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Citation

Rosendaal, F. R. (1998). Risk of stroke in young women with two prothrombotic mutations: factor V Leiden and prothrombin gene variant (G20210A), 577-580. Retrieved from <https://hdl.handle.net/1887/1701>

Version: Not Applicable (or Unknown)

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Note: To cite this publication please use the final published version (if applicable).

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 associ-

ation 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

Received October 17, 1997; final revision received December 4, 1997; accepted December 4, 1997

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King, Pierce, and Snohomish counties, three contiguous counties in western Washington state. The study was designed to evaluate the risk of cardiovascular and cerebrovascular diseases with the use of oral contraceptives.³⁵ Genotyping for factor V Leiden and the prothrombin variant were performed on a subset of case patients and control subjects. Associations of myocardial infarction with factor V Leiden was the focus of one previous study⁵ and with the prothrombin variant, another.⁶ This report is limited to stroke. As detailed previously,³⁵ eligible case patients were free of prior cardiovascular and cerebrovascular diseases, and diagnosis was made between July 1, 1991, and February 28, 1995, of their first fatal or nonfatal stroke. Stroke was defined by evidence of new focal neurological deficits lasting more than 24 hours or resulting in death in less than 24 hours. Strokes were classified as venous or arterial. Arterial strokes were further classified as hemorrhagic, ischemic, or other. For a stroke to be classified as hemorrhagic, imaging studies or lumbar puncture had to provide evidence of blood in the brain parenchyma, the subarachnoid space, or both. Arterial dissections that resulted in stroke were included in the "other" category.

Study personnel abstracted diagnostic information from hospital records. Results of brain imaging studies were available for 92% of the case patients. The study neurologist (W.T.L.) reviewed the hospital records of all potential case patients to confirm the diagnosis and to classify the type of stroke. We identified 249 eligible case patients through the review of discharge diagnoses from all hospitals within the study region; 198 were living at the time we initiated recruitment activities, and 149 were recruited and interviewed.

We used random-digit telephone dialing to identify a sample of women aged 18 to 44 years who were residents of King, Pierce, or Snohomish county during the time period of the study, as described previously.³⁵ Control subjects were frequency matched to case patients by age. Of the 684 eligible women, 526 were recruited and interviewed.

Participating case patients and control subjects were interviewed in person regarding cardiovascular and cerebrovascular risk factors. In addition, the interviewer obtained 30 mL nonfasting venous blood in EDTA-treated evacuated tubes from the antecubital vein. Samples were collected from 106 of 149 participating case patients (71%) and 391 of 526 participating control subjects (74%) who were interviewed. We compared the women who were interviewed and gave blood with those who were interviewed but declined venipuncture and found no important differences (data not shown). Blood specimens were genotyped for factor V Leiden and the prothrombin variant with use of published methods.^{5,6} Briefly, the presence of factor V mutation (1691, G-to-A replacement) was inferred from the loss of an *Mnl*I restriction site⁵ and the presence of the prothrombin variant (20210, G-to-A replacement) was confirmed by the presence of a *Hind*III 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%). Altogether, genotyping for both mutations were available in 381 control subjects (97%) and 104 case 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).³⁶ 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 stroke, 7 (31.8%) had a family history of myocardial infarction, and 10 (45.4%) had a family history of either stroke or myocardial infarction.

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 guanine at position 20210 (G20210A), consistent with a previous report.⁷ 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 stroke^{11-14,16,18,19,21,22,25,27,28,33} 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.³⁷⁻⁴⁷ 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 unable 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 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,^{15,24} childhood,^{23,26} an angiographic complication,³¹ oral contraceptive use and antiphospholipid syndrome,²² paradoxical embolus with deep-vein thrombosis and patent foramen ovale,²⁹ 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.

Acknowledgments

This study was supported in part by a contract from the National Institute for Child Health and Human Development (NO1-HD-1-3107). Dr Rosendaal is the recipient of a fellowship from the Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO). The authors are grateful to the many neurologists and other physicians and to the hospital administrators of medical records, who assisted in the identification of patients for this study. Fran Chard, Karen Graham, and Carol Handley-Dahl expertly abstracted medical records; Judy Kaiser, Marlene Bengelut, Carol Ostergard, Denise Horlander, and Barb Twaddell recruited and interviewed the patients and control subjects. Sandy Tronsdal and Jill Ashman supervised these activities. We thank Esther Vogels, who performed the DNA analyses. Finally, we are very grateful to all the women who participated in the study.

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