Prothrombotic Genetic Risk Factors in Patients With Coexisting Migraine and Ischemic Cerebrovascular Disease

J.A. Iniesta, MD; J. Corral, PhD; R. González-Conejero, PhD; J. Rivera, PhD; V. Vicente, MD

The role of hemostatic elements in stroke has been clearly defined but several prothrombotic polymorphisms of hemostatic factors, important for other thromboembolic disorders, seem not to be very significant in stroke. Recently, the high prevalence of factor V Leiden in patients with stroke and a history of migraine has suggested an association between migraine and prothrombotic genetic risk factors. Stroke being a multifactorial disease, the aim of this study was to test whether prothrombotic tendencies increase the risk of stroke in patients with migraine.

We determined the prevalence of four prothrombotic genetic risk factors (factor V R/Q 506, factor II 20210 G/A, decanucleotide insertion/deletion in the factor VII promoter, and the platelet HPA-1 alloantigen system) in 17 patients with coexisting ischemic cerebrovascular disease and migraine, 107 patients with ischemic cerebrovascular disease, 106 patients with migraine, and 202 control subjects. Genotyping for all polymorphisms analyzed in our study were performed after specific genomic polymerase chain reaction, and confirmed by single-strain conformation polymorphism analysis.

In the group of patients with coexisting ischemic cerebrovascular disease and migraine, the prevalence of prothrombotic genotypes (factor V Leiden, 5.8%; factor II 20210 A, 0%; factor VII A1, 70.6%; and HPA-1b, 35.3%) was similar to that obtained in all other groups. We can conclude that the studied polymorphisms do not seem to be associated with the development of ischemic cerebrovascular disease in those patients with migraine.

Key words: migraine, factor V Leiden, prothrombotic risk factors, ischemic cerebrovascular disease

Abbreviations: CVD cerebrovascular disease, FVL factor V Leiden, FII factor II, FVII factor VII

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Stroke is a multifactorial disorder in which the influence of genetic and environmental factors could affect the risk of a thromboembolic episode. Among the recognized risk factors for stroke, migraine has been considered an independent risk factor for ischemic cerebrovascular disease (CVD), particularly among young women, and in the absence of other well-established risk factors. Recently, Kontula et al have found high frequency of the procoagulant factor V Leiden (FVL) in patients with ischemic CVD and personal antecedents of migraine with aura. Therefore, we hypothesize that prothrombotic factors associated with migraine could increase the risk of stroke.

We have evaluated the synergism between migraine and prothrombotic genetic risk factors, including FVL, and the recently discovered factor II (FII) 20210 A, the decanucleotide deletion in the factor VII (FVII) promoter gene, and the platelet alloantigen system HPA-1b. These polymorphisms, affecting important proteins for the hemostatic system, increase the risk to develop arterial and/or venous thrombosis.

PATIENTS AND METHODS

Patients—This study involved 138 patients with ischemic CVD admitted to our hospital during an 18-month period. Fourteen patients were excluded because of aphasia. Personal antecedents of migraine

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were reported by 17 of the 124 recruited patients with ischemic CVD (Table 1). Migraine with aura was documented in 5 of these 17 patients, while 12 reported migraine without aura. The diagnoses of transient ischemic attack (n=46), minor stroke (n=53), and cerebral infarction (n=25) were made according to the classification of ischemic CVD of the National Institute of Neurological Disorder and Stroke Ad hoc Committee13 (Table 1). Additionally, we studied 106 patients with migraine (49 with aura, 57 without aura) (Table 1). Diagnosis of migraine was achieved according to International Headache Society criteria.14 All patients underwent brain computed tomography (CT) or magnetic resonance imaging (MRI).

Finally, the prevalence of the studied prothrombotic genetic risk factors in the normal population of the same area was determined from 202 control individuals with no documented history of migraine, venous and/or arterial thrombosis (Table 1). In order to avoid any effects of sex, age, and other risk factors, we selected a sample of 34 sex-matched control subjects of similar age and with the same risk factors as the patients with ischemic CVD and migraine (Table 1).

**Genotyping Analysis.**—Genotyping of the polymorphisms analyzed was performed after specific genomic polymerase chain reaction (PCR) testing, and confirmed by single-strain conformation polymorphism (SSCP) analysis according to the conditions summarized in Table 2,6,15-19

**RESULTS**

The prevalences of the prothrombotic alleles, FVL, FII 20210 A, FVII A1, and HPA-1b were similar in all groups (Table 1). It is important to point out that the only patient with coexisting ischemic CVD and migraine, positive for FVL, belonged to the subgroup of migraine without aura. This patient was 75 years old, he had a minor stroke affecting the right hemisphere, and did not have any of the known risk factors for ischemic stroke.

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* CVD indicates cerebrovascular disease.
† In the controls, group A consisted of individuals with no documented history of migraine, venous and/or arterial thrombosis. Group B was selected as sex- and age-matched individuals with the same risk factors as the patients with ischemic CVD and migraine.
Table 2.—Conditions and Methods for Genotyping of the Studied Prothrombotic Genetic Risk Factors

<table>
<thead>
<tr>
<th>Locus</th>
<th>Polymerase Chain Reaction Conditions</th>
<th>Genotyping</th>
<th>Conformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL</td>
<td>Corral et al\textsuperscript{15}</td>
<td>MnlI restriction</td>
<td>SSCP\textsuperscript{15}</td>
</tr>
<tr>
<td>FII</td>
<td>Poort et al\textsuperscript{16}</td>
<td>HindIII restriction</td>
<td>SSCP\textsuperscript{18}</td>
</tr>
<tr>
<td>FVII promoter</td>
<td>Bernardi et al\textsuperscript{16}</td>
<td>Direct electrophoresis</td>
<td>—</td>
</tr>
<tr>
<td>HPA-1</td>
<td>Jin et al\textsuperscript{17}</td>
<td>MspI restriction</td>
<td>SSCP\textsuperscript{19}</td>
</tr>
</tbody>
</table>

* SSCP indicates single-strain conformation polymorphism.

**COMMENTS**

It is intriguing that all prothrombotic genetic anomalies studied (FVL, FII, FVII, and HPA-1) have been involved in coronary heart disease and/or venous thrombosis,\textsuperscript{5,6,9-12} but none of them seem to be relevant risk factors for ischemic CVD.\textsuperscript{20,23}

Stroke, like other thromboembolic diseases (coronary heart disease and venous thrombosis), is a multifactorial disease in which the combined presence of risk factors significantly increases the possibility of a thromboembolic episode.\textsuperscript{1} Therefore, it could be suggested that these prothrombotic genetic factors, when combined with other well-established risk factors, would increase the likelihood of ischemic CVD. Noteworthy, recent studies have suggested that migraine (an independent risk factor for ischemic CVD)\textsuperscript{2-3} could be synergistic with risk factors for thrombosis.\textsuperscript{24,25} Interestingly, Kontula et al suggested that the combination of migraine with the FVL could increase the risk to develop ischemic CVD.\textsuperscript{4} They found that 6 (67%) of the 9 patients with cerebral ischemia and FVL had personal antecedents of migraine with aura. We studied the potential synergistic effects of migraine and four prothrombotic genetic risk factors in the development of ischemic CVD. Our results from 17 patients with coexisting migraine and ischemic CVD (including 5 patients with migraine with aura), showed that only 1 patient, with a history of migraine without aura, was positive for FVL. Likewise, the prevalences of the other three studied genetic variations (FII, FVII, and HPA-1) were similar in patients with coexisting ischemic CVD and migraine, patients with ischemic CVD, patients with migraine, and controls.

Unfortunately, the relatively small sample size of our study (resulting from the low frequency of ischemic CVD with migraine) did not allow us to perform statistical comparisons to establish strong conclusions. Therefore, further studies including a greater number of patients with migraine and ischemic CVD should be done.

In summary, the results of the present study suggest that the combination of prothrombotic polymorphisms and migraine do not increase the risk of developing ischemic CVD.

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**REFERENCES**


