Apolipoprotein E Isoform Influence on Outcomes After Pediatric Traumatic Brain Injury

Claire Usala, Rong Huang MS, Ana Hernandez PhD, Darryl Miles MD

University of Texas Southwestern Medical Center at Dallas

Background

In the United States traumatic brain injury (TBI) is the leading cause of death and disability among children and adolescents.[1] Allelic polymorphisms may in part account for patient heterogeneity seen in both the acute injury response and long-term recovery after TBI.[2,3] In adults with TBI, the ε4 allele of the apolipoprotein E gene (APOE) is associated with worse long-term neurocognitive outcomes, but its role in pediatric TBI is less certain.[4]

Objectives

The purpose of this study was to determine whether an association exists in the outcome of children with at least one ε4 allele vs. those with no ε4 alleles after pediatric TBI. The outcome variables studied between the two groups were as follows: 1) Glasgow Outcome Score (GOS) at hospital discharge, 2) GOS at long-term follow-up, and 3) the magnitude of change in GOS from discharge to > 6 month assessment (Δ GOS).

Methods

- Children ages 0-17 presenting with moderate to severe accidental blunt head trauma were prospectively recruited.
- Demographic, radiologic, clinical, and injury data were collected and APOE genotype obtained.
- Outcome was assessed at hospital discharge and at 12.7±8.4 months post-injury using the Glasgow Outcome Score (GOS). The GOS is an established five point score which categorizes patients as 1 = dead, 2 = vegetative state, 3 = severe disability, 4 = moderate disability, and 5 = mild to no apparent deficits. In addition, the frequency of post-traumatic seizure development was compared between APOE4 vs. non-APOE4 groups.
- Patients were also grouped by neurologic injury severity measured by the emergency department (ED) Glasgow Coma Scale (GCS). The GCS stratifies patients by their verbal, motor, and eye functioning, with a score of 15 representing no measurable deficits in these categories.
- Multiple regression model analysis was retrospectively conducted to determine if associations exist between the various genotypes and outcome variables.
- Neuropsychological testing was performed at follow-up in a subset of patients, including IQ, emotional functioning, adaptive behavior, and memory.

Table 1: APOE genotype frequency and Glasgow Outcome Score (GOS) at discharge, >6 months post-injury, and change in GOS.

Genotype	Number of Patients, (%)	Mean GOS at Discharge ± SD	Mean GOS at >6 months post-injury, ± SD	Mean Change in GOS ± SD
2/2	3 (1.7)	3.3 ± 0.6	4.3 ± 1.2	1.0± 1.0
2/4	4 (2.3)	4.0 ± 1.2	4.5 ± 1.0	0.5± 1.0
3/2	13 (7.4)	3.7 ± 1.2	3.8 ± 1.5	0.2± 0.9
3/3	118 (67.4)	4.2 ± 1.0	4.6 ± 0.8	0.4± 0.7
3/4	31 (17.7)	4.4 ± 0.8	4.5 ± 0.7	0.2± 0.7
4/4	6 (3.4)	4.8 ± 0.4	4.8 ± 0.4	0.0± 0.0

Table 2: GOS at discharge, >6 months post-injury, and change in GOS by injury severity category in APOE4 vs non APOE4 groups.

	Mean GOS at Discharge			Mean GOS at Follow-up			Mean Change in GOS		
ED GCS	At least one ε4	No ε4	p Value	At least one ε4	No ε4	p Value	At least one ε4	No ε4	p Value
Severe (3-8) n=117	4.1 ± 0.8 n=26	3.8 ± 1.1 n=91	0.13	4.4 ± 0.8 n=26	4.3 ± 1.0 n=91	0.6	0.3 ± 0.7 n=26	0.5 ± 0.8 n=91	0.20
Non-severe (9-15) n=54	4.8 ± 0.6 n=14	4.8 ± 0.5 n=40	0.95	4.9 ± 0.4 n=14	4.9 ± 0.3 n=40	0.9	0.1 ± 0.4 n=14	0.1 ± 0.6 n=40	0.85
Non-mild (3-12) n=138	4.2 ± 0.8 n=31	3.9 ± 1.1 n= 107	0.24	4.5 ± 0.8 n=31	4.4 ± 1.0 n= 107	0.76	0.3 ± 0.7 n=31	0.5 ± 0.8 n= 107	0.24
Mild (13-15) n=33	5.0 ± 0.0 n=9	4.8 ± 0.5 n=24	0.06	5.0 ± 0.0 n=9	4.9 ± 0.3 n=24	0.08	0.0 ± 0.0 n=9	0.1 ± 0.3 n=24	0.17

Results

Of the cohort (175), 23.4% had at least one ε4 allele, ε3/ε3 was the most common genotype (67.4%), and ε2/ε2 was the least prevalent (1.7%). Most children in each APOE allelic group improved from hospital discharge to GOS at follow-up time points.

Table 1 shows the GOS at discharge and follow-up in each genotype. After controlling for confounding variables: age, ethnicity, ICP monitor placement, and whether CPR was performed in each APOE allelic group, only patients with ε3/ε3 had a significantly higher GOS at >6 months than patients with the genotype ε3/ε2 ($p<0.05$). However ε3/ε2 had a lower discharge GOS. Likewise, patients with at least one ε2 allele in the non-mild injury category had significantly worse GOS at discharge. Table 2 shows that the GOS at discharge, > 6 months, and the change in GOS did not differ significantly in APOE4 vs. non-APOE4 groups when stratified by injury severity category. Neuropsychological function tests also did not differ between the APOE4 and non-APOE4 groups.

Conclusions

1) After accidental pediatric TBI, children having at least one APOE4 allele was not associated with hospital discharge or > 6 month outcome in any injury severity category, nor did APOE4 influence the magnitude of recovery potential or long-term neuropsychological functioning.
2) Patients with ε3/ε3 had significantly better long-term outcome than children with ε3/ε2.
3) Patients with at least one ε2 allele had worse outcome at hospital discharge.
4) Further research is needed on the longer-term effects of genotypes as more subtle sequelae may only be apparent years after the initial injury due to the pediatric brain's continuing growth and development.
5) When examining outcomes both the discharge and long-term outcomes should be measured to determine significance of genotype-phenotype associations.

Bibliography

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