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Interleukin-6 and apolipoprotein E as predictors of acute brain dysfunction and survival in ICU Patients

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INTRODUCTION

Delirium is an acute confusional state occurring in up to 80% of intensive care unit (ICU) patients¹ and has been associated with poor outcomes including difficulty weaning from the ventilator², longer ICU length of stay (LOS)³, longer hospital LOS⁴, higher mortality rates⁵, increased dependence upon discharge from the hospital⁶, worse recovery one year after ICU admission⁶ and a 31% higher cost of hospital care⁷. There are no biomarkers able to predict ICU delirium and biological mechanisms responsible for delirium development remain obscure. In the absence of a clear understanding of the process which leads to delirium, it remains difficult to reduce its occurrence or design effective therapeutic interventions.

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Most evidence supports a role for prolonged inflammation as a potential mechanism of delirium development. Elevated pro-inflammatory cytokine levels have been associated with delirium in general ICU patients with a variety of diagnoses; however this evidence is conflicting as some studies have not found this association^{8,9}. Apolipoprotein E genotype (APOE) has a role in neurodegenerative disorders, possibly by modulating neuroinflammatory responses¹⁰.

Recent literature suggests APOE genotype may be implicated in the development of ICU delirium with APOE 4 allele increasing frequency and duration of delirium^{11–13}, however others have found no association with delirium or more general cognitive impairment^{14–17}. Importantly, methodological differences may explain the inconsistent results of these studies and these relationships have not been explored in the context of apolipoprotein E protein (apoE) isoform or level. There are known apoE isoform specific effects on inflammation with apoE4 promoting stronger inflammatory response and increased neurotoxicity in animal^{18–21} and cell models^{22,23}. An increase in apoE, or apoE 4, may promote a stronger inflammatory response, delirium presence or longer delirium duration. The purpose of this study was to determine the association between inflammatory markers, apoE protein, APOE genotype and delirium presence, delirium duration, and outcome in ICU patients.

Patients and methods

Subjects were 21–75 years old admitted to the University of Pittsburgh Medical Center Presbyterian Hospital Medical and Surgical-Trauma ICUs requiring mechanical ventilation for 24 to 96 hours and without preadmission cognitive dysfunction. Cognitive dysfunction was identified by medical record review and interview with patient or next of kin. Data were collected for five days after study enrollment. The protocol was approved by the University of Pittsburgh Institutional Review Board.

Data collection

Demographic and clinical variables were extracted from medical records; Charlson comorbidity scores²⁴ and APACHE III scores²⁵ were determined by project personnel. Sedative-analgesic medication data, including specific drug(s) and dose(s), were extracted for the 24 hour period before delirium assessment. A 24 hour narcotic equivalency dose (fentanyl, oxycodone, or hydromorphone), benzodiazepine equivalency dose (midazolam or lorazepam) and propofol dose were generated for use as control variables.

Delirium determination

The Richmond Agitation Sedation Scale (RASS) was performed daily²⁶ and subjects with RASS scores rating between –3 to +4 underwent delirium assessment using the Confusion Assessment Method for the ICU (CAM-ICU)²⁷, while the remaining patients in either RASS –4 or –5 were designated as being in a comatose state (whether disease or drug induced). All patients were thus rated as either normal (CAM-ICU negative), delirious (CAM-ICU positive and RASS –3 or higher) or comatose (RASS –4 or –5). A significant proportion of our subjects were unable to participate in the CAM-ICU due to being in a coma due to disease process or the amount of sedation required. Since coma (RASS –4 and –5) and

delirium are both states of acute cognitive dysfunction in ICU patients, subjects in either coma or delirium states were included in the 'acute brain dysfunction positive' group for analyses (compared to the 'CAM-ICU negative' group).

Biomarkers

Samples were collected from existing arterial or central venous catheters. Sample dates were coded as days after admission. In some subjects (n= 10 to 55 depending upon specific biomarker) there was not enough serum collected to perform analyses of all biomarkers and analysis was done using the smaller sample.

DNA was extracted using a simple salting out procedure²⁸. APOE genotypes were determined using standard techniques²⁹ and genotypes were double called by individuals blinded to other data. For analyses, the sample was dichotomized based on APOE 4 allele presence (APOE4+ and APOE4-).

Daily serum apoE, IL-6, IL-8 and IL-10 were quantified using ELISA methodology as per manufacturer's instructions (MBL International Corp., Watertown, MA and Invitrogen Corporation, Carlsbad, CA).

Outcome measures

Days of mechanical ventilation within a 28 day period, total ICU length of stay (LOS) and total hospital LOS, mortality and discharge disposition (died, hospital inpatient, skilled nursing facility, long term acute care, rehabilitation or home) were collected from medical records.

Statistical Analyses

Measures of central tendency and dispersion were obtained for all continuous variables.. Absolute Frequency and percentage were reported for all categorical variables. Chi-square analysis was initially performed to explore the relationship between APOE genotype and delirium presence, presence of acute brain dysfunction, hospital discharge disposition, and 28 day mortality. Differences in days of mechanical ventilation, total ICU LOS, total hospital LOS and duration of delirium and acute brain dysfunction in groups based on APOE genotype, APOE 4 allele presence, delirium presence and acute brain dysfunction presence were examined with t-tests or ANOVA. Then multiple linear regression models and/or logistic regression models were used to determine relationships between predictor and outcome variables while controlling for covariates. Covariates were selected based on known relationships with outcome variables and included: age, sex, APACHE III, Charlson Comorbidity index, 24 hour propofol dose, 24 hour narcotic dose, 24 hour benzodiazepine dose. Given the repeated measurements of delirium status, acute brain dysfunction status, daily serum apoE protein or cytokine levels over 7 days, Generalized Estimating Equation (GEE) or repeated measure mixed effect modeling were used accordingly to determine the relationship between those outcomes and APOE4 allele controlling for covariates such as time-dependent sedative use.

RESULTS

Demographic and clinical characteristics (including delirium and coma frequency) of the 77 enrolled subjects are presented in table 1. Acute Respiratory Failure and/or acute respiratory distress syndrome (ARDS) were the most common admitting diagnosis (56%). Upon study enrollment, 25 (32.5%) subjects had no delirium or coma and 10 (13.0%) subjects had delirium. The majority of our sample developed delirium (45.5%) or were in a coma (31.2%) during the 5 day study period. There were 59 (76.6%) subjects in the acute brain dysfunction group (Delirium positive + Coma positive) and 18 (23.4%) in the delirium negative group. For the entire sample, average duration of delirium was 0.97 days, average number of coma days was 2.03 and average number of delirium free/coma free days was 2.0. For subjects developing delirium but not coma, average number of delirium days was 2.13 days and average number of coma free/delirium free days was 2.73 days. For subjects developing acute brain dysfunction (delirium + coma), average number of coma days was 3.7, average number of delirium days was 0.25 days and average number of coma free/delirium free days as 0.67 days.

APOE genotype distribution, delirium, and demographic/clinical characteristics are presented in table 2. There were 17 subjects in the APOE4+ group and 58 subjects in the APOE4- group. There were no differences in delirium presence by APOE genotype. The APOE4+ group had shorter duration acute brain dysfunction (0.67 vs 1.43; $p=.024$).

There were no differences in ICU length of stay by delirium group ($p=.08$), however subjects with delirium had more days of mechanical ventilation and a longer hospital length of stay compared to subjects without delirium or coma (Table 3). Subjects with coma were more likely to die than those with delirium, who were more likely to die than those without delirium or coma (Table 3). Subjects with acute brain dysfunction had 5.5 more days of mechanical ventilation ($p=.027$), a 5.5 day longer ICU LOS ($p=.0412$), and required higher level of care upon discharge ($\chi^2 = 11.24$; $p=.001$) (Figure 1) after controlling for covariates (age, sex, 24 hour medication dose, Charlson Comorbidity Index and APACHE III). This relationship was not modified by APOE genotype. There were no differences in days of mechanical ventilation, ICU LOS or hospital LOS between groups based on APOE genotype.

Five subjects died while on study; one in the delirium negative group (5.6%), one in the delirium group (2.9%) and 3 in the coma group (12.5%). The mortality rate was 19.5% ($n=15$); 5.6% ($n=1$) in those without delirium, 14.7% ($n=5$) in those with delirium and 39.1% ($n=9$) in those with coma. Mortality was higher in those with acute brain dysfunction compared to those without ($\chi^2 = 7.37$; $p=.025$) (Figure 1). The mortality rate differed based on genotype with the APOE4+ group more likely to survive ($\chi^2 = 4.80$; $p=.028$), after controlling for covariates (age, sex, 24 hour medication dose, Charlson Comorbidity Index and APACHE III) (OR = 13.565; $p=.0095$) and in fact all APOE4+ subjects survived.

Serum samples were available in 55 subjects (average of 4.3 per subject). Average IL-6 of the entire sample ($n=38$) was 182.16 p/mL at the start of the study; IL-10 ($n=36$) was 18.48p/mL and IL-8 ($n=16$) was 0.23 and apoE ($n=51$) was 6.48. Subjects with delirium had

higher IL-6 ($p=.027$; $n=55$) (Figure 2), but not IL-10 ($n=47$) or IL-8 ($n=10$). APOE 3 homozygotes had highest IL-6 levels, followed by those with APOE 2/3, 2/4, and 3/4 genotypes ($p=.05$; Figure 3).

There was no difference in apoE ($n=55$) over time by delirium status or APOE genotype. ApoE correlated with IL-8 (Pearson correlation = .624; $p<.001$) after controlling for genotype (Correlation = .653; $p<.001$) and delirium (Correlation = .613; $p<.001$). ApoE correlated weakly with IL-10 (Pearson correlation = .245; $p=.009$) but not IL-6, and after controlling for genotype (Correlation = .219; $p=.021$) and delirium (Correlation = .220; $p=.019$).

DISCUSSION

The main findings of this study are: 1) delirium and acute brain dysfunction in ICU patients is associated with higher IL-6, worse outcomes, and the APOE 3/3 genotype and 2) APOE 4 allele presence was associated with shorter duration of acute brain dysfunction and decreased mortality. This is also the first study to report serum apoE levels in ICU patients.

Elevated IL-6 appears to be a hallmark of ICU delirium³⁰ and the increased IL-6 in APOE 3/3 subjects is not particularly surprising. While all apoE isoforms are pro-inflammatory, the apoE 4 isoform is associated with the strongest inflammatory response. The APOE 4 allele correlates with increased pro-inflammatory cytokines in other populations and has interactive effects with the interleukin-6³¹ and other inflammatory genes (IL-10, HMGCR, ACT and IL-1 β)³². The lack of an association between IL-10 and delirium may be related to the temporal trajectory of IL-10 after acute physiologic injury. One study found that the T-helper 2 class of chemokines were elevated early in patients with delirium 6 hours post cardiac surgery, but decreased 4 days post-operatively³⁰. Our samples were drawn 2–9 days after admission, with higher numbers drawn closer to admission and it is possible that the peak in IL-10 that serves to dampen inflammation and stimulate immunity was not captured within our sample collection time frame. The complex response to acute illness promoting inflammation and culminating in cognitive dysfunction is likely influenced by multiple genes, their interaction and environmental factors. The lack of an association between IL-8 and delirium may be due to a small number of samples analyzed ($n=10$).

It is well documented that subjects who develop ICU delirium have worse outcomes⁶. Previous work has categorized patients with delirium together with comatose patients for some of this work and the acute brain dysfunction we describe is associated with higher mortality and worse recovery, as indicated by a higher level of care necessary upon discharge. ICU delirium leads to poorer cognitive recovery and persistent cognitive dysfunction for at least one year after admission³³ and APOE 4 is associated with worse cognitive functioning in a variety of populations. APOE likely modifies cerebral acetylcholine synthesis such that the apoE 4 isoform may lead to neurotransmitter dysfunction and cognitive impairment³⁴. In animal models, apoE-derived peptide administration impairs memory and cognitive function by blocking nicotinic acetylcholine receptors²¹. Our APOE 4 carriers had less delirium and a shorter duration of delirium. Much of the previous research in this area has included elderly subjects. The aging APOE 4 carrier

brain may be more vulnerable and therefore more susceptible to critical illness and delirium. Indeed, in pediatric studies, APOE 4 genotype has been associated with favorable cognitive function^{35,36}. Our study had a relatively younger population compared to previous literature and thus may be more resilient in their ability to recover regardless of genotype. The younger age of our sample may also equate to decreased morbidities that influenced our results. Additionally, there were no APOE 4/4 subjects in our sample which may have skewed results as the population with the most significant 'gene dose' is not represented. The complex response to critical illness leading to delirium and acute brain dysfunction and the pleiotropic role of the apoE protein in the human brain is likely a very complex relationship.

The finding that APOE 4 allele carriers had decreased mortality is a unique finding. This could have been significantly impacted by the lack of APOE 4/4 subjects and the young age of our population. The APOE 4 allele contributes to increased lipid load and may contribute to pre-admission comorbidities or in-hospital events impacting ICU recovery. This unique feature of our population makes it difficult to interpret the relationship we found between APOE genotype and mortality. Having one copy of the APOE 4 allele may not contribute enough to the pathology of delirium or acute brain dysfunction but having two copies might increase risk.

To our knowledge, this is the first study to report serum apoE levels in ICU patients. There were no differences in apoE protein over time regardless of delirium status or acute brain dysfunction. Elevated apoE levels may promote inflammation resulting in acute brain dysfunction and poor outcomes in ICU patients as serum apoE protein levels correlated with IL-8 and IL-10 levels over time suggesting interaction between the apoE protein and inflammation. It is not known if apoE modifies the chemotactic or neutrophil activating effects of IL-8 or inflammation dampening effects of IL-10. The mechanisms by which apoE protein modifies immune response are complex and most of this work has not fully evaluated genotypic/isoform specific response. ApoE synthesis is downregulated after acute inflammation, however serum levels are maintained via hepatic receptor downregulation and decreased clearance³⁷. This mechanism may be driving the stable apoE level such that there is no change regardless of delirium. Given the small sample size, these findings need to be validated in a larger sample.

Limitations to this study may impact findings and interpretation. Our sample was small and as such findings must be interpreted carefully particularly those related to genotype and the APOE 4 allele. Five subjects died while on study, and were used for analyses but we did not consider this in our analyses. Delirium is more common in the elderly and in patients who have previous cognitive impairment. Our study criteria specifically ruled out subjects >75 years old as a method to decrease bias related to preadmission dementia or cognitive impairment. We therefore anticipated a lower rate of delirium in our sample; however 45.5% of our sample developed delirium and 76.6% had acute brain dysfunction (delirium or coma). The inclusion of subjects in coma in this study was intentional as a measure of brain dysfunction. We found similar results with and without these subjects in our analysis; however findings should be interpreted carefully because other populations may be significantly different.

We were not able to analyze all serum samples for all biomarkers due to limited volumes in some subjects. This may lead to bias in our results. Certainly these preliminary findings are of interest and support previous work; however they do need to be replicated in larger sample sizes.

Our data support an association between IL-6 and acute brain dysfunction in critically ill patients. The lack of an association between APOE genotype and delirium or acute brain dysfunction presence, in combination with the paradoxical relationship between APOE 4 allele presence and decreased delirium duration and improved survival found in this study with a small sample size, highlight the complexity of the relationship. These findings need to be verified in a larger sample and in the context of biological pathways of brain function and recovery in ICU patients.

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Figure 1. Outcome measures by delirium

Discharge disposition by Acute Brain Dysfunction. A. Percent of subjects in each discharge disposition group. Individuals without Acute Brain Dysfunction were more likely to be discharged to home. B. Percent of subjects who lived/died in each Acute Brain Dysfunction group. Note that significantly more subjects with Acute Brain Dysfunction died compared to those without dysfunction. Acute Brain Dysfunction had a negative effect on recovery such that those with Acute Brain Dysfunction were more likely to die and, for those survivors, were more likely to be discharged to a high care need facility after controlling for age, sex, 24 hour medication doses, APACHE III, and Charlson comorbidity index.

Figure 2. Mean IL-6 ($\pm$ SE) over time

Mean IL-6 ($\pm$ SE) over time. A. Daily mean IL-6 in different delirium groups (CAM-ICU Negative, CAM-ICU Positive, Coma). B. Daily mean IL-6 concentrations over time by Acute Brain Dysfunction presence. IL-6 was higher in patients with delirium (CAM-ICU positive) and those with Acute Brain Dysfunction compared to those without dysfunction.

Figure 3. Mean IL-6 (±SE) over time by APOE genotype

Mean IL-6 (±SE) over time by APOE genotype. Daily mean IL-6 in groups based on APOE genotypes by hospital day. Subjects with IL-6 was greatest in APOE 3/3 genotype > APOE 2/3 genotype > APOE 2/4 genotype > APOE 3/4 genotype.

Table 1

Demographic and clinical characteristics of sample by delirium groups.

	Delirium Negative (n=18)	Delirium Positive (n=35)	Coma Positive (n=24)	Total (N=77)
Age Mean ($\pm$ SD)	46.4 (18.3)	47.2 (17.4)	50.0 (15.7)	47.9 (17.0)
Female n (%)	10 (55.6)	18 (51.4)	13 (54.2)	41 (53.2)
Race Caucasian n (%)	17 (94.4)	32 (91.4)	21 (87.5)	70 (90.9)
APACHE III Mean ($\pm$ SD)	59.3 (29.0)	68.5 (26.6)	80.6 (31.8)	69.9 (29.51)
Charlson Comorbidity Index Mean ($\pm$ SD)	1.5 (2.2)	1.9 (1.7)	2.2 (2.5)	1.9 (2.5)
Admission Diagnosis: Acute Respiratory Failure n (%)	7 (38.9)	20 (57.1)	15 (62.5)	42 (54.5)
Admission Diagnosis: Trauma n (%)	6 (33.3)	5 (14.3)	4 (16.7)	15 (19.5)
APOE 4 Positive n (%)	5 (27.8)	6 (17.1)	6 (25.0)	17 (22.1)

There were no significant differences in demographic/clinical variables between the three groups. * 2 subjects had missing genotype data.

Table 2

Demographic and clinical characteristics of sample by APOE genotype.

	APOE 2/3 (n=10)	APOE 2/4 (n=5)	APOE 3/3 (n=48)	APOE 3/4 (n=12)
Age Mean ($\pm$ SD)	55.0 (15.7)	54.0 (15.0)	44.8 (17.3)	50.6 (17.0)
Female n (%)	5 (50.0)	2 (40.0)	24 (50.0)	8 (66.7)
Race Caucasian n (%)	10 (100.0)	4 (80.0)	43 (89.6)	11 (91.7)
APACHE III Mean ($\pm$ SD)	58.2 (22.1)	71.2 (20.7)	69.2 (30.5)	76.9 (33.3)
Charlson Comorbidity Index Mean ($\pm$ SD)	1.9 (1.5)	1.2 (2.2)	2.0 (2.7)	1.6 (2.4)
Admission Diagnosis: Acute Respiratory Failure n (%)	7 (70.0)	2 (40.0)	25 (52.1)	7 (58.3)
Admission Diagnosis: Trauma n (%)	0 (0.0)	1 (20.0)	13 (27.1)	1 (8.3)
Delirium Negative n (%)	0 (0)	1 (5.6)	12 (66.7)	4 (22.2)
Acute Brain Dysfunction Positive n (%)	10 (16.9)	4 (6.8)	36 (61.0)	8 (13.6)

There were no differences in demographic or clinical characteristics by APOE genotype (*1 subject in each delirium group had missing genotype data). There were no APOE 2 or APOE 4 homozygotes.

Table 3

Outcome measures by delirium.

	No Delirium (n=18)	Delirium Positive (n=35)	Coma (n=24)
Mechanical Ventilation days ^a Mean (±SD)	7.55 (4.20)	14.43 (10.84)	10.91 (8.36)
ICU Length of stay Mean (±SD)	10.09 (4.40)	16.78 (10.22)	13.86 (11.94)
Hospital Length of stay ^b Mean (±SD)	16.39 (6.52)	25.09 (13.26)	16.58 (12.67)
Mortality ^c N (%)	1 (5.6)	5 (14.3)	9 (37.5)

There were significant differences in outcome measures by the 3 group delirium categories (no delirium, delirium positive and coma group).

^a p=.03.

^b p=.01,

^c p=.017.