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Original Research Article

Inherited thrombophilia in young Indian adults presenting with thrombotic vascular events

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ABSTRACT

Background: There is limited Indian data available regarding inherited thrombophilias. This study was to determine the prevalence of inherited thrombophilias in young Indian patients presenting with thrombotic events.
Methods: This study was done at a tertiary hospital in Western India over a period of 20 months. Epidemiological, clinical and laboratory data was recorded of all consecutive patients aged 16 to 45 admitted with arterial and venous thrombotic vascular events. Blood samples for the thrombophilia profile were sent. Data was tabulated and analyzed using microsoft excel and graph pad software.
Results: 49 patients aged 15 to 45 years, admitted with thrombotic vascular events a period of 20 months were included. 26 (53.1%) were male. The mean age was 22.2±7 years. 20 (40.8%) patients; 10 (38.5%) males and 10 (43.5%) females had at least one thrombophilia. The commonest thrombophilia in both arterial and venous thrombotic events was hyperhomocysteinemia.
Conclusions: Young patients with thrombotic vascular events should be tested for thrombophilias since they are an important risk factor in this subset of patients.

Keywords: Thrombophilia, Young

INTRODUCTION

Thromboses in the arterial system, commonly myocardial infarction (MI) and cerebrovascular accident (CVA); and in the venous system, commonly deep vein thrombosis (DVT) are predominantly diseases of the elderly. There is an exponential increase in the risk of both arterial and venous thrombotic events with age.[1,2] This could be explained by cumulative effects of risk factors on the arterial wall, decreased physical activity, increased immobility resulting in venous stasis, and systemic activation of blood coagulation.[3,4]

Venous and arterial thrombosis is less common in the young. The major risk factor for arterial thrombosis is atherosclerosis that is more common in the elderly than in the young. The risk factors for venous thrombosis are classically related to the 'Virchow's triad' that is injury to the vessel wall, stasis and hypercoagulability. Risk factors include immobility, surgery, underlying medical conditions such as malignancy, medications such as hormonal therapy, obesity, and genetic predispositions. Certain conditions are associated with both venous and arterial thrombosis such as hyperhomocysteinemia, malignancy, antiphospholipid antibody syndrome and hormonal therapy.[5]

Inherited thrombophilias are usually suspected when the patient has recurrent venous thromboembolism, is younger than 45 years of age, has no apparent risk

factors, has a significant family history or a history of recurrent abortions. Inherited and acquired causes of thrombophilia often interact and complicate the diagnosis.[6]

There is limited data regarding the magnitude of inherited thrombophilias in India.[7-10] This study attempted to contribute to the current understanding of the prevalence of inherited thrombophilias in young Indian patients presenting with arterial and venous thrombosis.

METHODS

This observational study was carried out at a tertiary care centre in Western India over a period of 20 months. After obtaining institutional ethics permission, the medical records of all consecutive patients aged 16 to 45 admitted with arterial and venous thrombotic vascular events were reviewed. Arterial thrombotic events included MI that was diagnosed by ECG and cardiac enzymes; and ischemic CVA that was diagnosed by CT or MRI brain. Venous thrombotic events were diagnosed by Doppler or CT/MRI venography as advised by the treating physician and included DVT, pulmonary thromboembolism (PTE), cortical venous thrombosis (CVT), hepatic venous thrombosis or Bud Chiari Syndrome (BCS), portal vein thrombosis (PVT). Patients with the following conditions were excluded:

- Vascular prosthesis in situ e.g. mechanical valves, central venous catheters, hemodialysis catheters.
- Use of oral contraceptive pills, hormonal therapy.
- History of major surgery in the immediate period preceding the thrombotic event.
- Malignancy or myeloproliferative disorder.
- Pregnancy or puerperium.
- Prolonged bed rest, immobilization, use of plaster cast.
- Sickle cell disease, thalassemia, paroxysmal nocturnal hemoglobinuria.
- Thrombotic thrombocytopenic purpura.
- Nephrotic syndrome.
- Valvular heart disease.
- Acute infections.
- Chronic infections (e.g. Tuberculosis, HIV).
- Cocaine or amphetamine use.

Epidemiological, clinical and laboratory data was recorded from their hospital records. Blood samples for the thrombophilia profile were collected before the patient was started on heparin or any oral anticoagulant. Data was tabulated and analyzed using microsoft excel and graph pad software.

RESULTS

51 patients aged 15 to 45 were admitted with thrombotic vascular events over a period of 20 months. Only 2 had MI and hence were excluded from the analysis.

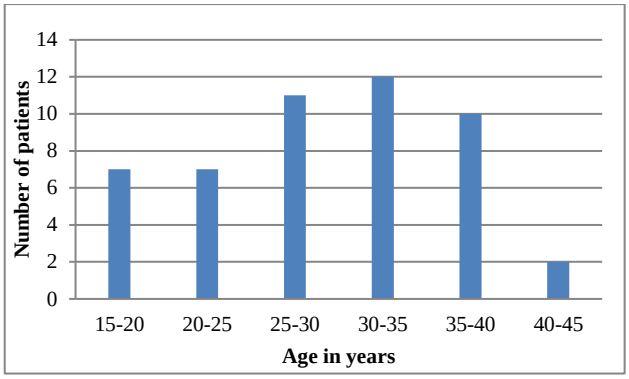

Figure 1: Age distribution of the study population.

Of the 49 patients included, 26 (53.1%) were male. The mean age was 22.2±7 years. The youngest patient was 17 years old, the oldest was 40 years. Figure 1 shows the age distribution of the study population. Maximum patients (12, 24.5%) were in the age group 30-35 years, followed by the age groups 25-30 years and 35-40 years. 33 (67.3%) of the patients were in the age group 25-40 years.

Table 1: Conventional risk factors in the study population.

	Total (49)	Male (26)	Female (23)
Mean age in years	22.2±7 years	28.0±6.9	30.6±7
Conventional risk factors: n (%)			
Smoking	10 (20.4)	10 (38.5)	0
Tobacco chewing	12 (24.5)	12 (46.1)	0
Chronic alcohol use	11 (22.5)	11 (42.3)	0
Diabetes	1 (2.0)	1 (3.8)	0
Hypertension	3 (6.1)	2 (7.7)	1 (4.4)
Dyslipidemia	7 (14.3)	5 (26.9)	2 (8.7)

Table 2: Thrombotic events in the study population.

Thrombotic vascular events	Total (49)	Male (26)	Female (23)
Arterial			
CVA	16 (32.7)	10 (38.5)	6 (26.1)
Venous			
CVT	10 (20.4)	4 (15.4)	6 (26.1)
BCS	9 (18.4)	4 (15.4)	5 (21.7)
PTE	5 (10.2)	4 (15.4)	1 (4.4)
DVT	5 (10.2)	2 (7.7)	3 (13.0)
Portal VT	4 (0.1)	2 (7.7)	2 (8.7)

Conventional risk factors were studied in the population. 1 (2%) patient had diabetes, 3 (6.1%) had hypertension and 7 (14.3%) had dyslipidemia. Smoking was present in 38.5%, tobacco chewing in 46.1% and chronic alcohol consumption in 42.3% of the male patients. None of the female patients had a history of smoking, tobacco

chewing, chronic alcohol use or diabetes. Table 1 shows various conventional risk factors in the study population.

Of the thrombotic events, 16 (32.7%) were in the arterial and 33 (67.3%) were in the venous vasculature. CVT was the most common venous thrombotic event in the entire study population and in female patients. In males, there were 4 cases each of CVT, BCS and PTE. The 16 arterial thrombotic events were all ischemic CVAs. Table 2 depicts the various thrombotic events in the study population (gender wise).

Table 3: Thrombophilias in the study population.

Thrombophilia	Total (49)	Male (26)	Female (23)
Protein C deficiency	2 (4.1)	1 (3.9)	1 (4.4)
Protein S deficiency	2 (4.1)	1 (3.9)	1 (4.4)
Antithrombin III deficiency	1 (2.0)	0	1 (4.4)
Factor V Leiden	2 (4.1)	0	2 (8.7)
ACLA	3 (6.1)	1 (3.9)	2 (8.7)
Hyperhomocysteinemia	14 (28.6)	9 (34.6)	5 (21.7)

Table 4: Type of thrombotic event and presence of thrombophilia.

Thrombophilia	Total (49)	Arterial (16)	Venous (33)
Hyperhomocysteinemia	14 (28.6	6 (37.5)	8 (24.2)
ACLA	3 (6.1)	1 (6.25)	2 (6.1)
Protein C deficiency	2 (4.1)	0	2 (6.1)
Factor V Leiden	2 (4.1)	0	2 (6.1)
Protein S deficiency	2 (4.1)	1 (6.25)	1 (3.0)
Antithrombin III deficiency	1 (2.0)	0	1 (3.0)

Table 5: Characteristics of patients with more than 1 thrombophilia.

Age	sex	Thrombotic event	Thrombophilia
19	Male	BCS	Protein C deficiency, Hyperhomocysteinemia
23	Male	Stroke	Protein S deficiency, Hyperhomocysteinemia
28	Female	CVT	Factor V Leiden, Hyperhomocysteinemia
34	Female	CVT	Protein C deficiency, Hyperhomocysteinemia

20 (40.8%) patients; 10 (38.5%) males and 10 (43.5%) females had at least one thrombophilia. Hyperhomocysteinemia was the most common thrombophilia amongst both genders and was observed in 14 (28.6%) patients. Table 3 shows the thrombophilias seen in the study population (gender wise). The commonest thrombophilia in both arterial and venous thrombotic events was hyperhomocysteinemia. Table 4 depicts the type of thrombotic event and presence of thrombophilia.

There were 4 patients (2 males) who had more than one thrombophilia, of which hyperhomocysteinemia was one. The characteristics of these 4 patients are depicted in Table 5.

12 (52.2%) female patients had no conventional risk factors or thrombophilias. Of these, 5 presented with stroke and 7 had venous thrombotic events (3 CVT, 2 BCS, 1 DVT and 1 PTE). The 5 (19.2%) male patients who did not haveconventional risk factors or thrombophilias presented with venous thrombotic events (2 BCS, 2 PTE, 1 portal VT).

Table 6: Characteristics of patients with past history of thrombotic events.

Age	Sex	Past thrombotic event	Current thrombotic event	Thrombophilia
26	Female	PTE	DVT	None detected
28	Female	Bad obstetric history	CVT	Factor V Leiden, Hyperhomocysteinemia
26	Male	DVT	PTE	None detected

3 patients had a significant past history of thrombotic events. Their characteristics are depicted in Table 6.

DISCUSSION

This study was undertaken to determine hereditary risk factors in young patients who presented with different thrombotic events. In present study, 53.1% patients were male. The age group 30-35 years had maximum number of patients. This is similar to a study of 428 patients in South India where the mean age for venous thrombotic events reported was 31.3 years.[10] Overall 81.6% events occurred in the third and fourth decade. A Danish study reported a steep increase in the incidence of cerebral ischemic events in young adults as a function of age.[11] Cumulative effects of hereditary risk factors, aging and environmental factors play a role in contributing to the risk for thrombosis. This is probably the reason why majority of the thrombotic events occurred in the third and fourth decades.

In this study, a possible etiology of thrombophilia was detected in about 40% of the patients. 20 (40.8%) patients; 10 (38.5%) males and 10 (43.5%) females had at least one thrombophilia. This finding underlines the significance of thrombophilias in young patients presenting with arterial and venous thrombotic events. Patients with thrombophilias causing thrombotic vascular events can be treated with anticoagulants to prevent further episodes and thereby decrease morbidity and mortality.

Hyperhomocysteinemia was the most common thrombophilia amongst both genders and was observed in 14 (28.6%) patients. This is similar to the observations of a study in 428 patients of CVT from South India where the second most common risk factor was hyperhomocysteinemia (78, 18.2%), after anemia (79, 18.4%).[10] In comparison, two Indian studies found Factor V Leiden to be the most common risk factor.[7,8] In present study, genetic mutations for methyl tetrahydrofolate reductase (MTHFR) C677T were not assessed. Hyperhomocysteinemia in present study may have been inherited or acquired. It would be interesting to study what proportion of patients with hyperhomocysteinemia and thrombotic events had an inherited cause of hyperhomocysteinemia. It was the most common risk factor for thrombophilia. Hyperhomocysteinemia is known to cause both arterial and venous thrombosis. Since thrombosis in both arterial and venous vasculature was studied, it is possible that more cases of hyperhomocysteinemia were detected in this study. This is contrast to the aforementioned studies where venous thrombosis (BCS, PVT) were studied and Factor V Leiden was the most common risk factor.[7,8]

There were 12 (52.2%) female patients and 5 (19.2%) male patients with no conventional risk factors or thrombophilias. There were a greater number of females without any risk factors who had thrombotic vascular events than males without any risk factors. It is possible that females are at a higher risk than males for thrombotic vascular events due to hormonal influences.

Modifiable risk factors were also studied. Smoking was present in 38.5%, tobacco chewing was present in 46.1% and chronic alcohol consumption was present in 42.3% of the male patients. A South Indian study compared 214 patients aged 5 to 45 with age and sex matched controls and found current smoking as a major risk factor for stroke.[12] In present study, smoking, tobacco chewing and chronic alcohol consumption were more of a problem in the male gender. None of the female patients had a history of smoking, tobacco chewing, chronic alcohol use or diabetes. These are modifiable or preventable risk factors that can potentially decrease morbidity if controlled. 1 (2%) patient had diabetes, 3 (6.1%) had hypertension and 7 (14.3%) had dyslipidemia. Diabetes, hypertension and dyslipidemia are considered to be risk factors in the older population. However, they may play a significant role even in young patients with thrombotic events.

We found that 3 patients had a significant past history of thrombosis at another site. Out of these, 2 patients had no risk factors. One was a male patient admitted for PTE who had a history of DVT. The other was a female patient admitted for DVT who had a history of PTE. Both of them may have benefitted from anticoagulation but had been non-compliant to therapy. The third patient was a female with a bad obstetric history who had presented with CVT. This patient had 2 risk factors; hyperhomocysteinemia and Factor V Leiden. A study of 238 patients had found that hereditary thrombophilic risk factors (deficiency of ATIII, Protein C and Protein S) are associated with recurrent thrombosis in 48%.[13] Patients with hereditary risk factor are at risk of recurrent thrombosis and are candidates for prophylactic anticoagulation.

One limitation of this study was the small sample size. Larger sample sizes are needed to understand the patterns of inherited thrombophilia in the Indian setting. Evaluating patients with hyperhomocysteinemia for genetic mutations would have added useful information to the study.

CONCLUSION

40.8% of the thrombotic vascular events could be explained by at least one risk factor studied. Hyperhomocysteinemia was the most common thrombophilia observed in this study. Young patients with thrombotic vascular events should be tested for thrombophilias since they are an important risk factor in this subset of patients.

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