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Regular Article

The impact of co-morbid conditions on family history of venous thromboembolism in Whites and Blacks ☆

Fatima D. Mili [a,*], W. Craig Hooper [a], Cathy Lally [b], Harland Austin [b]

[a] Clinical and Molecular Hemostasis Laboratory Branch, Division of Blood Disorders, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Road, N.E., Mail Stop D-02, Atlanta, GA 30333, USA
[b] Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA 30322, USA

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ABSTRACT

Introduction: Our objectives were to compare the magnitude of family history as a risk factor for venous thromboembolism (VTE) risk between Blacks and Whites, and to assess the impact of co-morbid conditions on familial risk for VTE.
Materials and methods: We used data from the Genetic Attributes Thrombosis Epidemiology (GATE) study, a matched case-control study which enrolled Blacks and Whites aged 18–70 years in Atlanta, Georgia. A total of 1,094 case patients with a deep vein thrombosis (DVT) or pulmonary embolism (PE) and 1,264 control patients were interviewed about their family history.
Results: Family history of VTE was a statistically significant risk factor for VTE among Blacks (odds ratio (OR) = 2.9, 95% confidence interval (CI) 2.0-4.1; *P* value < 0.0001) and among Whites (OR = 2.7, 95% CI 1.9-3.7; *P* value < 0.0001); among Blacks and Whites who were obese or had hypertension; among Blacks who had diabetes mellitus or cancer; as well as among males and females, and across all age categories. Family history of VTE increased the risk of VTE among Blacks with cancer by about 6-fold, whereas among Blacks without cancer the increased risk due to a positive family history was about 3-fold; a 2-fold relative difference. In addition, family history was a risk factor for VTE among case patients with DVT only or with PE only. The effect of family history generally was stronger among those with recurrent episodes of VTE compared with a first episode of VTE. For example, family history of any VTE was a strong risk factor among Black females with recurrent VTE compared with Black females with first VTE (OR = 3.9, 95% CI 2.0-7.5; *P* value < 0.0001).
Conclusion: Our study indicated that the adjusted attributable fraction for VTE was 16.9% among Blacks vs. 18.3% among Whites, and certain co-morbid conditions could further increase the risk of VTE associated with a positive family history of VTE.

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Introduction

Although the familial aggregation of venous thromboembolism (VTE) was recognized in the beginning of the 20th century, it was not until the late 1970s that the advances in the physiology of haemostatic and fibrinolytic systems were made and led to research on genetic defects associated with familial thrombosis [1]. Several studies found evidence of family history among patients with VTE, consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE) [2–7]. For example, in the Multiple Environmental and Genetic Assessment (MEGA) study, a large, population-based case-control study conducted in the Netherlands, investigators observed that a family history of VTE was a risk indicator for a first VTE regardless of having acquired or genetic risk factors, or both [2]. In addition, in the Genetic Attributes and Thrombosis Epidemiology (GATE) study conducted in the United States, family history of VTE appeared to be reported with comparable frequency in White and Black case patients [3].

The objective of our report was to evaluate family history as a risk factor for VTE among Blacks compared with Whites, as well as to assess the impact of co-morbid conditions, including obesity, diabetes mellitus, hypertension, and cancer, on familial risk for VTE among these two racial groups. Earlier data from several studies indicated that these co-morbid conditions were risk factors for DVT and PE [8–20], and the magnitude of increased risk of VTE varied by co-morbid condition. In addition, each of these co-morbid conditions is known to aggregate in families [21–26]. Our hypothesis is that these co-morbid conditions would increase the magnitude of the association between a family history of VTE and VTE among Whites or Blacks.

Abbreviations: AF, attributable fraction; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DVT, deep vein thrombosis; OR, odds ratio; PE, pulmonary embolism; SNP, single-nucleotide polymorphism; VTE, venous thromboembolism.

☆ The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

* Corresponding author. Tel.: +1 404 6390638; fax: +1 404 6391638.
E-mail address: fmili@cdc.gov (F.D. Mili).

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Materials and methods

Participants and study design

The GATE study is a case-control study of VTE designed to evaluate the roles of genetic polymorphisms and environmental factors, and their interaction in the etiology of VTE, and to compare risk factors of VTE between Blacks and Whites [3,27]. The study enrolled adults aged 18–70 years in Atlanta, Georgia, from March 1998 through September 2005 and comprised 1,145 VTE case and 1,309 control patients.

Case patients were adults with a recently confirmed first or recurrent episode of DVT or PE hospitalized at Crawford Long or Emory University Hospital [27]. Potential case patients were identified by a daily review of the records of the heparin services at each of these hospitals. Case patients included persons with idiopathic VTE, as well as those who developed a VTE following surgery, pregnancy, prolonged bed rest, or treatment of cancer. Case patients were interviewed during their hospitalization. Control patients were selected from a list of patients seen by primary care physicians at an Emory Healthcare clinic [27]. The list was sampled to produce subset lists of potential control participants frequency-matched to the case patients for race, sex, and age (in five-year age groups). Individuals with a history of VTE were excluded, as were individuals taking anticoagulant medication or those with mental impairment. Control patients were invited to the Centers for Disease Control and Prevention (CDC) laboratories to provide a blood specimen and to complete the interview.

Data collection and family history

Participants were interviewed at the time of enrollment about lifestyle characteristics (e.g., oral contraceptive use, smoking, and drinking), personal and family history of venous thrombosis, and general medical history. A self-reported family history of VTE was obtained by interview. Study participants were asked whether their parents, siblings (brothers or sisters), or offspring, or any combination thereof, had had a blood clot in the heart, brain, or other location, and the age at which their family members had blood clots for the first time. Respondents were classified as having a positive family history if they reported a history of a blood clot in a location other than the heart or brain for at least one first-degree relative. A positive family history could have included relatives with missing information, as long as at least one relative was identified with a positive history. Family history was defined as negative only if all first-degree family members were reported as not having experienced a blood clot. We excluded from the analysis 251 participants who did not identify a relative with a positive family history and were missing information on any first-degree relatives. We also considered two additional family history variables that reflected a strong predisposition to VTE. We defined a strong positive family history as a reported history of a blood clot either among any first-degree relatives before the age of 50 years or among multiple relatives regardless of age [2].

Statistical analysis

We compared the distribution of selected demographic and behavioral variables for case and control patients using the X^2 distribution. We computed odds ratios (ORs) to estimate the risk of VTE associated with a positive family history, 95% confidence intervals (CIs) for the odds ratios, and two-tailed P values using conditional logistic regression for matched data. The matching variables were race, sex, and age (the latter having four categories based on quartiles: 18–39, 40–49, 50–59, and ≥60 years). The odds ratios were interpreted as the risk of VTE for people with a positive family history divided by the risk of VTE for people with a negative family history. We ran the analysis separately for race, sex, and age (18–44, 45–54, and ≥55 years). Also, using conditional logistic regression models, we investigated whether each of these variables interacted with family history in their relationship with VTE. The P value for the product term was used to test for a statistical interaction. Since we evaluated many interaction terms, we considered only those with a P value less than 0.01 as significant to account for multiple testing.

Furthermore, we compared the association of VTE and each family history variable by categories of determinants that are known to be associated with DVT or PE, or both, including obesity (body mass index (BMI) ≥30.0 kilograms per square meter ($kg/m^{2)}$), diabetes mellitus, clinical or self-reported hypertension, and cancer (excluding nonmelanoma skin cancer). We also examined the association between the type of VTE (DVT only or PE only, as well as recurrent episodes of VTE versus a first episode of VTE (acute VTE)) and a family history of VTE. We ran the regression analyses of each variable adjusted for education because we identified education as a confounder. We also assessed potential confounding by age, sex, education, smoking, physical inactivity, blood type, oral contraceptive use, menopausal status, hormone replacement therapy, obesity, diabetes mellitus, hypertension, cancer, heart disease, kidney disease, lupus disease, and antiphospholipid syndrome. Statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA).

We used Stata 11.0 (StataCorp LP, College Station, TX, USA) to estimate the attributable fraction (AF) of VTE (excess fraction) due to family history and the 95% confidence interval adjusted for age, sex, and education [28–30] among Blacks and among Whites.

Results

The distribution of characteristics among case and control patients is summarized in Table 1. The proportion of VTE case patients among the study population who were related to any family history (adjusted

Table 1
Distribution of characteristics among case and control patients[1]: the Genetic Attributes and Thrombosis Epidemiology study, Atlanta, Georgia, 1998–2005.

	Case patients with VTE	Control patients
	(n = 1,094)	(n = 1,264)
Median age (5th–95th percentile) (years)	50.0 (25-68)	50.5 (27-68)
Blacks	537 (49)	586 (46)
Males	549 (50)	622 (49)
Education		
- ≤High school graduate	423 (39)	190 (15)
- Some college/junior college degree	355 (32)	429 (34)
- 4-year college degree	155 (14)	290 (23)
- Post-graduate work	161 (15)	355 (28)
Type of venous thrombosis		
- DVT	699 (100)	N/A
- PE	248 (100)	N/A
- DVT and PE	147 (100)	N/A
- First VTE	859 (79)	N/A
- Recurrent VTE	235 (21)	N/A
Family history of VTE		
- Negative	667 (72)	1,052 (89)
- Positive		
• Any relative	255 (28)	133 (11)
• Relative aged <50 years	108 (14)	44 (4)
• > 1 Relative	45 (6)	13 (1)
Co-morbid conditions		
- Obesity (BMI ≥ 30.0 kg/ m^2)	434 (40)	410 (32)
- Diabetes	223 (20)	133 (11)
- Hypertension	482 (44)	466 (37)
- Cancer[2]	291 (27)	89 (7)

BMI, body mass index; kg/m^2, kilograms per square meter; DVT, deep vein thrombosis; N/A, not applicable; PE, pulmonary embolism; VTE, venous thromboembolism.
[1]Data are given as number (percentage) of participants.
[2]Excluding nonmelanoma skin cancer.