Prothrombotic disorders in abdominal vein thrombosis

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ABSTRACT

Abdominal vein thrombosis is a rare, but potentially life-threatening form of venous thrombosis. It mainly involves the hepatic veins (Budd Chiari syndrome, BCS), portal veins (PVT) and mesenteric veins. In recent years several large-scale studies have been performed to study the underlying aetiiological factors in these thrombotic disorders. Both inherited and acquired thrombophilia factors are frequently observed in these patients. Factor V Leiden mutation is frequently found in patients with BCS and prothrombin gene variant is seen more frequently in PVT. Myeloproliferative neoplasms (MPNs), including polycythemia vera and essential thrombocythemia, are underlying disorders in 30-40% of patients with abdominal vein thrombosis. Other aetiological factors are paroxysmal nocturnal haemoglobinuria (PNH), autoimmune disorders and hormonal factors. Recently, several new risk factors have been reported and are discussed in this review. BCS and PVT are multi-factorial disorders. In nearly 50% of patients two, and in 16% even three prothrombotic risk factors were found at presentation. Because patients with abdominal vein thrombosis have a high risk of recurrence immediate anticoagulant treatment is necessary. The duration of treatment is still a matter of debate because these patients also have a high risk of bleeding, especially those with portal hypertension. For BCS patients life-long anticoagulant treatment is advised. In patients with PVT it is recommended to tailor treatment to the individual patient based on the presence of an underlying prothrombotic disorder and the risk of bleeding.

KEYWORDS

Portal vein thrombosis, Budd Chiari syndrome, thrombophilia, splanchnic vein thrombosis, thrombosis, myeloproliferative neoplasm

INTRODUCTION

Abdominal vein thrombosis or splanchnic vein thrombosis is a rare, but life-threatening form of venous thrombosis and includes hepatic vein thrombosis (Budd-Chiari syndrome, BCS), portal vein thrombosis (PVT) and mesenteric vein thrombosis (MVT). The splanchnic venous system consists of the portal vein and its branches that direct blood flow from the gastrointestinal organs to the liver. The portal vein is formed by the union of the superior mesenteric vein and the splenic vein, and subdivisions into a left and right branch, which are segmentally distributed throughout the liver. The terminal portal venules drain into the sinusoids, after which the blood flows from the small to large hepatic veins, ultimately reaching the inferior vena cava. Thrombosis can occur in the hepatic veins or the portal veins and sometimes extends to the mesenteric veins. BCS and PVT are the two most frequent manifestations of superficial venous thrombosis (SVT), and simultaneous involvement of these venous systems may occur.1 BCS is defined as an obstruction of the hepatic venous outflow tract from the level of the small hepatic veins to the entrance of the inferior vena cava into the right atrium. BCS is considered primary when obstruction of the venous tract is the result of an endoluminal lesion, i.e. thrombosis, and secondary if the obstruction results from compression or invasion of the venous system.2 BCS is a rare disorder with an incidence of around 1-2 per million inhabitants in the Western world. In the Netherlands an estimated number of 10-20 cases per year are seen, most of whom are young females.3 The main complications of BCS are the result of portal hypertension and liver dysfunction. The classical triad of presenting symptoms in BCS consists of abdominal pain, ascites and hepatomegaly. In addition, alterations in liver biochemical tests can be observed. Clinical presentation may range from absence of symptoms, in case of preservation of hepatic veins.
Local risk factors for the development of BCS include risk factors for more common venous thrombosis, such as deep venous thrombosis and pulmonary embolism. However, some risk factors are more specific for abdominal vein thrombosis.

### Aetiology

Local risk factors for the development of BCS include solid malignancies, cysts or abscesses that compress or invade the venous tract. This only accounts for the minority of BCS in the Western world. PVT, on the other hand, is most often seen as a complication of liver cirrhosis or hepatobiliary malignancies. Other frequent local risk factors are surgical trauma to the portal vein and infections or inflammation in the abdomen, which are often accompanied by an additional prothrombotic condition.

The aetiology of primary BCS and non-malignant, non-cirrhotic PVT often involves systemic, prothrombotic conditions. It should be kept in mind that most studies on aetiological factors for abdominal vein thrombosis included selected patient groups and only have a limited sample size. In a large multicentre European study (En-Vie study) 163 consecutive patients with primary BCS and 105 patients with non-malignant, non-cirrhotic PVT with a near-complete work-up for aetiological factors, reported prothrombotic factors in up to 84% and 42%, respectively. In table 1 the most common aetiological factors derived from these two large cohorts of patients with BCS and PVT are depicted. Several of these risk factors are also known risk factors for more common venous thrombosis, such as deep venous thrombosis and pulmonary embolism. However, some risk factors are more specific for abdominal vein thrombosis.

### Inherited and acquired thrombophilia

Thrombophilia defines conditions that are associated with an increased risk of venous thromboembolism (VTE), and is characterised by a hypercoagulable state. Common clinical features of thrombophilia are thrombosis at a young age, recurrent venous thrombosis, a positive family history of VTE, and thrombosis located at unusual venous sites. The role of thrombophilia in the aetiology of abdominal vein thrombosis has recently been established. The exact prevalence of inherited deficiencies of the natural anticoagulants antithrombin, protein C and protein S is difficult to determine in BCS and PVT patients, because low levels of these factors may also be caused by reduced liver synthesis function, which frequently occurs in these patients. In addition, most of these patients are treated with long-term anticoagulant treatment with vitamin K antagonists, which hampers the diagnosis of protein C and protein S deficiency. In some studies, an inherited deficiency was diagnosed if protein C or S levels were lower than other vitamin K dependent coagulation factors synthesised by the liver or when a clear isolated deficiency was found. In these studies the prevalence of antithrombin deficiency ranges from between 0-5% in both BCS and PVT, for protein C deficiency this is between 4-20% in BCS and 0-7% in PVT, and for protein S deficiency between 0-7% in BCS and 0-30% in PVT. In one study protein C deficiency was significantly associated with both BCS and PVT, whereas another large study did not find a significant association between these factors and PVT. Although the data are not entirely consistent,
primary deficiencies of these coagulation inhibitors are likely to contribute to the pathogenesis of BCS and PVT, and should be included in diagnostic work-up.

In BCS patients the prevalence of the Factor V (FV) Leiden mutation ranges between 7% and 32%, which resembles the percentage in patients with DVT. The prevalence of the FV Leiden mutation in patients with PVT is lower, ranging between 3% and 9% (reviewed in Smallberg et al.13). Case-control studies have confirmed that the FV Leiden mutation is more strongly associated with BCS than with PVT. FV Leiden carriers have a four- to 11-fold increased risk of BCS, whereas a recent meta-analysis reported only a twofold risk of PVT in FV Leiden carriers.15 On the contrary, the prothrombin G20210A gene variant is more common in PVT than in BCS with a prevalence ranging from 3%-8% in BCS.14 A recent meta-analysis reported a four- to five-fold increase in risk of PVT in carriers of the prothrombin gene variant,13 whereas the risk of BCS is approximately twofold increased.8 So far, the mechanism behind the difference in prevalence of the FV Leiden mutation and the prothrombin gene variant in BCS and PVT remains unresolved. Despite the increased relative risk, the absolute life-time risk for abdominal vein thrombosis in carriers of FV Leiden mutation or prothrombin gene variant is very low and mainly dependent upon other risk factors mentioned below.

Although antiphospholipid antibodies (APA) are considered a risk factor for BCS and PVT, they have hardly been studied in case-control studies. The prevalence of APA in BCS and PVT has been estimated to be around 5-15%.3,9 The importance as a risk factor is difficult to assess because anticardiolipin antibodies are also found in patients with chronic liver disease without thrombosis.14 However, large studies confirming the relationship between APA and BCS and PVT are still lacking. In most studies only one single measurement was carried out, whereas for the correct diagnosis of the antiphospholipid syndrome, these should be measured at two different occasions 12 weeks apart.9

More recent studies have investigated whether increased levels of coagulation factors are increasing the risk of abdominal vein thrombosis. Recently, Martinelli et al. described significantly elevated factor VIII levels in patients with primary PVT, both with and without underlying cirrhosis, even adjusted for the acute-phase reaction. However, factor VIII is known to be strongly increased in patients with liver dysfunction, which is frequently seen in BCS and PVT patients.16 These results were confirmed by Raffa et al. who studied several plasma coagulation factors in patients with non-cirrhotic PVT. They observed a significant increase of endogenous thrombin potential irrespective of the underlying prothrombotic or thrombophilic disorder.17

**Emerging new thrombophilic risk factors**

Only few studies have assessed the role of the fibrinolytic system in the pathogenesis of BCS and PVT. We recently observed an association between abdominal vein thrombosis (SVT) and genetic variation in the thrombin activatable fibrinolysis inhibitor (TAFI) gene.18 A decreased risk of SVT in 147Thr/Thr homozygotes and a slightly, but not significantly, increased risk in carriers of the 3451le variant was observed, suggesting a role for TAFI in the pathogenesis of SVT. The genotypes associated with an increased risk of SVT are associated with decreased TAFI levels.

Hockstra et al. extensively investigated components of the fibrinolytic system in 101 BCS patients included in the En-Vie study.19 This study showed significantly higher PAI-1 levels in BCS patients compared with controls, whereas TAFI and α2-antiplasmin levels were significantly lower. It was additionally shown that hypofibrinolysis, as determined using clot lysis times (CLT), was associated with an increased risk of BCS. A CLT above the 90th or 95th percentile of controls was associated with a 2.4-fold and 3.4-fold increase in risk of BCS, respectively. This study suggests that impaired fibrinolysis may also play a role in the pathogenesis of abdominal vein thrombosis. Recently, a potential new factor in the pathogenesis of BCS was identified. Using a proteomic approach assessing fibrin binding proteins in plasma obtained from patients with BCS compared with healthy controls, Talens et al. initially showed that apolipoprotein A1 (ApoA1) was decreased in BCS patients. This observation was validated in a large cohort of BCS patients, in which ApoA1 levels were also significantly lower compared with controls.20 ApoA1 is the principal component of high-density lipoprotein cholesterol, which has been shown to be inversely associated with other forms of VTE.21 Low ApoA1 levels have also been associated with an increased risk of recurrence of common VTE.22

**Other risk factors**

It has been known for several decades that myeloproliferative neoplasms (MPNs) are a common underlying cause of abdominal vein thrombosis. MPNs are chronic clonal haematopoietic stem cell disorders characterised by an overproduction of mature and functional granulocytes, red blood cells and/or platelets.23 It is estimated that MPNs are observed in 30-40% of patients with BCS or PVT, whereas this is rarely the cause of other types of VTE.24-27 Portal hypertension, resulting from pre- or post-hepatic venous obstruction, can lead to hypersplenism and haemodilution. This may mask the characteristic peripheral blood cell changes (i.e. high haemoglobin levels and thrombocytosis) and make diagnosis of MPN difficult. Previously, diagnosis of MPNs in these patients relied on bone marrow (BM) biopsy findings and growth of erythroid


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402
colonies in the absence of exogenous erythropoietin, referred to as spontaneous endogenous erythroid colonies (EEC). Patients were diagnosed with occult MPN in case of typical bone marrow changes, especially dysmegakaryopoiesis, or spontaneous EEC growth, but in whom blood cell counts were normal. The discovery of the \textit{JAK2V617F} mutation, a common gain of function mutation leading to development of MPN, has changed the diagnostic strategy of MPN. This mutation is present in nearly all patients with polycythaemia vera and in about 50% of patients with essential thrombocythaemia and primary myelofibrosis. The \textit{JAK2V617F} mutation has been described in a large number of unselected BCS and PVT patients. In a recent meta-analysis we determined the prevalence of MPNs and their subtypes as well as \textit{JAK2V617F} and its diagnostic role in these uncommon disorders. In BCS, mean prevalence of MPNs and \textit{JAK2V617F} was 28.4% and 41.1%, respectively. In PVT, mean prevalence of MPNs and \textit{JAK2V617F} were 19.5% and 27.7%, respectively. MPN and \textit{JAK2V617F} were more frequently found in BCS compared with PVT. Polycythaemia vera was more prevalent in BCS than in PVT. \textit{JAK2V617F} screening in SVT patients without typical haematological MPN features identified MPN in 17.1% and 15.4% of screened BCS and PVT patients, respectively. It can be concluded that besides bone marrow histology, screening for \textit{JAK2V617F} is an important diagnostic tool to detect MPN in these patients and should be performed in all patients with abdominal vein thrombosis as part of the standard diagnostic work-up. The exact pathogenetic mechanism of thrombosis in MPNs still remains to be resolved, but besides characteristic erythrocytosis and thrombocytosis, platelet and leucocyte functional abnormalities seem to have a pathogenetic role.

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired haematological disorder of haematopoietic stem cells, which is associated with thrombosis at unusual sites. Remarkably, thrombosis of the abdominal veins is a frequent complication and accounts for the majority of deaths in this disorder. PNH has been reported in 9-19% of tested BCS patients, whereas a prevalence of 0-2% has been reported in PVT. Several mechanisms, including intravascular haemolysis, increased platelet activation and aggregation, procoagulant microparticles resulting from complement-mediated platelet damage, hypofibrinolysis and increased tissue factor expression may contribute to the pathogenesis of venous thrombosis in PNH. Patients with a PNH cell population above 60% of the granulocytes appear to be at greatest risk for thrombosis. Testing for PNH should be routinely performed in all BCS and PVT patients, especially since treatment with eculizumab may be indicated in these individuals. A number of systemic, autoimmune-mediated diseases have been implicated in the pathogenesis of both BCS and PVT, including Behçet’s disease, inflammatory bowel disease, vasculitis, sarcoidosis and connective tissue disease. In the previously mentioned EnVie study these disorders occurred rarely.

Oral contraceptive use and pregnancy are well-known risk factors for VTEs. Since abdominal vein thrombosis occurs frequently in young women, hormonal factors may be of importance in the pathogenesis. In the recent En-Vie study, 50% of patients with BCS and 25% of the patients with PVT were women aged 15-45 years. Oral contraceptives have been shown to be associated with at least a twofold risk for BCS. For PVT the risk may be slightly increased, but this has not yet been well established.

Multifactorial aetiology
As is well known for other more common forms of venous thromboembolism (VTE) the aetiology of primary BCS and PVT is often multifactorial. In the En-Vie study a combination of two or more genetic or acquired prothrombotic factors was found in 46% of BCS and 48% of PVT patients. In BCS patients, 18% of the patients even displayed three risk factors. In over 60% of patients presenting with an inherited thrombophilia factor an additional risk factor was found. In a paediatric population of 31 patients with PVT it was shown that despite the fact that almost all children had a local underlying aetiological factor, deficiencies of the natural anticoagulants and prothrombotic mutations were observed in over 30% of the patients.

Based on these findings, a complete haematological work-up, including diagnosis of inherited thrombophilia, APA, MPN and PNH, should always be performed in BCS and PVT patients, irrespective of whether one prothrombotic factor has already been identified. This is in particular relevant for identifying MPN, which are also often accompanied by other prothrombotic factors, and may require additional treatment, such as aspirin and antiproliferative treatment, such as interferon or hydroxyurea.

\section*{Anticoagulant treatment of abdominal vein thrombosis}

The mainstay of therapy is the immediate institution of anticoagulant therapy with low-molecular-weight heparin followed by long-term use of vitamin K antagonists. In BCS, life-long therapy is warranted considering the severity of the disorders. In individuals with acute portal vein thrombosis, anticoagulant therapy is given for three to six months, but depending upon the underlying disorder is sometimes given indefinitely. The duration of anticoagulant therapy is strongly dependent upon the risk...
of recurrent thrombosis. So far, only a few studies have focused on the risk of recurrence in PVT. Condat et al. assessed the outcome of PVT in relation to prothrombotic conditions in a cohort of 136 patients of whom 84 received anticoagulant therapy. In this study, an incidence rate of 5.5 per 100 person-years for all types of thrombotic events was reported and an underlying prothrombotic state was shown to be an independent predictor of recurrent thrombosis. In another study with a median follow-up of 41 months in 121 patients with abdominal vein thrombosis, the recurrence rate of thrombosis was 10.5%. Nearly 75% of these recurrent events were abdominal vein thrombosis. Most of these patients had an MPN and none were on anticoagulant treatment. In a recent analysis of 120 PVT patients treated in the ErasmusMC we observed recurrent thrombosis in 4%, 8% and 27% of the patients after a follow-up of one, five and ten years, respectively. This was strongly dependent upon an underlying prothrombotic disorder.

As mentioned above, patients with abdominal vein thrombosis have a high risk of recurrence; however, they are also at a higher risk of bleeding. Because patients with acute PVT frequently present with variceal bleeding, local measures should be taken to stop bleeding and prevent rebleeding. In two previously mentioned studies the rates of bleeding after follow-up of 41 months and five years were 15% and 46% respectively. In the latter study anticoagulant therapy was a significant predictor of bleeding. Therefore it is very difficult to give strict recommendations on the duration of anticoagulant treatment in patients with PVT. It has been suggested to give long-term anticoagulant therapy only to those individuals with major underlying thrombophilic risk factors, such as homozygous FV Leiden mutation and prothrombin gene variant. Follow-up studies are needed in order to establish the duration of anticoagulant treatment, especially those with no or mild thrombophilic disorders.

In case of an underlying MPN, anticoagulant treatment should also be given indefinitely. It is still being debated whether aspirin should be added to the anticoagulant treatment with vitamin K antagonists in patients with MPN and abdominal vein thrombosis. In a recent retrospective study we showed a potential benefit of aspirin in patients with PVT and MPN with lower recurrent thrombosis rates in individuals also treated with oral anticoagulant therapy. This has to be confirmed in prospective studies. These patients should also be treated with antiproliferative therapy, such as alpha interferon or hydroxyurea, in order to normalise peripheral blood cell counts. Additional management of abdominal vein thrombosis with invasive procedures, stents or surgery is outside the scope of this article and has been reviewed before.

CONCLUSIONS

Abdominal vein thrombosis is a rare, but potentially life-threatening thrombotic event. The aetiology is multi-factorial, in which both genetic and acquired prothrombotic factors are frequently encountered simultaneously. Indefinite anticoagulant treatment is advised for patients with BCS and for patients with PVT with a major underlying prothrombotic risk factor; however, this must be balanced against an increased risk of bleeding. Long-term treatment studies are urgently needed to establish the optimal duration of anticoagulant treatment in these thrombotic disorders.

REFERENCES


