



**Karolinska
Institutet**

Department of Clinical Neuroscience

On Biomarkers in Traumatic Brain Injury

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Kugelbergsalen, Neurohuset U1 Karolinska Universitetssjukhuset Solna, Stockholm

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ABSTRACT

Traumatic brain injury (TBI) is a common cause of death and disability. Unfortunately, TBI patients will be affected by secondary insults, such as hypoxia and increased intracranial pressure, which may lead to secondary brain injuries. Because of this, these patients are treated in specialized neuro-intensive care units (NICU) where the brain is monitored in order to prevent secondary lesion development. Cerebral monitoring is limited by its locality and more generalized markers to monitor the injured brain are warranted. Biomarkers have been introduced in the field of TBI, where they may be evaluated to examine potential pathophysiological processes. S100B, a primarily astrocytic protein, is the most studied serum biomarker in TBI, but other candidates exist. The aims of this thesis were to validate biomarkers toward long-term functional outcome, to evaluate the effect of biomarkers and a new global method of microdialysis in multimodal monitoring of NICU patients and in a translational methodology assess how biomarkers may facilitate in the damage analysis in a hypoxic-TBI animal model.

In **Paper I**, a retrospective study including 265 NICU TBI patients, where S100B samples were acquired at admission and every 12 hours the first 48 hours after injury, we detected a significant, and independent, correlation between S100B levels and long-term functional outcome. The predictive capabilities increased sharply after 12 hours and remained high up to 36 hours after injury. S100B levels were only significantly correlated to pathology detected on computerized tomography (CT) and not to extracranial trauma.

In **Paper II**, a retrospective study including 250 NICU TBI patients, we analyzed S100B samples acquired later than 48 hours after injury. We noted that secondary increases of S100B even as low as $0.05\mu\text{g/L}$ is sensitive and specific enough to detect radiological verified cerebral deteriorations, undetected by conventional monitoring.

In **Paper III**, a prospective study including 14 NICU TBI patients, we monitored patients using microdialysis (MD) in flowing cerebrospinal fluid (CSF) for a more “global” overview of cerebral metabolism. We validated the method using conventional CSF samples, and found that the MD-CSF method yielded adequate results. Also, albeit a small sample size, we noted that lactate and pyruvate levels were significantly elevated in patients with an unfavorable outcome.

In **Paper IV**, a retrospective study including 182 NICU TBI patients, we analyzed serum and CSF levels of Neurofilament light, a protein of axonal origin thus different from S100B. We showed that NFL levels significantly correlated independently to outcome, even in the presence of S100B. However, we could not correlate NFL levels to injuries visible on CT and magnetic resonance imaging (MRI).

In **Paper V**, a preclinical study including 73 Sprague-Dawley rats, we analyzed how hypoxia exacerbates TBI. We detected increased neuronal death using immunohistochemistry and increased lesion size on MRI in the hypoxic animals compared to normoxic animals. A trend was found towards higher S100B levels in serum after 24 hours in the hypoxic group. Vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1-alpha (HIF1 α) expressions were significantly increased in the normoxic group.

In summary, the biomarker S100B provides important information towards long-term outcome, even more so than other known predictors of long-term outcome. Outcome prediction models including both S100B and NFL presents the highest explanatory variance, presumably by monitoring different pathophysiological processes. S100B is a valuable asset in the multimodal monitoring in order to detect secondary cerebral injuries and together with the MD-CSF technique; it could improve conventional NICU care with a more global approach. Hypoxic insults following TBI aggravate injury development and this pathophysiological process could presumably be monitored using S100B as an indicator of injury severity.