in the pathogenesis of SVT. However, the role of a single thrombophilic abnormality cannot be assessed because the prevalence and the role of these factors in patients with SVT have been evaluated only in small studies and the results are often conflicting or inconclusive.

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