Primary hypercoagulable states are quantitative and qualitative anomalies of coagulation-specific proteins. Many anomalies like these involve acquired mutations and polymorphisms leading to antithrombotic factor deficiency (thrombophilia by antithrombine deficit (III), protein S-deficit and protein C deficit), or increase of prothrombinic factors (by gain-of-function mutation) such as thrombophilia factor V Leiden (resistant to activated protein C), mutation in prothrombine G20210A or polymorphisms of MTHFR in homocysteine metabolism. Each is a factor of individual risk to thrombosis. Hence, when multiple prothrombotic mutations interact, these primary hypercoagulable states associate to increase predisposition to thrombosis for lifelong. Thromboembolic events in patients diagnosed with inherited or acquired thrombophilia are among the leading causes of mortality worldwide.

Keywords: thrombosis, protein C, protein S, antithrombin III, thrombophilia.

Abstract

Les états primaires d’hypercoagulabilité représentent des anomalies quantitatives ou qualitatives de certaines protéines spécifiques à la coagulation. Un grand nombre de ces anomalies impliquent des mutations acquises et des polymorphismes qui conduisent soit à un déficit de facteurs antithrombotiques (la thrombophilie par déficit d’antithrombine (III), le déficit de protéine S et le déficit de protéine C), soit à une croissance des facteurs prothrombiniques (par mutation avec gain de fonction) comme par exemple la thrombophilie à Facteur V de Leiden (résistante à la protéine C active), la mutation de la prothrombine G20210A ou les polymorphismes du gène MTHFR dans le métabolisme de l’homocystéine. Chacun de ceux-ci représente un facteur de risque individuel pour thrombose mais, une fois qu’une interaction des multiples mutations prothrombotiques apparait, ces états primaires d’hypercoagulabilité associent une prédisposition élevée pour thrombose tout au long de la vie. La prédisposition pour des évènements thrombotiques chez les patients diagnostiqués avec des formes héréditaires ou acquises...
When blood tends to clot too much, it is referred to as a hypercoagulable state or thrombophilia. Hypercoagulability, hemodynamic changes (like stasis or turbulence), endothelial injury or dysfunction, are the factors contributing to thrombosis (Virchow’s Triad). Several disorders are associated to higher or lower incidence of thrombosis.

Thrombosis is a multi-factor condition, because a patient can develop thrombosis out of several reasons. Thrombophilia is caused by blood consistency anomalies, given by various levels of coagulation factors and other blood proteins participating in clotting. In thrombophilia, the balance between procoagulant and anticlotting activity is altered. The severity of alteration determines the likelihood that somebody would develop a thrombotic event. Even small protein irregularities, such as decrease in level of AT-III to as little as 70—80 % of its normal values may increase chances for a thrombotic episode.

Besides the effects of thrombosis, hypercoagulable states significantly increase the risk of artery disease and myocardial infarction.

**Ethiopathogenesis of the primary hypercoagulable states**

Hypercoagulable states include inherited or acquired conditions highly prone to thrombosis. (Table 1). Thrombophilia disorders can be highlighted in half of the patients with venous thrombosis episodes. Hereditary thrombophilia represents a genetic tendency towards venous thrombosis, which is usually recurrent.1

**Factor V Leiden**

Factor V Leiden thrombophilia is characterized by a poor response to activated C protein (APC) and a high risk for venous thromboembolism (VTE). Factor V Leiden mutation results from a SNP mutation (single nucleotide polymorphism) G-A which is the result of Arg506-Gly substitution in the protein. This makes the factor V resistant to APC activity that will result in a defect in the natural process of anticoagulation. The mutation defect represents an alteration of the factor V anticoagulant properties. The mutation bears the name of the Holland city where it was first described. Proteolitic inactivation of activated V factor (FVa) is approximately 10 times slower for Gln506-FVa compared to Arg506-FVa which is partially resistant to APC.3

Factor V, like thrombine, has both anticoagulant and procoagulant properties. APC mediated splittings, if made to the factor V, may result in transforming it in a cofactor for APC (FVac). FVac acts in unison with APC and S protein to increase the inactivation rate for the factor VIII.

In contrast with other coagulopathies, the factor V Leiden poses a risk for developing PVT for life with a higher rate of thrombosis recurrence in the lower extremities compared to other regions. Nevertheless, not everyone who has the mutation will develop thrombotic episodes. Heterozygous patients have a lower risk per life (approximately 10%) compared to homozygous patients (approximately 50 – 100 times greater).4

**Prothrombine gene mutation (G20210A)**

Prothrombine is a glycoproteine synthesized by the liver (GM – 72 000). The proteine and its enzymatic form (thrombine) have important roles in de thrombophilie représente l’une des causes principales de mortalité au niveau global.

**Mots-clés:** thrombose, protéine C, protéine S, antithrombine III, thrombophilie.

### Table 1. Thrombophilia classification

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation inhibitor factor deficiency</td>
<td>High levels or functions of coagulation factors</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>Active protein C resistance</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>Factor V Leiden</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>Prothrombin gene mutation</td>
</tr>
<tr>
<td></td>
<td>High level of factors VII, IX, XI</td>
</tr>
<tr>
<td></td>
<td>High Lp</td>
</tr>
<tr>
<td></td>
<td>Change in strength fibrinogen</td>
</tr>
</tbody>
</table>

Other: HyperHomocisteinemia (MTHFR) – mixt, levels; high levels of fibrinolysis inhibitor

* adapted after2

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**Abbreviations**

aVF = activated V factor
PVT = profound venous thrombosis
AT (III) = antithrombine (III)
aXF = activated X factor
PC = protein C
WISN = Warfarin induced skin necrosis
FL (PF) = fetal loss
CID = disseminated intravascular coagulation
PS = protein S
MTHFR = methylenetetrahydrofolate reductase
some biological processes. The prothrombine gene is located on chromosome 11. A series of prothrombine polymorphisms has presented some rare genetic defects responsible for hypoprothrombinemia and dis-prothrombinemia. All these anomalies are associated with blood loss.5,6

Thrombophilia, as a result of prothrombine gene mutation (G20210A), is the second most common etiology after factor V Leiden. VTE is the first clinical manifestation and it includes PVT as well as pulmonary embolism. However, the clinical manifestations vary; many heterozygous or homozygous individuals with F2 alleles for 20210G>A will not manifest thrombosis. Some heterozygous individuals with thrombotic complications will remain asymptomatic until adulthood and others would develop recurrent thromboembolism until age 30. PVT risk in heterozygous adults for 20210G>A is 2.5 times higher; in children the relative risk for thrombosis is 3.4 times higher. Heterogeneity has, at most, a modest effect in the risk of recurrence after the first episode. Risk factors which may determine thrombosis: alleles number 20210G>A; presence or association with other genetic anomalies like factor V Leiden and acquired thrombophilia (antiphospholipid syndrome); circumstantial risk factors like pregnancy and oral contraceptive.5

Antithrombine III deficiency (AT – III)

Antithrombine III is one of the most potent inactivators of thrombine and X factor, being in the same time the main inhibitor of blood coagulation. Antithrombine congenital deficiencies are rare but patients with this type of pathology are prone to develop a thrombotic disease.

This type of deficiency was described for the first time by Olav Egeberg in 1965. He also was the one to establish its autosomal dominant transmission.7

Hereditary AT deficiency is dominant in heterozygous cases. Homozygotes with AT deficiencies are rare and they result in in utero death. The prevalence rate is between 1 in 500 and 1 in 5000 individuals.

Although in the general population, the type II deficiency is more frequent than type I, among the symptomatic patients type I is more frequent, representing almost 80% of total cases. Type IIb is less thrombogenic than type I (quantity speaking); being an autosomal dominant pathology, there is a 50% chance that the pathology may be transmitted to a new born if one of the parents has AT deficiency. Men and women can be equally infected, without racial or ethnic predilection.5

Hereditary AT – III deficiency may be caused by quality and quantity defects of the protein. Type I deficiency (quantity) represents the majority of cases, almost 80%. Family studies show that severe thromboembolic events usually start manifesting in late teenagers or in the early adult stages. Quality defects (type II deficiency) are characterised by a decrease in the activity of the heparine cofactor and doesn’t result in a decrease of AT – III molecular concentration. More than half the patients with type II deficiency will manifest recurrent PVT.3,8,9

Compared to the effects of the anticoagulant, the AT has more important anti-inflammatory effects which appear when it interacts with the endothelium. By inhibiting the thrombine and the factor X, it reduces the discharge of inflammatory cytokines, like interleukin-6 and interleukin-8, in the blood stream by using the thrombine/factor X complex. By binding to the endothelial heparan sulfate, AT increases its ability to bind to endothelial glycosamine and are not found in commercial or free heparine reactives.10

Protein C deficiency

Protein C deficiency (PC) is a congenital or acquired pathology with high risk of thrombosis. Therefore this is a type of hereditary thrombophilia. Protein C deficiency generates irregular fibrin because of bad inactivation of the factors VIII and V (factors essential in the coagulation cascade).4

The prevalence of heterozygous patients with protein C deficiency in the general population is between 1 in 200 and 500. In patients diagnosed with VTE, the protein C deficiency is found in approximately 3-5% of them.4

Clinical manifestations of protein C deficiency in heterozygous patients include VTE and warfarin induced skin necrosis (WISN). The risk of pregnancy loss is still controversial in this type of deficiency. Arterial thrombosis doesn’t appear to be associated with PC heterozygous deficiency. Persons with severe PC deficiency have PF recurrent episodes triggered by infection, trauma or even by minor decreases in optimal levels in anticoagulant therapy. Clinical manifestations include recurrent VTE, including PVT, pulmonary embolism, parenchymal thrombi and a tendency to CID.

Homozygous status is usually associated with neonatal purpura fulminans and intracranial thromboembolism (in the same group age). Occasionally in teenage stages or adult period, patients may express VTE.11

Protein S deficiency

Protein S (PS) is an anticoagulant protein dependent on vitamin K. Its main role is that of a cofactor
for facilitating the protein C activation (PCA), the activation of the factor V (FVa) and the factor VIIIa (FVIIia). A deficit in protein S predisposes the subject to venous thromboembolism (recurrent) and fetal loss.12

Hereditary deficiency in PS is of dominant autosomal type and thromboses are observed both in heterozygous and homozygous patients. Coding genes for PS, Pros α or PS-α and PROS2 or PS-β are located near the chromosome 3 centromer at 3q11.2 and 3p21-cen. There are over 200 mutations which result from loss of this protein function. Although PS deficiency isn’t commonly met in the general population, it can be found in approximately 2% of unselected patients and 1-13% in patients with VTE. The prevalence is higher because of the basic clinical criteria by which these patients were selected.12

PS deficiency is a hereditary pathology, but the age when thrombosis may manifest depends on the heterozygous or homozygous status. Majority of VTE in heterozygous patients manifest before the age of 40-45 years old. Homozygous patients rarely present neonatal purpura fulminans, like it was described in protein C deficiency.

MTHR polymorphisms and homocysteinemia

It has been suggested that the high plasmatic levels of homocystein (homocysteinemia) may be one of the predisposing factors for thrombosis. Two of the primary factors that influence the homocystein concentration in humans are: diet (especially vitamin B12 and folates consumption) and polymorphisms in the genes that code the transport proteins or enzymes which take part in dependent homocystein metabolism of folates and B12 vitamin. MTHR is the key enzyme in this metabolism. The enzyme catalyzes the 5,10-methylenetetrahydrofolate conversion to 5-methyltetrahydrofolate, the primary circulating form of the folate. 5-methyltetrahydrofolate is involved in homocystein remetilation (B12 dependent) in methionine. Methionine is converted in S-adenosylmethionine which has a donor role in the methylation of DNA, proteins, neurotransmitters and phospholipids.13

Two genetic polymorphisms are best characterized by MTHR:
• The first one consists in a transition 677C>T which resides in alanine-valine substitution in the catalytic domain of MTHR. Homozygous and heterozygous individuals have a reduced MTHR activity in vitro (70% for homozygous and 30% for heterozygous individuals). 677T homozygosity is associated with high levels of homocystein, especially in individuals with low levels of folates in plasmatic levels. Even more, the plasmatic level of homocystein may be low in some homozygous individuals who take folates supplements. Almost half of the population has at least one mutant allele. The frequency of homozygous genotype (677TT) is between 1-20%, depending on the population.14,15,16
• Another MTHR gene polymorphism is a transition 1298A>C which results in a glutamate-alanine substitution in the MTHR domain. 1298C alleles were reported of having a low enzyme activity, but not like 677T alleles.21 Some studies suggest that heterozygous individuals that are bearers of both alleles variants have a 40-50% higher enzymatic activity. Recent studies show that MTHR polymorphisms 1298A>C do not have a significant contribution towards homocysteinemia, neither as individual factor, nor

Table 2. Inherited primary hypercoagulable states (thrombophilia): epidemics and risk of venous thromboembolism (VTE)

<table>
<thead>
<tr>
<th>THROMBOPHILIA</th>
<th>PREVALENCE</th>
<th>RELATIVE RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>General population*</td>
<td>Patients with VTE</td>
</tr>
<tr>
<td>Antithrombin deficit</td>
<td>0.02-0.3</td>
<td>1-2</td>
</tr>
<tr>
<td>Protein C deficit</td>
<td>0.2-0.5</td>
<td>2-5</td>
</tr>
<tr>
<td>Protein S deficit</td>
<td>0.5</td>
<td>1-3</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>3-8</td>
<td>10-65</td>
</tr>
<tr>
<td>Factor II G20210A</td>
<td>1-6</td>
<td>3-8</td>
</tr>
<tr>
<td>Factor V Leiden and Factor II G20210A</td>
<td>0.1</td>
<td>–</td>
</tr>
</tbody>
</table>

* Statistics refers to the white population. The prevalence of Factor V Leiden and Factor II G20210A is below 0.1% in African, American and Asian populations.
** The relative risk for a first episode of VTE in homozygous patients with Factor V Leiden is up to 10 times higher (50-100).

Adapted from4
in combination with 677C>T polymorphism. However it shouldn’t be excluded when there is an important folate necessity, like pregnancy. Severe MTHR deficiency (<20% of enzyme) may lead to a clinical manifestation like homocystinuria.

MTHR polymorphisms are usually associated with hyper homocysteinemia. In pregnant women groups, this is a risk factor in determining neural tube defects and fetal loss.15-23

CLINICAL OVERVIEW

Primary hypercoagulable states associate predominantly venous thromboembolic complications. Deep vein thrombosis (DVT) of lower limbs and pulmonary embolism are the most common manifestations. Venous thrombosis of some rare sites include superficial thrombophlebitis and cerebral and mesenteric veins. Arterial thrombosis including coronary, cerebrovascular or peripheral circulation is not usually associated with hypercoagulable state. However, venous thrombosis can result from arterial occlusion by paradoxical embolism through a patent foramen ovale (4,24). Venous thrombosis is often a chronic condition with recurrence estimated to 5 to 7% annually after the first episode. Thrombophilia can be identified in about half of patients with venous thrombosis and appears to provide at least partially an explanation for a disease that was once hardly ever understood.25,26

Initial episode of venous thromboembolism (VTE) can occur at any age in patients with primary hypercoagulable states, but usually occurs in young adults. Family history of thrombosis is common. The risk of developing thrombosis varies in primary hypercoagulable states and is increased in antithrombotic-factor deficient patients (table 2); this risk is much higher when multiple prothrombotic mutations combine. Homozygous deficiency patients tend to have more severe thrombotic complications. Warfarin-induced skin necrosis occurs as a complication of anticoagulation therapy initiation in patients with heterozygous protein C or protein S deficiency. Since both proteins depend on vitamin K for proper functioning, their plasmatic levels in patients with inherited deficiencies may reach close to zero a few days after the start of warfarin therapy, an antagonist of vitamin K, and leads to a prothrombotic transient state and skin necrosis by dermal vasculature thrombosis. However, oral anticoagulant therapy has demonstrated long-term efficacy as antithrombotic prophylaxis in these patients.3,27,28

In most patients with primary hypercoagulable states, discrete thrombotic complications seem to be triggered by acquired prothrombotic phenomena (ex. pregnancy, use of oral contraceptives, surgery, trauma, immobilisation), many of which are secondary hypercoagulable states. For example, thrombosis complicates pregnancy, especially during the postpartum period in about 30-60% of women with antithrombin deficiency, 10-20% in those with protein C and S deficiency, and almost 30% in those resistant to APC (factor V Leiden), if anticoagulant prophylaxis is not administered during this period.4,29,30

Recurrent abortion is probably influenced by recurrent primary hypercoagulable states, but a certain association is not established, as it is with the antiphospholipid syndrome (secondary hypercoagulable state).

CONCLUSIONS

Although in the general population the incidence of thrombophilic defects may be low and the asymptomatic clinical overview may last for a lifetime, higher rates of such mutations in patients with a history of thrombosis show the importance of setting the correct diagnosis and how the anticoagulant therapy can reduce the risk of recurrent miscarriages.

REFERENCES