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APOLIPOPROTEIN E GENOTYPE AND CBF IN TRAUMATIC BRAIN INJURED PATIENTS

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1. INTRODUCTION

Prior to the discovery in 1993 of the link between apolipoprotein (ApoE) and Alzheimer disease[1], ApoE was primarily studied for its role in cholesterol transport and cardiovascular pathology [2]. Since that time, ApoE has been increasingly recognized for its function in hypercholesterolemia, vascular elasticity[3, 4], compliance[5] and endothelial dysfunction[6]. These studies suggest that vascular mechanisms of ApoE may contribute to neurodegeneration [7]. The mechanism for the ApoE role in cerebrovascular pathology is unknown but theories include increased production of O(2)(-) and inactivation of nitric oxide (NO) synthase enzyme activity [6, 8]. From this perspective, we hypothesize that ApoE 4 allele carriers have differential cerebral blood flow (CBF) immediately after injury that may affect outcomes in the traumatic brain injured (TBI) population.

2. SUBJECTS AND METHODS

This prospective study recruited 120 patients with severe TBI [Glasgow Coma Score (GCS) ≤ 8] admitted to a NeuroTrauma ICU at a University Hospital with a Level I Trauma Service from Aug. 06, 1994 to Feb. 02, 2001. This analysis includes those patients with a XeCT CBF test within the first 24 hours after injury (n=54). The Xe/CT CBF tests were ordered by the attending neurosurgeon as part of routine care. The medical records were reviewed to obtain information regarding demographics, symptoms, and treatmentj. Admission GCS were verified by the resident and on-call neurosurgeon.

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3. APOE GENOTYPING

Cerebrospinal fluid (CSF) samples were collected and stored in a -80°C freezer for future genotyping in batch. Genetic determinations were performed in Dr. Kamboh's laboratory. Genomic DNA was isolated from CSF samples by the Qiagen kit (Qiagen, Chatswirth, CA). ApoE genotyping was performed as described by Kamboh et al. (1995).

4. Xe CT CBF

A baseline 3 or 4 level stable xenon-enhanced CT (Xe/CT) CBF test was conducted and 20 2-cm circular regions of interest (ROI) were measured per level. The CBF software calculated the mean CBF within each of the 20 ROIs. The 20 ROIs were averaged per level and the 3 or 4 levels were averaged to determine hemispheric (right, left, ipsilateral, contralateral and difference between ipsilateral and contralateral) and global ROI CBF. XeCT CBF tests with poor confidence images were excluded. The baseline CT scan was reviewed independently by investigators blinded to the clinical data. The primary side of injury was coded as the ipsilateral hemisphere when the injury was greater than the contralateral side. If the primary side of injury could not be identified (e.g. diffuse axonal injury, diffuse punctate hemorrhage, bilateral injury), it was excluded from the analysis comparing ipsilateral to contralateral or "control" CBF (n=43).

5. STATISTICAL ANALYSES

SPSS (version 11.0, SPSS Inc,) and SAS (version 8.2, SAS Institute Inc., Cary, NC) were used for all analyses. An analysis of variance was used to compare the mean CBFs among patients with ApoE genotypes of 3|2, 3|3 and 3|4 (n=51). All patients were dichotomized based on the presence or absence of the ApoE 4 allele (n=54) and a t-test was used to compare mean differences in hemispheric and global ROI CBF values. A regression analysis was used to predict the effect of ApoE 4 allele on CBF while controlling for potential co-variates (PaCO2, severity of injury, race, and gender).

6. RESULTS

Out of 54 patients, the ApoE genotype distribution was 2|2 (n=0; 0%) 2|4 (n=1; 1.9%), 3|2 (n=11; 20.7%), 3|3 (n=30, 55.6%), 3/4 (n=10, 18.5%), and 4|4 (n=2, 3.7%). After classification by the presence or absence of the ApoE 4 allele, 13 (24.1%) subjects were positive for the ApoE 4 allele and 41 (75.9%) subjects were negative. Table 1 shows the means and standard deviations of the demographic characteristics and time of baseline XeCT for the total sample. There was no statistically significant difference in the median GCS, but a greater proportion of the patients that were positive for the ApoE 4 allele had a GCS of 5 through 8 indicating that they had less injury on admission.