

APOLIPOPROTEIN E GENOTYPE AND THE RISK OF RECURRENT LOBAR INTRACEREBRAL HEMORRHAGE

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ABSTRACT

Background Recurrent lobar intracerebral hemorrhage is the hallmark of cerebral amyloid angiopathy. The factors that predispose patients to early recurrence of lobar hemorrhage are unknown. One candidate is the apolipoprotein E gene, since both the $\epsilon 2$ and the $\epsilon 4$ alleles of apolipoprotein E appear to be associated with the severity of amyloid angiopathy.

Methods We performed a prospective, longitudinal study of consecutive elderly patients who survived a lobar intracerebral hemorrhage. The patients were followed for recurrent hemorrhagic stroke by interviews at six-month intervals and reviews of medical records and computed tomographic scans.

Results Nineteen of 71 enrolled patients had recurrent hemorrhages during a mean (\pm SD) follow-up period of 23.9 ± 14.8 months, yielding a 2-year cumulative rate of recurrence of 21 percent. The apolipoprotein E genotype was significantly associated with the risk of recurrence. Carriers of the $\epsilon 2$ or $\epsilon 4$ allele had a two-year rate of recurrence of 28 percent, as compared with only 10 percent for patients with the common apolipoprotein E $\epsilon 3/\epsilon 3$ genotype (risk ratio, 3.8; 95 percent confidence interval, 1.2 to 11.6; $P=0.01$). Early recurrence occurred in eight patients, four of whom had the uncommon $\epsilon 2/\epsilon 4$ genotype. Also at increased risk for recurrence were patients with a history of hemorrhagic stroke before entry into the study (two-year recurrence, 61 percent; risk ratio, 6.4; 95 percent confidence interval, 2.2 to 18.5; $P<0.001$).

Conclusions The apolipoprotein E genotype can identify patients with lobar intracerebral hemorrhage who are at highest risk for early recurrence. This finding makes possible both the provision of prognostic information to patients with lobar hemorrhage and a method of targeting and assessing potential strategies for prevention. (N Engl J Med 2000;342:240-5.)

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CEREBRAL amyloid angiopathy, defined by the deposition of congophilic material in vessels of the cortex and leptomeninges, is a major cause of intracerebral hemorrhage in the elderly.^{1,2} Hemorrhages related to amyloid angiopathy generally occur in the cortical and cortico-subcortical (lobar) brain regions where the vascular amyloid deposits are most frequent, and occur less commonly in the cerebellum.³ Most patients recover from an initial lobar hemorrhage.^{4,5} Recurrent lobar hemorrhages are relatively common, however, and may cause greater morbidity and mortality than first hemorrhages.⁶⁻⁸

Little is known about the factors that predict early recurrence in elderly patients with lobar hemorrhage. Such information would be useful both in determining the prognosis for individual patients and in furthering our understanding of underlying pathogenic processes, such as amyloid angiopathy.

In the current study we examined the apolipoprotein E genotype as a potential risk factor for recurrent lobar hemorrhage. Apolipoprotein E is present in three common allelic forms in humans, designated $\epsilon 2$, $\epsilon 3$ (the most common), and $\epsilon 4$. Previously implicated as a risk factor for dyslipidemia⁹ and Alzheimer's disease,¹⁰ the apolipoprotein E genotype also appears to have an important role in the pathogenesis of cerebral amyloid angiopathy. Clinical and pathological studies of amyloid angiopathy-related hemorrhage have suggested that both the $\epsilon 4$ and the $\epsilon 2$ alleles of apolipoprotein E are possible risk factors for the presence and early onset of the disease.¹¹⁻¹⁴ The prospective data reported here indicate a strong association as well with the risk of a recurrence of hemorrhage.

METHODS

Recruitment of Patients

We performed a prospective, longitudinal cohort study of survivors of acute lobar hemorrhage. Subjects were recruited from among consecutive patients at least 55 years old who presented with primary lobar hemorrhage to the Massachusetts General Hospital or the Spaulding Rehabilitation Hospital in Boston from July 1994 to June 1998. We identified potential subjects by screening lists of all admissions to the neurology, neurosurgery, and internal-medicine services. All patients underwent routine clinical evaluation, including history taking and physical examination, laboratory testing, stool guaiac examination, chest radiography, and computed tomography of the brain. Base-line evaluation also included conventional spin-echo magnetic resonance imaging (MRI) in 54 patients and gradient-echo MRI sequences (which are sensitive to small chronic hemorrhages^{15,16}) in 50 of the 71 patients in the final cohort.

Potential subjects were assessed by a study neurologist to determine whether they met the study criteria. The exclusion criteria were any hemorrhagic focus outside the lobar brain regions (e.g., basal ganglia, thalamus, or brain stem), the presence of another definite cause of hemorrhage (trauma, excessive warfarin therapy [as indicated by an international normalized ratio above 3.0], vasculitis, cerebral tumor, coagulopathy, or vascular malformation¹⁷), or death before hospital discharge. There were 103 patients with lobar intracerebral hemorrhage without another definite cause among the 197 elderly patients with intracerebral hemorrhage who were screened during this period, and 78 of them survived to hos-

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pital discharge. Among these 78 eligible patients, 71 (91 percent) consented to be followed as part of the study, and 70 (90 percent) gave blood samples for the determination of apolipoprotein E genotype. Most members of the cohort were white; the only exceptions were one Asian, one Hispanic, and one black patient.

All information on patients (clinical, radiographic, and pathological) was reviewed and recorded at the time of recruitment by staff members who had no knowledge of the genotype. Clinical information collected by the investigators at the time of index presentation included age, race or ethnic group, sex, history of hypertension (defined by the use of an antihypertensive agent before admission or for at least one week after presentation¹¹), dementia (defined as progressive decline in memory, language, or other cognitive function before the occurrence of hemorrhagic stroke¹¹), diabetes mellitus (defined by the regular use of a hypoglycemic agent before or after admission), and previous hemorrhagic stroke (i.e., occurring before the index lobar hemorrhage; defined by the presence of clinical symptoms with acute hemorrhage documented by neuroimaging). In the final study cohort of 71 patients, 49 met the criteria for probable cerebral amyloid angiopathy-related hemorrhage¹¹ on the basis of pathological demonstration of amyloid angiopathy (10 patients) or gradient-echo MRI evidence of two or more hemorrhagic lesions in the lobar regions (39 patients), and 22 were considered to have possible cerebral amyloid angiopathy¹¹ on the basis of radiographic demonstration of a solitary lobar hemorrhage.

This study was performed with the approval of and in accordance with the guidelines of the institutional review boards of Massachusetts General Hospital and Spaulding Rehabilitation Hospital and with the informed consent of all subjects or family members.

Follow-up

The patients were interviewed by telephone every six months through June 1999. During the interview, the patient, the care giver (typically a spouse or other family member), or both were asked whether the patient had had any type of stroke or new neurologic symptoms (with detailed examples provided) or a decline in memory, language, or other cognitive function over the previous six months. The care givers of 60 of the 71 patients were interviewed, including all care givers of patients with a history of dementia or any suggestion of cognitive impairment at follow-up. All reports of recurrent hemorrhagic stroke (in 19 of the 71 patients) were confirmed by direct review of pertinent medical records, computed tomographic (CT) scans, and available pathological specimens by a study investigator. The patients also continued to receive routine medical care from their primary physicians (internists or neurologists) during the follow-up period. Medical records from these visits were available for review for 42 of the 52 patients for whom there was no report of recurrent hemorrhage. In each case the medical records confirmed the absence of new symptoms or signs of stroke.

Determination of Apolipoprotein E Genotype

DNA was prepared from blood samples, and the apolipoprotein E genotype was determined by the polymerase-chain-reaction-restriction-enzyme method as previously described.¹⁷ The genotype was determined and recorded without knowledge of the patient's clinical characteristics.

Statistical Analysis

We used the Kaplan-Meier product-limit method to estimate the cumulative proportion of patients with recurrent hemorrhage in the overall sample and in groups stratified according to demographic, clinical, or genetic variables. The survival time was calculated from the date of onset of the index hemorrhage until the date of a recurrence or until the last known date without recurrence on the basis of interviews with the patient or care giver. Data were censored at the time of death from causes other than documented recurrent hemorrhage (14 patients) or loss of contact with the study personnel (4 patients); there was no association between these rea-

sons for censoring and apolipoprotein E genotype. Hypothesis testing was performed by the log-rank test; the effects of predictive variables are expressed as risk ratios and 95 percent confidence intervals, calculated by the Cox proportional-hazards method. Age at study entry was analyzed as both a continuous variable and a categorical variable according to the median age of the cohort (<75 vs. ≥75 years); age at the onset of a first clinical hemorrhage was handled similarly. Apolipoprotein E genotype was analyzed as a categorical variable according to the presence or absence of the ε2 and ε4 alleles. Multivariate analysis was performed with the Cox proportional-hazards model, with the use of variables associated (P<0.1) with the risk of recurrence in the univariate testing. Similar methods were used to estimate the proportion of patients who died or had evidence of cognitive decline.

All analyses were performed with Stata software (College Park, Tex.). All tests of significance were two-tailed.

RESULTS

The study cohort, consisting of 71 elderly survivors of lobar hemorrhage, was followed prospectively for an average (±SD) of 23.9±14.8 months (range, 0.2 to 53.9) after the initial hemorrhage. The baseline characteristics of the cohort, including the proportion with a clinical history of hypertension, diabetes mellitus, or dementia before the index hemorrhage, are shown in Table 1. The frequencies of the ε2 and ε4 alleles of apolipoprotein E were higher than those in control elderly populations, as noted previously.^{10,13} Just over half of the total cohort (38 of 70 patients for whom the genotype was determined) carried one or both of these alleles. One cohort member died from recurrent hemorrhage before a blood sample could be obtained for genotyping.

Nineteen members of the cohort had recurrent symptomatic hemorrhages during follow-up, yielding an estimated two-year cumulative incidence of 21 percent (Table 2), or an incidence of 14.3 per 100 person-years. Eighteen patients had recurrent lobar hemorrhages and one had a cerebellar hemorrhage. All recurrent hemorrhages were in a different site from that of the index hemorrhage. The in-hospital mortality rate associated with recurrent hemorrhage was 42 percent (8 of 19 patients). Pathological review of specimens obtained at the time of hematoma resection (in three patients, including one with cerebellar hemorrhage) or autopsy (one patient) demonstrated cerebral amyloid angiopathy in all instances.

Several clinical variables were examined for their effect on the risk of recurrence of hemorrhage (Table 2). The time to recurrence did not vary significantly with age (either at study entry or at the first clinical hemorrhage), sex, or the presence or absence of hypertension, dementia, or diabetes mellitus (P>0.4 for all variables). The risk was elevated, however, in the 10 patients with a history of hemorrhagic stroke before they entered the study (Fig. 1A).

The apolipoprotein E genotype was also a predictor of the risk of recurrence (Fig. 1B). Among the 18 patients whose genotypes were known who had a recurrent hemorrhage, 14 were carriers of the ε2 or ε4 allele; the two-year recurrence rate in this sub-

TABLE 1. CLINICAL AND GENETIC CHARACTERISTICS OF THE 71 PATIENTS.

CHARACTERISTIC	VALUE
Age at study entry — yr	
Mean ±SD	75.4±8.4
Range	57–98
Sex — F/M	34/37
Hypertension — no. (%)	38 (54)
Dementia — no. (%)	15 (21)
Diabetes mellitus — no. (%)	6 (8)
Previous hemorrhagic stroke — no. (%)*	10 (14)
Apolipoprotein E allele frequency — alleles present/total chromosomes examined (%)†	
ε2	21/140 (15)
ε3	89/140 (64)
ε4	30/140 (21)

*These hemorrhagic strokes occurred before the index lobar hemorrhages.

†DNA from one patient was unavailable, resulting in a total of 70 DNA specimens.

group was 28 percent. In contrast, only four patients with the common ε3/ε3 genotype had a recurrent hemorrhage; the two-year recurrence rate in this subgroup was 10 percent (risk ratio for carriers of ε2 or ε4, 3.8; 95 percent confidence interval, 1.2 to 11.6). An increased risk of recurrence was conferred by either ε2 or ε4 (Table 2). The ε2/ε4 genotype was associated with the earliest recurrences: four of the eight patients who had recurrences within the first six months of follow-up had this uncommon genotype. There were no differences in time to a recurrence between patients who were heterozygous for ε2 or ε4 and the small group of patients who were homozygous for ε2 (one patient) or ε4 (four patients).

A Cox proportional-hazards model was fitted to assess the independent contributions of the various predictor variables (Table 3). Analysis of apolipoprotein E genotype demonstrated that ε2 and ε4 each exerted independent effects on recurrence (model 1). Adding previous hemorrhagic stroke to the model (model 2) reduced the effect of the ε2 allele to borderline statistical significance (P=0.1).

DISCUSSION

The data demonstrate a clear relation between the ε2 and ε4 alleles of apolipoprotein E and the risk of recurrent lobar hemorrhage. This finding suggests that ε2 and ε4 alleles might identify the patients in whom cerebral amyloid angiopathy is sufficiently severe and widespread to cause early recurrence. Supporting this interpretation is the correspondence noted between these alleles and the severity of specific aspects of amyloid angiopathy. Apolipoprotein E ε4 is associated with increased vascular deposition of the β-amyloid peptide,^{12,17-20} an effect that is statistically

TABLE 2. PREDICTORS OF RECURRENCE OF HEMORRHAGE.

VARIABLE	NO. OF PATIENTS	2-YEAR CUMULATIVE RECURRENCE	RISK RATIO (95% CONFIDENCE INTERVAL)
Age at study entry			
<75 yr	36	0.19	
≥75 yr	35	0.23	1.4 (0.6–3.6)
Sex			
Female	34	0.26	
Male	37	0.15	0.8 (0.3–2.0)
Hypertension			
No	33	0.20	
Yes	38	0.21	0.9 (0.4–2.3)
Dementia			
No	56	0.20	
Yes	15	0.25	1.2 (0.4–3.4)
Diabetes mellitus			
No	65	0.20	
Yes	6	0.33	0.7 (0.1–5.2)
Previous hemorrhage			
No	61	0.14	
Yes	10	0.61	6.4 (2.2–18.5)*
Apolipoprotein E genotype			
ε3/ε3	32	0.10	
ε2+†	20	0.41	4.7 (1.4–15.9)‡
ε4+†	26	0.27	3.7 (1.1–11.7)‡
Total cohort	71	0.21	

*P<0.001 by the log-rank test.

†Eight patients with the ε2/ε4 genotype are included. Comparison is with the ε3/ε3 group.

‡P<0.02 by the log-rank test.

independent of the allele's association with plaque amyloid.¹⁷ Apolipoprotein E ε2, conversely, appears to promote degenerative changes, such as cracking and fibrinoid necrosis, in the amyloid-laden vessel wall.^{14,21} Both effects are specific to the vasculopathy of cerebral amyloid angiopathy, since neither allele is associated with other types of intracranial hemorrhage, such as hypertensive hemorrhage.^{11,22}

The lack of pathological confirmation of cerebral amyloid angiopathy in most of our cohort raises the alternative possibility that ε2 and ε4 distinguish patients who have amyloid angiopathy from those who do not. Although this explanation cannot be excluded, several considerations argue against it as the primary mechanism for the effect of apolipoprotein E. Even when the analysis was restricted to the subgroup of 49 patients who met the more stringent research criteria for “probable cerebral amyloid angiopathy–related hemorrhage,” carriers of the ε2 or ε4 allele had higher rates of recurrence than carriers of the ε3/ε3 genotype. It should also be noted that despite its association with ε2 and ε4, amyloid angiopathy–related hemorrhage is not at all uncommon in persons with the apolipoprotein E ε3/ε3 genotype.^{13,14} Indeed, the distribution of apolipoprotein E allele frequencies in pathologically documented cases of cerebral amyloid angiopathy² is quite similar to that in our cohort (Table 1).

The apolipoprotein E genotype did not predict the

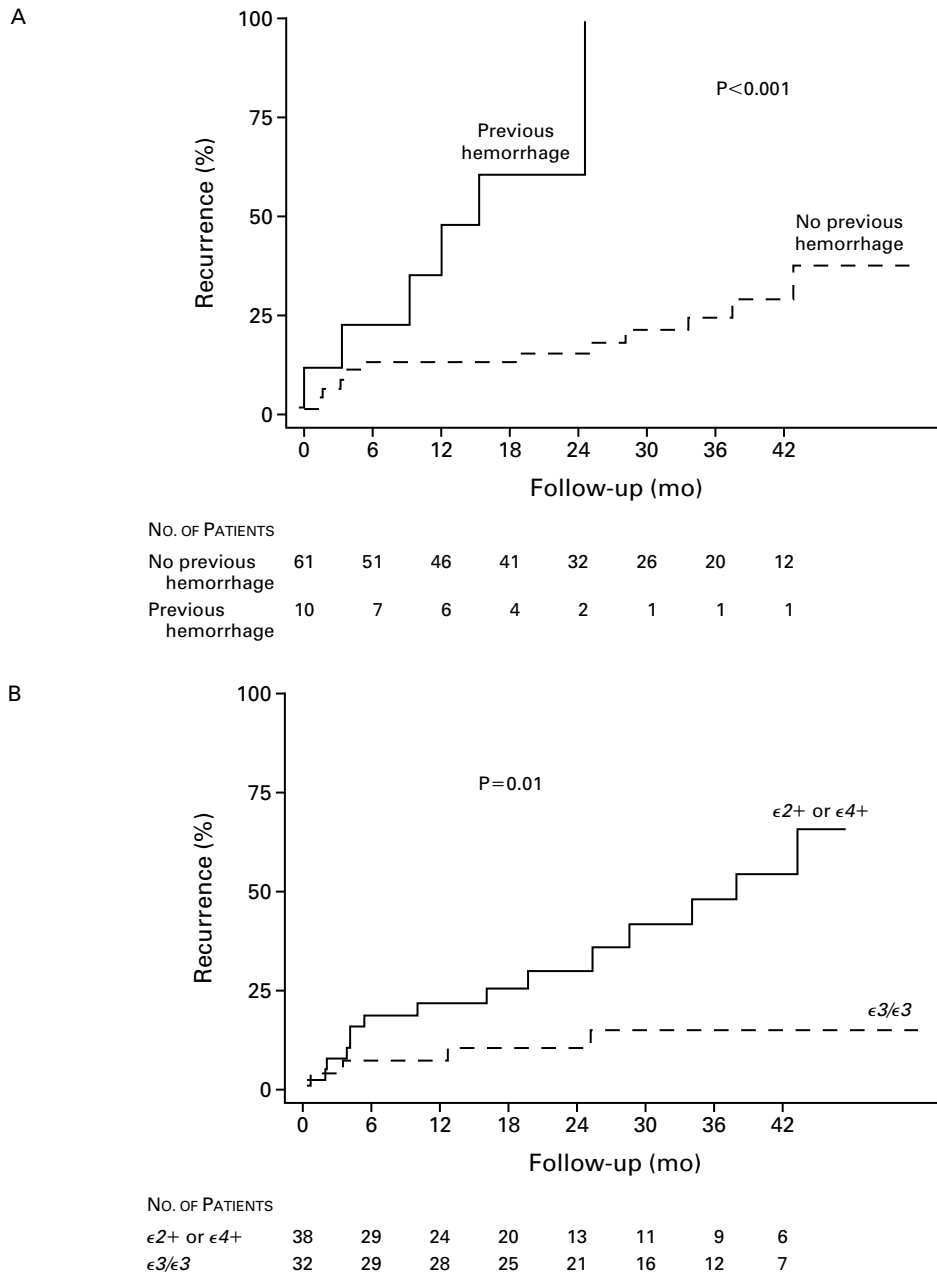


Figure 1. Kaplan–Meier Estimates of the Rate of Recurrence of Lobar Hemorrhage over Time. Data are stratified according to the presence or absence of a history of hemorrhagic stroke (Panel A) or the presence or absence of the apolipoprotein E ε2 or ε4 allele (Panel B). Testing for significance was by the log-rank method.

risk of recurrence with certainty, a finding that suggests the existence of other risk factors. One such predictive factor was hemorrhagic stroke before the index lobar hemorrhage, which was more directly linked to recurrence, in statistical terms, than was the apolipoprotein E genotype (Table 3). We interpret these two types of risk factors somewhat differently, since

previous hemorrhage, in contrast to a genetic factor, is unlikely to have a causal role in recurrence. Previous hemorrhage instead probably acts as a marker of other genetic or environmental risk factors for aggressive disease, both known risk factors (e.g., apolipoprotein E ε2, which is present at the markedly elevated allelic frequency of 40 percent among patients with

TABLE 3. MULTIVARIATE MODEL FOR TIME TO A RECURRENCE OF HEMORRHAGE.

VARIABLE	HAZARD RATIO (95% CONFIDENCE INTERVAL)
Model 1: Apolipoprotein E genotype	
$\epsilon 2+$	3.3 (1.3–8.7)
$\epsilon 4+$	2.5 (1.0–6.3)
Model 2: Apolipoprotein E genotype + previous hemorrhage	
Previous hemorrhage	5.9 (1.9–18.4)
$\epsilon 2+$	2.4 (0.8–6.8)
$\epsilon 4+$	2.9 (1.1–7.6)

previous hemorrhage) and those yet to be identified. The association between previous and recurrent hemorrhage also underscores the fact that recurrences do not occur at random, but are a characteristic of particularly aggressive diseases.

None of the other clinical risk factors we examined affected the risk of recurrence in this cohort. Hypertension, in particular, did not significantly affect the risk of recurrence, despite its important role as a risk factor for hemorrhage in the elderly²³ and for the recurrence of hypertensive-type hemorrhage.^{6,24} Several considerations make this conclusion somewhat tentative. Since the presence of hypertension was determined on the basis of the history or during hospitalization rather than through systematic outpatient monitoring, it is possible that variations in blood pressure during follow-up may have had a minor effect on the risk of recurrence. Another possibility that was not examined is that uncontrolled hypertension (probably precluded in our cohort by the primary care received by all patients) might substantially affect the risk of recurrence. From a practical standpoint, attentive control of hypertension remains the prudent course in patients with suspected amyloid angiopathy.

The association between the $\epsilon 2$ and $\epsilon 4$ alleles of apolipoprotein E and the progression of cerebral amyloid angiopathy adds independent support to the evidence implicating these alleles as risk factors for this disease. The data are particularly intriguing for the small group of patients with the apolipoprotein E $\epsilon 2/\epsilon 4$ genotype, who appear to have the earliest onset of amyloid angiopathy-related hemorrhage¹⁴ as well as the highest risk of early recurrence. Observations in this subgroup suggest that enhancement of both β -amyloid deposition (by $\epsilon 4$) and vascular degeneration (by $\epsilon 2$) may lead to a particularly malignant course of disease. The association between apolipoprotein E and the course of cerebral amyloid angiopathy also offers interesting contrasts with Alzheimer's disease, which, once established, appears not

to be accelerated by the presence of the apolipoprotein E $\epsilon 4$ allele.^{25–28} This distinction presumably arises from differences in the pathogenic pathways leading from amyloid deposition to tissue destruction in the two diseases.²

The results presented here pertain specifically to symptomatic hemorrhage that is sufficiently severe to bring the patient to medical attention and prompt the performance of CT. Future studies will determine whether similar risk factors govern the small, clinically asymptomatic hemorrhages that also characterize cerebral amyloid angiopathy.²⁹ These silent hemorrhages may be approximately twice as frequent as symptomatic hemorrhages, according to recent observations drawn from serial gradient-echo MRI studies of a subgroup of asymptomatic patients in the current cohort.³⁰

Recurrent hemorrhagic stroke appeared to be the principal contributor to poor outcome in our cohort of survivors of initial lobar hemorrhage. Among the 19 patients with recurrences, 8 did not survive to hospital discharge, another 4 died within six months of recurrence, and only 5 (26 percent) were able to return to even partially independent living. Members of the cohort who did not have recurrences, conversely, had a relatively good clinical course. The survival rate in this subgroup was 88 percent one year and 78 percent three years after entry into the cohort. Although cerebral amyloid angiopathy is also associated with an increased risk of Alzheimer's disease,¹ as well as subcortical ischemic dementia,^{31,32} our patients did not have extraordinarily high rates of cognitive decline. Among 53 patients who did not have dementia before or immediately after the index hemorrhage, 89 percent remained free of dementia after one year of follow-up and 77 percent after three years. These figures are similar to those for dementia-free survival after ischemic stroke.³³ Three of the eight new occurrences of dementia were related to recurrent hemorrhage. Taken together, these data indicate that prevention of recurrence would be an important step toward improving the outcome after lobar hemorrhage.

Our results raise the possibility that determination of the apolipoprotein E genotype might be clinically useful in assessing a patient's prognosis with respect to recurrent lobar hemorrhage. It should be emphasized, however, that the data refer expressly to recurrent rather than initial hemorrhage: the apolipoprotein E genotype is neither sensitive nor specific for the primary diagnosis of cerebral amyloid angiopathy. Another possible application of these data would be to identify the patients with the highest risk of recurrence for the purpose of testing potential protective agents in clinical trials.

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