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Review

Portal vein thrombosis in adults: pathophysiology, pathogenesis and management

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Pathophysiology

Portal vein obstruction can result from one or several of the following 3 mechanisms: thrombosis, invasion by a malignant tumor (mainly hepatocellular carcinoma) and constriction within a malignant tumor (adenocarcinoma of the pancreas or bile ducts). Compression in the absence of thrombosis, invasion or constriction does not produce portal vein obstruction. Usually, the vein passes round the space-occupying lesions. Clinically, portal vein thrombosis represents an almost pure form of portal vein obstruction.

The consequences of portal vein thrombosis are related to the extension of the thrombus. Upstream from the thrombus, there is little effect on the intestine as long as the mesenteric venous arches remain patent. Ischemia results from extension of the thrombus into the mesenteric veins and the mesenteric venous arches (1). It is likely that thrombosis of the arches prevents them from functioning as a collateral circulation to drain intestinal blood toward the adjacent patent territories. Alternatively, reflex arteriolar vasoconstriction might occur when the arches are thrombosed (1). When ischemia is prolonged for several days, intestinal infarction may follow. In 20–50% of the cases, intestinal infarction is responsible for death due to peritonitis and multiple organ failure, even when resection of the infarcted gut is carried out (1–3). Extensive intestinal resection due to venous thrombosis is one of the main causes of the short bowel syndrome. Short bowel stenosis can be a late sequela of mesenteric venous ischemia (4).

Downstream from the portal vein thrombus, the consequences for the liver are hardly discernible (5–8). Clinically, signs of liver disease are absent or transient (unless thrombosis occurs in a patient with cirrhosis). Biochemically, serum albumin level and prothrombin time ratio usually remain within low normal values, while serum bilirubin is normal. Histologically, there is little alteration in liver architecture when the obstruction is limited to the extrahepatic portal vein and its largest intrahepatic branches. However, there are indications of a deleterious influence of portal vein thrombosis on the liver. Experimentally, apoptosis of the liver cells can be demonstrated in rats with graded portal vein ligation (9). The degree of apoptosis is related to the grade of portal vein obstruction. There is a simultaneous increase in mitotic activity in the remaining well-perfused liver. Similar findings have been observed clinically following embolization of a portal vein branch to induce atrophy of the embolized lobe and hypertrophy of the other lobe in order to augment the tolerance of extensive liver resection (10). These subtle alterations in the liver may explain why, in particular circumstances (gastrointestinal bleeding or infection), transient signs of decompensated liver disease may develop (5).

There are two explanations for the fact that interruption of portal blood flow, which accounts for two thirds of total hepatic blood flow, has few clinical consequences. A first compensatory mechanism is the arterial "buffer" response, which consists of immediate vasodilation of the hepatic arterial bed in response to a decreased portal vein flow. This mechanism has been well demonstrated experimentally, but also in patients following portal vein clamping at hepatic surgery (11). The second compensatory mechanism is a rapid development of collateral veins bypassing the thrombosed portion of the portal vein (12). The development of these veins becomes visible within a few days. These collateral veins eventually make up the cavernoma, which was given this name because it was initially considered an anfractuous vascular tumor and thereafter a developmental anomaly in children. Collateral veins develop within the walls or at the periphery of the

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structures adjacent to the obstructed portion of the portal vein: bile ducts, gallbladder, pancreas, gastric antrum, duodenum. The collateral veins may alter the aspect of these structures at imaging and, occasionally, this will lead to erroneous diagnoses of bile duct or pancreatic tumor, pancreatitis or cholecystitis. In addition, bile duct varices may cause obstructive jaundice (13).

As a result of arterial buffer response and development of the cavernoma, total hepatic blood flow is only minimally reduced, at least in patients in stable condition (14). Portal pressure, however, is increased (14). The increase in portal pressure can be viewed as a compensatory mechanism allowing portal perfusion to be maintained through the collateral veins. In other words, portal perfusion is maintained at the expense of portal hypertension and, eventually, gastrointestinal bleeding from varices or portal hypertensive gastropathy. It is worth noting at this point that ruptured varices may belong to the portosystemic collateral circulation (in the esophagus and the gastric fundus) or to the portal cavernoma (in the gastric antrum and the duodenum). A hyperkinetic circulation similar to the one associated with cirrhosis, albeit of a smaller degree, is associated also with portal vein obstruction (14).

Pathogenesis

According to a recent hypothesis, venous thromboses in general occur only when several factors are combined (15). These factors comprise inherited or acquired prothrombotic disorders, other thrombophilic factors, and local factors. Prothrombotic disorders are characterized by features of coagulation activation, while thrombophilic factors refer to a more general tendency to thrombosis. *Inherited* prothrombotic disorders can be classified into 2 subgroups (Table 1) (16). The first one includes the long-identified deficiencies in protein C, in protein S and in antithrombin. The prevalence of these anomalies in the general Caucasian population is low (below 4/1000) and the associated relative risk of thrombosis in the heterozygous state is high (around 10). The second subgroup of inherited disorders includes conditions which were identified only recently despite being common in the general population (prevalence above 2%), and which are associated with a somewhat lower relative risk of thrombosis (2 to 8) (15). The *acquired* prothrombotic disorders and thrombophilic factors can likewise be separated into 2 subgroups, as depicted in Table 1, according to their prevalence and their associated relative risk of thrombosis.

This general multifactorial theory seems to apply well to portal vein thrombosis. In our current experience (17), general thrombophilic factors are identified in approximately 60% of patients with portal vein thrombosis, and local factors in 40%. In all patients with a local factor and most patients using oral contraceptives, a general prothrombotic condition is demonstrated. The main prothombotic disorders which, in our experience, are identified in association with portal vein thrombosis are presented in Table 2. The evidence implicating estroprogestative compounds and pregnancy is weak. This point has not been extensively investigated.

The *local* factors explain why in the course of a chronic and generalized (but latent) state of thrombophilia, thrombosis develops suddenly in the portal venous sytem. These local factors can be classified into 3 categories (Table 3). A first category refers to con-

TABLE 1

States of thrombophilia

Inherited prothrombotic disorders
Uncommon disorders (associated with a high risk of thrombosis)
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Common disorders
Factor V Leiden mutation
Factor II G20210 mutation
Acquired disorders
Uncommon disorders (associated with a high risk of thrombosis)
Primary myeloproliferative disorders
Antiphospholipid syndrome
Paroxysmal nocturnal hemoglobinuria
Common conditions
Oral estroprogestative contraceptives
Pregnancy and post-partum
Inflammatory states
Malignancy
Hyperhomocysteinemia

TABLE 2

Prevalence of etiological factors simultaneously investigated in 36 patients with portal vein thrombosis (adapted from ref. 17)

Etiological factor	%	95% confidence interval
Primary myeloproliferative disorder	22	9–36
Prothrombotic coagulation disorder	42	26–58
Primary myeloproliferative disorder plus prothrombotic coagulation disorder	8	0.7–17
Specific coagulation disorders		
Antiphospholipid syndrome	4	0.8–21
G1691 factor V gene mutation	3	0–8
G20210A factor II gene mutation	14	3–25
C677T MTHFR gene mutation	11	0.8–21
Protein S deficiency	30	11–49
Protein C deficiency	0	–
Antithrombin deficiency	4	0–8

TABLE 3

Local factors favoring or precipitating development of portal vein thrombosis

Local inflammatory lesions
Neonatal omphalitis
Diverticulitis
Appendicitis
Pancreatitis
Duodenal ulcer
Cholecystitis
Tuberculous lymphadenitis
Injury to the portal venous system
Surgical portacaval shunting
Splenectomy
Colectomy
Gastrectomy
Cancer of abdominal organs
Cirrhosis
Preserved liver function (splenectomy, portacaval shunting, thrombophilia)
Terminal liver disease

ditions characterized by local inflammation with or without a systemic inflammatory response. It is likely that the local or general prothrombotic state associated with inflammation plays a large role in precipitating thrombosis in this setting. Several particular conditions falling into this category merit additional comments. Neonatal thrombosis is well documented following omphalitis or umbilical vein cannulation complicated by septic phlebitis. However cannulation of the umbilical vein in the absence of sepsis or prothrombotic disorder is unlikely to play an important role (18). First manifestations of neonatal portal vein thrombosis can be delayed until adulthood. Septic portal vein thrombosis, the so-called septic pylephlebitis, is usually related to appendicitis or diverticulitis. It is so strongly associated to *Bacteroides bacteremia* that *Bacteroides bacteremia* of unknown origin should prompt the search for portal or mesenteric vein thrombosis (19). Portal vein thrombosis associated with chronic pancreatitis is related to compression by a pseudocyst or to acute pancreatitis in more than 90% of the cases (20).

A second category of local factors refers to operations that, intentionally or not, involve injury to the portal venous system. As a rule, this type of operation does not precipitate portal vein thrombosis unless there is an associated prothrombotic state or portal hypertension (21–23).

A third category refers to cancer of abdominal organs. Cancer may lead to thrombosis of the portal vein through a combination of cancer-related prothrombotic changes (24) and either compression or surgical injury. A more common mechanism of cancer-related portal vein obstruction is tumorous invasion or constriction.

A fourth category relates to cirrhosis. It is difficult to regard cirrhosis *per se* as a cause of portal vein thrombosis. Surveys of cirrhotic patients without hepatocellular carcinoma and in good condition showed a low prevalence of portal vein thrombosis (23). By contrast, studies performed at necropsy or in transplant candidates showed a much higher prevalence of portal vein thrombosis (25). It is a common experience to observe partial, spontaneously resolving, thrombi in the portal vein of patients with terminal liver failure and stagnant portal flow. In our experience, portal vein thrombosis occurring in patients without cancer and in good condition is usually associated with a prothrombotic condition. Therefore we conclude that cirrhosis should be considered only as a local factor.

To sum up, general thrombophilic factors should be investigated, even when a local factor for portal vein thrombosis is evident. Conversely, a local factor should be investigated even when a systemic thrombophilic factor is obvious. When portal vein thrombosis is discovered at a late stage, identification of the local factor becomes difficult if not impossible.

Management

Unfortunately, the natural history of portal vein thrombosis is unknown. In all the reported cohorts, many patients received some form of treatment for portal hypertension or for thrombophilia. In our cohort of adult patients with non-tumorous, non-cirrhotic portal vein thrombosis, we have analyzed the outcome after adjustment for those treatment variables (26) and we have found that the incidence of gastrointestinal bleeding was 17% patient-years (i.e. 17 episodes of gastrointestinal bleeding would have occurred in a group of 100 similar patients followed up for 1 year, or in a group of 50 similar patients followed up for 2 years). The size of esophageal varices was the main independent predictive factor for bleeding. We also found that the incidence of recurrent thrombosis, affecting mainly the portal venous system, was one third of that of gastrointestinal bleeding. The main independent predictive factor for recurrent thrombosis was an underlying documented prothrombotic condition. Mortality was low, about 5% in the average follow-up of 5 years. The cause of death was related to portal vein thrombosis in only half the cases. Based partly on these findings, the following recommendations can be proposed for the management of patients with portal venous thrombosis.

Diagnosis should be suspected in many different situations: abdominal pain, abdominal sepsis, gastroin-

testinal bleeding due to portal hypertension, fortuitous finding of portal hypertension (spleen enlargement, decreased blood cell counts, endocopic features). An accurate diagnosis is now allowed by duplex or color Doppler-ultrasound, and computed tomography (27,28). These non-invasive, or minimally invasive, procedures have permitted an earlier recognition of portal vein thrombosis in the setting of unexplained abdominal pain.

The next step following diagnosis should be to try to determine when thrombosis developed. Thrombosis can be considered recent when a thrombus is visible within the lumen of the portal vein and when there are no or minimal portoportal or portosystemic collateral veins. Computed tomography is most useful in this regard because spontaneous high luminal density prior to any contrast medium injection indicates a thrombus dating back to less than 10 days (28). Conversely demonstration of a well-developed cavernoma usually indicates an old thrombosis. An old portal vein thrombosis, however, can later be associated with a recently superimposed thrombus, this recent thrombus being responsible for the acute manifestations which lead to imaging studies.

The third step in management should be an investigation of the factors favoring or precipitating thrombosis. The purpose of this investigation is to identify a condition amenable to treatment. Investigation of the local factors is based mainly on abdominal computed tomography with contrast medium injection. It can be completed by endoscopic ultrasound in some cases. Barium X-ray studies and endoscopy in our experience rarely uncover an intestinal disease that was not clinically evident. Investigation of general thrombophilic factors must be extensive because an association of several factors is the rule rather than the exception (17). Some of these factors, such as myeloproliferative disorders, should be systematically investigated because they are commonly associated although their exploration need special procedures. Other factors are less commonly associated to portal vein thrombosis but they are easy to document and should therefore also be systematically investigated: the coagulation factor gene mutations, the natural coagulation inhibitor deficiencies, the antiphospholipid syndrome. Primary myeloproliferative disorders can manifest themselves as an overt form of polycythemia vera or essential thrombocythemia. Frequently, however, the peripheral blood picture is not suggestive. Indeed, portal hypertension can be responsible for: gastrointestinal blood losses leading to iron deficiency; increased plasma volume leading to a dilution of circulating blood cells; and hypersplenism. These forms of myeloproliferative disorders could be depicted as masked. In addition, there are occult or latent forms of myeloproliferative disorders which are not accompanied by suggestive peripheral blood changes and, yet, are associated with an increased risk of thrombosis. These myeloproliferative disorders include agnogenic myeloid metaplasia and the so-called *formes frustes* in myeloproliferative disorders. The latter are characterized by the spontaneous formation of erythroid colonies at culture of the circulating or bone marrow precursors in the absence of added erythropoietin to the culture medium (29). A similar test has also been developed for spontaneous colonies of megakaryocytes. These tests currently seem very specific. At least in the setting of portal vein thrombosis, they also appear to be much more sensitive than the conventional criteria (30,31). Where these tests are not easily available, diagnostic information can also be obtained using isotopic determination of the total red cell volume coupled with determination of serum erythropoietin, provided that iron deficiency has been corrected (29). Bone marrow biopsy is another means to demonstrate primary myeloproliferative disorder when the peripheral blood picture is not suggestive, but this procedure is too invasive to serve as a screening procedure. The antiphospholipid syndrome is diagnosed when high titers of antiphospholipid antibodies are found on two separate occasions or when a lupus anticoagulant is demonstrated. Determination of anti-β2 glycoprotein 1 antibodies may be both more sensitive and more specific than the first two tests (32). Interpretation of the results of antithrombin, protein C and protein S is particularly difficult in the context of portal vein thrombosis because their plasma level may be non-specifically decreased whenever there is slight liver insufficiency or coagulation activation (33,34). Therefore, comparisons with the results of prothrombin determination and familial studies are necessary before the conclusion of a primary (inherited) deficiency can be reached. Factor V Leiden mutation can be assessed directly using molecular technics or indirectly by evaluation of the resistance to activated protein C (15,16). Determination of factor II G20210A mutation uses molecular technics (15,16). Hyperhomocysteinemia is difficult to ascertain once portal vein thrombosis has developed because the plasma level is dependent on liver function. The allele C677T of the methylene tetrahydrofolate reductase gene is associated with an increased plasma homocysteine (15,16), but its not clear whether this genetic marker alone is as good a marker for the increased risk of thrombosis as plasma homocysteine level.

When a portal cavernoma has been recognized, portal hypertension can be postulated. Gastrointestinal

lesions that may be a source of bleeding need to be identified for adequate prophylactic measures to be taken. There has been no study specifically addressing the particular case of portal vein thrombosis. However, the available uncontrolled data indicate that the measures that are of established efficacy in patients with cirrhosis in good condition, namely propranolol (35) and endoscopic therapy (36), can be applied to patients with portal vein thrombosis. The place of surgery and the optimal type of operation is still being debated. A shunting procedure that would efficiently and permanently decompress the portal venous system with a low risk of encephalopathy would appear ideal. In particular, it would allow more general use of anticoagulant therapy (see below). Unfortunately, the risk of shunt thrombosis or stenosis is predictably high. Indeed, several precipitating factors are often present: underlying thrombophilia, surgery for portal hypertension, and splenectomy. Only the largest veins (superior or inferior mesenteric veins or splenic veins) should be used because of the high risk of thrombosis of the shunts using smaller veins. Because it leaves the spleen in place, distal splenorenal shunt appears most suited (37). Unfortunately, the splenic vein is frequently involved in thrombosis. Splenectomy and the Sugiura procedure have also been used (38). In desperate cases, total gastrectomy or esophagogastrectomy have been carried out (39). In our experience propranolol or nadolol in the first line and endoscopic therapy in the second line have permitted satisfactory prevention of recurrent bleeding despite the concurrent use of anticoagulant therapy in many patients.

Therapy for active gastrointestinal bleeding should, likewise, follow the guidelines for patients with intrahepatic portal hypertension. There is, however, a matter of concern about the use of vasoconstrictive agents. Theoretically, the profound decrease in splanchnic blood flow induced by bleeding and by the therapeutic vasoconstrictive agents might trigger recurrence or favor the extension of thrombosis in the portal venous system and precipitate intestinal ischemia. Indeed, peripheral vasopressin infusion has been reported to cause portal and mesenteric vein thrombosis, leading to intestinal ischemia in bleeding cirrhotic patients (40). Although we are not aware of any reported case documenting such a deleterious effect in patients with previous portal vein thrombosis, preference might be given to endoscopy as first-line hemostatic procedure. Therapy for ischemic intestinal injury should include aggressive resuscitation measures, anticoagulation, and surgery (41).

The issue of anticoagulant therapy is a central one. Recent and old portal vein thrombosis must be considered separately. The effects of early anticoagulant therapy on the outcome of recent thrombi has been reported only in a few small series of consecutive patients (42,43). We have recently presented in a preliminary form the findings from a combination of these experiences and of our own (44). To what extent spontaneous repermeation can be expected is not well known. Current experience suggests that spontaneous repermeation is possible but uncommon, whereas complete or extensive repermeation can be achieved with anticoagulant therapy in more than 80% of the patients. Repermeation prevents ischemic intestinal injury in the short term and extrahepatic portal hypertension in the long term. Therefore, like others (42,43), we recommend that anticoagulant therapy be given for at least 6 months, and then be continued if an underlying thrombophilia has been demonstrated or be stopped in the other cases. In the particular context of septic pylephlebitis, antibiotic therapy should be added (19); repermeation can follow efficient antibiotic therapy in the absence of anticoagulant therapy. Is there a place for aggressive therapeutic procedures such as thrombolytic agents (43) or emergency transjugular intrahepatic stent shunt placement coupled with fibrinolysis (45) for portal vein thrombosis of recent onset? Current data are insufficient to evaluate the benefit/risk ratio of these procedures. Turning to old portal vein thrombosis with portal hypertension due to cavernous transformation, the safety of anticoagulant therapy should be considered first. In a preliminary retrospective analysis of our cohort (26), we found that anticoagulant therapy increased neither the risk of gastrointestinal bleeding nor the severity of bleeding (as assessed by blood hemoglobin level on admission, volume of blood transfused or duration of hospital stay). This finding was confirmed in further analysis of the data from a larger cohort with a longer follow-up (unpublished data). There were no deaths due to bleeding on anticoagulant therapy. Moreover, we found in this further analysis that recurrent thrombosis, particularly in the portal venous sytem, was efficiently prevented. Therefore there is mounting evidence of an interesting benefit:risk ratio with anticoagulant therapy. It is too early, however, to advocate indiscriminate use of anticoagulant agents in patients with old portal venous thrombosis. Caution is needed in extrapolating the findings from this retrospective study because selection or treatment biases cannot be completely excluded. Review of experience in other centers in the first place, and a controlled therapeutic trial in the second place are needed. At present, however, there are patients for whom antigoagulant therapy should be considered without waiting. These are the patients who have a

documented thrombophilia that is not amenable to another therapy and who can be predicted to be at low risk of bleeding on anticoagulant therapy (age under 50 years; esophageal varices that are small or absent; and no potentially hemorrhagic extrasplanchnic lesions).

In conclusion, portal vein thrombosis should be considered as a clue to the presence of one or several prothrombotic disorders, whether or not a local precipitating factor has been identified. Early anticoagulation is followed by repermeation in a majority of the cases. In the absence of repermeation, the development of portal cavernoma allows maintenance of portal blood supply at the expense of portal hypertension. Despite the risk of gastrointestinal bleeding, anticoagulant therapy may be beneficial in patients with portal cavernoma.

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