The association between APOE ε4, age and outcome after head injury: a prospective cohort study

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Previous preliminary studies have suggested that possession of the APOE ε4 allele is associated with a poor outcome after head injury. This study was designed to confirm and extend those observations in a larger study with examination of additional variables. We prospectively identified admissions to a Neurosurgical Unit for head injury, collected demographic and clinical data, determined APOE genotypes and obtained follow-up information at 6 months. A total of 1094 subjects were enrolled (age range: 0–93 years, mean 37 years).

Outcome was assessed using the Glasgow Outcome Scale. There was no overall association between APOE genotype and outcome, with 36% of APOE ε4 carriers having an unfavourable outcome compared with 33% of non-carriers of APOE ε4. However, there was evidence of an interaction between age and APOE genotype on outcome (P = 0.007) such that possession of APOE ε4 reduced the prospect of a favourable outcome in children and young adults. The influence of APOE genotype in younger patients after head injury can be expressed as, at age <15 years, carriage of APOE ε4 being equivalent to ageing by 25 years. This finding is consistent with experimental data suggesting that the effect of APOE genotype on outcome after head injury may be expressed through the processes of repair and recovery.

Keywords: head injury; traumatic brain injury; genetics; outcome; apolipoprotein E

Abbreviations: GCS = Glasgow Coma Scale; GOS = Glasgow Outcome Scale

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Introduction

There is considerable variability in the outcome of acute head injury. An injury that initially appears to be severe can be followed by recovery, a mild injury may be followed by disability or even death, and injuries that are apparently similar in the acute stage may have very different outcomes (Thornhill et al., 2000). Clinical and investigative indices of the severity of damage in the acute stage explain only part of this variability and there is increasing interest in features that may indicate an individual response to brain damage, such as age, sex, health and social status before injury, and genetic factors. Apolipoprotein E (apoE, protein; APOE, gene) is an apparently multifunctional protein involved in the response of the brain to injury and in subsequent repair processes (Horsburgh et al., 2000a). In a pilot study (Teasdale et al., 1997), we found evidence of an association between APOE gene polymorphism and outcome: possession of APOE ε4 allele was associated with an almost 2-fold increase in unfavourable outcome, indicated by death or disabled survival 6 months after injury. Subsequent studies have indicated reduced prospects for recovery in APOE ε4 carriers during rehabilitation after head injury (Friedman et al., 1999; Lichtman et al., 2000; Crawford et al., 2002; Liberman et al., 2002; Chiang et al., 2003). Some studies have shown little or no evidence of an association between APOE genotype and outcome in relatively mild injuries (Sundstrom et al., 2004; Chamelian et al., 2004) or in a South African Black population in whom APOE ε4 is relatively...
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common (Nathoo et al., 2003). All of the studies referred to above differ in terms of patient selection, severity of injury and method of outcome assessment, and all suffer from small sample size with which to reliably detect genetic associations.

Our previous study (Teasdale et al., 1997) was limited to 93 patients, of whom only 30 possessed APOE e4 and the groups with and without e4 differed in several parameters including severity in the acute stage. Although association with adverse outcome remained significant even when these factors were taken into account, the numbers of patients studied did not permit reliable investigation of possible interactions between APOE genotype, other prognostic indicators and outcome. We have now prospectively studied a further series of almost 1000 patients in order to gain definitive evidence about the relationship between APOE genotype and outcome, and to investigate interaction with other factors such as age and injury severity.

Methods

Participants

The participants in the study were recruited from consecutive head injury admissions to the regional Neurosurgical Unit for the West of Scotland at the Institute of Neurological Sciences, Glasgow from 1996 to 1999.

Approval for the study was obtained from the local Research Ethics Committee of the Southern General Hospital University NHS Trust. In the acute stage, consent for recruitment and acquisition of a buccal swab sample as a source for DNA was obtained from patients’ next of kin or carer. When circumstances made this inappropriate, e.g. very rapid death or lack of a responsible person to provide consent, a buccal swab was not performed, but a portion of a blood sample taken for routine clinical purposes was retained and analysed later, after consent had been obtained. Approval for obtaining outcome information was obtained from survivors at late follow-up. In a small number of patients, who either died or were left too disabled to consent and who had no responsible relative, permission for genotyping to be performed anonymously was given by the ethics committee.

Clinical features in the acute stage

Research staff prospectively extracted information from clinical records to characterize the patient's demographic features and age, the cause of injury, clinical severity of brain damage in the acute stage as indicated by the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) and pupil reaction. The findings on CT scanning were classified according to the system of Marshall et al. (1991) and operative findings were obtained from case notes.

APOE genotyping

APOE genotypes were determined from buccal swabs or blood samples using methods described previously (Millar et al., 2003).

Outcome

Patients were contacted by post and telephone at 6 months after injury. A structured questionnaire was used to obtain information about their abilities to conduct activities at home and outside, including shopping, travelling, working and leisure activities, and the extent of any family disruption [Glasgow Outcome Scale (GOS), Jennett and Bond, 1975; Wilson et al., 1998]. This information was obtained by research staff who were unaware of the patient’s status in the acute stage and of the results of genotyping.

Analysis

Outcome was dichotomized into unfavourable (death, vegetative survival or severe disability at 6 months) and favourable outcome (moderate disability or good recovery). Some survivors were unfortunate individuals who, even before their injury, were functioning at a severely disabled level. Such participants were allocated to a group with a favourable outcome if they recovered to their previous state or to the unfavourable group if they were left with increased disability and dependency. Patients for whom, although some information was available, it was insufficient to discriminate between a moderate disability and a good recovery were allocated to the favourable group if it was clear that they were independent in society.

Associations between outcome, early features and APOE genotype were assessed using univariate and multivariate logistic regression models. Results are presented using odds ratios with corresponding 95% confidence intervals.

Results

In total, 1094 patients were recruited. Of these, 7 patients could not be genotyped from the available samples, 5 patients had no follow-up data and 7 were not included for other reasons. Of the remaining 1075, 91 patients were determined to have a chronic subdural haematoma rather than an acute head injury and were therefore excluded from further analysis leaving 984 patients with an acute head injury.

Of the 984 patients confirmed to have acute head injury, 324 (32.9%) were carriers of APOE e4. The characteristics of the patients, comparing e4 carriers with non-carriers of e4, including clinical features relating to their injuries at the time of admission to the Neurosurgical Unit are shown in Table 1. The features were very similar and there was no evidence of an association between the possession of APOE e4 and age, cause of injury, early severity or pattern of damage.

A full assignment of category on the GOS, 6 months after injury, together with an APOE genotype were available for 933 patients (Table 2). There is no evidence of an association between the possession of APOE e4 and the distribution of GOS ($\chi^2 = 5.46$, 4 df, $P = 0.24$, or, pooling the vegetative category with the dead category, $\chi^2 = 4.88$, 3 df, $P = 0.18$).

The full group of 984 patients is also shown in Table 2 divided into unfavourable and favourable outcome. Further, 29 patients, who were disabled before injury but were worse at 6 months, were allocated to the unfavourable outcome group according to the predetermined criteria; 19 patients, whose outcome was assessed as favourable but not further distinguished, were allocated to the favourable group. In this complete group, 118/324 (36%) of APOE e4 carriers had an unfavourable outcome compared with 215/660 (33%) of non-carriers of APOE e4. Overall, there is no evidence of an association between the possession of APOE e4 and unfavourable outcome ($\chi^2 = 1.43$, 1 df, $P = 0.23$).
An unfavourable outcome was associated with increased age, with greater severity of damage indicated by lower GCS, an absence of pupil reaction in both eyes and with pattern of findings on CT scan.

Inspection of odds ratios (Fig. 1) indicated an interaction between age, possession of \textit{APOE} \textit{e4} and outcome which was statistically significant (\(P = 0.01\)). Controlling for A&E motor score, pupil reaction and admission CT scan findings, the evidence for an interaction was strengthened (\(P = 0.007\)).

The association between possession of \textit{APOE} \textit{e4} and unfavourable outcome was most pronounced in participants aged 0–15 years (Table 3) (odds ratio 3.06, 95% confidence interval 1.22–7.65). This can be expressed as, at age <15 years, the carriage of \textit{APOE} \textit{e4} being equivalent to ageing by 25 years.

The adverse effect of carriage of \textit{APOE} \textit{e4} decreased steadily with age, being neutralized by age 55–60. Although the effect was heavily influenced by data from children, even in adults alone the effect was statistically significant (\(P = 0.03\)). In contrast to the foregoing effect, there was no evidence of an interaction between genotype and early features such as motor score or pupil reaction, CT scan and outcome.

### Table 1

| Characteristics of acutely head-injured patients related to possession of \textit{APOE} \textit{e4} | Non-\textit{e4} carriers | \textit{e4} carriers | All |
|---|---|---|---|
| Total | 660 (67%) | 324 (33%) | 984 (100%) |
| Sex | | | |
| Male | 536 (81%) | 261 (81%) | 797 (81%) |
| Female | 124 (19%) | 63 (19%) | 187 (19%) |
| Cause | | | |
| RTA | 156 (24%) | 80 (25%) | 236 (24%) |
| Assault | 146 (22%) | 76 (23%) | 222 (23%) |
| Fall | 308 (47%) | 148 (46%) | 456 (46%) |
| Other/not recorded | 50 (8%) | 20 (6%) | 70 (7%) |
| Age (years) | | | |
| Mean | 35 | 35 | 35 |
| SD | 21.6 | 21.8 | 21.7 |
| Range | <1–93 | <1–86 | <1–93 |
| Initial severity of brain injury | | | |
| GCS at A&E | | | |
| 3–8 | 191 (30%) | 76 (24%) | 267 (28%) |
| 9–12 | 121 (19%) | 57 (18%) | 178 (19%) |
| 13–15 | 332 (52%) | 181 (58%) | 513 (54%) |
| Not recorded | 16 | 10 | 26 |
| Pupils reactivity | | | |
| One or both | 603 (91%) | 299 (92%) | 902 (92%) |
| Neither | 57 (9%) | 25 (8%) | 82 (8%) |
| CT scan pattern | | | |
| Diffuse injury | | | |
| Normal | 154 (23%) | 86 (27%) | 240 (24%) |
| Lesions | 261 (40%) | 120 (37%) | 381 (39%) |
| Swelling | 40 (6%) | 21 (6%) | 61 (6%) |
| Swelling and shift | 6 (1%) | 3 (1%) | 9 (1%) |
| Mass lesion | 195 (30%) | 92 (28%) | 287 (29%) |
| Not recorded | 16 | 10 | 26 |
| Operation\* | | | |
| Yes | 189 (29%) | 98 (30%) | 287 (29%) |
| No | 471 (71%) | 226 (70%) | 697 (71%) |

\*Operation" means an intracranial operation other than for the placement of an ICP monitor.

### Table 2

| Outcome 6 months after acute head injury related to possession of \textit{APOE} \textit{e4} | Non-\textit{e4} carriers | \textit{e4} carriers | All |
|---|---|---|---|
| Total | 660 | 324 | 984 |
| Dead | 83 (13%) | 45 (14%) | 128 (13%) |
| Vegetative | 3 (0.5%) | 3 (0.9%) | 6 (0.6%) |
| Severe disability | 111 (17%) | 59 (18%) | 170 (17%) |
| Moderate disability | 177 (27%) | 65 (20%) | 242 (25%) |
| Good recovery | 256 (39%) | 131 (41%) | 381 (39%) |
| All unfavourable\* | 215 (33%) | 118 (36%) | 333 (34%) |
| All favourable\† | 445 (67%) | 206 (64%) | 651 (66%) |

\*Includes 29 patients disabled before injury but worse at 6 months. \†Includes 19 patients whose outcome was assessed as favourable but not further distinguished.

An unfavourable outcome was associated with increased age, with greater severity of damage indicated by lower GCS, an absence of pupil reaction in both eyes and with pattern of findings on CT scan.

### Discussion

This study extends the information available on the association between possession of \textit{APOE} \textit{e4} and unfavourable outcome after acute head injury. The association of this genetically determined difference with age of the subject after acute head injuries is a striking finding. It is particularly surprising that the effect is greatest in children in view of previous studies focusing on the role of \textit{APOE} \textit{e4} in ageing and in Alzheimer’s disease. The results of this study show that the effect was heavily influenced by data from children, even in adults alone the effect was statistically significant (\(P = 0.03\)). In contrast to the foregoing effect, there was no evidence of an interaction between genotype and early features such as motor score or pupil reaction, CT scan and outcome.

Inspection of odds ratios (Fig. 1) indicated an interaction between age, possession of \textit{APOE} \textit{e4} and outcome which was statistically significant (\(P = 0.01\)). Controlling for A&E motor score, pupil reaction and admission CT scan findings, the evidence for an interaction was strengthened (\(P = 0.007\)). The association between possession of \textit{APOE} \textit{e4} and unfavourable outcome was most pronounced in participants aged 0–15 years (Table 3) (odds ratio 3.06, 95% confidence interval 1.22–7.65). This can be expressed as, at age <15 years, the carriage of \textit{APOE} \textit{e4} being equivalent to ageing by 25 years. The adverse effect of carriage of \textit{APOE} \textit{e4} decreased steadily with age, being neutralized by age 55–60. Although the effect was heavily influenced by data from children, even in adults alone the effect was statistically significant (\(P = 0.03\)). In contrast to the foregoing effect, there was no evidence of an interaction between genotype and early features such as motor score or pupil reaction, CT scan and outcome.
admissions in a single regional centre and that follow-up was achieved in a very high proportion of the patients (only 5 of 1094 patients being lost during follow-up). Data on early severity and outcome, obtained blind to genotype, show associations in accord with well-established findings. However, the study has a number of limitations. First, the population was drawn from neurosurgical admissions and the findings do not directly extrapolate to unselected admissions to a general hospital. Nevertheless, a substantial number of patients included were not severely injured and so the bias is not substantial. Furthermore, there was no evidence of an interaction between injury severity and effect of \( \text{APOE} \) genotype on outcome. Secondly, early severity was characterized only at admission and there are no data to identify the stage between then and follow-up at 6 months at which the difference between patients grouped by \( \text{APOE} \) genotype appears. Thirdly, although the follow-up rate was extremely high, data are incomplete in some participants. Finally, outcome was assessed in terms of global psychosocial/life quality indicators, consequently interaction between \( \text{APOE} \) and specific sequelae were not investigated. The GOS that we used to compare the groups provides an overall index rather than identifying the relative contributions of the various factors (e.g. cognitive, behavioural, social, etc.) that may be responsible for any difference. Nevertheless, the status of the GOS as the most widely used method of assessment of outcome in groups of head injury victims (Teasdale et al., 1998) reflects its advantages. These include its applicability across all ranges of age, severity and outcome, including death. The high reliability and validity of assessment achieved by the new structured approach (Wilson et al., 1998; Pettigrew et al., 2003) used in this study and its high degree of correlation with the results of assessments more focused on specific but limited aspects of the state of survivors (e.g. cognitive, behavioural and emotional sequelae) and of detailed multidimensional assessments of health and psychosocial state such as the SF-36 questionnaire (Pettigrew et al., 2003). Although the sensitivity of the GOS has been questioned, this is relevant only to its ability to identify factors responsible for differences in outcome, not its outstanding ability to establish if a difference exists.

The findings extend those of our preliminary study (Teasdale et al., 1997) in a substantially larger cohort of patients, although the magnitude of the difference between carriers and non-carriers of \( \text{APOE} \) is substantially smaller in the present study. Other studies which have focused on specific sequelae of head injury have found that \( \text{APOE} \) carriers may have delayed (Friedman et al., 1999) or reduced likelihood of recovery (Sorbi et al., 1995) from post-traumatic coma. There is also evidence that \( \text{APOE} \) carriers have worse memory performance after head injury (Crawford et al., 2002), are less likely to have favourable outcome after rehabilitation (Teasdale et al., 1997; Friedman et al., 1999; Lichtman et al., 2000) and are more likely to have post-traumatic seizures (Diaz-Arrastia et al., 2003). In studies of outcome, such as these, it is important to note recent information that uninjured people do not appear to differ in general cognitive ability or temperament according to carriage of \( \text{APOE} \) (Turic et al., 2001; Jorm et al., 2003). The \( \text{APOE} \) allele carriage rate of the patients in this study reflects that of the Scottish population from which they are drawn (Cumming and Robertson, 1984).

Previous studies have identified several roles for apoE in the central nervous system which are potentially of importance after brain injury. First, several lines of evidence point to a critical role for apoE in maintaining the integrity of the cerebral vasculature. For example, apoE deficiency compromises the integrity of the blood brain barrier, especially after injury (Methia et al., 2001), and is associated with more marked cerebral oedema in head injury models (Lynch et al., 2001), although not confirmed in humans (Quinn et al., 2004). The \( \text{APOE} \) allele has a long known association with severity of atherosclerosis and also with predisposition to cerebral amyloid angiopathy (Greenberg et al., 1995) including in patients with traumatic brain injury (Leclercq et al., 2005). Furthermore, there is evidence that coagulation is relatively impaired in carriers of \( \text{APOE} \), providing a potential mechanism for more pronounced haemorrhage.

Support for the role of vascular integrity and coagulation being relevant to the association of \( \text{APOE} \) with outcome after head injury has come from a number of clinical studies. First, \( \text{APOE} \) genotype influences outcome in other types of acute brain insult in which haemorrhage is a feature, including spontaneous intracerebral haemorrhage (McCarron et al., 1998; McCarron et al., 2003) and possibly in subarachnoid

### Table 3: Outcome 6 months after head injury in children and adults related to possession of \( \text{APOE} \)

| Age group (years) | Non-carriers of \( \text{APOE} \) carriers of \( \text{APOE} \) | Total |
|------------------|-----------------|------|
|                  | Unfavourable | Favourable | % Favourable | Unfavourable | Favourable | % Favourable |
| Children         |               |           |            |               |           |            |
| ≤15              | 9             | 133       | 94         | 12            | 58         | 83          |
| Adults           | 206           | 312       | 60         | 106           | 148        | 58          |
| >15 (total)      | 31            | 130       | 81         | 25            | 59         | 70          |
| 16–30            | 53            | 92        | 63         | 29            | 42         | 59          |
| 31–45            | 72            | 70        | 49         | 29            | 33         | 53          |
| 46–65            | 50            | 20        | 29         | 23            | 14         | 38          |
| ≥66              |               |           |            |               |           |            |
haemorrhage (Dunn et al., 2001; Niskakangas et al., 2001; Leung et al., 2002; Tang et al., 2003) but not apparently after ischaemic stroke (McCarron et al., 1998; McCarron et al., 2000). Direct evidence of impaired cerebrovascular integrity after traumatic brain injury has come from studies showing that APOE ε4 carriers have larger volume intracranial haematomas (Liaquat et al., 2002), have more frequent insults involving hypotension and impaired cerebral perfusion pressure (Dunn L personal communication), and increased severity of contusions and higher prevalence of hypoxic–ischaemic brain damage in post-mortem cases (Smith C personal communication).

However, the main new finding in the present study is that the influence of APOE ε4 on outcome after acute head injury is substantially greater among younger victims. It is among children and young adults in whom there is greater potential for recovery following injury. Although little is known about the underlying neurobiological basis for functional recovery after injury in the young, this may, at least in part, be a consequence of repair processes including neuronal and synaptic plasticity (Grady et al., 1989). There is clear evidence from animal models that apoE is involved in the clearance of lipid cell debris after injury and recycles lipids to cells for sprouting and synaptogenesis. Clearance of lipid debris after injury is impaired in APOE-deficient mice (White et al., 2001a) and synaptogenesis in response to injury is impaired in APOE ε4 mice (White et al., 2001b). Transgenic mouse studies, in a trauma model, have also shown increased mortality in APOE ε4 mice and evidence of a neuroprotective effect in APOE ε3 mice (Sabo et al., 2000). Infusion of apoE (conjugated to lipid) into the CSF around the time of injury reduces the amount of neuronal damage, both in apoE-deficient and in wild-type mice (Horsburgh et al., 2000b). There is evidence of a substantial reduction in the concentration of apoE in the CSF following acute brain injury (Kay et al., 2003a, b), and it is possible that the APOE/lipid concentration may fall below levels required to fulfil critical functions, including maintenance and repair of cell membranes and synapses. In this respect, the alterations in apoE following injury (Kay et al., 2003a, b, c) may be relevant to both carriers and non-carriers of APOE ε4.

Manipulation of apoE and associated lipids could have benefits in terms of promoting neuronal sprouting and synaptogenesis following brain injury. Further work is needed to elucidate the mechanisms involved and the precise time course in order to define the most appropriate time and method of intervention to promote recovery.

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