Thrombophilia

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Thrombophilia or hypercoagulable state is a clinical condition characterized by a tendency to develop venous and (less frequently) arterial thrombosis. Thrombosis is defined as the obstructive clot formation within a vessel. Since the first observation of Virchow, three major pathogenic causes of thrombosis have been identified: changes in the vessel wall, in the blood flow and in the blood composition. Although all these mechanisms may contribute to thrombosis, arterial events are mainly determined by changes in the vessel wall, in particular atherosclerosis, while stasis and prothrombotic blood abnormalities play a major role in venous thrombosis. Venous thrombosis is a sudden event that occurs during a short- or long-lasting period of increased risk, but clinical symptoms may sometimes be mild, leading to diagnostic difficulties. The development of a venous thromboembolic episode (VTE) is often the result of multiple risk factors, including both congenital procoagulant defects and enviromental factors such as age, male sex, obesity, exposure to "risk periods" of immobilization, trauma, cancer, pregnancy, use of exogenous hormones or chemotherapy. Hereditary thrombophilia is a genetically determined increased risk of thrombosis; acquired or secondary thrombophilia is a physiologic or pathologic condition that predispose affected persons to thromboembolic diseases. Hereditary thrombophilia should be suspected in persons with a family history of thrombosis, especially if the thrombotic events occurred in young patients or when trigger factors are absent or minimal. A congenital or acquired hypercoagulable state should also be suspected in the case of idiopathic recurrent VTE or in thrombosis involving atypical locations, like upper extremities, visceral veins (hepatic, portal, mesenteric) or cerebral veins.[1]

Table 1 summarizes the most frequently inherited and acquired thrombophilic conditions in a population of patients with a first episode of VTE.

In patients with venous thrombosis before the early nineteen-ninties a biologic cause of thrombophilia was detectable in only 5% to 15% of cases and was confined to deficiencies of antithrombin, protein C, and protein S. The discovery of two prothrombotic mutations prevalent in white populations, the factor V-Arg506Gln mutation (factor V Leiden) and the prothrombin G20210A mutation has significantly increased the number of patients with recognizable hereditary risk factor. Factor V Leiden mutationis apparently not present in African blacks, Japanese or Native American populations and less than 1% in Chinese.[24] The incidence of VTE is higher in Africans and lower in Asian populations, however, the prevalence of hereditary or acquired thrombophilic factors in these ethnic groups is less known.

Hereditary Thrombophilia

The most common inherited defects include activated protein C resistance caused by the factor V Leiden mutation, the prothrombin gene G20210A mutation and hyperhomocysteinemia. Less common disorders include deficiencies of antithrombin, protein C, protein S, plasminogen and dysfibrinogenemias. These thrombophilic defects either enhancing procoagulant reactions or inhibiting natural anticoagulant mechanisms, promote hypercoagulability. Deep vein thrombosis (DVT) or pulmonary embolism are the most common manifestations of these disorders, although arterial thromboembolism can also manifest in a minority of patients.

The first identified coagulation defects were rare but strong prothrombotic factors whereas the more recently described abnormalities usually cause thrombosis only in the presence of additional risk factors.

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Table 1. Hereditary and acquired thrombophilia. For the most frequent conditions, the prevalence in patients presenting with a first episode of venous thromboembolism is reported.[1]

Hereditary thrombophilia	Prevalence
Antithrombin deficiency	1,1% [6]
Protein C deficiency	0,5–4% [78]
Protein S deficiency	1,3% [80]
Factor V Leiden mutation	12–40% [5,6]
Prothrombin gene G20210A mutation	6–18% [6]
MTHFR mutation	1,4–15% [79]
Factor XII deficiency	2,3% [81,§]
Dysfibrinogenemias, plasminogen deficiency	unknown
Acquired thrombophilia	
Elderly	
Trauma, Surgery, especially orthopedic	
Immobilization, Long distance travel	
Obesity	
Pregnancy and puerperium	
Oral contraceptives and hormone replacement therapy	
Disseminated intravascular coagulopathy (DIC)	
Malignancy	
Chemotherapy, tamoxifen, central venous catheter	
Heparin-induced thrombocytopenia	
Nephrotic syndrome, Congestive heart failure	
Antiphospholipid antibody syndrome	
Myeloproliferative disorders (Polcythemia vera; Essential thrombocythemia)	
Hyperviscosity (Waldenstrom's macroglobulinemia, Multiple myeloma)	
Paroxysmal nocturnal hemoglobinuria, Sickle cell anemia	
Unknown or mixed etiology	
Hyperhomocystinemia	
Acquired APC (activated protein C) resistance	
High levels of factor VIII, factor XI, factor IX	
High levels of TAFI (thrombin-activatable fibrinolysis inhibitor)	
Low levels of free TFPI (tissue factor pathway inhibitor)	

[§]Prevalenve in the general population.

The family history of the patient is itself an independent thrombotic risk factor because, even when a specific defect has been identified, carriers of thrombophilic defects that belong to a thrombophilic family have a worse clinical course. These patients are younger at onset and have a more severe phenotype compared to carriers of the same defects with a silent family history.[2,3] In fact, thrombophilic families harbor synergistic genetic defects (both characterized and uncharacterized) that contribute to the thrombotic risk.

Deficiencies of natural anticoagulant proteins are frequently identified in patients with thrombosis, while they are observed in less than 1% of the general population. Figure 1 illustrates the inhibitory activity of the natural anticoagulants (antithrombin, the protein C system) on the coagulation cascade. Deficiency of protein C, S or antithrombin increases the risk of thrombosis approximately 10-fold in heterozygotes, while homozygotes may develop purpura fulminans (with laboratory evidence of DIC) shortly after birth.[4] Levels of natural coagulation inhibitors should be measured if indicated before beginning anticoagulant therapy or after its discontinuation, because treatment affects the tests results.

Antithrombin deficiency

This a rare defect inherited in an autosomal dominant fashion which prevalence is estimated to be one in 1/2000 to 1/5000 persons.[5] The prevalence of antithrombin deficiency in patients presenting with a first thrombotic episode is 1%.[6] Antithrombin

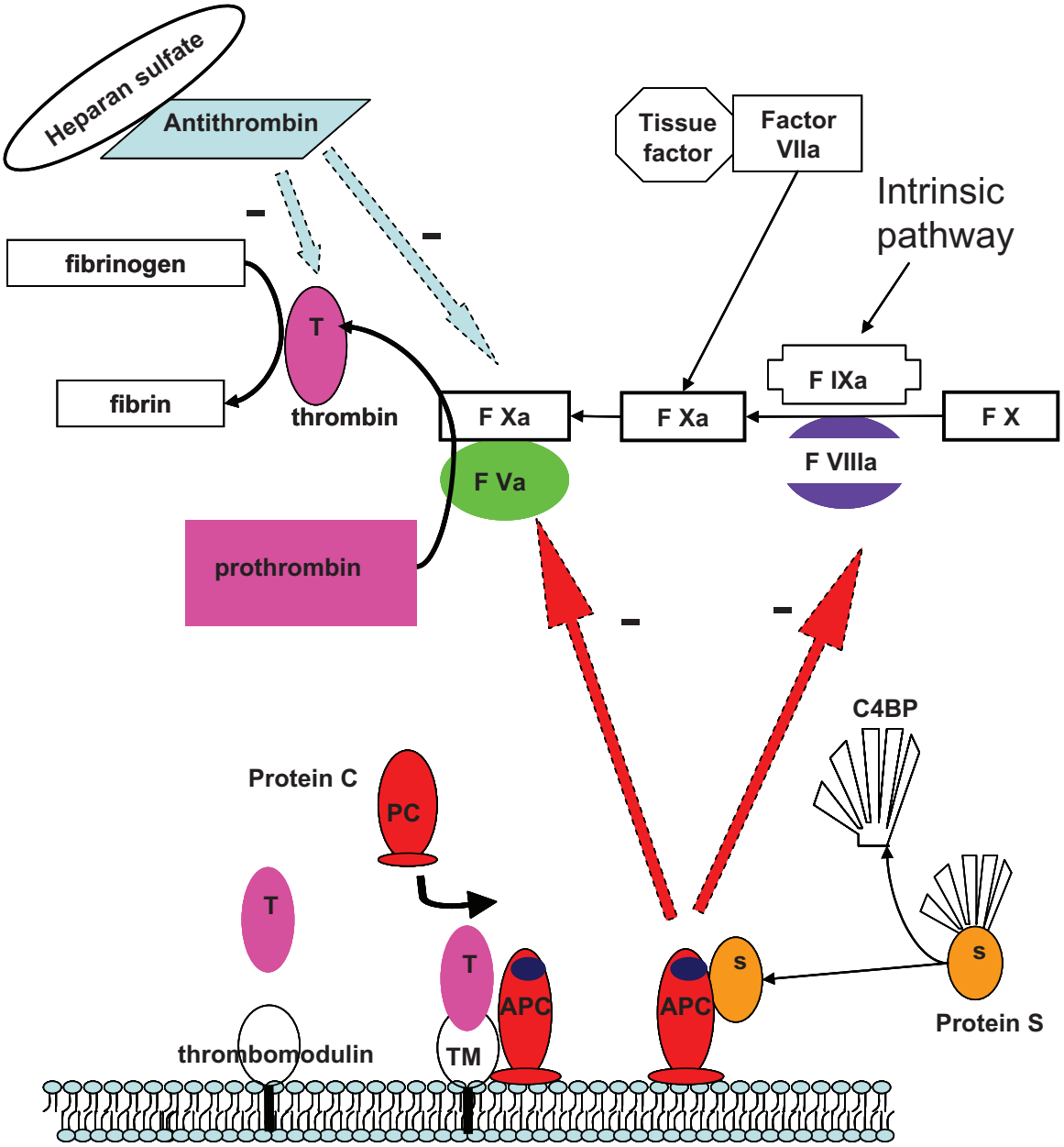

Figure 1. Inhibitory effect of natural anticoagulants on the coagulation cascade. Thrombin (T), beside its procoagulant enzymatic activity of fibrinogen activation, is able to bind thrombomodulin (TM) and activate protein C to activated protein C (APC). APC binds free protein S (S), which acts as a cofactor by enhancing the activity of APC. The complex can inhibit the coagulation cascade by the inactivation of factor Va and factor VIIIa. Antithrombin associated with heparan sulfate molecules on the surface of vascular endothelium inactivates thrombin and factor Xa.
Abbreviations: C4BP: C4b binding protein; PC: protein C; APC: activated protein C; TM: thrombomodulin; S: protein S; T: thrombin.

(or antithrombin III) is a plasma anti protease that belong to the serpin group inhibits thrombin by irreversibly binding in a 1:1 complex. Type I deficiency is characterized by low antithrombin antigen levels, whereas in type II is caused by a mutation in the thrombin binding site producing a dysfunctional molecule, with normal antigen level and reduced antithrombin activity.[7] There are no clinical differences between the two types. The best single screening test for this disorder is the antithrombin-heparin cofactor assay that measures factor Xa inhibition. Heterozygotes have 8.1 times higher probability of developing thrombosis.[8] Recurrent thrombotic episodes occur in 60% of patients[9] and 40% exhibit pulmonary embolism.[10] Patients with an acute thrombotic episode should be treated with heparin, although in some patients antithrombin III replacement may be useful.[11]

Protein C and protein S deficiencies

Protein C deficiency is a common defect in the general caucasian population, where the prevalence of heterozygous protein C deficiency in non symptomatic subjects ranges from 1/200 to 1/500 and 1/3000–1/5000 in symptomatic patients. Heterozygous protein C deficiency can be inherited in an autosomal dominant fashion or in a more severe autosomal recessive manner.[5] Type I (reduced enzymatic and immunological activity) and type II (dysfunctional protein C) deficiencies have been described.[12] Heterozygous protein C deficiency produces a 7.3 fold increase risk of thrombosis.[8] Warfarin-induced skin necrosis has been associated with this disorder, but it is not specific for this condition. This syndrome develops in the first few days of warfarin treatment, when protein C levels can decrease to 50% of normal level, causing an active prothrombotic state.[13] Rare cases of purpura fulminans have been described in newborns with less than 1% protein C activity, which resulted from homozygous or double heterozygous mutations for protein C deficiency.[14] In order to avoid skin necrosis in patients with known protein C deficiency warfarin treatment should start at a low dose and only after full heparinization. In patients with a previous episode of skin necrosis, administration of protein C concentrates (or alternatively fresh frozen plasma) can be protective at the beginning of oral anticoagulant therapy. Protein C deficiency can be acquired in conditions like liver diseases, DIC, sepsis,and in malignancies treated with L-asparaginase, methotrexate, fluorouracil, cyclophosphamide.[15]

Protein S deficiency is a common thrombophilic abnormality that can originate both from a congenital genetic defect or, more often, from acquired plasma perturbations. Inherited heterozygotes prevalence at first thrombotic episode is between 1% and 7%. Patients with protein S deficiency have an increased risk of VTE but a clear association with arterial thrombosis has not been demonstrated. Heterozygotes have an 8.5 times higher risk of developing thrombosis.[8] Neonatal purpura fulminans or recurrent VTE at a young age have been described in homozygotes or double heterozygotes.[18] Under normal conditions, about 60% of protein S is bound in plasma to C4b binding protein (C4BP). It is generally accepted that only the free protein S (about 40% of the total) is functionally active, consequently an increase of C4BP levels produces a reduced protein S activity, despite normal antigen levels.[19] Recent report never less has shown that protein S-C4B couples retain APC cofactor activity (20). Total protein S levels are 15% to 30% of normal in healthy newborns, but C4BP is also reduced (20% of normal levels), with only slightly reduced functional level compared to adults. Acquired deficiency of protein S is observed during pregnancy, oral contraceptive use, during an acute thromboembolic disease, anticoagulant therapy, DIC and liver diseases.[20] Free protein S antigen and functional activity can decrease during inflammatory disorders, possibly due to higher levels of C4BP.[21] Symptomatic cases should be treated with full anticoagulation; like for protein C deficiency, warfarin treatment should start at a low dose and only after full heparinization.

Factor V Leiden mutation

The most common inherited prothrombotic condition is due to a mutation of factor V, called factor V Leiden. The mutation is at the cleavage site, where APC inactivates factor Va. This single point mutation leads Factor V Leiden to be relatively resistant to proteolytic inactivation by APC. The slower inactivation of factor Va results in its persistent presence in the blood, producing a prothrombotic state. This defect was identified in 1993, when Dahlbäck observed that plasma from a patient with a personal and family history of VTE showed a reduced response to the addition of APC in an APTT-based test. This phenomenon called APC resistance has been associated in most cases to a single amino acid substitution (ARG residue at position 506 is replaced by GLN).[22,23] The prevalence of this mutation in the general caucasian population is between 1% and 7%, while it is very rare in other ethnic groups.[24] Patients with heterozygous factor V Leiden mutation have a relative risk 7-fold increased in overall risk of VTE (relative risk corrected for sex and family status is 2.2),[8] relative risk increases to 50–80 fold in homozygous patients.[25,26] Compared with deficiency of natural anticoagulants, factor V Leiden is a weaker risk factor for VTE, but it is far more common, as it can be found in about 20% of patients with venous thrombosis. Homozygotes are not so rare, with a prevalence of 1/500 in the general population.[26] The main clinical manifestation of this defect is the increased VTE development. Of particular interest is the observation of a high incidence of VTE in women with factor V Leiden mutation taking oral contraceptives; in these cases the risk of thrombosis

is 35 fold higher.[27] Discordant results have been obtained from different studies testing the correlation between factor V Leiden and the risk of myocardial infarct or arterial thrombosis: it seems that factor V Leiden can increase the risk of arterial events only in patients with an already present cardiovascular risk factor like cigarette smoking.[28] The presence of factor V Leiden mutation, as well as other hereditary thrombophilic factors, has been associated with a high risk of fetal loss.[29] Resistance to APC is caused in most cases by the factor V Leiden mutation; however, an acquired state without any genetic mutation (acquired APC resistance) has been associated to pregnancy, use of estroprogestone therapy and cancer (see below).

Prothrombin G20210A mutation

This is a quite common mutation observed almost exclusively in caucasian people. It is present in about 2% of healthy individuals and in 6% of patients with VTE.[30] As a consequence of this mutation, levels of prothrombin in the blood are increased and the risk of VTE is 3 times higher in patients with this mutation. This defect is not a risk factor for arterial thrombosis or fetal loss.[31]

MTHFR mutation

The gene for methylenetetrahydroflate reductase (MTHFR) plays a role in homocysteine metabolism; in particular it is essential for the methylation of homocysteine and formation of methionine. The C677T mutation is quite common and has been shown to be associated with mildly elevated homocysteine levels. As later explained, elevated homocysterine levels are associated with an increased risk of thrombosis. Although this variant is common (about 10% of the general population are homozygous carriers), it produces a slight elevation of homocysteine levels and only a small number of patients with the homozygous defect shows premature vascular disease and thrombosis.[32,33] A less common genetic defect in the homocysteine metabolism is the deficiency of cystathionine-β-synthase, which causes elevated homocysteine levels in the blood and result in early death due to CV disease.

Factor XII deficiency

Patients with factor XII deficiency show a prolonged activated partial thromboplastin time (APTT), but they do not have a bleeding diathesis. An increased rate of VTE has been observed in subjects carrying this abnormality. The thrombophilic tendency associated with severe factor XII deficiency (<1% factor XII activity) has been attributed to reduced plasma fibrinolytic activity.[34] However, different rates of VTE have been reported in different studies including patients with factor XII deficiency and a clear role of this defect for the risk of VTE has not been established.[35,36]

Dysfibrinogenemias

This group of disorders is characterized by qualitative abnormalities of fibrinogen, usually inherited in an autosomal dominant fashion. Some variants are associated with an increased risk of thrombosis and can be detected by a prolonged thrombin time (TT) and reptilase time and by the discrepancy between the functional and the antigenic levels of fibrinogen.[1]

Treatment

Treatment of acute episodes of VTE begins with heparinization to obtain a full coagulation, that can be switched to oral anticoagulant therapy with INR in range 2–3. The decision to extend therapy beyond 6–12 months After a thrombotic event must be made on an individual basis, depending on the presence of concomitant transient risk factors, location and severity of the thrombosis. The risk of VTE associated with the inherited thrombophilic defect should be weighted against the hemorrhagic risk associated with a long-term anticoagulant therapy. Current guidelines suggest continuing anticoagulation for individuals with antithrombin deficiency and a previous thrombotic event, with homozygous thrombophilic defects or with two or more prothrombotic abnormalities (see also below).[82]

Acquired Thrombophilia

Classic risk factors for VTE include cancer, surgery, prolonged immobilization, fractures, puerperium, paralysis, use of oral contraceptives, and antiphospolipid antibody; these may trigger thrombosis in people with inherited thrombophilic abnormalities. Combined genetic defects as well as the combination of a genetic defect with one or more acquired risk factors and the combination of

two acquired risk factors result in a risk of VTE that exceeds the sum of single factors effect.

Pregnancy, puerperium, oral contraceptives and hormone replacement therapy

The risk of VTE is approximately 10-fold increased during pregnancy and puerperium, leading to an overall rate of VTE of about 1%.[37,38] It has been estimated that 12% of the fatalities during pregnancy are attributable to pulmonary embolism;[37,39] the presence of a hereditary thrombophilia represents a major risk factor in this setting. Thrombosis during pregnancy and puerperium is attributable both to venous stasis (caused by the compression from the gravid uterus), to estrogen-dependent alterations of the hemostatic mechanisms like elevation of procoagulant factors (thrombin, tissue factor, fibrinogen, factor VII, IX, X, XII, XIII VWF), to the decline of the natural anticoagulant protein S and antithrombin[40,41,42] and to impaired fibrinolysis.[43,44]

The prothrombotic effect of the estrogens produces also a 2-to 5-fold increased risk of venous and arterial thrombosis in women taking oral contraceptives.[45] It is noteworthy that incidence of arterial thrombosis is significant in this setting. This risk decreased slightly after the reduction of the estrogens dose content in contraceptives (from first to second generation pills), but further dose reduction in the latest contraceptives preparation did not produce any additional benefit on the thrombotic risk. Many studies have observed that third-generation contraceptives containing the progestogens desogestrel or gestodene carry a higher thrombotic risk compared to second generation pills containing levonorgestrel. This difference is not due to different estrogens content but presumably by the less compensated effect of desogestrel compared to levonorgestrel. Hormone replacement therapy, which often consists in a combination of conjugated estrogens with medroxyprogesterone, is associated with a 2- to 4-fold higher risk of venous and arterial thrombosis.[46,47] For either oral contraceptives or hormone replacement therapy, the risk of thrombosis is highest shortly after the beginning of therapy.

Acquired factors like obesity, age, and the coexistence of hereditary thrombophilic disorder further increase the thrombotic risk. In particular, antithrombin, protein S or C deficiency and factor V Leiden greatly enhance this risk: women with factor V Leiden have a 15- to 30-fold thrombotic risk while taking oral contraceptives.[48,27]

Cancer

After the first report of an association between malignacies and thrombosis, many large studies have confirmed the higher risk of thromboembolic events in the cancer population. The rates of VTE in cancer patients have a wide variability in different trials. In women with breast cancer, the VTE rate ranges from 0.1% in untreated stage I patients to 17% in chemotherapy treated women for advanced stages. The MEGA study accrued 3220 unselected patients with VTE and 2131 controls; the presence of a malignancy increased the thrombotic risk 4.3 fold.[49] In patients with cancer VTE represents an important case of morbidity and mortality. It has been estimated that mortality in one of every 7 hospitalized cancer patients is associated to pulmonary embolism. According to "Medicare Provider Analysis and Review Record", the rate of initial or recurrent thromboembolism in patients with cancer greatly exceeds the cardiovascular complications recorded in those without malignancy, and occurs with similar frequency among cancers of virtually all body systems. The most common co-morbidities which produce a higher risk of VTE in cancer patients include immobilization, surgery, chemotherapy with or without adjuvant hormone therapy, and the insertion of central venous catheters. The relationship between cancer and venous thromboembolism is further emphasized by the high rate of cancer development in patients with unprovoked venous thrombosis.[50] Multiple studies have consistently shown 4–5 times higher risk in patients with idiopathic rather than in subjects with secondary thrombosis. Three large-scale prevention studies involving over 5500 medically ill patients have shown that 11%–15% will have VTE and 4%–5% will have proximal-vein thrombosis as identified by screening studies in the absence of prophylaxis. Carriers of the factor V Leiden mutation who developed cancer had a 12-fold higher DVT risk compared to individuals without malignancy and factor V Leiden mutation; similar results were observed in carriers of prothrombin gene 20210A variant.

Serine proteases such as thrombin and TF/VIIa operate not only in promoting clot formation but

function as signaling factors modulating cellular behavior.[51,52] Serine proteases communicate with cells through a family of protease activated receptors (PAR1, PAR2, PAR3, PAR4). Thrombin can activate PAR 1, 3 and 4 while either the TF/FVIIa or the more effective TF/VIIA/XA complex activates PAR 2. PAR is expressed primarily by cells in the vasculature, but also by tumor cells with high metastatic potential. Thrombin and the TF/FVIIa or TF/FVIIa/Xa complex also initiate signal transduction activating a number of pathways that shapes the microenvironment of the tumor. TF has been found a wide variety of tumor cells.[53,54] Increasing expression of TF correlates with advanced stages of disease and poorer survival rate.[55,56]

The fibrinolytic system functions either within the vascular space or in the tissue compartment. Plasminogen plays a critical role in the extravascular space serving as the key mediator of *extracellular* proteolysis a process that is essential for cell migration. Plasmin-mediated degradation of extracellular matrix enables malignant cells to invade surrounding tissue and also facilitates a tumor's ability to metastasize. Angiogenesis is also dependent on the tissue plasminogen system.[57]

Different model systems have now provide evidence that oncogene activation or tumor suppressor gene inactivation upregulate clotting pathways in vivo. Targeting activated human MET oncogene to mouse liver with a lentivrial vector and liver-specific promoter has recently been described as a model for human liver carcinoma.[58] Progressive hepatocarcinogenesis was preceded and accompanied by a thrombohemorrhagic state, which was indistinguishable from Trousseau's Syndrome with disseminated intravascular coagulation (DIC).[57]

The contribution of platelet activation to tumor dissemination has been recently elucidated; Palumbo and colleagues have been studied mice lacking Gαq, a G protein critical for platelet activation. Loss of platelet activation resulted in a profound decrease in both experimental and spontaneous metastases after injection of either Lewis Lung carcinoma cells or B16 melanoma cells. Radiolabeled tumor cells distribution demonstrated that diminished platelet function and decreased fibrinogen, significantly improved the survival of circulation tumor cells in the pulmonary vasculature. The prometastatic effect conferred by either platelets or fibrinogen was linked to a reduction in natural killer cell function.[59]

Medically ill patients

The frequency of DVT in medically ill patients, in the absence of prophylaxis, varies from 10% to 26%. About 10% of deaths that occur in hospitals are associated to pulmonary embolism and 75% of fatal pulmonary emboli develop in medical population. Numerous risk factors for VTE have been identified. These clinical risk factors include increasing age, heart and respiratory failure, prolonged immobility, stroke or paralysis, previous VTE, cancer chemotherapy and, acute infection, dehydration, hormonal treatment, varicose veins; incidence of DVT has been also noted to rise in association with acute inflammatory bowel disease, rheumatologic disease, and nephrotic syndrome. Patient carriers of proximal-vein thrombosis have an unexpectedly high risk of in-hospital death.

Risks factors for VTE in medically ill patients have a cumulative effect; hospitalized subjects with thrombophilia or a history of thrombosis are at increased risk of VTE, as well as patients with lower limb paralysis from acute ischaemic stroke.

Acquired activated protein C (APC) resistance

Abnormally increased resistance to APC has been observed in patients not carrying factor V Leiden mutation; this phenomenon has been defined as acquired APC resistance. In a large cohort of 15,109 unselected subjects, 2.3% showed an APC resistance in the absence of Factor V mutation.[60] The presence of an APC resistance increases the thrombotic risk, independently from presence of a genetic defect.[61,62] Resistance to APC has been also described with cerebrovascular diseases and pre-eclampsia.[63,64]

Many physiologic and pathologic conditions have been associated with the presence of acquired APC resistance:[65] pregnancy, oral contraceptives and hormone replacement therapy, lupus anticoagulant syndrome, and neoplasia. Several authors have recently described the presence of APC resistance in patients with malignancies; in addition, multiple reports indicated an association between low APC levels and increased thrombotic risk in cancer.[66,67,68] Testing cancer patients for baseline APC resistance seems to be an appealing screening method to identify hypercoagulable subjects with impaired natural anticoagulant system. However, the initiation of an anticoagulant therapy or

prophylaxis based only on the presence of APC resistance is not fully justified by current data.

Antiphospholipid antibodies

Antiphospholipid antibodies are a heterogenous group of autoantibodies directed against anionic phospholipids. There are two classes of antiphospholipid antibodies: anticardiolipin antibodies and lupus anticoagulants. Anticardiolipin antibodies, which can be IgG or, less often, IgM, may be directed against β_2-glycoprotein 1 and quantified by ELISA that uses cardiolipin as the antigen.[69] High-titer IgG anticardiolipin antibodies are most strongly associated with clinical manifestations. Lupus anticoagulants are very common in normal children and are frequently identified prior to scheduled tonsillectomy/adenoidectomy or the basis of a prolonged APTT. In this setting, they are not a significant risk factor for thrombosis. Lupus anticoagulants induce a dose dependent prolongation in phospholipid-dependent clotting assays such as the APTT using a sensitive reagent, the dilute PT, Russell Viper Venom time or kaolin clotting time. The presence of such antibodies can be indicated by the failure of APTT to correct when normal plasma is added in mixing studies. The mechanism by which antiphospholipid antibodies cause thrombosis is unclear. There is evidence that the antibodies interfere with the protein C pathway by impairing both protein C activation and the function of APC. Endothelial cell dysfunction with reduced prostacyclin synthesis and antibody-induce platelet activation have also been described. The antiphospholipid antibody syndrome is defined by thrombosis or pregnancy morbidity in association with a persistent elevation (>12 weeks) of lupus anticoagulant, anticardiolipin, or antiβ2 glycoprotein I antibodies.[69] Clinical manifestations are venous or arterial thrombosis, recurrent fetal loss, and livedo reticularis. The clinical significance of transient antiphospholipid antibodies is unclear and testing should be repeated at 6–12 weeks. Although antiphospholipid antibody syndrome can be idiopathic, it is frequently associated to systemic lupus erythematosus, or cancer (such as lymphoma) or infections (Pneumocystis carinii pneumonia, in HIV patients), and in association with drugs such as hydralazine or procainamide. All patients <65 years of age who present with transient ischemic attacks or ischemic stroke should be screened for antiphospholipid antibodies.

Management of thrombotic defects

Asymptomatic patients with hereditary thrombophilia identified through family studies should not receive long-term oral anticoagulation. They should, however, receive counselling regarding their diagnosis and need for prophylaxis during high-risk periods.[70] In patients who have a first venous thrombotic even in the setting of a transient triggering factor, anticoagulation can be discontinued after 3 to 6 months after removal of the triggering factor. Patients with idiopathic thromboembolism without triggering factors are generally treated for 6 months. Extended anticoagulation should be considered for single unprovoked venous thrombotic events in the presence of more than one allelic abnormality (for example, homozygous factor V Leiden and combined heterozygosity for factor V Leiden and prothrombin G20210A mutation), and initial life-threatening thrombosis (such as massive pulmonary embolism or cerebral, mesenteric, portal, or hepatic venous thrombosis), after second unprovoked thrombotic episode. In the setting of acute thrombosis, the presence of Factor V Leiden of prothrombin G20210A does not alter the initial anticoagulation regimen. Patients with a diagnosis of one of the less common thrombophilias (deficiencies of antithrombin, protein C, or protein S) are generally initially treated as patients without one of these defects. Treatment therapy for patients with deep venous thrombosis and pulmonary embolism typically includes administration of unfractionated or low-molecular-weigh heparin in therapeutic doses, followed by anticoagulation with warfarin at an INR between 2 and 3 for 3 to 6 months. After cessation of anticoagulant therapy for patients with a first episode of symptomatic venous thromboembolism the cumulative incidence of recurrent venous thrombosis is 5% to 15% at 1 year and approximately 25% at 5 years. Recurrences are much less frequent when the initial event was associated with surgery or trauma. It is unclear whether risk of recurrence is higher among patients with a first episode of venous thromboembolism associated with the factor V Leiden or prothrombin G20210A mutations than in those without a prothrombotic mutation.[71] A statistically significant higher incidence of recurrence has been reported

in a subset of patients who are heterozygous for both mutations.[72] In patients with unprovoked thromboembolism, the risk of recurrent thrombosis in the presence of antithrombin, protein C, and protein S deficiencies is not known. It is common practice that patients with heterozygous antithrombin deficiency receive anticoagulation for an indefinite period of time because they appear more prone to thrombosis than patients with other single heritable abnormalities. In the setting of arterial thrombosis, most studies indicate that the presence of hereditary thrombophilias does not constitute a risk factor. It is not recommended to investigate for the hereditary thrombophilias in patients who have isolated arterial thrombosis, in the presence of other independent cardiovascular risk factors (hypertension or diabetes mellitus or if they smoke or have hyperlipidemia).

Most patients with an antiphospholipid antibody are adequately treated with warfarin administered to achieve an INR of 2.0–3.0. The addition of aspirin to warfarin for those patients with arterial thrombosis is reasonable. Patients with recurrent thrombosis despite "usual intensity warfarin" therapy can be treated with heparin or Low Molecular Weight Heparin (LMWH) administered subcutaneously in therapeutic doses. Higher doses of warfarin (target INR of 3.0–4.0 in combination with aspirin) might also be considered in such patients. Because of the high risk of recurrent thrombosis off anticoagulation, retrospective studies have suggested that patients with antiphospholipid antibody syndrome require indefinite treatment.

Even if a significant body of evidence[73,74] suggests a survival advantage in cancer patients treated with LMWH, routine administration of anticoagulant is not recommended. Primary prophylaxis for thromboembolism is recommended unfractionated Heparin (UFH), or LMWH in cancer patients who are to undergo surgery; such patients have a post operative thromboembolic risk 3 times higher of non cancer individuals. All hospitalized acutely ill individuals with active cancer should receive anticoagulant prophylaxis with low dose UFH or LMWH.[75,76] With the current practice in oncology being dominated by outpatient care with the more frequent use of active anticancer drugs with prothrombogenic activity, the physician should watch for signs or symptoms of VTE and patients seeking immediate medical attention for symptoms such as chest pain, shortness of breath or lower extremities swelling. In patients treated with a combination of immunomodulatory drugs such as thalidomide, with chemotherapy or steroids, has now become common practice with the use of a prophylactic dose of LMWH or coumadin, especially during the early courses of cancer chemotherapy.[77]

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