AETIOLOGY

APOE ε4 allele, age, and duration of unconsciousness were associated with unfavourable outcomes in traumatic brain injury


Question
In patients who survive traumatic brain injury (TBI), what is the relation between the apolipoprotein E (APOE) ε4 allele and outcome?

Design
Cohort analytic study with 6–8 months of follow up.

Setting
A hospital department for brain injury and rehabilitation and an outpatient rehabilitation clinic in Israel.

Participants
69 patients (mean age 36 y, 75% men) with blunt trauma. Patients with penetrating injuries or anoxic brain damage were excluded.

Assessment of risk factors
APOE genotype, Glasgow Coma Scale score, duration of unconsciousness, admission to an intensive care unit (ICU) in hospital, age, and duration of education.

Main outcome measures
Independence in activities of daily living (ADL), cognitive and behavioural abnormalities, dysarthria, dysphasia, epilepsy, and overall function. A good outcome was defined as no dysarthria, neurological abnormalities, or dysphasia; no severe cognitive abnormalities; and the ability to live independently. Outcome assessors were blinded to APOE status.

Main results
Patients who were unconscious for > 7 days were more likely to have an APOE ε4 allele (78% v 38%, p = 0.001). Fewer patients with an APOE ε4 allele had a good outcome than those without such an allele (4% v 31%, p = 0.006, odds ratio [OR] 0.1, 95% CI 0.0 to 0.7). More patients with an APOE ε4 allele had dysarthria (63% v 33%, p = 0.02, OR 3.4, CI 1.1 to 10.7). No statistically significant associations existed between the presence of an APOE ε4 allele and independence in ADL, behavioural abnormalities, severe cognitive abnormalities, dysarthria, or epilepsy. In multivariate analysis, the independent risk factors for an unfavourable outcome were the presence of an APOE ε4 allele (p = 0.02), increasing age (p = 0.01), and being unconscious for > 7 days (p = 0.02) (table).

Conclusions
In patients who survived traumatic brain injury, those having an apolipoprotein ε4 allele were more likely to be unconscious for > 7 days. At 6 months, independent risk factors for poor outcome were presence of the APOE ε4 allele, older age, and unconsciousness for > 7 days.

Risk factors for an unfavourable outcome in patients who have survived traumatic brain injury

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Adjusted odds ratio (95% CI)*</th>
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<tbody>
<tr>
<td>APOE ε4 allele present</td>
<td>13.9 (1.5 to 134.0)</td>
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<tr>
<td>Age</td>
<td>1.1 (1.0 to 1.2) per year</td>
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<tr>
<td>Unconscious for &gt; 7 days</td>
<td>7.6 (1.4 to 40.0)</td>
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*Adjusted for Glasgow Coma Scale score, duration of unconsciousness, age, and education.

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Commentary

Psychiatrists working in rehabilitation settings and in general hospitals frequently have to assess the prognosis of patients with TBI. This task is a challenging one because long term outcome depends on an interaction of susceptibility to injury, severity of insult, and capacity to repair and regenerate. To date, the prediction of long term outcome has relied largely on measures of short term outcome, such as duration of unconsciousness or post-traumatic amnesia, or coma score.1 Risk factors that are not themselves aspects of outcome offer hope of more accurate and earlier prediction. Such factors are likely to relate to susceptibility to injury or to repair.

Investigation of the biochemical and genetic basis of neuronal growth and repair has led to the identification of the ε4 allele of APOE as one potential factor. Its clinical relevance has been confirmed in the degenerative brain disorder Alzheimer’s disease, for which APOE ε4 is a risk factor, at least in whites.2 This study by Friedman et al extends previous work on TBI and APOE ε4, and provides further support for the role of this allele in the determination of prognosis.

However, there are 2 clear caveats. Firstly, the influence of race on the association between this allele and outcome from TBI is not yet known. In Alzheimer’s disease, the association seems much clearer among whites than other racial groups. Secondly, the magnitude of the association awaits further clarification. The confidence intervals around the point estimate of effect are very wide, such that it is quite possible that the odds ratio for the allele is much higher or much lower than that for > 7 days of unconsciousness. It is therefore too early to say whether this study marks a step forward in the prognostic assessment of TBI.

At the very least, however, this study should stimulate further research and encourage clinicians with relevant interests to maintain a watchful and critical eye on the growing literature about APOE ε4.

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