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Review article: portal vein thrombosis – new insights into aetiology and management

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SUMMARY

Portal vein thrombosis may occur in the presence or absence of underlying liver disease, and a combination of local and systemic factors are increasingly recognized to be important in its development. Acute and chronic portal vein thrombosis have traditionally been considered separately, although a clear clinical distinction may be difficult. Gastrooesophageal varices are an important complication of portal vein thrombosis, but they follow a different natural history to those with portal hypertension related to cirrhosis. Consensus on optimal treatment continues to be hampered by a lack of randomized trials, but recent studies demonstrate the efficacy of thrombolytic therapy in acute thrombosis, and the apparent safety and benefit of anticoagulation in patients with chronic portal vein thrombosis.

INTRODUCTION

The management of portal vein thrombosis (PVT) has been complicated by a lack of randomized controlled trials in the area, the clinical difficulty of differentiating acute from more chronic disease, and perceived risks of anticoagulant therapy. Over the last few years, the aetiology of PVT, including the role of inherited and acquired prothrombotic factors, has been better defined, and large case series have improved our understanding of the natural history of this condition, particularly with regards to bowel infarction and the merits of therapy. These advances allow a reappraisal to be made of the approach to treatment of patients with PVT, possibly tailored for the individual patient according to the duration and aetiology of the disease. Increasing evidence supports the use of early thrombolytic therapy in patients with acute PVT, and of the relative benefit and safety of oral anticoagulation in the management of chronic PVT. The focus of this review will be on PVT in the absence of cirrhosis, although reference will be made to the aetiology and clinical features of PVT in patients with chronic liver disease.

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AETIOLOGY, PATHOGENESIS

Portal vein thrombosis refers to the development of thrombosis within the extrahepatic portal venous system draining into the liver. Anatomically PVT may be classified into four categories: (i) thrombosis confined to the portal vein beyond the confluence of the splenic and superior mesenteric vein (SMV); (ii) extension of thrombus into the SMV, but with patent mesenteric vessels; (iii) diffuse thrombosis of splanchnic venous system, but with large collaterals; (iv) extensive splanchnic venous thrombosis, but with only fine collaterals.[1] Whilst this anatomical classification is

mainly applicable to issues of operability, it may also be of aetiological and prognostic relevance, as those patients with thrombus involvement of the mesenteric vasculature carry a higher risk of bowel infarction and a lower risk of variceal bleeding, than those with isolated PVT.[2] Bowel infarction is an important cause of mortality in patients with thrombosis of the portal venous system.[3]

Both local and systemic factors may contribute to the development of PVT (Table 1). Disruption of portal blood flow may occur due to a range of causes, including local tumour compression or inflammation. Although pancreatitis has been identified as the cause of PVT in only 1% of cases in the study by Condat *et al.*,[3] at least temporary PVT has been shown by colour Doppler ultrasound in 23% of patients with acute pancreatitis (57% in those with pancreatic necrosis).[4] 'Sinistral' portal hypertension, with localized thrombosis of the splenic vein, occurs in 7% of patients with chronic pancreatitis.[5] PVT follows splenectomy in 6–8% of cases,[3, 6] but other interventions, including local ablative therapy for hepatocellular carcinoma[7, 8] and fine-needle aspiration of a pancreatic mass[9] have also been linked with its development.

PVT is an important complication of cirrhosis, with incidences in those with well-compensated disease reported between 0.6 and 16%.[10–12] An increased frequency is seen in those with decompensated disease, and in up to 35% of cirrhotic patients with hepatocellular carcinoma,[13] in whom the thrombosis may also be due to extension of the tumour.

Systemic or general factors associated with PVT include inherited prothrombotic disorders, acquired haematological diseases associated with thrombosis, and miscellaneous factors including sepsis. Early reports suggested an association with intra-abdominal or systemic sepsis in nearly 40% of patients with PVT,[14] in particular in children who had undergone neonatal umbilical vein catheterization.[15] Although more recent studies have not found as a high frequency,[16] abdominal sepsis has been identified as a risk factor in 11% of PVT cases in a recent large retrospective study.[3] The apparent strong association of *Bacteroides fragilis* infection with PVT has led to a recommendation that this complication should be excluded in all cases where *B. fragilis* bacteraemia of unknown origin has been demonstrated.[17, 18] The transient development of anticardiolipin antibodies has been suggested as the pathophysiological link between *Bacteroides* sp. infection and PVT.[19]

Over the last decade significant advances have been made in identifying prothrombotic predispositions in patients with thromboses in a range of vascular beds, including the portal venous system (Table 2). Genetic polymorphisms, including factor V Leiden and G20210A prothrombin gene mutations[20, 21] may be important in PVT. Acquired causes also play a role, and Valla and Condat have found evidence of overt or latent myeloproliferative disorders in 48% of cases of isolated PVT.[18] Although other groups have reported a lower figure,[22] the number of cases of truly 'idiopathic' PVT appears to be falling, with an underlying cause identified in 80% of patients who are rigorously investigated. In those patients with an identified cause, general thrombophilic factors account for 60% of cases, and local factors for 40%.[20] Nevertheless, it appears that isolated systemic or local risk factors infrequently lead to PVT. Despite the relatively high prevalence of inherited prothrombotic tendencies in the population (3% carriage of factor V Leiden mutation and 2% carriage of prothrombin gene mutation in Holland[23]), PVT remains a rare complication in the non-cirrhotic population. There is increasing awareness of the importance of multiple factors contributing to the

Table 1. Aetiology of portal vein thrombosis

Cirrhosis/portal hypertension
Prothrombotic tendency (see Table 2)
Malignancy (local/distant)
Sepsis (local/systemic)
Schistosomiasis
Pancreatitis
Postsurgical (e.g. liver transplantation, splenectomy)
Umbilical vein catheterization
Portal vein compression by nodes (e.g. TB, lymphoma)
Drugs (e.g. oral contraceptive)
Pregnancy/post-partum

Table 2. Prothrombotic factors associated with portal vein thrombosis

Myeloproliferative disorders (e.g. polycythaemia rubra vera, essential thrombocytosis, myelofibrosis)
Antiphospholipid syndrome
Anticardiolipin antibody
Protein C, S, antithrombin III deficiency
Factor V Leiden deficiency
G20210A prothrombin gene mutation
Hyperhomocysteinaemia
Paroxysmal nocturnal haemoglobinuria

development of venous thrombosis.[24] In support of this hypothesis, a study of 700 cirrhotic patients showed the presence of a genetic thrombophilic predisposition in 70% of patients with PVT, with a fivefold higher frequency of the G20210A prothrombin gene mutation in patients with PVT, compared to those without.[25] In patients with PVT or Budd-Chiari syndrome, more than one prothrombotic tendency was found in 40% of cases.[23] In patients undergoing splenectomy, the presence of cirrhosis or a myeloproliferative disorder increases the risk of subsequent PVT to 13–18%.[26, 27]

CLINICAL ASPECTS OF PVT

The presentation of PVT has been divided into the two broad clinical categories of acute or chronic PVT. These categories are somewhat arbitrary, and it may in clinical practice be difficult to distinguish between the types. However, although either condition may present with symptoms related to the underlying disease, particular clinical features enable a distinction to be made in most cases between those patients with recent-onset PVT, and those with chronic disease. No definitive time-frame distinguishes acute from chronic PVT, but studies of the former have considered patients who developed symptoms <60 days prior to hospital assessment.[28]

The typical presentation of acute PVT is with abdominal pain, nausea and fever. The severity of symptoms may correlate with the extent of mesenteric venous thrombosis, because of associated bowel ischaemia,[29] and up to 10% of cases of bowel ischaemia are due to mesenteric venous thrombosis.[30] The acute onset of ascites may also be seen in this syndrome. In a patient with proven PVT the absence of clinical, endoscopic or radiological evidence of portal hypertension may also suggest that the thrombosis is of recent onset. The aetiology of acute PVT is similar to that of chronic PVT, although associated sepsis is more commonly reported.[31] The natural history of acute PVT is uncertain, in part because of medical intervention. Significant variations in mortality of 0–76% have been reported,[29] with a poor prognosis associated with bowel infarction. Spontaneous resolution of acute PVT undoubtedly occurs, as suggested by the high rate of temporary PVT in acute pancreatitis. The proportion of patients with symptomatic acute PVT who later develop complications related to chronic thrombosis has not been established. Perhaps due to an increased clinical awareness of acute PVT, improved imaging, and the potential for treatment, this pattern of disease appears to be increasingly diagnosed. In a retrospective review of 141 patients with PVT, recent-onset PVT was diagnosed in only 7% of cases before 1990, and 56% of cases after 1994.[31]

Established or chronic PVT most frequently presents with problems related to portal hypertension, including gastrointestinal bleeding, splenomegaly and hypersplenism. Ascites rarely occurs in the absence of established liver disease, except in the elderly, in whom an erroneous diagnosis of cirrhosis may be made. In a retrospective study of 172 adult patients with established PVT, the overall 10 year survival was 54%, but this figure increased to 81% in those without cirrhosis, cancer or mesenteric vein thrombosis. Concomitant disease was a more important cause of death than variceal bleeding (6% of deaths), even in those who presented with variceal bleeding.[16] In the 83 patients without malignancy or mesenteric thrombosis, only one died from variceal bleeding. There certainly appears to have been a significant reduction in variceal bleeding related deaths in patients with PVT over the last 20 years. In patients followed during the period of 1960–1989, bleeding related deaths occurred in 13–20% of patients with PVT,[14, 22] compared with 1–2% in studies from 1983 to 1998[3] and 1984 to 1997.[16] Although the relatively short period of follow-up in the latter studies might partly explain the difference, improvements in the management of acute bleeding may also have been important. However, despite the low mortality from variceal bleeding, this remains an important complication. It is the presenting problem in approximately 30% of patients with PVT not related to established liver disease, and the most common complication during the natural course of the disease. Large varices are an independent risk factor for bleeding in patients with PVT, as is the case for those with liver disease and portal hypertension. However, although the varices are often large, and with red signs, the frequency of bleeding in patients with PVT (12.5 episodes per 100 patient-years,[3, 16] approximating to 0.25% over 2 years) appears to be far less than in cirrhotics with similar variceal characteristics (20–30% bleeding over 2 years of follow-up[32]). This strongly suggests that the severity of the liver disease is the principal cause of the increased bleeding risk, although the lower rate in those with isolated PVT might also be due to the effect of an associated prothrombotic

tendency. It also reiterates the fact that in patients with PVT in association with cirrhosis, the prognosis is more dependant on the underlying liver disease, than the PVT *per se*.

It is increasingly recognized that abnormalities of the extrahepatic biliary tree may occur in more than 80% of patients with chronic PVT who develop a portal 'cavernoma' (mass due to a leash of collateral vessels related to thrombosed portal vein).[33, 34] Various mechanisms for these abnormalities have been suggested, including biliary compression by choledochal or periportal varices, external compression by the cavernoma, pericholedochal fibrosis, or ischaemic stricturing.[35–38] Complications occur in <30% of cases, but may include jaundice and cholangitis because of biliary stricturing by external compression, or choledocholithiasis,[34, 39] and cholecystitis because of cavernoma involvement of the wall of the gall-bladder. A hilar mass may be seen on imaging, which comprises a leash of collateral vessels and inflammatory tissue,[40] and the appearances at ERCP (endoscopic retrograde cholangiography) may be confused with those of cholangiocarcinoma.[41] Haemobilia due to rupture of choledochal varices may also occur, either spontaneously or as a result of endoscopic intervention.[42]

In children, PVT may be associated with growth retardation.[43]

Investigation

A range of imaging modalities may be used in the diagnosis of PVT. An accurate diagnosis is made in most cases using colour Doppler-ultrasound, contrast-enhanced computerized tomography (CT) scanning, or magnetic resonance angiography,[44] precluding the need for other effective, but more invasive, techniques, including carbon dioxide portography[45] or intra-arterial digital subtraction angiography.[46] CT scanning may be more useful than ultrasound in demonstrating portosystemic collaterals and the development of a cavernoma, both suggestive of well-established PVT.[18] Endoscopic ultrasound has recently been shown to be 81% sensitive, and 93% specific in the diagnosis of PVT, in patients whose diagnosis was confirmed by CT or surgery.[47] Non-invasive imaging is less reliable at diagnosing thrombus extension into the mesenteric vasculature.

If an underlying local cause for PVT is established (e.g. pancreatitis, cirrhosis), there is rarely a clinical need to search for other cofactors. Where no local cause is found, investigation of a systemic cause is indicated, and will include exclusion of a myeloproliferative disorder and a prothrombotic tendency (see Table 2). This is important, as specific treatment may be required for the underlying condition (e.g. polycythaemia), and the finding of a prothrombotic tendency may influence decisions concerning the use and duration of anticoagulation.

Treatment

It is important to clarify the goal of therapy for PVT. As a means to reduce PVT-associated morbidity and mortality there are two broad intentions: (i) to reverse or prevent the advancement of thrombosis within the portal venous system, and (ii) to treat the complications of established PVT, most specifically gastrointestinal varices or biliary complications.

Studies of the management of portal hypertension have mainly involved patients with cirrhosis, as 30% with compensated, and 60% with decompensated disease, have varices.[48] Over the last two decades the management of gastro-oesophageal varices, including the use of primary and secondary prophylaxis for bleeding, and the treatment of acute bleeding, has been better defined (for review see Ref.[49, 50]). Both B-blockers (±nitrates) and endoscopic therapy have been shown to reduce the rate of first variceal bleed in those with at least moderate sized varices compared with no prophylaxis, and recent studies have suggested that variceal band ligation (VBL) is as effective as B-blockade for the prevention of a first bleed[51, 52] when both treatments have been directly compared. Endoscopy and VBL remain central to the acute management of variceal bleeding. In the secondary prevention of variceal bleeding, both B-blockers ± nitrates and VBL have been shown to reduce the rate of rebleeding, with recent randomized studies showing similar outcomes[53–55] In patients with PVT, complete endoscopic eradication of varices following an initial bleed has been shown to significantly reduce the risk of recurrent bleeding, with a 5 year survival of 95% and no mortality related to recurrent bleeding.[56]

The only randomized trial which was specific to patients with portal hypertension in PVT relates to the management of acute variceal bleeding. In this study from India, where extrahepatic portal vein obstruction in children is more common than in the West, the

effectiveness of endoscopic sclerotherapy and VBL were compared.[57] Initial endoscopic control of bleeding was achieved in all 49 cases, with subsequent variceal eradication performed in 92% using sclerotherapy, and 96% using VBL. These findings reiterate the relatively benign nature of variceal bleeding in patients with isolated PVT,[58] when one considers the 20% mortality from a variceal bleed in patients with underlying liver disease.[48, 59] No studies have addressed the role of primary or secondary prophylaxis on bleeding complications in patients with PVT, but there may be a theoretical argument for favouring endoscopic therapy over B-blockade. Sluggish portal vein flow, as seen in cirrhotics with portal hypertension, may predispose to PVT, particularly in the presence of other prothrombotic tendencies. By reducing splanchnic blood flow further B-blockade might encourage thrombotic progression, but this is unproven, and B-blockers are known to be effective for variceal bleeding prophylaxis in general. Concern has also been raised about the use of vasoconstrictors (e.g. terlipressin) for acute variceal bleeding related to PVT, because of the theoretical risk of inducing thrombus extension, again as a result of marked reductions in splanchnic blood flow.[18] Although this scenario has not been reported in patients with established PVT, the development of PVT has been reported in association with the use of vasopressin for variceal bleeding.[60]

The question of anticoagulation in patients with PVT is a crucial one, and the evidence for its benefit for recent-onset/acute PVT and established thrombosis may be considered separately. Again there are no randomized trials of its use in either pattern of disease. The effectiveness of anticoagulation in patients with evidence of acute PVT has been reported in a number of small studies and case reports.[61, 62] In a retrospective study of recent PVT, recanalization occurred in 25 of 27 patients given anticoagulation, but in 0 of 2 who received none.[31] Although the rate of spontaneous recovery of vein patency is not known, these studies suggest that anticoagulation may result in recanalization in more than 80% of cases. Thrombolytic therapy, given either into the systemic venous circulation,[63] the superior mesenteric artery[64, 65] or into the portal vein via a transjugular[66] or transhepatic route,[67, 68] has also been reported to lead to resolution of acute PVT. In patients who develop acute PVT before or after liver transplantation, transjugular intrahepatic portosystemic shunt (TIPSS) insertion, with subsequent anticoagulation, has been shown to result in recanalization.[69, 70] Thrombosis in the SMV can also be disrupted, provided that the thrombus is not too long.[70] It is probable that TIPSS should be reserved for cases where anticoagulation fails, but it has a definite role in acute bleeding when endoscopic therapies are ineffective, and possibly in sinistral portal hypertension if the splenic vein thrombosis can be disrupted.

The available evidence suggests that treatment should be considered in patients in whom a diagnosis of acute PVT is made. There is no trial data on whether initial thrombolysis should be given in preference to anticoagulation, but retrospective reports of patients with acute PVT have shown high rates of recanalization with thrombolysis compared with conservative treatment,[28] and thrombolysis has been shown to be effective when initial heparin therapy has failed.[63] In those reports in which initial heparin therapy has been given this has usually been followed by oral anticoagulants. The duration or degree of anticoagulation (i.e. optimal INR [International Normalised Ratio]) has not been standardized. As a result, it may be pragmatic to adopt the management algorithm as applied to deep vein thromboses in the lower limb.[71] Where a self-limiting cause for acute PVT has been identified (e.g. acute pancreatitis, abdominal sepsis) a finite treatment course of 3–6 months, with maintenance of the INR at 2–3 may be appropriate. In those patients in whom a prothrombotic tendency is identified, and/or an ongoing local predisposition to PVT, there may be advantage in continued anticoagulation. Extensive thrombosis, including involvement of the splanchnic bed, may also justify long-term treatment. Although the absence of comparative studies prevent a definitive view being made of the relative merits of thrombolysis compared with anticoagulation in acute PVT, it appears clearer that the sooner the treatment is given the better the outcome. In a recent retrospective analysis of 28 patients who received thrombolysis for acute PVT, recanalization and rapid improvement in clinical parameters was seen in the 10 patients who received treatment within 14 days of first symptoms. The effectiveness of thromobolysis was significantly reduced in those treated after this period.[28]

Considerably more controversy has surrounded the role of anticoagulation in patients with chronic PVT. Large variation exists between clinicians in the use of anticoagulants in this setting with studies reporting <30% usage, and often intermittently. This variability undoubtedly reflects concern about the use of anticoagulation in

the setting of gastro-oesophageal varices. The study by Condat *et al.* of 136 adults with PVT, but no cirrhosis or malignancy, has recently shed light on the role of anticoagulation in established PVT. The cohort was followed for a median of 46 months, and 84 received anticoagulants. In total, 84 bleeding episodes occurred in 42 patients.[3] There was no difference in the bleeding rate, haemoglobin level on admission in bleeders, or subsequent transfusion requirement, between those patients taking, and those not taking, anticoagulation. It is not clear from the data whether those on anticoagulation were in a better risk group, with less comorbidity, than those who were not anticoagulated, or whether they had previously bled from varices. Nevertheless, neither of the bleeding-related deaths in their study occurred in patients on warfarin. Interestingly, the use of anticoagulant therapy was associated with a significant reduction in new thrombotic episodes, either within the portal venous bed or other systems. Eight cases of mesenteric venous infarction were reported, none of which occurred in adequately anticoagulated patients. These findings support those of Janssen *et al.*, who found that reduced survival on follow-up was associated with prior evidence of mesenteric vein thrombosis, and not a history of variceal haemorrhage.[16] In the absence of randomized-controlled trials, they provide supportive, albeit not definitive evidence, for the benefit of anticoagulation in non-cirrhotic patients with chronic PVT. This benefit appears to be obtained through the prevention of thrombus propagation, and without an increase in variceal bleeding. Nevertheless, a pragmatic approach, particularly in the patient with chronic PVT who presents with bleeding varices, may be to endoscopically eradicate the varices prior to commencing anticoagulation.

Although good results from operative porto-systemic shunting for extrahepatic PVT have been reported from dedicated units,[72] earlier reports of high mortality in surgical patients,[14] in conjunction with the low observed mortality associated with bleeding, and effective medical/endoscopic therapy, has led to a broad consensus that shunt surgery for PVT has little role to play. However, new approaches to surgical treatment, including the creation of a splanchnic-intrahepatic portal bypass, have shown promise,[73] and surgical shunts have been shown to increase growth potential in children with PVT.[74] In patients with PVT associated with splenomegaly and clinical features of hypersplenism, splenectomy may be of benefit. Surgical devascularization of gastro-oesophageal varices has been reported as being safe and effective in patients with PVT (certainly in comparison with this approach in patients with underlying liver disease),[75, 76] but should rarely be necessary, in view of the availability of endoscopic approaches to controlling acute and recurrent variceal bleeding.

Despite the high prevalence of bile duct abnormalities in patients with PVT, intervention is only indicated in those with clinical manifestations of biliary obstruction. Surgical management of strictures (e.g. with hepatico-jejunostomy) is associated with high morbidity and mortality, because of the collateral vessels around the bile duct and in the porta hepatis,[77] and is not used as first-line treatment. Decompression of the hypertensive portal venous system, with either TIPSS[78] or surgical porto-systemic shunting,[78] has been shown to reduce biliary stricturing, presumably through a reduction in the size of choledochal varices. Endoscopy is the principal therapy used to treat biliary obstruction because of PVT. Although bleeding has been reported in association with balloon dilatation of biliary strictures,[79] and on stent removal,[80] endoscopic therapy in patients with choledochal varices appears safe, and biliary sphincterotomy does not appear to be associated with a significantly increased risk.[80] Studies have demonstrated the effectiveness of long-term biliary stenting for benign bile duct strictures,[81] and the few case reports and small cohort studies of patients with biliary obstruction because of PVT suggest that it is also safe and beneficial in this setting.[80]

CONCLUSION

Our understanding of the aetiology, natural history, and treatment options for extrahepatic PVT have improved over the last few years. The recognition that multiple risk factors, including inherited and acquired thrombophilic predispositions, are involved in the majority of cases merits a methodical search for these, as their identification may influence management. The prognosis from variceal bleeding in non-cirrhotic patients with PVT is good, and it is hoped that advances in the management of varices, including endoscopic eradication and primary and secondary prophylaxis with drugs, may improve outcome further. In particular, recent data suggest that the perceived risks of anticoagulation therapy in patients with chronic PVT may be overstated, and that new consideration should be given to this treatment, particularly in those at risk of thrombus extension, as mesenteric infarction is an important cause of death.

Large cohort studies have improved our understanding of the disease and its treatment, but a clear consensus on the optimal management of patients with PVT is unlikely to be reached in the absence of evidence derived from much-needed randomized-controlled trials. These will need to be coordinated in a multicentre setting, because of the relative rarity of the condition.

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