

Prediction value of genetic and neuromarkers in blood and liquor in patients with severe traumatic brain injury

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- I. A. Olsson, L. Csajbok, M. Öst, Höglund, K. Nylén, L. Rosengren, B. Nellgård and K. Blennow. Marked increase of β -amyloid₍₁₋₄₂₎ and amyloid precursor protein in ventricular cerebrospinal fluid after severe traumatic brain injury. *Journal of Neurology* (2004) 251:870–876
- II. M. Öst, K. Nylén, L. Csajbok, A. Olsson, O. Öhrfelt, M. Tullberg, MD, C. Wikkelson, P. Nellgård, L. Rosengren, K. Blennow and B. Nellgård. Initial CSF total tau correlates with 1-year outcome in patients with traumatic brain injury. *Neurology* (2006) 67:1600–1604
- III. M. Öst, Nylén, L. Csajbok, K. Blennow, L. Rosengren and B. Nellgård. Apolipoprotein E polymorphism and gender difference in outcome after severe traumatic brain injury. *Acta Anaesthesiologica Scandinavica* (2008) 52:1364–1369
- IV. M. Öst, L. Csajbok, K. Nylén, K. Blennow and B. Nellgård. CSF concentrations of glial fibrillary acidic protein and neurofilament light correlate with 1-year outcome after severe traumatic brain injury. *Submitted for publication* (2015)



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ABSTRACT

Background: Severe traumatic brain injury (sTBI) is the most common cause of mortality in young adults. sTBI induces variable brain damage, invisible in Computer Tomographic scans early post-trauma. Further, neurology is difficult to evaluate in sedated patients. Therefore, biochemical neuromarkers (BNMs) in blood or cerebrospinal fluid (CSF) may be valuable tools to both evaluate trauma and to prognosticate patient outcome.

Aims: The aim of the thesis was to evaluate if concentrations of the BNMs; Glial Fibrillary Acid Protein (GFAP, CSF, study IV), Neurofilament light (NFL, CSF, study IV), Tau (CSF, study II), β -amyloid (1-42) and amyloid precursor-proteins (CSF & plasma, study I) were enhanced after a sTBI. Further, we investigated if these levels were correlated to outcome, neurology and patient ability of daily living 1-year post-trauma. Finally, we explored if patient-genotype, specifically Apolipoprotein E, (*gene APOE*), influenced 1-year outcome in sTBI-patients, (plasma, study III).

Methods: Patients were consecutively included if; aged ≥ 7 years, < 9 in Glasgow Coma Scale, receiving an indwelling ventricular catheter allowing CSF sampling), were artificially ventilated and admitted to the Neurointensive care unit (NICU) within 48h post-trauma. NICU-care was performed according to a standardized protocol. CSF samples were collected on days 0-4, 6, 8 and once on days 11-18. Surviving patients were assessed at 1-year evaluating; 1) outcome by Glasgow Outcome Scale (GOS), 2) neurology and 3) activities of daily living. NFL, GFAP, Tau, β -amyloid (1-42) and amyloid precursor-proteins were all analyzed by ELISA-methods. *APOE* genotyping was performed by polymerase chain reaction and solid-phase mini-sequencing.

Results: During the inclusion period, patients (n=28-96) were included into studies I-IV for CSF and/or blood sampling. Study I; β -amyloid (1-42) and amyloid precursor-proteins increased from day 0 until day 11 in the CSF, but not in plasma. In study II we found enhanced levels of CSF-Tau on days 2-3 correlated to mortality (GOS 1) at 1-year. In study III we found that patients with *APOE allele 4* had worse outcome (GOS) at 1-year. Finally, in paper IV we found increased CSF levels of GFAP and NFL both correlating to outcome (GOS) at 1-year.

Conclusions; In this thesis we have found in sTBI-patients that genetic and BNMs in the plasma and/or CSF correlate to outcome at 1-year post-trauma. The result may be clinically applicable to prognosticate outcome and influence treatment paradigms in these patients.

Keywords; *Traumatic brain injury, outcome, NFL, GFAP, tau, β -amyloid, apolipoprotein E, biochemical neuromarkers.*