

Thrombophilia testing in patients with venous thrombosis

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Background: Routine thrombophilia testing is controversial because of the low yield of positive tests, costs involved, and debate about the clinical usefulness of the data obtained from testing.

Laboratory investigations are rarely done for those with superficial venous thrombosis (SVT) or isolated calf vein thrombosis (CVT) that, in some cases, are not even treated with anticoagulants.

Objective: The purpose of this study was to identify the incidence of markers of thrombophilia in patients with deep vein thrombosis (DVT), SVT, isolated CVT or a history of thrombosis in a referral practice.

Methods: One hundred and sixty-six patients were referred to our thrombosis unit for consultation, including patients with SVT, DVT, and preoperative patients with a previous history of SVT or DVT. Patients underwent thrombophilia screening and patients with a diagnosis of SVT or DVT were confirmed by full-leg bilateral duplex ultrasonography.

Thrombophilia testing included factor V Leiden (FVL), prothrombin 20210A mutation (P2), methylene tetrahydrofolate reductase deficiency (MTHFR), fasting serum homocysteine (HC), lupus anticoagulant (LA), anticardiolipin antibodies (ACA), antithrombin deficiency (AT), protein S deficiency (PS), and protein C deficiency (PC).

Results: The incidence of any significant abnormality in patients with DVT was 27/44 (61%; 95% Confidence Interval [CI], 47-76%) and 10 of these patients were positive for FVL (22.7%; 95% CI, 10-35%). Twelve patients with only CVT were seen and 5 had at least one abnormality (41.7%; 95% CI, 14-70%) including one with FVL (8.3%; 95% CI, 0-24%). Thirty-nine patients with only SVT were seen including 14 with at least one abnormality (35.9%; 95% CI, 21-51%) and 5 of these patients with SVT had FVL (12.8%; 95% CI, 2-23%). Nine patients with recurrent DVT were seen and 5 of these had at least one abnormal test (55.6%; 95% CI, 23-88%). Finally, 18 of the 166 patients had more than one abnormality (10.8%; 95% CI, 6-16%).

Conclusion: The presence of one or more markers of thrombophilia was significantly higher in this patient population compared to reports from other centers. This study identified 18/166 (10.8%; 95% CI, 6-16%) with more than one defect where life-long anticoagulation may be necessary. The results in this subset of patients as well as the serious defects found in some patients with provoked, isolated CVT or isolated SVT demonstrate the value of this screening program to both these patients and their blood relatives. On the other hand, this is a small series from a referral practice where the incidence of these defects is greater than one would expect in the general population. These studies are preliminary and it is not recommended that all VTE patients should be screened on the basis of the current report.

The introduction of the term thrombophilia by Egeberg in 1975 followed his description of a tendency to develop deep vein thrombosis (DVT) in a Norwegian family that was subsequently shown to have antithrombin deficiency.¹ Since that time a number of additional defects in patients with venous thromboembolism (VTE) have been described.² The overall incidence of these disorders in the general population is low, so routine testing is not justified. There are no clear-cut guidelines regarding routine testing of patients with VTE^{3,4} and even less information regarding testing of patients with superficial venous thrombosis (SVT) or isolated calf vein thrombosis (CVT). Zwicker⁵ has reported that patients testing positive for certain combinations of 2 or more defects may result in a 70-90% risk of recurrent thrombosis during their lifetime.

We embarked on a program of routine thrombophilia testing in patients referred for thrombosis management or preoperative consultation because of a previous DVT. The intent was to determine the incidence of thrombophilic defects in these patients and to speculate on the clinical usefulness of the information obtained from this screening.

METHODS

Patient referral and duplex scan verification. Patients referred to the primary author's practice included those with SVT, DVT, patients with venous disease, or with a personal or family history of DVT who required elective surgery and needed advice regarding the type and extent of thrombosis prophylaxis. All of these patients underwent bilateral leg duplex scanning and were questioned regarding past episodes of personal VTE and family history to uncover any

thromboembolic events in blood-related individuals. Each patient underwent a careful thrombosis risk assessment, including specific questions regarding previous major surgery, cancer, prior myocardial infarction, past major trauma, or other serious medical disease. We also recorded medications, including oral contraceptives and hormone replacement therapy. Bilateral venous duplex ultrasonography was done using a high-resolution color scanner (Ultramark9-HDI, Advanced Technology Laboratories, Bothell, WA). The patients were placed in reverse Trendelenburg position at approximately a 10 to 20 degree angle to examine the common femoral, superficial femoral, profunda femoral, and greater and lesser saphenous veins. The examination began at the level of the common femoral vein just below the inguinal ligament. The distal superficial femoral, popliteal, and calf veins were examined, when possible, in the dependent position with a leg resting on the operator's lap. This maneuver induces vein dilatation and improves vein visualization. If the patient was unable to sit, the leg was externally rotated and the test performed in the supine position. All the veins were examined in the transverse and longitudinal views.

The abnormal examination criteria that indicated DVT included: no venous Doppler scan signals noted with respiration or augmentation maneuvers, echogenic filled vessel lumen, and the inability to compress the vein with gentle probe pressure that was not as a result of extra vascular causes. At least two criteria were required for the diagnosis of DVT. Thrombi that extended to the popliteal vein or above were considered proximal, whereas those clots that were limited to the calf were considered distal. This technique has previously been reported and validated.⁶

Thrombophilia Screening. Thrombophilia tests were ordered for patients based on the risk factors associated with the development of VTE at the time of their clinical evaluation. Specific indications for testing included patients with a personal or family history of VTE, women with a

history of unexplained stillborns, or patients with a personal or family history of stroke or myocardial infarction.

The three genetic mutations examined included factor V Leiden, prothrombin 20210A, and methylene tetrahydrofolate reductase deficiency (MTHFR). The remaining thrombophilia markers consisted of antithrombin, protein C and S functional, and acquired antiphospholipid antibodies which included lupus anticoagulant, and fasting serum homocysteine.

The first three mutations were evaluated using a signal amplification program known as the 'Invader method' (Third Wave Technologies [Madison, WI]). All remaining tests involved a blood draw using standard venous phlebotomy at Glenbrook Hospital, Glenview, IL. A 2.7-mL buffered sodium citrate (9:1) vacutainer tube was used to obtain blood for protein S, C, and antithrombin levels. A chromogenic method was employed for antithrombin and protein C activity (Dade Behring [Deerfield, IL]), whereas a clotting method determined results for protein S (Biopool) and lupus anticoagulant (Dade Behring [Deerfield, IL]). Homocysteine values were obtained on a specimen of blood drawn into a 3-mL potassium EDTA (Ethylene Diamine Tetra-Acetic Acid) 5.4-mL vacutainer tube. Normal homocysteine ranges were produced with an adviaventaur (Bayer™ [Pittsburgh, PA]). Finally, blood for anticardiolipin antibodies was drawn into a 5-mL serum separator (SST) vacutainer tube gel and clot activator. An enzyme immunoassay kit manufactured by Diamedix was used to evaluate ranges. These assays were all obtained either prior to the institution of anticoagulation therapy or after the patients had completed their course of anticoagulation treatment.

Table I displays the normal values for these tests and indicates what we considered significant abnormalities. Heterozygous MTHFR mutations were not considered abnormal since these defects exist in up to 30% of normal individuals.⁷ We also excluded borderline or mild elevations of anticardiolipin antibodies as positive test results. None of these abnormalities has been shown to be important in thrombosis management.^{7,8} Table II shows the number of

patients in each group. The breakdown between significant and overall findings in various patient groups is seen in Table III.

Statistical methods. SPSS version 11.5 package (Statistical Package for Social Sciences Inc., Chicago, IL) was used for all statistical analyses. Cross-tabulation of variables was performed and included the frequency of each abnormality. Along with exact proportions, 95% confidence intervals were calculated.

RESULTS

The study included 166 patients with some form of thrombosis or history of thrombosis who were referred for primary or secondary VTE management over a two-year period. This included patients referred for evaluation before an elective surgical procedure or for management of venous disease. Table II lists the location of thrombi as well as important historical information. A broad range of abnormal tests was seen in the various patient groups. Some patients had more than one thrombotic location and some individuals had more than one defect. We defined a personal or family history of VTE as those cases with objective evidence of a thrombosis (i.e., duplex scan, venogram, lung scan).

The results of thrombophilia testing for these same categories are seen in Tables III, IV, and V. Forty-four patients with a DVT were seen and 27/44 (61.4%; 95% CI, 47-76%) of these individuals had a significant abnormality. Twelve of the DVT patients shown in Table III had CVT only and 5 of these 12 (41.7%; 95% CI, 14-70%) individuals had a positive marker for thrombophilia. Also included in the DVT group seen in Table III were 9 patients with recurrent DVT and 5 of these (55.6%; 95% CI, 23-89%) had a significant abnormality.

Superficial thrombosis not associated with DVT or PE was seen in 39 patients in the study, including 14 individuals with a positive marker as seen in Table III (35.9%; 95% CI, 21-51%). Five of these patients with a positive marker had a factor V Leiden defect including two

homozygous and three heterozygous defects. Finally, we found 18 patients with more than one defect and 14 of these individuals had a past history of thrombosis (78%; 95% CI, 59-97%). Other categories of patients with 2 defects included: acute DVT 9/18 (50%; CI, 95% 27-73%), history of PE 5/18 (27%; 95% CI, 6-48%), 4/18 (22%; 95% CI 3-41%) patients each had recurrent DVT or a family history of DVT, and 2/18 patients had SVT only (11%; 95% CI, 0-25%).

Table V shows the incidence of thrombophilic markers in patients with provoked versus idiopathic clots. As expected, a greater percentage of idiopathic clots were associated with positive markers. It is interesting to note the relatively high percentage of positive markers in those with provoked clots.

DISCUSSION

It is important for the reader to understand that we screened everyone with DVT since they were referred to us to get some answers as to why they developed DVT in the first place. We screened even those with provoked causes since some of them, as mentioned later, had defects and this we felt added to the value of our consultation.

Provoked Thrombosis

An interesting finding from our study is the percentage of patients with so-called “provoked” thrombosis who were found to have a thrombophilic defect. “Provoked events” in this study were defined as those where it was felt that the clot resulted from surgery, leg injuries, prolonged travel, birth control pills or hormonal replacement. None of these provoked cases was due to intravenous catheters or post-partum, and the numbers are too small to break down according to type of event. Eleven of the 44 DVT patients (25%; 95% CI, 12-38%) were judged to have a provoked event. Surprisingly, 5 of the 11 provoked DVT patients (45.5 %; 95% CI, 16-75%) were found to have a positive marker for DVT. It should be noted that this is

simply an observation to alert the clinician that even though the event is provoked, a thrombophilic defect still may be present. It is for the reader to decide which of these patients needs to be screened. An idiopathic event was seen in 33/44 (75%; 95% CI, 62-87%) of the DVT patients and 22/33 (66.7%; 95% CI, 51-83%) of these idiopathic DVT individuals had a positive marker for thrombophilia, as seen in Table V.

Although the sample size is small and the confidence interval wide, individual patient care was potentially improved by finding these defects. While many physicians do not recommend testing those with known causes of thrombosis (provoked), if a serious defect were found, extended anticoagulation may be necessary.

Isolated SVT

At least one abnormality was found in 14/39 (35.9%; 95% CI, 21-51%) patients with isolated SVT and 3 of these individuals were considered to have a provoked event. The most important defects identified included one patient each with protein C, protein S, antiphospholipid antibodies, and lupus anticoagulant. Two of these patients also had homozygous factor V Leiden. Most investigators treat these patients with life-long anticoagulation.^{9, 10} To our knowledge, testing for markers of thrombophilia in those with provoked SVT has not been done and may represent one tiny contribution that is unique to this paper.. We know that women of child-bearing age found to have positive markers would be at increased risk for developing thrombosis during subsequent pregnancies. This is just an observation, however, and the authors are not suggesting that every female with SVT be subjected to screening.

An interesting perspective is provided by the recently published long-term epidemiologic studies from Heit at the Mayo Clinic that showed a startling 25% of patients with acute PE presented as sudden death. Recurrent thromboembolism over 16,430 person-years of follow-up resulted in a 7-day case fatality of 16.7%. The authors concluded that routine screening of

patients with a first episode of thrombosis, and long-term treatment of those with positive markers, could have lowered this death rate.¹¹

In our study the overall values of positive markers are somewhat higher than those seen by others in patients with VTE.^{7, 12} The reader should be careful to note that the management of the patient is not necessarily influenced by the presence of the heterozygous form of this defect. However, the incidence of factor V Leiden in 22% of these individuals does agree with some other reports.¹³ Investigation of selected patient groups by Eichinger revealed a 20-50% incidence of FVL in patients with primary or recurrent VTE, with the highest figures being seen in women with a history of thrombosis during pregnancy or the puerperium.¹⁴ Clark has suggested that selective screening of pregnant patients with a history of thrombosis or pregnancy-related complications may identify the factor V Leiden gene in 20-40% of patients.¹⁵ Factor V Leiden has been found to be the most common defect and is seen in approximately 20% of patients developing venous thrombosis. There is a great deal of controversy regarding the significance of factor V Leiden increasing the risk of recurrent venous thrombosis compared to patients without the gene. This controversy has led some investigators to omit screening for FVL defects since studies have shown that this finding will not change the length of anticoagulation in persons with a first DVT event.²

Calf Vein Thrombosis

Two additional findings in this study are the incidence and type of defects seen in patients with CVT alone. Treatment of patients with isolated CVT or SVT is not routinely done in some centers despite the fact that significant morbidity and mortality can occur in some of these cases.¹⁶ In addition, most physicians do not measure thrombophilia markers in such patients. While there were only 12 patients in this group, 2 individuals had a lupus anticoagulant, which many physicians feel merits life-long anticoagulation.¹⁰ Abnormal homocysteine levels were seen in 2 other patients with calf thrombosis only. Many experts

would advocate prophylactic vitamins to help prevent stroke, myocardial infarction, and arterial and venous thrombosis in such patients, although randomized controlled clinical trials have not been done to prove the value of this prophylaxis.¹⁷ One patient in the calf thrombosis group had a heterozygous factor V Leiden defect, which would not change the approach to treatment for the calf vein thrombosis but may have other implications for blood relatives, especially those who are contemplating birth control pills or hormonal replacement therapy.¹⁸

The value of knowing about positive markers such as factor V Leiden, prothrombin 20210A and MTHFR in this group is less evident. However, some of these patients were of child-bearing age and developed SVT during or after a previous pregnancy. If these women were to become pregnant again, the incidence of DVT without prophylaxis during pregnancy could be higher than in the general pregnant population. We feel that thrombosis prophylaxis with anticoagulants during and following such a pregnancy may be of value. Similarly, if patients who develop an SVT during pregnancy subsequently wish to use oral contraceptives to space out their pregnancies but do not know they are carrying one of these defects, they may have a much higher incidence of VTE compared to patients without a positive thrombophilia marker taking oral contraceptives.

Multiple Thrombophilic Defects

We found 18 patients in our population with more than one significant thrombophilia defect, including 2 patients with SVT. The incidence of recurrent venous thrombosis in patients with more than one defect has been estimated to be 70-90% according to Zwicker.⁵ In our opinion, the potential high thrombotic risk in these individuals would have been missed were it not our policy to test those with SVT for thrombophilia defects. In both of our patients, these events occurred during pregnancy and we treated both patients with anticoagulants. We also cautioned them not to take oral contraceptives since the incidence of serious VTE events is much higher than in those without defects of thrombophilia.² Westrich has reported that the

presence of multiple genetic defects was more frequent in patients developing postoperative pulmonary emboli compared to those not developing postoperative thrombosis.¹⁹ He suggested that more aggressive thrombosis prophylaxis was indicated in these individuals.

Family History of Thrombosis

Also of great importance was the finding that 22% of patients with a family history of VTE had 2 defects. This is the same rate we found in patients with recurrent venous thrombosis where one would expect to find a marker of thrombophilia. This fact highlights the value of eliciting a careful family history in all patients, particularly those who require surgery. The most frequent observation we have made during hospital consultations on patients with a postoperative thrombosis is that no one asked them about their family history of VTE. These patients require careful attention since they are candidates for life-long anticoagulation and the most intense perioperative thrombosis prophylaxis should additional surgery be necessary.

General remarks

The fact that 61% of DVT patients had at least one abnormality may reflect the nature of our referral practice. We would be the first to caution about routine testing based on these data because the sample size is very small. The wide confidence intervals of most of these findings emphasize the pilot nature of our study. On the other hand, we discovered a number of patients with potentially serious defects. It should be noted that this is a referral practice where most of the patients seen have a personal or family history of VTE. The incidence of thrombophilic defects in this group is much higher than in the general population. The data set is too small to allow a multivariate model to predict the risk of recurrent thrombosis.

We acknowledge the important work of Baglin, who pointed out that in unselected patients with a first episode of venous thrombosis, the presence of hereditary thrombophilia did not predict a recurrent event within 2 years of stopping anticoagulation. We do not have enough numbers or data to make any statement except to agree with his conclusions.²⁰ As previously

mentioned the small size of this study which is from a referral practice where the incidence of thrombophilia is higher than in the average clinical practice should caution the reader that it is premature to advocate routine screening of all DVT patients. However, we feel that this study does point out that even those with SVT or calf only DVT may harbor a thrombophilic defect.

The nature of our data collection and the small size of this seriesw preclude making any statements regarding the cost effectiveness of this approach. Again, a larger study needs to be done before such an analysis would be appropriate.

We hope others will expand on these data and provide larger studies to validate or refute our preliminary results.

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Table I: Thrombophilia Tests

Test	Results	Significant Positive Results
1) Factor V Leiden Mutation	Heterozygous, Homozygous, Negative, Not Performed	Heterozygous, Homozygous
2) Prothrombin Mutation	Heterozygous, Homozygous, Negative, Not Performed	Heterozygous, Homozygous

3) MTHFR Mutation	Heterozygous, Homozygous, Negative, Not Performed	Homozygous
4) ACA-IgG (GPL Units)	< 10: Negative 10-20: Low Positive 21-80: Medium Positive >80: High Positive	>21: Positive
5) ACA- IgA (APL Units)	<12: Negative 12-15: Borderline >15: Positive	>15: Positive
6) ACA- IgM (IGM Units)	< 10: Negative 10-20: Borderline 21-80: Medium Positive >80: High Positive	>21: Positive
7) Homocysteine	0-13 μ mol/L = Normal >13 μ mol/L = Abnormal	>13 μ mol/L = Abnormal
8) Lupus Anticoagulant	Positive, Negative, Not Performed (Ratio \leq 1.30)	Positive
9) Antithrombin III	Normal Range: 72-148% activity	< 72 = Abnormal
10) Protein C Functional	Normal Range: 66-142% activity	< 66 = Abnormal
11) Protein S Functional	Normal Range: 64-140% activity	< 64 = Abnormal

Table II: Number of Patients

	Number of Patients
All DVT*	44/166 (26.5%)
CVT only**	12/166 (7.2%)
SVT only	39/166 (23.5%)
Recurrent DVT	9/166 (5.4%)
Hx DVT	73/166 (44.0%)
Hx PE	32/166 (19.3%)
Family Hx DVT	54/166 (32.5%)
Any DVT/SVT with >1 abnormality	18/166 (10.8%)

- * Proximal DVT with or without calf involvement
- ** Calf only DVT excludes patients with proximal clots

Table III: Genetic Mutations

Reason for Test	Significant Abnormality	Factor V Leiden	Prothrombin 20210A	MTHFR*	Antithrombin	Protein C	Protein S	Homocysteine
All DVT	27/44 (61.4)	10/44 (22.7)	6/44 (13.6)	6/44 (13.6)	1/44 (2.3%)	3/44 (6.8%)	2/44 (4.5%)	4/44 (9.1%)
CVT only	5/12 (41.7)	1/12 (8.3)	0/12 (0)	0/12 (0)	0/12 (0%)	0/12 (0%)	0/12 (0%)	2/12 (16.7%)
SVT only	14/39 (35.9)	5/39 (12.8)	3/39 (7.7)	1/39 (2.6)	0/39 (0%)	1/39 (2.6%)	1/39 (2.6%)	4/39 (10.3%)
Recurrent DVT	5/9 (55.6)	3/9 (33.3)	1/9 (11.1)	1/9 (11.1)	0/9 (0%)	1/9 (11.1%)	3/9 (33.3%)	1/9 (11.1%)
History of DVT	41/73 (56.1)	17/73 (23.3)	9/73 (12.3)	3/73 (4.1)	1/73 (1.4%)	5/73 (6.8%)	1/73 (1.4%)	10/73 (13.7%)
History of PE	16/32 (50)	3/32 (9.4)	4/32 (12.5)	2/32 (6.3)	0/32 (0%)	1/32 (3.1%)	1/32 (3.1%)	5/32 (15.6%)
Family History of DVT	23/54 (42.6)	11/54 (20.4)	6/54 (11.1)	2/54 (3.7)	0/54 (0%)	1/54 (1.9%)	0/54 (0%)	5/54 (9.3%)
Any DVT/SVT with >1	18/18 (100)	7/18 (38.9)	6/18 (33.3)	5/18 (27.8)	1/18 (5.6%)	3/18 (16.7%)	5/18 (27.8%)	7/18 (38.9%)

Table IV: Antiphospholipid Antibodies

Reason for Test	IgG	IgA	IgM	Lupus Anticoagulant
All DVT	0/44 (0%)	0/44 (0%)	0/44 (0%)	4/44 (9.1%)
CVT only	0/12 (0%)	0/12 (0%)	0/12 (0%)	2/12 (16.7%)
SVT only	0/39 (0%)	1/39 (2.6%)	0/39 (0%)	1/39 (2.6%)
Recurrent DVT	0/9 (0%)	0/9 (0%)	0/9 (0%)	0/9 (0%)
History of DVT	0/73 (0%)	1/73 (1.4%)	3/73 (4.1%)	3/73 (4.1%)
History of PE	0/32 (0%)	0/32 (0%)	2/32 (6.3%)	3/32 (9.4%)
Family History of DVT	0/54 (0%)	0/54 (0%)	1/54 (1.9%)	2/54 (3.7%)
Any DVT/SVT with >1 abnormality	0/18 (0%)	1/18 (5.6%)	1/18 (5.6%)	3/18 (16.7%)

Table V: Provoked vs. Idiopathic Events

Reason for Test	Total Patients	Positive Markers	Patients with a Provoked Event		Patients with an Idiopathic Event	
			No Marker	Positive Marker	No Marker	Positive Marker
DVT	44	27	(11/44) 25%	(5/11) 45%	(33/44) 75%	(22/33) 67%
Calf Only	12	5	(5/12) 42%	(1/5) 20%	(7/12) 58%	(4/7) 57%
SVT Only	39	14	(11/39) 28%	(3/11) 27%	(28/39) 72%	(11/28) 39%