of aspirin and ticlopidine before continuing long-term treatment. Our patients, however, were homogeneous in terms of infarct size and clinical severity.

As Dr Öztürk and colleagues state, further studies based on a large number of patients (with more appropriate controls) are necessary to determine the significance of the coagulation-fibrinolysis markers for stroke and stroke recurrence and the effects of antiplatelet medication on the markers.

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Reference

Apolipoprotein E e4 Allele Frequency in Vascular Dementia and Alzheimer’s Disease

To the Editor:

The issue of apolipoprotein E (apo E) polymorphism has been receiving a great deal of attention in the neurological literature. It has been suggested in Stroke that the frequent e3/e4 phenotype may protect against vascular morbidity and that the e4 allele might be a predisposing genetic marker for ischemic cerebrovascular disease. However, the e4 allele has recently been reported to also be more frequent in patients with sporadic Alzheimer's disease (40% in patients with Alzheimer's disease compared with 10% to 16% of control subjects), raising questions about the specificity of e4 as a risk factor for cerebrovascular or Alzheimer's disease.

We assessed apo E allele frequencies in 51 elderly control subjects, 23 subjects with vascular dementia, 6 and 93 patients with Alzheimer's disease compared with 10% to 16% of control subjects, raising questions about the specificity of e4 as a risk factor for cerebrovascular or Alzheimer's disease.

We assessed apo E allele frequencies in 51 elderly control subjects, 23 subjects with vascular dementia, and 93 patients with Alzheimer's disease. Apo E phenotype was determined by isoelectric focusing in immobilized pH gradients and immunodetection by sheep anti-apo E antibodies. Frequency of the e4 allele is higher in both patients with vascular dementia and those with Alzheimer's disease than in age-matched control subjects or a younger Italian population.

The association of the apo E allele with vascular disease has been repeatedly reported, and it should not be surprising that it appears more frequently in patients with vascular dementia than in control subjects. However, this casts doubt on its specificity as a risk factor for Alzheimer's disease.

The synthesis of apo E isoforms in the repair processes in the nervous system. Apo E is synthesized in the central nervous system and plays a role in normal brain lipid metabolism. It can be hypothesized that different insults, either degenerative or vascular, might result in greater damage when a particular apo E isoform allele is present.

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Letters to the Editor

References

Response

The specificity of the linkage between the apolipoprotein E (apo E) e4 allele and Alzheimer’s disease is indeed a very important issue. In a study by Saunders et al, there were no differences in e4

Frequency of the Apo E Allele in Selected Groups

<table>
<thead>
<tr>
<th>Population</th>
<th>n</th>
<th>No. of Alleles</th>
<th>Age*</th>
<th>e2†</th>
<th>e3†</th>
<th>e4†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>51</td>
<td>102</td>
<td>69.2 (3.6)</td>
<td>.10 (.02)</td>
<td>.72 (.05)</td>
<td>.18 (.04)</td>
</tr>
<tr>
<td>Young†</td>
<td></td>
<td>704</td>
<td>35.2 (5.7)</td>
<td>.04 (.00)</td>
<td>.86 (.02)</td>
<td>.10 (.02)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>93</td>
<td>186</td>
<td>73.6 (8.2)</td>
<td>.02 (.01)</td>
<td>.53 (.03)</td>
<td>.45 (.03)§</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>23</td>
<td>48</td>
<td>77.0 (7.5)</td>
<td>.00 (.00)</td>
<td>.54 (.07)</td>
<td>.46 (.07)§</td>
</tr>
</tbody>
</table>

*Mean (standard deviation); †Frequency (standard error).
†Data taken from Gabelli et al.
§P<.0005 on z-test for difference with controls.
allele frequency between control subjects and patients with amyloid-forming diseases such as Creutzfeldt-Jakob disease, familial amyloidotic polyneuropathy, and Down's syndrome. Vascular dementia is a poorly defined disease and its diagnostic criteria are still a matter of debate.3

We examined e4 frequency in 19 patients with mixed and vascular dementia (mean age, 81.7 years; SD, 9.5) and in 76 patients with Alzheimer's disease (mean age, 78.4 years; SD, 7.7)a by using a phenotyping technique.5 Our results are different from those of Frisoni et al (Table). Several factors might account for the discrepancy. First, the two groups in our study were small and interpretation of the results should be made cautiously. Second, the populations of the two studies had different mean ages. Moreover, other environmental or genetic risk factors such as diet and hypertension should be taken into account. Far more patients need to be studied and additional clinical, biological, and genetic information will be necessary to determine whether the apo E e4 allele is indeed a specific risk factor for Alzheimer's disease.

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References

Familial Aggregation of Cervical Artery Dissection and Cerebral Aneurysm

To the Editor:
Familial aggregation of intracranial aneurysms and aortic aneurysms is well established; 6.7% of patients with cerebral aneurysm and 18% of patients with aortic aneurysm have a family history of a similar disease.2 An autosomal recessive mode of inheritance has been suggested on the basis of statistical analysis of families of patients with aortic aneurysms. The underlying gene defect is known only when the aneurysms are part of a syndrome, such as the Marfan syndrome or the Ehlers-Danlos type IV syndrome, although a mutation in the type III procollagen gene was found in 1 of 50 patients with a family history of aortic aneurysm not associated with a syndrome.3 No such mutations were found in patients with cerebral aneurysms or carotid dissections.4

Familial aggregation of carotid dissection has been reported in only two families5 and of carotid dissection and cerebral aneurysm in three.6 Therefore, we examined the epidemiology of familial aggregation of cervical artery dissection and cerebral aneurysm in 22 consecutively diagnosed patients with spontaneous carotid artery dissection and 38 randomly selected control subjects (Table 1). None of the control subjects had a history of cerebrovascular disease, cerebral artery dissection, or aortic aneurysm. The diagnoses of all the patients were based on the clinical features of the disease and on the typical angiographic findings at the acute stage. Carotid dissection was unilateral in 18 cases (14 on the left, 4 on the right) and bilateral in 4.

The prevalence of family history of cervical artery dissection and cerebral aneurysm was determined among the patients with carotid dissection and the control subjects. They were interviewed about family history of cerebrovascular disease, and all positive responses were confirmed. Definitive diagnosis of the affected relative's condition was acquired before including the case in the analysis. Relatives over 65 years of age with cervical artery dissection, cerebral aneurysm, or subarachnoid hemorrhage were excluded from analysis to minimize the inclusion of atherosclerotic diseases. One case of subarachnoid hemorrhage, two of cerebral aneurysm, and two of carotid dissection in four families were verified among the first-degree relatives of the patients with carotid dissection, and one case of cerebral aneurysm was found among the first-degree relatives of the controls. The prevalence of family history of cervical artery dissection and cerebral aneurysm was thus 18.2% among the patients with carotid dissection and 2.6% among the control subjects.

Genealogical data were also obtained at the interview. The siblings of the patients and the control subjects were then defined as study cohorts, comprising 114 and 189 persons, respectively, for calculation of the risk ratios. The prevalence of cervical artery dissection and cerebral aneurysm was 3.5% among the siblings of the patients and 0.53% among those of the controls, suggesting a relative risk of 6.6 (Table 1). The relative risk was 32 among the siblings of the probands with family history of cervical artery dissection or cerebral aneurysm.

There are clinical and biochemical data to suggest that the integrity of the walls of the carotid arteries depends largely on collagen8 and that a collagen disorder may be a factor in aneurysm formation.6 Therefore, we also studied the biosynthesis of the two major collagen types in skin fibroblast cultures established from three patients with cervical artery dissection who had a family
Apolipoprotein E epsilon 4 allele frequency in vascular dementia and Alzheimer's disease.
G B Frisoni, C Geroldi, A Bianchetti, M Trabucchi, S Govoni, G Franceschini and L Calabresi

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