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Acute and longterm neurorecovery after TBI

May 18, 2021

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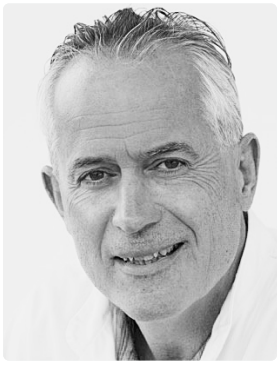
Webinar EVER Pharma (May 18, 2021)

Acute and longterm neurorecovery after TBI

Participants



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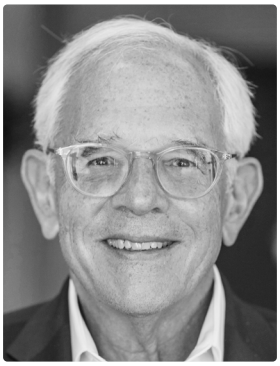

Michael Chopp

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Topic: **Exosomes mediate the therapeutic benefit of Cerebrolysin for TBI**

Christian Matula

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Topic: **Advances in acute Neurotrauma treatment**

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Topic: **Long-term neurocognitive consequences of TBI – The CAPTAIN-trials**

Order of the webinar

Exosomes mediate the therapeutic benefit of Cerebrolysin for TBI

M. Chopp

The elucidation of benefits of Cerebrolysin treatment, as well as the mechanisms through which Cerebrolysin mediates its benefits as a highly effective neurovascular therapeutic treatment in traumatic brain injury (TBI) and stroke, is a continuous effort undertaken by Dr. Chopp's group at Henry Ford Healthcare System. The results of the most recent investigations were summarized in his lecture. Cerebrolysin has been studied in several well-established animal models of TBI, including moderate closed head injury (CHI, classic Marmarou model).[1] The treatment was initiated 4 hours after the injury and lasted for 10 days. Among the functional outcomes measured, was the Morris Water Maze behavior. In this model, the injured animals swim in the pool and have to find the hidden (underwater) platform. Normal animals can find the platform quickly but injured animals spend a much longer time searching for the platform, indicative of a compromised ability to learn the spatial cues. In the same environment, the injured animals spend a much longer time finding the platform, indicative of a compromised ability to learn the spatial cues. However, Cerebrolysin treated injured animals are no different than sham animals in the speed of learning. Another functional aspect highly relevant for TBI is social behavior, as many TBI patients get depressed and lose their normal social capacities. In the Three Chamber Test, Cerebrolysin fully restored social interactions suppressed by the closed head injury and resulting in the lack of curiosity and drive to meet and interact with other animals (**Fig. 1**).

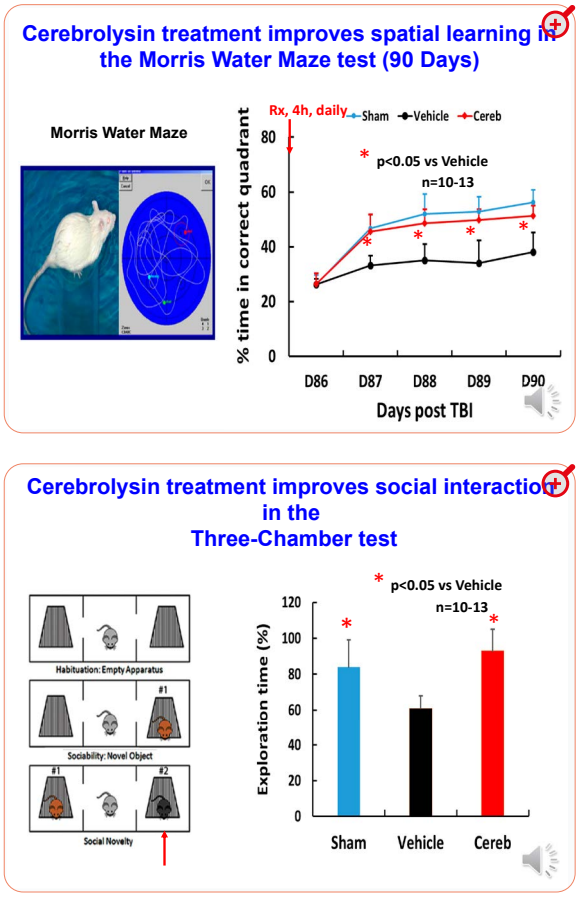

Fig. 1. Impact of Cerebrolysin on spatial learning and social behavior in animals suffering from CHI

The structural and molecular changes induced by Cerebrolysin, were also examined. For example, the axonal integrity can be measured with the phosphorylated neurofilament factor (pNfH+). When this parameter was assessed in various brain regions, like the dentate gyrus, hippocampus, and cortex, there were no differences between the sham and the Cerebrolysin treated injured animals. However, the injured animals' brains suffered from highly damaged axonal structures in the absence of Cerebrolysin, when assessed 90 days post-TBI. One of the toxic protein conglomerates described in the literature as closely associated with TBI, Alzheimer's disease, and dementia is amyloid precursor protein (APP). Cerebrolysin was shown to prevent the accumulation of APP in the same key functional brain structures. Again, no difference was noted in comparison with sham/control animals in the Cerebrolysin treated CHI animals after 90 days (**Fig. 2**).

What is mediating this therapeutic benefit of Cerebrolysin seen at the functional and physiological levels? To address this matter, Dr. Chopp investigated the relationship between Cerebrolysin treatment and nanoparticles (exosomes) that are produced by endothelial cells of the brain's vascular system. They contain various proteins, messenger RNAs (mRNAs), and also micro RNAs (miRNAs). These little (30-130 nm in size) bilipid layer structures protect and contain a significant amount of information and act as the vehicles in the intercellular communication controlled by the vascular system. First, Dr. Chopp described Cerebrolysin's impact on inflammatory processes affecting the brain's vascular system and blood brain barrier (BBB) integrity. Then, he related these findings to research showing the role of Cerebrolysin in modifying the exosomes-mediated intercellular communication.

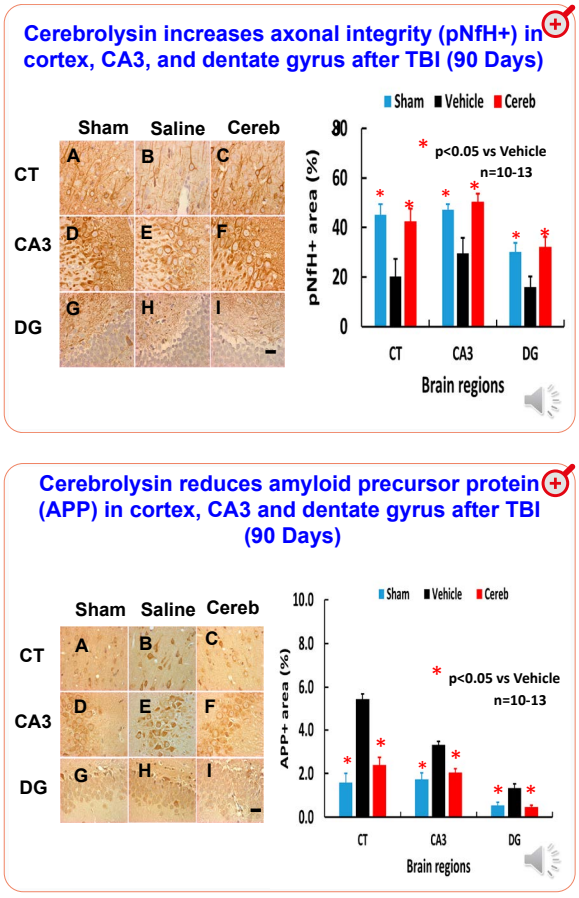

Fig. 2. Cerebrolysin preserves the key brain structures in experimental animals after CHI

After TBI or stroke, the vasculature of the brain becomes pro-coagulant, pro-inflammatory, and pro-thrombotic. In this state, the vasculature promotes secondary brain injuries, while aggravating and further extending the functional deficits of a patient. Dr. Chopp's experimental work showed that Cerebrolysin counteracts these pathological changes and promotes neurorecovery. He shared with the audience the key experimental data leading to this conclusion. After a closed head injury, there is a significant buildup of fibrin within the brain of the studied animals. Fibrin acts toxically, leading to increased production of pro-inflammatory cytokines, like IRAK1, PAI-1, and NF-kB by the endothelial cells. This, in turn, leads to increased vascular permeability. In the in vitro experimental model of blood-brain barrier (BBB) integrity, the layer of the human brain endothelial cells was subject to treatment with fibrin and the leakage of the fluorescent dye through this layer was measured. Cerebrolysin showed a significant dose-dependent protection effect against fibrin-induced cellular leakage. This set of experiments also showed that Cerebrolysin reduces the production of the pro-inflammatory cytokines induced by fibrin (e.g. HMGB1, TNF alfa, NF-kB). In effect, Cerebrolysin reduces the inflammatory response within the endothelial cells and reverses the fibrin-dependent damage to BBB. Concomitantly, the delayed (to 24hours) administration of Cerebrolysin increases the numbers of the endothelial cell tight-junction proteins (reduced by fibrin deposits) and reduces the levels of ICAM1, the adhesion molecule responsible for the adhesion of inflammatory cells to the vasculature. In these experiments, Cerebrolysin protected the integrity of the vasculature counteracting the inflammatory processes triggered by an injury within the brain tissue (**Fig. 3**).

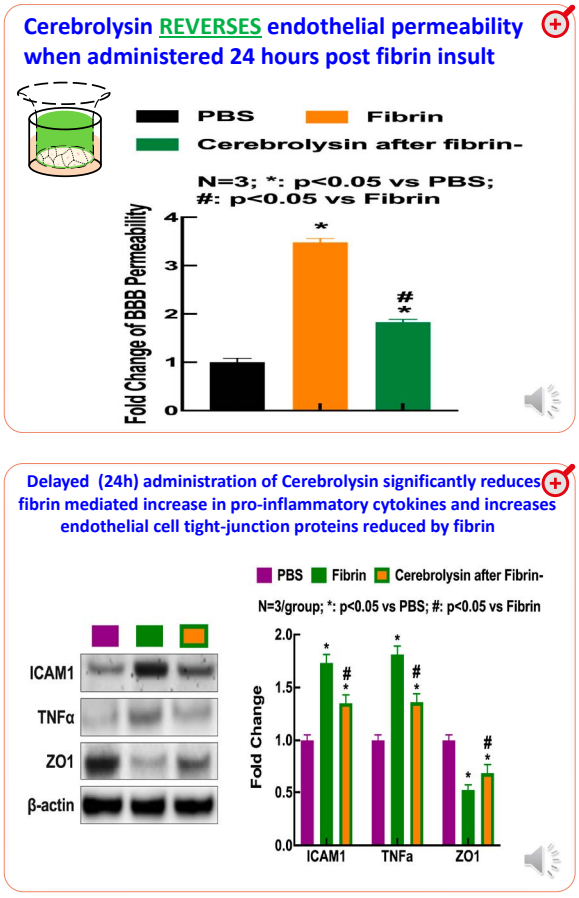

Fig. 3. Cerebrolysin reverses fibrin-dependent damage to BBB in the experimental models of brain injury

Dr. Chopp's team has found that the endothelial cells treated with Cerebrolysin generate exosomes that mediate the described here therapeutic effects (**Fig. 4**). To find out what kind of information do these exosomes contain, Dr. Chopp conducted the proteomics study in which 1,942 total proteins were identified. The exosomes derived from the endothelial cells treated with Cerebrolysin contained 567 proteins that were increased and 87 that were decreased in comparison with the exosomes derived from the untreated cells. The investigators found that the Cerebrolysin-induced proteins were associated with cell junction and cellular energy metabolism as well as represented proteins active in various metabolic pathways and endocytosis signaling. The downregulated proteins represented the pro-inflammatory proteins and coagulation factors as well as those associated with coagulation cascades and synaptic vesicle cycle signaling. This study confirmed, that Cerebrolysin generates exosomes within the vasculature which, in turn, act as strong multimodal therapeutic agents (**Fig. 4**).

The take-home message is that Cerebrolysin has a profound effect on the vasculature in the animal models of brain injury. It reduces endothelial permeability as well as the pro-inflammatory and pro-thrombotic protein expression induced after the brain injury by fibrin. It protects and restores the endothelial function which underlies the integrity of BBB. Finally, Cerebrolysin mediates these therapeutic effects via exosomes that are produced in response to Cerebrolysin treatment. This is probably the most interesting and transformative finding in Cerebrolysin's research to date, as the observed therapeutic effects of Cerebrolysin are secondary to the exosomes that are generated as a result of Cerebrolysin treatment.

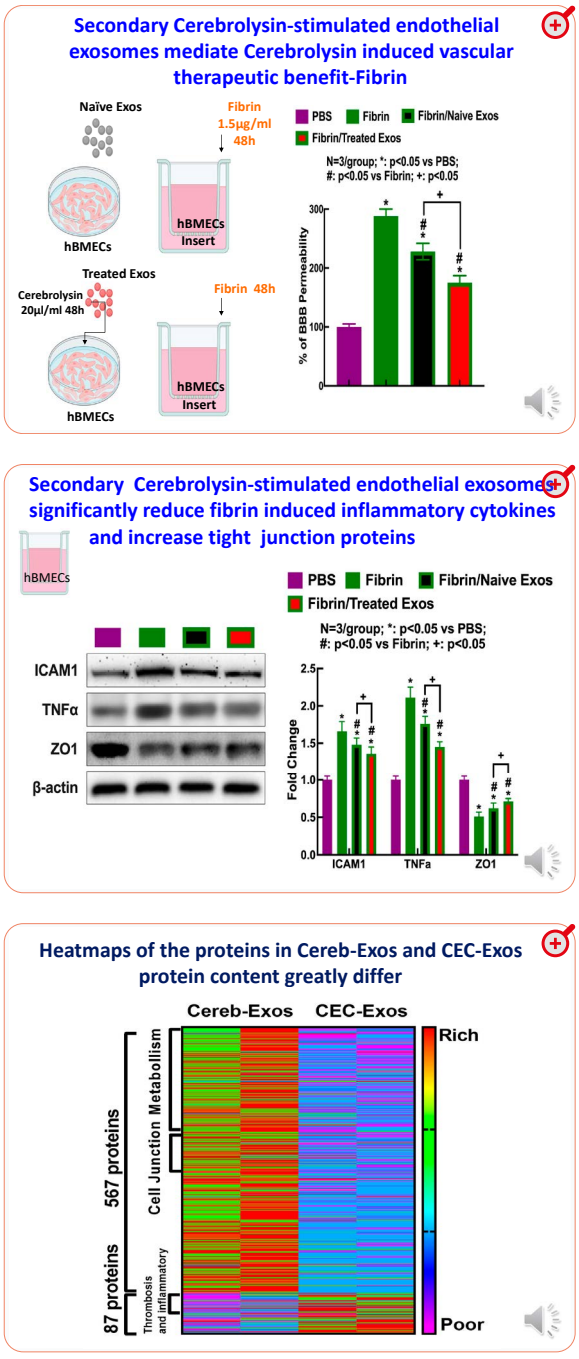

Fig. 4. Cerebrolysin-induced exosomes mediate its benefits in the experimental models of brain injury

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1. M.A. Foda, A. Marmarou. J Neurosurg 1994 Feb;80(2):301-13. doi: 10.3171/jns.1994.80.2.0301.
2. N.J. Abbott et al., Neurobiol Dis. 2010 Jan;37(1):13-25. doi: 10.1016/j.nbd.2009.07.030.
3. All published and unpublished experimental data - curtesy Michael Chopp et al.

Advances in acute Neurotrauma treatment from the neurosurgeon's perspective

Ch. Matula

In the '50s and '60s, TBI was considered a surgeon's disease and the focus was on decreasing the intracranial pressure (IP) and maintenance of the cerebral perfusion pressure (CPP) employing the craniotomy to evacuate the hematoma. Neurosurgery did not exist at that time and the procedures were performed by specialized general surgeons. Nowadays, after the implementation of pharmacological therapies and big advances in neuroscience, TBI is viewed more as a cytopathological disease. Especially, the last decade witnessed the explosion of research in various related areas, including a better understanding of ICP reduction by mass removal, awareness of the role of ischemia, mechanisms of brain edema, and better understanding of mechanisms of secondary injury based on cellular physiology. The pharmacological therapies were attempted leading to discussions about the meaning of cerebral protection and recovery. The improved ICP monitoring systems, increased knowledge about cerebral flow mechanisms, while multimodal monitoring systems, as well as microdialysis became part of the clinical routine.

For a neurosurgeon, the reduction of mass lesions is still the primary focus in the treatment of more severe TBI cases, but the second branch of useful modalities did emerge with the implementation of neurorecovery and neurorestoration.

When we consider the so-called neurotrauma classics (epidural hematoma, subdural hematoma, intracerebral bleeding, subarachnoid bleeding, diffuse swelling, and diffuse axonal injury), we have to understand that in the clinical reality the pathological picture is always very complex and cannot be contained within the narrow classification. It all happens at the same time (**Fig. 1**).

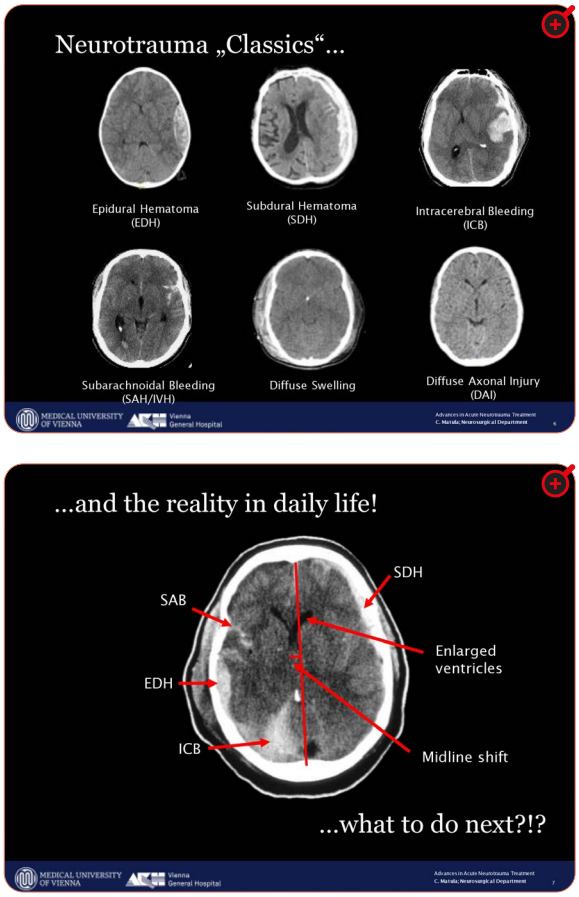

Fig. 1. The complexity of the TBI - it all happens at the same time!

Importantly, the damage is not only of primary nature, but also includes the secondary pathological mechanisms, like ischemia, reperfusion, hypoxia, swelling, and infection. The TBI is now seen as a sequence of events and the therapeutic intervention as resuscitation of the injured brain. It involves various identified biological and pathological response mechanisms underlying the primary and secondary injuries as well as the choice of therapeutic modalities aimed at minimizing the damage and enhancing the biological response to achieve improved outcomes. While the major enemies in neurotrauma are still hyper- and hypocapnia, hypoxia, and hypotonia, the key overarching problem with the treatment of TBI remains the time. The moment of intervention is crucial to break the chain of events leading to death: hypoventilation, hypercapnia, hypoia, increase in the intracerebral volume and increase in ICP. Even the most potent therapeutic will fail to bring its benefits if this "circle of disaster" is not broken by the timely intervention, said Dr. Matula. Therefore, the neurosurgeon's credo in severe TBI cases circles around intracranial pressure which grows exponentially after all "intracranial reserve" has been exhausted.[1] The primary goal is to prevent secondary brain damage (**Fig. 2**).

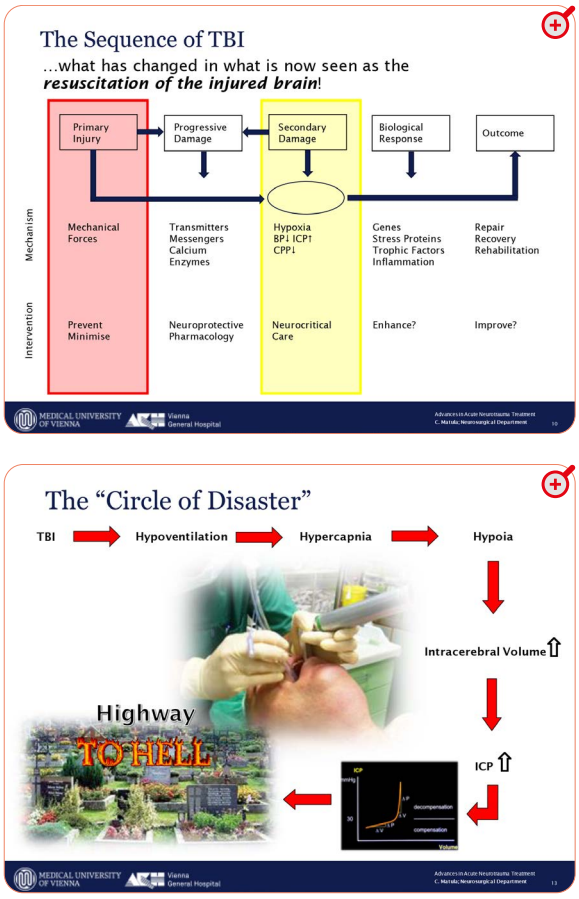

Fig. 2. The sequence of TBI and prevention of secondary injury as a major therapeutic target

Dr. Matula described the key phases of action within the interdisciplinary neurotrauma management team. The Acute or Reanimation Phase starts within 1-3 hours post-accident and involves classical life-saving acute surgery, the so-called 1st surgical phase. The Primary Phase starts between 4 and 72 hours and is called a stabilization phase. Many urgent surgery procedures in poly-trauma appear in this phase, which is also known as 2nd surgical phase. It is followed by the Secondary Phase lasting from 4 to 10 days post-trauma. It is a period during which most of the decompressive craniectomies occur (3rd surgical phase). Finally, the tertiary phase starts after 10 days and involves the rehabilitation and reconstruction phase (the 4th surgical phase). Among the main surgical options available, Dr. Matula listed: the primary evacuation of the mass lesion (EDH, SDH, ICH, penetrating trauma); the decompressive craniectomy with the removal of bone flap and opening of the dura to achieve additional reserve space; any kind of drainage systems, like ventricular drainage and lumbar drainage in case of skull base fractures and rhinorrhea; addressing the postoperative complications, like hydrocephalus (shunt); and reconstruction, including osteoclastic bony defects (e.g., Patient-Specific Implants, PSI), and also impression ("PingPong" fractures). These complicated procedures and processes are covered by clear guidelines for the treatment of TBI, which unfortunately quite often are not observed in clinical practice.[2] The complementary integrated approach to prevention, clinical care, and research emerged in recent years to further guide the practice and define priorities. Multimodal neuromonitoring is currently a reality in many centers and is affording us a completely different set of advantages in the care of patients with severe trauma (**Fig. 3**).

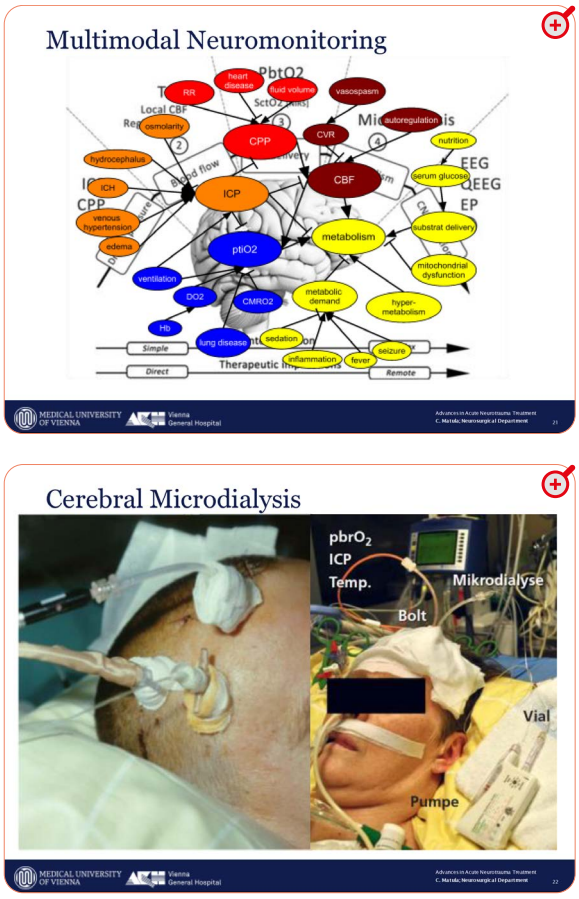

Fig. 3. The multimodal monitoring and cerebral microdialysis are the hallmarks of modern interdisciplinary TBI care

Neuro-intensive care includes interdisciplinary monitoring & therapy (e.g. anesthesia) and the use of contemporary statistical tools to identify the therapies associated with the best clinical outcomes. The continuous monitoring of intracranial pressure allows for the necessary control of the intracranial pressure therapy with the overall goal not to exceed 20 mmHg. The intracranial pressure probe allows for continuous ICP measurement. Finally, ventricular drainage allows to dispose off the excessive liquid and cerebral microdialysis allows for the control of the oxygen level.

In the final part of his lecture, Dr. Matula outlined the CAPTAIN trial project which addressed the issue of the heterogeneity and the inter-rater variability characteristic of clinical trials performed in this area of research. The primary aim of the CAPTAIN was to investigate the safety and efficacy of Cerebrolysin in patients with traumatic brain injury. Since its inception in 2011, four papers have been published by the researchers involved in this project (**Fig. 4**).

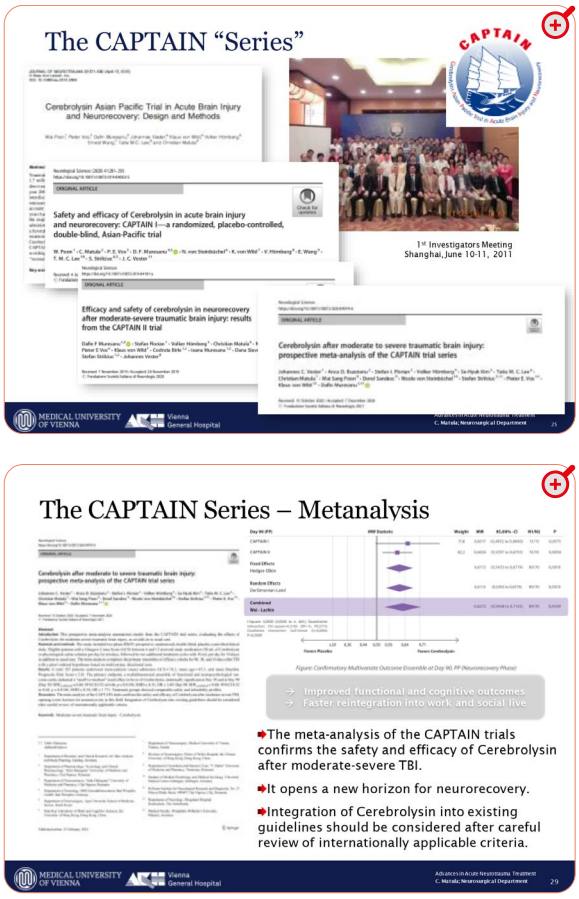

Fig. 4. The CAPTAIN trial series and its major related publications

The first step in this important endeavor was to prove that the novel methodology chosen for the trial, including the multidimensional analysis, is feasible. It showed that multidimensional analysis provides a new direction for clinical and statistical thinking. The CAPTAIN trial has been the first TBI trial with a "true" multidimensional approach based on full outcome scales while avoiding previous weaknesses, such as loss of information through 'dichotomization', unrealistic assumptions such as "normal distribution," or bias by insensitivity to outcome clusters. The first paper coming out gave mixed results, much to the surprise of the involved investigators, who expected better results. The data showed some beneficial effects of Cerebrolysin in the treated TBI patients, but the conclusion was to recommend confirming the results in a larger RCT of similar design. The CAPTAIN II trial was initiated and, in line with existing literature, confirmed the benefits of Cerebrolysin in moderate to severe TBI. Importantly, it also consolidated the case for the use of multimodal agents and the multidimensional approach in clinical research. The final act of the CAPTAIN series to date happened a few months ago with the CAPTAIN-series meta-analysis.[3] It showed the improved functional and cognitive outcomes after treatment with Cerebrolysin as well as a faster reintegration into work and social life, in the investigated group of moderate-severe TBI patients. From the trial design standpoint, the CAPTAIN trials concept opened a new horizon for neurorecovery after trauma and also resulted in the recommendation of the authors that the integration of Cerebrolysin into existing guidelines should be considered after careful review of internationally applicable criteria.

Regarding the opening of new horizons in the treatment of TBI, Dr. Matula mentioned also the paper by Olsen et al., 2021, in which the multidisciplinary character of neurotrauma care has been summarized. The multidisciplinary team approach is not only a big change in our thinking but also a big chance for improving our care of TBI patients (**Fig. 5**).

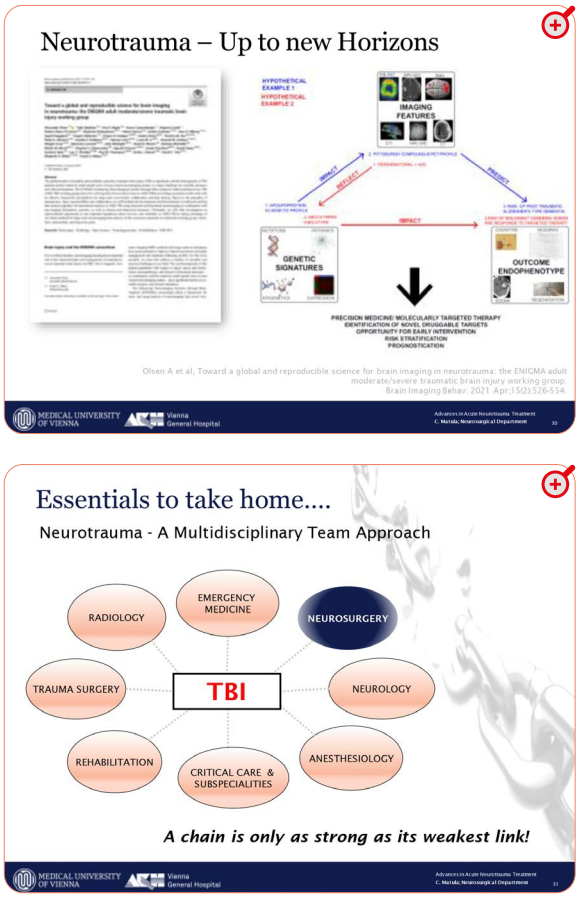

Fig. 5. Towards the new horizon of TBI care

Selected Literature

1. B. Mokri. Neurology. 2001 Jun 26;56(12):1746-8. doi: 10.1212/wnl.56.12.1746.
2. N. Carney et al., Neurosurgery. 2017 Jan 1;80(1):6-15. doi: 10.1227/NEU.0000000000001432.
3. J.C. Vester et al., Neurol Sci (2021). https://doi.org/10.1007/s10072-020-04974-6

Long-term neurocognitive consequences of TBI – The CAPTAIN-trials

P. Lackner

Dr. Lackner closed the presentation section of the webinar with a topic introduced already by Dr. Matula: the CAPTAIN trials series. He began by showing the broader epidemiological and pathophysiological picture of TBI. The heavy burden of TBI worldwide is uneven in its geographical distribution. The same must be told about a clinical picture after TBI. It all depends on the circumstances. TBI can lead to death or a vegetative state, but one can also recover quite quickly after a mild TBI. The complex pathophysiology and its underpinning molecular mechanisms of damage and repair are the function of the primary, secondary, and tertiary brain injuries. Such a complexity inevitably leads to a variety of neurological deficits and their clinical consequences. Among them, the neurocognitive deficits characteristic of diffuse brain injuries are of special interest to Dr. Lackner and his clinical practice and research. The temporal dynamics of TBI are frequently foreshadowed by more obvious clinical effects and a picture of immediate damage. It is, however, the key to understanding the therapeutic challenges in front of a TBI care team. The use of biomarkers helped to see and to understand the long-term consequences of TBI reaching far beyond the primary and the secondary damage mechanisms. Neurodegeneration is a process that initiates early but also takes place even months after the initial insult. As expected, this translates into the temporal dynamics of the neurocognitive deficits (**Fig. 1**).

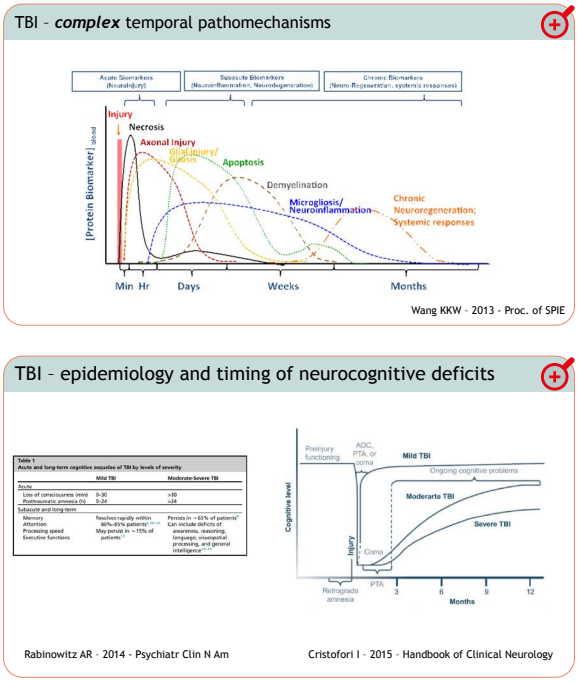

Fig. 1. The temporal dynamics of TBI damage and its neurocognitive consequences

They are seen at all stages of TBI, increasingly so among the mild TBI population. About 15% of these patients will suffer from long-term cognitive disorders. Certainly, the neurocognitive problems will manifest themselves even more frequently and with even higher intensity in more severely affected patients. What are the major neurocognitive domains affected in patients with neurotrauma? The frequent involvement of the frontal lobe and the connective structures of the brain means that learning and memory, executive functions, complex attention, and processing speed are often compromised. However, we should not forget about the neurobehavioral consequences of TBI, like sleep disturbances, increased susceptibility to social and environmental stressors, and seizures together with indirect effects of their medications. All these effects are intertwined with motor deficits and are multimodal in their nature and impact. This poses a tough challenge for both clinical practice and also for designing clinical trials which are supposed to bring in new insights leading to improvement of our TBI care standards. This challenge was undertaken in large projects like CENTER-TBI and TRACK-TBI, in which the neuropsychological tests batteries were extensively used. For example, the mild TBI population investigated in the CENTER-TBI core data set was divided into normal initial CT scan group (uncomplicated mTBI; n=648) and abnormal initial CT scan group (complicated mTBI; n=599). The frequency and the progress of neurocognitive symptoms were monitored and compared between the two groups. The conclusion after the observation period between 3 and 6 months was that the neurocognitive scores of both groups did not change significantly and only a few patients migrated between the respective categories.[1] The symptoms appear to persist irrespective of CT-based classification. This is bad news, as the impact of cognitive functions and performance in everyday life is significant. There was a good correlation between the results of the extended version of the Glasgow Outcome Scale (GOSE) and the mental or physical scores in the mild-severe TBI population. However, cognitive outcomes cannot differentiate equally well the patients in the more favorable status category of GOSE.[2] Therefore, cognition itself seems to be not a good outcome tool (used alone), especially in mild TBI patients. Instead, patients should be evaluated with various behavior-oriented outcome tools as well (**Fig. 2**).

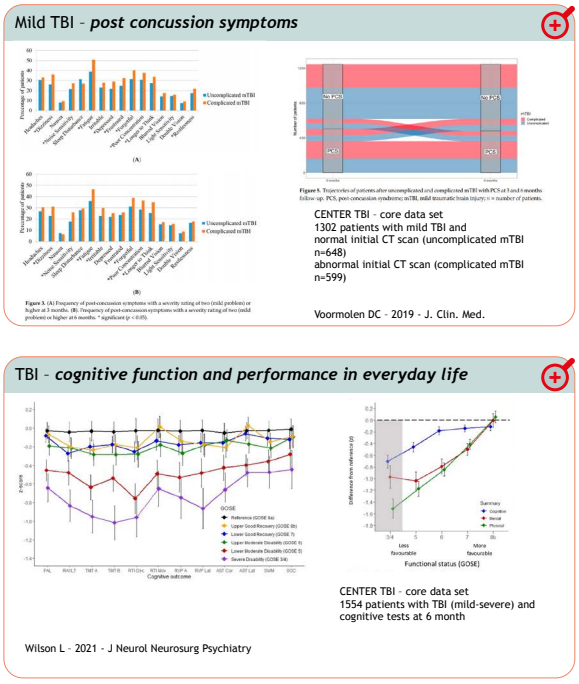

Fig. 2. The CENTER-TBI: neurocognitive battery tests and the dissociation of cognitive outcomes and overall patient status as measured with GOSE

The CAPTAIN trials were the first TBI trials that did a good job in applying the real multidimensional outcome approach by not only including general outcome parameters but also neurocognitive scales, together with depression and anxiety. Patients with moderate to severe TBI were included presenting with mainly isolated TBI, in both CAPTAIN 1 and 2. The idea of the multidimensional outcome design reflected the pleiotropic, multimodal mechanism of action of the investigated agent - Cerebrolysin. The objective of this trial was to evaluate the efficacy and safety of Cerebrolysin in treating patients after moderate to severe TBI as an adjunct component to standard care protocols. The trial was designed to investigate the clinical effects of Cerebrolysin in both the acute (neuroprotective) stage, and during early and long-term recovery as part of a complex neurorestorative strategy. Nine outcome scores for evaluating different consequences of TBI were employed. The time to the first injection was very short (6h) and the assessment of the first treatment period was conducted on day 10. It was then followed by additional 2 treatment periods and assessments at day 30 and day 90 (**Fig. 3**).

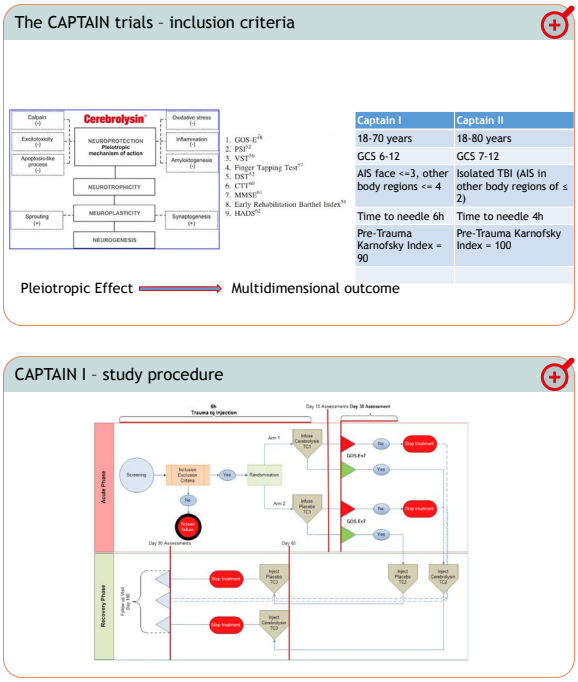

Fig. 3. The design of the CAPTAIN trials series

This approach reflected quite well the modulation patterns of TBI, underlined Dr. Lackner. It covered the acute phase, during which many primary and secondary pathophysiological mechanisms are taking place leading to the initial damage. After that period, during the following weeks and months, the processes of neurodegeneration, as well as the processes of neurorepair, are active. As shown in the work of Dr. Chopp, Cerebrolysin is capable of reintegrating the vasculature into the processes of neurorepair. Therefore, the addition of the third cycle of treatment was the right move, in Dr. Lackner's opinion. The outcome scales employed for the study included: Glasgow Outcome Scale Extended (GOSE), Mini-Mental State Examination (MMSE), Processing Speed Index (PSI; a part of the Wechsler Adult Intelligence Scale), Stroop Color-Word Test 1 + 2 (Victoria Version, VST), Digit Span (a part of Wechsler Adult Intelligence Scale), Color Trails Test (CTT), Hospital Anxiety and Depression Scale (HADS), and Finger Tapping Test (used only in CAPTAIN I due to low sensitivity). One of the achievements of the CAPTAIN project was the use of these various scales for measuring the consequences of TBI on the neurocognitive domains (learning and memory, executive functions, and complex attention), while not omitting the neurobehavioral aspect of neurotrauma. The populations included in the trials were quite well matched and the results showed shifts toward positive outcomes for the majority of scales, with the overall composite effect (Wei-Lachin procedure) reaching the statistical significance in both trials. All efficacy criteria were then evaluated as pre-defined for the confirmatory analysis of the 2 studies. Already at day 10 observation point, the effect of the treatment in the per-protocol (PP) group reached statistical significance. This positive outcome was confirmed for day 30 and day 90 observation points (medium-size superiority for PP and ITT populations). Interestingly, 90 days post-trauma there was a marked decrease in HADS score indicating significantly decreased prevalence of depression among the Cerebrolysin treated patients, in comparison with the standard care. Cerebrolysin was well tolerated with a safety profile similar to the control group (**Fig. 4**).

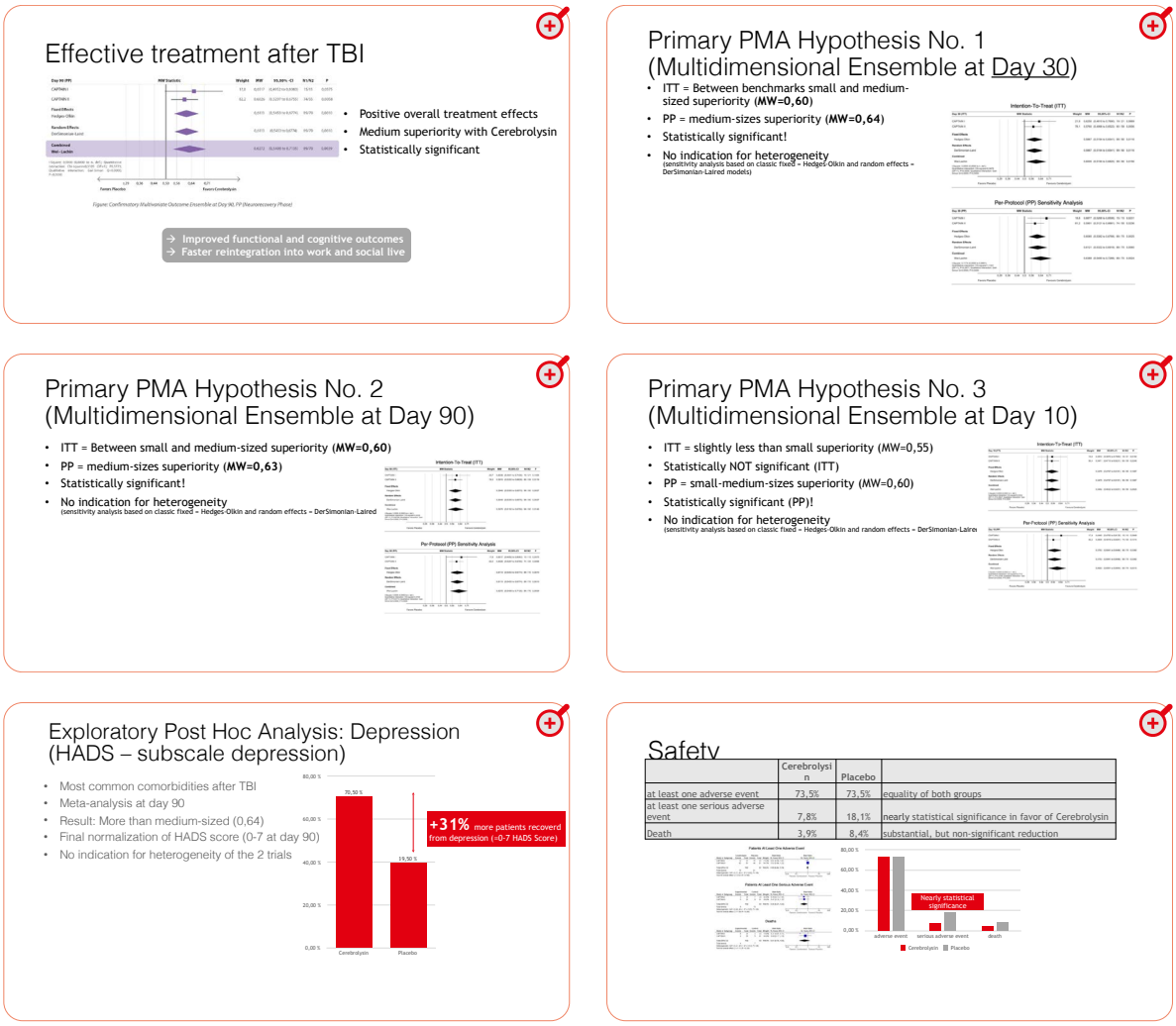

Fig. 4. The results of the CAPTAIN trials were confirmed in the confirmatory meta-analysis

Concluding his lecture, Dr. Lackner underlined that cognitive deficits are frequent among mild TBI (15%), and especially among moderate-severe TBI (65%) patients. In these patients, memory, attention, executive functions, processing speed are the most affected neurocognitive domains. In most of these domains, the CAPTAIN trials series showed benefit from Cerebrolysin treatment, which were further confirmed in the meta-analysis showing a statistically significant overall positive effect at day 30 and day 90 post-trauma in the multidimensional outcome, together with the statistically significant positive effect on anxiety and depression.

Selected literature

1. D.C. Voormolen et al., J. Clin. Med. 2019, 8(11), 1921; https://doi.org/10.3390/jcm8111921
2. L. Wilson et al. J Neurol Neurosurg Psychiatry 2021;92:407–417. doi:10.1136/jnnp-2020-324492
3. J.C. Vester et al., Neurol Sci (2021). https://doi.org/10.1007/s10072-020-04974-6

Questions and Answers session, discussion

P. Vos, Ch. Matula, M. Chopp, P. Lackner

The general question to Dr. Chopp concerned the impact of his impressive work with the pre-clinical models of TBI on the treatment and prevention of the TBI. The major underlying hypothesis of brain injury and degenerative disease is that the vasculature plays a primary role in their pathophysiological picture. The vasculature becomes highly permeable, pro-inflammatory as it starts to produce pro-inflammatory cytokines. The inflammatory state subsequently impacts the parenchyma and microglia. What happens with the endothelial cells in the injured region has also downstream effects on the microvasculature. What Dr. Chopp's work has shown is that when an agent such as Cerebrolysin is used for the treatment, the vasculature itself produces the biological agents of repair contained within the exosomes. They move to the microvasculature and prevent processes of inflammation, coagulation, and secondary thrombosis. This leads not only to a healthier vasculature but also potentially prevents cognitive dysfunction, dementia, and motor dysfunction, which are secondary to the initial impact of the injury. To control the disease, we must understand how to manipulate the regulatory nanoparticles (exosomes) that are produced by the endothelial cells after the injury and are responsible for the communication within the injured brain. Cerebrolysin appears to be able to shift the injury response of the vasculature toward the production of beneficial, protective, and repair-oriented exosomes while, at the same time, reducing the production of those related to accelerating the secondary brain injury.

Another question to Dr. Chopp related to potential clinical benefits of Cerebrolysin in patients with TBI in comparison with intracranial hemorrhage and subarachnoid hemorrhage patients, as in all these patients the underlying pathology has a strong vascular component. Which group then, can be most successfully treated with Cerebrolysin? Dr. Chopp's work focused on TBI, ischemic stroke, and also ICH. It seems that the generalized answer to this question is that vasculature has for long been neglected in brain injury research. However, it has critical significance from the clinical standpoint as it determines the outcomes in the parenchymal tissue. To have a healthy organ, you have to have a healthy vasculature that mediates the communication between the various regions of the body and produces key factors involved in processes of secondary damage and repair. Based on the vascular hypothesis, one can assume that Cerebrolysin treatment can bring benefits in all these cases.

The question to Dr. Matula related to the decompressive craniectomy after 4 days and what, in his opinion, are the key indications in favor and also against performing it in the neurosurgical practice. His response: Decompressive craniectomy happens often much later than we initially thought. When we are doing it, it means that nothing else worked until that moment. The mass lesion removal (emergency surgery), does not constitute the proper decompressive craniectomy and is not problematic from the standpoint of timing. However, you have to be very accurate and in time for the decompressive craniectomy. The good rule of thumb for an experienced neurosurgeon is to perform it whenever one thinks of doing it. It appears, that postponing the surgery more often than not is a mistake. Again, this is the team- and interdisciplinary work, and a neurosurgeon is not alone in the decision-making process.

The 2nd question directed at him: Is it true that neurosurgeons are interested mostly in the short-term effects of their work rather than in the long-term outcomes? Answer: This thinking was common 50 years ago, said Dr. Matula. It is completely different nowadays and modern neurosurgeons are focused much more on the functional outcomes than on morphological ones. Especially, multimodal neuromonitoring changed this landscape and mentality among young neurosurgeons and shifted their focus on the functional end of TBI care.

The question for Dr. Lackner was to state his opinion about the current role of Cerebrolysin in neurotrauma treatment, taking into account the long and unsuccessful history of preventive therapies in TBI (e.g. NMDA receptors antagonists, calcium channel blockers). Cerebrolysin, with its pleiotropic nature, appears to be a true recovery drug. Should it then be used as such in TBI, while we do not have anything similar available right now for the treatment? Dr. Lackner underlined that the smart approach of CAPTAIN design allowed for detection of treatment signals that would probably be missed in the conventional design, using conventional outcome scales, like GOSE. When you scrutinize the outcome from many different angles (per CAPTAIN design) and then combine the positive signals in the multivariate analysis, you can better describe the complexity of TBI, on one hand, but also the impact of the therapeutic intervention, on the other hand. This is a valid model, from the standpoint of granularity of observation and statistical analysis, that is going to be adopted widely for future clinical trials in TBI. Cerebrolysin should be initiated early in the TBI care, but the effects will be observed later due to the pleiotropic effects and continuation of the treatment in the post-acute phase. *Another question was if Dr. Lackner would recommend Cerebrolysin for the treatment guidelines.* Taking into account the relatively small sample size of CAPTAIN trials, the 1a recommendation is still not warranted. However, Cerebrolysin should be included in the treatment guidelines with the appropriate recommendation level, stated Dr. Lackner.

Another question was directed to Dr. Chopp: How, in his opinion, Cerebrolysin should be employed in the clinic? Prof. Chopp answered: Indeed, Cerebrolysin has multimodal effects and therefore can be used acutely, post-acutely, and also chronically. Some of the treatment effects of Cerebrolysin are delayed and occur as secondary to its impact on the vasculature. The vascular damage mediates the secondary injuries characteristic of brain injuries that translate into all kinds of neurological deficits. By treating the vasculature with Cerebrolysin, we can reverse some of the adverse effects of the injury on the vasculature. That would hold or greatly reduce the downstream damage and, therefore, also the neurobehavioral disfunction.

Finally, Dr. Lackner was asked to comment on the new project: the Vienna TBI Treatment Simulation Center. This project is about defining the treatment chain of TBI, akin to what was achieved previously in the stroke care arena. We want to create the treatment chain school and training for developing the whole process of trauma care, from pre-hospital to hospital to neurorehabilitation facility. The project will be open to all medical centers interested in cooperation.

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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CERE/INT/06/2021/13