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Case study

APOE ε4 positive patients suffering severe traumatic head injury are more prone to undergo decompressive hemicraniectomy

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ABSTRACT

Object: In this paper we tested the hypothesis if patients with severe traumatic brain injury and presence of the apolipoprotein E (APOE) ε4 allele are more prone to undergo the surgical procedure decompressive hemicraniectomy (DC) in order to bring the intracranial pressure (ICP) under control.
Methods: In this prospective consecutive study patients with sTBI were enrolled (n = 48). Inclusion criteria were arrival to our level one trauma university hospital within 24 h after trauma, patient age between 15 and 70 years, Glasgow Coma Scale (GCS) score ≤8 at the time of intubation and sedation, an initial cerebral perfusion pressure >10 mm Hg. Venous blood was sampled for APOE genotype determination. Clinical outcome at 6 months after injury was assessed with the Extended Glasgow Outcome Scale (GOSE). All surgical procedures needed for each patient were registered.
Results: Patients with the APOE ε4 allele were significantly overrepresented in the DC group. In the APOE ε4 + DC group, ICP_{max} and ICP_{mean} during the first 36 h were significantly higher and GOSE was significantly worse at 6 months.
Conclusion: Our data suggest that patients with the APOE ε4 allele are predisposed for the need of DC more often than patients without the APOE ε4 allele. Thus, it seems to be of importance to consider the APOE genotype in patients suffering severe traumatic brain injury in order to forecast the need for a more exquisite intensive care.

1. Introduction

ApoE is a multiform protein arising from three alleles at a single gene locus. The three major isoforms, ApoE4, ApoE3 and ApoE2, differ from one another by single amino acid substitutions. However, these changes have explicit functional effects at both cellular and molecular levels. The APOE ε4 allele has been connected to Alzheimer's disease [1,9]. Worse outcome after brain injury in subjects expressing the APOE ε4 allele has been reported [10]. However, it has also been reported that the APOE ε4 allele does not influence outcome after TBI [27,31]. APOE genotype has also been demonstrated to play a significant role in recovery after TBI, with APOE ε4 associated with poor recovery after TBI compared to APOE ε3 in humans [39].

It has been reported that S-100B and NSE is more pronounced in subjects presented with the APOE ε4 allele [19,29].

Traumatic brain injury (TBI) elicits inflammation, cerebral oedema and vascular changes resulting in an increase in intracranial pressure (ICP), which can lead to further secondary damage. Decompressive hemicraniectomy is a surgical option in the management of ICP ([7,27,1,2,26,36,40]).

Although DC has been shown to improve both survival and functional outcome in patients suffering malignant cerebral infarctions, evidence of benefit in patients with TBI has been more inconsistent ([27,7]). Although DC is effective in reducing ICP as a second tier therapy, its impact on clinical outcome has been less clear. However, the recently published rescue-ICP study reported lower mortality in the DC group as compared to the medical treatment group at 6 and 12 months [17].

One of the most important controversial points in the randomized controlled trial setting is how to standardize the surgical technique, in particular, the location and the extent of bone removal [34].

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Interestingly, little is known about the correlation of the APOE genotype and the need for DC in patients suffering severe head injury.

The primary aim of this study was to investigate the possible association of the APOE ε4 allele and the need for DC in patients with sTBI treated by an ICP targeted therapy based on the Lund concept. Secondary aims were to study the temporal ICP pattern and to explore whether the outcome at 6 months differed in the two groups.

2. Materials and methods

The department of neurosurgery in Umeå has a regional responsibility of about 900,000 inhabitants in the northern region of Sweden.

All patients treated for sTBI during the time between January 1st 2001 and December 31st 2005 were included in the study if inclusion criteria were met. The inclusion criteria were: age 15–70 years, arrival in the department within 24 h of trauma, verified traumatic brain injury, Glasgow coma score (GCS) at intubation and sedation of 8 or less, a first measured CPP of 10 mmHg or more. Exclusion criteria were: pregnant or breastfeeding woman and penetrating head injury. The patients are part of a prospective randomized blinded placebo controlled study on the effect of prostacyclin in sTBI [28].

Initially, all the patients were sedated with fentanyl and midazolam. Multimodal monitoring was applied. An ICP oriented therapy was applied [21]. Arterial blood pressure was measured invasively and ICP measured continuously by using an intraparenchymal pressure-measuring device (Codman MicroSensor, Johnson & Johnson Professional Inc., Raynham, MA, USA). CPP was automatically calculated. By using the Picis system (Picis, Inc., Wakefield, MA, USA) and the LabPilot (CMA Microdialysis, Solna, Sweden), data were digitally stored. Patients were treated with the body positioned flat and the arterial baseline level was set at the heart level. Thereby, no correction for CPP was needed. The patients were intubated and ventilated ($P_aO_2 \geq 12$ kPa and P_aCO_2 4.5–5.5 kPa). The goal of the treatment is to keep ICP < 20 mmHg, not allowing CPP < 50 mmHg. Hourly ICP_{max} and CPP_{min} were calculated by using all the minute-to-minute ICP and CPP values during the first 5 days. The hour with the highest ICP and lowest CPP was identified. The mean ICP and CPP for the 5 days were also calculated. The patients were kept normovolemic. By infusion of red blood cells, albumin, glucose solutions and Ringer's acetate (S-Hb > 110 g/l, S-alb > 40 g/l), the colloid and cristalloid osmotic pressure was kept normal. The fluid balance was kept neutral and furosemide was used when indicated. Clonidine and metoprolol were given, as continuous intravenous infusions, in order to normalise the blood pressure and to reduce the transcapillary hydrostatic pressure. These medicines also reduce the stress level caused by the sympathetic nervous system. Further, mass lesions were surgically removed. If ICP despite first tier therapy was not brought under control, additional sedation with low-dose thiopental monitored by continuous EEG, ventriculostomy and uni- or bilateral hemicraniectomy with duraplasty were used.

Blood samples for analysis of the APOE alleles were drawn after arrival and inclusion in the study. The samples were analyzed at the department of clinical chemistry, Malmö University Hospital, Malmö, Sweden. Parts of the actual gene is amplified by PCR technique from isolated genomic DNA, where after florescence marked allele specific probes hybridize with specific products evolving florescence at a specific wave length which is analyzed in an automatized system.

Independent staff members evaluated the clinical outcome at 6 months according to the GOSE [45]. The results were also dichotomized into deceased/alive.

In accordance to the aim of the study the subjects were dichotomized into groups representing those with APOE ε4 + DC, non-APOE ε4 + DC and non-DC. Continuous variables are reported as mean ± standard error of the mean (SEM) and discrete variables as median and range. The two-tailed Student's *t*-test and Wilcoxon rank-sum test was used for calculations of significant differences between groups, and χ^2-test was used for evaluation of significant difference between proportions. In multiple comparisons ANOVA followed by Dunnett's test was used for continuous variables and Kruskal–Wallis test followed by Dunn's test for discrete parameters. Likelihood ratios and Fisher's Exact test were used as noted.

The study was approved by the internal review board at Umeå University (00-175, 05-007M) and the study is registered in Clinical Trials (ClinicalTrials.gov Identifier NCT01363583).

3. Results

Forty-eight patients were included in the study. Due to 2 missing APOE values all the calculations are on 46 subjects (15 females, 31 males). No effect of the prostacyclin treatment on the actual parameters was observed and thus all subjects are considered as one group. No patients were lost to follow up.

Demographics, GCS and ISS for the different groups are given in Table 1. There was no statistically significant difference in GCS, age and ISS between the groups.

The APOE ε4 allele was present in 39.1% of the patients. In 19 subjects DC was performed (41%). The likelihood ratio for DC in the APOE ε4 group was 4.811 ($p = 0.028$, Chi Square test) and the difference in probability of DC between the APOE groups was statistically significant ($p = 0.037$, two-tailed Fishers's test), see Table 2.

Fig. 1 shows the ICP_{mean}, CPP_{mean}, ICP_{max} and CPP_{min} in the groups during the first 5 days. ANOVA showed a significant difference in ICP_{max} ($p = 0.023$) between the groups and ICP_{max} was significantly higher in the APOE ε4 + DC group ($p = 0.027$ Dunnett's test) as compared to the non-DC group. Fig. 2 depicts the temporal profile of the mean ICP during the first 5 days in the groups. ICP_{mean} was significantly higher in the APOE ε4 + DC group during the first 36 h as compared to non-DC (ANOVA followed by Dunnett's test).

A comparison of the outcome measured as GOSE at 6 months after injury showed a significant difference between the groups ($p = 0.018$, Kruskal-Wallis test) and was significantly worse in the APOE ε4 + DC group as compare to non-DC ($p = 0.031$, Dunn's test). The likelihood ratio for dead or alive at 6 months in the APOE ε4 + DC was 4.338 ($p = 0.037$) and two-tailed Fisher's Exact test ($p = 0.046$) showed a significant risk of death in that group.

4. Discussion

We have demonstrated that significant more patients with the APOE ε4 allele compared to non-ε4 underwent DC after sTBI. To our best knowledge, this has never been reported before.

The most essential pathophysiological processes following brain injury are brain swelling, increased ICP, insufficient oxygen delivery, reduced cerebral blood flow, ischemia and further brain edema. One of the aim of treatment is to interrupt this harmful cycle by controlling intracranial hypertension and maintaining an adequate blood and oxygen supply to meet the metabolic demands of the injured brain [16]. DC is one option in the treatment of elevated ICP and can clearly be life-saving in the presence of medically intractable ICP levels [1,2,12,17,20,26,27,36,40].