Is Hormone Replacement a Risk Factor for Ischemic Stroke in Women With Factor V Leiden Mutation?

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Objective: To describe a patient with multifocal cerebral ischemia whose only identified potential risk factors were use of postmenopausal hormone replacement and heterozygosity to factor V Leiden mutation.

Design: A case report.

Setting: A tertiary care center.

Patient: A 51-year-old woman taking hormone replacement (0.625 mg/d of estrogen alternating with 10 mg/d of medroxyprogesterone) presented with a generalized tonic-clonic seizure. She had persistent multifocal non-enhancing lesions on magnetic resonance imaging of the brain. A stereotactic biopsy of the brain performed to exclude gliomatosis cerebri was consistent with cerebral ischemia. An extensive evaluation to uncover the cause of stroke revealed only heterozygosity to factor V Leiden mutation.

Main Outcome and Results: Hormonal replacement was discontinued and the patient had no recurrent ischemic strokes.

Conclusions: Postmenopausal hormonal replacement may be a risk factor for ischemic stroke in women with the factor V Leiden mutation. Ongoing trials of hormonal replacement provide an opportunity to test this hypothesis.

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CASE-CONTROL studies predominantly point to a reduction in coronary heart disease with postmenopausal hormonal replacement (PHR). However, the effect of PHR on the risk of ischemic stroke is less clear. Recently, the Nurses Health Study showed a nonsignificant trend toward an increased risk of stroke with PHR. While methodological issues may be confounding the detection of an association between PHR and ischemic stroke, another plausible explanation is that the response to PHR may vary with genetic differences among patients.

A G to A substitution at nucleotide position 1691 of the factor V gene results in a substitution of Gln for Arg at position 506, rendering factor V resistant to inactivation by activated protein C. This mutation, known as factor V Leiden, is associated with deep venous thrombosis in otherwise healthy individuals and cerebral venous thrombosis in individuals with additional prothrombotic risk factors. An overall association of the Leiden mutation with cerebral arterial thrombosis has not been found. We describe a woman with factor V Leiden heterozygosity and a history of PHR who had multiple, bilateral cortical, and subcortical focal areas of cerebral ischemia suggesting that PHR may be a risk factor for ischemic stroke in women with the factor V Leiden mutation.

REPORT OF A CASE

A 51-year-old right-handed white woman was seen at a local emergency department after having a generalized tonic-clonic seizure. Four weeks earlier she had had a severe headache lasting 12 hours associated with nausea, vomiting, photophobia, and phonophobia. She complained of persistent mild memory impairment following her seizure.

The patient had no history of venous or arterial thrombotic events or miscarriages and no antedating viral illnesses or vaccinations. She was taking 0.625 mg/d of conjugated estrogen (Premarin) (days 1-25 per month) and 10 mg/d of medroxyprogesterone (Provera) (days 15-25 per month) for hot flashes. She did not smoke tobacco or drink alcohol. Her mother had late-onset Alzheimer disease.

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Cerebrospinal fluid analysis showed the following values: white blood cells, 4 × 10^9/L; red blood cells, 4 × 10^12/L; protein, 0.7 g/L; and glucose, 3.8 mmol/L. Routine, fungal, and mycobacterial cultures of cerebrospinal fluid were negative. Oligoclonal bands were negative. Cerebrospinal fluid IgG index was normal. Ambulatory electrocardiogram, electroencephalogram, and transesophageal echocardiogram findings were normal. Evaluation for systemic vasculitis was negative. She was found to be heterozygous for the Leiden mutation using polymerase chain reaction amplification of a portion of the factor V gene followed by restriction digestion with MnII. Antithrombin III, fibrinogen, homocyst(e)ine, protein C, and protein S activities were normal. Dilute Russell viper venom time was 30.7 seconds (reference range, 25-37 seconds). Erythrocyte sedimentation rate was 5 mm/h. Extractable nuclear antigen SS-A and SS-B were negative. Anticardiolipin IgG was less than 20 GPL and IgM was less than 20 MPL. Serologic studies for human immunodeficiency virus type 1 antibody, rapid plasma reagin, and Lyme disease were negative. Mammography and bone density studies were normal. There were no meningeal signs. She had minor problems with simple calculations. She had bilateral palmo-mental reflexes but no chewing or hand or foot grasp reflexes. Magnetic resonance imaging obtained 3 days after her seizure demonstrated multiple bilateral non-enhancing frontal and frontoparietal white matter signal abnormalities with extension into the cortex particularly in the right frontoparietal region. The right frontoparietal lesions were associated with some effacement of the right lateral ventricle. Results of a bilateral carotid and left vertebral angiogram were normal. Carotid and vertebral angiograms were normal. Cerebrospinal fluid IgG index was normal. Ambulatory electrocardiogram, electroencephalogram, and transesophageal echocardiogram findings were normal. Evaluation for systemic vasculitis was negative. She was found to be heterozygous for the Leiden mutation using polymerase chain reaction amplification of a portion of the factor V gene followed by restriction digestion with MnII. Antithrombin III, fibrinogen, homocyst(e)ine, protein C, and protein S activities were normal. Dilute Russell viper venom time was 30.7 seconds (reference range, 25-37 seconds). Erythrocyte sedimentation rate was 5 mm/h. Extractable nuclear antigen SS-A and SS-B were negative. Anticardiolipin IgG was less than 20 GPL and IgM was less than 20 MPL. Serologic studies for human immunodeficiency virus type 1 antibody, rapid plasma reagin, and Lyme disease were negative. Mammography and bone density studies were normal. There were no meningeal signs. She had minor problems with simple calculations. She had bilateral palmo-mental reflexes but no chewing or hand or foot grasp reflexes. Magnetic resonance imaging obtained 3 days after her seizure demonstrated multiple bilateral non-enhancing frontal and frontoparietal white matter signal abnormalities with extension into the cortex particularly in the right frontoparietal region. The right frontoparietal lesions were associated with some effacement of the right lateral ventricle. Results of a bilateral carotid and left vertebral angiogram were normal. Carotid and vertebral angiograms were normal. Cerebrospinal fluid IgG index was normal. Ambulatory electrocardiogram, electroencephalogram, and transesophageal echocardiogram findings were normal. Evaluation for systemic vasculitis was negative. She was found to be heterozygous for the Leiden mutation using polymerase chain reaction amplification of a portion of the factor V gene followed by restriction digestion with MnII. Antithrombin III, fibrinogen, homocyst(e)ine, protein C, and protein S activities were normal. Dilute Russell viper venom time was 30.7 seconds (reference range, 25-37 seconds). Erythrocyte sedimentation rate was 5 mm/h. Extractable nuclear antigen SS-A and SS-B were negative. Anticardiolipin IgG was less than 20 GPL and IgM was less than 20 MPL. Serologic studies for human immunodeficiency virus type 1 antibody, rapid plasma reagin, and Lyme disease were negative. Mammography and computed tomographic scan of thorax, abdomen, and pelvis showed no malignancy.

Follow-up magnetic resonance imaging (Figure) obtained 1 month after the first magnetic resonance imaging showed slight decrease in the size of the parietal lesions bilaterally, but other previously noted lesions now appeared to involve the cortex. Two new small round-enhancing lesions were identified in the right temporal lobe. One of these lesions had a hemorrhagic component. A stereotactic biopsy of a 10 × 2 × 2-mm region of the right parietal white matter was performed 2 months after her initial presentation. Permanent sections of the first block showed white matter with numerous gemistocytic astrocytes. The second block demonstrated astrocytic gliosis and focal petechial hemorrhages. In one area, the white matter appeared disrupted with loosening of the cytoplasm and presence of petechial hemorrhages. There was no pathologic evidence of a demyelinating disorder, granulomatous angiitis, neoplastic angioendotheliosis, or gliomatosis cerebri. The patient was placed on a regimen of carbamazepine and had no additional seizures. She was anticoagulated with warfarin sodium, and hormone replacement therapy was discontinued. Magnetic resonance venography showed no dural sinus thrombosis.

**COMMENT**

Postmenopausal hormone replacement has proven efficacy in reducing the risk of myocardial infarction and osteoporotic fractures. There is also mounting evidence that PHR may delay onset or reduce occurrence of Alzheimer disease. Although the absolute increase in risk is small, PHR increases the risk of deep venous thrombosis and pulmonary embolism. Our patient with multifocal cerebral ischemia was relatively young and lacked the more well-established risk factors for ischemic stroke. The absence of right-to-left shunting on transesophageal echocardiography in our patient suggests that her lesions were not attributable to transcerebral embolism, in a patient made doubly susceptible to venous thrombosis by having the factor V Leiden mutation and taking PHR.

A link between PHR and the Leiden mutation is biologically plausible. Both exogenous estrogen use in the form of oral contraceptives and the Leiden mutation can cause activated protein C resistance, and activated protein C resistance has been associated with ischemic stroke. There is also an increased risk of venous thrombosis in users of oral contraceptives with the Leiden mutation. It remains to be seen whether the prothrombotic interaction seen between the use of oral contraceptives and the Leiden mutation applies to PHR as well.

Long-term anticoagulation for secondary stroke prevention has unknown efficacy in patients with ischemic stroke and the Leiden mutation. Anticoagulation is probably not indicated for primary stroke prevention in asymptomatic people who carry the Leiden mutation because mutation status does not significantly alter life expectancy. It is unknown whether discontinuation of PHR, as was done in our patient, reduces the risk of recurrent
ischemic stroke. In one study, past use of PHR did not increase the risk of pulmonary embolus whereas current use did. This suggests that at least in venous disease a possible prothrombotic state induced by PHR may be reversible with discontinuation of the hormones. Ongoing randomized trials of PHR such as the Women’s Health Initiative and the Heart and Estrogen/Progestin Replacement Study present unique opportunities to investigate a possible association between PHR and ischemic stroke and the Leiden mutation.

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REFERENCES