SHORT REPORT

Influence of APOE polymorphism on cognitive and behavioural outcome in moderate and severe traumatic brain injury

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Aim: To analyse the influence of apolipoprotein (APOE) ϵ4 status on the cognitive and behavioural functions usually impaired after moderate and severe traumatic brain injury (TBI).

Methods: In all, 77 patients with TBI selected from 140 consecutive admissions were genotyped for APOE. Each patient was subjected to neuropsychological and neurobehavioural assessment at least 6 months after injury.

Results: Performance of participants carrying the ϵ4 allele was notably worse on verbal memory (Auditory Verbal Learning Test), motor speed, fine motor coordination, visual scanning, attention and mental flexibility (Grooved Pegboard, Symbol Digit Modalities Test and part B of the Trail Making Test) and showed considerably more neurobehavioural disturbances (Neurobehavioral Rating Scale—Revised) than the group without the ϵ4 allele.

Conclusions: In particular, performance on neuropsychological tasks that are presumed to be related to temporal lobe, frontal lobe and white matter integrity is worse in patients with the APOE ϵ4 allele than in those without it. More neurobehavioural disturbances are observed in APOE ϵ4 carriers than in APOE ϵ2 and ϵ3 carriers.

Apolipoprotein (APOE) is the gene responsible for the production of apolipoprotein E (apoE) and has been widely studied in relation to outcome after traumatic brain injury (TBI). In humans, there are three common isoforms of apoE, encoded by the alleles ϵ2, ϵ3 and ϵ4. Clinical and experimental studies suggest that APOE ϵ4 is associated with an unfavourable functional outcome after TBI,[1–5] in some cases in association with other factors such as age.[6] The inheritance of APOE ϵ4 allele has even been mentioned as a risk factor for Alzheimer's disease after TBI, although this has not yet been conclusively shown.[7]

The relationship between inheritance of APOE ϵ4 and cognitive outcome in humans after TBI has been dealt with in some studies.[8–12] Some degree of impairment of neuropsychological functions has been shown after mild head injury in people with the APOE ϵ4 allele.[9 11] In a group with more severe TBI, possession of at least one APOE ϵ4 allele has been related to memory impairment within 6 months of injury.[8] In this study, the association of the frontal lobe was assessed only by verbal fluency, and no differences were observed between people with APOE-ϵ4 and those without. In a study of mainly severe TBI, however, cognitive decline after 15–25 years of injury was not related to the APOE genotype.[10]

As moderate to severe TBI usually induces disseminated injury throughout the frontotemporal regions and white matter, these areas will be noticeably affected in any patient with TBI.[13–15] Therefore, impairment of memory and executive function, mental flexibility, attention, speed, motor function and visual scanning is expected. To date, the influence of the APOE genotype on behaviour and neuropsychological functions usually impaired after TBI in moderate and severe chronic survivors has only partially been demonstrated.

The aim of this study was to analyse the influence of APOE ϵ4 status on the neuropsychological and behavioural functions usually impaired after moderate and severe TBI.

METHODS

Participants

Patients were selected from a cohort of 140 consecutive patients admitted to the Neurotraumatology Unit, Vall d'Hebron University Hospital, Barcelona, Spain, between January 2000 and December 2001, who had a Glasgow Coma Scale (GCS) score $\leqslant$12. GCS was estimated initially (at the place of injury) and on arrival at hospital. The worst GCS value was used. Head injury was moderate (GCS from 9 to 12) in 50 patients and severe (GCS $\leqslant$8) in 90. In all, 25 (27%) patients with severe TBI and 7 (14%) patients with moderate TBI died as a consequence of the injury. Of the 108 TBI survivors, eight patients could not be contacted and six refused to participate in the neuropsychological study; six patients were too severely impaired to undergo neuropsychological testing, five did not have proficiency in Spanish and five had a psychiatric history. This left 78 patients for the neuropsychological study, aged between 16 and 65 years. All patients included were literate and had no aphasia, dysarthria or motor impairment that would preclude neuropsychological evaluation. None of them had a history of TBI or neurological or psychiatric diseases. Oral informed consent was obtained from the patients or parents (of patients who were underaged) in all cases.

APOE genotype

Genomic DNA was extracted from the leucocyte fraction by using the phenol or chloroform method. PCR was used to amplify the common alleles of APOE genes, following the protocol published elsewhere.[16]

Neuropsychological and neurobehavioural assessment

Each patient with TBI underwent cognitive and behavioural assessment at least 6 months after injury (mean: 215 (SD 23) days, range 182–272 days). A modified version of Rey's Auditory Verbal Learning Test was used to measure verbal learning and memory.[17] Visual memory was assessed by

Abbreviations: APOE, apolipoprotein; apoE, apolipoprotein E; GCS, Glasgow Coma Scale; TBI, traumatic brain injury

short-term recall (3 min) of the Rey–Osterrieth Complex Figure Test.[18] Verbal fluency was evaluated with the Controlled Oral Word Association Test. Speed and fine motor coordination were assessed with the Lafayette Grooved Pegboard Test. Visual scanning, tracking and motor speed were also assessed by the Symbol Digit Modalities Test. Parts A and B of the Trail Making Test were given to measure visual scanning, motor speed and attention, and mental flexibility.

Behaviour was assessed with the five-factor model of the Neurobehavioral Rating Scale—Revised.[19]

Global adjustment to activities of daily living and general outcome was assessed by using the extended Glasgow Outcome Scale.

Statistical analyses

All statistical analyses were carried out using SPSS V.11.0 for Windows. χ^2 test or Fisher's exact probability test was used to compare categorical variables between the genetic groups. The continuous variables were compared by means of the Student's t test for independent samples. Allele group comparisons were carried out by using analysis of covariance to control for the effects of age on cognitive and behavioural performance among people with TBI.

RESULTS

The APOE genotype was determined in the whole cohort, except in one patient. The final sample thus included 77 patients.

In the whole cohort, inheritance of the APOE ϵ4 allele was not related to mortality (20% of ϵ4 and 23.5% of non-ϵ4 died; $p = 1.00$) or to suitability for neuropsychological testing in survivors (62.5% of ϵ4 and 73.6% of non-ϵ4 underwent neuropsychological testing; $p = 0.38$). Survivors who underwent neuropsychological testing and those who did not were also comparable in sex ($\chi^2 = 0.00$; $p = 1.00$) and initial findings on CT ($\chi^2 = 2.67$; $p = 0.11$), but differed in age ($t = 2.23$; $p = 0.03$), GCS ($t = 2.66$; $p = 0.01$) and Glasgow Outcome Scale ($\chi^2 = 15.08$; $p = 0.001$).

Demographic and clinical variables of participants with and without the APOE ϵ4 allele were compared in the final sample. Sex (ϵ4, 7 men and 3 women; non-ϵ4, 53 men and 14 women; $p = 0.68$), years of formal education (ϵ4, mean 9.6 (SD 2.63) years; non-ϵ4, mean 10.25 (SD 2.86) years; $t = 0.68$; $p = 0.50$), GCS (ϵ4, mean 7.10 (SD 2.81); non-ϵ4, mean 7.82 (SD 2.24); $t = 0.92$; $p = 0.36$), duration of coma, finishing with eyes opening (ϵ4, mean 13.50 (SD 8.16); non-ϵ4, mean 11.15 (SD 7.08); $t = 0.95$; $p = 0.34$), post-traumatic amnesia measured by means of the Galveston Orientation and Amnesia Test (ϵ4, mean 38.44 (SD 16.29); non-ϵ4, mean 31.93 (SD 17.48); $t = 1.05$; $p = 0.30$) and initial findings on CT coded with a regrouping of the Traumatic Coma Data Bank categories (ϵ4, 7 with diffuse injury and 3 with focal mass lesion; non-ϵ4, 50 with diffuse injury and 17 with focal mass lesion; $p = 0.71$) did not differ between the genetic groups. The differences in age were, however, significant (ϵ4, mean 37.70 (SD 18.31); non-ϵ4, mean 28.87 (SD 11.47); $t = 2.08$; $p = 0.04$). In a recent study, Teasdale *et al*[6] confirmed the interaction between age and APOE genotype. We therefore carried out an analysis of covariance, entering age as a covariable to rule out its effect on neuropsychological and neurobehavioural outcome.

Participants carrying the ϵ4 allele performed notably worse on almost all neuropsychological and behavioural measures than the group without the ϵ4 allele (table 1).

DISCUSSION

This APOE study in a cohort of survivors with moderate and severe TBI is based on a broad neuropsychological and neurobehavioural assessment. Participants with the ϵ4 allele showed poorer learning and long-term memory. Outcomes of tests on frontal lobe participation, such as speed, motor coordination, visual scanning, and executive function or mental flexibility, were also worse in the ϵ4 allele carriers than among non-carriers.

Furthermore, the neurobehavioural assessment showed a markedly poor score for the global score on the Neurobehavioral Rating Scale—Revised, as well as on some of its components, for the ϵ4 allele carriers. The lack of differences in oral or motor component may be related to excluding patients with severe aphasia, dysarthria or motor impairment. The exclusion of patients whose GCS and Glasgow Outcome Scale scores differed from those in the final sample may explain the homogeneity in coma duration and length of post-traumatic amnesia between the APOE genotype groups studied.

Our data support and extend the results of previous studies examining cognitive dysfunction after mild TBI. Liberman *et al*[9] showed that an APOE ϵ4-carrier group performed worse on almost all neuropsychological tests, with marked differences for some measures of frontal lobe involvement. In a study of pre-injury and post-injury within-person comparisons of neuropsychological measures, Sundstrom *et al*[11] found that participants with the APOE ϵ4 allele had poorer post-injury performance compared with their pre-injury performance on memory and divided attention tests, whereas the performance of participants without the ϵ4 allele remained unchanged. Our results are also in agreement with a study of mainly severe TBI. Crawford *et al*,[8] in a sample of 110 patients with TBI, showed that patients with APOE ϵ4 performed worse on verbal memory than those without this allele. As in our study, they found no relationship between the presence of the ϵ4 allele and certain measures that presumably require the participation of the frontal lobe (verbal fluency).[8]

In a recent study, Chamelian *et al*[12] analysed the relationship between possession of the APOE ϵ4 allele and both cognitive and behavioural measures in a sample with predominantly mild TBI at 6 months after injury. They found no association between the presence of the APOE ϵ4 allele and poor cognitive or behavioural outcome.[12] We did observe a relationship between APOE ϵ4 carriers and both poor neuropsychological measures and an unfavourable neurobehavioural outcome, and these differences may be due to the greater severity of our TBI sample.

The study by Millar *et al*[10] did not find differences either. The most important difference between the present report and that of Millar *et al*[10] is the significantly longer follow-up after injury in their study: 15–25 years. This may mean that APOE ϵ4 possession is related more to acute than to chronic cognitive decline after severe TBI. It may also be related to the lack of consensus on the relationship between the APOE genotype, TBI and later cognitive decline such as Alzheimer's disease.[7]

The mechanisms underlying the modulating effect of APOE in the acute response to brain injury remain unclear. ApoE is associated with synaptic repair, remodelling and regeneration in an isoform-specific way.[3 20] The apoE ϵ4 isoform is believed to provide less neuroprotection and a lower ability for brain tissue recovery and functional restoration than apoE ϵ2 and ϵ3 isoforms.[3] Therefore, APOE ϵ4 carriers are apparently less able to avoid secondary damage, remove injury-induced degeneration products or repair damaged tissue than those without this allele. The combined effect of these mechanisms may result in poorer neuropsychological performance and greater behavioural disturbances in the subacute phase.

Table 1 Neuropsychological and neurobehavioural performance for the genetic groups

	ε4 present (n = 10), mean (95% CI)	ε4 absent (n = 67), mean (95% CI)	F	p
AVLT immediate recall	31.20 (20.88 to 41.52)	37.66 (34.94 to 40.38)	5.86	0.005
AVLT long-term recall	5.00 (3.09 to 6.91)	7.50 (6.63 to 8.37)	5.66	0.005
CFT short-term recall	18.10 (11.48 to 24.72)	21.28 (19.3 to 23.26)	2.16	0.12
Grooved peg right	147.90 (89.81 to 205.99)	93.85 (78.53 to 109.17)	11.15	<0.001
Grooved peg left	149.40 (98.30 to 199.97)	99.00 (84.01 to 113.99)	7.33	0.001
SDMT	33.78 (16.11 to 51.44)	47.36 (43.56 to 51.15)	11.37	<0.001
TMT A	71.00 (29.45 to 112.55)	53.67 (44.25 to 63.09)	2.82	0.066
TMT B	137.00 (39.15 to 234.85)	105.12 (88.85 to 121.38)	5.16	0.008
COWAT (FAS)	15.80 (7.65 to 23.95)	21.98 (19.34 to 24.63)	2.87	0.063
NRS–R				
Executive/cognition	15.00 (9.80 to 20.20)	9.79 (7.77 to 11.82)	4.68	0.012
Positive symptoms	13.60 (10.11 to 17.09)	8.37 (6.73 to 10.01)	2.89	0.062
Negative symptoms	9.50 (5.98 to 13.02)	4.12 (2.99 to 5.25)	7.81	0.001
Mood/affect	12.30 (8.94 to 15.66)	6.54 (5.24 to 7.83)	6.98	0.002
Oral/motor	8.80 (5.55 to 12.05)	6.37 (5.02 to 7.73)	1.56	0.22
Global score	59.20 (44.04 to 74.36)	35.19 (28.78 to 41.61)	5.60	0.005
GOS extended	6.00 (4.93 to 7.07)	6.61 (6.21 to 7.01)	2.85	0.064

AVLT, Auditory Verbal Learning Test; CFT, Complex Figure Test; COWAT, Controlled Oral Word Association Test; GOS, Glasgow Outcome Scale; NRS—R, Neurobehavioral Rating Scale—Revised; SDMT, Symbol Digit Modalities Test; TMT, Trail Making Tests A, B.

In addition to the small sample size, other possible limitations, such as the fact that premorbid ability was not well controlled, should be borne in mind. Years of education may not be a very good proxy for premorbid ability and the differences found may have been related to pre-existing cognitive differences.

In summary, we showed an association between APOE isoforms and typical impairment after moderate and severe TBI. The poor cognitive and behavioural outcome of the APOE ε4 carriers in moderate and severe TBI may be attributable to the worsening of the initial brain injury and the poor effectiveness of recovery in the presence of the apoE ε4 isoform.

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