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Clinical Impact of Thrombophilia Screening in Young Adults with Ischemic Stroke

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Abstract

Objective: We evaluated the ability of genetic and serological testing to diagnose clinically relevant thrombophilias in young adults with ischemic stroke.

Methods: We performed a retrospective cohort study of patients aged 18-65 years diagnosed with acute ischemic stroke at a comprehensive stroke center between 2011-2015 with laboratory testing for thrombophilia. The primary outcome was any positive thrombophilia screening test. The secondary outcome was a change in clinical management based on thrombophilia testing results. Logistic regression was used to assess whether the prespecified risk factors of age, sex, prior venous thromboembolism, family history of stroke, stroke subtype, and presence of patent foramen ovale were associated with outcomes.

Results: Among 196 young ischemic stroke patients at least one positive thrombophilia test was identified in 85 patients (43%; 95% CI, 36-51%) and 16 (8%; 95% CI, 5-13%) had a resultant change in management. Among 111 patients with cryptogenic strokes, 49 (44%) had an abnormal thrombophilia test and 9 (8%) had a change in management. After excluding cases of isolated hyperhomocysteinemia or methylenetetrahydrofolate reductase or Factor V Leiden gene mutation heterozygosity, the proportion of patients with an abnormal thrombophilia screen decreased to 24%. Prespecified risk factors were not significantly associated with positive thrombophilia testing or a change in management.

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Conflicts-of-Interest/Disclosures

None.

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Conclusions: Two-of-five young patients with ischemic stroke who underwent thrombophilia screening at our institution had at least one positive test but only one-in-twelve had a resultant change in clinical management. Neither cryptogenic stroke subtype nor other studied clinical factors were associated with a prothrombotic state.

Keywords

ischemic stroke; thrombophilia; stroke in the young; hypercoagulable state

Introduction

At least 10% of ischemic strokes occur in young persons (i.e., age less than 65 years), and this incidence may be increasing.(1) Nearly half of these strokes in the young have no identified cause (i.e., cryptogenic) after standard evaluations.(2) Not identifying a specific stroke mechanism is problematic because it prevents clinicians from directly targeting responsible pathologies with tailored treatments, which might translate into unnecessarily high recurrent stroke risks.(3)

Inherited and acquired thrombophilias explain a proportion of cryptogenic strokes that may benefit from tailored treatment.(4) Prior studies have suggested associations between various thrombophilias and ischemic stroke,(5-7) particularly in young adults.(5, 6) However, these studies were generally small, underpowered, or focused on individual thrombophilias. Conversely, other studies have not found associations between thrombophilia and ischemic stroke risk.(5, 8, 9) Furthermore, the clinical utility of extensive thrombophilia testing in patients with ischemic stroke remains controversial and is not routinely endorsed by the American Heart Association.(3, 10) This is partly because thrombophilia testing is expensive and often requires delayed confirmatory testing.(8, 11)

Nonetheless, in clinical practice, thrombophilia screening is often performed in young stroke patients.(12) Therefore, identifying subgroups of stroke patients with high pretest probability for thrombophilia could result in more efficient testing and reduced costs. Such subgroups might include very young persons (<45 years of age), (5, 6) patients with cryptogenic mechanisms,(13, 14) patients with personal or family histories of thromboembolism,(15) and patients with patent foramen ovale (PFO).(15, 16) Diagnosing thrombophilia in these individuals could change clinical management through prescription of anticoagulation or PFO closure.

Herein, we aimed to determine if thrombophilia screening had a clinical impact in young adults with ischemic stroke. We also assessed whether the diagnostic yield of thrombophilia screening would be higher in select subgroups of patients, such as patients with cryptogenic stroke.

Methods

Study Design

We performed a retrospective cohort study evaluating the clinical utility of thrombophilia screening in young adults with ischemic stroke. Patients were selected from the Cornell

Acute Stroke Academic Registry (CAESAR), a prospective database of patients diagnosed with acute stroke at a large, academic, Joint Commission-certified comprehensive stroke center in New York City. Characteristics of CAESAR have been published previously.⁽¹⁷⁾ Patients were included if they were 18 to 65 years of age, were hospitalized for an acute ischemic stroke of any subtype from 2011 through 2015, and had any laboratory testing for thrombophilia within 6 months of index stroke. Standard thrombophilia testing at our institution includes serum evaluation for antiphospholipid syndrome comprising the anticardiolipin and anti-beta-2 glycoprotein-1 antibodies (IgG and IgM isotypes) and lupus anticoagulant; Factor V Leiden gene mutation; prothrombin gene G20210A mutation; protein C, protein S, and antithrombin deficiencies; increased homocysteine; and methylenetetrahydrofolate reductase (MTHFR) gene mutation (Table 1). Testing for any of these thrombophilias, alone or in combination, was sufficient for study inclusion. Patients with transient ischemic attack were excluded. This study was approved by the Weill Cornell Medicine Institutional Review Board with a waiver of the requirement for informed consent.

Measurements

Patients' strokes were subtyped per the TOAST classification by two independent neurologists with a third neurologist resolving disagreements.⁽¹⁸⁾ Study neurologists collected data on patients' demographics, relevant clinical history (previous stroke in the patient or a first degree relative; conditions associated with thrombophilia including history of systemic lupus erythematosus, venous thromboembolism, hormone contraceptive use, and spontaneous abortions), stroke characteristics including brain imaging and echocardiography findings, thrombophilia screening, and prescribed secondary stroke prevention treatments in the 6 months after index stroke hospitalization. Data variables were predefined in a data dictionary prior to chart review and they were collected using standardized abstraction forms.

The primary outcome was a positive thrombophilia screen, defined as any abnormal thrombophilia screening test, except for the antiphospholipid antibody syndrome tests which required two abnormal values at least 12 weeks apart, and the protein C and S deficiency tests which required two abnormal values at least 4 weeks apart (Table 1). The secondary outcome was a change in clinical management based on the results of patients' thrombophilia testing, defined as a change in antithrombotic treatment or PFO closure.

Statistical Analysis

Descriptive statistics with exact confidence intervals and the chi-square, Fisher's exact, and Student's T tests were used to evaluate: 1) patients' clinical characteristics including demographics, medical comorbidities, stroke severity and subtype, and clinical factors associated with thrombophilia, and 2) rates of the primary (e.g., positive thrombophilia screen) and secondary (e.g., change in clinical management based on the screen) outcomes.

Logistic regression was used to evaluate the association between the following prespecified risk factors and study outcomes: age, sex, prior venous thromboembolism, stroke subtype, presence of PFO, and family history of stroke. The choice and number of analyzed risk

factors (n=6) was based on investigator consensus and the expected rate of the primary outcome among a planned sample size of ~200 patients (30% equating to ~60 outcomes).

Two sensitivity analyses were performed to expand upon our findings. In the first, cases of isolated hyperhomocysteinemia, MTHFR gene mutation heterozygosity, and Factor V Leiden gene mutation heterozygosity were excluded from the definition of a positive thrombophilia screen. In the second, patients whose only performed thrombophilia test was a homocysteine evaluation were excluded. Statistical significance was set at a two-sided α of 0.05. All statistical analyses were performed by AM and GG using Stata/MP, Version 13 (College Station, TX).

Results

Patient Characteristics and Outcomes

Among 1710 patients hospitalized with acute ischemic stroke at our institution from 2011 through 2015, 196 (12%) met study eligibility criteria and were included in the final analysis. Mean age was 47 years (standard deviation, ± 10) and 51% were women (Table 2).

The primary outcome of at least one positive thrombophilia screening test result was identified in 85 patients (43%; 95% confidence interval [CI], 36-51%). Vascular risk factors were similar among patients with and without positive thrombophilia testing. The most common positive tests were MTHFR gene mutation heterozygosity (n=22), lupus anticoagulant (n=17), and antithrombin deficiency (n=10); 7 patients had more than one positive test (Figure 1). Among 111 patients whose stroke was deemed cryptogenic at hospital discharge, 49 (44%; 95% CI, 0.35-0.54%) had an abnormal thrombophilia screen.

The secondary outcome of a change in clinical management based on the results of thrombophilia testing was identified in 16 patients (8%; 95% CI, 5-13%), of whom 10 (63%) had the initiation of anticoagulation and 6 (37%) had PFO closure. The most common thrombophilia screening test to affect management was the detection of antiphospholipid antibodies, which were present in 20 patients (10% of total cohort) and which changed management (i.e., anticoagulation or PFO closure) in 11 patients (6%) (Figure 2). Among those with cryptogenic strokes (n=111), 9 had a change in clinical management (8%), of whom 4 had the initiation of anticoagulation and 5 had PFO closure.

Risk Factor Analysis

There were no significant associations between any of the 6 prespecified risk factors and a positive thrombophilia screen or a change in management (Table 3). This included cryptogenic stroke subtype, which had an odds ratio of 1.1 (95% CI, 0.6-1.9; $p=0.61$) for a positive thrombophilia screen and 1.0 (95% CI, 0.4-2.8; $p=0.97$) for a change in management. Since no factors were significantly associated with outcomes at the univariate level, multivariable regression was not performed.

Sensitivity Analyses

After excluding cases of isolated hyperhomocysteinemia, MTHFR gene mutation heterozygosity, and Factor V Leiden gene mutation heterozygosity from the definition of a

positive thrombophilia screen, 47 of 196 patients (24%) had at least one positive thrombophilia test. Meanwhile, after excluding 11 patients whose only performed thrombophilia test was a homocysteine evaluation, 81 of 185 patients (44%) had at least one positive thrombophilia test. In both analyses, the number of patients with a change in management remained the same. Logistic regression analyses evaluating for predictors of a positive thrombophilia screen or a change in management were materially unchanged in these sensitivity analyses cohorts.

Discussion

In a large cohort of young patients with ischemic stroke evaluated for thrombophilia, about 40% had at least one positive thrombophilia test and about 8% had a resultant change in management. The most common abnormal thrombophilia test in our cohort was MTHFR gene mutation heterozygosity, which in the absence of folate and/ or vitamin B12 deficiency, is of uncertain clinical relevance. When excluding these cases, as well as isolated hyperhomocysteinemia and Factor V Leiden gene mutation heterozygosity from the definition of a positive thrombophilia screen, the proportion of patients with a positive test decreased to 24%. Contrary to our prespecified study hypothesis, cryptogenic stroke subtype was not associated with a positive thrombophilia screen nor a change in management; similarly, neither was age, sex, history of prior venous thromboembolism, presence of PFO, and family history of stroke. However, there were nonsignificant trends with male sex and prior venous thromboembolism, and therefore it is possible that a larger study could find these variables to be significant predictors.

Our results build upon previous studies. In a systematic review by Bushnell et al, the frequency of thrombophilia conditions was low (lupus anticoagulant 3%, anticardiolipin antibodies 17%, Factor V Leiden 7%, prothrombin gene mutation 4.5%) in all ischemic stroke patients, but the prevalence increased when restricted to patients <50 years of age (8%, 21%, 11%, and 6%, respectively).(19) Using factors that may increase the pretest probability of identifying thrombophilia, including personal and family history of thromboembolism and stroke onset at a young age, the authors created a scheme to increase the diagnostic yield of thrombophilia screening in ischemic stroke patients. We analyzed some of these factors in our study but did not find them to substantially affect the diagnostic yield of thrombophilia screening. These discrepant findings may be due to differences in study populations, particularly the younger age of our cohort and variable racial distributions. Factor V Leiden and prothrombin gene mutation are more prevalent in patients of European descent, and are rarely seen in African-Americans;(20) while protein C levels are generally lower in African-Americans than Caucasians, and protein C and S deficiency may be more common in Japanese, Taiwanese, and Thai populations.(21) Additionally, in a single-center study, Pahus et al evaluated the association between several different forms of ischemic cerebrovascular disease (e.g., ischemic stroke, transient ischemic attack, and amaurosis fugax) and positive thrombophilia testing.(22) They reported laboratory evidence for individual thrombophilias in less than 10% of ischemic stroke patients. Furthermore, there was no association between ischemic stroke and positive thrombophilia testing, as the prevalence of thrombophilia was not increased among patients with ischemic stroke as compared to the general population. In our study, the estimated prevalence of positive

thrombophilia testing was 43%; however, most positive tests were not clinically impactful, as only 8% of patients had changes in their clinical management based on this testing.

Given the high cost of thrombophilia screening, which can range from \$1,300 to \$2,500 depending on which tests are performed,(23) clinicians may be inclined to reserve testing for stroke patients with high pretest probabilities for carrying a thrombophilia. Florez et al examined 280 patients with ischemic stroke to determine whether thrombophilia is more common in patients with PFO.(16) In their study, which included patients of all ages and examined fewer thrombophilias, they, like us, did not find an association between thrombophilia and presence of PFO. Other studies have similarly reported a lack of association between thrombophilia and PFO. (24, 25)

This study has limitations. First, it was conducted at a single, tertiary care center, mostly comprising white patients, so our results may not generalize to other populations. Second, despite analyzing nearly 200 patients—which, to our knowledge, is more than most prior studies on this topic—and over 80 outcomes of interest, our analysis may have been underpowered to identify factors associated with positive thrombophilia testing, making type 2 error possible.(14, 24, 26) Third, the rate of positive thrombophilia tests identified in our study may be falsely elevated because their measurement was performed during the index stroke hospitalization and some thrombophilia tests are acute phase reactants. However, we addressed this potential bias by requiring delayed confirmatory testing for positive cases of protein C deficiency, protein S deficiency, and antiphospholipid antibody syndrome. Additionally, the rate of abnormal tests in this study was dependent on our institution's laboratory criteria, which may vary from other institutions. Fourth, thrombophilia screening was not systematically performed in all study patients so diagnostic yield estimates may be inflated because of selection bias. Fifth, changes in clinical management in our study were based on the individual decision making of treating physicians; while the evidence for anticoagulation or PFO closure in patients with stroke and thrombophilia is limited. For instance, prior studies have not found a clear benefit of anticoagulation over antiplatelet therapy in this population, although these studies may have been underpowered. (27, 28) Similarly, to the authors' knowledge, there is no convincing evidence that history of thrombophilia should influence the decision to perform PFO closure. Lastly, because this study was designed to simulate current clinical practice, the specific type of performed thrombophilia tests varied among study patients.

Conclusion

Two-of-five young patients with ischemic stroke who underwent thrombophilia screening at our institution had at least one positive test, and one-in-twelve patients had a resultant change in clinical management. Antiphospholipid antibodies were responsible for the majority of changes in clinical management. Neither cryptogenic stroke subtype nor other studied clinical factors were associated with positive thrombophilia testing in this analysis. Larger, multicenter studies are needed to determine the diagnostic yield of thrombophilia testing amongst different stroke populations, which tests provide the highest yield, and whether thrombophilia testing is cost-effective for young patients with ischemic stroke. In

the meantime, routine thrombophilia screening in all young adults with ischemic stroke is not justified by the current data.

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Figure 1. Yield of Thrombophilia Testing in Young Adults with Ischemic Stroke.

Proportions represent the number of patients with a positive screening result (numerator) over the number of patients who underwent the specific screening test (denominator).

MTHFR indicates Methylenetetrahydrofolate Reductase gene.

Figure 2. Percentage of Patients with a Change in Management due to an Abnormal Thrombophilia Screen.

Proportions represent the number of patients with a change in clinical management due to the results of the thrombophilia screening test (numerator) over the number of patients with that positive test result (denominator). Numbers do not sum to group total, as some patients had more than one positive screening test leading to a change in management. MTHFR indicates Methylene tetrahydrofolate Reductase gene.

Table 1.**Panel and Definitions for Thrombophilia Screening**

Thrombophilia Screening Test	Cut-off for Positive or Abnormal Value
Antiphospholipid antibodies	
Lupus anticoagulant [†]	DRVVT 1.2, Silica clotting time > 1.2
Beta-2-glycoprotein I antibodies [‡]	IgM and/or IgG > 20 units
Cardiolipin antibodies [‡]	IgM > 12 units, IgG > 14 units
Factor V Leiden gene mutation	Homozygous and heterozygous mutant allele
Prothrombin gene mutation	Homozygous and heterozygous mutant allele
Protein C deficiency [§]	Functional assay for protein C activity is <70%
Protein S deficiency [§]	Functional assay for protein S activity is <57%
Antithrombin deficiency	Functional assay for AT activity is <83%
MTHFR genotype	Homozygous and heterozygous mutant allele
Homocysteine	>15 µmol/L

Abbreviations: DRVVT, Dilute Russell Viper Venom Time; IgG, Immunoglobulin G; IgM, Immunoglobulin M; AT, Antithrombin; MTHFR, Methylene tetrahydrofolate Reductase

[†] At least one prolonged screening assay on two or more occasions 12 weeks apart demonstrating presence of a lupus anticoagulant.

[‡] Antibodies were considered clinically present if standardized enzyme-linked immunosorbent assay (ELISA) demonstrated IgG and/or IgM isotypes present in serum on two or more occasions at least 12 weeks apart.

[§] Deficiency must be demonstrated with functional assay testing on two separate occasions at least four weeks apart. Only included values if patients were not treated with warfarin within two weeks of testing.

^{||} Only included values if patients were not treated with therapeutic heparinoid within 48 hours.

Table 2.

Baseline Characteristics of study patients

Characteristic [†]	Positive Thrombophilia Testing (N=85)	Negative Thrombophilia Testing (N=111)
Age, mean year, SD	46 (10)	48 (10)
Female	38 (45%)	61 (55%)
Race [‡]		
White	73 (86%)	87 (78%)
Black	8 (9%)	15 (14%)
Other	4 (5%)	9 (8%)
Atrial fibrillation	0 (0%)	5 (5%)
Chronic kidney disease	0 (0%)	2 (2%)
Heart failure	1 (1%)	2 (2%)
Coronary artery disease	5 (6%)	4 (4%)
Diabetes	9 (11%)	19 (17%)
Dyslipidemia	18 (20%)	30 (27%)
Hypertension	36 (42%)	48 (43%)
Prior stroke	11 (13%)	17 (15%)
Peripheral vascular disease	3 (4%)	4 (4%)
Active tobacco use	11 (13%)	15 (14%)
First degree relative with stroke	8 (9%)	15 (14%)
History of SLE	5 (6%)	0 (0%)
History of prior VTE	10 (12%)	9 (8%)
History of spontaneous abortion	2 (2%)	2 (2%)
Recent hormone contraceptive use	6 (7%)	5 (5%)
Initial NIHSS, mean, SD	6 (1)	5 (1)
Stroke subtype [§]		
Large artery atherosclerosis	6 (7%)	11 (10%)
Cardioembolic	11 (13%)	14 (13%)
Small-vessel occlusion	4 (5%)	8 (7%)
Other determined mechanism	11 (13%)	12 (11%)
Cryptogenic	49 (58%)	62 (56%)
Right-to-left shunt	17 (28%)	23 (29%)

Abbreviations: SD, Standard Deviation; SLE, Systemic Lupus Erythromatosus; VTE, Venous Thromboembolism; NIHSS, National Institutes of Health Stroke Scale.

[†]Data are presented as numbers (%) unless otherwise specified. Percentages have been rounded and may not add up to 100%.

[‡]Race was self-reported by patients.

[§]Determined using TOAST Criteria. Numbers do not sum to group totals because of incomplete workup in less than 5% of patients.

^{||} Diagnosed based on passage of bubbles through a patent foramen ovale on transthoracic or transesophageal echocardiography.

Table 3.

Univariate Regression Analyses Evaluating the Association Between Prespecified Risk Factors and a Positive Thrombophilia Screen and Change in Management

Prespecified Risk Factor	Thrombophilia Screening			Resultant Management Change		
	Positive Testing (N=85)	Negative Testing (N=111)	Odds Ratio (95% CI)	Yes (N=16)	No (N=180)	Odds Ratio (95% CI)
Age, mean, y ($\pm$ SD)	46 (10)	48 (10)	1.0 (0.9-1.0)	46 (9)	48 (10)	1.0 (0.9-1.0)
Female sex	38 (45%)	61 (55%)	0.7 (0.4-1.2)	8 (50%)	91 (51%)	1.0 (0.4-2.7)
Stroke in 1 st degree relative	8 (9%)	15 (14%)	0.7 (0.3 -1.7)	0 (0%)	23 (13%)	N/A
PFO	17 (28%)	23 (29%)	1.0 (0.5-2.1)	4 (44%)	36 (27%)	2.1 (0.5-8.3)
Prior VTE	10 (12%)	9 (8%)	1.5 (0.6-3.9)	2 (13%)	17 (9%)	1.4 (0.3-6.5)
Cryptogenic stroke subtype	49 (58%)	62 (56%)	1.1 (0.6-1.9)	9 (56%)	102 (57%)	1.0 (0.4-2.8)

Abbreviations: SD, Standard Deviation; PFO, Patent Foramen Ovale; VTE, Venous Thromboembolism; CI, Confidence Interval; N/A, Not Applicable.