Apolipoprotein E ϵ 4 Allele and Outcomes of Traumatic Spinal Cord Injury

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Abstract

Background/Objective: To test the hypothesis that apolipoprotein E (APOE) polymorphisms are associated with outcomes after spinal cord injury (SCI).

Methods: Retrospective cohort study, from rehabilitation admission to discharge.

Participants: Convenience sample of 89 persons with cervical SCI (C3–C8) treated from 1995 through 2003. Median age was 30 years (range 14–70); 67 were male (75%) and 83 were white (93%).

Main Outcome Measures: American Spinal Injury Association (ASIA) motor and sensory scores, ASIA Impairment Scale (AIS), time from injury to rehabilitation admission, and length of stay (LOS) in rehabilitation.

Results: Subjects with an APOE ϵ 4 allele ($n = 15$; 17%) had significantly less motor recovery during rehabilitation than did individuals without an ϵ 4 allele (median 3.0 vs 5.5; $P < 0.05$) and a longer rehabilitation LOS (median 106 vs 89 days; $P = 0.04$), but better sensory-pinprick recovery (median 5.0 vs 2.0; $P = 0.03$). There were no significant differences by APOE ϵ 4 allele status in sensory–light touch recovery, likelihood of improving AIS Grade, or time from injury to rehabilitation admission.

Conclusions: APOE ϵ 4 allele was associated with differences in neurological recovery and longer rehabilitation LOS. Genetic factors may be among the determinants of outcome after SCI and warrant further study.

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Key Words: Apolipoprotein E; Polymorphism; Genotype; Spinal cord injuries, cervical; Tetraplegia; Rehabilitation, physical

INTRODUCTION

Genetic factors in central nervous system function and disease are only beginning to be elucidated (1) and may be important in influencing severity of and recovery from spinal cord injury (SCI) (2). In humans, the apolipoprotein E (APOE) gene codes for a 299-amino acid protein (apoE). There are 3 common APOE alleles, ϵ 2, ϵ 3, and ϵ 4, each coding for a different apoE isoform, E2, E3, and E4, which differ only by a single amino acid. Each person has 2 alleles that together compose that person's APOE genotype (eg, ϵ 2/ ϵ 3 or ϵ 3/ ϵ 3). Initially, apoE was thought to be important mainly in lipid transport and metabolism. It was later found to be produced abundantly in the

brain, and its role in the cell biology of tissue repair after injury was recognized (3). Subsequently, the ϵ 4 allele was associated with an increased risk of Alzheimer's disease, in both its familial and sporadic forms (4).

The effect of APOE genotypes on outcomes after SCI has not been studied, but that they might have an effect is a plausible hypothesis. Basic science and clinical evidence suggest that APOE polymorphism might affect outcome after traumatic brain injury (TBI) (5). Mechanisms by which the ϵ 4 allele might adversely affect the severity of and recovery from TBI may include: (a) less efficient transport of lipids, (b) more accumulation of beta amyloid, (c) a cytoskeleton more vulnerable to mechanical damage, (d) less protection against oxidative injury, (e) more brain inflammation, (f) poorer brain perfusion acutely, (g) diminished growth and branching of neurites (poorer repair), (h) diminished clearance of degenerative products, (i) worse pre-existing atherosclerotic vascular disease, (j) more widespread pre-existing amyloid deposits, and (k) worse disruption of the blood-brain barrier (5). The ϵ 4 allele may, therefore, adversely

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influence neuronal protection, repair, and remodeling (6). Clinical studies have found that the $\epsilon 4$ allele is associated with higher risk of ischemic vascular disease (7) and more severe injury after some insults to the central nervous system, such as cardiac surgery (8), TBI in adults (9–14), intracerebral hemorrhage (15,16), and cardiopulmonary arrest (17), but not after other insults, such as ischemic stroke (18) and ischemic hippocampal injury (19). The effect of APOE genotypes on outcomes after SCI has not been studied.

This retrospective cohort study of a convenience sample of individuals with traumatic cervical SCI was conducted to determine associations between APOE $\epsilon 4$ allele status and short-term outcomes.

METHODS

Subjects

Participants for the study were recruited from a registry of all patients discharged from a single facility for rehabilitation after acute traumatic SCI from 1995 through 2003. The registry contains demographic and clinical data, including dates of injury, dates of rehabilitation admission and discharge, level of injury (LOI), and completeness of injury. The LOI was recorded for the left and right side at admission and discharge. Cervical injury (C5–C7) on either side at either admission or discharge was chosen as an inclusion criterion to ensure clinical uniformity among subjects and because of the broader anatomical distribution of segmental motor function recovery that is measurable in the zone of injury (20). We reasoned that this potential variation of outcome might increase the chance of detecting associations of outcomes with gene polymorphisms. The institutional review boards at both facilities approved the study protocol.

An introductory letter inviting participation in the study and a consent form were mailed to 282 potential study participants. Fifty-nine potential study participants refused participation. Nineteen additional potential study participants could not be contacted. Buccal swab kits with instructions for sample collection were mailed to the 204 consenting potential study participants. Of these, 109 returned buccal swab samples. DNA was extracted and genotype determined using standard techniques (21) by a research assistant unaware of the study participant's clinical condition. Twelve samples could not be analyzed for genotype, 6 participants were excluded because they did not have admission or discharge information in the registry, 1 was excluded because admission was more than 90 days after injury, and 1 was excluded because of a missing level of injury. A maximum of 89 participants were available for analysis.

Outcome Measures

As part of clinical care at the study site, neurological data were collected systematically on all patients with SCI on admission and at discharge. Neurological condition was

assessed using the American Spinal Injury Association (ASIA) International Standards for Neurological Classification of SCI (22). Perceptions of light touch and pinprick stimuli are scored as 0 for absent, 1 for impaired, and 2 for normal. Each sensory dermatome is tested for light touch and pinprick, and a summary score that ranges from 0 to 112 is calculated by adding up the dermatome scores. Motor function is scored on the Medical Research Council Scale of 0 for total paralysis to 5 for normal strength. Ten muscles are tested bilaterally and individual muscle scores are added together, yielding an ASIA motor score that ranges from 0 to 100. The LOI is assigned by determining the lowest spinal level with normal neurological function. In addition, an ASIA Impairment Scale (AIS) grade (A, B, C, D) is assigned using ASIA Motor and Sensory Scores. Briefly, AIS grade A denotes no motor function beneath the LOI and no sensory function at the lowest sacral level (ie, on rectal examination), AIS grade B denotes presence of rectal sensation but no motor function below the LOI, AIS grade C denotes sensory function and some motor function below the LOI, and AIS grade D denotes sensory function and substantial motor function beneath the LOI (22).

A research assistant unaware of the participants' APOE genotypes collected data from clinical records and entered them into a research database, which was then imported into a statistical software package (SAS, Cary, NC).

Incomplete Data

For some of the 89 participants, fractures and orthotics made determining motor and sensory level problematic. An investigator who was unaware of the participants' genotypes reviewed all such cases and determined motor and sensory function by assessing for symmetry between left and right, completeness of the injury, LOI, and neurological findings at other points in time. This resulted in approximately 5.1% of all individual myotome and dermatome data points being changed from an initially missing value. However, the approach was conservative, erring on the side of leaving values as missing. Thus, despite these efforts, AIS Grade could not be determined for 4 participants, and 14 participants were missing a motor, sensory-pinprick, or sensory–light touch score.

Statistical Analysis

Medians and proportions were used to describe the study population. For hypothesis testing, the independent variable in all analyses was $\epsilon 4$ allele status. The small number of participants required collapsing them into two groups, those with and those without an $\epsilon 4$ allele. Participant characteristics were compared using a Wilcoxon rank sum test (for age) and Fisher exact test (for sex, race, LOI, and changes in AIS grade). The Wilcoxon rank sum test was used to compare days between injury and rehabilitation admission, rehabilita-

Table 1. Comparison of Demographic and Clinical Characteristics of Study Participants to NSCISC Database

Participant Characteristics	Participant Data (n = 89)	NSCISC Data*, †, ‡
Male sex	67 (75.3%)	80.2%†
Median age	30	31†
White	83 (93.3%)	60%†
Complete injury on admit	42 (49.4%)	51.8%*
Acute LOS (days)	18 (median)	20‡ (1997)
Rehabilitation LOS (days)	90.9 days (mean) 28.6 (SD)	60.8‡ (mean, 1997)

*See reference 20.

†See reference 24.

‡See reference 25.

NSCISC studies used different subsamples of the entire database. Statistical comparisons between the study population and NSCISC are not possible because sufficient data to do so are not presented in the cited references.^{20,24,25}

tion length of stay (LOS), and changes in ASIA sensory and motor scores. (ASIA admission scores were subtracted from the ASIA discharge scores, and the Wilcoxon rank sum test was performed on these differences). The genotypes of the cases were tested for Hardy-Weinberg equilibrium using a chi-square test with 3 degrees of freedom. The allele frequencies were then compared with the well-established general population allele frequencies of 8% (APOE ϵ 2), 77% (APOE ϵ 3), and 15% (APOE ϵ 4) (23) using a chi-square test with 2 degrees of freedom. In all analyses, a *P*-value less than 0.05 was considered statistically significant.

RESULTS

Table 1 presents demographic and clinical characteristics of our study sample, compared with published analyses of the National Spinal Cord Injury Statistical Center (NSCISC) database (20,24,25). Although direct comparisons are difficult because of varying time periods used and limited information reported in the references, whites may be over-represented in our sample (93% vs 60%) and rehabilitation LOS may be longer (mean 90.9 days vs mean 60.8 days) than in the NSCISC database.

Figure 1 presents APOE genotype distribution in the study population, with the 3/3 genotype being the most common (*n* = 58, 65.2%), followed by 2/3 (*n* = 16, 18.0%), 3/4 (*n* = 12, 13.5%), 4/4 (*n* = 2, 2.2%), and 2/4 (*n* = 1, 1.1%). No study participants had the 2/2 genotype. The genotypes in the case sample did not deviate from the Hardy-Weinberg equilibrium (*P* = 0.33), and the allele frequencies of 9.6% for ϵ 2 (*n* = 17), 80.9% for ϵ 3 (*n* = 144), and 9.6% for ϵ 4 (*n* = 17) were not significantly different from the general population (*P* = 0.11). Fifteen participants (16.8%) had at least one ϵ 4 allele and 74 (83.2%) did not.

Table 2 presents demographic characteristics and LOI by APOE ϵ 4 allele status. There were no significant differences in these characteristics by ϵ 4 allele status. Table 3 presents associations of APOE ϵ 4 allele status with outcomes. Participants with an ϵ 4 allele had significantly

worse motor recovery in rehabilitation than those without, as reflected in a smaller change in median ASIA motor score during rehabilitation (3.0 vs 5.5; *P* = 0.05). Median rehabilitation LOS was longer in participants with an ϵ 4 allele (106 vs 80.9 days; *P* = 0.04). In contrast, sensory-pinprick recovery was better during rehabilitation in ϵ 4 participants, as reflected in a greater change in median sensory-pinprick score (5.0 vs 2.0; *P* = 0.03). No association was found between ϵ 4 status and sensory–light touch recovery nor in time between injury and rehabilitation admission.

Table 4 presents changes in AIS Grade during rehabilitation, by rehabilitation admission AIS grade, for ϵ 4 allele–positive and ϵ 4 allele–negative participants. On admission to rehabilitation, only one of the 14 ϵ 4-positive participants (7.1%; 1 participant was missing discharge AIS grade and is not included in Table 4) had a motor-incomplete lesion, as compared with 18.1% of ϵ 4-negative participants, but the difference was not significant. Across all AIS grades A to C, the proportion improving in AIS grade during rehabilitation hospitalization was not significantly different in those with and without an ϵ 4 allele (23.1% vs 23.1%).

Figure 1. APOE genotype distribution in participants (*n* = 89).

Table 2. Demographics and Level of Injury by APOE ϵ 4 Allele Status

	ϵ 4 Positive (%) (n = 15)	ϵ 4 Negative (%) (n = 74)	Significance (P-value)
Age (median)	28	30	0.87
Sex: n (%)			0.10
Male	14 (93.3)	53 (71.6)	
Female	1 (6.7)	21 (28.4)	
Race: n (%)			0.32
White	14 (93.3)	69 (93.2)	
Hispanic	0	4 (5.4)	
Native American	0	1 (1.4)	
African American	1 (6.7)	0	
Level of injury on admission: n (%)			> 0.99
C3–C4	3 (20.0)	15 (20.3)	
C5–C6	12 (80.0)	56 (75.7)	
C7–C8	0	3 (4.0)	

Table 3. Association of APOE ϵ 4 Allele Status to Outcome

Outcome	ϵ 4 Positive			ϵ 4 Negative			P-value
	n	Median	Range	n	Median	Range	
ASIA: motor	14	3.0	–1 to 37	66	5.5	–1 to 38	0.05
ASIA: light touch	13	6.0	–2 to 36	66	4.5	–11 to 40	0.17
ASIA: pinprick	13	5.0	–5 to 36	66	2.0	–8 to 36	0.03
Acute LOS	15	18.0	8 to 36	74	18.5	5 to 85	0.59
Rehabilitation LOS	15	106.0	51 to 158	74	89.0	11 to 162	0.04

Table 4. Changes in AIS Grade by ϵ 4 Allele Status*

Genotype	Admission AIS Grade	Discharge AIS Grade			
		A	B	C	D
ϵ 4 Positive	A	6 (46.2%)	1 (7.7%)		
	B		4 (30.8%)	1 (7.7%)	
	C			0	1 (7.7%)
	D				0
ϵ 4 Negative	A	30 (41.7%)	4 (5.6%)		
	B		16 (22.2%)	8 (11.1%)	
	C			4 (5.6%)	2 (2.8%)
	D				7 (9.7%)

*There was no association between ϵ 4 allele status and change in AIS grade.

DISCUSSION

In this first study of associations of polymorphisms of a candidate gene to outcomes in traumatic SCI, we found that the APOE ϵ 4 allele was associated with worse motor recovery during rehabilitation hospitalization and longer rehabilitation LOS, but better sensory-pinprick recovery.

Our sample was similar to that in the National Spinal Cord Injury Database, with the exceptions of overrepresentation of whites and a longer rehabilitation LOS. The longer LOS probably reflects that in our study all participants had a cervical LOI, compared with a mixture of cervical and lower LOIs in the National Spinal

Cord Injury Statistical Center Database. Lower LOIs in general require a shorter rehabilitation LOS than do cervical LOIs (25). Furthermore, although limited by a small sample size, APOE allele frequencies in our sample were not significantly different from those of the general population.

That the ϵ 4 allele was associated with a seemingly contradictory pattern of motor and sensory recoveries in our study may have several explanations. First, sensory testing may be more subjective and less reliable than motor testing. Second, given the longer length of stay seen in the ϵ 4 group, it may simply reflect a longer time

between assessments in the $\epsilon 4$ -positive group, allowing greater improvement in pinprick and light-touch testing. Third, it might be evidence that the effect of APOE is very small relative to all the other factors influencing outcome. Moreover, the clinical, functional, and scientific significance of such a small statistically significant difference is not clear. Finally, the observed patterns of motor and sensory recoveries may suggest that the role of apoE in SCI might be complex.

This complexity of apoE is evident in studies of the brain. The $\epsilon 4$ allele has been associated with worse outcome after TBI (5,9–14), but not after some purely ischemic brain injuries (18,19). Mechanisms by which the $\epsilon 4$ allele might affect outcome after brain injury have been studied (5), but little is known about their relevance in traumatic SCI. In an experimental animal study of SCI, the apoE protein is up-regulated and stays up-regulated for at least 3 weeks after the experimental injury, evidence that APOE may have a role in repair (26). It is possible, for instance, that the $\epsilon 4$ allele might have different effects on recovery in the different types of pathological lesions seen in traumatic SCI (mechanical tissue damage, hemorrhagic injury, and ischemic injury) or in injuries to different types of spinal neurons or different types of tracts. That types of spinal neurons might differ in susceptibility to traumatic injury is suggested by the relatively more frequent occurrence of preservation of sensation in motor-complete lesions than preservation of motor function in sensory-complete lesions after SCI.

We do not know why patients with the $\epsilon 4$ allele had a longer mean rehabilitation LOS. Possible explanations might include slower or worse recovery from SCI, more frequent or worse TBI associated with SCI, or more frequent or worse sepsis in rehabilitation (27). Because we did not collect data about the clinical course or complications during rehabilitation, we cannot test these hypotheses.

Our study has some limitations. First, the study sample size was small. For instance, it was not possible for us to determine whether there was a gene-dose effect for $\epsilon 4$ on outcomes (assessed by evaluating outcomes in subjects with the $\epsilon 4/\epsilon 4$ genotype). Second, there was only a single-site recruitment of participants, but the demographic characteristics of our sample were similar to the NSCISC database population. Third, the study was retrospective in design, but data for the registry were collected at the time of discharge from the rehabilitation hospital. Despite this, data were incomplete for some subjects. Fourth, the outcome was short-term, but outcome at discharge from rehabilitation likely correlates with longer-term outcome after SCI. Finally, we did not have data on processes of care during the acute hospitalization that may have had an influence on neurological outcomes. However, lengths of acute stay were not significantly different, and it is unlikely that factors such as methylprednisolone administration pro-

ocols or timing of surgical decompression would vary systematically by genotype.

There are two strengths of our study. First, there was no observer bias. Genotypes were determined by research assistants unaware of clinical outcomes, and outcomes were determined by investigators unaware of genotypes. Second, standard, accepted, and valid outcome measures were used, in keeping with the NSCISC standards. This makes comparison of our results to those of future studies possible.

The admission criteria of cervical LOI minimized clinical variation in the sample. In this respect, our study might serve as a model for future studies of relationships of polymorphisms of candidate genes to outcomes after SCI. It is also possible that genotype-phenotype associations in traumatic injury to the central nervous system might be more easily studied in SCI than in TBI, while acknowledging that there might be differences in response to traumatic injury in the spinal cord and the brain.

As polymorphisms of candidate genes affecting outcome in TBI are found, it will be necessary to study them also in individuals with traumatic SCI. Interventions based on understanding of genetic factors influencing outcome in TBI are being developed and might have use also in SCI. For instance, an apoE-mimetic protein is being developed in experimental animals as a potential treatment for TBI (28).

CONCLUSION

In conclusion, in individuals with traumatic cervical SCI, the APOE $\epsilon 4$ allele is associated with worse motor outcome and longer rehabilitation stay, but better sensory-prick outcome. This is the first study associating polymorphisms of a candidate gene to outcomes in SCI, demonstrating that further studies are warranted.

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