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Apolipoprotein E e4 Allele Increases the Risk of Early Postoperative Delirium in Older Patients Undergoing Noncardiac Surgery

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Background: **Whether patients who subsequently develop early postoperative delirium have a genetic predisposition that renders them at risk for postoperative delirium has not been determined.**

Methods: **The authors conducted a nested cohort study to include patients aged ≥ 65 yr who were scheduled to undergo major noncardiac surgery requiring anesthesia. A structured interview was conducted preoperatively and for the first 2 days postoperatively to determine the presence of delirium, defined using the Confusion Assessment Method. Blood was drawn for measurement of the apolipoprotein genotypes. Bivariate tests of association were conducted between delirium and apolipoprotein genotypes and other potentially important risk factors. Variables that had significant bivariate association with postoperative delirium were entered in a forward multivariable logistic regression model.**

Results: **Of the 190 patients studied, 15.3% developed delirium on both days 1 and 2 after surgery. Forty-six patients (24.2%) had at least one copy of the apolipoprotein e4 allele. The presence of one copy of the e4 allele was associated with an increased risk of early postoperative delirium (28.3% *vs.* 11.1%; $P = 0.005$). Even after adjusting for covariates, patients with one copy of the e4 allele were still more likely to have an increased risk of early postoperative delirium (odds ratio, 3.64; 95% confidence interval, 1.51–8.77) compared with those without the e4 allele.**

Conclusions: **Apolipoprotein e4 carrier status was associated with an increased risk for early postoperative delirium after controlling for known demographic and clinical risk factors. These results suggest that genetic predisposition plays a role and may interact with anesthetic/surgical factors contributing to the development of early postoperative delirium.**

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POSTOPERATIVE delirium is common in older patients after noncardiac surgery and is associated with increased rates of nursing home placement and hospital mortality.[1] Despite this prevalence and clinical importance, no specific etiologic factor has been identified. Genetic studies in population-based investigations[2,3] have demonstrated a relation between certain genotypes and the risk of dementia and cognitive decline. Specifically, elevated risk of Alzheimer disease has been demonstrated among individuals with the E4 allele of the apolipoprotein E (APOE) gene in many populations.[4,5] The E4 allele of APOE is associated with a shift to an earlier age at onset of Alzheimer disease.[6] However, the APOE E4 genotype is neither necessary nor sufficient for the occurrence of Alzheimer disease.[6] The APOE polymorphism also affects response to trauma, age-related cognitive decline,[7] and several other disorders.[8–10]

APOE is a polymorphic protein associated with plasma lipoproteins. Three major isoforms can be recognized, designated as APOE2, APOE3, and APOE4, according to their relative position after isoelectric focusing.[11] APOE is unique among apolipoproteins in that it has a special relevance to nervous tissue.[12] APOE is involved in the mobilization and redistribution of cholesterol in repair, growth, and maintenance of myelin and neuronal membranes during development or after injury.[13–15] Whether patients who subsequently develop postoperative delirium have a genetic predisposition that renders them at risk for early postoperative delirium has not been determined.

This investigation hypothesized that the APOE4 allele increased the incidence of early postoperative delirium in older patients undergoing noncardiac surgery after controlling for covariates.

Materials and Methods

Patient Recruitment

The study was approved by the institutional review board for human research at the University of California, San Francisco, California, and informed consent was obtained preoperatively from each study patient. This nested cohort study was conducted from 2001 to 2006 at the University of California, San Francisco Medical Center, and the patients included were a subset of an ongoing investigation of the pathophysiology of postoperative delirium in elderly surgical patients. The inclusion criteria were consecutive English-speaking patients

aged ≥ 65 yr who were scheduled to undergo major elective noncardiac surgery requiring anesthesia, and who were expected to remain in the hospital postoperatively for more than 48 h. Excluded were patients who did not provide or were incapable of providing informed consent.

Neurocognitive and Delirium Assessments

Each patient was interviewed by the same trained research assistant preoperatively and postoperatively on days 1 and 2 after surgery. The preoperative interview typically occurred less than 48 h before surgery in the preoperative clinic. During the preoperative interview, in addition to the assessment of medical history, the presence of depressive symptoms, pain, and functional status were also measured. Cognitive status was measured preoperatively using the Telephone Interview of Cognitive Status instrument,[16] which was adapted from the Mini-Mental Status Examination. During both the preoperative and the two postoperative interviews, the presence of delirium was measured using the Confusion Assessment Method (CAM).[17] The CAM assessments typically occurred 24–48 h after surgery and followed a brief structured interview that helped to determine the patients' ability to converse logically by asking several questions about the patients' postoperative experiences, including their levels of pain. This method was developed as a screening instrument based on operationalization of *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised criteria for use by nonpsychiatric clinicians in high-risk settings. Based on a structured interview, the CAM algorithm consists of four clinical criteria: acute onset and fluctuating course, inattention, and disorganized thinking, and altered level of consciousness. For delirium to be defined, both the first and the second criteria have to be present, plus either the third or the fourth criterion. CAM has a sensitivity of 94–100%, a specificity of 90–95%, a high interobserver reliability,[17] and convergent agreement with four other mental status tests.

Genotyping of APOE

Genomic DNA was prepared, from whole blood, using the Puregene DNA Purification System (Gentra Systems, Minneapolis, MN). Initially, APOE genotypes were determined using the restriction isotyping method described by Hixson and Vernier.[18] Subsequently, a method was developed based on template directed dye terminator incorporation with fluorescence polarization detection as described by Hsu *et al.*[19] to assay the two single nucleotide polymorphisms. These single nucleotide polymorphisms were rs429358 (p.Cys130Arg) and rs7412 (p.Arg176Cys). For the polymerase chain reaction (PCR), 2.4 ng DNA (dried) was amplified in 6 μl reaction solution containing 3 μl PCR primer mix (0.2 μm each primer), and PCR reagent mix using the following protocol: 95° for 2 min, 35 cycles of 92° for 10 s, 63° for 20 s, 68° for 30 s; 10 min at 68° to complete the elongation. The PCR reagent mix was as follows: 0.02 μl Platinum *Taq* (5 U/μl; Invitrogen, Carlsbad, CA), 0.5 μl 10X buffer, 0.25 μl $MgCl_2$ (50 mM), 0.1 μl dNTP (2.5 mM), 0.5 μl Betaine–DMSO, and 1.63 μl water. The primers used were as follows: sense, AGACGCGGGCACGGCTGTCCAAGGA; antisense, CCTCGCGGGCCCCGGCCTGGTACAC. After exo-sap cleanup of the PCR product, the following primers were used for the two separate TDI reactions: TGCCGATGACCTGCAGAAG and GCGGACATGGAGGACGTG. We tested both methods (the DNA Purification System and the fluorescence polarization detection) independently against a large collection of isoelectric focusing gel data that records the phenotype (*i.e.*, at the protein level) and found a high agreement (95%) between the genotype and phenotype.

Definition of Delirium

During the three interviews, trained interviewers determined the presence of delirium using the CAM.[17] All assessments of postoperative delirium were validated by a second investigator (L.P.S.). We defined the occurrence of delirium as the patient meeting CAM criteria for delirium on both the first and second postoperative day assessments.

Assessment of Descriptive Characteristics and Covariates

The potential covariates included were those that in previous research were determined to be associated with postoperative delirium.[20–22] The covariates included age, education, amount of alcohol intake, history of central nervous system disorders, preoperative depressive symptoms, preoperative functional status, and pain levels. Each of the covariates were collected either at the preoperative or postoperative interviews or abstracted from medical records. Preoperative demographics included age, highest education level achieved, amount of alcohol intake (more than 2 drinks *vs.* 2 drinks or fewer per day), depression, and functional status. Depression was measured using the Geriatric Depression Scale and defined as the presence of six or more symptoms of depression.[23] Functional status was measured using the Activities of Daily Living[24] and the Instrumental Activities of Daily Living.[25] Assessment of pain at rest occurred both preoperatively and postoperatively using an 11-point rating scale in which 0 represents no pain and 10 represents the worst imaginable pain. Based on these assessments, it was determined whether the patient experienced an increase in level of pain after surgery. Medical record review was conducted to obtain information on perioperative blood pressure measurements. Other perioperative data obtained from chart review included the type of surgery; the American Society of Anesthesiologists physical status,[26] which incorporates the number and severity of preoperative co-

morbid conditions; and the type of anesthesia (general, regional, or combined). Surgical risk was estimated using the guidelines from the American College of Cardiology and American Heart Association update for the perioperative cardiovascular evaluation for noncardiac surgery, which takes into consideration the type and duration of surgery, and intraoperative blood loss.[27]

Statistical Analysis

Bivariate associations between postoperative delirium and covariates that had been demonstrated in previous research to be associated with the presence of delirium were tested using Pearson chi-square tests for nominal predictor variables and Mantel-Haenszel chi-square tests for trend for ordinal predictor variables. Two-sample *t* tests or Wilcoxon rank sum test were used to test the association between the presence of delirium and continuous predictor variables. Variables that had a bivariate association with a *P* value of 0.20 or less were included in multivariate analyses to determine whether the association between apoE4 is associated with delirium after adjusting for potential explanatory variables. Bootstrapping techniques were used to determine the most consistent set of candidate variables for the final model. The procedure consisted of randomly drawing with replacement 1,000 samples and for each such sample, fitting the full model with all of the candidate variables. A threshold of $P = 0.05$ was used for eliminating a variable from the model. For each predictor variable, the percentage of models in which it was found significant was recorded. A multivariate logistic regression analysis was then computed to determine the independent effect of the e4 allele of APOE after adjusting for covariates that were associated with presence of delirium. Covariates included in the model were those variables that were associated with the outcome variable with a *P* value of 0.05 or less in at least 70% of the bootstrapped samples.

Table 1. Demographics, Functional and Cognitive Status (n = 203)

	Patients, %
Age, yr	72.5 ± 5.9
Sex	
Female	48.5
Male	51.5
Race	
White	90.6
Nonwhite	9.4
Education level	
High school graduate or less	24.1
Incomplete college or more	75.9
Independent in five ADLs	88.6
Independent in seven IADLs	70.2
Alcohol intake	
No	41.2
Yes	58.8
History of CNS disorders	
No	57.0
Yes	43.0
History of stroke	
No	96.0
Yes	4.0
History of vascular disease	
No	87.6
Yes	12.4
GDS	2.5 ± 2.4
0–2	59.4
3–5	28.7
6+	11.9
TICS score	33.0 ± 3.2
Preoperative use of benzodiazepine	
No	86.6
Yes	13.4
Preoperative use of opioids	
No	74.3
Yes	25.7

ADL = activities of daily living; CNS = central nervous system; GDS = Geriatric Depression Score; IADL = independent activities of daily living; TICS = Telephone Interview of Cognitive Status.

Results

A total of 203 patients were initially included, but only 190 were ultimately assessed for the presence of both APOE e4 allele and postoperative delirium. Delirium assessment was not performed in 13 patients because of postoperative intubation, unexpected early discharge from the hospital, or refusal/unavailability for testing. There was no difference in the demographics between patients who had missing delirium data *versus* those who were assessed for delirium.

Our study included an older cohort with a mean age of 72.5 ± 6 yr. The majority of the patients completed high school or higher education. Other preoperative and surgical characteristics are shown in tables 1 and 2.

Overall, 29 of 190 patients (15.3%) developed delirium that persisted for 2 days after surgery. By bivariate analysis, patients who developed postoperative delirium that persisted for 2 days after surgery were older, dependent in one or more independent activities of daily living, had a history of central nervous system disorder, had lower systolic postoperative blood pressures on postoperative day 1, and had increased pain levels at rest on postoperative day 1 (table 3). Patients who had postoperative delirium that persisted for 2 days after surgery had significantly longer hospital stay than those without delirium (8.1 ± 6.7 *vs.* 5.1 ± 3.5 days; $P = 0.0008$).

Of the 190 patients studied, 46 (24.2%) had at least one copy of the e4 allele. The presence of one copy of the e4 allele was associated with an increased risk of postoperative delirium that persisted for 2 days after surgery (28.3% *vs.* 11.1%; $P = 0.005$). Even after adjusting for covariates associated with postoperative delirium, which included age, change in postoperative pain levels, history of central nervous disorders, and so on, patients with at least one copy of the e4 allele were still more likely to have an increased risk of postoperative delirium

Table 2. Anesthetic and Surgical Data

	Patients, %
Type of surgery	
Ear, nose, and throat; plastic; general; thoracic; vascular; urologic; gynecologic	48.0
Spine surgery; hip and knee replacement	52.0
Surgical risk categories	
Low	4.0
Intermediate	78.7
High	17.3
ASA physical status	
I and II	52.0
≥ III	48.0
Anesthesia duration, min	303 ± 137
Anesthesia technique	
General anesthesia only	75.8
General plus regional anesthesia	18.2
Regional only	6.0
Postoperative use of benzodiazepines	
No	83.1
Yes	16.9
Postoperative use of other CNS drugs	
No	72.5
Yes	27.5
Postoperative analgesia	
PCA only	46.3
Epidural/PCEA/spinal	13.4
PCA plus epidural/PCEA/spinal	14.2
Oral analgesics	26.1
Intraoperative blood loss, ml	832 ± 1,696
POD1 hemoglobin, g/dl	10.8 ± 1.4
POD2 hemoglobin, g/dl	10.4 ± 1.4
POD1 lowest postoperative systolic blood pressure, mmHg	107 ± 18
POD2 lowest postoperative systolic blood pressure, mmHg	113 ± 19

ASA = American Society of Anesthesiologists; CNS = central nervous system; PCA = patient-controlled analgesia; PCEA = patient-controlled epidural analgesia; POD = postoperative day.

(odds ratio, 3.64; 95% confidence interval, 1.51–8.77) compared with those without the e4 allele (table 4).

Discussion

Changes in cognitive status after surgery may present in the form of a frank delirium or more subtly as postoperative cognitive dysfunction (POCD). Delirium refers to observable changes in consciousness and attention,[17,28] whereas POCD refers to a patient exhibiting significant declines from his or her own baseline level of performance in one or more neuropsychological domains.[29–32] POCD presents more subtly than delirium and because it is detected with the administration of neuropsychological tests and often goes unrecognized in the clinical setting.

Our study is the first to report an association between APOE e4 status and the occurrence of postoperative delirium. Direct comparison of our results to previous studies is difficult because there is no information at present that directly compares the relation between

Table 3. Bivariate Analysis of Factors Associated with Postoperative Delirium (n = 190)

	No Delirium	Delirium	*P* Value
APOE			0.005
Without e4	128 (67.4)	16 (8.4)	
With e4	33 (17.4)	13 (6.8)	
Age, yr	72.3 ± 5.7	74.2 ± 6.5	0.10
Highest level of education			0.03
High school or less	34 (17.9)	12 (6.3)	
High school graduation and greater	121 (63.7)	17 (8.5)	
Independent in five ADLs			0.12
No	16 (8.4)	6 (3.2)	
Yes	144 (75.8)	23 (12.1)	
Independent in seven IADLs			0.02
No	43 (22.6)	14 (7.4)	
Yes	117 (61.6)	15 (7.9)	
Alcohol intake			0.15
No	62 (32.6)	15 (7.9)	
Yes	97 (51.1)	13 (6.8)	
History of CNS disorders			0.007
No	100 (52.6)	10 (5.3)	
Yes	60 (31.6)	19 (10)	
TICS score	33.3 ± 2.8	31.4 ± 4.4	0.05
GDS	2.4 ± 2.4	3.0 ± 2.3	0.24
0–2	100 (52.6)	13 (6.8)	0.17
3–5	42 (22.1)	12 (6.3)	
6+	19 (10)	4 (2.1)	
Change in pain levels at rest on POD1	1 ± 2.7	2 ± 4.1	0.09

Cross-tab for delirium *vs.* personal characteristics; numbers shown in parentheses represent percentages of total patients studied.

ADL = activities of daily living; APOE = apolipoprotein E; CNS = central nervous system; GDS = Geriatric Depression Score; IADL = independent activities of daily living; POD = postoperative day; TICS = Telephone Interview of Cognitive Status.

postoperative delirium and POCD. One small study in critically ill patients, however, recently reported that apolipoprotein E4 was associated with longer duration of delirium.[33] Several studies in surgical patients demonstrated conflicting results as to the impact of the APOE allele on POCD as determined by change from baseline in performance on neuropsychological tests.[34–40] With the exception of one study,[37] all were small and lacked the statistical power to detect a clinically significant effect of APOE allele on the occurrence of postoperative cognitive decline. The three smaller studies that demonstrated an association between APOE allele and cognitive decline were conducted in patients undergoing carotid endarterectomy and cardiac operations.[34,39,40] The largest study that did not demonstrate an association be-

Table 4. Multivariate Analysis of Factors Associated with Postoperative Delirium (n = 189)

	Odds Ratio	95% Confidence Interval
APOE, with e4 *vs.* without e4	3.64	1.51–8.77
Age	1.08	1.00–1.16
History of CNS disorders, yes *vs.* no	3.42	1.44–8.09

APOE = apolipoprotein E; CNS = central nervous system.

tween apolipoprotein E genotype and POCD did not measure postoperative delirium, and also likely underestimated the incidence of POCD because the investigators considered any patients who were not "fit enough for testing" as not having POCD.[37] The APOE e4 frequency of 24.2% observed in our study is consistent with that previously reported, which ranged from 16% to 39.5%.[34–40] If POCD and postoperative delirium are similar phenomena on a continuum, our results along with those from previous investigations would suggest that decline in cognitive status postoperatively does have a genetic predisposition.

What is the possible mechanism between apolipoprotein and postoperative delirium? Previous studies suggest that the effects of APOE are mediated through alterations in lipid transport in regenerating neurons, proinflammatory cytokine release from activated microglia, amyloid precursor protein metabolism, increased blood brain carrier permeability, alterations in platelet function, and systemic inflammation.[41,42,43] One hypothesized mechanism is that APOE e4 allele diminishes the capacity for repair in cases of cerebral injury or capacity for homeostasis/maintenance. Whether this mechanism occurs to increase the likelihood of developing postoperative delirium remains to be proven.

In addition to the apolipoprotein genotype which was a novel finding in this study, several factors found to be independent predictors of postoperative delirium in our previous studies were also demonstrated. This includes older age and having a history of central nervous system disorders.

Potential Study Limitations

Although we have described an association between apolipoprotein genotype and postoperative delirium, we cannot determine the mechanism by which this genotypic appearance is related to postoperative delirium. We focused on measuring delirium in the early postoperative period, because subjects in this investigation were included in a larger studying examining perioperative management and delirium. As a result, incidents of later onset delirium may have been missed. Our study focuses on the comparison of the E4 alleles only; the study sample size precludes additional analyses to be performed in patients with other allele combinations. Finally, it is not known whether postoperative delirium is reversible, and the long-term prognostic significance, including whether patients with postoperative delirium and APOE e4 allele have higher risk for further cognitive impairment, is not known.

In conclusion, APOE e4 carrier status was associated with an increased risk for early postoperative delirium after controlling for known demographic and clinical risk factors. These results suggest that genetic predisposition plays a role and may interact with anesthetic/surgical factors and aging, contributing to the development of early postoperative delirium. Future studies on postoperative delirium and cognitive decline should consider the potential importance of genetic influence as one of the several etiologic factors.

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