Risk of Stroke in Young Women and Two Prothrombotic Mutations: Factor V Leiden and Prothrombin Gene Variant (G20210A)

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Background and Purpose—Factor V Leiden and a prothrombin gene variant, G20210A, are mutations associated with a thrombotic risk. The aim of our study was to assess whether these mutations increase the risk of stroke in women under 45 years of age.

Methods—We conducted a case-control study in western Washington state. Case patients were women aged 18 to 44 years with a first stroke \( n = 106 \). Control subjects were women without stroke recruited from the same region by use of random-digit telephone dialing \( n = 391 \). All were interviewed and provided blood specimens, which were genotyped for these mutations.

Results—Factor V Leiden was found in 0.9% of case patients, a single patient with a subarachnoid hemorrhage, and in 4.1% of control subjects. The odds ratio (OR) for any stroke was 0.2 (95% confidence interval [CI], 0.03 to 1.7). The prothrombin variant was found in 1.9% of case patients, 1 with a venous stroke and 1 with an ischemic stroke, and in 1.6% of control subjects. The OR for any stroke was 1.48 (95% CI, 0.14 to 9.17). ORs for stroke types were also not statistically significant.

Conclusions—In this study, neither factor V Leiden nor the prothrombin variant (G20210A) was an important risk factor for stroke in young women. In this setting, screening for these mutations cannot be recommended. Unanswered by this study is whether screening would be useful in select patients, such as those with a strong family history of thrombophilia or those with venous strokes. (Stroke. 1998;29:577-580.)

Key Words: cerebrovascular disorders ■ mutation ■ factor V ■ prothrombin

Factor V Leiden and a recently described variant of the prothrombin gene are both clotting factor mutations that are associated with an increased tendency for venous thrombosis.1-4 Factor V Leiden is a single-point mutation on the factor V gene in which adenine is substituted for guanine at nucleotide position 1691. The mutation results in a change in the factor V molecule where activated protein C would normally cleave and partially inactivate factor V. The result is a resistance to activated protein C.1,2 In a recently described prothrombin variant, adenine is substituted for guanine at position 20210 (G20210A) in the noncoding 3’ terminal end of the prothrombin gene.3,4 This variant is associated with increased prothrombin levels. Although the prothrombin molecule is normal, its expression is not. Factor V Leiden is a relatively common hereditary abnormality with a 3% to 5% prevalence of heterozygous carriers,2 whereas the prothrombin variant, at 1% to 3%, is less prevalent.3,4 Although the association of these mutations with venous thrombosis has been demonstrated,1-4 the association with arterial disease has not. As recently reviewed, the studies have not been consistent with respect to an association of factor V Leiden with coronary artery disease and myocardial infarction,5 and the studies of the prothrombin variant are limited.6 Although information on the prothrombin variant in patients with ischemic stroke is limited to a single negative report,7 many reports have concerned factor V Leiden and have not found the risk of ischemic stroke to be elevated consistently.8-34 Using data collected as part of a recent population-based case-control study,35 we examined the association of stroke in young women with these two mutations.

Subjects and Methods
We conducted a population-based case-control study of myocardial infarction and stroke among women aged 18 to 44 years residing in...
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published methods.5,6 Briefly, the presence of factor V mutation (1691, G-to-A replacement) was confirmed by the presence of an MnlI restriction site in an A allele–specific polymerase chain reaction fragment.6 These determinations were accomplished without knowledge of whether the specimen came from a case patient or control subject. Determinations for factor V Leiden were available in 105 of the 106 case patients (99%) and 388 of the 391 control subjects (99%) and for the prothrombin variant in 105 case patients (99%) and 382 control subjects (98%).

The association of these two mutations with stroke was examined by the calculation of the odds ratio (OR), as an estimate of relative risk, and 95% confidence interval (CI). The study was approved by the Human Subjects Review Committee at the University of Washington, and those who participated in the study all provided informed consent.

Results

In the 106 case patients with blood specimens available for analyses, 2 strokes were venous and 104 were arterial (of which 54 were hemorrhagic, 41 were ischemic, and 9 were dissections). The 1 patient for whom the factor V Leiden determination was missing had an ischemic stroke, and the 1 for whom the prothrombin variant determination was missing had an arterial dissection. The mean age of the 106 case patients was 36.6 years (range, 18 to 44 years), with 88 (83%) being white, 6 (6%) black, and 12 (11%) classified as other. The mean age of the 391 control subjects was 37.7 years (range, 19 to 44 years), with 350 (90%) being white, 9 (2%) black, and 32 (8%) other. Sixteen of the 388 control subjects (4.1%) but only 1 of the 105 case patients (0.9%) had the factor V Leiden mutation. The patient was a 33-year-old white woman with a subarachnoid hemorrhage who had treated hypertension, diabetes, and obesity. The OR for any stroke was 0.2 (95% CI, 0.03 to 1.7); for hemorrhagic stroke, 0.4 (95% CI, 0.1 to 3.4); and for ischemic stroke, 0 (95% CI, 0 to 2.5). All of these CIs are broad and include 1.

Six of the 382 control subjects (1.6%) and 2 of the 105 case patients (1.9%) had the prothrombin variant. One, a 33-year-old white woman who was using oral contraceptives at the time of her event, was free of other recognized stroke risk factors and had a venous stroke. The other was a 32-year-old white woman with long-standing hypertension and epilepsy who had an ischemic stroke 11 days postpartum. Evaluation failed to suggest a right-to-left shunt through the heart, and venous thrombosis of the lower extremities was not clinically evident. The OR for any stroke was 1.2 (95% CI, 0.1 to 6.9); for hemorrhagic stroke, 0 (95% CI, 0.0 to 6.8); and for ischemic stroke, 1.6 (95% CI, 0.03 to 13.4). Again, these CIs are broad and include 1.

Carriership of either mutation was found in 22 of 382 control subjects (5.8%) and 3 of 104 case patients (2.9%). The OR for any stroke was 0.49 (95% CI, 0.09 to 1.7). No one carried both mutations, although 1 control subject who had factor V Leiden and who was included among the 22 control subjects above could not be genotyped for the prothrombin variant. None of the 3 case patients with one of these mutations had a family history of stroke, and the only case patient with the factor V Leiden (who suffered a subarachnoid hemorrhage) had a family history of myocardial infarction. This patient’s brother was reported to have suffered a myocardial infarction at age 27 years. Of the 22 control subjects with either of the mutations, 3 (13.6%) had a family history of myocardial infarction, 1.6 (95% CI, 0.03 to 13.4). Again, these CIs are broad and include 1.

Discussion

Our inability to find a strong association between stroke and factor V Leiden is consistent with the findings of many previous studies.18–34 We also were unable to find an association between stroke and the prothrombin variant with adenine substituted for thymine at position 20210 (G20210A), consistent with a previous report.1 In the studies of factor V Leiden, which have included different types of patients with stroke but almost exclusively ischemic stroke, 0 to 13.8% of patients carried factor V Leiden. In the current study, none of the 40 women with ischemic strokes had factor V Leiden (95% CI derived from the binomial distribution, 0 to 8.8%). Considering prior reports on series of patients with stroke11–14,16,18,19,21,22,5,27,28,33 and the results of this study for ischemic stroke, we calculated that 73 of 1610 stroke patients (4.5%) who have been genotyped carry factor V Leiden, similar to the 3% to 5% reported for the general population.2 The associa-
tion between factor V Leiden and hemorrhagic stroke was also not statistically significant (OR, 0.4; 95% CI, 0.1 to 3.4).

We had only two women with venous strokes in the current study. Neither had factor V Leiden, but one had the prothrombin variant. We had too few patients with venous strokes to reach any conclusions about associations, but other reports have described patients with venous strokes and factor V Leiden.37–42 In these series, 11% to 21% of patients with cerebral venous thrombosis have carried factor V Leiden.40,43,46 More patients will need to be studied before a conclusion can be reached about a possible association between the prothrombin variant and venous stroke.

One potential problem in the current study arises because blood specimens were obtained at the time of interview. Patients who died or were disabled as a consequence of their stroke were not represented among those who were studied. If these mutations were associated with more severe strokes and consequently death or disability, we would be underestimating the effect of these mutations with this study design. We cannot exclude such a possibility in this study. Eleven patients with ischemic strokes who were eligible for this study did not participate because of death or disability. If we assume that all were carriers of the mutations, the recalculated OR is 3.0 for factor V Leiden and 9.9 for the prothrombin variant. Such extreme assumptions are unlikely to hold, but these ORs give an idea of what could be possible.

Other studies that have also been able to identify an association between factor V Leiden and stroke have suffered from the same potential problem because blood samples were collected some time after the acute event.12,18,33 Nonetheless, in one study in which blood samples were collected at presentation, 15 of 348 patients (4.3%) with an ischemic infarction carried factor V Leiden.11 In addition, the mutation was not related to mortality at 1 or 3 months after the initial stroke.20 In another study in which patients provided blood within 7 days of their stroke, only 4 of 161 (2.5%) carried the mutation.27 Whether patients who were unable to provide consent were excluded from these two studies is unclear. Finally, in the Physicians’ Health Study,16 209 men for whom blood samples were available from baseline went on to experience a stroke during follow-up. Nine of the 209 (4.3%) had the mutation, a figure somewhat lower than the 6% found in men who remained free of vascular disease. Although the results of these studies may not entirely apply to women under 45 years of age with stroke who were enrolled in the current study, these results suggest that exclusion of women with severe strokes was unlikely to have had a major effect on our findings.

The current study included too few Hispanic and black patients to address the question of ethnic or racial variations. In one study,22 although some Hispanic patients with ischemic stroke had resistance to activated protein C, none of the them had factor V Leiden nor did any of the Hispanic controls. Also of note, factor V Leiden does not seem to play an important role among black patients with sickle cell disease. Only 1 of 82 such patients (1.2%) had factor V Leiden, and none of the 15 with a history of stroke had the mutation.32

The current study and others do not support the routine screening for these mutations in patients with ischemic strokes. Unanswered by this study is whether screening would be more useful in select patients, such as those venous strokes. Other investigators have suggested that such select groups may include patients with an ischemic stroke combined with one of the following features: a strong family history of thrombophilia;17 pregnancy and puerperium;12,24 childhood;12,26 an angiographic complication,20 oral contraceptive use and antiphospholipid syndrome,22 paradoxical embolus with deep-vein thrombosis and patent foramen ovale,20 migraine,13 and young age without any risk factors.9,10 Given the relative rarity of such ischemic strokes, the utility of screening for these two mutations in these settings will remain difficult to define.

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References

7. Bentolila S, Ripoll L, Drouet L, Mazoyer E, Woimant F. Thrombophilia include patients with an ischemic stroke combined with one of the following features: a strong family history of thrombophilia;17 pregnancy and puerperium;12,24 childhood;12,26 an angiographic complication,20 oral contraceptive use and antiphospholipid syndrome,22 paradoxical embolus with deep-vein thrombosis and patent foramen ovale,20 migraine,13 and young age without any risk factors.9,10 Given the relative rarity of such ischemic strokes, the utility of screening for these two mutations in these settings will remain difficult to define.
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