ORIGINAL ARTICLE

Thrombophilia Profile of Portal Vein Thrombosis in Young

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Abstract

The abdominal vein thrombosis is an unusual and rare, but potentially a life threatening form of thrombosis. Much is known, studied and published about the venous thrombosis in the lower limbs and to some extent in upper limbs, where as the abdominal vein thrombosis still remains an unexplored area. The diagnosis of abdominal venous thrombosis has increased with awareness of the entity and the availability of better imaging modalities. Despite advances made in the management of venous thrombosis, the knowledge of events predisposing to abdominal thrombosis is largely unknown. This gap in knowledge needs to be studied and analyzed for better patient management. The study aims at analysing various risk factors in patients of abdominal venous thrombosis.

Portal vein thrombosis is common among abdominal vein thrombosis. It can occur in patients without co-existent liver disease and its prevalence has been reported to lie between 0.6% and 44%. Both hereditary and acquired risk factors have been implicated in the etiopathogenesis. Many of these risk factors are also known risk factors for more common venous thrombosis such as deep vein thrombosis of lower limbs and pulmonary thromboembolism, whereas some are specific for abdominal vein thrombosis. Most studies on etiological factors for abdominal vein thrombosis included selected patient groups and only have a limited sample size. This study enrolled 70 patients of abdominal vein thrombosis, out of 70, 38 patients were diagnosed as PVT. Mean age of patients was 37.6±10.3 years.

Among hereditary causes, hyperhomocysteinemia was the most common cause. Acquired risk factors like Myeloproliferative Neoplasms present in 06 patients (15.8%) and Anti Phospholipid Antibody syndrome was diagnosed in 04 (10.5%). Exposure to high altitude present in 09 (23.7%) patients of Portal vein Thrombosis. Hence abdominal venous thrombosis requires extensive thrombophilia evaluation, as management differs in various acquired factors like Myeloproliferative neoplasms and Anti Phospholipid Antibody syndrome.

Introduction

The abdominal vein thrombosis is an unusual and rare, but potentially a life-threatening form of thrombosis. Most commonly it includes hepatic vein thrombosis (Budd- Chiari syndrome), portal vein thrombosis (PVT), rare forms such as splenic vein thrombosis, and mesenteric vein thrombosis. The splanchnic venous system consists of the portal vein (formed by the union of the superior mesenteric vein and the splenic vein) and its branches that direct blood flow from the gastrointestinal organs to 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.

PVT, a rare disorder, occurs commonly in patients with chronic liver disease, characterized by thrombosis in extra-hepatic portal veins with or without involvement of intra hepatic branches. Patients may present with variceal bleed, splenomegaly or in rare cases with bowel infarction, if it extends to involve mesenteric veins. Though PVT can occur in patients without co-existent liver disease, its prevalence has been reported to lie between 0.6% and 44% with an increasing frequency in decompensated disease and/or concomitant hepatocellular cancer.[1,2]

Both hereditary and acquired risk factors have been implicated in the etiopathogenesis of abdominal vein thrombosis. Several of these risk factors are also known risk factors for more common venous thrombosis such as DVT and PTE, whereas, some are specific for abdominal vein thrombosis. Most studies on etiological factors for abdominal vein thrombosis included selected patient groups and only have a limited sample size. The exact prevalence of inherited deficiencies of the natural anticoagulants anti thrombin,[1] protein C and protein S is difficult to determine in patients of abdominal vein thrombosis, because low levels of these factors may also be caused by reduced liver synthesis function, which frequently occurs in these patients. Timing of testing for these factors, as well as long term treatment with Vitamin K antagonists in these patients also hampers the accurate diagnosis.

Myeloproliferative neoplasms (MPN) defined as clonal haematopoietic stem cell disorders characterised by an excessive production of mature and functional granulocytes, red blood cells and/or platelets are implicated in 30-40% of patients with abdominal vein thrombosis as well as rarely in other types of VTE. JAK2V617F mutation, a common gain of function mutation leading to development of MPN, is present in nearly all patients with polycythemia vera and in about 50% of patients with essential thrombocythemia and primary myelofibrosis. The same mutation has been described in large number of patients with abdominal vein thrombosis. Though the exact pathogenetic mechanism of thrombosis in MPNs is not known, but besides characteristic erythrocytosis and

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Received: 12.06.2018; Accepted: 16.08.2018

Table 1: Types of abdominal vein thrombosis

Vessel involved	No. of cases (n)	Percentage
PVT	38	54.3%
MVT	21	30.0%
SVT	6	8.6%
HVT	5	7.1%
Total	70	

PVT: Portal vein thrombosis; MVT: Mesenteric vein thrombosis; SVT: Splenic vein thrombosis; HVT: Hepatic vein thrombosis

thrombocytosis, platelet and leucocyte functional abnormalities seem to have a pathogenetic role.[3-10]

There is limited Indian data regarding thrombophilia profile in patients with portal vein thrombosis. In this study we analyzed the clinical and risk factor profile in patients of PVT. Also, we tried to determine the prevalence of MPNs and JAK2V617F mutation as well as their diagnostic role in these uncommon disorders.

Materials and Methods

Our study was a cross sectional observational study, including 38 patients of PVT, who presented to Gastroenterology and Hematology departments of Army Hospital Research and Referral, New Delhi from October 2015 to April 2017. The diagnosis of PVT was confirmed by appropriate radiographic imaging such as Doppler ultrasonography, computed tomography and magnetic resonance imaging. A recently formed thrombus is virtually anechoic. Doppler imaging will show absence of flow in part or all of the lumen. A CT scan without contrast can show hyper attenuating material in the PV. After injection of contrast agent, lack of luminal enhancement is seen. Interview technique was used to collect the information 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. All cases of cirrhosis were excluded in this study.

Blood samples were collected in 3.2% trisodium citrate (1:9), EDTA vials and plain vials. A complete hemogram, liver function tests and renal function tests were done in all cases. Extensive thrombophilia workup was done in all patients, but focusing on acquired risk factors especially JAK2 mutation analysis, Anti phospholipid antibodies (Lupus anti coagulant, Anti B2 glycoprotein I antibodies and Anti cardiolipin antibodies) and Paroxysmal nocturnal hemoglobinuria (PNH), which are not affected either by the timing of testing or does not require stopping of anticoagulant therapy. JAK2 mutation study was done by PCR followed by polyacrylamide gel electrophoresis. PNH flow cytometry was done by FLAER (Fluorescein labeled proaerolysin method). The LAC (lupus anticoagulant) and ACA (anticardiolipin antibody) were tested twice twelve weeks apart in positive cases.

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Pearson correlation was used to assess the relationship between Haemoglobin, Total Leukocyte count and JAK2 Mutation. p value less than 0.05 will be taken to indicate a significant difference.

Table 2: Thrombophilia profile of portal vein thrombosis

	N (%)
Hereditary causes	
Hyperhomocysteinemia	10 (26.3)
Protein C deficiency	6 (15.8)
Protein S deficiency	4 (10.5)
Increased factor VIII levels	3 (7.9)
Factor V Leiden mutation	3 (7.9)
SCT	1 (2.6)
AT III deficiency	1 (2.6)
Acquired causes	
JAK 2 positive MPN	5 (13.2)
APLA syndrome	4 (10.5)
JAK 2 Negative MPN (ET)	1 (2.6)
Total	38

MPN: Myeloproliferative neoplasms; AT III: Antithrombin III; ET: Essential thrombocytosis; SCT: Sickle cell trait

Results

Out of 70 patients of abdominal vein thrombosis, 38 were diagnosed as PVT (Table 1). There were 29 (76.3%) males and 09 (23.7%) females in the study group. Mean age of patients was 37.6±10.3 years with majority of patients in age group 30-40 years.

Pain abdomen was most common presenting symptom in 26 (68.4%) patients, whereas 12 patients had an incidental diagnosis. Among hereditary causes of thrombophilia, hyperhomocysteniemia was the most common entity found in 10 (26.3%) patients, followed by Protein C and S deficiency in 06 and 04 patients respectively. Acquired thrombophilic risk factors for thrombosis were present in 10 (26.3%). JAK2 mutation positive with MPN was detected in 05 (13.2%) patients, whereas JAK2 negative MPN (Essential thrombocytosis) was present in one patient of PVT (Table 2). Antiphospholipid antibody (APLA) positivity was diagnosed in 04 (10.5%) of 38 patients. PNH flowcytometry was positive for none of the patients. Exposure to high altitude present in 09 (23.7%) patients of PVT.

Discussion

Both hereditary and acquired risk factors have been implicated in the etiopathogenesis of abdominal vessel thrombosis, however some factors are specific for it. Our present study conducted at tertiary care hospital of armed forces primarily focuses on acquired and inherited thrombophilic factors with special emphasis on exposure to high altitude, JAK2 mutation and myeloproliferative neoplasms (MPN). There is an ease with evaluation of acquired thrombophilic factors in comparison to most of the inherited factors as testing for acquired factors is independent of timing of tests, and does not require cessation of oral anticoagulants. There is very limited data on incidence of these acquired thrombophilic factors including exposure to high altitude, JAK2, PNH and APLA syndrome in patients with abdominal vein thrombosis.

We found Portal vein thrombosis (PVT) as the most common site of thrombosis, detected in 38 (54%) of 70 patients diagnosed as abdominal vein thrombosis, which is commensurate with previous Indian and Western studies. An Indian Study by Prabha Sawant et al has reported 90% PVT among patients with abdominal vein thrombosis, in a study consisting of 30 patients.[11]

There is very limited data regarding association of abdominal vein thrombosis and exposure to high altitude area (HAA). It was

suggested that at such extreme altitudes, pronounced dehydration due to increased respiration might predispose to thrombosis. Reduced activity, decreased thirst and appetite, compounded by hyperviscosity, associated endothelial damage and alterations in coagulation factors are implicated in pathogenesis of thrombosis.[12] Anand et al reported 17.4 % cases of abdominal vein thrombosis in patients exposed to HAA with mean duration of 10.2 months.[13] Since our centre is a service hospital mainly catering to serving soldiers posted at different locations in the country, association with HAA exposure was extensively evaluated in our study. We found 09 (23.7%) patients had exposure to HAA, with stay above 3000 meters for mean duration of 12 months.

JAK2 mutation was detected in 13.2% (5/38) of PVT. Hemoglobin and leucocyte counts were significantly higher in JAK2 positive patients as compared to JAK2 negative patients ($p<0.01$) with the mean hemoglobin (16.05 ± 2.02 gm/dl) and the mean total leukocyte count (9246 ± 4251.21/ mm^3) was found. 05 patients of PVT with JAK2 mutation had MPN on bone marrow evaluation. Most of the studies have not included JAK2 and MPN evaluation in patients with abdominal vein thrombosis. Our study has demonstrated significantly higher prevalence of JAK2 in these patients as compared to study published by Shetty et al which has found JAK2 in 8.8% and 5% in patients of BCS and PVT respectively.[14] We should suspect and consider testing for JAK2 mutation whenever there is normal to high hemoglobin, leucocyte or platelet counts in a patient with large spleen or portal hypertension.

Anti phospholipid antibodies as a risk factor for abdominal vein thrombosis is not extensively studied, and also there is lack of definite Indian or western data about its prevalence in such patients. Our data concludes higher prevalence of APLA syndrome in patients with PVT as compared to the study by Rajani et al (10.8 vs 7%). Though prevalence of APLA has been estimated to be around 5-15%, but most of these studies have taken single measurement, whereas for the correct diagnosis of the antiphospholipid syndrome, these should be measured at two different occasions 12 weeks apart.[15-18]

Hence abdominal venous thrombosis requires extensive thrombophilia evaluation especially for acquired factors like JAK 2 mutation analysis for MPN in patients with high counts and APLA antibodies for diagnosis of APLA syndrome. It will be helpful for appropriate management as treatment differs in each one of them.

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