Cerebral Amyloid Angiopathy–Related Hemorrhage
Interaction of APOE ε2 With Putative Clinical Risk Factors

Mark O. McCarron, MA, MRCP; James A.R. Nicoll, MD, FRCP; James W. Ironside, FRCP; Seth Love, PhD, FRCP, FRCP; Mark J. Alberts, MD; Ian Bone, FRCP

Background and Purpose—Current evidence suggests that the apolipoprotein E (APOE for gene; apoE for protein) ε4 allele predisposes to cerebral amyloid angiopathy (CAA) whereas ε2 is associated with CAA-related hemorrhage (CAAH). The clinical risk factors for other forms of intracranial hemorrhage are a less-frequent feature of CAAH. In this study we examined potential clinical risk factors in patients with CAAH and assessed these with respect to APOE genotype.

Methods—Thirty-six patients were identified with a pathological diagnosis of CAAH. Clinical notes were reviewed to document age of hemorrhage onset, history of dementia, antiplatelet/anticoagulant medication, hypertension, minor head trauma, or transient neurological events. In a review of reported cases of CAAH, the frequency of these clinical features was also recorded. APOE genotypes were determined with use of polymerase chain reaction techniques.

Results—There were 24 women and 12 men; the mean age was 70.3 years. One third (n = 12) had been taking antiplatelet medication, and a similar number were demented. Nine patients were hypertensive, and 4 had a history of recent minor head trauma. The relative frequency of each of these clinical features was similar to that in previous reports. Forty-four percent (16 of 36) possessed an ε2 allele. Antiplatelet or anticoagulant medication, hypertension, or minor head trauma were significantly more frequent antecedents of CAAH in ε2 carriers than in non–ε2 carriers (81% versus 35%, P = 0.008), antiplatelet/anticoagulant medication in particular (P = 0.038).

Conclusions—Our findings suggest that antiplatelet or anticoagulant medication, hypertension, or minor head trauma are most likely to precipitate cerebral hemorrhage in patients with CAAH who are also ε2 carriers. This may result from isoform-specific effects of apoE on the structure of amyloid-laden blood vessel walls.

Key Words: apolipoproteins • cerebral amyloid angiopathy • intracerebral hemorrhage

Sporadic cerebral amyloid angiopathy (CAA) is characterized by the deposition of amyloid β-protein (Aβ) in small to medium-sized leptomeningeal and cortical blood vessels. The incidence of CAA increases with age, but the process usually remains asymptomatic. However, a minority of patients develop single or multiple CAA-related hemorrhages (CAAH). This observation prompted us to search for specific risk factors (genetic or environmental) that may precipitate hemorrhage from amyloid-laden vessels.

Recent evidence implicates the apolipoprotein E gene (APOE) in the etiology of CAAH. We previously hypothesized that whereas the APOE ε4 allele increases Aβ deposition in the cerebral vasculature, APOE ε2 is associated with rupture of Aβ-laden blood vessels, possibly by predisposing to the development of recognized vasculopathic complications of CAA. The clinical risk profile in CAAH has not, however, been firmly established. Although previous reports of CAAH have included patients who were taking antiplatelet or anticoagulant medication, had suffered minor head trauma or had hypertension, it is unclear whether these clinical features are risk factors for CAAH that are independent of the effects of APOE genotype. In the present study we have established the frequency of these putative clinical risk factors in a large series of patients with a pathological diagnosis of CAAH and compared our findings with those in previous reports. In addition, we have examined the relationship between these clinical risk factors and APOE genotype.

Methods
Thirty-six unselected patients with CAAH were identified from the records of 4 neuropathology departments within the United Kingdom (Glasgow, n = 17; Bristol, n = 10; Edinburgh, n = 4; and Manchester, n = 2) and the intracerebral hemorrhage database at Duke University Medical Center, Durham, NC (n = 3), between 1986 and 1997. The clinical records were retrieved. Only patients fulfilling the Boston...
TABLE 1. Clinical Features in Patients Presenting With CAAH in the Current Series and in Reported Cases

<table>
<thead>
<tr>
<th>Feature</th>
<th>Current Series</th>
<th>Reported Cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>36</td>
<td>312</td>
</tr>
<tr>
<td>Putative clinical risk factors for hemorrhage†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet/anticoagulant</td>
<td>12</td>
<td>43</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>9</td>
<td>55</td>
</tr>
<tr>
<td>Minor head trauma</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>Other features‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>12</td>
<td>60</td>
</tr>
<tr>
<td>Previous transient deficits</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*References 3, 5–10, 13–15, 20, 23, and 25–60. †No significant differences between any of the clinical features.

CAH group criteria with a diagnosis of definite or probable and with supportive pathological evidence of CAAH were included. Clinical histories were reviewed, including age at hemorrhage onset, number of intracerebral hemorrhages, evidence of minor head trauma, antiplatelet and anticoagulant medications, and a clinical history of hypertension preceding the first CAAH. Dementia, defined as evidence of progressive cognitive decline, was also noted. The frequency of dementia and the putative clinical risk factors was similarly recorded from a literature search using MEDLINE (Ovid and PubMed) databases as well as references from these reports between 1977 and January 1999 in pathologically proved cases of CAAH. Clinical profiles were established only from those reports that explicitly described the absence or presence of these features.

APOE genotypes (28 already established) were determined from either blood or paraffin-embedded tissue by use of the polymerase chain reaction (PCR), as previously described. The PCR products were digested with HhaI and separated on a polyacrylamide gel. The clinical data and APOE genotypes were analyzed with the Mann Whitney and Fisher exact tests.

Results

There were 24 women and 12 men (mean age, 70.3 years; range, 46 to 89 years). The youngest patient, previously reported, had Down’s syndrome, the extra copy of amyloid precursor protein probably enhancing Aβ deposition in the cerebral vasculature. Table 1 demonstrates the clinical profile in this group of patients at the time of their first hemorrhage. Dementia (n=12) was prominent among the patients, supporting its recognized association with Alzheimer’s disease. Fifteen (42%) had multiple hemorrhages (demonstrated radiologically and/or pathologically). All of the hemorrhages were in a lobar distribution in the cerebral hemispheres.

One third of the patients (n=12) were taking regular antiplatelet medication (aspirin in all cases) for secondary prevention of coronary heart disease and ischemic stroke; 2 of these 12 were also taking anticoagulant medication. One of the patients on anticoagulant medication had had a deep venous thrombosis and the other had recurrent transient neurological deficits thought to be associated with a 40% stenosis of the internal carotid artery. Because of continuing transient deficits, warfarin sodium (Coumadin, Du Pont) was prescribed, and while therapeutically anticoagulated the patient developed a right temporal lobe hematoma.

The reported cases of CAAH in the literature had clinical profiles very similar to those of our series of patients, with no statistically significant differences between the 2 groups (Table 1).

In our group, 44% of the patients (n=16) had 1 or more APOE ε2 alleles. The presence of 1 or more of the 3 putative risk factors (antiplatelet/anticoagulant medication, hypertension, and minor head trauma) was significantly more frequent in ε2 carriers compared with non–ε2 carriers (P=0.008). When analyzed individually all of these features were more common in ε2 allele carriers (Table 2), but only antiplatelet/anticoagulant medication was significantly associated with patients possessing the ε2 allele compared with those without ε2: 9 of 16 ε2 carriers (56%) versus 4 of 20 non–ε2 carriers (20%; P=0.038). No such associations were found among APOE ε4 carriers. Patients carrying an ε2 allele had their first documented hemorrhage at an earlier age than did patients without the ε2 allele, although the difference was not statistically significant (P=0.088). In APOE ε4 carriers the age of hemorrhage onset was similar to that in non–ε4 carriers (median age, 72.0 versus 69.0 years; P=0.877). Clinical evidence of dementia was not significantly more frequent in ε2 carriers compared with non–ε2 carriers (44% versus 25%) or in ε4 carriers compared with non–ε4 carriers (38% versus 36%).

TABLE 2. Clinical Features in CAAH in Patients With and Without the APOE ε2 Allele

<table>
<thead>
<tr>
<th>Feature</th>
<th>ε2 Positive</th>
<th>ε2 Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAAH patients, n</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Age at first hemorrhage,* y</td>
<td>66.5</td>
<td>72.5</td>
</tr>
<tr>
<td>Putative clinical risk factors for hemorrhage†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any of the 3 putative risk factors below</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Antiplatelet/anticoagulant</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Minor head trauma</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test; † Fisher exact test.
Discussion

Both the APOE ε4 and ε2 alleles have been reported to be overrepresented in CAAH.\textsuperscript{2,3,12} It has been proposed that whereas age and the ε4 allele increase Aβ deposition in the cerebral vasculature,\textsuperscript{4} the APOE ε2 allele promotes subsequent hemorrhage.\textsuperscript{2,13} Our current findings suggest that patients who have CAA and are exposed to antiplatelet or anticoagulant medication, hypertension, or minor head trauma are at a higher risk of intracerebral hemorrhage if they are ε2 carriers.

There is accumulating evidence implicating the ε2 allele in CAAH. The allele occurs at a higher frequency in patients with CAAH than in control subjects,\textsuperscript{2,12} and CAAH has been documented to occur at a significantly younger age in ε2 carriers,\textsuperscript{2,13} although we did not replicate this finding in the current study. Some of the recognized vascular pathological complications of CAA have also been associated with the APOE ε2 allele. Greenberg et al\textsuperscript{13} found an elevated ε2 frequency in the brains of CAA patients demonstrating a combination of vessel wall concentric splitting (a “vessel-within-a-vessel” appearance) and evidence of paravascular bleeding. In a systematic analysis of the vascular complications of CAA (vessel stenosis, vessel dilatation, or microaneurysm formation, fibrinoid necrosis, vasculitis, a vessel-within-a-vessel appearance, and evidence of previous microscopic hemorrhage\textsuperscript{1,14,15}), we have recently found a statistically significant excess of fibrinoid necrosis in patients possessing the ε2 allele compared with non–ε2 carriers.\textsuperscript{16} Further work is required to clarify the underlying mechanism associated with apoE-induced vascular changes in CAA, but whatever the mechanism, the present study suggests that CAA patients exposed to clinical risk factors such as antiplatelet/anticoagulant medication, hypertension, and minor head trauma may be most at risk of lobar hemorrhage if they also have an ε2 allele. Although our present findings form the basis of a testable hypothesis that ε2 carriers with CAA may have a differential clinical risk profile for cerebral hemorrhage than non–ε2 carriers, the results probably do not justify revision of the indications for antiplatelet and anticoagulant medications, which have been shown to benefit patients over and above the risk of cerebral hemorrhage.\textsuperscript{17,18} Caution should, however, be exercised in prescribing these medications to elderly patients with transient neurological deficits in the absence of significant carotid stenosis, because CAA can imitate transient ischemic attacks. This phenomenon, which may be due to focal seizures secondary to petechial hemorrhages, is a recognized feature of CAAH.\textsuperscript{1,14,15} and some reports have implicated aspirin\textsuperscript{7} or anticoagulant medication\textsuperscript{6,8} as precipitants of CAAH in this setting, a feature documented in 1 of our series. In addition, none of our patients had a family history of CAA-related hemorrhage, and amyloid precursor protein mutations have never been found in sporadic cases of CAAH-related hemorrhage.\textsuperscript{20–23} Although there is 1 published case of “sporadic” CAA-related hemorrhage due to a cystatin C mutation,\textsuperscript{21} we have not identified this mutation in our series.\textsuperscript{24}

There are several potential limitations to our study. Although systematic searches ensured high ascertainment of pathological cases of CAAH (and hence accurate diagnoses), the study’s reliance on autopsy cases (n=27) inevitably introduces selection bias. However, many of the patients had multiple hemorrhages, and the clinical details were confined to the first recorded intracerebral hemorrhage. Although the retrospective nature of the study limited the amount of clinical data, hospital admission helped in accurate data acquisition, which was often confirmed by family members and primary care physicians. Despite the relatively large size of this group of pathologically confirmed CAAH patients, the small size of subgroups with specific clinical features may have limited the sensitivity of some of the analyses. Our findings are preliminary and need to be interpreted cautiously, particularly those in the small subgroups with hypertension and minor head trauma, which individually were not significantly associated with possession of the ε2 allele. Larger studies, ideally also with pathologically verified diagnoses, are required to confirm whether hypertension and minor head trauma are significant risk factors for CAA-related hemorrhage in ε2 carriers.

In conclusion, clinical factors associated with other forms of intracranial hemorrhage (antiplatelet/anticoagulant medication, hypertension, and minor head trauma) appear to be more significant risk factors in APOE ε2 carriers with CAA than in similar patients without the APOE ε2 allele. This may result from an apoE isoform-specific effect (ε2) on amyloid-laden blood vessels that renders the vessels more vulnerable to rupture in the presence of these clinical factors.

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References


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