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Assessment of Risk Factors for Recurrence of Deep Vein Thrombosis in a Cohort of 125 Patients

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ABSTRACT

A combined prospective and retrospective descriptive analysis of a cohort of patients with recurrent lower limb DVT was conducted. The study included 125 patients studied for a series of risk factors including clinical evidence of Behcet's disease, internanal malignancy and laboratory evidence of APC resistance, Prothrombin gene mutation G>A 20210 by PCR, Protein C, S and Antithrombin. Ancticardiolipins aCL, Homocysteine or evidence of Paroxysmal nocturnal haemoglobinuria or a myeloproliferative disorder.

In our study, 51.2% of patients with recurrent DVT had an idiopathic aetiology, 26.6% had a single endogenous risk factor, 13.6% had two endogenous risk factors, 8.8% had both endogenous and exogenous risk factors and 5.6% had an exogenous risk factor.

Statistical analysis was done to difference in relation to site, bilaterality, recurrence and patency of the affected vessels. A correlation was statistically significant between the site and recurrence (p=0.05) as well as between incomplete patency and recurrence (p=0.000).

Key Words: *Risk factor - DVT.*

INTRODUCTION

Deep vein thrombosis (DVT) is a common disease, with an annual incidence in the general population of approximately 1 per 1000. It is defined as a partial or complete occlusion of a deep vein by thrombus. DVT is an important complication of several inherited and acquired disorders, but may also occur spontaneously. The clinically important problems associated with venous thromboembolism (VTE) are death from pulmonary embolism (PE), morbidity resulting from the acute event, recurrent thromboembolic events and the post-thrombotic syndrome. Prevention of recurrent VTE and PE is the main reason for accurate diagnosis and adequate treatment **[1]**.

The risk of recurrent thromboembolism after the discontinuation of anticoagulant therapy is highly dependent on patient-specific risk factors. Patients who have thrombosis in the absence of known risk factors (i.e., who have idiopathic venous thrombosis) or in association with persistent risk factors (such as cancer and thrombophilia) are at higher risk of recurrence than patients with thrombosis associated with time-limited, reversible risk factors **[2]**.

The pathophysiology of vein thrombosis involves three interrelated factors “Virchow’s triad”: Damage to the vessel wall, slowing down of the blood flow and increase in blood coagulability. The first two components of Virchow’s triad, in most instances, represent acquired conditions but blood hypercoagulability has both intrinsic and extrinsic causes **[3]**.

Several conditions enhance the chances of thrombosis. Atheromatous vessels, myeloproliferative disorders, polycythaemia, paroxysmal nocturnal haemoglobinuria (PNH), associated malignancies, Behcet syndrome, abnormalities of lipid profile, antiphospholipid syndrome, oral contraceptives and prolonged bed rest are some conditions attributed to cause thrombosis **[4]**.

These states not only predispose apparently healthy people to thrombosis, but are also likely to trigger thrombosis in people with inherited

thrombophilic abnormalities. The well - established inherited prothrombotic abnormalities are deficiencies of antithrombin III (ATIII), protein C (PC), protein S (PS) as well as factor V Leiden and prothrombin gene mutation (G20210A) **[5]**. Hyperhomocysteinaemia, dysfibrinogenaemia, abnormalities of the fibrinolytic system and increased plasma levels of coagulation factors VIII, IX and XI are additional prothrombotic risk factors **[5]**.

Co-existing thrombophilic abnormalities increase the risk of thrombosis. Compound heterozygotes with both factor V Leiden and prothrombin gene mutation are relatively common. The risk of thrombosis may be further increased by the co-existence of antiphospholipid antibodies or hyperhomocysteinaemia **[6]**.

Similarly; other hereditary or acquired abnormalities may co-exist substantially increasing the risk of venous thrombosis. For example, it has been shown that women who have the prothrombin gene mutation increase the risk of developing a DVT by about 16 times by using oestrogen-containing oral contraceptives. Hormone replacement therapy also increases the risk of DVT by 2 to 4 times in females with the prothrombin 20210 mutation **[7]**.

Study objectives:

To determine the prevalence of endogenous and exogenous risk factors for venous thrombosis in patients with recurrent lower limb DVT and to evaluate the risk of recurrence in patients with incomplete patency.

MATERIAL AND METHODS

A combined prospective and retrospective descriptive analysis of a cohort of patients with recurrent lower limb (LL) DVT was conducted. The study included 125 patients referred for evaluation of thrombosis from August 1999 to December 2005. All patients had recurrent LL DVT (second episode) proved by Doppler.

Detailed history was taken to exclude reversible precipitating causes like prolonged bed rest, diabetes mellitus, prolonged use of oral contraceptives, atherosclerosis, cardiovascular or congenital heart disease, surgical procedures and preceding infections. Hence, the study predominantly included only those patients who needed further evaluation for the cause of recurrent thrombosis.

Detailed epidemiological and clinical data were obtained. All patients were subjected to meticulous clinical examination and routine laboratory investigations. In addition, specific laboratory tests were performed in an attempt to identify the cause of thrombophilia. The latter included testing for PC, PS and ATIII deficiencies, anticardiolipin antibodies (aCL), prothrombin gene mutation and activated PC resistance (APCR).

The patients' plasmas were tested for PC and PS deficiencies by enzyme-linked immunosorbent assay (ELISA) using Corgenix kit; while ATIII deficiency was tested by colorimetric analysis using kits supplied by Organon Tekinka. The patients' sera were used to test for aCL IgG antibodies by using the commercially available Orgentek ELISA kits.

Testing for prothrombin gene mutation was performed by DNA polymerase chain reaction (PCR). Although a definitive diagnosis of factor V Leiden can be done by PCR, yet the relatively simple plasma screening test for APCR was used instead.

Patients were categorized on the basis of tests' results as being with or without thrombophilia. Those without thrombophilia were further classified as having idiopathic or secondary DVT. All patients received therapeutic doses of clexane and oral anticoagulants.

Patients were followed up to document the incidence of symptomatic recurrent DVT or PE. They were educated about the main signs and symptoms of recurrent VTE and received a card with the telephone numbers of the thrombosis clinic. They were instructed to return to the study center if they noted clinical manifestations suggestive of recurrent venous thrombosis (edema, redness, tenderness, pain, or swelling) in either leg or suggestive of PE (dyspnea, chest pain, or tachycardia).

Patients were also seen at the time of ultrasonographic assessments and were contacted at least twice yearly to ascertain whether signs and symptoms had occurred in which case they were invited to come to the study center for additional diagnostic procedures.

Recurrent DVT was diagnosed by compression ultrasonography. Patients with suspected PE had ventilation-perfusion lung scanning.

RESULTS

The studied group included 125 patients with recurrent LL DVT. They were 52 females and 73 males. Their age ranged between 14 and 75 years with a mean ± SD of 47.2±13.1 years.

An endogenous risk factor for thrombophilia was found in 54 patients representing 43.2% of the entire studied group. Twenty six patients (20.8%) had a single risk factor while 17 patients (13.6%) had two risk factors of thrombophilia. Both an exogenous and an endogenous risk factor were detected in 11 patients (8.8%) and seven patients had a secondary cause for thrombosis (myeloproliferative, malignancy and PNH). The different aetiologies are shown in Table (1).

Table (1): The distribution of patients according to the risk factors (n=125).

Risk Factor	n	%
APCR	18	14.4
Prothrombin G20210A mutation	3 (2 homozygous and 1 heterozygous)	2.4
ATIII deficiency	6	4.8
PC deficiency	7	5.6
PS deficiency	3	2.4
Behcet	11	8.8
Hyperhomocysteinaemia	2	1.6
aCL	16	14.4
PNH	3	2.4
Myeloproliferative disorders	6	4.8
Malignancy	9	7.2

The detected risk factors varied widely with the highest incidence (14.4%) in patients having APCR and aCL (18 and 16 cases respectively). The lowest incidence (1.6%) was in patients with hyperhomocysteinaemia (2 cases).

No definite aetiology could be detected in 64 patients (51.2%), *p* value was not significant. Clinically detectable pulmonary emboli occurred among the LL DVT patients. Three patients had minor post-phlebitic symptoms and 8 patients experienced recurrent DVT. The descriptive statistics of the study subjects is shown in Table (2).

Patients were divided into 5 groups according to the aetiology of LL DVT:

1- Group 1: Included patients with one endogenous risk factor.

2- Group 2: Included patients with two endogenous risk factors.

3- Group 3: Included patients with both exogenous and endogenous risk factors.

4- Group 4: Included patients with exogenous risk factor.

5- Group 5: Included patients with idiopathic aetiology.

Table (2): The descriptive statistics of the study subjects (n=125).

Variable	n	%
Group:		
1	26	20.8
2	17	13.6
3	11	8.8
4	7	5.6
5	64	51.2
Site:		
Peripheral	105	84
Ilio-femoral	20	16
Bilaterality:		
Unilateral	115	92
Bilateral	10	8
Recurrence:		
No	117	93.6
Yes	8	6.4
Patency:		
Complete	107	85.6
Incomplete	18	14.4

Statistical analysis was done to detect any correlation and if there is statistical difference between the different groups in relation to site, bilaterality, recurrence and patency of the affected vessels.

Significant statistical differences were found in the rate of recurrence in group 2, patency in group 3, site in group 4 and all the previous variables in group 5 when compared to other groups.

Group 1 with one risk factor showed no significant correlation with recurrence, patency or the site when compared to other groups [Table (3)].

Table (3): Chi square to test for statistical differences between group 1 (n=26) and other aetiologies.

	One risk factor		Other subjects		*p**
	n	%	n	%	
Site:					
Peripheral	23	18.4	82	56.6	0.49
Ilio-femoral	3	24	17	13.6	
Bilaterality:					
Unilateral	25	20	90	72	0.38
Bilateral	1	0.8	9	7.2	
Recurrence:					
No	26	20.8	91	72.8	0.13
Yes	0	0	8	6.4	
Patency:					
Complete	21	16.8	86	68.8	0.43
Incomplete	5	4	13	10.4	

* *p* value <0.05 is considered statistically significant.

Group 2 with two thrombophilic risk factors showed significant correlation with recurrence *p* value =0.000, but no significant correlation with patency or the site when compared to other groups [Table (4)].

Table (4): Chi square to test for statistical differences between group 2 (n=17) and other aetiologies.

	Two risk factor		Other subjects		*p**
	n	%	n	%	
Site:					
Peripheral	12	9.6	93	74.4	0.15
Ilio-femoral	5	4	15	12	
Bilaterality:					
Unilateral	16	12.8	99	79.2	0.73
Bilateral	1	0.8	9	7.2	
Recurrence:					
No	11	8.8	106	84.4	0.000
Yes	6	4.8	2	1.6	
Patency:					
Complete	13	10.4	94	75.2	0.25
Incomplete	4	3.2	14	11.2	

* *p* value <0.05 is considered statistically significant.

Group 3 with both exogenous and endogenous risk factors showed significant correlation with incomplete patency, *p* value =0.000, but no significant correlation was found with recurrence or the site when compared to other groups [Table (5)].

Table (5): Chi square to test for statistical differences between group 3 (n=11) and other aetiologies.

	Exogenous and endogenous risk factors		Other subjects		*p**
	n	%	n	%	
Site:					
Peripheral	8	6.4	97	77.6	0.29
Ilio-femoral	3	2.4	17	13.6	
Bilaterality:					
Unilateral	11	8.8	104	83.2	0.31
Bilateral	0	0	10	8	
Recurrence:					
No	9	7.2	108	86.4	0.09
Yes	2	1.6	6	4.8	
Patency:					
Complete	5	4	102	81.6	0.000
Incomplete	6	4.8	12	9.6	

* *p* value <0.05 is considered statistically significant.

Group 4 with endogenous risk factor showed significant correlation with ilio-femoral affection, *p* value =0.04, but no significant correlation with the other parameters [Table (6)].

Table (6): Chi square to test for statistical differences between group 4 (n=9) and other aetiologies.

	Exogenous risk factors		Other subjects		*p**
	n	%	n	%	
Site:					
Peripheral	4	3.2	101	80.8	0.04
Ilio-femoral	3	2.4	17	13.6	
Bilaterality:					
Unilateral	6	4.8	109	87.2	0.53
Bilateral	1	0.8	9	7.2	
Recurrence:					
No	7	5.6	110	88	0.48
Yes	0	0	8	6.4	
Patency:					
Complete	5	4	102	81.6	0.27
Incomplete	2	1.6	16	12.8	

* *p* value <0.05 is considered statistically significant.

Group 5 with idiopathic aetiology showed significant correlation with incomplete patency, recurrence and ilio-femoral affection, *p* value =0.000, 0.003 and 0.04 respectively, but no significant correlation with bilaterality when compared to other groups [Table (7)].

Table (7): Chi square to test for statistical differences between group 5 (n=64) and other aetiologies.

	Idiopathic aetiology		Other subjects		*p**
	n	%	n	%	
Site:					
Peripheral	58	46.4	47	37.6	0.04
Ilio-femoral	6	4.8	14	11.2	
Bilaterality:					
Unilateral	57	45.6	58	46.4	0.21
Bilateral	7	5.6	3	2.4	
Recurrence:					
No	64	51.2	53	42.4	0.003
Yes	0	0	8	6.4	
Patency:					
Complete	63	50.4	44	35.2	0.000
Incomplete	1	0.8	17	13.6	

* *p* value <0.05 is considered statistically significant.

The association between the site of thrombosis, bilaterality, recurrence and patency was tested by Chi square and the results are shown in Tables (8,9,10) respectively.

Table (8): The association between the site of thrombosis and other variables.

	Peripheral		Ilio-femoral		*p**
	n	%	n	%	
Bilaterality:					
Unilateral	95	76	20	16	0.15
Bilateral	10	8	0	0	
Recurrence:					
No	100	80	17	13.6	0.05
Yes	5	4	3	2.4	
Patency:					
Complete	92	73.6	15	12	0.14
Incomplete	13	10.4	5	4	

* *p* value <0.05 is considered statistically significant.

Table (9): The association between bilaterality of thrombosis and other variables.

	Unilateral		Bilateral		*p**
	n	%	n	%	
Recurrence:					
No	107	85.6	10	8	0.4
Yes	8	6.4	0	0	
Patency:					
Complete	97	77.6	10	8	0.18
Incomplete	18	14.4	0	0	

* *p* value <0.05 is considered statistically significant.

Table (10): The association between recurrence of thrombosis and other variables.

	No recurrence		Recurrence		*p**
	n	%	n	%	
Patency:					
Complete	104	83.2	3	2.4	0.000
Incomplete	13	10.4	5	4	

* *p* value <0.05 is considered statistically significant.

A correlation was statistically significant between the site and recurrence (p=0.05) as well as between incomplete patency and recurrence (p=0.000).

DISCUSSION

Prospective studies in asymptomatic carriers of inherited thrombophilic defects have shown rather low annual incidence of VTE (between 0.2 and 2% patient-years), which however, is 2-20 times higher than in non-carriers **[9]**.

In the last few years, questions have been raised on whether these thrombophilic conditions are also responsible for an increased risk of recurrent VTE. It is indeed generally expected that carriers are more prone to develop recurrent thrombotic events than non-carriers. This has been shown to be the case for conditions like ATIII, PC and PS deficiencies, mild hyperhomocysteinaemia, increased factor VIII levels, and antiphospholipid antibodies. Surprisingly, there is still some debate on whether heterozygous FV Leiden mutation and G20210A prothrombin variant, which are the most common causes of thrombophilia, are associated with an increased risk of VTE, as some studies are in favour of and others against this association. Homozygous or double heterozygous carriers of either defect, however, appear to be consistently exposed to a higher risk of recurrent VTE **[5]**.

In our study, 51.2% of patients with recurrent DVT had an idiopathic aetiology, 26.6% had a single endogenous risk factor, 13.6% had two endogenous risk factors, 8.8% had both endogenous and exogenous risk factors and 5.6% had an exogenous risk factor.

The detected risk factors varied widely with the highest incidence (14.4%) in patients having APCR and aCL (18 and 16 cases respectively). The lowest incidence (1.6%) was in patients with hyperhomocysteinaemia (2 cases).

Prandoni et al., reported an increased risk of recurrent VTE in patients who showed ultrasound findings compatible with persistent residual thrombus after a first episode of proximal-vein thrombosis compared with those who did not. Interestingly, in a multivariate analysis including thrombophilic abnormalities, persistent residual thrombus appeared to be an independent risk factor for recurrent VTE. This is in accordance with our study in which a statistically significant correlation was found between patency and recurrence.

It is well established that patients who are deficient in one of the natural coagulation inhibitors (i.e., AT-III, PC, or PS) have a markedly increased risk for VTE. Retrospective studies revealed an increased risk for thromboembolism in the inhibitor-deficient compared with the inhibitor-nondeficient individuals. In our study, ATIII deficiency was found in 6 patients, PC deficiency in 7 patients and PS deficiency in 3 patients.

In almost 50% of patients with recurrent DVT, decrease of at least one plasma coagulation inhibitor (ATIII, PC, and PS) level was observed in a study by Swiatkiewicz et al. **[11]**. Also, among 30 patients with ATIII, PC, and PS deficiencies (2, 21 and 7 cases respectively) studied by Lefrancois et al., ten of the 30 cases have had recurrent venous thrombosis at the time of bed rest, trauma, surgery, pregnancy, postpartum or during oral contraceptive treatment. Spontaneous DVT occurred in 3 cases. Seventeen patients had remained asymptomatic till then **[12]**.

In a study by Pabinger et al. **[13]** the probability of developing thrombosis in patients with hereditary AT III, PC and PS deficiency was high (80-90% by the fifth to sixth decade of life). Although a significant difference among the three deficiency states with regard to age at the first thrombotic event was not detected in males, females with ATIII deficiency developed thrombosis significantly earlier in life compared with females with PC or PS deficiency. This difference is due to the extremely high thrombotic risk associated with pregnancy and oral contraceptive use in ATIII-deficient females.

Interestingly, these results in patients with AT-III, PC, or PS deficiency are different from those of patients with resistance to APC, since Svensson and Dahlbäck **[14]** reported only a 30% risk of thrombosis at age 60 for APC-resistant individuals. Hereditary AT-III, PC and PS deficiencies seem to be stronger risk factors for thrombosis than is APC R. However, in our study 18 patients (14.4%) showed APCR while 16 patients (12.8%) collectively had AT-III, PC and PS deficiency.

Many investigators have reported that factor V Leiden is a stronger risk factor for DVT than PE. Prothrombin gene mutation is associated with DVT in the lower extremities alone or when complicated by PE, but it is not associated with isolated PE. Carriers of inherited thrombophilic risk factors were less frequently found among patients with PE alone. Also, carriers of two inherited thrombophilic defects were more frequent among patients with DVT only than among those suffering from isolated PE **[15,16,17]**.

Margaglione et al. **[15]** stated that in patients from different ethnic groups, factor V Leiden has been found in up to 20% and the prothrombin gene mutation in up to 14% of cases of unselected patients with DVT. Double heterozygotes showed higher risk of VTE **[18]**.

When patients with a known alternative risk factor for thrombosis (factor V Leiden mutation or deficiency of ATIII, PC or PS) were excluded, the G20210 variant was found to increase the risk for venous thrombosis by approximately 5 fold **[19]**. Varga and Moll **[20]** also agreed that having a heterozygous prothrombin mutation increases the risk of developing a first DVT by about 2 to 3 times the background. Having homozygous prothrombin mutations increases the risk further, but is not yet known how much the risk is increased.

Surprisingly, De Stefano et al. **[21]** found that patients with the prothrombin mutation had a risk for spontaneous recurrent VTE similar to that of patients with normal genotype. The circumstances of the first event (spontaneous or secondary) did not produce any substantial variation in the risk of recurrence.

Some investigators reported that the risk of recurrent DVT is similar among carriers of factor V Leiden and patients without this mutation. They did not corroborate a stronger association of factor V Leiden in DVT than PE or

in older than in younger participants. Thus, for them, whether factor V Leiden is associated with recurrent events is somewhat controversial **[22,23]**.

In our study, recurrence of VTE was not statistically significant between the idiopathic cases and those with a definite aetiology 51.2 and 49.8% respectively. However, group 2 with two endogenous risk factors showed the highest statistically significant recurrence rate (p= 0.000). Ten of our patients developed recurrent thrombosis in the unaffected leg and three developed isolated PE. These results are in accordance with Paolo et al. **[23]** who confirmed that both idiopathic cases and those with a definite risk factor are associated with increased risk for recurrent VTE. Also, one third of their cases developed recurrent thrombosis in the initially unaffected leg and another third developed isolated PE.

The presence of an identifiable cause among our patients was associated with an increased risk for incomplete patency and development of ilio-femoral rather than peripheral DVT when compared to the idiopathic group. There was a strong correlation between recurrence and incomplete patency, the latter showed statistical significance in group 3 patients with both endogenous and exogenous risk factors.

Ginsberg and others suggested that the risk for recurrence is considerably higher in patients with residual venous thrombosis on repeated ultrasonography than in patients with early vein recanalization **[24,25]**. Residual thrombosis could impair venous outflow, resulting in blood stasis with consequent clot formation. Piovella and colleagues suggest that the thrombus in proximal venous segments (ilio-femoral) increase the incidence of recurrence risk **[26]**.

Prins and Marchios suggested that patients with proximal venous thrombosis whose veins do not recanalize are likely to develop recurrent thrombotic events after withdrawal of oral anticoagulant therapy **[6]**. Recurrence of DVT, in our study, occurred in 3 out of 8 patients (37.5%) who did not receive adequate warfarin treatment. This was statistically significant in comparison to those who received adequate treatment; 5 out of 117 patients (4.2%).

In patients with thrombosis associated with time-limited, reversible risk factors, oral anticoagulant therapy can be limited to 3 months after the elimination of the risk factor. More prolonged courses of anticoagulant therapy are recommended for patients in whom thrombosis is associated with persistent risk factors or idiopathic thrombosis **[2]**. However, in all patients, the risk for recurrence after a short, fixed period of anticoagulation varies greatly. Approximately 70% of patients with unexplained thrombosis do not develop a recurrence, and 10% of patients with transient risk factors do **[27]**.

In their study, Angelli et al., reported that prolonging anticoagulant therapy beyond 3 months in patients with idiopathic DVT simply delays recurrence until anticoagulant therapy is stopped, rather than reducing the risk of recurrence **[2]**. Pinede et al., showed equivalence between two treatment regimens for recurrence, namely, 6 or 12 weeks of anticoagulant therapy for isolated calf DVT and 3 or 6 months for proximal DVT and/or PE without a significant increase in bleeding complications **[28]**.

Christiansen et al., stated that prothrombotic abnormalities do not appear to play an important role in the risk of a recurrent thrombotic event. Testing for prothrombotic defects has little consequence with respect to prophylactic strategies. Clinical factors are probably more important than laboratory abnormalities in determining the duration of anticoagulation therapy **[29]**.

There is no doubt that discrepancy of results among the many studies now available on the role of thrombophilia in predisposing to VTE recurrences are largely due to the complexity of interactions of component causes. Unfortunately, discrepancies of results often generate discordance in the management of thrombotic patients. Future studies with the potential to provide physicians with consistent and reassuring answers are warranted.

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