Review Article

Haematologic Disorders and Cerebral Venous Thrombosis

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Abstract

This review focuses on the several coagulation disorders (the so called hypercoagulable states) that are associated with cerebral venous thrombosis. Hypercoagulable states likely explain the high percentage of cases of cryptogenic cerebral infarction in young people. The most common of the hereditary defects appear to be deficiency of antithrombin III, protein C or protein S, activated protein C resistance and prothrombin 20211A mutation. In a large majority of cases activated protein C resistance is due to the presence of factor V Leiden. Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) represent an acquired disorder of coagulation. Rare defects include heparin cofactor II (HC II), plasminogen or tissue plasminogen activator deficiency (TPA), elevated plasminogen activator inhibitor-1 (PAI-1) and dysfibrinogenemia. Hyperhomocystinemia is responsible for both arterial and venous thrombosis. A work-up to identify one of the recognizable hypercoagulable states is indicated, especially in younger patients with stroke. Laboratory evaluation for hypercoagulable states may also often be indicated in those patients who do not have other obvious risk factors for their stroke. If from clinical history, family history and/or laboratory studies, a patient is felt to have a hypercoagulable state, the decision for long term chronic anticoagulation needs to be individualized. If a hereditary hypercoagulable state is found, it also may be appropriate to recommend screening of other family members.

Introduction

Over the last few decades, substantial progress has been made towards a better comprehension of the pathophysiological mechanisms involved in venous thrombosis. Numerous conditions are known to predispose to venous thrombosis. Generally accepted or "classically" acquired risk factors for venous thromboembolism include advanced age, prolonged immobilisation, surgery, fractures, use of oral contraceptives and hormone replacement therapy, pregnancy, puerperium, cancer and antiphospholipid syndrome. In addition to these well-established risk factors, several lines of evidence over the past few decades specify a role of novel genetic risk factors, mainly related to the haemostatic system, in influencing thrombotic risk. The most significant breakthrough has been the confirmation of the concept that inherited hypercoagulable conditions are present in a large proportion of patients with venous thromboembolic disease. These include mutations in the genes that encode antithrombin, protein C and protein S, and the factor V Leiden and factor II G20211 A mutations.[1] Moreover, plasmatic risk indicators, such as hyperhomocysteinemia and elevated concentrations of factors II, VIII, IX, XI and fibrinogen, have also been documented.[2-6] This broad list of genetic and acquired factors emphasizes that a single cause of venous thrombosis does not exist and that this condition should be considered as a complex or multifactorial trait.

The aim of this review is to highlight the significance of these factors in cerebral venous sinus thrombosis. The specific factors discussed in this article include factor V Leiden (ie, resistance to activated protein C); deficiencies of proteins C and S and antithrombin III; hyperhomocystinemia; and antiphospholipid antibody syndrome, and prothrombin gene mutation.

Pathophysiology

Haemostasis is provided by an interaction of normal vessel responses, platelet plug formation, and activation of the coagulation cascade (Figure). The coagulation cascade involves activation of blood coagulation factors with formation of prothrombin activator, which catalyzes the conversion of prothrombin to thrombin. Thrombin acts as an enzyme to convert fibrinogen into fibrin fibers that enmesh platelets, blood cells, and plasma to form a clot.

Counteracting haemostasis are normal vascular endothelial cells, which inhibit platelet adhesion and aggregation, and proteins such as thrombomodulin. Thrombomodulin activates protein C, which in turn activates protein S; together, the 2 factors play a role in inactivating factors V and VIII. Antithrombin III also plays a role in inactivating factor X and thrombin, thus inhibiting thrombosis. In this way, interactions among multiple plasma proteins, protein C, and protein S; resistance to APC; antithrombin III; and normal vascular endothelial cells form an important barrier to thrombosis.

Factors that accelerate the haemostatic mechanism or inhibit mechanisms that counteract haemostasis contribute to an increased state of thrombogenicity

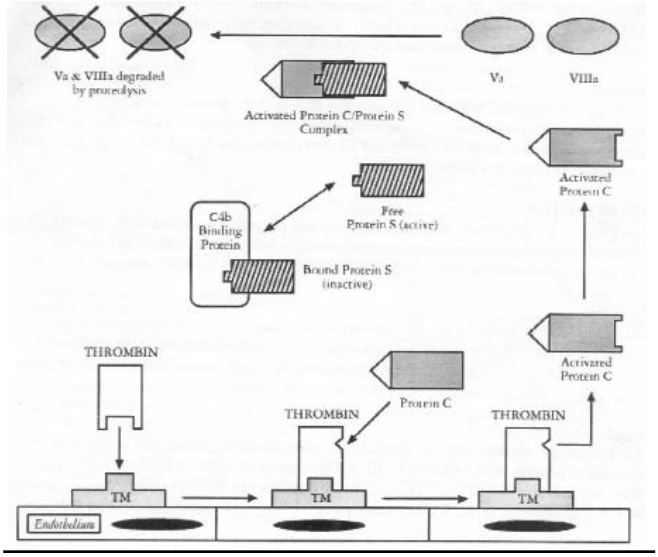

Figure. The coagulation of cascade and other mechanisms of haemostasis.

(i.e. hypercoagulability) and thereby play an etiological role in infarction (arterial or venous).

Factor V Leiden and Activated Protein C Resistance

Activated protein C resistance is a common cause of hereditary predisposition to venous thrombosis.[1] The most common cause of activated protein C (APC) resistance is the Factor V Leiden mutation, which occurs in 5-7% of the normal population, 20% of patients with deep vein thrombosis (DVT), and 60% with recurrent DVT. The incidence of this factor in patients with stroke is not known; in general, however, this factor correlates more with venous mechanisms of thrombosis than arterial ones.[7,8]

A mutation in factor V (factor V Leiden) renders activated factor V unable to be cleaved by APC. More than 95% of patients with resistance to APC have the Arg506Gln mutation defect.

APC resistance can occur in the absence of the Leiden Factor V gene mutation. This abnormality has been reported in patients with stroke.[9,10] Therefore, it may be important to perform a functional assay for activated protein C resistance in addition to testing for the Leiden Factor V mutation in these patients.

Protein C, protein S, and Antithrombin III deficiencies

Protein C binds to the thrombomodulin-thrombin complex and becomes converted into activated protein C (Figure). APC along with protein S as a cofactor inhibits coagulation by degrading the activated Factor V and Factor VIII. Protein C and protein S deficiency occur in approximately 0.5% and 0.7% of the general population. Deficiencies in both of these factors are well-recognized etiologies of venous thrombosis. The role of protein C and protein S deficiency in arterial thrombotic disease and stroke is less clear. There are, however, several studies that have demonstrated the presence of protein C deficiency in stroke, either alone or in combination with other causes of a hypercoagulable state.[11-14]

No clear-cut association has been found between protein C or antithrombin III deficiency and arterial strokes, though patients with low protein C levels at the time of acute stroke have had poor outcomes. A prospective study did find free protein S deficiency in 23% of young patients with stroke of uncertain cause, but this finding could be associated with higher levels of C4b (an acute phase reactant that decreases free protein S levels). Once a deficiency of protein C, protein S, or antithrombin III is identified, differentiating between congenital and acquired cases is important.

Antiphospholipid antibody syndrome

Antiphospholipid antibodies (APLs) consist of several related, but somewhat clinically distinct subgroups, including lupus anticoagulants (LA), anticardiolipin antibodies (ACAs), and a number of less well characterized and investigated antiphospholipid antibodies.[15,16] ACAs and LA occur in approximately 5% and 4%, respectively, of the general population. Antiphospholipid antibodies have been associated with venous thromboembolism as well as arterial thrombosis, including coronary thrombosis, stroke, and transient ischemic attacks. The presence of APLs is considered a risk factor for stroke by some authors; however, some studies have shown no such association.[15]

APLs are polyclonal and polyclass antibodies that bind to anionic and neutral phospholipid-containing moieties. Recognizing APLs is important, as they are associated with a hypercoagulable state characterized by foetal loss, thrombocytopenia, and venous and arterial thrombosis. Initially associated with systemic lupus erythematosus (SLE), these antibodies now are known to be found also in patients without SLE; patients without SLE who have these antibodies are diagnosed as having the "primary antiphospholipid antibody syndrome" (APS).

Cerebrovascular symptoms associated with APS include amaurosis fugax, occlusion of retinal arteries and veins, transient ischaemic events of the brain, thrombosis of cerebral arteries and veins, and dementia. The mechanisms of thrombosis are heterogenous and include cardiac valve lesions that embolize, hypercoagulable states, and cerebral vascular endotheliopathy. They tend to interfere in some way with normal endothelial cell functions via the protein C and protein S anticoagulant pathway.

Hyperhomocystinaemia

Elevated levels of homocysteine and related disulfide compounds are clear risk factors for stroke. Moderate (15-30 mumol/l) or intermediate (> 30-110 mumol/l) hyperhomocysteinaemia is caused by defects in genes encoding for enzymes of homocysteine metabolism or by inadequate intake of those vitamins that are involved in homocysteine metabolism (folic acid, cobalamin, and vitamin B6). Today, hyperhomocysteinaemia should be considered an important risk factor for atherosclerotic vascular and venous thromboembolic diseases.[17] Homocysteine plasma levels above the 95th percentile were found to be associated with a 2 to 3-fold elevated relative risk for deep vein thrombosis and pulmonary embolism. Moreover, mild hyperhomocysteinaemia has been shown to be associated with a 2 to 4-fold increased relative risk for coronary artery disease, cerebrovascular disease, and peripheral arterial occlusive disease. Several mechanisms have been proposed by which hyperhomocysteinaemia contributes to atherogenesis and thrombogenesis.[18]

Individuals who are homozygous for cystathionine beta-synthase deficiency develop premature atherosclerosis and often experience a stroke early in life. Homozygous patients clinically manifest a marfanoid habitus, lenticular dislocations, and other skeletal abnormalities in addition to strokes. These patients excrete homocysteine in the urine and have 20-fold or greater elevations of homocysteine and related amino acids in the plasma. Patients who are heterozygous for cystathionine beta-synthase deficiency can develop a mild clinical picture.

Prothrombin gene mutation

Fairly recently another common genetic variation, prothrombin gene G20211A, has been described. This mutation causes elevated plasma prothrombin concentrations and is a relatively common cause of venous thrombosis. It has been found in the heterozygous form in 2.3% of normal controls.[1] The prothrombin G20211A mutation is found to be associated with increased risk of stroke and may be a factor in the etiology of cerebral ischemia in young patients.[19] Other studies[20] have not shown this association. Reuner[21] showed an association with the prothrombin G20211A mutation and cerebral vein thrombosis, but not with acute ischaemic stroke or transient ischaemic attack. Likewise, Martinelli[22] did show an association of cerebral vein thrombosis with the prothrombin gene mutation as well as with the Factor V Leiden mutation. This study also showed a strong and independent association of oral contraceptives to cerebral vein thrombosis. The presence of both prothrombin gene mutation and oral contraceptive use raised the risk of cerebral vein thrombosis additively.

Hereditary abnormalities of fibrinolysis

Dysplasminogenaemia results in hypofibrinolysis by various mechanisms, including a decreased level of circulating plasminogen, an abnormally functioning plasminogen, an increase in the concentration of plasminogen activator inhibitor, or a decrease in the level of plasminogen activator. Although an association with stroke per se has yet to be described, these abnormalities should be considered in a young patient with stroke and a history of recurrent DVT.

Dysfibrinogenaemia is caused by genetic mutations that produce fibrinogen molecules that form clots resistant to fibrinolysis or that bind with increased avidity to platelets to promote thrombosis. These mutations thereby increase the risk of venous and arterial thrombotic episodes. Most strokes result from cerebral venous occlusion, but large arterial thrombotic strokes also are described in relatively young individuals and in those without other recognized risk factors.

Conclusion

Hypercoagulable states, both congenital and acquired, may be causes of both ischaemic stroke and cerebral vein thrombosis. A work-up to identify one of the recognizable hypercoagulable states is indicated, especially in younger patients with stroke. Laboratory evaluation for hypercoagulable states may also often be indicated in those patients who do not have other obvious risk factors for their stroke.

In the acute setting, several studies may be obtained in the evaluation of a possible hypercoagulable state. These include the Factor V Leiden mutation, the prothrombin G20211A mutation, homocysteine levels and ACAs. It may also be useful to measure them. Studies that are not helpful in the setting of an acute event include determination of fibrinogen levels, protein C, protein S, and antithrombin-III levels. It is also important to recognize other conditions, which may in and of themselves be associated with a hypercoagulable state. These may be synergistic with one of the above described abnormalities causing the development of thrombosis. These include the use of oral contraceptives or hormones, systemic inflammatory disorders, and malignancies.

For those patients who are placed on oral anticoagulation with warfarin, it may be appropriate to reevaluate them and stop anticoagulants after 4 to 6 months of treatment. If from clinical history, family history and/or laboratory studies, a patient is felt to have a hypercoagulable state, the decision for long term chronic anticoagulation needs to be individualized. This decision needs to occur after a thorough discussion of the risks of recurrent thrombosis, as well as the risks of long-term anticoagulation. If a hereditary hypercoagulable state is found, it also may be appropriate to recommend screening of other family members. There may

be recommendations that can be made to other affected family members that may be able to reduce their risk of thrombosis in the future.

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