M U N I

COMMENTARY TO HABILITATION THESIS

Factors with a negative impact on the overall outcome of treatment in patients with severe brain injury

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1. Brief characteristic of the investigated matter

1.1. General information

The presented habilitation thesis represents over two decades of the author's profound interest in the field of severe brain injuries and their consequences.

Severe traumatic brain injuries (GCS ≤ 8) (TBI) represent a significant medical challenge, characterized by high morbidity and mortality rates. These injuries often lead to long-term neurological deficits, cognitive impairments, and a reduced quality of life for patients. The pathophysiology of severe brain injuries is multifactorial, involving primary damage from the initial trauma and secondary injury mechanisms such as ischemia, inflammation, oxidative stress, and excitotoxicity. Historically, it was thought, that some aspects of these secondary processes could not be influenced, but on the other hand, they have been shown to contribute significantly to the generally poor prognosis of these TBI patients.

1.2. Compromised Host Defence Mechanisms

However, emerging research suggests that previously underestimated factors - such as subtle biochemical cascades, microvascular dysfunction, and epigenetic modifications - may play a pivotal role in determining patient outcomes. For instance, recent studies have highlighted the potential influence of neuroinflammation and blood-brain barrier disruption in exacerbating neuronal damage. Additionally, advances in neuroimaging and biomarker analysis have provided new insights into the dynamic nature of brain injury progression, revealing opportunities for targeted therapeutic interventions.

While the overall prognosis for severe brain injuries remains poor, these findings underscore the importance of reevaluating traditional paradigms and exploring novel strategies to mitigate secondary injury mechanisms. By addressing these overlooked factors, there is potential to improve functional recovery and reduce the long-term burden of disability in affected patients.

Severe TBI can affect the homeostasis and integrity of the entire organism. This seems to occur through the hypothalamic-pituitary-adrenal axis. Another factor is the autocrine and paracrine release of cytokines and interleukins. One of the consequences of high levels of

catecholamines and corticosteroids and cytokine imbalance leading to an unfavourable overall treatment outcome may be the impairment of the immune system. Cortisol released during the acute stress response from the adrenal glands has a significant immunosuppressive effect.

1.3. Pathophysiology of secondary – ischemic brain injuries

Ischemia in brain tissue develops within minutes, so adequate and timely treatment is crucial. Patients with severe brain injuries are unable to adequately maintain airway patency and adequate spontaneous breathing. They are indicated for sedation and intubation, which immediately reduces the level of consciousness to three points. However, altered consciousness is one of the main indicators of increasing intracranial pressure. Intubated and sedated patients require multimodal monitoring. Standard multimodal monitoring involves invasive measurement of intracranial pressure, tissue oxygen levels (oximetry), and cerebral blood flow (CBF). A recent invasive monitoring technique is microdialysis. Invasive monitoring provides immediate data on the monitored variables and allows for timely responses to pathological changes. Measuring intracranial pressure is considered a global method. Although the sensor is always inserted in the Kocher's point for safety reasons, intracranial pressure values are comparable within the supratentorial space. The oximeter and the sensor for direct measurement of cerebral blood flow provide information from a small area of tissue located around the sensor. Therefore, it is important to implant the sensors, if possible, in the penumbra area. The last monitoring method is microdialysis. Its principle is to monitor the parameters of anaerobic glycolysis and excitatory amines released from broken-down cells. The last substance is diacylglycerol. Parameters are obtained from the plasma ultrafiltrate, the acquisition of which takes several minutes. A certain limitation of this monitoring method may be the time, during which the plasma ultrafiltrate is obtained.

A recent trend and the subject of further research by the author in the field of neurotrauma is the autoregulation of cerebral arteries and the determination of PRx.

2. Work Objectives

Weakened immune defences lead to an increased risk of developing extracranial inflammatory complications. Pneumonia, urinary tract infections, and subsequent sepsis worsen the course of treatment. In patients after craniocerebral injury, these inflammatory complications occur in statistically significant numbers. However, observations from previous years suggest that craniocerebral injuries do not cause simple immunosuppression, but rather an imbalance leading to immune dysfunction. The cellular component (T-lymphocytes) is primarily affected, while the humoral component is inadequately stimulated, with an excessive

synthesis of IgE antibodies. The imbalance is further influenced by the age of the patients and the localization of the injury. Another important factor is the extent of the injury, expressed by the initial GCS score. The immune defence of patients after severe craniocerebral injury changes gradually during hospitalization. In patients without infection, it gradually improves. An independent predictor of the severity of immune impairment is the severity of brain injury.

The basic principle of treating brain injuries is to influence intracranial hypertension. This arises from the acceleration of cytotoxic oedema or intracranial bleeding. Intracranial hypertension reduces cerebral blood flow and limits the supply of oxygen to the nerve tissue. The resulting ischemia exacerbates cytotoxic oedema and increases intracranial pressure. Secondary brain injury occurs. Brain tissue is generally very sensitive to oxygen deficiency. Terminal areas of the vascular bed with minimal collateral circulation are most at risk. Before definitive cell death occurs due to ischemia, brain cells enter a state with minimal energy and oxygen requirements; this part of the tissue is called the penumbra and represents a potentially salvageable area.

This thesis is focused on an acute consequence of an impaired immune system and host defence failure in the patients suffered from severe brain injury. Extracranial inflammatory complications, resulting from the immune system disorders, are demonstrated to be a strong independent factor of a poor outcome.

Secondary (ischemic) brain injuries belong to the influenceable part of early intensive care. Adequate and fast approach requires an adequate and a very certain information obtained from the impaired brain tissue. The saying, that time is brain seems to be truer than ever.

3. Applicant contribution

I hereby submit this habilitation thesis, which consists of a collection of 7 published peer-reviewed articles, that I have selected and commented on. I declare that I have made significant impact to all these articles. My contributions were as follows - conceptualization and design of the research, data collection and analysis, interpretation of results, writing and revising the manuscript

This habilitation thesis represents the culmination of my extensive and dedicated research in this field. I am confident that this work offers new and original insights that will contribute significantly to the advancement of the scientific domain.

Thank you for considering my habilitation thesis.

1. SMRCKA, M., **A. MRLIAN** and M. KLABUSAY. Immune system status in the patients after severe brain injury. *Bratislavské lekárske listy*. 2005, **106**(3), 144–146. ISSN 0006-9248.

Original publication. WoS classification: Medicine (miscellaneous) – SJR Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	10	90	40

2. **MRLIAN, Andrej**, Martin SMRCKA, Vilem JURAN, Ondrej NAVRATIL, Eduard NEUMAN and Kamil DURIS. Immune system disorders in the early post-injury period in patients after severe brain injury from the perspective of the severity of the injury. *Neurological Sciences* [online]. 2023, **44**(3), 1031–1038. ISSN 1590-3478. Available at: doi:10.1007/s10072-022-06482-1

Original publication. WoS classification: Neurology (clinical) Q2

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	10	99	40

3. **MRLIAN, A.**, M. SMRCKA and M. KLABUSAY. The importance of immune system disorders related to the Glasgow Outcome Score in patients after severe brain injury. *Bratislavske lekarske listy*. 2007, **108**(8), 329–334. ISSN 1336-0345.

Original publication. WoS classification: Medicine (miscellaneous) – SJR Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	10	90	50

4. **MRLIAN, A.**, M. SMRCKA and M. KLABUSAY. The use of controlled mild hypothermia and immune system status in patients with severe brain injury. *Bratislavské lekárske listy*. 2006, **107**(4), 113–117. ISSN 0006-9248.

Original publication. WoS classification: Medicine (miscellaneous) – SJR Q3

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
75	20	90	50

5. SMRCKA, M., **A. MRLIAN**, K. DURIS, J. KARLSSON-VALIK and M. KYR. IgE antibody serum level changes in patients after severe head injuries [Změny hladin IgE protilátek v séru u těžkého poranění mozku]. *Ceska a slovenska neurologie a neurochirurgie*. 2007, **70**(3), 259–265. ISSN 1210-7859.

Original publication. WoS classification: Surgery Q4

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	20	90	50

6. **MRLIAN, A.**, M. SMRCKA, M. DUBA, R. GAL and P. SEVCIK. The Use of Continuous Cerebral Blood Flow Monitoring after Severe Head Injury [Využití kontinuálního monitoringu průtoku krve mozkem po těžkém mozkovém poranění]. *Ceska a slovenska neurologie a neurochirurgie*. 2010, **73**(6), 711–715. ISSN 1210-7859.

Original publication. WoS classification: Surgery Q4

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40	50	90	50

7. MUZIKÁŘOVÁ, Sabina, **Andrej MRLIAN**, Martin SMRČKA and Vilém JURÁŇ. Multimodální monitoring u těžkých mozkových poranění. *Neurologie pro praxi*. 2021, 22(6), 466-470. ISSN 1213-1814.

Original publication. WoS classification: no classification

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	90	90	90