

# Clinical aspects of venous thrombophilia

Antonio Girolami, Fabrizio Fabris, Bruno Girolami

University of Padua Medical School, Department of Medical and Surgical Sciences, Second Chair of Medicine, Padua, Italy.

## Abstract

Venous thrombophilia is the result of clotting changes namely of a hypercoagulable state together with blood flow and vessel wall changes. There is no need for all these components to be present in order for thrombosis to occur. As the matter of fact, thrombosis may occur even if only one of these conditions is present. In clinical practice a combination of factors is usually seen. In comparison with arterial thrombophilia, clotting changes and blood flow seen to play a major role in venous thrombosis. Venous thrombophilia may remain asymptomatic or may result in a series of clinical syndromes. The commonest of these are:

1. Superficial vein thrombosis
2. Deep vein thrombosis of legs
3. Deep vein thrombosis of arms
4. Caval veins thrombosis
5. Portal vein thrombosis
6. Hepatic veins thrombosis
7. Renal vein thrombosis
8. Cerebral sinuses thrombosis
9. Right heart thrombosis
10. Miscellaneous (ovarian, adrenal veins thrombosis, etc.)

Since the first two are widely and easily recognized, there is no need for an extensive discussion. Deep vein

thromboses of upper limbs are not as frequent as those of lower limbs or of superficial phlebitis but they can still be recognized on clinical grounds and non invasive techniques. The remaining 7 syndromes are less common and therefore less frequently suspected and recognized. Of particular interest, among these less common manifestations of venous thrombophilia are hepatic vein and renal vein thrombosis. Hepatic vein thrombosis, sometimes part of inferior vena cava thrombosis is most frequently due to an isolated occlusion of hepatic veins thereby causing a form of venocclusive disease. Occasionally diagnosis may be difficult because of slow onset of symptoms (hepatomegaly, right flank pain, fever, ascitis etc.). The same is true for renal vein thrombosis which may also be of difficult diagnosis since it causes proteinuria and flank pain. The proteinuria is often interpreted as due to a nephrotic syndrome which, incidentally, may be caused by its renal vein thrombosis. Portal vein thrombosis and cerebral sinuses thrombosis on the contrary are more easily suspected because of ascitis, abdominal pain, jaundice or headache, eye proptosis, vomiting. Right heart thrombosis should be suspected in cases of recurrent pulmonary embolization. Ovarian or adrenal vein thrombosis are rare. The competent physician should always consider, given certain congenital or acquired

conditions, the possibility to be facing a special form of venous thrombosis or a venous thrombosis in unusual sites. An early diagnosis, as often in medicine, is of paramount importance for a prompt treatment and a satisfactory outcome.

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Venous thrombophilia is the result of clotting changes namely of a hypercoagulable state together with blood flow and vessel wall changes. The terms hypercoagulable state and thrombophilia therefore are not synonymous and should not be used interchangeably (1-3). There are several types of hypercoagulability, namely due to: 1) activation of contact phase 2) increased levels of coagulation factors (ex FVII or FVIII) 3) decrease of inhibitors and 4) inhibition of fibrinolysis (2,4-7). Sometimes more than one of these changes are present in the same individual. Therefore, thrombophilia is a more complex condition as compared to hypercoagulability which is only part of it. There is no need for all these components to be present in order for thrombosis to occur. As the matter of fact, thrombosis may occur even if only one of these conditions is present. In clinical practice a combination of factors is usually seen. In comparison with arterial thrombophilia, clotting changes and blood flow seem to play a major role in venous thrombosis. Clotting changes may be characterized by an increase in the levels of activity, by the lack or malfunctioning of inhibitors (2, 8-11) or by a decreased fibrinolysis (2, 4, 8-10). Unfortunately there is a discrepancy between the laboratory tests available for the study of the hypercoagulable states and those available to evaluate the presence of blood flow and/or endothelial damage (2). Endothelial lesions are particularly difficult to evaluate. This may explain why some venous thrombosis may occur even in the presence of a normal blood coagulation. In this case the culprit should be looked for, if possible, in the evaluation of blood flow and in the study of the venous wall. It has to be remembered that decreased blood flow is regulated by the simplified formula  $F=AP/h$  where AP is the pressure gradient existing between two points of a given vessel and h is the blood viscosity. In the pathogenesis of venous thrombosis the impact of blood viscosity is often underestimated (2). This is wrong since in some patients an increase in blood viscosity is often present (polycythemia vera, dehydration, Hb abnormalities, stress-induced increase in HT, etc.). These conditions, even minor, if persistent, given certain associated circumstances such as congenital clotting defects, may cause thrombosis.

Venous thrombophilia may remain asymptomatic or may result in a series of clinical syndromes. The commonest of these are:

1. Superficial vein thrombosis
2. Deep vein thrombosis of legs and arms

3. Hepatic veins thrombosis
4. Renal veins thrombosis
5. Portal vein thrombosis
6. Caval veins thrombosis
7. Cerebral sinuses thrombosis
8. Right heart thrombosis
9. Retinal vein thrombosis
10. Miscellaneous (ovarian vein thrombosis, adrenal vein thrombosis, etc.)

Since the first two are widely and easily recognised, these is no need for an extensive discussion. Therefore for these two aspects of venous thrombophilia only most important data will be dealt with in this regard.

## 1. Superficial vein thrombosis

This is probable the most common thrombotic manifestation.

It is usually associated with varicose veins and the post-phlebitis syndrome due to a previous deep vein thrombosis. The cause may be chronic and relapsing with further worsening of a pre-existing post-phlebitic syndrome. It is rarely associated with pulmonary embolism but for the forms which involve proximal great saphena vein close to the cross and its merger with the deep femoral vein.

Superficial vein thrombosis of upper limbs are usually secondary to i.v. administration of antitubercular drugs, in-dwelling catheters for parenteral feeding, traumas.

## 2. Deep vein thrombosis

Deep vein thrombosis (DVT) may be subdivided in upper limb and lower limb thrombosis. The site of the DVT is divided in proximal or distal, in both limbs.

Lower limb venous thrombosis are common and constitute the bulk of anticoagulated patients. Altogether, they are the most frequent manifestation of venous thromboembolism and also are the most extensively studied. Main causes are known: congenital thrombophilic conditions, traumas, surgery, cancer, immobilisation from any cause (stasis), oral contraceptives therapy, pregnancy, puerperium, splints, casts, central catheter nutrition.

The usual features of the condition are well known. Peculiar features are the following: proximal vein thrombosis of legs are associated with an increased risk of pulmonary embolism, upper limb thrombosis may be indicative of a mediastinal tumor, cancer associated deep vein thrombosis of lower limbs are often bilateral. The relation between deep vein thrombosis and pulmonary embolism is a complex, still not completely clarified, one. It has to be remembered that about 30% of patients with proximal DVT of legs have overt or

covert pulmonary embolism. Conversely about 30% of patients with overt pulmonary embolism have no detectable DVT of limbs. In the latter case venous thrombosis of pelvic veins is often the culprit.

It has to be remembered that still today about 40% of DVT appear to be idiopathic, namely without an apparent either congenital or acquired predisposing conditions. This may be an artifact since these venous thrombosis may be due to a still unknown clotting defect or to acquired conditions which went unnoticed or were underestimated.

The diagnosis of idiopathic deep vein thrombosis is a difficult but a very important one.

In fact, as a well known paraneoplastic syndrome, it is strongly associated with occult cancer (11, 12). Therefore once a diagnosis of idiopathic deep vein thrombosis is made, the need for a careful follow up is clearly established.

The remaining syndromes are less common and therefore less frequently suspected and recognized.

### **3. Hepatic veins thrombosis**

Hepatic veins thrombosis, sometimes part of inferior vena cava thrombosis, is most frequently due to an isolated occlusion of hepatic veins thereby causing a form of venocclusive disease (13-15). Occasionally diagnosis may be difficult because of slow onset of symptoms (hepatomegaly, right flank pain, fever, ascitis etc.). Main causes of hepatic vein thrombosis are: congenital thrombophilic conditions, vena cava thrombosis, antituberculous drugs, alkaloids found in certain beans or leaves (bush tea), abdominal neoplasias, recent bone marrow transplantation, pregnancy or puerperium.

The condition needs prompt attention and immediate therapy.

Suspicion should arise, in the presence of the above mentioned predisposing conditions, whenever the patient presents abdominal pain, enlarging liver, anorexia, ascitis.

U.S., MRI or CT are useful for the diagnosis. If standard anticoagulation therapy fails, liver transplantation may be considered.

### **4. Renal vein thrombosis**

This form may also be of difficult diagnosis since it causes proteinuria and flank pain. The proteinuria is often interpreted as due to a nephrotic syndrome which, incidentally, may cause by its turn renal vein thrombosis (13, 15, 16).

The most common renal vein thrombosis is the chronic form secondary to nephrotic syndrome. There are other acute forms in children and in adults. The relationship between nephrotic syndrome and renal vein thrombosis is not clear yet. It seems likely that nephrotic syndrome causes vein thrombo-

sis and not viceversa. The loss of AT and other inhibitors with the heavy proteinuria seem to play an important role in the pathogenesis. Sometimes it may be associated with thrombosis of the inferior vena cava.

Congenital deficiencies of clotting inhibitors may also be responsible for the occurrence of renal vein thrombosis in the absence of nephrotic syndrome. Acute forms are typical in infants because of dehydration. Acute forms of renal vein thrombosis in adult women are usually secondary to extension from ovarian vein thrombosis secondary to puerperium.

### **5. Portal vein thrombosis**

Portal vein is formed by the merging of the splenic vein with the superior mesenteric vein, the inferior mesenteric vein ending usually at the area of the confluence of the two. Portal vein thrombosis may be secondary to any abdominal disease (acute appendicitis, pancreatitis, ileitis etc.) and post surgical procedures (13, 15). However liver cirrhosis and myeloproliferative diseases are common causes of portal vein thrombosis. Some forms appear to be idiopathic. The conditions can be suspected on the basis of abdominal pain, appearance or worsening of ascitis, appearance or worsening of splenomegaly, fever, worsening of dyspepsia, appearance of bloody ascitis.

US, CT or MRI are useful to confirm the diagnosis. Therapy is not fully standardised yet, but the use of heparin and/or coumadin are the usual procedures. Removal or control of underlying condition, when possible, is of paramount importance.

### **6. Caval thrombosis**

Superior vena cava thrombosis is usually associated with lung or mediastinal tumors.

It may sometimes originate as an extension of a jugular or subclavian veins thrombosis.

Vein distension of the neck and arms and a variable oedema involving face, neck and arms are the most frequent clinical findings. Inferior vena cava thrombosis may be associated with renal vein or hepatic veins thrombosis.

The clinical presentation varies with the level of obstruction, being more and extensive in occlusion occurs above the hepatic veins. In this case hepatomegaly, signs or symptoms of renal stasis and oedema of legs are present.

### **7. Cerebral sinuses thrombosis**

Cerebral sinuses represent a peculiar venous system which allows drainage of blood from the brain and skull into the jugular veins system.

The central part is represented by the cavernous sinus which may be equated to a large, low flow vein in the center of the head. Other potential areas of thrombosis are the superior sagittal sinus which continues on each side in the transverse sinus and the sigmoid sinus which may also be the site of thrombosis. The latter, at the exit of the skull, becomes the jugular vein.

Main cause are: congenital thrombophilic states, APA syndrome, trauma, brain or cranial surgery, oral contraceptives, myeloproliferative conditions (13, 15).

Diagnosis may be difficult. Headache and papilledema are present in about 50% of cases. Fever is present in about 25% of cases. A high level of suspicion is of paramount importance particularly in the absence of focal signs. The lack or rarity of focal signs in a patient with headache, mental confusion and papilla oedema should immediately raise the suspicion. The presence of such findings and symptoms in a woman on oral contraceptive therapy usually allows to establish the correct diagnosis.

## 8. Right heart thrombosis

Right heart has to be considered as part of the venous system. Thrombosis of this area is often due to extension into the right atrium of caval vein thrombosis. Alternatively may be secondary to right heart acute endocarditis as seen in i.v. drug users (13, 15, 17).

The clinical picture is often characterised by multiple pulmonary embolization which is the case of endocarditis associated with i.v. drug use. This may evolve into a picture of multiple pulmonary abscesses.

## 9. Retinal veins thrombosis

Thrombosis of retinal veins is not rare and its recognition seems on the rise. It has been associated with several acquired conditions, but very rarely, apparently, in congenital thrombophilia. The idiopathic form seems more frequent.

Since the central retinal vein drains into the cavernous sinus, the possibility of an extension into such cerebral sinus has to be always taken into due consideration.

A prompt diagnosis is mandatory. Variable visual disturbances: dark spots, diplopia, ambliopia are common. Thrombosis of branches of central vein have also to be considered in this chapter and are usually associated with the same signs and/or symptoms even though less severe. The condition is usually unilateral. Fluorangiographic studies are useful. Patients benefit from the usual anticoagulant treatment (SH or LMWH plus coumarin medication). Nothing or little is known yet about the evolution of this thrombosis. Residual variable visual defects are common.

## 10. Miscellaneous

Ovarian vein thrombosis and adrenal vein thrombosis may be included in this group (13, 15, 18).

Ovarian vein thrombosis is almost always a post-partum complication. It is rarely associated also with pelvic inflammatory disease, pelvic surgery and post-abortion sepsis and pelvic surgery. In the past diagnosis was difficult if not impossible and usually made at exploratory surgery.

Patients show, early in the post-partum period, low abdominal pain, tenderness, flank pain, fever, tachycardia. The picture is similar to that of endometriosis. Differential diagnosis may be impossible for woman known to have had in the past such condition. The diagnostic role of d-dimer has not been clarified yet. Sonography, C.T. and MR are supposed to play an important role.

Adrenal vein thrombosis is a rare condition.

It causes secondary adrenal haemorrhage and adrenal gland incompetence. It has been described in heparin-induced thrombocytopenia and in APA sometimes.

Diagnosis is difficult: vague abdominal pain and hypotension may be present together with decreased cortisol levels.

## Conclusions

A clear understanding of all clinical and laboratory conditions predisposing to thrombosis should be part of the cultural background of every physician.

A venous thrombosis may be an isolated self-limited episode or it may be part of a more complex occult condition. It may in fact indicate an occult cancer, a myeloproliferative disease, a congenital prothrombotic defect.

The distinction between idiopathic and secondary thrombosis as mentioned above, is of paramount importance (2, 11). This includes, on the part of the caring physician, the need to exclude both known congenital predisposing conditions (AT, PC, PS deficiency, FV Leiden etc) and all known acquired conditions (casts, oral contraception therapy, etc.). However, one has to remember that still unknown clotting defects may exist and also that minor acquired but undetected conditions potentially predisposing to thrombosis may play a role (minor stasis, minor endothelial lesions, etc.).

The concept of idiopathic venous thrombosis is therefore a temporary and a changing one. The number of idiopathic venous thrombosis has considerably shrunk in recent years and it may further diminish in the future. Today, unfortunately, at least 40% of venous thrombosis have still to be considered as idiopathic. The best cure for a secondary thrombosis, besides the proper anticoagulant treatment, is the elimination of the condition that has caused the thrombosis to occur. Unfortunately this is feasible only in some of the instances. If not, continuous anticoagulation is indicated. A continuous

alert on the part of the caring physician is needed together with the understanding that, as often in medicine, a prompt diagnosis is of paramount importance for an adequate treatment and a satisfactory outcome.

This is more so if one takes into account that the prompt diagnosis of a venous thrombosis in usual or unusual sites may lead, with appropriate screening and investigation, to the diagnosis of an underlying disease.

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