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Venous thromboembolism (VTE) is a disease that is caused by genetic and environmental factors that interact in a dynamic, time-dependent model. Therefore, it is not astonishing that, although VTE is seen throughout the world, the rate of its clinical manifestations, deep venous thrombosis (DVT) and pulmonary embolism (PE), varies. Thus, Asian and Native American individuals have been reported to have a significantly lower rate of VTE than whites and blacks; the latter present with the highest rate and worst 90-day prognosis.

Among the genetic causes of the disease, 2 traits have been recognized as more prevalent than others, affecting several percent of the population: the so-called Leiden mutation of coagulation factor V and the G3469A transition at nucleotide 20210 of prothrombin (coagulation factor II). Factor V Leiden has a mutation at one of the cleavage sites in position 506 (factor V R506Q) that activates protein C, a natural inhibitor of coagulation, which renders its activated form (activated factor V) less sensitive to inactivation by activated protein C. The prothrombin mutation is associated with increased plasma concentration of prothrombin. These 2 mutations confer an increased risk of thrombosis to the affected individual. Thus, in the heterozygous form, the factor V Leiden is associated with a 6-fold increased risk, and the 20210A prothrombin mutation is associated with a 3-fold increased risk. Even though the absolute risk of VTE in heterozygous carriers is low for the 2 mutations, 0.6% per year for factor V Leiden and 0.4% per year for the prothrombin mutation, they are, because of their high prevalence, responsible for around 20% for all venous thrombotic events (population-attributable risk). All these figures are valid only for whites, and wide geographic variations point to likely ethnic/racial differences (Table).

In the current issue of Circulation, Tang et al add an interesting piece to the puzzle. Taking advantage of a large consecutive series of patients who died of out-of-hospital PE in the New York City area, they were able to compare incidence rates and personal characteristics of these individuals, including ethnicity. In brief, fatal out-of-hospital PE was 3 times more frequent in blacks (3.7 per 100 000 people per year) than in whites (1.15) and in Hispanics (0.9). Interestingly, the heterozygous factor V Leiden status was strongly correlated with earlier age-at-death from PE. As expected, however, the 2 previously mentioned mutations were very rare or absent among nonwhites. The authors also report data on the molecular testing of the methylenetetrahydrofolate reductase C677T variant, which is not, however, a prothrombotic factor. From a clinical perspective, there is no point at all in measuring it, and indeed it did not stand out in this study.

The table displays the incidence rates of VTE and fatal PE and age-at-death in fatal PE as well as the prevalence of the factor V Leiden and prothrombin 20210A mutations according to ethnicity, based on the literature and on the report by Tang et al. In aggregate, these figures reveal not only a few consistent facts, but also some intriguing clues.

Compared with nonblacks, blacks experience 40% more VTE and 3 times more frequent fatal PE and die at a 10-year younger age in the case of fatal PE, but they do not carry the factor V Leiden and prothrombin 20210A mutations. It is noteworthy that the Leiden mutation was strongly associated with earlier age-at-death, but not with the risk of fatal PE itself. Interestingly, this mutation had been suggested to predispose to DVT much more strongly (with an odds ratio of 5 to 6 in comparison with controls without the mutation) than to PE (odds ratio of only 2.5), the so-called factor V Leiden paradox, in a mainly white population. The earlier age at death in blacks should be viewed in the light of the younger age of the black population than of the white population: according to the New York City Department of Health and Mental Hygiene summary of vital statistics, 11% of blacks are 65 years or older compared with 17% of whites. Now, if we compare 2 populations of which one is very much younger, the average age at death will invariably also be younger in that population. So, the large reported difference...
of 9 years of age at death will, at least in part, be explained by this age difference in the 2 populations.

There are several other potential limitations to the data presented, starting from the definition of ethnic groups, especially in the United States, where mixed ethnic backgrounds are not uncommon. In addition, the methodological quality of the epidemiological studies in the field is far from ideal. In the report by Tang et al, the focus is on the end point of fatal PE, which implies that we observe the tip of the iceberg, and 2 denominators are missing: first, there is a population with a distribution of risk factors, from which, second, originate cases with PE, of whom some subsequently die. When focusing on the last group, and comparing results with the general population, results should be interpreted with caution. For instance, factor V Leiden genotypes are higher among those with fatal PE than in the general population, but this does not imply that factor V Leiden specifically increases the risk of embolic death; it is a risk factor for PE, and so increased in those with all forms of VTE (the second denominator). Similarly, when factor V Leiden prevalence among white and black PE deaths are compared, they are different because they differ in the 2 denominators: in the population as a whole, there is a racial difference in factor V Leiden prevalence, whereas in PE patients (the population at risk to die of PE), there are more carriers of the Leiden mutation than in the population as a whole, because it is a risk factor for PE. When one only looks at the fatal cases, one cannot see in which of the 2 denominators the difference actually occurs, and whether a factor increases risk of all PE, or specifically fatal PE.

Nevertheless, these observations point to the large disparity of clinical presentation of VTE, ranging from isolated DVT to extensive proximal DVT with or without PE, isolated PE, and fatal PE. It also suggests that these clinical presentations might not just occur by chance as one type or the other, which is further supported by the fact that patients who have a recurrence after a DVT often again have DVT, whereas patients who experienced a PE often experience recurrence of a PE.12 This leads us to postulate yet unrecognized genetic predispositions to the one clinical type or the other. If this were true, blacks would have a particular predisposition to VTE, and specifically to PE, causing death at an early age, possibly in relation with a particular thrombus composition that makes it less stable, less attached to the vessel wall, and more prone to embolize. It is certain that the last word has not been said about this, and genetic breakthroughs in the future will provide new insight into a disease that may prove less simple than most clinicians believe.

But before this happens, what should be done based on our present knowledge? First, thoroughly designed epidemiological research should focus on nonwhite populations to identify genetic and other risk factors for VTE, especially fatal PE. Second, public policies such as outlined in the recent Surgeon General’s call13 should particularly target ethnic groups that are at higher risk. Third, clinicians should integrate the higher risk of VTE in blacks in their clinical assessment in patients clinically suspected of DVT or PE, and monitor treatment with utmost care in these patients once diagnosis has been confirmed.

Disclosures

None.

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