Update on evidence for a genetic predisposition to cerebral vasospasm

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The only accepted predictor for the occurrence of cerebral vasospasm after SAH is the amount of subarachnoid blood detected on head CT scans, which is classified as Fisher Grades 1 through 4. Anecdotally, however, the occurrence and neurological effects of vasospasm have been found to vary markedly, even among patients with the same Fisher grade. Such observations raise the possibility that genes encoding key proteins implicated in cerebrovascular regulation may exhibit functionally significant variations that can account for individual differences in vasomotor integrity after aneurysmal rupture. That is, the possibility exists for a genetic susceptibility to cerebral vasospasm. This article is intended as an update on the evolving evidence supporting such a possibility.

Data From the Coronary Vasospasm Literature

The notion of genetic predisposition to coronary vasospasm or Prinzmetal angina has been present in the cardiology literature for decades. The higher incidence of coronary vasospasm in Japanese individuals compared with Caucasians and isolated reports of vasospastic angina in siblings have supported this notion. The idea is further strengthened by evidence from large epidemiological studies involving several hundred monozygotic and dizygotic twin pairs in addition to cohorts of unrelated individuals.

Molecular evidence for a genetic predisposition to coronary vasospasm has been the subject of several studies. In some of these studies, individual variations or polymorphisms in the eNOS gene have been reported. Although certain other candidate genes, including those related to oxidative stress, have been implicated as the cause of a predisposition to coronary vasospasm, the eNOS gene is the strongest candidate.

Nakayama, et al., reported that the incidence of SNP in the T-786C eNOS gene was significantly higher in patients with coronary vasospasm than in matched control volunteers. The aberrant allele was found to be cytosine. In the same study, this polymorphism was, in vitro at least, associated with a significant reduction in eNOS gene promoter activity. The presence of this polymorphism also is associated with increased basal tone of coronary arteries in vitro and with enhancement of these vessels’ contractile function.
response to acetylcholine in vivo. Reduced eNOS protein expression and enzymatic activity also have been reported to be associated with eNOS polymorphisms, including the T-786C SNP. Together, these clinical and molecular genetic data substantially implicate the involvement of the polymorphic eNOS gene in causing a susceptibility to coronary vasospasm. Although the pathogenesis of coronary vasospasm and cerebral vasospasm is dissimilar, impairment in NO signaling has been implicated in both.

Putative Predictors of Cerebral Vasospasm

Risk factors for cerebral vasospasm include having a Fisher grade of SAH as exhibited on CT scans, young age, and a history of smoking. However, only the Fisher grade has widely accepted predictive value. Nonetheless, the anecdotal and independent observations of many physicians have been that the radiological confirmation and clinical severity of vasospasm are often unrelated to the amount of subarachnoid blood present on a patient’s initial head CT scan. We clinically confirmed and quantified such observations. In a prospective study of 51 consecutive patients with aneurysmal SAH from ruptured saccular aneurysms, we found 23 patients with Fisher Grade 1, 2, or 4 SAH (that is, grades typically not strongly associated with the development of cerebral vasospasm). Of these 23 patients, radiologically confirmed vasospasm, clinically confirmed vasospasm, or both developed in seven (30%).

Of the 28 patients with Fisher Grade 3 SAH (that is, a grade typically strongly associated with the development of cerebral vasospasm), seven (25%) experienced no radiologically or clinically confirmed vasospasm. Such observations spurred our interest in studying other factors that might be related to a predisposition toward this condition.

Why Study the eNOS Gene?

Of the array of molecular candidates potentially relevant to the pathogenesis of aneurysmal SAH, we deliberately chose the gene encoding the endothelial isoform of NOS as the focus of our investigation for several reasons. First, NO derived from constitutive isoforms of NOS acts as a potent vasodilator and inhibitor of inflammation, smooth muscle cell proliferation, and platelet aggregation. Second, there is biochemical, immunohistochemical, and functional evidence for impairment of NO signaling after induced SAH in experimental animals. 

Of the 51 patients, 28 presented with Fisher Grade 3 SAH. Among these 28 patients, the eNOS T-786C SNP significantly differentiated between the presence and severity of cerebral vasospasm (p = 0.04). Among these 28 patients, 21 experienced cerebral vasospasm. Of these 21, 19 (90%) were cytogenic allele heterozygous (T/C; 18 patients) or cytogenic allele homozygous (C/C; one patient) for this SNP. The cytogenic allele, reported to be the normal allele that causes a predisposition toward coronary vasospasm, occurred in four (57%) of the seven patients without cerebral vasospasm, in eight (80%) of the 10 patients with asymptomatic cerebral vasospasm, and in all 11 patients with symptomatic cerebral vasospasm. This trend was significant (p = 0.046). Among the 28 patients with Fisher Grade 3 SAH, the odds ratio for spasm for those with at least one cytogenic allele was 7.1 (95% confidence interval 4.8–11.3, p = 0.065). These findings are preliminary in that they need to be confirmed in a larger cooperative study. However, they do support the findings of Nakayama, et al., indicating that there might be a genetic susceptibility to vasospasm, particularly one involving the T-786C SNP of the eNOS gene.
Evidence for a genetic predisposition to cerebral vasospasm

**Actions and Effects of Apolipoprotein E**

Apolipoprotein E is a protein that is a component of very-low-density lipoproteins involved in cholesterol transport. The APOE is encoded by the polymorphic gene \( \text{APOE} \) on chromosome 19q13. The most common allele of this gene is the \textit{epsilon} 3 allele (\( \text{APOE e3} \)), encoding APOE e3. The presence of the less common \textit{epsilon} 4 allele of this gene (\( \text{APOE e4} \)), encoding APOE e4, has been implicated in causing susceptibility to hyperlipoproteinemia Type III, coronary artery disease, oxidative stress, Alzheimer disease, and modulation of ET-1–mediated vasoconstriction. Recently, Lanterna, et al., reported that the presence of the \( \text{APOE e4} \) allele in patients with SAH negatively affected their overall cognitive morbidity, conferred a greater likelihood of their experiencing cerebral vasospasm, and increased their susceptibility to neurological impairment from vasospasm. These findings were based on a prospective study of 101 patients with SAH who were admitted after aneurysmal SAH. The researchers used an \( \text{APOE} \) allele genotyping assay of genomic DNA purified from peripheral blood samples in addition to serial tests of cognitive and functional outcome. The clinical characteristics of their patient cohort in terms of ruptured aneurysm site and size distribution were consistent with other published series. The authors postulated that the adverse effects of \( \text{APOE e4} \) in patients with SAH may be due to it being a less efficient free-radical scavenger and a modulator of amyloid-beta protein and ET-1–mediated vasospasm.

**TABLE 1**

<table>
<thead>
<tr>
<th>Protein Encoded by PMG</th>
<th>PMG on Chromosome</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>eNOS</td>
<td>7q35</td>
<td>atherosclerosis, coronary artery disease, hypertension, cerebral vasospasm</td>
</tr>
<tr>
<td>APOE e4</td>
<td>19q13</td>
<td>Alzheimer disease, coronary artery disease, hyperlipoproteinemia Type III, cerebral vasospasm</td>
</tr>
<tr>
<td>haptoglobin</td>
<td>16q22</td>
<td>atherosclerosis, coronary artery disease, cerebral vasospasm</td>
</tr>
</tbody>
</table>

* PMG = polymorphic gene.
Actions and Effects of Haptoglobin

Haptoglobin is composed of two subunits, alpha and beta. The former subunit is encoded by the haptoglobin alpha gene and the latter by the haptoglobin beta gene. The gene complex is located on chromosome 16q22.4

The haptoglobin alpha gene is dimorphic, encoding alpha 1 and alpha 2 variants of the alpha subunit. Haptoglobin containing the alpha 2 subunit is less capable of inhibiting hemoglobin-induced free-radical production, and it promotes inflammatory responses in vitro. Haptoglobin polymorphism has been implicated as a cause of susceptibility to atherosclerotic coronary artery disease.29 Researchers have recently suggested that knowing the haptoglobin subtype of a patient may be helpful in predicting the occurrence of cerebral vasospasm. Borsody, et al.,1 postulated that types of haptoglobin that have greater affinity for extracorporeal hemoglobin could neutralize the effects of hemoglobin, which induces cerebral vasospasm. These authors studied 32 patients with Fisher Grade 3 SAH and used genotyping to identify their haptoglobin alleles. Vasospasm was significantly more common in patients with the alpha 2 allele than in those with the alpha 1 allele. Furthermore, the risk of vasospasm among patients with the alpha 1/alpha 1 genotype was unexpectedly low for those with Fisher Grade 3 SAH, suggesting that the haptoglobin variant encoded by this genotype confers protection against vasospasm.1,29

Conclusions

The three independent studies of the functional genomics of cerebral vasospasm that we have described have several important clinical implications (Table 1). First, the volume and distribution alone of subarachnoid blood on a CT scan (that is, the Fisher grade) are not the sole factors governing predisposition to cerebral vasospasm after SAH. Rather, genetic factors that are specific to individuals may also govern such a predisposition. Second, if a subset of patients with SAH can be defined by identifying a genetic profile linked to increased vasospasm susceptibility, these patients can be observed more closely and treated more aggressively when appropriate. Third, elucidating the precise molecular pathogenesis of cerebral vasospasm, which probably involves multiple proteins and their encoding genes, will be key to tailoring more effective therapy. Tailored treatment options may involve pharmacotherapy, immunotherapy, and/or gene therapy (Fig. 1). Finally, the findings in these studies need to be confirmed by larger series.

References

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