Thrombophilia Profile in Budd-Chiari Syndrome and Splanchnic Vein Thrombosis: A Study from Western India

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Abstract

Aim: To estimate the prevalence of inherited prothrombotic risk factors in patients with splanchnic venous thrombosis (SVT) and Budd-Chiari syndrome (BCS) and to compare the risk factor profiles between these two groups.

Methods: In this prospective study, patients with abdominal venous thrombosis were studied. The patients were divided into two groups on the basis of the veins involved; splanchnic venous thrombosis group [portal (PVT), splenic, superior mesenteric veins (SMV)] and Budd-Chiari group (hepatic vein, IVC thrombosis). Thrombophilia profile including protein C, protein S, antithrombin III, factor V Leiden mutation, activated protein C, factor VIII level, CD55, CD59, IgM cardiolipin, IgG cardiolipin, anti-β2 glycoprotein, JAK2 mutation, homocysteine levels, MTHFR and lupus anticoagulant was done in all patients.

Results: Out of 30 patients, 23 patients had SVT, 7 had BCS, including 2 of the 23 patients with SVT had mixed venous thrombosis, PVT and SMV thrombosis. Risk factors were found in 21/30 (70%) patients [17/23 (73.9%) of PVT. 4/7 (57.1% of BCS] and multiple risk factors were overall present in 8/23(34.7%) patients of SVT.

Conclusion: Hereditary risk factors play an important role in the etiopathogenesis of abdominal venous thrombosis and hyperhomocysteinemia and protein S deficiency are the most common risk factors.

Introduction

Abdominal venous thrombosis may present as splanchnic venous thrombosis (SVT) (occlusion of portal, splenic, superior or inferior mesenteric veins) and Budd-Chiari Syndrome (BCS) (thrombosis of inferior vena cava and/or hepatic veins). Both hereditary and acquired risk factors have been implicated in the etiopathogenesis of abdominal vessel thrombosis.

Budd-Chiari syndrome (BCS) results from occlusion of the hepatic venous outflow tract at the level of the hepatic veins or the inferior vena cava (IVC). Portal vein thrombosis (PVT) causes reduced portal flow, and clinically manifests as features of portal hypertension. In BCS most patients have abdominal pain, jaundice, and gastrointestinal bleeding. Physical signs on examination are tender hepatomegaly, ascites, tortuous veins on the abdominal wall and back, and pedal edema. BCS and PVT may be associated with inherited deficiencies of coagulation factor inhibitors such as protein C, protein S, and antithrombin III. Prothrombin G20210A mutation is a risk factor for idiopathic PVT, but it is not a prominent factor in causation of BCS. Factor V Leiden mutation has been found to be the most common inherited risk factor in BCS, but it has not been found that commonly in PVT. The MTHFR C677T mutation and hyperhomocysteinemia were also important thrombophilic factors.
risk factors specially for BCS.\textsuperscript{12} The evaluation of thrombophilic factors in PVT and BCS have been done in limited studies. One study from Western India on inherited thrombophilia in BCS and PVT has been reported that showed factor V Leiden mutation as the most common inherited risk factor in BCS and protein C deficiency in PVT.\textsuperscript{13}

**Materials and Methods**

Patients with SVT (portal vein/superior mesenteric vein/splenic vein) and BCS admitted in the gastroenterology ward or attending gastroenterology outpatient department were included in the study. Patients underwent workup of a hypercoagulable state from January 2009 to December 2012 in this study. The diagnosis of SVT or BCS was confirmed by appropriate radiographic imaging such as Doppler ultrasonography, computed tomography and magnetic resonance imaging. History was taken regarding acquired risk factors such as oral contraceptive use, pregnancy, cirrhosis, infection, neoplasm, abdominal surgery, regarding prior episode of thrombosis and family history of thrombosis. Blood samples were collected in 3.2\% trisodium citrate (1:9), EDTA vials and plain vials. A complete hemogram was done in all cases. JAK2 mutation and factor V Leiden mutation study was done by PCR followed by polyacrylamide gel electrophoresis. Clotting assay was done for APC resistance, protein C activity and factor VIII activity. Protein S assay was done by ELISA based method. MTHFR mutation study was done by PCR based restriction digestion method. Antithrombin III activity was measured by chromogenic assay. Homocysteine level was assessed by CMIA (Chemiluminescent microparticle immunoassay) method.

The study was approved by the institutional ethics committee.

**Results**

The majority of patients belonged to age group of 20-40 years (Figure 1). In our study of 30 patients, 23 (76.6\%) patients had SVT while seven patients had BCS. Of the patients with SVT and BCS, 14 (60.8\%) and 4 (57.1\%) were males, respectively. Out of patients with PVT, SMV thrombosis was present in 2 (8\%) patients. The mean age of patients with BCS was 41.5 years (range 15 to 65 years), 32.6 years (range of 5 to 56 years) and 52 (range 52 to 56 years) in patients with combined PVT and PVT with SMV thrombosis, respectively.

Patients with BCS presented with abdominal pain, hepatomegaly, pedal oedema, ascites and jaundice while those with PVT presented with splenomegaly and gastrointestinal bleeding. Patients with SMV thrombosis mostly presented with post-prandial abdominal pain.

The most common site of obstruction in BCS was hepatic vein block, seen in 57.1\% cases, followed by combined block of IVC and hepatic veins seen in rest of the patients; isolated IVC block was not seen in our patients.

The most common inherited thrombophilic state associated with PVT was hyperhomocysteinemia (34.7\%), followed by protein S deficiency (30.4\%) and increased factor VIII activity (21.7\%). In BCS, the risk factors seen were protein S deficiency, MTHFR
mutation, JAK 2 mutation, and hyperhomocysteinemia. There were six patients below the age of 20 years and none of them turned out JAK 2 positive. Protein C deficiency, protein S deficiency, MTHFR mutation, raised factor VIII levels and hyperhomocysteinemia were found in one patient each. Fourteen patients were between the age of 20 to 40 years and the risk factors were protein S deficiency (36%), MTHFR mutation (14%), raised factor VIII levels (21%), anticardiolipin antibodies (7%) and hyperhomocysteinemia (35%). For patients above 40 years of age, the risk factors were JAK 2 mutation (40%), hyperhomocysteinemia (40%), anticardiolipin antibodies (10%), protein C deficiency (10%), protein S deficiency (10%) and antithrombin III resistance (10%).

Multiple risk factors were present in 26.6% patients. None of BCS patients had multiple risk factors. 34.7% patients with SVT had multiple risk factors, six patients had two risk factors while two patients had three risk factors. Two patients with PVT had additional SMV thrombosis. JAK 2 was seen in 14.2% of BCS and 13% of SVT patients. Hyperhomocysteinemia was seen in nine patients, of which six had additional risk factors. A summary of all the patients is included in Table 1.

Discussion

Hypercoagulability due to inherited thrombophilic factors have been implicated in the causation of both PVT and BCS. The present study found inherited prothrombotic defects in a significant number of patients with PVT and BCS. Prothrombotic abnormalities were more pronounced in PVT (16/23 [73.9%]) than in BCS (4/7 [57.1%]). None of the patients in our study had acquired risk factors such as abdominal surgery, malignant neoplasm, and oral contraceptive pill use compared to study by Bhattacharyya et al where acquired risk factors were present in 17% patients with PVT and 7% of patients with BCS.14

Hyperhomocysteinemia was the most common inherited risk factor (9/30 [30%]). Though 6/9 (67%) patients with hyperhomocysteinemia had additional prothrombotic risk factors like MTHFR mutation, protein S deficiency, anticardiolipin antibody and increased factor VIII activity. Patients with portal or mesenteric vein thrombosis, most of the times have an additional risk factor associated with hyperhomocysteinemia.15-18 So we should always investigate for an additional risk factor whenever hyperhomocysteinemia is diagnosed in a patient with abdominal vein thrombosis.

Protein S deficiency was present in 30.4% patients overall with 14.2% of BCS and 30.4% of PVT having this deficiency. This has been the second most common risk factor in our patients. This is in contrast to other Indian studies which show low incidence of protein S deficiency. Dutta et al didn’t find a single protein S deficiency in their study.19 It was seen in 7% in BCS patients and 4% in PVT in a study from Bhattacharyya et al20 whereas in a study from western India by Mohanty et al21 states that 5.7% of BCS and 3.03% of PVT showed protein S deficiency.

Protein C deficiency was seen in only one patient of PVT. None of BCS patients showed protein C deficiency. This is again in contrast to the other studies which state it to be present in 8% of PVT and 12% of BCS patients as per Bhattacharyya et al24 It was seen in 13.2% of BCS and 9.09% of PVT as per study from Mohanty et al.23

Though, the prevalence of protein C and protein S deficiency was present in 1 (14.2%) patient of BCS in accordance with findings of the study by Janssen et al.25 Both BCS and PVT are associated with reduced synthesis of protein C, protein S and antithrombin III by the liver but the acquired deficiency of these factors was ruled out by documenting normal liver function test and prothrombin time. There is significant extrahepatic synthesis of protein S so the level of protein S remains substantially greater compared to protein C deficiency in liver disease which parallels the deficiency of other vitamin K–dependent factors (II, VII, and X).20 None of our patients were on anticoagulation at the time of estimation of protein C and protein S.

Many studies had factor V Leiden mutation as the most common risk factor. In Deltenre et al study factor V Leiden mutation was detected in 31% of patients with BCS.21 Even another Indian study by Mohanty et al23 showed a prevalence as high as 26.2%. However, factor V Leiden mutation and prothrombin gene mutation was not detected in any of the patients studied.

JAK 2 mutation was positive in 14.2% of BCS and 13% of SVT patients in our study. The other studies have not included JAK 2 mutation analysis in thrombophilic work up of patients with SVT and BCS.13,14 The prevalence values for the JAK2 mutation were 8.8% (12/137) and 5% (4/78), in BCS and PVT respectively in a study by Shetty et al.22 We should suspect JAK 2 mutation whenever there is normal to high platelet count in a patient with large spleen or portal hypertension. JAK 2 mutation was seen mainly in individuals above the age of 40 years.

SMV thrombosis was seen in two patients. One was male and another was female. The mean age was 54 years. The risk factors turned out were hyperhomocysteinemia and JAK 2 mutation. Both the cases had the thrombus extension from portal vein. None of the two patients had bowel ischemia.

Hyperhomocysteinemia and protein S deficiency were the most common risk factors identified.
in our study. However, we should investigate for additional prothrombotic states in patients with hyperhomocysteinemia as it is most commonly an additional risk factor and not an isolated cause of hypercoaguable state.

We conclude that all patients with BCS or SVT should undergo evaluation for thrombophilia. These tests not only help in identifying the prevalent risk factors in the defined population but can help guide the management. Patients with JAK 2 mutation, hyperhomocysteinemia and paroxysmal nocturnal hemoglobinuria will require management beyond anticoagulation. Patients with BCS who require liver transplant for management have an additional advantage in form of a cure from hypercoaguable state caused by protein C, S and antithrombin III deficiency. Hence, such patient may not require lifelong anticoagulation.

Evaluating all patients with BCS and SVT before anticoagulating helps in planning the future management of patients.

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References