Blood biomarkers for traumatic brain injury

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i Torgny Segerstedt, Göteborgs Universitets huvudbyggnad i Vasaparken, fredagen den 4 december 2015 kl 13.

av

Pashtun Shahim

Fakultetsopponent:
Associate Professor David L Brody, MD, PhD
Washington University School of Medicine, Department of Neurology
Saint Louis, MO, USA

Avhandlingen baser på följande delarbeten:

I. **Shahim P**, Tegner Y, Wilson DH, Randall J, Skillbäck T, Pazooki D, Kallberg B, Blennow K, Zetterberg H. *Blood biomarkers for brain injury in concussed professional ice hockey players*. JAMA Neurology 2014; **71**(6): 684-92.

II. **Shahim P**, Linemann T, Inekci D, Karsdal MA, Blennow K, Tegner Y, Zetterberg H, Henriksen K. *Serum tau fragments predict return to play in concussed professional ice hockey players*. Journal of Neurotrauma 2015; doi: 10.1089/neu.2014.3741.

III. Siman R, **Shahim P**, Tegner Y, Blennow K, Zetterberg H, Smith DH. *Serum SNTF increases in concussed professional ice hockey players and relates to the severity of postconcussion symptoms*. Journal of Neurotrauma 2015; **32**(17): 1294-300.

IV. **Shahim P**, Mattsson N, Macy EM, Crimmins DL, Ladenson JH, Zetterberg H, Blennow K, Tegner Y. *Serum visinin-like protein-1 in concussed professional ice hockey players*. Brain Injury 2015; **29**(7-8): 872-6.

V. **Shahim P**, Gren M, Liman V, Andreasson U, Norgren N, Tegner Y, Mattsson N, Andreasen N, Öst M, Zetterberg H, Nellgård B, Blennow K. *An ultrasensitive method for quantitating serum neurofilament light protein after traumatic brain injury*. Submitted.

UNIVERSITY OF GOTHENBURG

Blood biomarkers for traumatic brain injury

Pashtun Shahim

Department of Neurochemistry

Institute of Neuroscience and Physiology

Sahlgrenska Academy University of Gothenburg

Abstract

Traumatic brain injury (TBI) is the major cause of death and disability following blunt head trauma. The term mild TBI (mTBI) or concussion are used interchangeably in the literature. Concussion or mTBI is recognized as a clinical syndrome caused by biochemically induced alterations of brain function secondary to head trauma, typically affecting memory and orientation and may involve loss of consciousness. The diagnosis of mTBI is mainly based on clinical symptoms. Objective tools such as computed tomography or magnetic resonance imaging are mainly used to exclude structural brain damage, e.g., intracranial bleeding.

Biomarkers are molecules that can be measured in accessible biological fluids, that reflect physiological, pharmacological, or disease processes and can suggest the etiology of, susceptibility to, activity level of, or progress of a disease.

The overall aim of this dissertation was to assess both novel and previously studied blood biomarkers reflecting neuronal injury and dysfunction in individuals with mild to severe traumatic brain injury (sTBI). The main research question we sought to answer was whether mTBI was associated with biomarker evidence of axonal injury. For this purpose we used sera from ice hockey players competing in the Swedish Hockey League. In addition, we developed a novel ultrasensitive digital ELISA based on Single molecule array (Simoa) platform for detection of neurofilament light protein (NFL) in serum. NFL is a neuron-specific protein, which is difficult to measure in blood using standard immunochemical techniques due to suboptimal analytical sensitivity. We assessed the diagnostic and prognostic utility of this assay in patients with sTBI, who were treated at the Neurointensive Care Unit at the Sahlgrenska University Hospital.

The main findings of these studies were that mTBI in professional ice hockey players is associated with altered serum levels of biomarkers associated with neuronal injury. The levels of these biomarkers were also related to the number of days it took for the athletes to return to play. In the context of sTBI, NFL levels assessed in serum showed high diagnostic accuracy, and the levels in serum were also related to overall clinical outcome at follow-up 12 months after the injury.

Our overall conclusion is that the novel blood biomarkers presented in this thesis are promising diagnostic and prognostic tools for mild to severe TBI. Furthermore, the findings of this thesis may be extended to other neurological disorders associated with axonal injury, where tracking disease progression and evaluating the efficacy of novel therapy were previously limited to analyses of cerebrospinal fluid.