Acquired and Congenital Thrombo-Hemorrhagic Disorders: The Clinical Plot Has Thickened

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Abstract

Hemorrhagic and Thrombotic disorders, either congenital or acquired, constitute an important aspect of clinical practice. During the past, few decades several conditions characterized by the concomitant or sequential presence of both bleeding and thrombosis in the same patient (disseminated intravascular coagulation, Fibrinogen Defects, Thrombotic thrombocytopenic purpura, Antiphospholipids syndrome and Heparin induced thrombocytopenia) have been extensively investigated. Subsequently other conditions have been added to this chapter, namely: Myeloproliferative Diseases, acute promyelocytic leukemia, FV and FII polymorphisms. Recently, dysprothrombinemias, FIX abnormalities and liver cirrhosis have been also included. Therefore, the chapter of Thrombo-Hemorrhagic or Hemorrhagic-Thrombotic conditions have become an important subject involving several aspects of medicine. Of particular interest are the studies on dysprothrombinemias which have indicated that the same clotting factor may be associated either with a bleeding diathesis or a thrombotic condition according to the site of the mutation. It is conceivable that other clotting factors, for example FX may present the same pattern. These reports have considerable spurred research in the field and improved our knowledge of the clotting mechanism.

Introduction

Coagulation disorders have been known to be either hemorrhagic or thrombotic. For many decades, this was the accepted classification. In the early 1960s the attention of practicing internists and hematologists was first called to the disseminated intravascular coagulation (DIC) and to the thrombotic complications observed after replacement therapy in congenital a fibrinogenemia [1-4]. About three months later the heparin induced thrombotic thrombocytopenia was described (HIT) [5, 6]. In this condition too, symptoms were both thrombotic and hemorrhagic. Actually, thrombotic manifestations prevail in HIT contrary to what occurs in DIC where bleeding prevails. Thrombotic phenomena may follow or precede the bleeding in a sequential pattern. The clinical picture depends often on the time of observation. Myeloproliferative Disorders (MPD), Thrombotic thrombocytopenia purpura, Acute promyelocytic leukemia, Antiphospholipid antibodies syndrome (APAS), coumarin necrosis and other conditions were also added to the group [7-19].

Recently, congenital coagulation disorders concerning FII (Prothrombin) and FIX were described in which venous thromboses,
were reported to occur, rarely, together with bleeding and, often, without bleeding [20, 21].

These two latter conditions could also be included among the Thrombo-Hemorrhagic (T-H) conditions. This chapter has therefore increased its role and impact in the study and evaluation of coagulation disorders. Finally, there are conditions in clinical practice characterized by the concomitant presence in the same patient of thrombosis and bleeding (for example, thrombosis occurring after replacement therapy in patients with bleeding disorders or in patients bad-ridden because of a brain hemorrhage).

The purpose of the present Review is to deal in a systematic way with T-H disorders placing particular attention on the new and congenital defects. A review that dealt mainly with acquired vascular T-H diseases was published in 2001 [22].

Classification: A fundamental fact to be kept in mind is the frequent sequential behavior of events whereby thrombosis occurs first and then bleeding ensues or the reverse occurs.

Thrombotic phenomena at the beginning may be undetected whereas bleeding is always evident. In other conditions bleeding may be mild or even absent, such as that seen in APAS syndrome or in congenital FII or FIX abnormalities. Thrombohemorrhagic syndromes can be distinguished in Acquired and Congenital. For example, DIC and HIT are acquired whereas Prothrombin and FIX defects are congenital (Table 1).

The former involves both venous and arterial thrombosis whereas the latter show only venous thrombosis. Furthermore, the former is usually severe and occasionally lethal; the latter are less severe, safe for the potential event of pulmonary embolism. There is no age preference but the former affect both sexes whereas the latter show a bivalent behavior involving both sexes in case of prothrombin and FVII abnormalities and only male in the case of FIX (Hemophilia B).

A. Acquired forms

The acquired forms of T-H disorders have received considerable attention during the past two decades and will be dealt only briefly in this review.

I Disseminate intravascular coagulation (DIC)

DIC was the first one to be investigated and have been the object of extensive studies [1, 2, 23-27].

The condition has been repeatedly dealt with in the literature, during the past 40 years. It may be subdivided in an acute form (sepsis, acute promyelocytic leukemia) and in a chronic one (solid neoplasias). It may be subdivided in forms with hypofibrinolysis (sepsis), forms with hyperfibrinolysis (acute promyelocytic leukemia) and in those with normal fibrinolysis (solid tumors) [24].

Management depends on the stage in which the condition is recognized. Heparin is mainly indicated at onset during the thrombotic phase whereas replacement therapy mainly Fresh Frozen plasma (FFP) and clotting Factors concentrates are needed during the hemorrhagic phase. Several therapeutic guidelines have been suggested [27].

II Thrombo hemorrhagic syndrome during replacement therapy

Replacement therapy with FFP or clotting factor concentrates are occasionally associated, not only with the control of bleeding, but also with the appearance of both arterial or venous thrombosis.

The most dangerous concentrates are FEIBA, Fibrinogen or FXI concentrates and aFVII preparations [19-33]. The list of patients who had these thrombotic complications is large and involves most clotting factor deficiencies [34-36].

Today, most of the thrombotic complications occur with aFVII concentrates for their large, often unjustified and off label use, due to the purported definition of these concentrates as general or global hemostatic agents [28]. The concomitant or sequential presence of bleeding and thrombosis in these patients has to be considered as a form of T-H Disorder or Hemorrhagic-Thrombotic disorder.

Table 1: Thrombo-hemorrhagic disorders.

<table>
<thead>
<tr>
<th>Acquired</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Discriminated Intravascular coagulation (DIC)</td>
<td></td>
</tr>
<tr>
<td>2 Thrombohemorrhagic conditions during replacement therapy</td>
<td></td>
</tr>
<tr>
<td>3 Thrombosis and bleeding during anticoagulant therapies</td>
<td></td>
</tr>
<tr>
<td>4 Thrombotic thrombocytopenia purpura (TTP). Hemolytic Uremic Syndrome (HUS)</td>
<td></td>
</tr>
<tr>
<td>5 Antiphospholipids Antibodies Syndrome (APAS)</td>
<td></td>
</tr>
<tr>
<td>6 Heparin Induced Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>7 Liver cirrhosis</td>
<td></td>
</tr>
<tr>
<td>8 Myeloproliferative Diseases (MPD)</td>
<td></td>
</tr>
<tr>
<td>9 Acute promyelocytic leukemia</td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
</tr>
<tr>
<td>1 Coumadin necrosis</td>
<td></td>
</tr>
<tr>
<td>2 Abnormal prothrombins</td>
<td></td>
</tr>
<tr>
<td>3 Abnormal FIX (FIX Padua)</td>
<td></td>
</tr>
<tr>
<td>4 Fibrinogen defects</td>
<td></td>
</tr>
<tr>
<td>5 Factor VII defects</td>
<td></td>
</tr>
</tbody>
</table>

III Thrombohemorrhagic syndrome during anticoagulant therapy

It is a common clinical observation to assist a patient with thrombosis, usually venous, and a concomitant bleeding due to excess of anticoagulation. Another example is represented by an elderly patient immobilized for a brain hemorrhage who develops deep venous thrombosis in the legs due to the protracted immobilization. These are too cases of T-H diseases which have to be faced by the caring physician. In the first example one has to take into account the status of the patient,
the control of bleeding, the type of the defect before discontinuing the replacement therapy.

In the second case, the evolution of the brain hemorrhage is of paramount importance before starting anticoagulant therapy. Sometimes local antithrombotic measures may be sufficient. LMWH at low dosage may also be necessary.

IV Thrombotic thrombocytopenic purpura (TTP) and Hemolytic Uremic Syndrome (HUS)

Thrombotic thrombocytopenic purpura is an acute disease characterized by anemia, thrombocytopenia, arterial and capillary occlusions with multi organ involvement [32-40]. Hemolytic uremic syndrome is a clinical entity that has some similarity with the TTP. In this case bleeding, arterial thrombosis and renal failure prevail.

TTP is often due to ADAMTS13 acquired or congenital defects. The defective ADAMTS13 activity results in persistence of high molecular weight multimers (HMWM) of VW Factor in the circulation. Such HMWM cause thrombotic occlusions of several arterial and capillary vessels in several organs.

It can be seen from the above that medicinal properties are summarized on the basis of efficacy. However, there are deficiencies in the description of medicinal properties and efficacy still needs to be studied due to improper description, which makes the potency and efficacy of Chinese medicine not establish a good relationship.

Table 2: Variations of Bleeding and Thrombosis in T-H Disorders. Indications are only tentative.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Bleeding</th>
<th>Thrombosis</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>+++</td>
<td>++</td>
<td>Picture variable in time</td>
</tr>
<tr>
<td>Due to replacement therapy</td>
<td>+++</td>
<td>++</td>
<td>Bleeding conditions treated with clotting factor</td>
</tr>
<tr>
<td>During anticoagulant therapy</td>
<td>+++</td>
<td>++</td>
<td>Patients with Brain hemorrhage who develop Deep</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vein thrombosis</td>
</tr>
<tr>
<td>TTP-HUS</td>
<td>+-</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>APAS</td>
<td>+-</td>
<td>+++</td>
<td>Adrenal gland hemorrhage</td>
</tr>
<tr>
<td>HIT</td>
<td>+-</td>
<td>+++</td>
<td>Adrenal gland hemorrhage</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>++</td>
<td>+-</td>
<td>Portal Vein thrombosis</td>
</tr>
<tr>
<td>MPD</td>
<td>+-</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Acute promyelocitic leukemia</td>
<td>++</td>
<td>+-</td>
<td></td>
</tr>
<tr>
<td>Coumadin necrosis</td>
<td>+++</td>
<td>+++</td>
<td>Thromboses involve skin veins</td>
</tr>
<tr>
<td>Abnormal prothrombins</td>
<td>+-</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Abnormal FIX (FIX Padua)</td>
<td>No</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen defects</td>
<td>+++</td>
<td>+-</td>
<td>Thrombosis in afibrinogemia usually secondary to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>replacement therapy</td>
</tr>
<tr>
<td>FVII defects</td>
<td>+++</td>
<td>+-</td>
<td></td>
</tr>
</tbody>
</table>

VII Liver cirrhosis

Patients with liver cirrhosis are commonly believed to be prone to bleeding due to decreased Vik.K dependent factors, low platelets due to platelet sequestration by an enlarged spleen. However, it is not to be forgotten that these patients present often thrombosis of the portal vein. Therefore, the cirrhotic patient could represent a case of T-H disorders. Recently the prothrombotic states of cirrhotic patients has been the object of extensive investigations. These studies indicate that in cirrhotic patients there is an increased ratio between FVIII (which is often
increased) and Protein C (which is often decreased as the result of the liver failure). In the presence of this increased ratio, the anticoagulant effect of thombomodulin (TM) is impaired.

This results in a decreased activation of Protein C (PC) to activated Protein C (APC) and therefore in the appearance of a thrombophilic or prothrombotic state. This has been obtained in vitro by the determination of the endogenous thrombin potential (ETP) carried out in the absence or in the presence of added TM [22].

VIII Myeloproliferative Disorders (MPD) or myeloproliferative neoplasias (MPN)

This heterogeneous group of diseases or neoplasias provides a typical example of T-H syndromes. The problem concerns mainly Polycythemia Vera (PV) and especially Essential Thrombocythemia (ET).

In PV arterial or venous thrombosis prevail due to the increased blood viscosity. In ET, both bleeding and thrombosis occur. The increased number of platelets could indicate a potential risk of thrombosis. But this is not so because these platelets are defective and may impair the formation of an adequate clot. It is probably an expression of different stages of the disease: thrombosis being more frequent at onset when platelets are still efficient and bleeding more frequent when platelet count has become very high, over one million / μl. The main features of MPD is the involvement of arterial, capillary and veins [6-9].

IX Acute promyelocytic leukemia

Acute promyelocytic leukemia is a variant of acute myelogenous leukemia characterized by bleeding and thrombosis. The defect is due to a chromosomal alteration (usually a translocation between chromosomes 15 and 17). The condition has the peculiarity to be successfully treated with all trans retinoic acid (ATRA) and arsenic trioxide (ATO). The thrombotic manifestations accompanied by variable bleeding are present at the onset (about 4-5% of cases) but its prevalence seems to increase during or after the treatment.

Both venous and arterial thrombotic events such as deep vein thrombosis, myocardial infarction and ischemic stroke have been described. The pathogenesis is due to tissue factor release from the abnormal promyelocytes [18, 19] (Table 3).

The management of these patients includes Fresh Frozen Plasma (FFP), platelet concentrate administration and sometimes it has to include also LMWH as a prophylaxis against thrombosis [18, 19].

Table 3: Approximate prevalence of Type of thrombosis (arterial, capillary or venous) in H-H Disorders.

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Arterial Thrombosis</th>
<th>Capillary thrombosis</th>
<th>Venous thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>++</td>
<td>+++</td>
<td>+/-</td>
</tr>
<tr>
<td>Due to replacement therapy</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>During anticoagulant therapy</td>
<td>+--</td>
<td>+--</td>
<td>++</td>
</tr>
<tr>
<td>TTP-HUS</td>
<td>++</td>
<td>++</td>
<td>+--</td>
</tr>
<tr>
<td>APAS</td>
<td>+--</td>
<td>++</td>
<td>+--</td>
</tr>
<tr>
<td>HIT</td>
<td>+++</td>
<td>--</td>
<td>+--</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>++</td>
<td>--</td>
<td>+--</td>
</tr>
<tr>
<td>MPD</td>
<td>++</td>
<td>+--</td>
<td>+--</td>
</tr>
<tr>
<td>Acute premyelocytic leukemia</td>
<td>+--</td>
<td>+--</td>
<td>+--</td>
</tr>
<tr>
<td>Coumadin necrosis</td>
<td>++</td>
<td>+++</td>
<td>---</td>
</tr>
<tr>
<td>Abnormal prothrombins</td>
<td>--</td>
<td>--</td>
<td>+++</td>
</tr>
<tr>
<td>Abnormal FIX (FIX Padua)</td>
<td>--</td>
<td>--</td>
<td>+++</td>
</tr>
<tr>
<td>Fibrinogen defects</td>
<td>+++</td>
<td>++</td>
<td>+--</td>
</tr>
<tr>
<td>FVII defects</td>
<td>+--</td>
<td>--</td>
<td>+++</td>
</tr>
</tbody>
</table>

B. Congenital Forms

The congenital forms of T-H disorders represent a small part of the problem. However, they had an important role in stimulating research on blood coagulation. Furthermore, they have been less studied and are often only partly known. Finally, it is likely that new conditions will be discovered in the future.

I Coumarin Necrosis

This severe T-H condition should be classified among the congenital forms since it is almost always due to congenital deficiency of Prot. C or Prot. S. Thrombosis involves skin arteries and veins with consequent appearance of large ecchymotic areas involving mainly the limbs [14-17].

II Prothrombin abnormalities

Congenital prothrombin deficiency is one of the rarest coagulation disorders [47, 48]. Homozygotes or compound heterozygotes with FII
levels of less than 10% of normal, present a severe bleeding tendency. Complete absence of Prothrombin seems incompatible with life. Heterozygotes with FII levels around 40-50% of normal may present occasional bleeding during surgery or tooth extractions [49]. No thrombotic event has ever been reported in “true” Prothrombin deficiency [50].

On the contrary a few cases of prothrombin abnormalities or dysprothrombinemias have been associated with a thrombotic tendency [20, 51-53]. These patients have no bleeding tendency but their inclusions in this chapter is justified by the involvement of a clotting factor that is usually associated with bleeding.

These abnormal prothrombins show a gain of function towards antithrombin. Antithrombin (AT) is a small glycoprotein of a molecular weight of 58000 Dalton produced by the liver and circulating at a concentration of about 0.12 mg/ml. When coupled with heparin it exerts mainly an anti FII and anti FX activity. Without heparin the activity of antithrombin is markedly reduced. The increased resistance of these abnormal prothrombins (thrombins) to the action of AT creates a condition of prolonged thrombin activity which may cause thrombosis. The condition has been termed “antithrombin resistance” [20].

This is a new clinical entity characterized by a relative decrease of antithrombin (AT) activity due to the presence of abnormally resistant prothrombins (thrombins) which show a gain of function and have mutations in a special region of the molecule, encoded by exon 12, that is supposed to interact with AT. Due to these mutations the generation of the complex Thrombin-Antithrombin (T-AT) is defective whereby antithrombin activity is decreased, thrombin persists in the circulation and a thrombophilic state ensues.

The first prothrombin abnormality responsible for this effect was reported in 2012 (Prothrombin Yukuhashi) [20]. Subsequently other similar cases were published in Serbia, India and Italy [20, 51-53]. These families involve three different mutations on the same amino acid, Arginine596: Prothrombin Yukuhashi Arg596Leu, Prothrombin Belgrade Arg596Gln and Prothrombin Padua 2, Arg596Trp, Prothrombin Amrita has also an Arg596Gln mutation [20, 51-53].

Prothrombin Greenville shows an Arg517Gln mutation and a doubtful tendency but no thrombosis [54]. It is still unknown at what level of the codon sequence; a mutation can cause the shifting of a bleeding condition into a thrombophilic one. It is interesting to note that all these patients are heterozygotes for the mutation. This indirectly confirms the fact that homozygosis for prothrombin defects are very severe and sometimes incompatible with life [48, 49].

The main laboratory and clinical features of these patients are gathered in Table 4. All patients had venous thrombosis; there is no information about arterial thrombosis.

Table 4: Cases of Prothrombin abnormalities that cause antithrombin resistance and therefore cause a thrombophilic state. Het. = Heterozygote; n.r. = not reported. a) data supplied in “Correspondence”. N. Engl Med 2012; 367:1069-1070.

<table>
<thead>
<tr>
<th>Authors, Year</th>
<th>Age, Sex</th>
<th>FII Act</th>
<th>FII ant</th>
<th>Bleeding</th>
<th>Venous thrombosis (age at first episode)</th>
<th>Associated Risk</th>
<th>Mutation</th>
<th>Genotype</th>
<th>Eponym</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyawaki et al. (2012)</td>
<td>17, F</td>
<td>37.6</td>
<td>63.8</td>
<td>No</td>
<td>Yes (11 Years)</td>
<td>No</td>
<td>Arg596Leu</td>
<td>Het.</td>
<td>Prothrombin Yukuhashi</td>
<td>Patient from Japan</td>
</tr>
<tr>
<td>Djordeyevic et al. (2013) Fam 1 Fam 2</td>
<td>n.r., F n.r., F</td>
<td>n.r. n.r. n.r. n.r.</td>
<td>n.r. n.r.</td>
<td>Yes (17 years) Yes (16 years)</td>
<td>No No</td>
<td>Arg596Leu Arg596Leu</td>
<td>Het. Het.</td>
<td>Prothrombin Belgrade</td>
<td>Six patients in two families</td>
<td></td>
</tr>
<tr>
<td>Sivasundar et al. (2013)</td>
<td>60, M</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>Yes</td>
<td>n.r.</td>
<td>Arg576Gln</td>
<td>Het.</td>
<td>Prothrombin Amrita</td>
<td>No founds study</td>
</tr>
<tr>
<td>Kishimoto et al. (2016)</td>
<td>23, F</td>
<td>n.r.</td>
<td>n.r.</td>
<td>No</td>
<td>Yes (15 years)</td>
<td>No</td>
<td>Arg596Leu</td>
<td>Het.</td>
<td>Prothrombin Belgrade</td>
<td>Patient from Japan</td>
</tr>
<tr>
<td>Bulato et al. (2016) Fam. 1 Fam. 2</td>
<td>47, M 29, F</td>
<td>54 29</td>
<td>80 89</td>
<td>No No</td>
<td>Yes (38 years) Yes (27 years)</td>
<td>No No</td>
<td>Arg596Trp Arg596Trp</td>
<td>Het. Het.</td>
<td>Prothrombin Padua</td>
<td>Seven patients in two families</td>
</tr>
</tbody>
</table>
It is likely that other cases will be discovered. A clinical suspicion should arise from the following observations: 1) venous thrombosis in a young patient known to have no other prothrombotic defect (AT, Prot. C etc. deficiencies); 2) slightly decreased or borderline low prothrombin activity level; 3) Prothrombin antigen level higher than the activity counterpart; 4) positive family history for venous thrombosis. Needless to say, that genetic analysis is needed to confirm the suspicion.

The occurrence of thrombosis at a young age is of paramount importance. The mean age, excluding the case from India, is 20.1 (range 11-38). The patient from India had a venous thrombosis at the age of 60 [52]. Furthermore, there is no information about a familiar predisposition to thrombosis.

Recently a patient with dysprothrombinemia (Arg382His) with a severe bleeding tendency who developed Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) 28 day after delivery was described [55]. The patient had received weekly 600 Units of a Prothrombin Complex Concentrate (PCC), starting on the sixth week of pregnancy for bleeding therapy and prophylaxis for a total amount of approximately 20.400 Units [55]. This could be a case of thrombosis during replacement therapy or a hemorrhagic-thrombotic condition.

It is worth noting that so far, no abnormality of FX has been described which could generate an impairment in the activity of antithrombin with a consequent antithrombin resistance. On theoretical grounds the possibility that such mutation in the FX gene exist is fully plausible, and even likely.

**III T-H syndrome involving a FIX abnormality (FIX Padua)**

By a strict definition this condition should also not be included since no concomitant bleeding or a sequential thrombosis and bleeding is present in these patients [21]. However, its inclusion is justified by the fact that FIX, which is deficient in hemophilia B, is involved. An abnormal FIX characterized by an elevated FIX clotting activity in the presence of normal or only borderline increased antigen was described in a patient with venous thrombosis. The defect is X-linked and has been named FIX Padua [21]. The hemizygous mutation found in this patient is Arg338Lys in exon 8; a brother is similarly affected but is asymptomatic whereas the mother is a carrier and also asymptomatic [21].

**IV Fibrinogen defects**

Fibrinogen defects are usually divided in 1) Afibrinogemia 2) Hypofibrinogemia 3) Disfibrinogemia and 4) Hypodisfibrinogemia [56, 57].

Several dysfibrinogemias have been described. About 50% of them are asymptomatic, 25% show thrombosis and 25% bleeding. They are usually heterozygotes. The defect is due to: 1) an impairment of the transformation of fibrinogen in fibrin or 2) an impairment of the conversion of fibrin monomers in polymers [56]. Several mutations have been described. The Arg554Cys mutation has been reported in a few unrelated families with dysfibrinogemia and thrombosis [56]. These conditions have also to be considered as thrombohemorrhagic or hemorrhagic-thrombotic disorders [56-58]. In congenital afibrinogemia, thrombosis, mainly arterial, but also venous, occurs usually after replacement therapy, with fibrinogen concentrates or Fresh Frozen plasma (FFP). The same is true for hypofibrinogemia. Thrombosis is often massive and occasionally fatal. Because of these complications, replacement therapy requires extreme attention and sometimes the concomitant administration of heparin or another anticoagulant [59-61].

Contrary to what occurs in afibrinogemia thrombosis in Dysfibrinogemia may be spontaneous and is usually arterial [56, 57, 62].

**V Congenital FVII Deficiency**

Congenital FVII deficiency is the most frequent defect among the rare coagulation disorders. Its prevalence is estimated to be about 1:500.000 [63]. The main features of these autosomal recessive clotting disorders are represented by the lack of a correlation between FVII activity levels and bleeding manifestation. There are several reports of patients with low (<5% of normal) or very low (1% of normal) and only a mild bleeding tendency if any. Furthermore, it was demonstrated that thrombosis, mainly venous was non-exceptional in patients with FVII deficiency [63, 64]. Subsequently it was found that patients with a type II defect, namely conditions with low FVII activity but normal FVII level, were more prone to develop thrombosis. Some mutations (Arg304Gln and Ala294Val) were also indicated as to be more frequently related with the occurrence of thrombosis [65]. These mutations were all associated with the presence of normal levels of FVII antigen, they were Type II defects. In reality thrombotic events have been described rarely also in patients with Type I defects. Despite this limitation, the attention of research was focused on the Type II defects. It was also discovered that these patients showed little bleeding, if any. This had been noted in Afro- Americas carriers of the Arg304 mutation [66, 67].

The overall picture suggests that FVII defects could not protect from prothrombotic risk factors such as surgery, oral contraceptives, immobilization etc. [64]. So far, no specific unifying mechanism for the occurrence of thrombosis in FVII deficiency has been established [64, 65].

A plausible speculation might be that in the presence of FVII antigen the Tissue Factor (T.F.). aFVII complex can be only partly downregulated or neutralized by the Tissue Factor Pathway Inhibitor (TFPI). The defective action of this inhibitor could cause a prolongation of the activity of the TF-aFVII complex with consequent occurrence of a thrombophilic state.

**Discussion and Conclusions**

The new acquisitions on congenital forms, mainly the dysprothrombinemias, that may present thrombotic events, besides the expected bleeding, have increased the significance of T-H disorders. They represent surely a minor part of the problem being rare, but they have added important information to the understanding of the intricacies and complexity of blood coagulation.

These congenital forms are associated only with venous thrombosis whereas the acquired conditions involve often arteries, capillaries and
veins. The latter are therefore more severe and involve several organs and tissues and may be fatal.

Due to variable prevalence of thrombosis or bleeding in some forms and vice versa in others, the former could be termed Thrombotic-Hemorrhagic Syndromes whereas the latter could be defined as Hemorrhagic-Thrombotic. However, this may be of little value since it is known that the clinical observation of such prevalence may vary with time and depends on the evolution of the process. The importance of congenital forms will probably increase with time as demonstrated by FIX Padua and by FVII defects studies.

The strict relation existing between bleeding and thrombosis is well demonstrated by what occurs in DIC and APS or HIT. DIC is known to cause a diffuse intravascular clotting with consequent depletion of platelet and clotting protein and the onset of bleeding.

On the contrary, the adrenal gland hemorrhage seen in APS and HIT may be envisaged as the result of a local (adrenal vein) occlusion with secondary upstream stasis, rupture of vessels, bleeding and endocrine failure [41-43]. The inclusion of FVII defects among the H-T conditions should be of no surprise. It was known that about 4% of patients with this defect presented thrombotic events [63]. Recent studies have confirmed this finding, but it remains to be clarified the underlying mechanism even though it seems that the Type II defects, namely those with low FVII activity but normal antigen are specifically affected [65]. It is also plausible, that a FX abnormality with a resistance to antithrombin might be discovered.

Since antithrombin is supposed to neutralize both FII and FX, there is no reason to suppose that only resistant prothrombin (thrombin) exist. The same may occur for FX. Due to the genetic similarities existing between FIX and FVIII, it is also conceivable that an abnormal FVIII associated with high levels of activity will be discovered. This possibility is supported by the observation that families with elevated FVIII levels and venous thrombosis have been reported [68]. However no genetic explanation has been supplied so far. The recent studies on prothrombin and FX have considerably amplified the chapter of T-H conditions. Since they have added a congenital, hereditary dimension to the subject.

They have also demonstrated that known clotting factors may cause both bleeding and thrombosis according to the site of the mutation.

Congenital deficiency of FII or FIX are associated with variable, but usually severe bleeding. Mutation in certain areas of the FII or FIX gene are instead associated with thrombosis, usually venous. This is a remarkable observation because it changes completely our usual approach to the study of clotting factors [20, 21].

Finally, as a further demonstration of the great significance of the thrombohemorrhagic mechanism in medicine we cannot abstain from indicating that such a pathogenesis has been recently postulated to play a role also in Alzheimer’s disease [69].

This study was supported in part by the “Associazione Emofilia ed altre coagulopatie delle Tre Venezie”

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

6. Amiral J, Bidey F, Dreyfus M, Vissoc AM, Fressinaud E, et al. (1992) Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thromb Haemost 68: 95-96. [Crossref]
10. [No authors listed] (1993) Thrombosis and thrombocytopenia in antiphospholipid syndrome (idiopathic and secondary to SLE): first report from the Italian Registry. Italian Registry of Antiphospholipid Antibodies (IR-APA). Haematologica 78: 313-318. [Crossref]


25. Ito T (2014) PAMPs and DAMPs as triggers for DIC. J Intensive Care 2: 67-70. [Crosstref]


