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APOE Genotype and Functional Outcome Following Aneurysmal Subarachnoid Hemorrhage

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Abstract

Apolipoprotein E (apoE), the major apolipoprotein in the central nervous system, has been shown to influence neurologic disease progression and response to neurologic injury in a gene-specific manner. Presence of the APOE4 allele is associated with poorer response to traumatic brain injury and ischemic stroke, but the association between APOE genotype and outcome following aneurysmal subarachnoid hemorrhage (SAH) remains unclear. The purpose of this project was to investigate the association between APOE genotype and outcome after SAH. We also explored the association of APOE4 genotype and cerebral vasospasm (CV) presence in a subsample of our population with available angiographic data. A sample of 206 aneurysmal SAH participants had APOE genotyping performed, Glasgow outcome scores (GOS) and modified Rankin scores (MRS) collected at 3 and 6 months after aneurysm rupture. No significant association was found between the presence of the APOE4 genotype and functional outcomes controlling for age, race, size of hemorrhage (Fisher grade), and severity of injury (Hunt & Hess grade). However when controlling for CV and the covariates listed above, individuals with the APOE4 allele had worse functional outcomes at both time points. The presence of the APOE2 allele was not associated with functional outcomes even when considering presence of CV. There was no difference in mortality associated with APOE4 presence, APOE2 presence, or presence of CV. These findings suggest APOE4 allele is associated with poor outcome after aneurysmal SAH.

Keywords

apolipoprotein E; subarachnoid hemorrhage; cerebral vasospasm; Modified Rankin Score; Glasgow Outcome Score

Apolipoprotein E (apoE), a protein primarily responsible for lipid transport and metabolism, is the major apolipoprotein present in the central nervous system (CNS) and has been shown to influence neurologic disease progression and response to neurologic injury (Laskowitz, Horsburgh, & Roses, 1998). The exact mechanisms by which apoE influences CNS recovery are unclear; however several relevant pathways have been shown to be influenced by apoE including cellular membrane maintenance and repair (Hayashi et al., 2002; Mahley, 1988; Weisgraber, Roses, & Strittmatter, 1994), intracellular calcium maintenance (Tolar et al., 1999), neurite development and extension (DeMattos, Rudel, & Williams, 2001), astrocyte

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migration (Blain, Sullivan, & Poirier, 2006), and neuronal apoptosis (Hayashi, Campenot, Vance, & Vance, 2007; Ji et al., 2002).

Single nucleotide polymorphisms in the apolipoprotein E gene (APOE) result in six common genotypes (APOE 2/2, APOE 2/3, APOE 2/4, APOE 3/3, APOE 3/4, and APOE 4/4) and the formation of the three common protein isoforms (apoE2, apoE3, and apoE4) in the North American population. Differences in a single amino acid at position 112 and 158 of the protein create the three isoforms with differences in structure and charge distribution resulting in genotype-specific function. The APOE4 genotype has been associated with increased incidence of Alzheimer's disease (Corder et al., 1993, 1994; Okuizumi et al., 1994; Roses, 1994; Roses et al., 1994; van Duijn et al., 1994), and poorer outcome after cerebral hemorrhage (Alberts et al., 1995), subarachnoid hemorrhage (SAH; Lanterna et al., 2005; Leung, Poon, Yu, Wong, & Ng, 2002; Niskakangas et al., 2001; Tang et al., 2003), and traumatic brain injury (Isoniemi, Tenovu, Portin, Himanen, & Kairisto, 2006; Jiang et al., 2006; Sorbi et al., 1995; Teasdale, Nicoll, Murray, & Fiddes, 1997). Although this literature supports the role of APOE4 in poorer outcomes, there is some controversy in the traumatic brain injury and SAH populations.

Aneurysmal SAH results from blood entering the subarachnoid space. The initial hemorrhage can cause increased intracranial pressure (Voldby & Enevoldsen, 1982), decreased cerebral perfusion pressure (Fisher, 1975), and decreased cerebral blood flow (Bederson, Germano, & Guarino, 1995). After the initial hemorrhage, 30–70% of patients are likely to experience a secondary injury because of cerebral vasospasm (CV; Kassell, Sasaki, Colohan, & Nazar, 1985). Recovery from SAH is a complex process with few known prognostic factors including severity of hemorrhage, age, and presence or absence of CV. These factors do not explain all variation in recovery suggesting a possible genotypic influence exists. Presence of the APOE4 allele has been associated with poorer prognosis after some neurological disease and injuries (Corder et al., 1993; Lanterna et al., 2005; Leung et al., 2002; Niskakangas et al., 2001; Tang et al., 2003). In the SAH population specifically, some literature has suggested that the presence of the APOE4 allele is associated with poorer outcome (Lanterna et al., 2005; Leung et al., 2002; Niskakangas et al., 2001; Tang et al., 2003), while others have not found any relationship (Dunn, Stewart, Murray, Nicoll, & Teasdale, 2001; Morris, Wilson, Dunn, & Nicoll, 2004). The above mentioned studies are comparable in their demographic makeup. The differences in the studies may stem from their small sample size and possibly being underpowered. No relationship has been found between APOE2 allele presence and outcome after SAH (Ruigrok et al., 2005). The current state of the literature investigating APOE genotype and SAH recovery is conflicting. Therefore, the purpose of this project was to investigate a potential association between APOE genotype and outcome after SAH in our larger sample. Because of severe confounding effects of CV on SAH recovery, we explored the association in light of CV presence in a subsample of our population with available angiographic data.

Materials and Methods

Sample

The cohort of 206 participants was prospectively recruited as part of an ongoing NIH-funded study. This study was approved by the Institutional Review Board (IRB) and the experiments were undertaken with the understanding and written consent of each participant. The sample included adult patients (aged 18–75 years) with the diagnosis of SAH from a ruptured cerebral aneurysm verified by digital subtraction angiography (DSA) or CT angiography (CTA) with a Fisher Grade > 1. Patients were excluded if they had a preexisting neurological disorder or if SAH resulted from a mycotic aneurysm, arterio-venous malformation, or trauma. Patients were admitted to the neurovascular intensive care unit (NICU) at the University of Pittsburgh Medical Center (UPMC) from July 2000 to May 2006. All patients received standard nursing

and medical care in the NICU including triple-H therapy, nimodipine, and early surgical or endovascular intervention. Fisher and Hunt & Hess grades were collected from the attending physician's admission note in the patient's medical record. Age, race, and gender were extracted from medical records.

APOE Genotyping

Genotyping was performed on DNA extracted from cerebrospinal fluid (CSF) samples collected from a ventriculostomy bag or from whole blood from the first sample available (i.e., before blood transfusion). DNA was extracted using a commercially available kit (Qiagen, Chatsworth, CA). APOE genotyping was conducted using restriction fragment length polymorphism techniques as previously described (Hixson & Vernier, 1990; Kamboh, Aston, & Hamman, 1995). Genotypes were double called in a blinded manner and discrepancies between genotypes identified and resolved by retyping the sample. The sample was dichotomized into two groups based on genotype, APOE4+ (which included APOE 2/4, APOE 3/4, and APOE 4/4) and APOE4- (which included APOE 2/2, APOE 2/3, and APOE 3/3). Statistical analysis was performed on this dichotomized sample. Then the original sample was dichotomized into two groups based on APOE2 genotype, APOE2+ (which included APOE 2/2, APOE 2/3, and APOE 2/4) and APOE2- (which included APOE 3/3, APOE 3/4, and APOE 4/4) analyses were repeated to explore a possible influence of the APOE2 allele on recovery from SAH.

CV

A subset of the sample ($n = 108$) had a cerebral angiography performed at 3 to 10 days after aneurysm rupture as a result of neurologic deterioration. Evidence and degree of CV, defined as narrowing of cerebral vessels, was determined via cerebral angiography, which was interpreted and graded by neuroradiologist and neurosurgeons. The degree of vasospasm was categorized as the percentage of narrowing in the cerebral vessels as follows: 0–25% = *none to minimal* narrowing, 26–75% = *moderate* narrowing, and 76–99% = *severe* narrowing. Patients with either moderate or severe vasospasm were considered positive for CV.

Outcome

Outcome measurements consisted of modified Rankin score (MRS) and Glasgow outcome score (GOS) at 3 and 6 months post-hemorrhage and were obtained during a face-to-face or telephone interview by a neuropsychological technician. Both measures have been shown to be reliable and valid administered in person or by telephone (Wilson, Pettigrew, & Teasdale, 1998). Interviews were conducted with the participant when it was possible and with the primary caregiver when it was not possible to interview the participant.

MRS

MRS is a measure of gross functional outcome, which incorporates mental and physical adaptations to neurological deficits following a neurological injury (stroke, traumatic brain injury, etc). It is easy to use and has been widely adopted for use in stroke trials, including SAH trials. Scores range from 0 to 6 with 0 representing normal ability to perform activities and 6 indicating death (Sturm et al., 2002; Sulter, Steen, & De Keyser, 1999). MRS was measured at 3 and 6 months after the initial aneurysm rupture. The MRS has demonstrated excellent interobserver reliability within the stroke population ($\kappa = 0.56$ and weighted $\kappa = 0.91$; van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988).

GOS

GOS is a measure of gross functional outcome often used in the neurologically injured population. GOS was defined as follows: 1 = *death*; 2 = *persistent vegetative state* (unable to

interact with the environment; 3 = *severe disability* (unable to live independently but able to follow commands); 4 = *moderate disability* (capable of living independently but unable to return to work or school); and 5 = *good recovery* (able to return to work or school; Jennett, 1976; Jennett & Bond, 1975). GOS was measured at 3 and 6 months after the initial aneurysm rupture. Interrater reliability has been reported from 68% to 95% with kappa values from .62 to .79 (Gennarelli et al., 1982; Maas, Braakman, Schouten, Minderhoud, & van Zomeren, 1983), and the GOS has correlated well with severity of illness and other measures of function (Hall, Cope, & Rappaport, 1985). The GOS has wide acceptance and established validity (Jennett & Bond, 1975; Maas et al., 1983).

Mortality

Mortality was obtained from medical records or caregiver report.

Statistical Analysis

To determine differences in age between the two groups, *t*-tests were used. Analysis of variance (ANOVA) was used to determine differences in racial distribution and severity of hemorrhage (Fisher grade) between the two groups. Differences in GOS and MRS between the APOE4+ and APOE4- groups were determined using ANOVA controlling for age, race, Hunt & Hess grade (severity of injury), and Fisher grade (size of hemorrhage). To elucidate the role of CV in long-term outcomes, we repeated the analysis above controlling for CV in a subsample of participants with angiographic data. Differences in mortality rates based on APOE4 allele presence were examined using chi-square analysis. ANOVA controlling for age, race, Hunt & Hess grade, and Fisher grade was also performed on the subset of patients with cerebral angiographies to elucidate any possible differences between outcomes that may be associated with vasospasm. The above described analyses were then performed on the APOE2+ and APOE2- groups. A chi-square analysis was also performed on the APOE4 and APOE2 groups to see if there was an association with mortality rates at 3 or 6 months.

Results

There were 206 participants with genotyping, demographic information, and outcome information available. Of these 206 participants, 108 had angiographic CV data available. The sample was primarily White (91.7%) and women (69.9%) with a mean age of 53.7 years; these demographics parallel the demographics of the SAH population in the Pittsburgh area. Of the 206 participants, 46 (22.3%) were in the APOE4+ group and 160 (77.7%) were in the APOE4- group. The APOE2+ group consisted of 29 (14.1%) individuals and the APOE2- group consisted of 177 (85.9%). The sample was in Hardy-Weinberg equilibrium. Demographic information for the sample by APOE4 and APOE2 groups are presented in Tables 1 and 2. Frequency counts of APOE genotypes are presented in Figure 1. There were no significant differences in demographic information between the APOE2+ and APOE2- groups. Because there are so few racial minorities in our population, race was dichotomized into White and non-White to compare the groups. The racial distribution was significantly different between the two groups based on APOE4 genotype with the APOE4+ having far more non-White participants than would have been expected (Table 1).

MRS

MRS of APOE4+ and APOE4- groups were not significantly different at 3 months ($n = 189$; $p = .054$) or at 6 months ($n = 181$; $p = .311$) after controlling for age, race, Hunt & Hess, and Fisher grade (data not shown). However, when controlling for vasospasm in addition to the above covariates in the subset of this population with angiographic vasospasm data available, there were significant differences between the APOE4+ and APOE4- groups at 3 months ($n = 94$; $p = .002$) and 6 months ($n = 95$; $p = .008$). Specifically, MRS was significantly worse in

individuals with the APOE4 allele (Table 3). MRS of APOE2+ and APOE2- groups were not significantly different at 3 months ($n = 189$; $p = .660$) or 6 months ($n = 181$; $p = .945$) after controlling for age, race, Hunt & Hess, and Fisher grade (data not shown). Controlling for vasospasm in the APOE2 groups did not show significant differences in outcome (data not shown).

GOS

Mean GOS of APOE 4+ and APOE4- groups were not significantly different at 3 months ($n = 190$; $p = .201$) or at 6 months ($n = 182$; $p = .463$) after hemorrhage after controlling for age, race, Hunt & Hess, and Fisher grade (data not shown). However, when controlling for vasospasm in addition to the above covariates in the subset of this population with angiographic vasospasm data available, there were significant differences between the APOE4+ and APOE4- groups at 3 months ($n = 94$; $p = .012$) and 6 months ($n = 95$; $p = .013$). Specifically, GOS was significantly worse in individuals with the APOE4 allele. GOS of APOE 2+ and APOE2- groups were not significantly different at 3 months ($n = 190$; $p = .675$) or at 6 months ($n = 182$; $p = .814$) after hemorrhage after controlling for age, Hunt & Hess, and Fisher grade (data not shown). Controlling for vasospasm in the APOE2 groups did not show significant differences in outcome (data not shown).

Mortality

Mortality rates were not significantly different between the APOE4+ and APOE4- groups at 3 months ($p = .777$) or 6 months ($p = .591$; data not shown). There was also no significant difference between the mortality rates of the APOE2+ and APOE2- groups at 3 months ($p = .918$) or at 6 months ($p = .617$) after hemorrhage (data not shown).

Discussion

Although we did not find a difference in development of CV based on APOE allele, it was a significant covariate included in all analyses. The major findings of this study are that individuals with an APOE4 allele had worse functional outcome (GOS and MRS) at 3 and 6 months after injury when controlling for age, race, severity of hemorrhage, and CV. However there was no difference in mortality based on APOE4 allele presence in our population. There was also no difference in mortality in patients with CV compared to patients without CV. The presence of the APOE2 allele was not associated with improved outcomes or a decline in mortality.

Our findings are similar to those of Morris et al. (2004) and Dunn et al. (2001) in that there were no significant differences in outcome by APOE4 allele presence alone. These findings conflict with results of others (Niskakangas et al., 2001). Niskakangas et al. (2001) found the APOE4 allele was associated with poorer outcome 7–8 months after SAH ($N = 168$). Leung et al (2002) also found the APOE4 allele to be associated with poor outcomes 6 months after SAH ($n = 58$); however they did not find APOE4 allele presence/absence added predictive value in a model considering age, poor Fisher grade, and poor World Federation of Neurological Surgeon's grade. Our sample size is the largest to date (206 participants). We were also able to analyze a subset of our sample (95 participants) with available angiographic data to control for influence of CV on outcome. To our knowledge, a role for APOE genotype in outcomes attained after SAH taking CV into account has not been previously explored, and interesting results arose in the analysis of this subset. Although we did not find a significant difference in the number of individuals having CV based on APOE4 allele presence, when used as a control variable, there were significant differences between the APOE4+ and APOE4- groups' functional outcome with participants with an APOE4 allele having poorer MRS and GOS scores at both 3 and 6 months. These differences may explain the conflicting results

presented in the literature. CV is a common occurrence after SAH and is associated with poor outcomes. Although APOE genotype does not appear to influence development of CV, it may impact neuronal response. Individuals with the APOE4 allele may have ineffective neuronal membrane repair response leading to decreased neuronal survival and poorer long-term outcomes. Although this study was not designed to identify mechanisms by which different APOE genotypes impact recovery, other studies do provide potential rationales. Others have found that genotype-specific differences in response to severe TBI are present in animal models and in humans. Fleischer and associates (2005) found decreased hippocampal volume and function in individuals with the APOE4 allele, particularly in women, recovering from moderate head injury (Fleisher et al., 2005). Animal studies of TBI in transgenic mice expressing human apoE4 and human apoE3 proteins and compared to APOE knockout mice have shown that mice expressing human apoE4 protein had increased neuronal damage in hippocampal regions and associated memory impairment (Sabo et al., 2000). ApoE has been shown to decrease the inflammatory response in a protein-specific fashion with the apoE4 protein less efficiently downregulating this response and thereby increasing oxygen free-radical formation, as compared to the apoE3 protein (Laskowitz et al., 1998; Lynch, Morgan, Mance, Matthew, & Laskowitz, 2001). An increase in oxygen free-radical formation or decreased/slower clearance of oxygen free radicals in an apoE protein-specific manner may be exhibited as poorer long-term recovery in our sample.

Morris et al. (2004) found no differences in advanced neuropsychological tests at a mean of 16 months after SAH. Our sample included functional outcome assessments at 3 and 6 months after hemorrhage. It may be that the effects of APOE are exerted later in the recovery process and impact long-term recovery, which would not be shown in our study. The early timing of our outcome assessment may be masking long-term genotypic influences on recovery. This hypothesis is supported by the work of Sun and associates (1998), who found that in vitro neurons exposed to astrocytes producing the apoE3 protein in vitro (versus apoE4 or no apoE) had significantly greater neurite outgrowth. This study was not designed to assess neuronal survival or outgrowth; however, our findings support the idea that individuals producing apoE4 protein may have decreased outgrowth/neuronal survival ultimately exhibited as poorer functional outcome.

No differences were found between the APOE2 groups when controlling for CV. There were no differences found in mortality rates between the APOE4 groups or the APOE2 groups. There is little literature exploring the influence of the APOE2 allele on CNS response to injury. There has been no work exploring APOE2 allele presence in the SAH population. Our findings about APOE2 were similar to that of Ruigrok et al. (2005) and suggest that there is no influence exerted by the APOE2 allele.

This study was limited in the short follow-up period. Limiting assessment time periods to only 3 and 6 months provided a larger sample size in that there were fewer missing data; however, it does not allow us to estimate genotypic influences on long-term recovery after SAH. Because of the low number of homozygous APOE4 allele participants and homozygous APOE2 allele participants, we were unable to investigate if there was a difference between these homozygous participants and their heterozygous counterparts.

Our findings suggest that APOE genotype influences recovery from SAH. They further support the hypothesis that the influence is exerted over the longer term. Additional work needs to be done exploring the association between APOE genotype and recovery from SAH controlling for CV. This may shed light into the mechanism by which apoE proteins influence neuronal recovery to a variety of insults. Genomic research is in its infancy in the nursing realm. The suggestion of APOE genotype influencing outcome has direct implications to nursing practice. If nurses and other health providers are aware of genotype influences that may worsen

outcomes, then resources can be focused on patients with these higher risk factors. In the long term this may influence hospital stay and cost of health care in patients with genetic risk factors. Additionally, results from genetic data can be used to inform future work identifying mechanistic pathways of CV and recovery from SAH. As mechanistic pathways are identified, points of intervention to improve outcomes will also be identified and ultimately may improve long-term recovery of SAH and other neurologically injured patients.

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Figure 1.

Frequency distribution of APOE genotypes of subarachnoid hemorrhage (SAH) patients. The numbers above the histogram are the exact count for that APOE genotype.

Table 1
Demographic Information Based on APOE4 Allele Presence^a

	APOE4- (<i>n</i> = 46)	APOE4+ (<i>n</i> = 160)	<i>p</i> -Value
Gender			
Male	13 (6.3%)	49 (23.8%)	.758
Female	33 (16.0%)	111 (53.9%)	
Age (years; <i>M</i> [<i>SD</i>])	53.0 (11.9)	53.9 (11.5)	.671
Race			
White	38 (18.5%)	151 (73.3%)	.011
Non-White	8 (3.9%)	9 (4.4%)	

^a. Values are expressed as *n* (%) unless otherwise indicated.

Table 2
Demographic Information Based on APOE2 Allele Presence^a

	APOE2+ (<i>n</i> = 29)	APOE2- (<i>n</i> = 177)	<i>p</i> -Value
Gender			
Male	10 (4.9%)	52 (25.2%)	.579
Female	19 (9.2%)	125 (60.7%)	
Age (years; <i>M</i> [<i>SD</i>])	53.0 (11.1)	53.8 (11.7)	.753
Race			
White	25 (12.1%)	164 (79.6%)	.242
Non-White	4 (1.9%)	13 (6.3%)	

^a. Values are expressed as *n* (%) unless otherwise indicated.

Table 3

ANOVA Results for APOE4 Groups Controlling for Age, Race, Hunt & Hess Score, Fisher Grade, and Cerebral Vasospasm

Outcome Measure	<i>N</i>	<i>F</i>	<i>p</i> -Value
MRS 3 months	94	10.138	.002
MRS 6 months	95	7.371	.008
GOS 3 months	94	6.57	.012
GOS 6 months	95	6.412	.013

NOTES: GOS = Glasgow Outcome Scores; MRS = Modified Rankin Scores.