Venous Thrombosis in Blacks
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Case Presentation: A 42-year-old black woman is diagnosed with idiopathic (unprovoked) lower-extremity deep vein thrombosis (DVT) after presenting with leg swelling. She is treated with anticoagulation for 6 months without major complications and with stable international normalized ratios, and her lower-extremity symptoms completely resolve. She has sickle cell trait but no other chronic conditions. The patient’s mother also had an idiopathic DVT at 53 years of age. Physical examination is notable only for obesity (body mass index 33 kg/m²) and absence of lower-extremity swelling, redness, and pain. D-dimer and follow-up lower-extremity Doppler ultrasound testing are negative. Testing for antiphospholipid antibodies was negative at the time the clot was diagnosed; further tests for thrombophilia have not been performed. She wants to know whether she should continue taking warfarin.

Venous Thromboembolism and Ethnicity
In 2008, the US Surgeon General issued The Surgeon General’s Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism, which highlighted the scope and impact of venous thromboembolism (VTE). In the United States alone, as many as 100 000 to 180 000 deaths occur annually due to DVT and pulmonary embolism (PE). Many of these events are preventable by implementation of standard prophylactic measures in certain high-risk populations (eg, hospitalized patients with reduced mobility); however, a large proportion of VTE events occur spontaneously, without clear inciting factors. Identification of novel risk factors for VTE might allow clinicians to better identify at-risk patients and modify both primary and secondary prevention strategies accordingly.

The incidence of VTE depends on a complex interaction of inherited and environmental risk factors. The prevalence of inherited risk factors depends on the population being studied. To date, the genetics of VTE has been studied most frequently in patients with European ancestry; as a result, our current understanding of inherited VTE risk factors is weighted toward the genetic thrombophilias that are more (or even exclusively) prevalent in that population.

Over the past 2 decades, evidence has emerged revealing that the clinical characteristics of VTE differ among ethnic groups. Blacks have both an increased incidence of VTE and poorer disease outcomes than other racial groups. These observations have led to further efforts to discover novel risk factors (inherited or acquired) that might explain the disproportionate impact of VTE on blacks.

Race and the Epidemiology of VTE
Studies of hospital discharge data and large observational cohorts show that the incidence of VTE varies by race, with blacks having the highest rates, followed by whites and then Hispanics and Asians. The overall incidence of VTE is 30% to 60% higher in blacks than in whites. This holds true across age groups and for both men and women. The overall incidence of PE is higher for blacks, as is the proportion of VTE patients who have a PE. Pregnancy-associated VTE rates are also higher in blacks than in other groups.

A recent study of New York City autopsies found that the incidence of out-of-hospital fatal PE was more than 3 times higher for blacks than for whites (3.73 versus 1.15 deaths per 100 000 people per year). Idiopathic PE was more common among blacks.
Outcomes After VTE

Multiple studies have shown that blacks have higher mortality rates after VTE, particularly after PE. This does not appear to be because of differential access to health care or differences in treatment approach, although evidence suggests that blacks are less likely to receive a full course of anticoagulation after VTE. In addition, nonwhite patients may be less likely to follow up with their physicians regularly while undergoing anticoagulation treatment, which may in turn contribute to the higher incidence of major bleeding after hospitalization for DVT seen in this population. Very few studies have examined race as it relates to the risk of VTE recurrence. One such study found significant inter racial differences in recurrence rates only among women, with Hispanic women having the highest rates of recurrence, followed by blacks and then whites.

Potential Reasons for Interracial Differences

History of thrombosis in a parent or sibling has been shown to be an independent risk factor for VTE. This remains true regardless of the presence of other genetic or environmental risk factors, which suggests that other unmeasured or unknown risk factors are present. In a case-control series of 370 patients with VTE, black patients with VTE were equally likely to have a positive family history of thrombosis as white patients; however, the genetic VTE risk factors most often found in white patients with VTE (factor V Leiden and prothrombin G20210A mutations) were much less common in the black population, which suggests that a different set of VTE risk factors is at work in blacks.

Inheritance of hemoglobin S (as in sickle cell disease and sickle cell trait) may confer an increased risk of thrombosis. Although the prevalence of sickle cell disease is relatively small (approximately 100,000 patients in the United States), sickle cell trait is fairly common, found in 7% to 8% of blacks. Individuals with sickle cell disease are well known to show laboratory evidence of a chronically overactivated coagulation system. Clinically, this appears to correlate with an increased prevalence of PE (but not DVT) in patients with sickle cell disease compared with black patients who do not have sickle cell disease. In addition, sickle cell disease is a significant risk factor for VTE in pregnancy. Sick cell trait is also associated with increased VTE risk; individuals with sickle cell trait have nearly a 2-fold increased incidence of VTE and a nearly 4-fold increased incidence of PE compared with control subjects.

Many genetic variants known to affect risk of VTE have been investigated to determine whether they might confer a disproportionate risk of VTE in blacks; however, none of these known defects have been clearly shown to contribute significantly to the increased risk. Investigations of genetic variants in other pathways potentially related to venous thrombosis (such as the renin-angiotensin axis) have also failed to identify novel risk factors that differentially affect blacks with VTE.

Several chronic conditions are more common among blacks with VTE than among whites with VTE, including hypertension, diabetes mellitus, and chronic kidney disease. Because these conditions are also more common among blacks without VTE, their relative contribution to overall VTE risk has not been determined.

Higher levels of factor VIII and von Willebrand factor are known to be associated with increased risk of VTE, and blacks have the highest levels of factor VIII and von Willebrand factor among all ethnic groups studied. In addition, markers of activation of the coagulation system such as plasma D-dimer and plasmin-antiplasmin complexes are higher in blacks. Whether these findings represent an underlying genetic defect or are simply markers of increased coagulation due to another cause is unknown.

Impact on Clinical Practice

Race and ethnicity generally do not play a role in clinical decision making regarding diagnosis, treatment, and follow-up of VTE. The utility of

| Table. Relative Impact of Race on Risk Factors and Findings Associated With Venous Thromboembolism |
| Inherited | Factor V Leiden | Anti-thrombin III deficiency | Sickle cell trait |
| Prothrombin G20210A | Protein C deficiency | |
| Non-O blood group | Protein S deficiency | |
| Fibrinogen gamma 10034T | |
| Underlying defect | Hyperhomocysteinemia | Increased factor VIII |
| unknown | Increased fibrinogen | |
| | Decreased TFPI | Increased D-dimer |
| | Increased TAFI | Decreased protein C |
| TFPI indicates tissue factor pathway inhibitor; TAFI, thrombin-activatable fibrinolysis inhibitor; and vWF, von Willebrand factor. |
thrombophilia testing for all patients with idiopathic VTE should be considered carefully, but race and ethnicity may have minimal impact on decisions about testing. The current testing for thrombophilia is likely less revealing in blacks than whites for detecting inherited clotting tendencies, particularly in the setting of a positive family history of VTE.

Clinical Case: Resolution

The patient expressed concern about stopping anticoagulation because her mother developed debilitating postthrombotic syndrome after her second DVT. The patient’s risk of VTE recurrence was judged to be intermediate (with a low risk of bleeding on anticoagulation), so she was advised to continue taking warfarin and follow up for annual reevaluation. Further thrombophilia testing was not performed because the results would not have altered this clinical decision.

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Disclosures

None.

References


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