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RAPID COMMUNICATION

Risk factors of thrombosis in abdominal veins

Amit Kumar Dutta, Ashok Chacko, Biju George, Joseph Anjilivelil Joseph, Sukesh Chandran Nair, Vikram Mathews

Amit Kumar Dutta, Ashok Chacko, Biju George, Joseph Anjilivelil Joseph, Department of Gastrointestinal Sciences, Christian Medical College & Hospital, Vellore 632 004, India
Sukesh Chandran Nair, Department of Clinical Pathology, Christian Medical College & Hospital, Vellore 632 004, India
Vikram Mathews, Department of Hematology, Christian Medical College & Hospital, Vellore 632 004, India
Author contributions: Dutta AK, Chacko A, George B, and Joseph AJ were involved in patient care, data analysis, and writing up the paper; Mathews V conducted the mutations analyses; Nair SC estimated Protein C, S and, AT Ⅲ levels.
Correspondence to: Dr. Ashok Chacko, MD, MNAMS (Gastro), DM, Professor & Head, Department of Gastrointestinal Sciences, Christian Medical College & Hospital, Vellore 632 004, India. gastro@cmcvellore.ac.in
Telephone: +91-416-2282148 Fax: +91-416-2232035
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Abstract

AIM: To estimate the prevalence of inherited and acquired thrombophilic risk factors in patients with abdominal venous thrombosis and to compare the risk factor profiles between Budd-Chiari syndromes (BCS) and splanchnic vein thrombosis (SVT).

METHODS: In this retrospective study, 36 patients with abdominal venous thrombosis were studied. The patients were divided into Budd-Chiari group (hepatic vein, IVC thrombosis) and splanchnic venous thrombosis group (portal, splenic, superior mesenteric veins) based on the veins involved. Hereditary and acquired thrombophilic risk factors were evaluated in all patients.

RESULTS: Twenty patients had SVT, 14 had BCS, and 2 had mixed venous thrombosis. Ten patients (28%) had hereditary and 10 patients (28%) acquired thrombophilic risk factors. The acquired risk factors were significantly more common in the SVT group (SVT *vs* BCS: 45% *vs* 7%, χ^2 = 5.7, P = 0.02) while hereditary risk factors did not show significant differences between the two groups (SVT *vs* BCS: 25% *vs* 36%, χ^2 = 0.46, P = 0.7). Multiple risk factors were present in one (7%) patient with BCS and in 3 patients (15%) with SVT. No risk factors were identified in 57% of patients with BCS and in 45% of patients with SVT.

CONCLUSION: Hereditary and acquired risk factors play an important role in the etiopathogenesis of abdominal venous thrombosis. Acquired risk factors are significantly more common in SVT patients while hereditary factors are similar in both groups.

Key words: Budd Chiari syndrome; Splanchnic vein thrombosis; Risk factors; Hereditary; Risk comparison

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INTRODUCTION

Abdominal venous thrombosis may present as Budd-Chiari Syndrome (BCS) (thrombosis of inferior vena cava and/or hepatic veins) or splanchnic venous thrombosis (SVT) (occlusion of portal, splenic, superior or inferior mesenteric veins). Hereditary and acquired risk factors have been implicated in the etiopathogenesis of abdominal venous thrombosis[1,2]. Hereditary risk factors for thrombophilia include Factor V Leiden gene mutation, prothrombin gene mutation, homozygous methyl tetrahydrofolate reductase (*MTHFR*) gene mutation, and deficiencies of coagulation inhibitor protein C, protein S and antithrombin Ⅲ (AT Ⅲ)[3-7]. Causes of acquired thrombophilia are myeloproliferative disorders, malignancy, surgery, antiphospholipid syndrome, pregnancy, oral contraceptives, and infection[8-11]. Identification of these risk factors may help in evaluation, planning therapy, or screening family members to evaluate an individual risk.

There are few studies from South Asian regions which have comprehensively evaluated prothrombotic risk factors in BCS and portal venous thrombosis (PVT)[12,13]. These studies did not assess risk factors in patients with mesenteric venous thrombosis. Other studies have evaluated individual risk factors or multiple risk factors in single venous thrombosis[14-17]. The aim

of the study was to analyse prothrombotic etiological profiles (hereditary and acquired) in patients with abdominal venous thrombosis and to compare the profiles of the BCS and SVT groups.

MATERIALS AND METHODS

Patients admitted with abdominal venous thrombosis that had complete etiological work up during the period July 1997 to June 2006 were included in the study. Patients with incomplete evaluation (acute thrombosis or on anticoagulants) were excluded. Diagnosis of thrombosis was based on Doppler sonography, abdominal computed tomography (CT), or venography. For all selected patients, clinical information and laboratory data were collected by a standardized review of medical charts using uniform structured data forms. Details of acquired prothrombotic risk factors like abdominal surgery, oral contraceptives, pregnancy, liver cirrhosis, antiphospholipid syndrome, infection, or others were also obtained.

Genetic tests for mutation in Factor V Leiden gene (1691, G-A), *MTHFR* gene (677 C-T), and prothrombin gene (20210, G-A) were done in all the patients by PCR amplification of the respective gene segments[18-20]. The amplified products were subjected to restriction digestion fragment length polymorphism (RFLP) analysis. Protein C and AT Ⅲ were assessed using chromogenic assays, done on the coagulation analyzer (Dade Behring's Sysmex CA 1500). Free protein S was estimated by an immunoassay (Chromogenix Coamatic Protein S Free, IL) done on the ACL Advance (Instrumentation Laboratory). The assays for protein C, protein S, and AT Ⅲ were run concurrently with normal control and abnormal control (substrate present in low level simulating deficiency states) samples for validation as well as comparison with normal. The normal reference ranges of various tests were protein C: 50%-150% of normal; protein S: 50%-150% of normal; AT Ⅲ: 80%-120% of normal. Patients were considered to have protein C, protein S, or AT Ⅲ deficiency only if liver dysfunction was ruled out.

Statistical analysis

Comparison between the BCS and the SVT group was done by Fischer's exact test for categorical variables and Mann Whitney *U* test for continuous variables. A *P* value of < 0.05 was considered significant. All analysis was performed in SPSS for Windows Version 11.

RESULTS

Thirty-six patients with thrombosis of abdominal veins were studied. The mean age of the patients was 36.7 years (range: 3-69 years). There were 24 males (67%) and 12 females (33%). Abdominal pain, the commonest symptom, was seen in 16 (44%), hepatomegaly in 4 (11%), splenomegaly in 10 (28%), and ascites in 13 (36%) patients. Acute presentation was more common in SVT (40%) than in BCS (21%). Diagnosis of abdominal venous thrombosis was made by Doppler sonography in 21 patients (58%), CECT abdomen in 10 (28%), and venography in 5 (14%) patients. Twenty patients had thrombosis of splanchnic veins (SVT), 14 had thrombosis of inferior vena cava and/or hepatic vein (BCS) and 2 had thrombosis in both splanchnic and IVC/hepatic veins.

The site of thrombosis along with details of hereditary and acquired risk factors in all patients studied is shown in Table 1. Hereditary risk factors were present in 10 (28%) patients and acquired risk factors in 10 (28%) patients. The most common hereditary risk factors were Factor V Leiden gene mutation (11%) and AT Ⅲ deficiency (11%) followed by protein C deficiency (8%). None of the patients had a prothrombin gene mutation, protein S deficiency, or was homozygous for *MTHFR* gene mutation. *MTHFR* mutation (heterozygous) was seen in 22% patients, which is not considered a risk factor for thrombosis. In the BCS group (14 patients): IVC obstruction alone was present in 5 patients, hepatic vein (HV) obstruction alone in 6 patients, and IVC + HV obstruction in 3 patients. Hereditary risk factors were present in 5 (36%) patients and acquired risk factor in one (7%) patient. In SVT group (20 patients): portal vein (PV) obstruction alone was present in 4 patients, splenic vein (SV) obstruction alone in 2 patients, superior mesenteric vein (SMV) obstruction alone in 1 patient, PV + SMV obstruction in 3 patients, and PV + SV + SMV obstruction in 10 patients. Hereditary risk factors were present in 5 (25%) patients and acquired risk factors in 9 (45%) patients.

Comparison of risk factor profiles between the BCS and the SVT group is shown in Table 2. Hereditary risk factors were higher in the BCS group (BCS *vs* SVT: 36% *vs* 25%, $P = 0.7$), but this difference did not reach statistical significance. Acquired risk factors were significantly higher in the SVT group (SVT *vs* BCS: 45% *vs* 7%, $P = 0.02$). The prevalence of multiple risk factors in the BCS and the SVT group are shown in Table 3. More than one risk factor was seen in 1 (7%) patient in the BCS group and in 4 (20%) patients in the SVT group. No risk factor was identified in 57% of patients in the BCS group and in 45% of patients in the SVT group.

DISCUSSION

This study evaluated hereditary and acquired risk factors in 36 patients with abdominal venous thrombosis. Hereditary risk factors were identified in 36% of patients with BCS and in 25% of patients with SVT. Acquired risk factors were detected in 7% of patients with BCS and in 45% of patients with SVT.

Prevalence of Factor V Leiden mutation (FVLM), the most common cause of inherited thrombophilia, is variable in different populations[21]. Risk of venous thrombosis is 5- to 8-fold in heterozygotes and 50- to 80-fold in mutation homozygotes[3]. Janssen *et al* showed that prevalence of FVLM in BCS (26%) and PVT (8%) was higher than in controls (3%) suggesting that FVLM is an important risk factor for BCS (OR 11.3) and PVT (OR 2.7)[22]. Mohanty *et al* also found FVLM to be an important risk factor in BCS (26%; OR 14.5) and in PVT (6%; OR 2.3)[12]. Bhattacharyya *et al* demonstrated FVLM mutation in 17% of BCS and in 3% of patients with

Table 1 Site of thrombosis and presence of risk factors in individual patients

Patient No.	Group	Site	Age(yr)	Sex	Hereditary risk factors						Acquired risk factors
					FVL	PT	MTHFR[1]	PrC	PrS	AT Ⅲ	
1	IVC and/or	Ⅳ	12	M	-,-	-,-	-,-	N	N	N	
2	Hepatic vein	Ⅳ	43	M	-,-	-,-	-,-	N	N	N	Past peripheral DVT
3	thrombosis	Ⅳ	45	M	-,-	-,-	-,-	N	N	N	
4	(BCS)	H	20	F	+,-	-,-	-,-	N	N	N	
5		Ⅳ + H	39	M	-,-	-,-	-,-	N	N	N	
6		H	42	F	-,-	-,-	-,-	N	N	N	
7		H	20	M	-,-	-,-	+,-	N	N	N	
8		Ⅳ	49	M	-,-	-,-	-,-	N	N	N	
9		H	4	M	-,-	-,-	-,-	N	N	N	
10		Ⅳ	46	M	-,-	-,-	+,-	N	N	Y	
11		Ⅳ + H	54	M	+,-	-,-	+,-	N	N	N	
12		Ⅳ + H	5	M	-,-	-,-	+,-	Y	N	Y	
13		H	40	F	-,-	-,-	-,-	N	N	N	
14		H	28	M	-,-	-,-	+,-	N	N	Y	
15	Splanchnic	P + SP + SM	55	F	-,-	-,-	-,-	Y	N	N	
16	vein	P + SP + SM	49	F	-,-	-,-	-,-	N	N	N	
17	thrombosis	P + SP + SM	44	F	-,-	-,-	-,-	N	N	N	Abdominal surgery
18	(SVT)	SP	35	M	-,-	-,-	-,-	N	N	N	
19		P	3	M	-,-	-,-	+,-	Y	N	N	Abdominal surgery
20		P	22	F	-,-	-,-	-,-	N	N	N	Cirrhosis
21		P + SP + SM	51	F	-,-	-,-	-,-	N	N	N	Past peripheral DVT
22		P + SM + IM	47	F	-,-	-,-	-,-	N	N	N	
23		P	30	M	-,-	-,-	-,-	N	N	N	
24		P + SM	37	M	-,-	-,-	-,-	N	N	N	Cirrhosis
25		P + SM	43	M	-,-	-,-	-,-	N	N	N	
26		SM	31	M	+,-	-,-	-,-	N	N	N	APLA
27		P	30	M	-,-	-,-	-,-	N	N	Y	
28		P + SP + SM	28	M	-,-	-,-	-,-	N	N	N	
29		SP	20	M	-,-	-,-	-,-	N	N	N	Acute pancreatitis
30		P + SP + SM	62	M	-,-	-,-	-,-	N	N	N	
31		P + SP + SM	69	M	-,-	-,-	-,-	N	N	N	Cirrhosis, HCC
32		P + SM	49	F	-,-	-,-	-,-	N	N	N	
33		P + SP + SM	53	M	+,-	-,-	-,-	N	N	N	Polycythemia, APLA
34		P + SP + SM	42	F	-,-	-,-	+,-	N	N	N	
35	BCS + SVT	Ⅳ + H + P	50	F	-,-	-,-	+,-	N	N	N	
36		H + P	25	M	-,-	-,-	-,-	N	N	N	

Ⅳ: Inferior vena cava; H: Hepatic vein; P: Portal vein; SP: Splenic vein; SM: Superior mesenteric vein; IM: Inferior mesenteric vein; FVL: Factor Ⅴ Leiden gene; PT: Prothrombin gene; MTHFR: Methyl tetrahydrate folate reductase gene; PrC: Protein C deficiency; PrS: Protein S deficiency; AT Ⅲ: Antithrombin Ⅲ deficiency; Y: Yes; N: No; APLA: Antiphospholipid antibody. -,-: Wild type; -,+: Heterozygous mutation. [1]Heterozygous *MTHFR* gene mutation is not considered a risk factor of thrombosis.

Table 2 Characteristics and risk factors of patients with BCS and SVT

	BCS (n = 14)	SVT (n = 20)	P[1]
Age: Median (IQR)	39.5 (27.25) yr	42.5 (20.5) yr	0.18
Female	21.4%	40%	0.30
Acute presentation	21.4%	40%	0.30
Hereditary risk factors	35.7%	25%	0.70
Factor Ⅴ Leyden mutation	14.3%	10%	0.55
Prothrombin gene mutation	0%	0%	-
Homozygous *MTHFR* gene mutation	0%	0%	-
Protein C deficiency	7.1%	10%	1.0
Protein S deficiency	0%	0%	-
AT Ⅲ deficiency	21.4%	5%	0.28
Acquired risk factors	7.1%	45%	0.02
No risk factor	57.1%	45%	0.70

[1]Fisher's exact test for categorical variables and Mann Whitney's U test for continuous variable.

Table 3 Prevalence of multiple risk factors (inherited and acquired) among patients with BCS and SVT n (%)

Number of risk factors	BCS (n = 14)	SVT (n = 20)	Total (n = 34)
0	8 (57)	9 (45)	17 (50)
1	5 (36)	7 (35)	12 (35)
2	1 (7)	3 (15)	4 (12)
3	-	1 (5)	1 (3)

PVT[13]. Koshy *et al* showed that the prevalence of FVLM was similar in patients with PVT (3%) and controls (1%) and suggested that FVLM is not associated with PVT in India[14]. Similar observations were made by Sharma *et al* who demonstrated FVLM in 1.6% of patients with PVT and in 4% of controls[15]. In the present study, 14% of patients with BCS and 10% with SVT were heterozygotes, both higher than control data (1%-4%) reported earlier from India[12,14,15]. Though the numbers of patients in the study are small, results suggest that FVLM may be a risk factor in BCS and SVT.

Prothrombin gene mutation, a risk factor for venous thrombosis (homozygote: 10-fold; heterozygote: 2- to 4-fold) is rare in African and Asian populations compared to Caucasians[23]. None of the five Indian

studies have shown this gene mutation in cases or controls[12,13,15-17]. We also did not detect this mutation in any of our patients. Prevalence of heterozygote *MTHFR* gene mutation in patients with venous thrombosis is similar to healthy controls suggesting that this mutation is not an important prothrombotic factor[24]. It has been shown that homozygote *MTHFR* mutation, one of the causes of hyperhomocystinaemia (risk factor for vascular disease), is a risk factor for venous thrombosis[19,24]. None of the patients in the present study were homozygous for the *MTHFR* mutation. Three patients had heterozygote *MTHFR* mutation as the only abnormality. They were presumed to have idiopathic abdominal venous thrombosis as heterozygote *MTHFR* mutation alone is not considered a significant prothrombotic risk factor. Five heterozygous patients had additional hereditary or acquired risk factors. In a study from Northern India, Bhattacharyya *et al* investigated 57 BCS and 48 PVT patients, and reported none were homozygous for *MTHFR* gene mutation. Heterozygous mutations were seen in 24% of BCS and 21% of PVT patients[13].

Indian and Western studies have shown that protein C deficiency is the second most common cause of inherited thrombophilia in patients with BCS and PVT[12,13,22]. Amarapurkar *et al* showed that protein C deficiency was the commonest hereditary risk factor (26%) in a study on 28 patients with mesenteric venous thrombosis[25]. Protein C was also the commonest risk factor (38% patients) in a series of 16 patients with mesenteric venous thrombosis reported by Harward *et al*[26]. In the present study, protein C deficiency was demonstrated in 7% of patients with BCS and in 10% of patients with SVT. Prevalence of protein S, and AT Ⅲ deficiency as risk factors for inherited thrombophilia in patients with BCS and PVT were low in Indian and Western studies[12,13,22]. Protein S deficiency was not detected in any of our patients. AT Ⅲ deficiency was higher in patients with BCS (21%) as compared to those with SVT (5%). Diagnosis of inherited deficiencies of protein C, protein S, and AT Ⅲ, as a cause of abdominal venous thrombosis is difficult, because acquired deficiencies develop in liver failure, acute thrombosis, and during anticoagulant therapy[27]. None of the patients in the present study with protein C and AT Ⅲ deficiency had liver failure or were on anticoagulant therapy.

Comparison of prothrombotic risk factor profiles between BCS and SVT showed a trend for hereditary risk factors to be more frequent in BCS (BCS *vs* SVT: 35.7% *vs* 25%; $P = 0.7$); two other Indian studies have made similar observations of hereditary factors being more frequent in BCS group compared to PVT group[12,13]. Studies on prevalence of acquired risk factors in abdominal venous thrombosis have shown variable results. Denninger *et al* and Janssen *et al* have shown that acquired risk factors are more frequent in PVT than in BCS[22,28]. Mohanty *et al* found the frequency of acquired risk factors to be similar in BCS and PVT[12]. In our study, acquired risk factors were significantly more common in the SVT group (BCS *vs* SVT: 7% *vs* 45%; $P = 0.02$) suggesting that SVT is a heterogeneous disease where hereditary and local risk factors play important roles.

No risk factor was identified in 57% of BCS and 45% of patients with SVT. One possible reason may be the low prevalence of myeloproliferative disorders in our series (one patient). Myeloproliferative disorders (overt or latent) have been shown as an important risk factor in previous studies on abdominal vein thrombosis[28-31]. Tests for detecting latent myeloproliferative disorders (formation of "spontaneous" erythroid colonies in cultures of bone marrow progenitor cells in erythropoietin-poor medium[32,33]) were not performed on our patients. In a study from Western India, an etiological factor could be found in 59% of the BCS and 30% of the PVT patients[12]. Interestingly, in this study also, none had a myeloproliferative disorder.

Previous studies have suggested that venous thrombosis results from coexistence of several risk factors[28]. In the present study, ⩾ 2 risk factors were detected in 7% of BCS and in 20% of patients with SVT.

Hereditary and acquired risk factors play an important role in etiopathogenesis of abdominal venous thrombosis. Acquired risk factors are significantly more common in patients with SVT while hereditary risk factors are similar in patients with BCS and SVT. Recognition and evaluation of these risk factors may help in therapy and prevention of disease progression. As a significant number of patients lack obvious etiology further research is required to identify as yet unrecognized risk factors.

COMMENTS

Background

Abdominal venous thrombosis may present as Budd-Chiari Syndrome (BCS) or splanchnic venous thrombosis (SVT). Hereditary and acquired risk factors are implicated in the etiopathogenesis of abdominal venous thrombosis. There are few systematic studies that have comprehensively evaluated both hereditary and acquired factors in BCS and SVT. Most studies have evaluated either a single prothrombotic risk factor or multiple risk factors in a single vein.

Research frontiers

Concept of multifactorial theory of thrombogenesis suggests that thrombosis occurs by activation of a trigger factor (acquired) in a thrombophilic milieu (hereditary). The prevalence of inherited risk factors is variable between populations throughout the world. Possible reasons are small numbers of patients studied, non-standardized evaluation of parameters tested, and genetic differences between patient populations. Data need to be generated by good studies from different geographical areas in the world. Etiological factors for abdominal venous thrombosis were identified in 70%-80% of patients in Western studies. In Indian studies, no risk factor was identified in half the patients suggesting that other unknown hereditary/risk factors may be operating in these patients.

Innovations and breakthroughs

The present study suggests that acquired risk factors which are preventable are important in etiopathagenesis of SVT. As no risk factors were identified in about half the patients, research needs to be ongoing to identify unknown hereditary/ acquired risk factors operating in these patients.

Applications

Abdominal venous thrombosis is a life threatening condition caused by single or multiple, hereditary or acquired prothrombotic risk factors. Prevention and therapy with non-invasive techniques and new anticoagulant drugs are now possible. Complete thrombophilia screening is, therefore, important for risk assessment, and therapy in patients with abdominal venous thrombosis. With continuing search for hereditary risk factors (genetic molecular defects), true

idiopathic thrombotic disease will become uncommon.

Peer review

This paper investigates genetic and acquired risk factors in patients with thromboembolism in abdominal veins. The authors make a difference between hereditary and acquired risk. It's a nice study.

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