Apolipoprotein E polymorphism and neuropsychological outcome following subarachnoid haemorrhage

Apolipoprotein E Polymorphism and Neuropsychological Outcome following Subarachnoid Haemorrhage

Abstract

Objectives - To investigate the association between *APOE* genotype and cognitive and emotional outcome following spontaneous subarachnoid haemorrhage (SAH).

Materials and Methods - Neuropsychological assessments were conducted with 70 SAH survivors derived from a consecutive series of neurosurgical admissions. Outcomes, including cognitive tests, health questionnaires and Glasgow Outcome Scale at a mean of 16 months after SAH, were compared with presence or absence of the ε4 allele.

Results – There was no evidence that SAH survivors possessing the ε4 allele had poorer outcome. The only suggestion of an association between the ε4 allele and outcome was in a subgroup of patients with a Fisher Grade 4 haemorrhage, though this trend did not reach statistical significance.

Conclusions – Overall, possession of the *APOE* ε4 allele is not significantly associated with neuropsychological outcome following subarachnoid haemorrhage. However there may be an effect amongst those with a Fisher Grade 4 haemorrhage.

APOE Polymorphism and Subarachnoid Haemorrhage Outcome

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Introduction

Several studies have suggested that polymorphism of the Apolipoprotein E (*APOE*) gene influences recovery from brain injury, with the ε4 allele associated with poorer outcome. Nicoll and colleagues first reported altered neuropathological findings amongst ε4 patients who suffered fatal head injury (1). Other studies of outcome following head injury have indicated poorer recovery amongst those with the ε4 allele. The first prospective clinical study reported that ε4 patients were more than twice as likely to have a poor outcome as determined by the Glasgow Outcome Scale (2). Poorer outcome in ε4 survivors of head injury has also been reported amongst brain injury patients who have participated in rehabilitation programmes (3, 4).

These findings have been reflected by studies of outcome following intracerebral haemorrhage, in which patients with ε4 alleles were more likely to die or to have a poor outcome if they survived than were non-ε4 patients (5, 6). However this apparently deleterious effect of the ε4 allele has not been reported in outcome studies of ischaemic stroke (6, 7), suggesting that the effect may be influenced by the type of brain insult.

Recent studies of the association between the apolipoprotein E gene and outcome following subarachnoid haemorrhage have reported conflicting findings. Two studies, one prospective and the other retrospective, have found significantly poorer outcome in patients with the ε4 allele (8, 9), whilst a prospective study involving 100 SAH patients found no association between *APOE* genotype and outcome (10). However these studies have been limited by the use of a relatively simple categorisation of death or disability as the sole measure of outcome.

The current study reports the results of a detailed neuropsychological assessment of outcome in 70 patients derived from a consecutive series of neurosurgical admissions with suspected SAH. A comparison of the current study with previous studies that have reported an association between the ϵ4 allele and outcome following brain injury is given in Table 1.

<Insert Table 1 around here>

(2-9)

Material and Methods

Patients: From a consecutive series of 125 neurosurgical admissions with suspected SAH, 19 died as a consequence of the haemorrhage, 12 did not have SAH confirmed by CT or lumbar puncture, one was excluded due to a previously clipped aneurysm and nine did not consent to the earlier part of the study (10). The remaining 84 patients were contacted by letter and asked to participate in the neuropsychological assessment. Of these patients, no contact could be established with seven, six either declined to participate or repeatedly did not attend arranged appointments and one lived too far from the unit to travel. The remaining 70 patients participated in the neuropsychological assessment either in their own homes or at the neurosurgical unit depending on their preference. The study was approved by the local ethics committee and informed consent was obtained from all patients prior to the assessment.

Clinical indices for the 70 participating patients and the 14 non-participants are outlined in Table 2. There were no significant differences between participants and non-participants. Of those who participated in the neuropsychological assessment (N = 70, 43 females), the mean age was 45.2 years (SD 15.2) with a range from 25 to 74 years. Mean years of education was 12.21 (SD 2.1) ranging from 9 to 19 years. Mean time between initial admission to the neurosurgical unit and neuropsychological assessment was 16.3 months (SD 2.1) with a range from 14 to 23 months. The majority (80%) of patients were married or in a stable cohabiting relationship.

<Insert Table 2 around here>

APOE genotypes were determined using polymerase chain reaction as described previously (10, 11). All assessments and scoring were conducted blind to genotype.

Neuropsychological Assessment

The neuropsychological interview involved the assessment of cognitive performance, including measures of visual and verbal memory, information processing, attention and executive functioning. The extended Glasgow Outcome Scale (GOS) was completed as part of a semistructured interview. Questionnaire measures of emotional and functional outcome were given and explained to patients to be returned by post. An overview of the assessment employed is given in Table 3.

<Insert Table 3 around here>

(12-24)

There were no notable differences between ε4 and non-ε4 patients in terms of educational level or social class. There was a slight difference in mean age at assessment (ε4 52.1 vs non-ε4 48.2) which was not statistically significant. In order to control for any possible influences of this slight age difference, the relationship between the APOE ε4 allele (present or absent) and cognitive task performance was determined using analysis of covariance, with age at assessment entered as co-variate. The relationship between the ε4 allele and measures of emotional and functional outcome was determined using non-parametric Mann-Whitney tests.

Results

The *APOE* ε4 allele was present in 16 (23%) of the 70 patients who participated in assessments at 14 months. There were no significant differences between ε4 and non-ε4 patients in terms of aneurysmal origin (ε4 88% vs non-ε4 81%), anterior communicating artery aneurysm (ε4 25% vs non-ε4 28%), or admission World Federation of Neurological Surgeons (WFNS) grade (grade I: ε4 63% vs. non-ε4 70%). A Fisher Grade of 4 was more common amongst ε4 patients, with six (38%) of sixteen ε4 patients having a Fisher Grade 4 relative to fourteen (26%) of fifty-four non-ε4 patients, though this difference did not reach statistical significance. None of the sixteen ε4 patients had an intraparenchymal haematoma, whereas haematoma was present in ten of the non-ε4 patients. The Fisher Grade 4 ε4 patients all had intraventricular haemorrhages.

< Insert Table 4 around here >

As shown in Table 4, there were no consistent associations between presence of the ε4 allele and performance on the neuropsychological measures. The WAIS comprehension task difference was the only difference to be statistically significant at the $p < 0.05$ level, with this difference in the opposite direction to that expected and no longer significant after Bonferroni correction. Possession of the ε4 allele was not associated with the presence of anxiety or depression amongst patients and there were no differences in outcome assessed using the GOS or SF-36. There was also no association between presence of the ε4 allele and change in GOS between assessments at 6 & 16 months.

There was a suggestion of an interaction between the ε4 allele and Fisher Grade. Only one (17%) of the six ε4 Fisher 4 patients improved on GOS, relative to 6 (43%) of 14 non-ε4 Fisher 4 patients. At the 16 month assessment four (67%) of the six ε4 Fisher 4 patients remained severely disabled relative to five (36%) of fourteen non-ε4 Fisher 4 patients. By contrast amongst patients with Fisher Grades 1-3, none of the ten ε4, and only two of the forty non-ε4 patients were severely disabled at 16 months. There was also a non-significant trend for the ε4 Fisher 4 patients to perform more poorly than non-ε4 Fisher 4 patients on verbal memory tasks such as logical memory and verbal paired associates (Table 5).

<Insert Table 5 around here >

Discussion

Previous studies investigating the association between *APOE* genotype and recovery from stroke have used relatively crude indices of outcome, but have generally found poorer outcome amongst ε4 ICH patients, with little if any effect of the ε4 allele upon outcome following ischaemic stroke (5-7). Additionally, evidence suggests that the ε4 allele has an independent rather than a synergistic influence upon the risk of cognitive decline or dementia following stroke (25). Recent studies have reported conflicting findings in relation to the association between ε4 and outcome following SAH (8-10).

The current study reports findings from a detailed neuropsychological assessment of SAH survivors which did not identify an association between the ε4 allele and outcome amongst patients in whom haemorrhage was confined to the subarachnoid space (Fisher Grades 1-3). There were however suggestions of an effect of the ε4 allele upon outcome and verbal memory amongst Fisher Grade 4 patients, in whom haemorrhage extended into the ventricles or brain parenchyma. These Fisher 4 patients might be viewed as having more in common with intracerebral haemorrhage patients than do the lower Fisher Grade patients and thus it might be expected that they would be more likely to demonstrate an effect of the ε4 allele.

It is possible that the ε4 patients were disposed towards greater severity of haemorrhage, which resulted in a greater proportion of them having a Fisher Grade 4. Evidence from the acute stage of this patient cohort suggested that ε4 patients may be less susceptible to vasospasm but more susceptible to re-haemorrhage (10). This would be consistent with findings of an association between ε4 and recovery from ICH but not ischaemic stroke (5-7).

The suggestions of greater initial haemorrhage and risk of re-haemorrhage amongst ε4 patients are also consistent with emerging evidence suggesting that ε4 individuals may have deficient blood clotting mechanisms and larger haematoma volumes (26, 27).

Alternatively it is possible that greater secondary damage occurs amongst Fisher 4 ε4 patients following subarachnoid haemorrhage. Previous studies have demonstrated that the cytotoxic effects of amyloid β-protein (Aβ) may be mediated by oxidative damage (28, 29). Aβ deposits are more likely to be present in the vessels of *APOE* ε4 carriers and may increase oxidative damage following haemorrhage, particularly amongst Fisher 4 patients in whom extravascular blood is present in the parenchyma or ventricles. However the current findings indicate that the ε4 allele is not an important factor in the neuropsychological outcome of those who survive the initial haemorrhage when all patients are considered as a group. Earlier findings of an association between the ε4 allele and outcome were limited by their use of a relatively simple scale of death / disability as their sole outcome measure and as such may reflect an association with survival rather than functional outcome following SAH.

In summary, the current study does not find an overall association between the *APOE* ε4 allele and neuropsychological outcome following SAH. However, the study raises the possibility that the presence of ε4 may be associated with outcome in a subgroup with Fisher Grade 4.

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Table 1. Studies comparing APOE genotype with outcome following brain injury

Study	N	Patient Group	Outcome Measures
Teasdale G. et al (2)	89 *	Head Injury	GOS
Lichtman (3)	31	Head Injury	Telephone FIM
Friedman (4)	69	Head Injury	Clinician determined outcomes
Alberts M J (5)	44 *	ICH	Bartel index
McCarron et al (6)	69 *	ICH	Return Home vs In care or Death
Catto et al (7)	592 *	Acute stroke	Mortality
Leung et al (8)	72 *	SAH	GOS
Niskakangas et al (9)	108 *	SAH	GOS
Current Study	70	SAH	15 Neuropsychological tasks, 4 Emotional outcome measures, Extended GOS

GOS: Glasgow Outcome Scale; FIM: Functional Independence Measure; ICH: Intracerebral Haemorrhage;

SAH: Subarachnoid Haemorrhage

*: Includes deceased patients

Table 2: Clinical Variables. Number of cases (with percentage in parentheses)

	Participants	Non-Participants		Participants	Non-Participants
Fisher Grade 0	1 (1.4)	0	WFNS Grade I	47 (67.1)	10 (71.4)
Fisher Grade I	6 (8.6)	2 (14.3)	WFNS Grade II	12 (17.1)	2 (14.3)
Fisher Grade II	6 (8.6)	0	WFNS Grade III	2 (2.9)	0
Fisher Grade III	37 (52.9)	6 (42.9)	WFNS Grade IV	3 (4.3)	0
Fisher Grade IV	20 (28.5)	6 (42.9)	WFNS Grade V	6 (8.6)	2 (14.3)
No Clinical Deterioration	50 (71.4)	10 (71.4)	Aneurysmal SAH	56 (80.0)	12 (85.7)
Deteriorated Once	7 (10.0)	2 (14.3)	Negative Angio †	12 (17.1)	2 (14.3)
More than Once	13 (18.6)	2 (14.3)			
Surgical Intervention	54 (77.1)	12 (85.7)	Haematoma	10 (14.3)	2 (14.3)
No Surgery	16 (22.9)	2 (14.3)	No Haematoma	60 (85.7)	12 (85.7)

† : No angio performed for two of the participating patients

Table 3: Neuropsychological Assessment Battery

Cognitive Tasks	**Global Outcome**
Digit Span - WAIS-R (12)	Extended Glasgow Outcome Scale (13)
Comprehension - WAIS-R (12)	UK Short Form-36 Health Survey (SF-36) (14)
Block Design - WAIS-R (12)	
Digit-Symbol - WAIS-R (12)	
PASAT (2 and 4 second interval) (15)	**Emotional Outcome**
National Adult Reading Test (16)	Hospital Anxiety and Depression Scale (17)
McKenna Graded Naming Test (18)	State Trait Anxiety Inventory (19)
Logical Memory (20)	Beck Depression Inventory (21)
Verbal Paired Associates (20)	General Health Questionnaire (22)
Figural Memory WMS-R (20)	
Brixton Spatial Anticipation Test (23)	
Verbal Fluency ‘F’ ‘A’ ‘S’	
Rey-Osterreith Complex Figure	
Trail Making A & B	
Stroop Test: (24)	

Table 4: *APOE* ε4 allele and Cognitive Performance

	ε4 allele present		No ε4 allele			
	Mean	SD	Mean	SD	F	p
Digit Span	15.47	3.85	15.39	4.43	0.64 (1,65)	0.429
Comprehension	19.93	3.94	18.22	6.07	4.68 (1,65)	0.034 *
Block Design	22.00	9.74	22.56	9.59	0.98 (1,66)	0.326
Digit Symbol	40.20	11.43	45.15	12.78	0.01 (1,63)	0.946
PASAT 4 seconds	47.54	14.32	46.80	13.97	0.69 (1,55)	0.411
PASAT 2 seconds	30.08	9.78	32.31	11.93	0.01 (1,47)	0.940
GNT	20.07	5.66	19.81	5.60	0.94 (1,65)	0.337
Logical Memory	22.93	7.71	23.56	8.40	0.31 (1,65)	0.579
Delayed Logical Memory	17.43	11.03	18.83	8.82	0.11 (1,63)	0.741
Paired Associates	15.36	5.21	16.00	4.75	0.04 (1,61)	0.845
Delayed Associates	5.43	2.77	6.38	1.58	1.02 (1,58)	0.318
Figural Memory	6.54	1.94	6.69	1.68	0.65 (1,60)	0.424
Brixton Spatial †	22.36	6.42	19.54	8.66	0.22 (1,60)	0.642
Verbal Fluency FAS	31.53	13.58	33.36	15.05	0.38 (1,64)	0.542
Rey Copy	27.72	6.19	29.39	5.41	0.02 (1,62)	0.893
Rey Immed Recall	11.47	9.62	14.45	7.49	0.12 (1,61)	0.727
Trailmaking A †	54.93	33.31	42.28	19.22	1.39 (1,64)	0.242
Trailmaking B †	95.31	30.24	87.59	38.77	0.14 (1,58)	0.709
Stroop Interference	0.97	6.51	-0.74	6.54	1.14 (1,56)	0.291

Analysis of covariance with age at assessment as co-variate

† Denotes task in which higher score represents worse performance; * $p < 0.05$

Table 5: Mean Verbal Memory Performance in Fisher 4 Patients by ε4 allele

(Standard deviation in parentheses)

Verbal memory Task	ε4 (n=6)	Non-ε4 (n=14)
Logical Memory	15.8 (5.9)	20.8 (8.6)
Delayed Logical Memory	6.0 (6.7)	16.2 (9.1)
Verbal Paired Associates	9.3 (3.3)	14.9 (4.8)
Delayed Verbal Paired Associates	2.0 (1.2)	6.1 (1.5)