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ESICM LIVES 2023 MILAN

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Evidence-based, cerebroprotective treatment strategies in neurotrauma and delirium

Chair: Katarzyna Kotfis (Poland)

- **Can the devil be driven out of critically ill patients? – Introducing a new cerebroprotective treatment option**
  Wojciech Dabrowski (Poland)
- **Multimodal treatment strategies for TBI patients – Why do we need them?**
  Helmut Trimmel (Austria)

General information

The **European Society of Intensive Care Medicine (ESICM)** organized one of the largest congresses in this field of medicine with over 6,000 delegates. EVER Pharma took part for the first time with a satellite symposium. The management of severe traumatic brain injury and delirium were the topics discussed and presented in connection with Cerebrolysin.

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Katarzyna Kotfis

Dr.
University Szczecin, Poland

Introduction

The moderator, Dr. Katarzyna Kotfis, Professor in Anesthesiology and Intensive Care Medicine at Pomeranian Medical University in Szczecin, Poland, emphasized the importance of the two presentations by Dr. Trimmel and by Dr. Dabrowski.

Dr. Kotfis expertly guided the speakers and the audience through the symposium, which was very well attended and led to many interesting and meaningful discussions about the clinical development of Cerebrolysin in the indications presented.

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Wojciech Dabrowski

MD, PhD
First Department of Anaesthesiology and
Intensive Therapy Medical University of Lublin, Poland

Can the devil be driven out of critically ill patients? – Introducing a new cerebroprotective treatment option

ABSTRACT

Delirium is an acute alteration in mental status characterized by confusion, inattention and a fluctuating level of arousal. It is a serious clinical problem that is associated with prolonged hospital stay and an increased risk of mortality. The pathomechanisms of delirium are not well recognized, however a disturbances in the cholinergic system, dopamine synthesis, neuronal plasticity, inflammation and oxidative stress following cerebral ischemia or hyperoxia appear a key role in this process. A lot of drugs have been tested to reduce or treat delirium. Some of them have been shown to reduce brain disorders that can cause delirium. From this point of view Cerebrolysin seems to be the most effective drugs. It improves neuronal plasticity, attenuates post-ischemia disorders, improves cholinergic activity and attenuates post-ischemic disorders reducing the severity of oxidative stress. Hence, it may be useful in prevention and treatment of delirium. A single-center study documented that Cerebrolysin significantly reduces the risk of postoperative delirium in cardiac surgery patients. The adjunctive treatment with Cerebrolysin significantly improves neuropsychological outcome in septic shock patients, reducing the risk of delirium and subsequent the length of stay in the intensive care unit. The use of Cerebrolysin in patients undergoing abdominal surgery at high risk of delirium significantly reduced the incidence of postoperative neuropsychological disorders and improved circadian rhythm. All these results suggest that Cerebrolysin may be effective drug for prevention and treatment of delirium in critically ill patients. Interestingly, the properties of Cerebrolysin also suggest, that its administration from the first day of treatment in the intensive care unit (ICU) may effectively prevent delirium in critically ill patients, however this hypothesis should be confirmed in a large clinical trials.

LECTURE SUMMARY

In the second part of the symposium, a possible new indication for Cerebrolysin was presented, which affects several million patients worldwide every year with a rapidly increasing incidence - post-operative delirium (POD).

Dr. Wojciech Dabrowski, Professor of Anaesthesiology and Intensive Care at the Medical University of Lublin, Poland, began his presentation with a definition of delirium as a mental state in which patients are confused and disorientated and unable to think logically or remember clearly.

After outlining the extent of the problem *(figure 6)*, Dr. Dabrowski mentioned various risk factors, such as age, alcohol or drug abuse, protracted infections, and prolonged artificial respiration.

He then listed the pathomechanisms that lead to delirium *(figure 7)*, but which to date cannot be effectively treated with pharmacological agents such as haloperidol or benzodiazepines. Only dexmedetomidine has achieved a moderate level of recommendation in the guidelines.

Dr. Dabrowski made a strong plea for more intensive focus on agents that are able to address the various pathophysiological mechanisms of POD. He impressively demonstrated that the multimodal agent Cerebrolysin should be able to play a role in the treatment of this difficult medical complication *(figure 8)*. He also showed several neuroscience studies in which Cerebrolysin demonstrate the ability to reduce neuronal loss after ischaemia, improve neuronal plasticity, inhibit neuronal apoptosis, inhibit neurotransmitters dysfunction, improve dendritic cell activity, and improve memory.

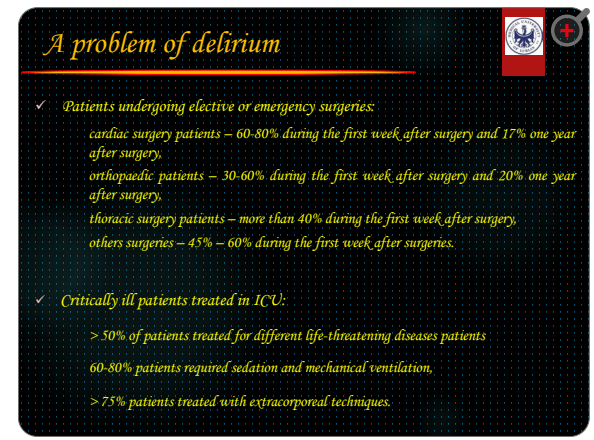

Figure 6

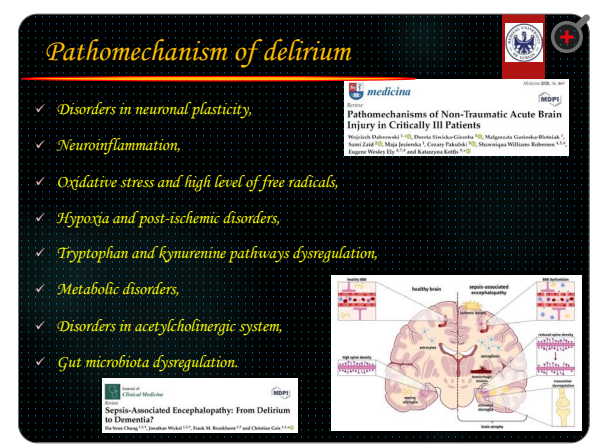

Figure 7

In the final part of his presentation, Dr. Dabrowski presented his own clinical experience with the use of Cerebrolysin in POD patients, with each individual example showing a very impressive reduction in symptoms.

He began by presenting the preliminary results of a study that is currently being analysed.

The patients treated with Cerebrolysin showed a significantly lower incidence of POD – 2 out of 30 patients treated with Cerebrolysin developed delirium compared to 8 out of 20 patients in the control group. The duration of delirium was also significantly shorter in the Cerebrolysin group *(figure 9)*. The full results of the study will be published shortly.

Dr. Dabrowski also showed the results of a small case series and the overall benefit of treatment with Cerebrolysin using data from his hospital records, and concluded with the following messages:

- Delirium is a serious problem in all hospitalised patients.
- Cerebrolysin reduces the symptoms of delirium and improves outcome.
- Cerebrolysin may improve circadian rhythm.
- Cerebrolysin appears to be a promising drug for the treatment of delirium.
- A large international study should be conducted to confirm this indication for Cerebrolysin.

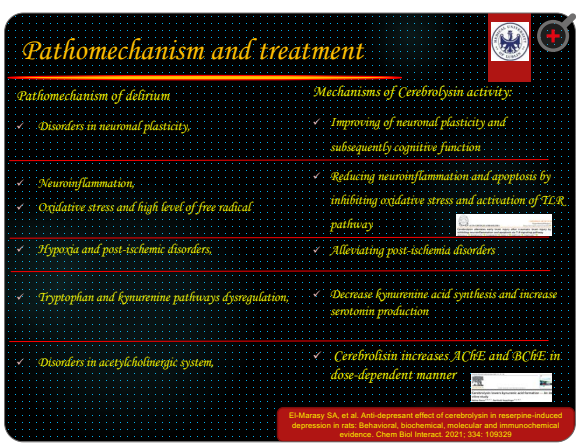

Figure 8

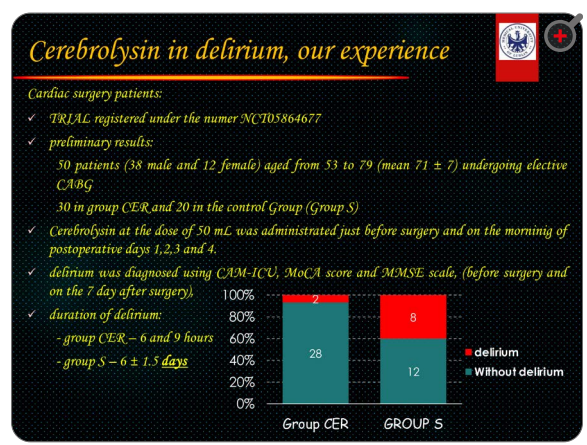

Figure 9

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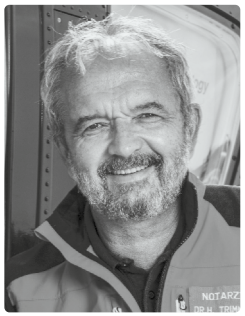

Helmut Trimmel

Prof. Dr.
Landesklinikum Wiener Neustadt, Austria

Multimodal treatment strategies for TBI patients – Why do we need them?

ABSTRACT

Traumatic brain injury (TBI) affects over 10 million people each year, causes more lost productive years of life than any other disease and is the leading cause of death and disability in people under the age of 45. In particular, cognitive deficits and depression are frequent consequences. Stringent treatment and rehabilitation concepts are crucial. In addition to the primary injury, secondary damage is a focus of current research and treatment strategies: following the trauma, increased glutamate levels lead to excitotoxicity, cellular and humoral immune response is strongly activated and the integrity of the blood-brain barrier (BBB) is disrupted. The consequences are excessive neuroinflammation, unbridled excitation spread over the cortex, excessive cellular influx of Ca++ and Na+ with cerebral edema formation, disruption of the energy balance, apoptosis and cell death. However, there are also regenerative processes in the injured brain: neurotrophic factors initiate repair of damaged cell membranes, sealing of the BBB and protection of the mitochondrial energy supply; Neurogenesis, angiogenesis and neuroplasticity are stimulated. Current guidelines (e.g. Brain Trauma Foundation) provide clear recommendations for surgery, emergency and intensive care treatment. They essentially focus on limiting intracranial pressure, maintaining cerebral perfusion, reducing cerebral oxygen consumption and the homeostasis of the organism in the acute and post-acute phases. Nevertheless, the use of neurotrophic substances is controversial, despite promising preclinical and clinical data. This presentation discusses the use of the most interesting clinically available substances and provides current evidence for higher survival rates, shorter intensive care stays and better cognitive outcomes.

LECTURE SUMMARY

Professor Dr. Helmut Trimmel, from Wiener Neustadt Regional Hospital began his lecture on multimodal treatment strategies for severe TBI patients with a reference to the high and increasing epidemiological burden of neurotrauma worldwide. No other disease costs more productive lives worldwide than traumatic brain injury.

He continued by pointing out what makes traumatic brain injury such a complex and heterogenous medical problem *(figure 1)*, which – as a consequence – requires a high degree of multimodal treatment, including neuroprotection and neuroregeneration *(figure 2)*.

In discussing the various treatment algorithms for TBI, Dr. Trimmel emphasized the importance of:

- Ensuring cerebral blood flow (CBB) and cerebral perfusion pressure (CPP)
- Reduction of cerebral oxygen metabolisms (CMRO2)
- Reduction of oedema
- Maintenance of homeostasis.

These could be specific therapeutic targets for neuroprotective agents such as Cerebrolysin, which could have a positive effect on resilience to brain injury - a new approach in neuroprotection.

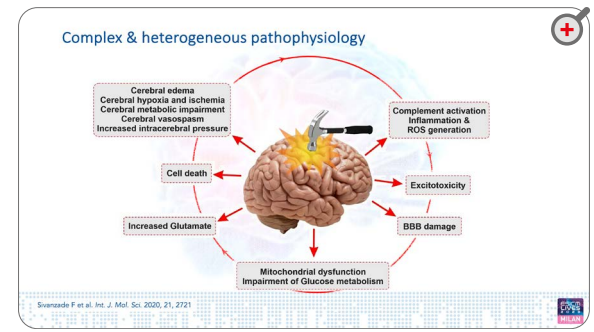

Figure 1

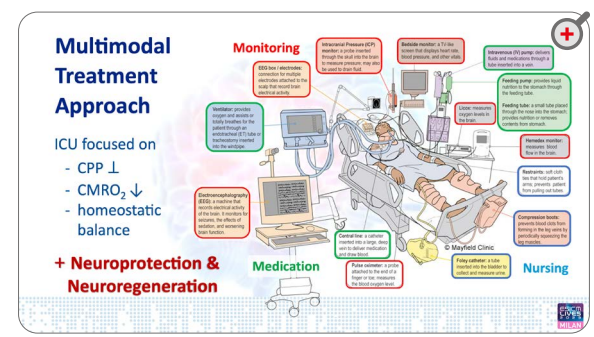

Figure 2

In the final part of Dr. Trimmel's presentation, different processes following brain injury were linked to various preclinical studies with Cerebrolysin *(figure 3)*, demonstrating the multimodality of the compound at different time points *(figure 4)*. Dr. Trimmel then briefly reviewed the results of the CAPTAIN study, which not only showed a significantly positive overall outcome, but also particularly strong data in areas often overlooked in patients with traumatic brain injury – cognition, depression and anxiety, and attention deficits.

He concluded his presentation with a reference to the recent inclusion of Cerebrolysin in the Canadian ERABI guideline for the improving attention function with a 1b recommendation *(figure 5)*.

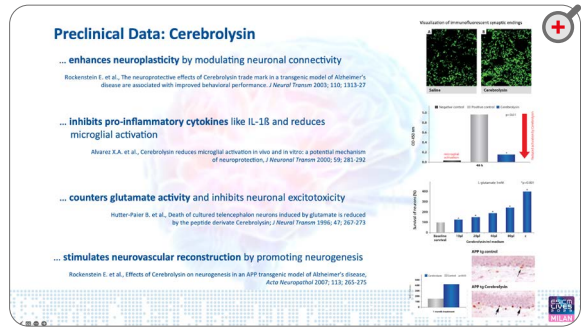

Figure 3

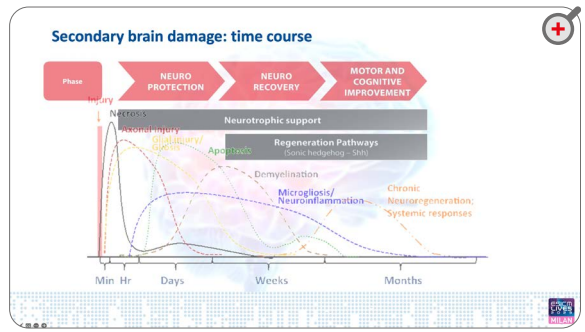

Figure 4

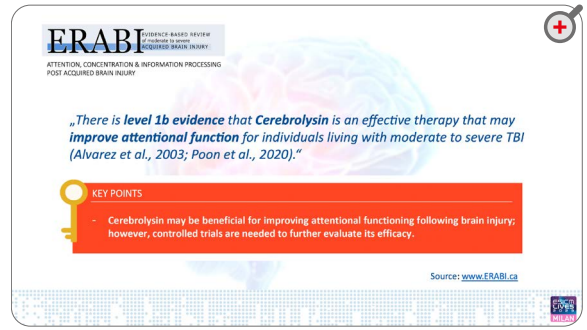

Figure 5

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ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin - Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of Cerebrolysin concentrate in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: For treatment of cerebrovascular disorders. Especially in the following indications: Senile dementia of Alzheimer's type. Vascular dementia. Stroke. Craniocerebral trauma (commotio and contusio). Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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