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Neurorecovery in acute stroke treatment.

Complications and rehabilitation after stroke.

Salzburg, Austria / September 15th, 2017

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Program of the symposium

Keynote speaker

Neurorecovery in acute stroke treatment

Chairmen: Natan M. Bornstein, Steven R. Zeiler

Complications and rehabilitation after stroke

Chairmen: Dafin F. Muresanu, Andreas Winkler

Challenges & opportunities in motor recovery after Stroke

Dafin F. Muresanu

Chairman Department of Neurosciences, University of Medicine and Pharmacy 'Iuliu Hatieganu', Cluj-Napoca, Romania

ABSTRACT:

Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes.

Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone.

Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization- related complications cause over 50% of stroke patients' deaths, rehabilitation plays an important role in stroke care.

It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke.

The results of recently published large and well-controlled clinical studies show a positive effect of Cerebrolysin on neurological recovery after acute ischemic stroke.

The newly published CARS study assessed the efficacy and safety of Cerebrolysin in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper limb motor functions. Cerebrolysin was administered for 21 days, starting within 48-72 hours after ischemic stroke.

The study showed a statistically significant group difference in the upper limb motor function (ARAT) at day 90 – primary end point. Cerebrolysin was also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with Cerebrolysin showed less depressive symptoms and better quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of Cerebrolysin. Analysis of the safety parameters did not show any clinically and statistical significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach.

Prof. Muresanu was a keynote speaker of the conference, and his intention was to give an overview on the challenges and opportunities in a rapidly changing stroke recovery arena.

As a reminder for the audience, Prof. Muresanu mentioned epidemiological data indicating that stroke is the 2nd cause of death and disability and that 75% of stroke survivors remain with disabilities with the parameter of Disability Adjusted Life Year (DALY) showing that the burden of stroke is relatively high in the European populations **(Fig. 1)**. He then outlined major progress elements in subsequent stages of stroke management. In primary stroke prevention, significant steps have been made toward reduction of most dangerous behavioral and diet related risk factors (e.g. BP, smoking, exercise) while in the acute treatment phase, thrombectomy has been proven as a highly efficacious method (albeit for a relatively small subset of stroke patients), whereas neuroprotection remains an unfulfilled promise. During hospitalization, strong progress in the prevention of complications (e.g. through early mobilization) has been shown, also because an increasing number of patients is treated in stroke units. Finally, rehabilitation was demonstrated as the most powerful multimodal and pleiotropic intervention with the biggest impact on stroke recovery, both on cognition/mood and motor functions recovery **(Fig. 1)**.

In this context, neurorecovery must be seen as a holistic approach with many important stages. The neurobiology of stroke recovery is a fast developing discipline with increasingly clinically useful discoveries. One of the fundamental new insights, is the discovery of the interdependence between pathological and beneficial processes. These processes appear to be anti-correlated. For example, glutamate excitotoxicity can be defined as a signaling imbalance triggered by stroke. However, blocking glutamate receptors disturbs neuroplasticity. The glutamate signaling is a necessary element in stroke recovery. **Many anti-correlated mechanisms happen after stroke and all historical efforts utilizing monomodal, suppressor drugs failed to recognize their existence and significance for stroke recovery.** Moreover, anti-correlation is a widespread means of normal brain regulation at all levels of complexity, extending to the circuitry level. Therefore, it makes sense to use multimodal pleiotropic agents that have modulatory, rather than suppressor properties. Such agents should be capable of enhancing endogenous recovery processes of the lesioned brain through modulation of both neuroprotection and long-term recovery. Interestingly, even today the old neuroprotective/suppresive approach continues to be researched in clinical trials, remarked Prof. Muresanu, and opined that this is a wasteful approach with low probability of successful clinical development.

The major question for stroke recovery is: how can rehabilitation efforts be enhanced? In clinical

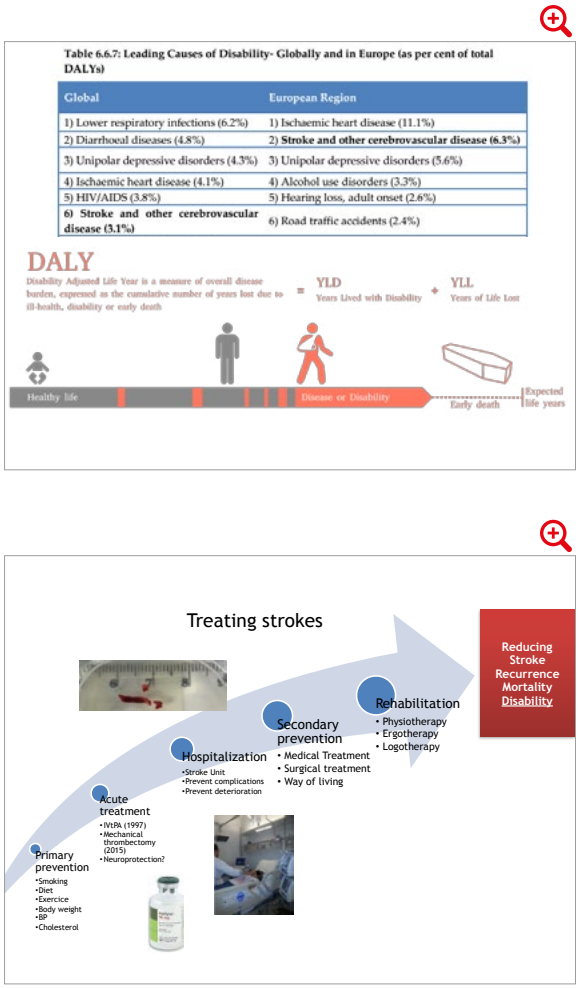


Fig. 1. DALY in Europe and major milestones in stroke management

practice two models exist: the medical model and the rehabilitation model. While the medical model relies on evidence based medicine, specific diagnosis and treatments, the rehabilitation model relies on patient's participation and activities. It focuses on multidisciplinary approaches addressing individual patient's needs. In addition to specific treatment, it is also related to adaptation. While evidence based approaches are important, it must be recognized that successful rehabilitation has to remain a personalized therapy. Another important aspects are timing and intensity of rehabilitation. Clearly, if rehabilitation begins already in the stroke unit then the chances of good outcome are higher, which explains the successful concept of early mobilization.

Appropriate pharmacological support can enhance rehabilitation. So far, clinical data in this area are scarce (only 12 RCTs). The majority of rehabilitation trials were conducted later in the rehabilitation process, while the clinical practice of rehabilitation is to act early. One of the most promising trials is the FLAME - study, employing fluoxetine (SSRI), which showed effective support for early motor rehabilitation. SSRIs are an example of stimulating, pleiotropic agents and these new data suggest that they have direct utility in supporting motor rehabilitation post-stroke.

Prof. Muresanu briefly outlined the history of a multimodal approach utilizing modulating agents, which began with the article by Rogalewski et al., (2006) titled: "Toward the multimodal neuroprotective treatment of stroke". Prof. Muresanu convincingly demonstrated that Cerebrolysin is such a multimodal and modulating agent, as it acts like the endogenous neurotrophic factors. Due to this mechanism of action, Cerebrolysin supports underlying mechanisms of brain recovery, rather than interferes with the ischemic cascade processes (in contrast to monomodal, neuroprotecive drugs). The pre-clinical research data of Cerebrolysin reflect and target the earlier discussed neurobiological anti-correlated processes of recovery after stroke. These findings were, to a significant extent, confirmed in the clinic with almost 5500 stroke patients included in the clinical trials to date.

While early trials investigated the short-term treatment effects of Cerebrolysin used as a monotherapy, more recent trials evaluated the combination of Cerebrolysin and motor rehabilitation in both the very early and the post-acute period (Fig. 2). The CARS trial focused on upper limb motor impairment and investigated recovery of motor functions using the Action Research Arm Test (ARAT) scale. Some important secondary parameters included NIHSS, Barthel Index and mRS; in total, 12 different outcome parameters were used. In Prof. Muresanu's opinion, this design allowed to assess the turning point between natural neuroprotection and neurorecovery and potential influence of Cerebrolysin and motor rehabilitation on these processes. The ARAT results showed significantly improved upper limb motor functions in the Cerebrolysin group. The positive impact of the double intervention was seen already after two

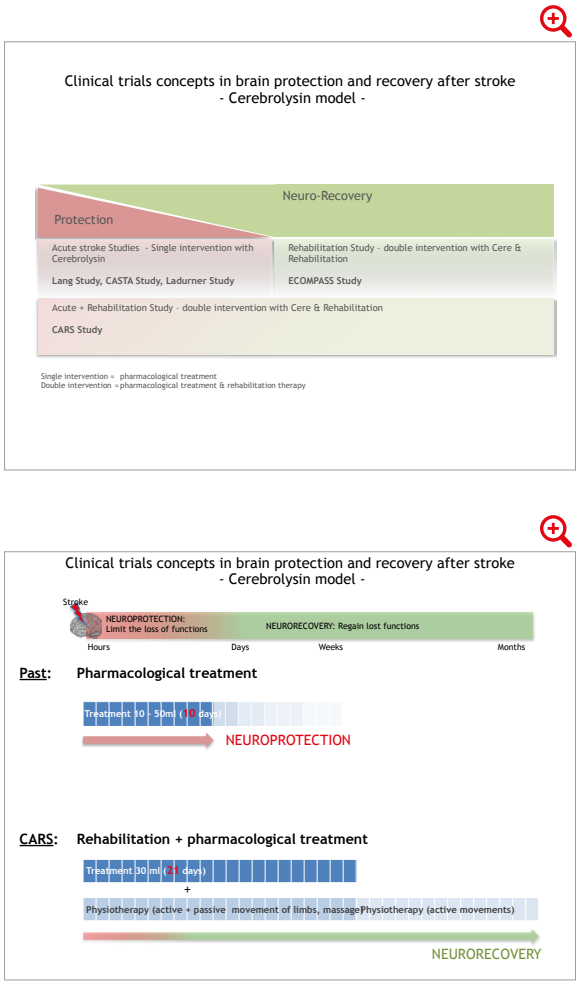
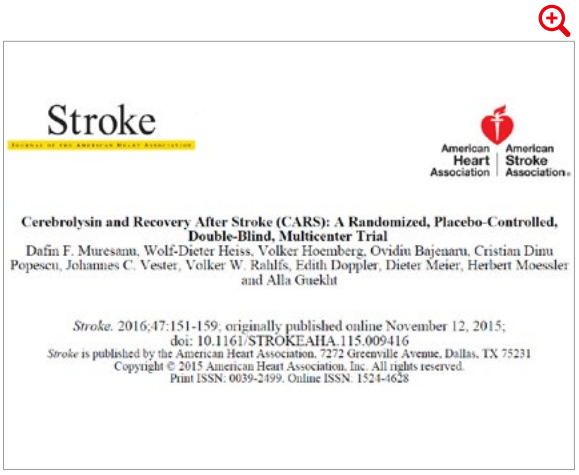


Fig. 2. The clinical trials concept - Cerebrolysin's therapeutic development model

weeks. The mRS results confirmed positive impact of Cerebrolysin plus rehabilitation on clinical outcome. Six out of 12 efficacy measures used in this trial showed significantly positive results at the day 90 endpoint **(Fig. 3)**. The safety data were similar for both groups.

Finally, Prof. Muresanu addressed shortly the methodological aspects of the ECOMPASS trial, in which Cerebrolysin and motor rehabilitation were applied from the eighth day after stroke (focus on recovery-enhancing properties of the drug). The investigators evaluated Fugl Meyer Motor Scale (FMMS) scores of upper and lower extremities. They found, that in the more severely affected group, the combination Cerebrolysin plus motor rehabilitation significantly improved



Stroke

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Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial

Dafin F. Muresanu, Wolf-Dieter Heiss, Volker Hoemberg, Ovidiu Bajenaru, Cristian Dinu Popescu, Johannes C. Vester, Volker W. Rahlfs, Edith Doppler, Dieter Meier, Herbert Moessler and Alla Guekht

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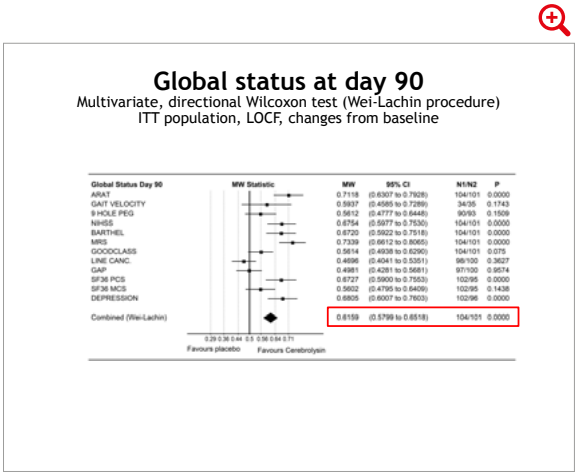
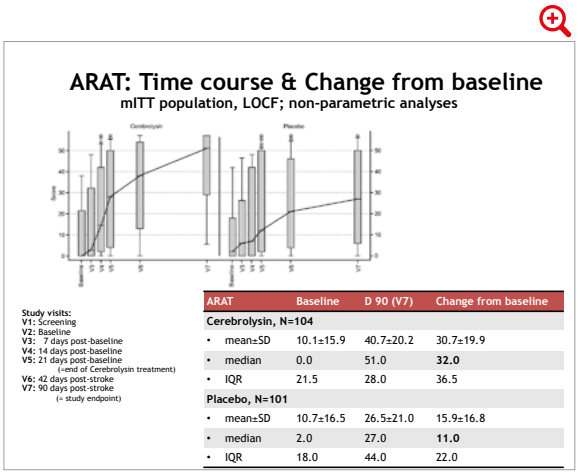


Global status at day 90

Multivariate, directional Wilcoxon test (Wei-Lachin procedure)
ITT population, LOCF, changes from baseline

Global Status Day 90	MW Statistic	MW	95% CI	N1/N2	P
ARAT		0.7118	(0.6307 to 0.7928)	104/101	0.0000
GAIT VELOCITY		0.5937	(0.4585 to 0.7289)	34/35	0.1743
9 HOLE PEG		0.5612	(0.4777 to 0.6448)	90/93	0.1509
NIHSS		0.6754	(0.5977 to 0.7530)	104/101	0.0000
BARTHEL		0.6720	(0.5922 to 0.7518)	104/101	0.0000
MRS		0.7339	(0.6612 to 0.8065)	104/101	0.0000
GOODCLASS		0.5814	(0.4938 to 0.6290)	104/101	0.075
LINE CANC.		0.4696	(0.4041 to 0.5351)	98/100	0.3627
GAP		0.4981	(0.4281 to 0.5681)	97/100	0.9574
SF36 PCS		0.6727	(0.5900 to 0.7553)	102/95	0.0000
SF36 MCS		0.5602	(0.4795 to 0.6409)	102/95	0.1438
DEPRESSION		0.6805	(0.6007 to 0.7603)	102/96	0.0000
Combined (Wei-Lachin)		0.6159	(0.5799 to 0.6518)	104/101	0.0000

Favours placebo | Favours Cerebrolysin

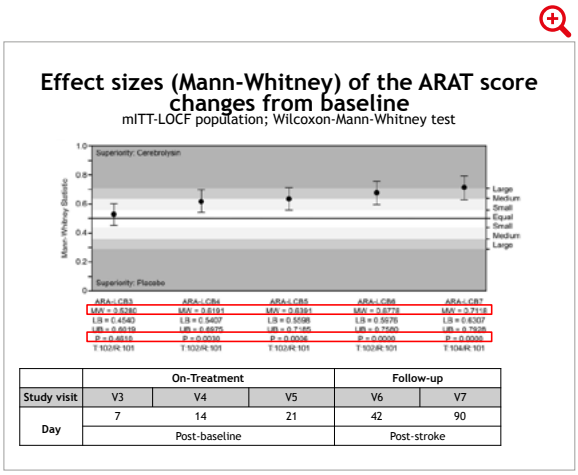


ARAT: Time course & Change from baseline

mITT population, LOCF; non-parametric analyses

Study visits:
V1: Screening
V2: Baseline
V3: 7 days post-baseline
V4: 14 days post-baseline
V5: 21 days post-baseline
(-end of Cerebrolysin treatment)
V6: 42 days post-stroke
V7: 90 days post-stroke
(= study endpoint)

ARAT	Baseline	D 90 (V7)	Change from baseline
Cerebrolysin, N=104			
• mean±SD	10.1±15.9	40.7±20.2	30.7±19.9
• median	0.0	51.0	**32.0**
• IQR	21.5	28.0	36.5
Placebo, N=101			
• mean±SD	10.7±16.5	26.5±21.0	15.9±16.8
• median	2.0	27.0	**11.0**
• IQR	18.0	44.0	22.0

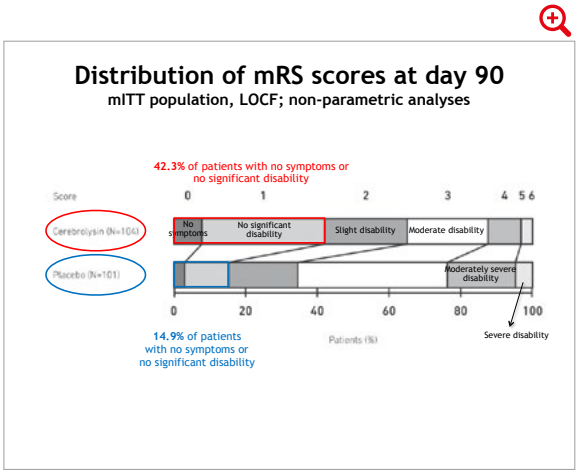


Effect sizes (Mann-Whitney) of the ARAT score changes from baseline

mITT-LOCF population; Wilcoxon-Mann-Whitney test

Superiority: Cerebrolysin
Superiority: Placebo
Mann-Whitney Statistic
Large / Medium / Small / Equal / Small / Medium / Large

	On-Treatment			Follow-up	
Study visit	V3	V4	V5	V6	V7
Day	7	14	21	42	90
	Post-baseline			Post-stroke	



Distribution of mRS scores at day 90

mITT population, LOCF; non-parametric analyses

42.3% of patients with no symptoms or no significant disability

Score: 0 | 1 | 2 | 3 | 4 5 6
Cerebrolysin (N=104)
Placebo (N=101)
No symptoms | No significant disability | Slight disability | Moderate disability | Moderately severe disability | Severe disability
0 | 20 | 40 | 60 | 80 | 100
Patients (%)

14.9% of patients with no symptoms or no significant disability

Fig. 3. The CARS results: pharmacological support of motor rehabilitation with Cerebrolysin

measured parameters. Moreover, the secondary efficacy criteria-imaging analysis using rsfMRI and DTI-showed that Cerebrolysin improved lateralization index as well as plasticity processes involved in the recovery of the structure and function of the corticospinal tract. Together, these results confirm the right direction for the future clinical development, and help in fine-tuning the future trials designs **(Fig. 4)**. **Cerebrolysin and the multimodal treatment concept are the opportunities for development of the effective stroke rehabilitation strategies.**

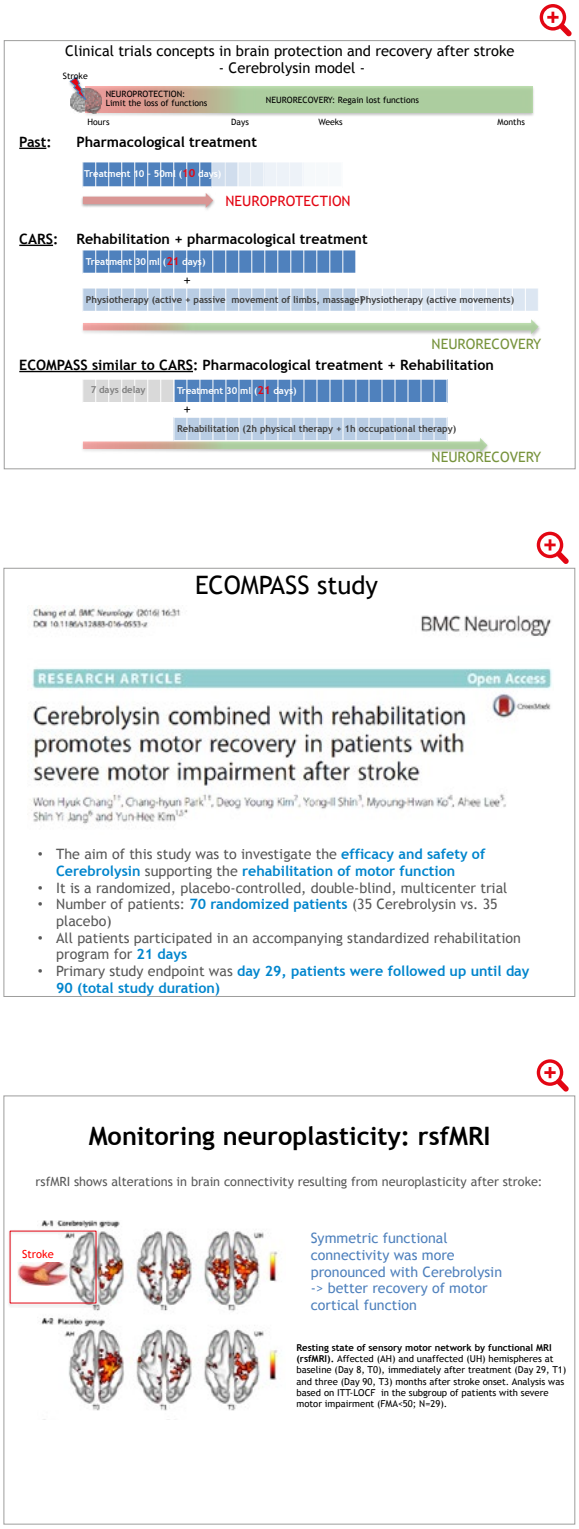


Fig. 4. The ECOMPASS trial demonstrated positive impact of Cerebrolysin on structural and functional recovery of the corticospinal tract when combined with motor rehabilitation

Neurorecovery properties of Cerebrolysin for stroke and neural trauma - Novel mechanisms of action

Michael Chopp

Henry Ford Hospital, Detroit, Michigan and Oakland University, Rochester, Michigan, USA

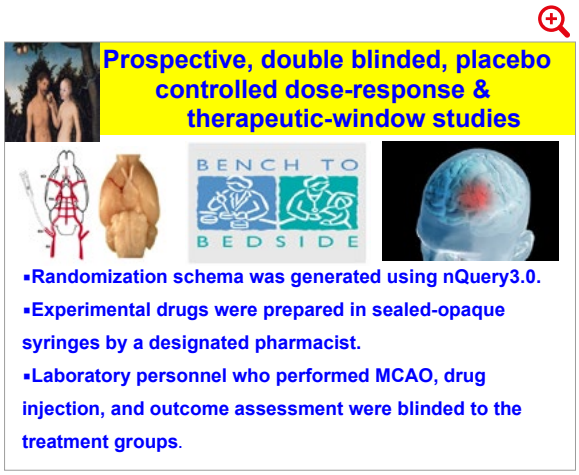
ABSTRACT:

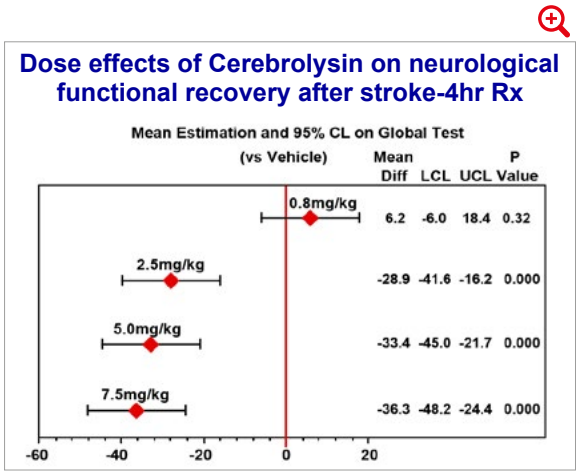
I will review our data on prospective, double blinded, placebo controlled preclinical studies, performed under rigorous clinical trial conditions for the treatment of stroke and TBI. These data clearly indicate that treatment of neural injury with Cerebrolysin potently promotes neurological recovery, even under conditions with no changes in infarct volume or other indices of neural damage. I will then provide new insight into the multiple mechanisms of action of Cerebrolysin. Data will be shown that Cerebrolysin evokes expression of Angiopoietin 1 (Ang1) in endothelial cells, which promotes blood brain barrier integrity, is anti-inflammatory and mediates axonal outgrowth. Cerebrolysin also up-regulates the expression of select developmental proteins, such as Sonic-Hedgehog (Shh), a morphogen, that is critically important in the developing brain. Shh stimulates parenchymal cellular expression of tissue plasminogen activator (tPA), which acts as both an endogenous thrombolytic agent and plays a pivotal role in promoting neurite outgrowth and neurological recovery. In addition, I provide novel insight into how Cerebrolysin stimulates specific sets of microRNAs (miRs). miRs are small non-coding RNAs, master gene regulatory switches, each of which post-transcriptionally regulates the translation of many genes. Specifically, I will show that Shh stimulates a specific cluster of miRs, which promotes axonal outgrowth. Thus, we demonstrate that Cerebrolysin has multifactorial protective and neurovascular remodeling effects on tissue which drive neurological recovery.

The neuropathophysiology of stroke was the underlying theme of the lecture by Prof. Chopp. He began by asking about the right way to undertake clinical development, and why companies with promising neuroprotective compounds have failed in the past? Launching clinical trials without the necessary, extensive pre-clinical research is one major problem. In case of Cerebrolysin research, Prof. Chopp and his team decided to do the opposite, and test the drug in the most rigorous research projects. They used the embolic stroke rat model which reproducibly creates an infarct zone encompassing 30-40% of the total brain volume. Based on this model, a prospective, double-blind, placebo-controlled dose response and therapeutic window studies were performed **(Fig. 1-2)**.

The first study successfully established the dose response for Cerebrolysin, as measured with the neurological functional recovery battery after administering the compound 4 hours post-stroke. The researchers assessed the efficacy of Cerebrolysin in both male and female rats and confirmed similar neurological response for both sexes. In the therapeutic window study, similar proven design features and outcomes measures were used. The treatment starting points were 4, 24, 48, and 72 hours post-stroke, and it was demonstrated that the therapeutic window for Cerebrolyin in this research model was up to 48 hours post-stroke.

Prof. Chopp's laboratory performed complementary studies on closed head injury models in order to see if Cerebrolysin's action in stroke can also be successfully translated into clinical approaches in a broader group of TBI patients. A prospective, randomized, blinded, and placebo-controlled study of dose response effects on the long-term functional and histological outcomes in rats with mild closed head injury (CHI) investigated





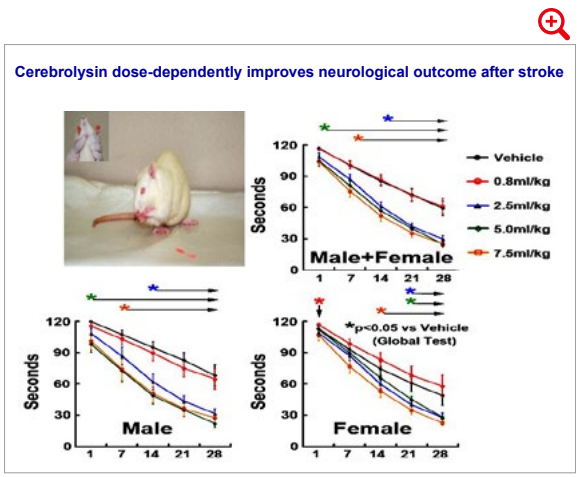
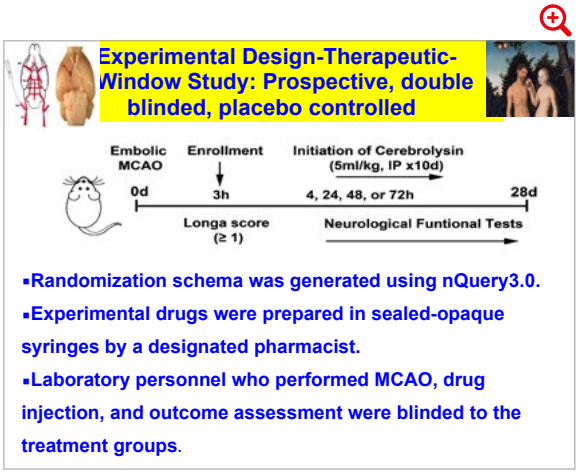
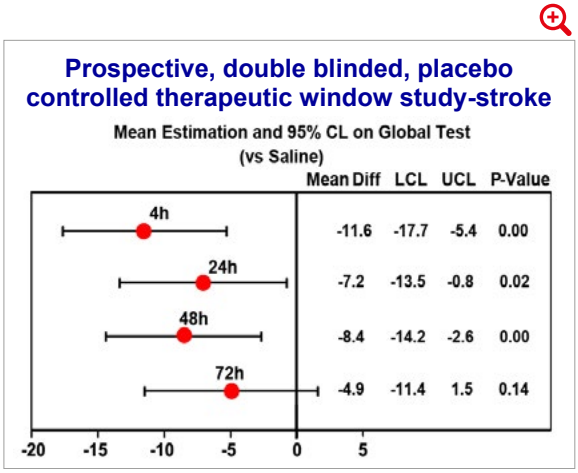


Fig. 1. The dose response study of Cerebrolysin in the embolic rat model.

the same doses of Cerebrolysin as previously tested in the embolic stroke model. The primary outcome measures were: Morris Water Maze, Novel Object Recognition Test, Social Interaction, Somatosensory Outcomes, and the Global Test. The statistically significant improvements in all outcome measures with all tested doses of Cerebrolysin were observed.

Why does Cerebrolysin evoke these important therapeutic effects? In order to answer this question, one has to look into the mechanism of action of the drug. Prof. Chopp went on to present the results of the relevant experiments. It is important to underline the fact that treatment of stroke, or generally brain injuries, requires involvement of many concerted mechanisms underlying natural recovery. One of the important properties of Cerebrolysin is that it affects blood vessels, particularly the microvasculature. For example, it induces the production of Angiopoietin 1 (ANG-1) in the endothelial cells. ANG-1 is an essential component maintaining the integrity of the blood brain barrier (BBB) as well as supporting the maturation of endothelial cells and tight junctions. This may be the reason why Cerebrolysin plays a role in reducing hemorrhagic transformation, BBB leakage, and re-establishment of homeostasis in the entire central nervous system. The molecular pathways regulated by ANG-1 are multiple and Prof. Chopp presented them suggesting that the impact of Cerebrolysin can be seen at many additional levels, like: pro-survival regulation, anti-inflammatory action and neuronal plasticity. Next, Prof. Chopp talked about a new pharmacological target in medicine and its relationship to Cerebrolysin. Humans and animals share 97 to 99% of genes, yet humans are remarkably different from other species. The main difference can be traced to the regulation of gene translation by the noncoding micro RNA (miRs) molecules. They act as molecular master switches and, on the phylogenetic scale, the highest numbers and complexity of miRs are observed in humans. miRs regulate simultaneously an extraordinary number of pathways including those responsible





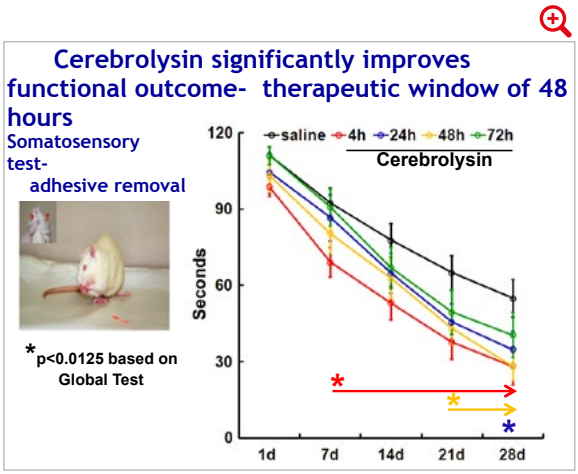
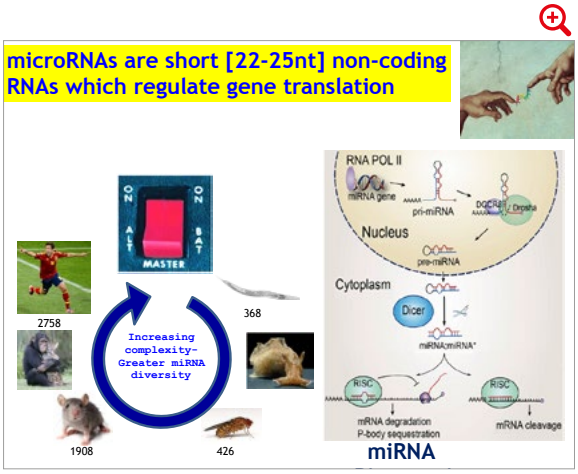
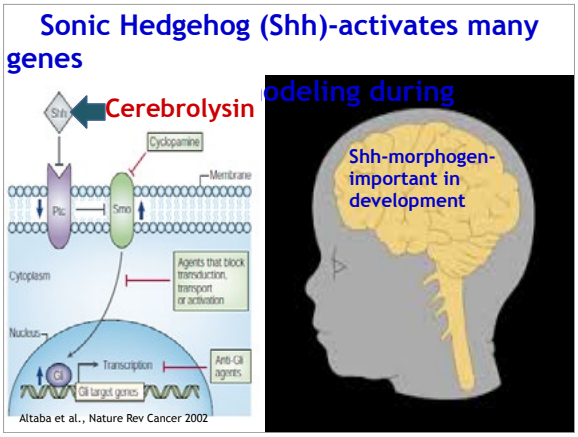


Fig. 2. The therapeutic window study of Cerebrolysin in the embolic rat model.

for the natural recovery processes after brain injuries. It appears, that Cerebrolysin turns on these critically important, recovery-related miRs. **The Cerebrolysin activation mechanism operates through stimulation of the sonic hedgehog (Shh) signaling pathway. Shh than increases expression of miRs cluster called miR17-92, which in turn activates several critically important regulatory pathways including MTOR, PI3K/AKT, GSK3b, PTEN, VEGF.** This action translates into promotion of axonal outgrowth that is vital for neural plasticity **(Fig. 3)**.

Another aspect of the Cerebrolysin-mediated action involving miRs is related to sequelae of arterial occlusion, a primary cause of stroke. It is often forgotten that downstream of the major occlusion, microvessels become occluded too, especially with fibrin. This is a secondary effect that precipitates further damage, mainly through inflammation (activation of pro-inflammatory and pro-coagulation processes). It was found, that miR17-92 activates various anti-inflammatory mechanisms and also down-regulates plasminogen activator inhibitor (PAI). This leads to an increased production of endogenous tPA and tips the balance of microvasculature-localized processes towards anti-inflammatory, anti-coagulant and pro-fibrinolytic action. Obviously, stimulation of this endogenous pro-recovery mechanism can help a patient in natural recovery from stroke. Prof. Chopp summarized his lecture by saying that the multimodal treatment mechanism for stroke, as explained earlier by Prof. Muresanu, is well represented by Cerebrolysin, a drug that fulfills criteria of a multimodal-acting agent.





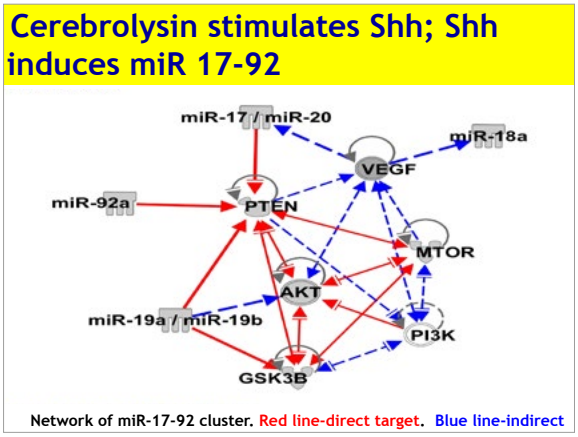


Fig. 3. Cerebrolysin stimulates Shh-miRs-mediated regulatory pathways leading to stimulation of natural recovery processes post-stoke

Pharmacological support in the management of Subarachnoid Hemorrhage.

Peter Woo

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ABSTRACT:

BACKGROUND: Aneurysmal subarachnoid hemorrhage (SAH) is a devastating form of hemorrhagic stroke that results in a mortality rate approaching 50% within a month, and moderate to severe disability in a third of surviving patients. The most important determinant for morbidity is delayed cerebral ischemia (DCI), a unique complication that occurs in 20- 50% of patients. For 30 years, the standard-of-care for DCI has remained largely unchanged. Cerebrolysin is a neurotrophic agent proven to be beneficial for functional performance among ischemic stroke patients, but its role in SAH has never been explored.

METHODOLOGY: The Cerebrolysin for Aneurysmal Subarachnoid Hemorrhage Study: a Randomized, Placebo Controlled Trial (CESAR), was initiated for patients 18-70 years of age. It is a single-center 2-arm pilot study (n=50) in which the intervention group subjects are given standard treatment and systemic Cerebrolysin within 4 days of symptom onset for a total duration of 2 weeks. The aim of the study is to explore the safety and feasbility of this intervention. Secondary endpoints are: DCI, 6-month functional performance (modified Ranking scale; Glasgow Outcome Scale), stroke-specific quality of life, cognitive performance (Montreal Cognitive Assessment and neurobehavioural cognitive state examination).

RESULTS: 29 patients have been recruited with 21 having completed the study. 14/21 (66%) patients were female with a mean age of 66 years (range 34-66). The median World Federation of Neurological Surgeons SAH grade was IV. 11 (52%) were in the intervention group. Administration of Cerebrolysin in the acute phase of SAH was safe and feasible. No adverse effects were observed. Delayed cerebral ischemia developed in 5 (24%) patients: 3 (intervention) and 2 (control). The median 6-month modified Rankin Scale functional performance was 2 (slight disablility) in the intervention group, and 3 (moderate disability) in the control group. The 6-month mean Montreal Cognitive Assessment score was 22 (intervention) and 18 (control).

CONCLUSION: According to current trial progress results, Cerebrolysin administration in acute SAH is safe and feasible. Further recruitment is ongoing to determine its efficacy in improving 6-month outcomes.

As a neurosurgeon and neurocritical care specialist, Dr. Woo introduced the audience to topics of aneurysm and related hemorrhagic brain injuries. The prevalence of aneurysm, located usually at the bifurcation of the middle cerebral artery (MCA), at the bottom of the brain, is about 2.3% and this means that in Hong Kong itself there are about 150 000 people suffering from this serious health problem. Aneurysms cause subarachnoid hemorrhage (SAH) which is responsible for up to 5% of all stroke forms. SAH is predominantly a female disorder and concerns persons from 40 to 60 years. Up to 15% die before they reach the hospital and 1/3 of the survivors remain severely disabled. One of the most catastrophic complications of SAH is delayed cerebral ischemia (DCI). It usually happens 3 days after SAH and resolves within 14 days. One of the major causes of DCI appears to be the angiographic vasospasm that, apart from the obvious hemodynamic effect, creates local emboli which additionally block the blood flow in the large area downstream of the vasospasm. Another explanation for SAH-caused ischemia is related to release of cytotoxic factors by the blood within the hemorrhage, which in turn leads to glutamate cytotoxicity and diffused depolarization affecting large brain areas. For a neurosurgeon, the delayed cerebral ischemia is a big problem because even after successful surgery of the aneurysm, it can damage large areas of the brain. Interestingly, only 1/3 of vasospastic patients develop DCI. For the majority of SAH patients, neurological decline or a new infarct must be attributed to other causes than vasospasm.

What kind of pharmacological intervention is conceivable for SAH? There are basically two theories trying to address this issue: the mechanistic theory and the organic theory. The first one points to hemodynamic, vasospasm related events while the second one points to cellular events and the delayed cerebral ischemia as treatment targets. The mechanistic strategies focus on opening up the constricted vessels, like a "triple H therapy" (Hypertension- Hypervolemia Hemodilution). However, it was found that this approach, while improving cerebral blood flow, does not improve DCI and long-term outcomes. In the CONCIOUS-I trial, a very selective vasodilator (endothelin A receptor antagonist, clazosentan) was used, and again the vasospasm was reversed while DCI and long-term outcomes did not improve. Endovascular therapy does help if applied within a short time window, however there is no proof yet for the long-term benefits. The only drug that consistently improves patients' outcomes is Nimodipine and Dr. Woo mentioned a 30-years-old study that described its benefits; namely a 30% reduction of cerebral ischemia as well as a 40% reduction in poor outcome. It can be speculated that calcium channel blockers can alter the vascular architecture and de facto act as hemodynamic agents. However, other studies showed that there is no vasodilatation effect of the treatment. The drug showed efficacy despite being used for the wrong reason!

Interestingly, the very precise methods the surgeons use to address the problem do not work as needed. Therefore, neurosurgeons turn their attention to neuroprotective and neurorestorative methods which have been explored continuously throughout the last 30 years. None of them worked so far, including a study utilizing Magnesium in which Dr. Woo took part as an investigator. Current therapeutic concept is a multi-targeted approach as potentially most promising in this area, and Cerebrolysin, with its multimodal properties, appears to fit exactly to the profile of the required agent. Dr. Woo mentioned a preclinical study by Hanson et al., (2009) in which Cerebrolysin reduced cerebral infarct size and cerebral ischemia; dose dependently, in an MCA occlusion rat model. He also indicated that the already discussed CARS trial results can be considered a landmark achievement since the study used a very specific outcome measure, the ARAT score. On the basis of currently available information about benefits of Cerebrolysin treatment, Dr. Woo and co-investigators from Hong Kong decided

to launch the CESAR-trial (CErebrolysin for Sub-Arachnoid Hemorrhage; see study description in the Abstract). The interim results of this study are currently analyzed and Dr. Woo showed some of them for the first time. There was a notable advantage in mRS for the Cerebrolysin group in comparison to placebo. This is considered as an encouraging result, which validates continuation of this trial. He further illustrated the results with one particularly interesting case of a female patient randomized into Cerebrolysin group after successful aneurism clipping, who developed DCI due to several vasospasm episodes with resulting hemiparesis. This patient recovered fully until day 40, which can be regarded as a remarkable outcome.

Concluding his lecture, Dr. Woo underlined the complex nature and the catastrophic impact of ischemia after SAH, with no breakthrough treatment approved so far. It seems that research should focus on organic therapeutic approaches rather than mechanistic ones, and on multimodal rather than single pathway treatments. A very suitable candidate for ongoing clinical investigations is Cerebrolysin as it was established as a safe treatment.

Hemorrhagic transformation after thrombolysis – What are the mechanisms and can multimodal agents reduce the occurance?

Dina Khasanova

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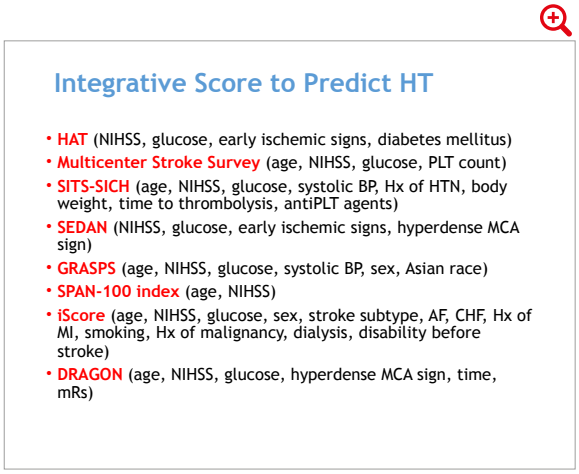
ABSTRACT:

Reperfusion therapy for ischemic stroke is the most effective and evidence based method of treatment improving clinical outcome. There are several approved methods of reperfusion therapy: IV thrombolysis (rtPA), mechanical recanalization and step-by-step technology (rtPA bridging). Good outcome after rtPA is closely linked to using a strict inclusion protocol, especially implemention during the "therapeutic window". At the same time, recanalization does not always lead to real reperfusion and is associated with complications. Symptomatic hemorrhagic transformation (SHT) spontaneous hemorrhage in the ischemic area - is the most serious complication of rtPA that influences especially mortality and bad outcome. Hemorrhagic transformation (HT) occurs due to an increased permeability of the BBB. The HT pathogenesis is linked to damage of neurovascular units by leukocytes and brain metalloproteinkinases (MMP-9 and MPP-2), activation of brain proteases and neuroinflammation. According to clinical data analysis the frequency of HT reaches 71% and SHT – 15% and higher. There are known markers of HT, identification of which is very important for the safety prognosis of rtPA. The most important clinical markers are age, stroke severity, previous usage of anticoagulants and antiaggregants, hypocoagulation, arterial hypertension, onset of stroke before reperfusion. Biochemical predictors are the level of MMP-9, fibronectin, TAFI, PAI-1 and others. Neurovisualizational markers: early reperfusion MRI, markers of ischemia, the volume of the ischemic core, symptoms of hyperdensity of arteria, amount of residual lacunar ischemic cores, a high BBB permeability indicated by perfusion MRI PS regimen (permeability surface area product). Exploring the mechanism of SHT and searching for its markers, also the methods of protection, is an actual task for neurologists. The decrease of HT occurrence could help not only in the reduction of unfavorable outcomes after rtPA, but also could influence the rehabilitation potential of patients. In this field, a large opportunity has been observed in pharmacological prevention of HT when using drugs with a multimodal mode of action influencing the pathological links of HT.

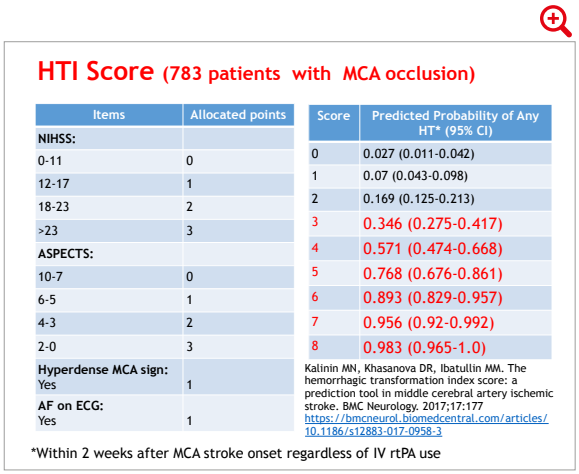
The major question regarding hemorrhagic transformation (HT) after stroke is if the occurrence can be reduced, also by using multimodal agents like Cerebrolysin, stated Prof. Khasanova. She quickly reviewed reperfusion therapies and relevant key selection criteria. In most cases, HT is a result of reperfusion injury with most important causative factors being time to reperfusion, speed of reperfusion, certain preconditions, and also unsuccessful reperfusion itself. The increased permeability of the blood brain barrier (BBB) is a major factor at the cellular level. It is very important to understand the predictors of HT which include: clinical, biochemical, genetic and imaging factors. The various predictive scores help during the decision making process and Prof. Khasanova and coworkers developed their own score (HTI Score) based on the results published recently in the journal BMC Neurology **(Fig. 1)**.

Prof. Khasanova then went on to present two typical cases from her hospital with both symptomatic and asymptomatic hemorrhagic transformations. In the first case, unsuccessful thrombolysis was followed by recanalization using the Solitaire device with resulting reperfusion and asymptomatic HT. In the second case, very late thrombolysis (280 min.) led to recanalization, but also large symptomatic HT. The use of anticoagulants in patients with atrial fibrillation is another important factor to consider as is imaging predictor in clinical practice. There are 4 Ps in multimodal assessment: Parenchyma, Pipes (blood vessels), Penumbra, and Permeability of BBB. A recent study by Australian investigators also added the aspect of tPA dosage to the discussion about HT prediction. They found out that the higher dosage correlated with increased rate of HT and therefore with increasing precision in predicting HT we now might be able to use a lower dosage of tPA in patients with increased risks. Prof. Khasanova addressed the pharmacological strategies with Cerebrolysin noting the study by Lang et al. (2012), in which Cerebrolysin sped up



Integrative Score to Predict HT

- **HAT** (NIHSS, glucose, early ischemic signs, diabetes mellitus)
- **Multicenter Stroke Survey** (age, NIHSS, glucose, PLT count)
- **SITS-SICH** (age, NIHSS, glucose, systolic BP, Hx of HTN, body weight, time to thrombolysis, antiPLT agents)
- **SEDAN** (NIHSS, glucose, early ischemic signs, hyperdense MCA sign)
- **GRASPS** (age, NIHSS, glucose, systolic BP, sex, Asian race)
- **SPAN-100 index** (age, NIHSS)
- **iScore** (age, NIHSS, glucose, sex, stroke subtype, AF, CHF, Hx of MI, smoking, Hx of malignancy, dialysis, disability before stroke)
- **DRAGON** (age, NIHSS, glucose, hyperdense MCA sign, time, mRs)



HTI Score (783 patients with MCA occlusion)

Items	Allocated points
NIHSS:	
0-11	0
12-17	1
18-23	2
>23	3
ASPECTS:	
10-7	0
6-5	1
4-3	2
2-0	3
Hyperdense MCA sign: Yes	1
AF on ECG: Yes	1

Score	Predicted Probability of Any HT* (95% CI)
0	0.027 (0.011-0.042)
1	0.07 (0.043-0.098)
2	0.169 (0.125-0.213)
3	0.346 (0.275-0.417)
4	0.571 (0.474-0.668)
5	0.768 (0.676-0.861)
6	0.893 (0.829-0.957)
7	0.956 (0.92-0.992)
8	0.983 (0.965-1.0)

Kalinin MN, Khasanova DR, Ibatullin MM. The hemorrhagic transformation index score: a prediction tool in middle cerebral artery ischemic stroke. BMC Neurology. 2017;17:177 https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-017-0958-3

*Within 2 weeks after MCA stroke onset regardless of IV rtPA use

Fig. 1. Integrative scores for HT prediction and HTI Score developed by Prof. Khasanova et al., (2017)

the recovery processes in patients treated with rtPA without increasing the rate of HT. The positive influence of Cerebrolysin on BBB integrity as well as its pro-plasticity properties can contribute to the potential of rehabilitation, indicated Prof. Khasanova.

Finally, Prof. Khasanowa reported on two pilot trials performed in her center **(Fig. 2)**. In the first study, the patients with carotid-origin ischemic stroke after successful rtPA recanalization were undergoing multimodal therapy with Cerebrolysin (right after rtPA) or no other therapy. The Cerebrolysin group demonstrated excellent progress in NIHSS scores showing significantly higher reduction of impairment. In the second

study, the researchers tested protective effects of **Cerebrolysin when administered concomitantly with rtPA. Cerebrolysin treatment resulted in a 32% reduction in the occurrence of symptomatic hemorrhagic transformation (SHT) and very much improved imaging results overall.**

In conclusion, Prof. Khasanova noted that we should consider using lower rtPA doses in patients with identifiable risks of HT. We should also combine rtPA with pharmacological agents like Cerebrolysin which might have a potential to lower the incidence of HT as well as supporting the rehabilitation after stroke.

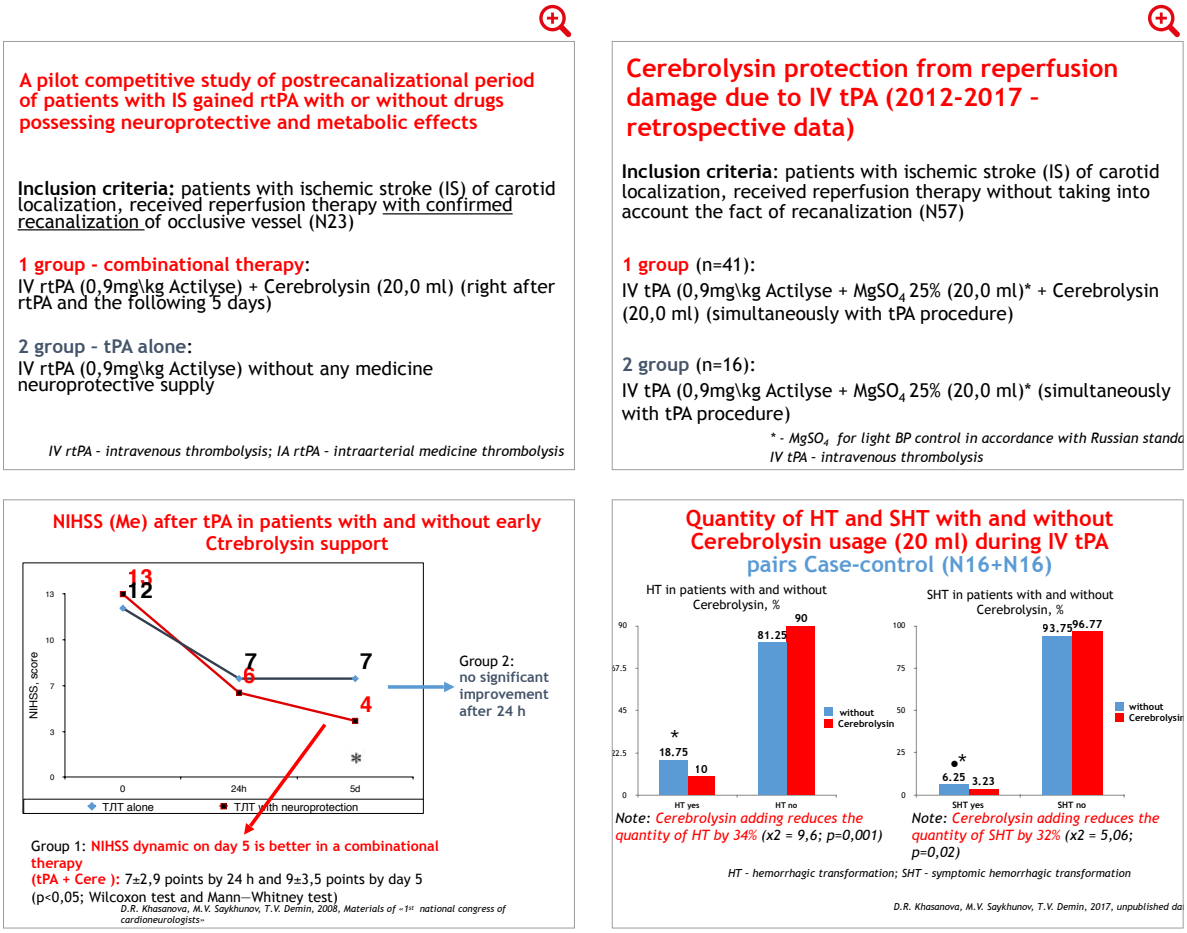


Fig. 2. The pilot trials investigating Cerebrolysin as add-on therapy to reperfusion in ischemic stroke patients

Cerebrolysin in ischemic stroke - A clinical overview with emphasis on Cerelyse trial.

Milan Vosko

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ABSTRACT:

Early recanalisation, brain protection and neurorecovery are the main goals of the acute stroke treatment. Rapid recognition of stroke symptoms, immediate application of systemic thrombolysis within 4.5 hours, rapid performance of mechanical thrombectomy in selected patients, as well as early recognition and prevention of complication guarantee better outcomes of stroke patients.

There are numerous clinical and experimental data showing neuroprotective and neurorestorative effect of Cerebrolysin. In the CASTA study, Cerebrolysin was tested in a large double-blind, placebo-controlled randomized clinical trial in 1070 patients with acute ischemic stroke. Stratification by severity showed a trend in favour of Cerebrolysin in patients with NIHSS>12. A significant beneficial effect of Cerebrolysin on function and global outcome in early rehabilitation in stroke patients as well as safety comparable to placebo was shown also in the CARS Trial.

Combination of Cerebrolysin with thrombolysis (CERELYSE Trial, Lang et al., 2013) found in patients additionally treated with Cerebrolysin earlier recovery seen on the NIHSS compared to placebo treated patients. Although this difference did not remain at 3 month follow up, the notion is upheld that earlier recovery of such patients can be effective for early mobilization. Better early outcome shown in Cerelyse trial could be beneficial for patients to get in the rehabilitation centres and to optimize further rehabilitation therapy.

Dr. Vosko shared with the audience his experience in acute stroke management and also in the implementation of multimodal therapy with Cerebrolysin. He started by showing the brain imaging data and explaining the intrinsic heterogeneity of the ischemic stroke. This heterogeneity is the reason why in Dr. Vosko's center, despite its high (30%) thrombolysis rate, the majority of patients cannot benefit from modern recanalization therapy. The addition of thrombectomy to the routine of acute management does not change this overall picture and there is still a need for further development of supportive, complementary therapies **(Fig. 1)**.

It is well known that the ischemic cascade leads to endothelial, neuronal, glial cell injuries and to a loss of collagen type IV, which is a sign of damage occurring to blood vessels after several hours of ischemia **(Fig. 1)**. Therefore, the sooner the patients are recanalized, the better is the outcome.

In acute stroke management, the whole vascular unit consisting of neurons, astrocytes, glial cells and blood vessels, should be in the focus. **Taking into account the growing body of evidence that Cerebrolysin can potentially help in reducing hemorrhagic transformation, it is important to consider its use as soon as possible in the acute management phase. Another reason is that brain recovery starts concomitantly with the acute therapy.**

Dr. Vosko gave a quick overview of Cerebrolysin's mode of action, underlining its ability to reduce apoptosis as well as to enhance neural plasticity, neurogenesis and maturation of the precursor cells. This involves the activation of sonic hedgehog (Shh) and neurotrophic factors (NTF) pathways. It is nowadays one of the best studied agents in this respect, said Dr. Vosko. He reviewed the available clinical data to illustrate the translation of Cerebrolysin's research data into the bed-side practice.

One of the first well designed studies was done by Prof. Ladurner (Ladurner et al., 2005) in which 146 patients were investigated. 50 ml of Cerebrolysin were given daily for 21 days, and leading to significant improvement of motor functions, activities of daily living and of cognitive functions. Safety and tolerability were no concerns at all. The large-scale trial, CASTA (Heiss et al., 2012), just missed the primary endpoint efficacy criteria. However, the study population was only mildly affected with an average of NIHSS = 9 at inclusion, which led to a therapeutic ceiling effect. The mild stroke patients often recover rapidly by themselves and this spontaneous recovery masks the pharmacological effect of the drug. A pre-planned subgroup analysis, with patients suffering from more severe strokes (NIHSS ≧ 12), confirmed this interpretation by showing that

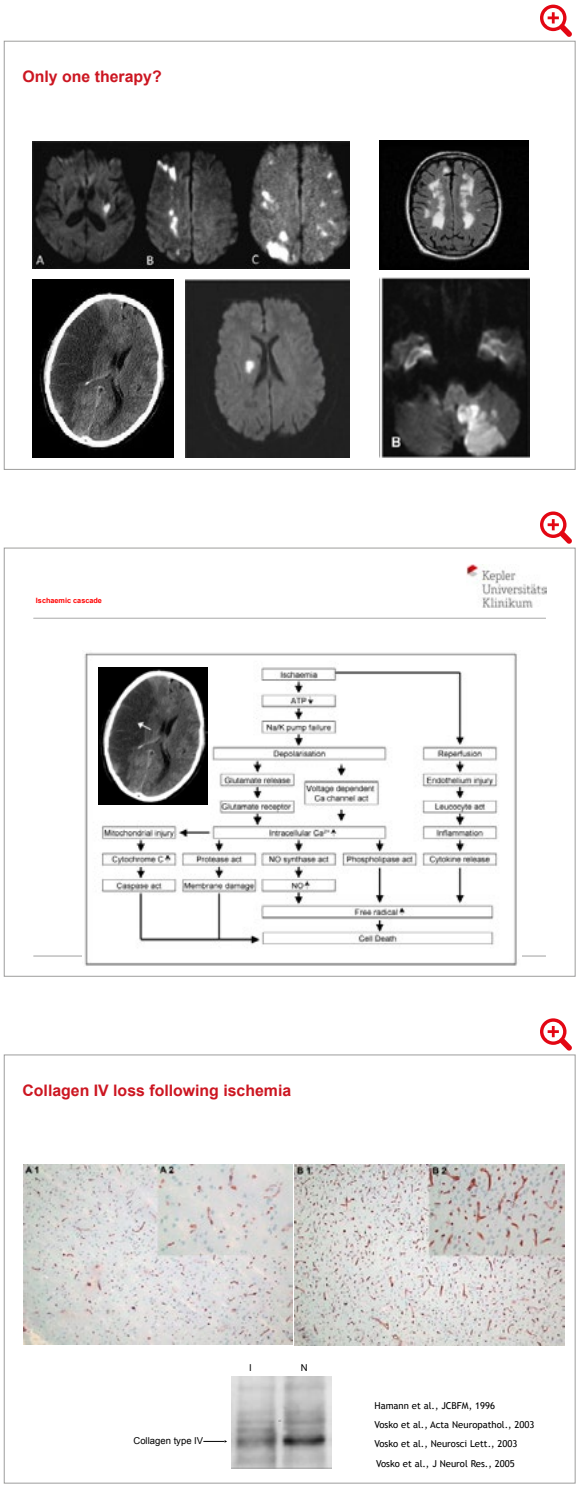

Fig. 1. The heterogeneity of the acute ischemic stroke and the ischemic damage cascade

the difference between the placebo group and the Cerebrolysin group was significant.

Dr. Vosko then moved to the main focus of his lecture, the CERELYSE trial (Lang et al., 2013) in which he played an active role as one of the investigators **(Fig. 2)**.

It was a combination trial using 30 ml daily dosage of Cerebrolysin for 10 days as add-on to rtPA treatment. The trial was organized by Prof. Lang from Vienna. It included 119 patients and significant differences in NIHSS and mRS in favor of the Cerebrolysin group in the weeks after the treatment could be observed. At day 90 however, the difference for the whole study population was not significant anymore. Dr. Vosko suggested, that one reasonable explanation could be that patients entered a highly heterogeneous environment after discharge, which precluded proper monitoring of long-term treatment effects. In order to gain better insight and understanding of the results, a subgroup analysis was performed. Similarly to the CASTA trial, the more severely affected subgroup of patients benefited from the combination Cerebrolysin plus rtPA treatment also at day 90. Additionally, the improvement differences, for this subgroup, remained significant throughout the observation period. One additional conclusion, apart from the need to include patients with a more severe stroke, is that the length of treatment and dosage of Cerebrolysin in future investigations need to be increased. Dr. Vosko highlighted also that the AHA/ASA stroke guidelines include Cerebrolysin and that the wording points into the direction of a Level IIB recommendation. Dr. Vosko stressed the need for producing new evidence and introduced the CREGS-S trial which finished enrollment in January 2017 and for which results are expected in 2018.

Summarizing his lecture, Dr. Vosko encouraged the audience to start therapies supporting neuroprotection and neurorecovery already very early in the acute phase. The need for multimodal therapies is obvious and support from clinicians to collect more data through the CREGS-S registry remains a high priority in Cerebrolysin research.

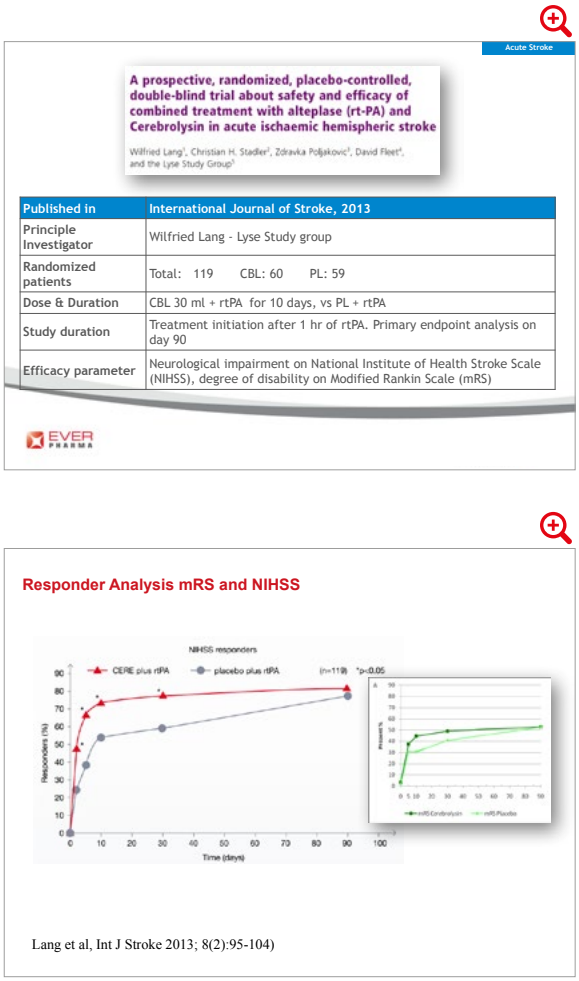

Fig. 2. The CERELYSE trial - combination of rtPA and Cerebrolysin

BDNF as a drug target for the treatment and prevention of cognitive impairment after stroke.

Anton Alvarez

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ABSTRACT:

Cognitive impairment after stroke, including post-stroke dementia (PSD), is present in at least third of stroke survivors and represents a main cause of disability. Overlapping of vascular and degenerative pathologies is common in post-stroke brains, and stroke contributes to cognitive deterioration during aging and to dementia of all types, and not only of the vascular dementia type. Cognitive impairment was found to be significantly associated with the 5-year prevalence of post-stroke disability as assessed with the modified Ranking Score (mRS); and showed a significant association with the presence of neuropsychiatric symptoms, another cause of disability in stroke patients.

Almost all studies with neuroprotective drugs, statins, anti-inflammatory and blood pressure lowering agents failed to show efficacy in preventing or improving post-stroke cognitive deterioration. Recent studies involving lifestyle interventions, physical activity, cognitive rehabilitation, and treatment with Actovegin or Citicoline reported significant cognitive improvements in stroke patients that need to be confirmed in large controlled trials.

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin within the brain. It regulates neurovascular functions such as neural and vascular plasticity, angiogenesis, neurogenesis and neuroinflammation; and has been implicated in post stroke recovery, showing a positive influence on cognition. BDNF mediates the beneficial effects of pharmacological interventions (progesterone, fluoxetine, Cerebrolysin), repetitive transcranial magnetic stimulation (rTMS), aerobic exercise, and social interaction on cognition after stroke. Therefore, strategies aimed at enhancing endogenous BDNF seem to represent an effective option for the treatment and probably the prevention of post-stroke cognitive impairment.

The lecture's first part focused on the impact of post-stroke cognitive impairment (PSCI) on patient's recovery. Stroke causes a wide range of disabilities that can be grouped into: brain damage, sensory-motor deficits, emotional and behavioral alterations, and cognitive deterioration. There is a significant contribution of other factors to cognitive impairment (e.g. chronic pain, apathy, depression, brain damage). Therefore planning treatment of cognitive impairment has to take all these factors into consideration. At least 1/3 of patients succumb to cognitive impairment

and until now little attention was given to this problem. The neurovascular continuum shows an overlap between vascular and degenerative features; this complicated etiology makes it even more difficult to find effective treatments **(Fig. 1)**.

It must be noted that stroke is a contributing factor to different types of pre-existing dementia conditions, like frontotemporal dementia and Alzheimer's disease. Therefore, the term poststroke dementia (PSD) must be used for all types of dementia with a temporal relationship to stroke. Several important domains are affected by post-stroke dementia including: attention and executive functions, psychomotor processing speed, visuospatial abilities, expressive fluency/language and verbal fluency, and memory. However, the evaluation of particular domains remains a difficult task as this depends on the clinical status of a patient, which often makes testing obsolete. The prevalence of cognitive impairment without dementia is at 40% level at 12-24 months. In 10% of the cases after a first stroke and in 40% of cases after recurrent stroke, dementia can also be detected. The transformation rate from cognitive impairment post-stroke to dementia is 3 times higher compared to stroke patients without cognitive impairment. It was found that there is a synergistic interaction between vascular and degenerative pathologies (White Matter Hyperintensities, Medial Temporal Atrophy) on cognitive deficits in PSD and AD. Dr. Alvarez indicated that appropriate treatment of cognitive impairment after stroke may be relevant for clinical outcome and PSD prevention.

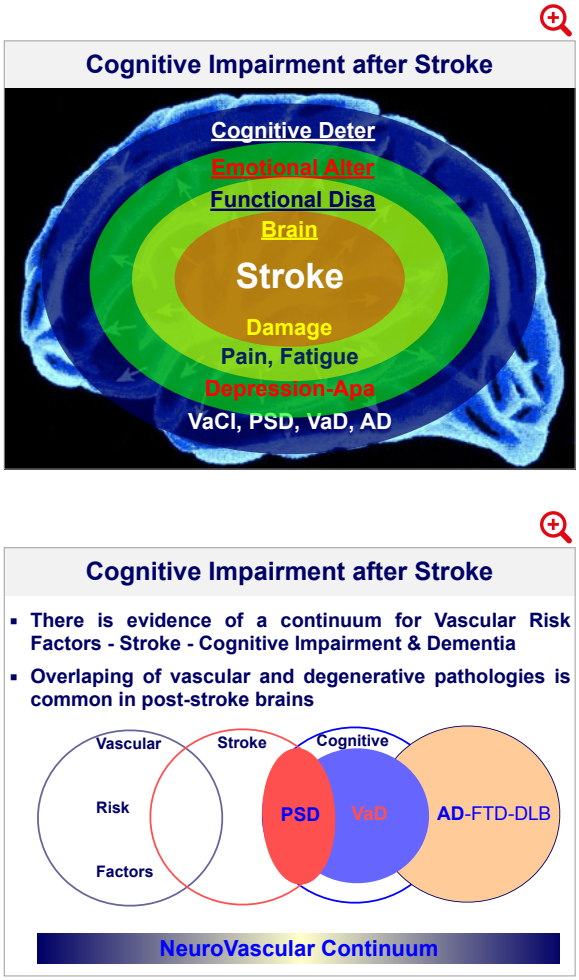

Fig. 1. The brain damage and the neurovascular continuum

He continued to address treatment options for post-stroke dementia with special focus on brain derived neurotrophic factor (BDNF) as a promising drug target. It is recognized as one of the essential regulators of neurovascular unit functions. Endothelial cells produce several neurotrophic factors, including BDNF, which in various ways contribute to the recovery after stoke. In a short overview, Dr. Alvarez explained the expression, synthesis and processing of BDNF, including cleavage of proBDNF by furin and tPA, and its interaction with specific receptors (TrkB with BDNF and p75NTR with proBDNF).

The non-specific interaction of the precursor form with its receptor was shown to trigger apoptosis, while specific interactions of the mature form (BDNF) with TrkB receptor induces pro-survival pathways **(Fig. 2)**. **The key signaling cascades regulated by BDNF are to great extent overlapping with and contribute to the pro-recovery pathways described earlier by Prof. Chopp.**

Dr. Alvarez addressed a question of the involvement of BDNF in poststroke cognitive impairment. BDNF circulating levels are associated with better memory after stroke. On the other side, low levels of BDNF correlates with poor prognosis, in terms of functional status of a patient. Also neurocognitive recovery of patients treated with rtPA was correlated positively with levels of circulating BDNF. Higher levels of serum BDNF can be expected in this context, as tPA is one of the enzymes involved in the processing of mature BDNF. In these patients (with highest levels of BDNF), the decrease in neurological impairment was also most pronounced, as measured with NIHSS. Additionally, it was shown that patients doing aerobic exercises have higher levels of circulating BDNF which correlated with better cognitive recovery. Higher BDNF levels were also associated with a lower risk of depression after stroke. All these recently published data indicate that BDNF is involved in neurorecovery and that it is indeed contributing to ameliorating cognitive impairment after stroke. Regarding the preventive strategies of PSCI-PSD, primary and secondary stroke prevention, as well as some available therapeutic strategies should be mentioned. A reduction of the total vascular burden by use of antihypertensives, antiaggregants and statins leads to a reduction of cognitive impairment at 3 months after stroke. However, multimodal lifestyle intervention had no effect on CI. Other treatments associated with

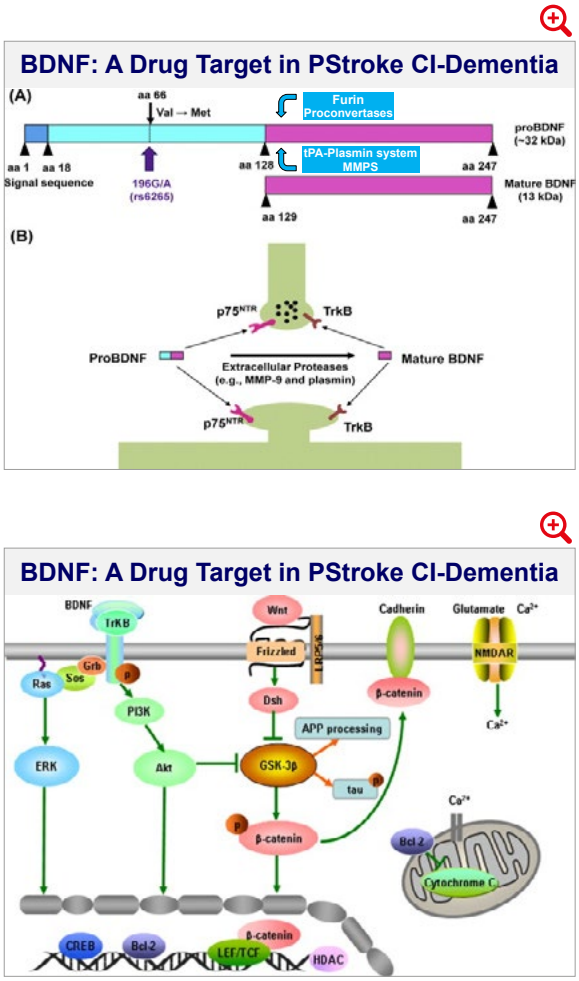

Fig. 2. The expression, maturation and signaling transduction pathways controlled by BDNF

improved cognitive performance after stroke were: treatment of neuropsychiatric symptoms, neurorehabilitation, neuroprotective drugs and BDNF-enhancing agents like Cerebrolysin or SSRIs **(Fig. 3)**. Different treatment options have been associated with increased stroke survival, prevention of post-stroke depression, improvement of motor recovery and the enhancement of cognitive performance together with serum BDNF levels in VaD patients (no data are available for stroke patients, as yet). Finally, **Dr. Alvarez mentioned his own publication reporting the increase of serum BDNF-levels after treatment of AD patients with Cerebrolysin or with a combination Cerebrolysin plus donepezil (Fig. 3)**.

This effect correlated with significantly increased cognitive performance of the treated patients. It was also recently shown that Cerebrolysin enhances expression of BDNF, in particular its mature form, in an animal model of AD. These results highlight and corroborate other research and clinical data explaining the role of Cerebrolysin in enhancing neurorecovery processes, increasing survival rates and ameliorating depression-apathy after stroke.

In summary, Cerebrolysin appears as a good option for the treatment of stroke patients to improve their cognitive functions, but more large scale trials are needed to confirm this benefit.

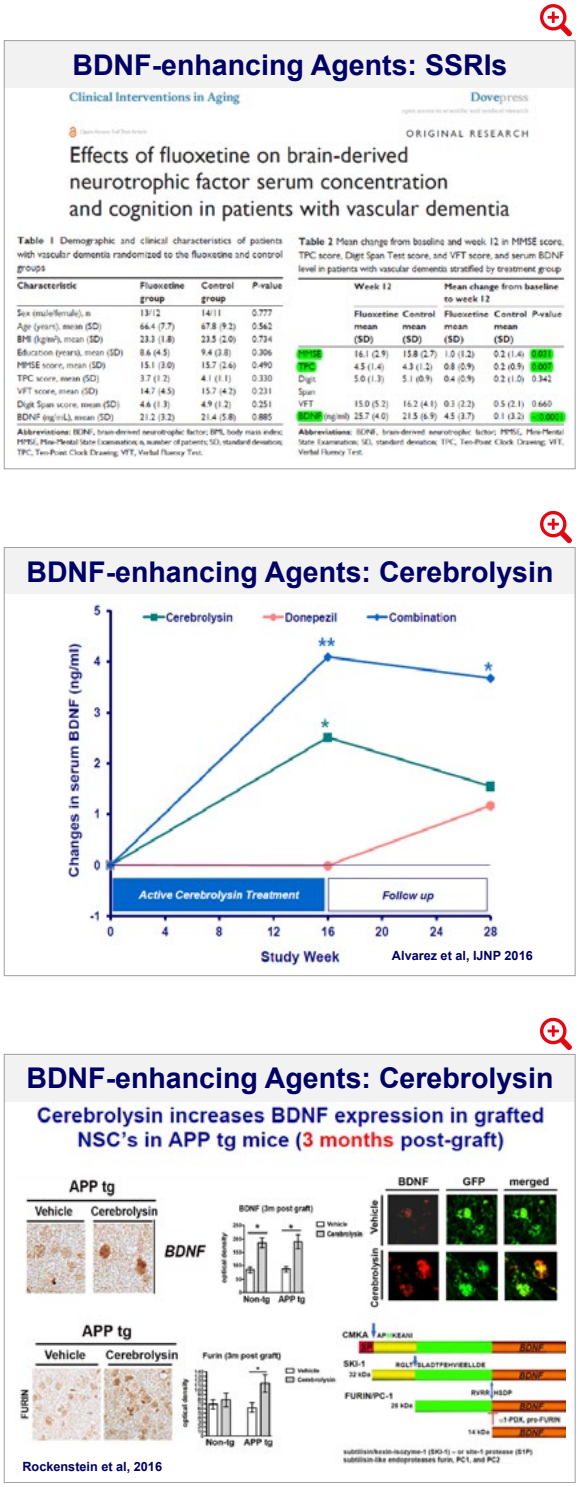

Fig. 3. SSRIs and Cerebrolysin increase BDNF levels in VaD and AD patients

Geriatric stroke care – Epidemiological challenges and special considerations

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ABSTRACT:

Numerous investigations indicate that 75–89% of stroke patients are older than 65 years. By 2025, the global population aged >60 years is estimated to rise to 1.2 billion - double the number 30 years before. Since incidence and prevalence of stroke increase with age, a corresponding increment exists in the age of stroke patients, and most survivors will require rehabilitation.

The brain changes during aging as a result of subtle alterations, such as neuronal atrophy and a decrease in the levels of neurotransmitters and receptors, resulting in impaired neuroplasticity. All these changes have an impact on both, stroke severity and capability for successful rehabilitation.

Furthermore, age-related conditions like musculoskeletal pain, reduced joint mobility and cardiovascular diseases restrict the ability to exercise. Sarcopenia - loss of muscle mass and strength - is present in almost all old stroke patients, thus immobilisation bears a high risk of being left bedridden. Malnutrition due to dysphagia may intensify this problem. Deficits in cognition also affect the success of rehabilitation.

Methods and concepts of therapy are not particularly age related, but have to be adapted in intensity and frequency to patients` capabilities.

The effect of age on the outcome of rehabilitation has been reported by numerous studies. Although the success rate for rehabilitation is lower in the old, the results justify the effort invested in rehabilitation in the geriatric group.

The world population is aging and the life expectancy is increasing by about 2 months per year in the Western Hemisphere. People over 65 years constitute the fastest growing age group worldwide and that trend correlates with the age when the incidence of stroke dramatically rises. This means, that cerebrovascular disease will be an even bigger burden in the future; the number of events will probably double within the next 30 years. Additionally, prognosis of stroke worsens with increasing age in terms of both mortality and potential for recovery from stroke. For a one year mortality after stroke, the following main negative prognostic factors have been established: advanced age, frailty, hemorrhagic stroke, hypertension, ischemic heart disease, hyperglycemia at admission. By evaluating changes in the methylation of DNA as function of aging, it was found that stroke patients are indeed biologically older (by about 2.5 years) than the comparable healthy population.

One of the concepts explaining these data postulates that the aged brain is probably a prodromal disease brain. **The healthy aged brain presents changes in many different domains, like: neurotransmission, neurogenesis, blood brain barrier, neuroinflammation, neurodegeneration, demyelination, and axonal damage.** These changes have a cumulative impact on stroke patients. In animal models of stroke, both necrosis and apoptosis occur earlier in aged animals compared to younger animals implying that we need to take this difference into consideration while treating patients. The treatment window may be different for older patients. It can also be assumed that rehabilitation efforts strictly depend on neuroplasticity and there are several key plasticity mechanisms inhibited in the aged brain (e.g. synaptogenesis, neural outgrowth, neurotrophin expression, neurogenesis). Beyond the age of 70, patients usually are multi-morbid and suffer on average from 5 diseases **(Fig. 1)**.

The general physical condition of an old patient depends on genetic, environmental and lifestyle variables and the phenotypes of aging vary by about 20 years. However, there is a common constant reduction of physiological reserve which limits the functions of all important organs. Therefore measuring frailty using e.g. the WHAS - Frailty Score is important. One of the prevailing factors triggering frailty is malnutrition which is usually related to dysphagia (present predominantly in patients suffering from cerebrovascular diseases). The lack of proteins leads to a resorption of proteins from muscles. The same occurs with immobilization. A healthy old man loses up to 25% of muscle power and lean tissue after 10 days in bed and we need to be aware that especially geriatric patients should be mobilized regularly. Nosocomial events, including infections, falls and delirium (potentially leading to dementia), are major problems as well as hospital acquired pneumonia which is also related to dysphagia.

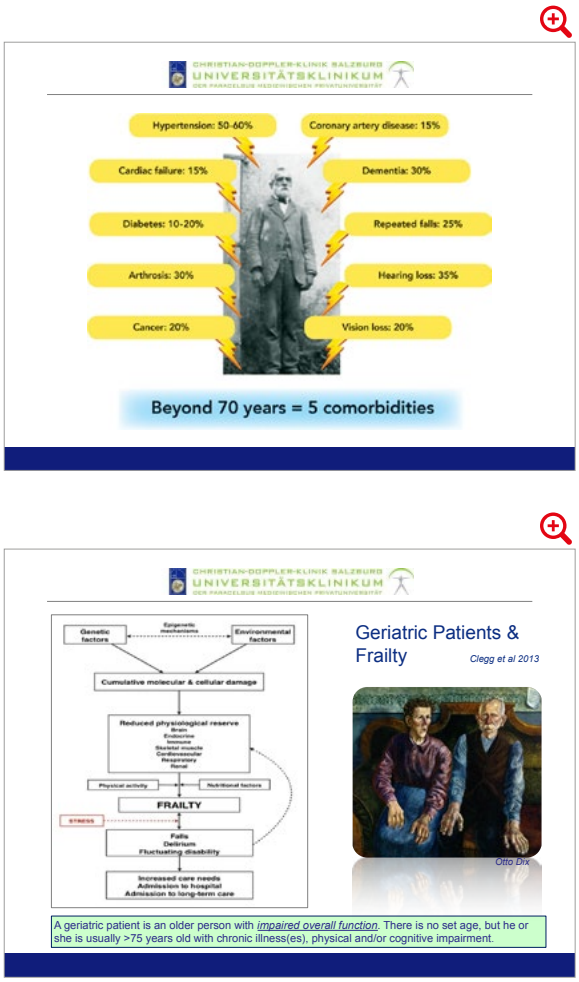


Fig. 1. Comorbidities of old age and the frailty as major factors influencing stroke care

Discussing geriatric patients rehabilitation and understanding their "pyramid of needs" leads to conclusion that their most important requirement is quality of life, followed by autonomy while life extension is considered less important. This finding supports the decision-making for the rehabilitation process as well as the evaluation of geriatric patients, usually done by geronto-scope. This tool is a multidisciplinary approach to assess the functional ability, different domains of health and the socio-environmental situation from the perspective of the future life of a patient. Several other related conditions interfere with rehabilitation and Dr. Igleseder reviewed them shortly **(Fig. 2)**.

Dr. Iglseder noted that it is possible to work with old patients in spite of all these difficulties. He and his team found out that the rehabilitation of motivated patients with an average age of 85 resulted in 25-30% increase in muscular strength of lower extremities within 6-8 weeks of training.

Another issue typical for geriatric patients is multi-medication, resulting in an elevated risk of drug-drug interactions. Treatment of vascular risk factors is as effective as it is in young patients. At the same time, all tranquilizers and antipsychotic drugs negatively influence neurorehabilitation while drugs with a positive effect on neurorehabilitation should be added to the mix (e.g. SSRIs, dopamine, Cerebrolysin).

Dr. Iglseder summed up his lecture by saying that we will face increasing challenges form the growing population of geriatric patients in coming decades. The worse prognosis in these patients is associated with neurobiological background, frailty, sarcopenia and malnutrition, higher risk of complications, and nosocomial events (delirium, ADE, falls, pneumonia). However, old age is not a reason to postpone or deny treatment and rehabilitation.

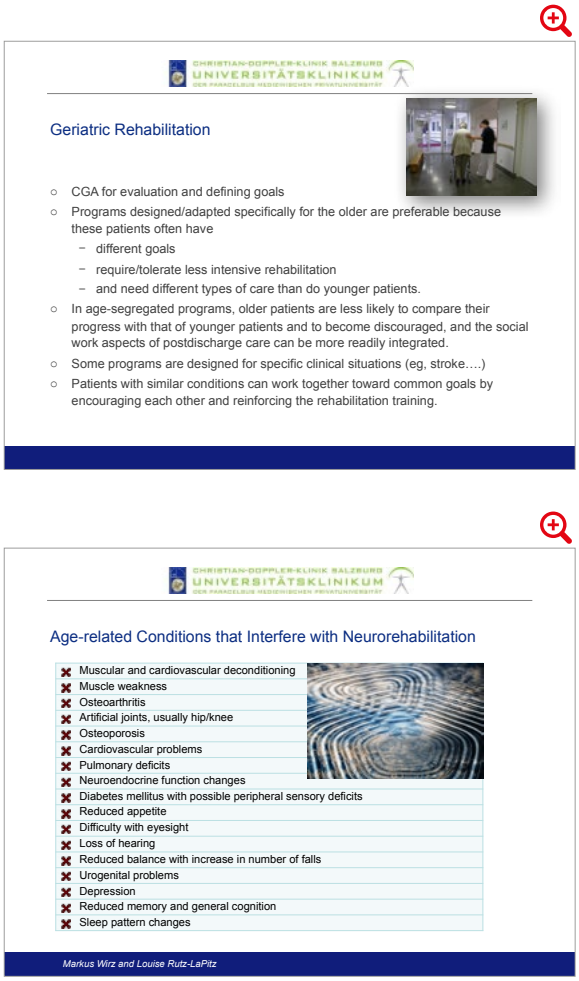


Fig. 2. Geriatric rehabilitation and age-related conditions interfering with rehabilitation

Timing, training, and tinctures – Reorganization & recovery after stroke

Steven R. Zeiler

Johns Hopkins Neurology Phipps 4-4446, Baltimore, MD, USA

ABSTRACT:

Studies in humans and nonhuman animal models show that most recovery from impairment occurs in the first 1–3 months after stroke as a result of both spontaneous reorganization and increased responsiveness to enriched environments and training. Improvement from impairment is attributable to a short-lived sensitive period of postischemic plasticity defined by unique genetic, molecular, physiological, and structural events. Data suggests that there are three important variables that determine the degree of motor recovery from impairment all else being equal: (i) the timing, intensity, and approach to training with respect to stroke onset, (ii) the unique post-ischemic plasticity milieu, and (iii) The extent of cortical reorganization. I will present data regarding both the biology of the brain's post-stroke sensitive period and the difficult question of what kind of interventions best exploit this period. I will describe limitations of current post-stroke rehabilitation methods and suggest novel interventions, which incorporate robotics, video-gaming, and pharmacological interventions including SSRIs and Cerebrolysin. Of importance, Cerebrolysin has allowed us for the first time to model spontaneous recovery in an animal model of motor stroke.

Prof. Zeiler discussed about what we are doing right versus what we are doing wrong in stroke rehabilitation. 80 billions USD annually is being spend on stroke care in the USA alone, and only a third of that is accounted for acute stroke care as chronic stroke and recovery cost more. With improving acute care standards more patients are surviving and require further medical assistance; about 70% of stroke survivors suffer from motor deficits affecting their daily lives.

As with any complex matter, the question of terminology is important, therefore, Prof. Zeiler defined the term "recovery" as an improved success at a specific task reducing neurological impairment. The true recovery of motor functions should not be mistaken with compensation. For example, true recovery of right hand functions means that a patient can use his right hand again as he did before stroke, whereas compensation means that a patient can use his left healthy hand to compensate for a dysfunctional right hand.

How good our efforts are right now in post-stroke interventions? asked Prof. Zeiler. Until now, data suggest that current physical and occupational therapies have no effect on true functional recovery. Rehabilitation therapies

help patients to compensate for lost functions and to get patients back home, but they do not reduce the impairment.

Prof. Zeiler introduced the audience to the data driven model of recovery from stroke used in his lab as a blueprint for the experimental setup **(Fig. 1)**.

He showed, that after stroke a short period of time exists, called the sensitive period of plasticity, during which spontaneous recovery (true recovery) of lost motor functions occurs to a certain level. In humans, the maximum recovery

In the animal model suitable for assessment of the learning-based motor task performance, mice are being trained in upper arm prehension. They have to grab a food pellet through a hole in a plastic cage. At the beginning of the learning process the animals are poor performers, but with time they learn the skill very well. Afterwards, a small and reproducible stroke is induced in the primary motor cortex **(Fig. 2)**. It targets the area responsible for learning and the maintenance of the learned prehension skill. After the stroke, animals are allowed to rest for 7 days. When the skill performance is measured after this period,

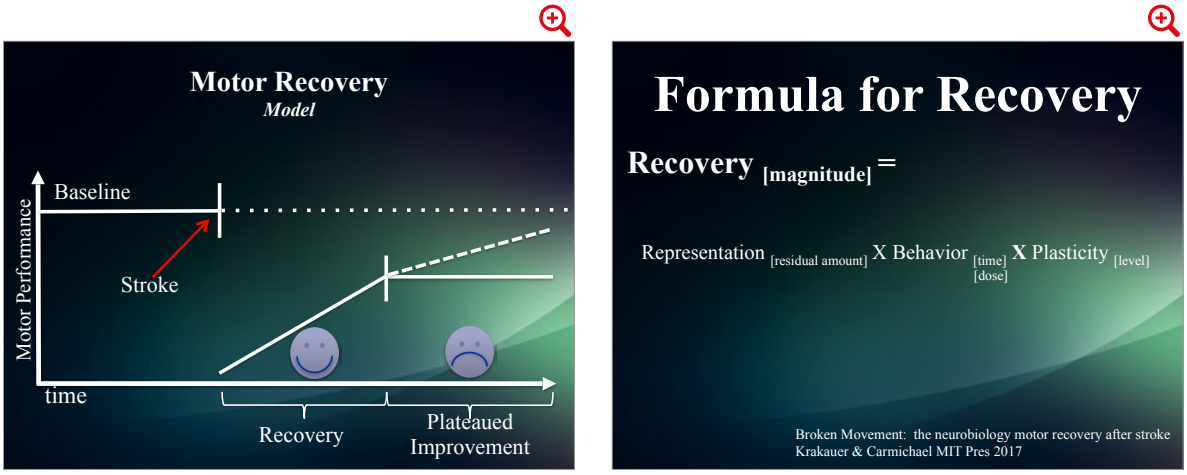
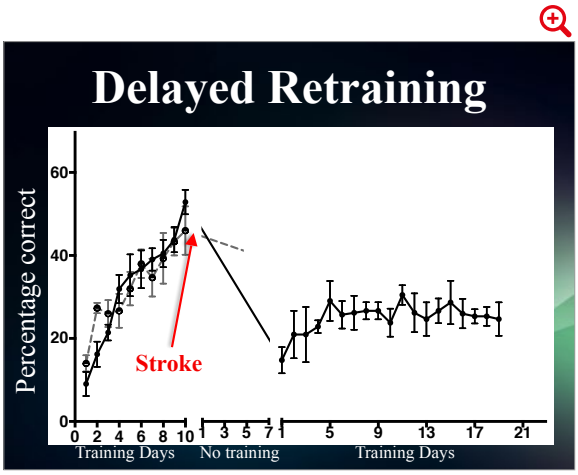


Fig.1. A model explaining sensitive recovery period after stroke and the Formula For Recovery

level can be reached within the period of initial 3 months post-stroke. Prof. Zeiler went on to introduce the Formula For Recovery developed by John Krakauer and S. Thomas Carmichael and published in 2017. It represents how much of the brain (motor cortex) is left intact, how the remaining brain interacts with input (behavior) of the subject, and how the resulting environment then interacts with plasticity **(Fig. 1)**. The representation of the remaining brain is a topic of acute stroke care, while the topic of this lecture was the impact of behavior and plasticity on recovery after stroke.

a strong impairment of this skill can be measured and after rehabilitating the animals intensely during next 3 weeks they improve only a little bit, but do not reach the skill level from before the stroke. This doesn't happen because the mice forgot the skill; the control sham animals do just fine. When the experiment is modified and the animals rest only 1 day instead of 7 days, they get back to their pre-stroke skill level in a couple of days. In other words, there is something very special happening in this short period after stroke that allows the animals to take advantage of rehabilitation. This knowledge opens an opportunity to test new therapeutic strategies for stroke recovery and this is what Prof. Zeiler and his team did.



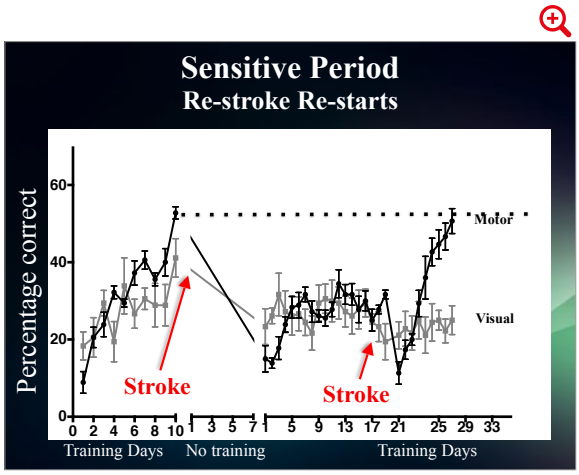
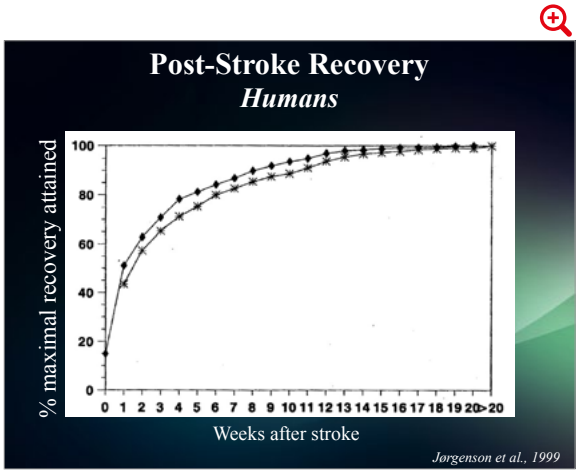


Fig. 2. The experimental setup for studying the sensitive recovery period using the mice stroke model

When a 2nd stroke was induced in the animals which rested for 7 days and were rehabilitated for 3 weeks **(Fig. 2)**, the repeated rehabilitation within the new sensitive period allowed them to quickly re-gain the initial motor skill level. It almost seems as if the second stroke created an opportunity through re-opening this short sensitive plasticity period for effective rehabilitation of motor skills and for true functional recovery.

Can we apply this knowledge to our patients? asked Prof. Zeiler. Is there a similar time window for recovery in humans? It seems, that the answer is positive. The mentioned earlier data indicate that recovery occurs within the initial 3 months. Cortes et al., (2017) compared different upper limb motor tests to find out how long after stroke the recovery of motor functions is possible. The most sensitive of these tests, the AMD test, which eliminates any influence from compensation on the recovery outcome, showed that the true recovery period is in fact much shorter and plateaus at 2 weeks **(Fig. 3)**.



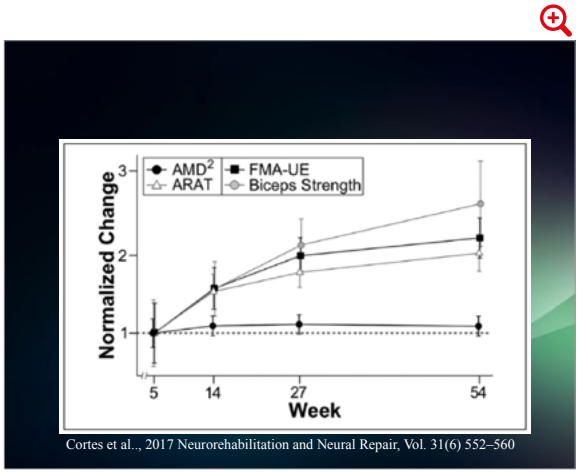
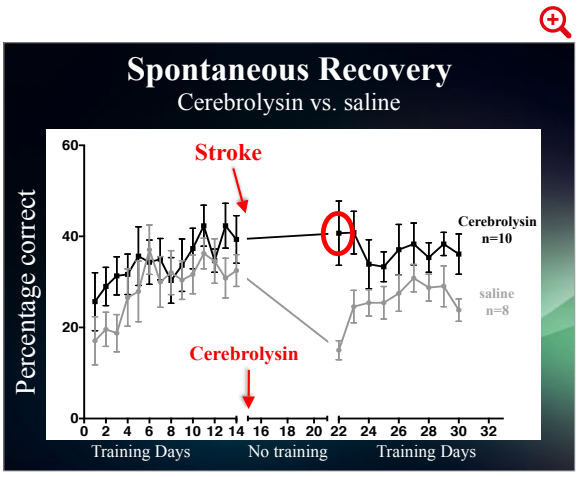


Fig. 3. The motor recovery post-stroke in patients is limited to a relatively short time window

In contrast to the situation observed in the normal brain as well as in the chronic post-stroke brain, in the acute post-stroke brain there is an increased amount of plasticity going on, and we can probably take advantage of this situation for improving our rehabilitation efforts.

Finally, to enhance recovery, we can alter or prolong the sensitive period. Here, Cerebrolysin may play a role. Cerebrolysin showed properties that are closely linked to mechanisms of brain recovery. Also, some clinical trials showed a benefit after stroke. Prof. Zeiler and his team tested Cerebrolysin in their mouse stroke model. Treatment started 24 hours after stroke and the animals that received Cerebrolysin improved, even without rehabilitation. **When Cerebrolysin was given as add-on therapy to rehabilitation, noticeable improvement of prehension skills were observed. This is the first instance when a pharmacological agent enhanced spontaneous recovery after stroke (Fig. 4)**.

In conclusion, Prof. Zeiler stated that we should replace the current in-hospital environment with the enriched one, where patients can also exercise task-independently and with higher daily intensities/repetitions to recover their motor functions. Additionally, pharmacological enhancers of spontaneous recovery, like Cerebrolysin should be administered. All these interventions should happen early after stroke.



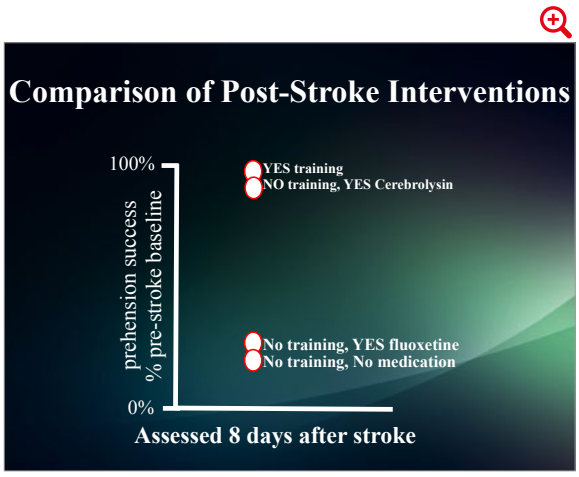


Fig. 4. Cerebrolysin enhances natural recovery processes active within the sensitive period; a comparison of different post-stroke interventions

Consequences after stroke – When they occur and how they are treated

Natan M. Bornstein

Director of the Brain Division, Shaare-Zedek Medical Center, Israel

ABSTRACT:

Stroke is the leading cause of death and one of the most frequent causes of the global burden of disabilities. Therefore, recovery from the consequence of stroke is an important goal. However, the definition of global recovery from stroke and the goals are not well defined by the professional stroke neurologists and neuro-rehabilitation physicians. Currently, most of the efforts are invested in the early stages after stroke and is focused on improvement of the neurological deficit measured by the NI- HSS (impairment), where improvement of 4 points is considered clinically relevant. Later on, the functional outcome is measured, usually at 90 days, by the mRS (disability), which is also mainly based on the motor functional ability.

And what about handicap? It is a completely different definition than impairment or disability, as it relates to the deficiencies that the patient experiences and the way he perceives his function in his daily life, even if by the current measurements he is defined as fully recovered.

None of the above mentioned measurements consider the patient in a holistic manner and don't take into consideration the behavioral-emotional and cognitive impairments which have a significant impact on the patient's functional recovery. Moreover, none of these actually takes into account the patients' perspective. What is the definition of recovery from the patients' point of view?

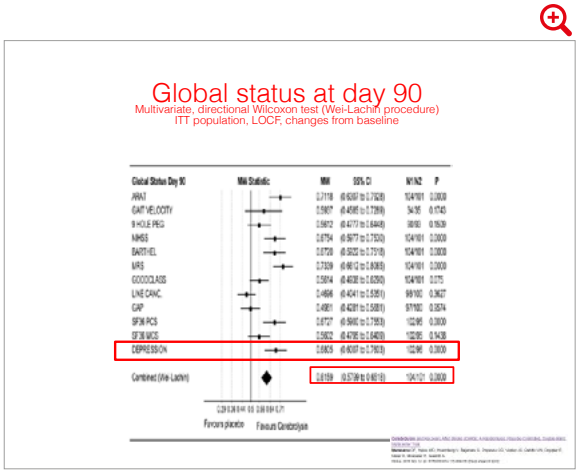
Recently, the Patients Report Outcomes (PROMs) index has been introduced in order to improve care experience, health outcomes and value the ways that matter to the patients and not just to the physicians.

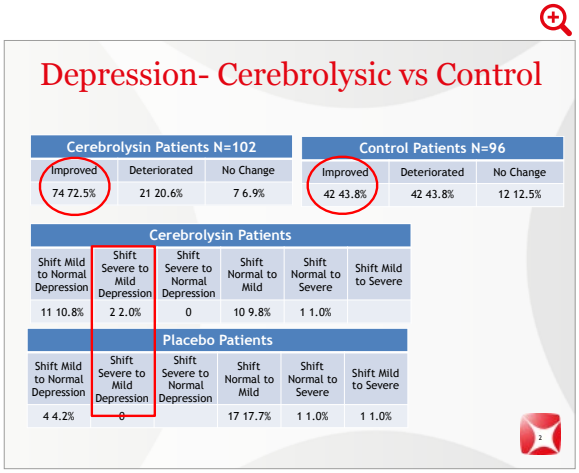
Everybody has a different idea about the term "Neurorecovery" said Prof. Bornstein introducing the audience to a leading theme of his lecture. He outlined what is known about this field of medicine and what kind of goals can be realistically considered in general and specifically in rehabilitation.

Epidemiological data indicate that dementia and cerebrovascular diseases are the most prevalent disabilities worldwide, which underlines one goal to redefine rehabilitation needs of patients. This should have major implications for the organization of all institutions involved in rehabilitation. Medical institutions need to apply the available knowledge about brain recovery processes

which could lead to a reduction in post-stroke complications. Starting rehabilitation earlier than currently practiced is, for most patients, still an unmet need, as is a longer, more patient focused rehabilitation, especially for chronic stroke patients. Furthermore, cognitive and emotional disorders should be strongly prioritized and targeted.The post-stroke rehabilitation should be done in a multidisciplinary way. The mood, emotional and cognitive disorders are key factors influencing and determining the success of rehabilitation.

Post-stroke depression is a huge problem, because depression is such a difficult entity to deal with medically and also it is the most common neuropsychiatric consequence of stroke. 30% of all patients have mood disorders and/or depression. Depression also has a negative impact on recovery and is linked directly to survival as well as functional and cognitive disability. The depressive symptoms are often under-diagnosed and under-treated, due to a lack of follow-up systems after patients are discharged from primary care institutions. **Much more awareness about the catastrophic consequences of post-stroke depression and diagnosis, treatment or even prevention is needed. Cerebrolysin should also be discussed in this context as the CARS trial results revealed that this compound also has anti-depressive activities (assessed with the Geriatric Depression Scale, GDS) (Fig. 1)**





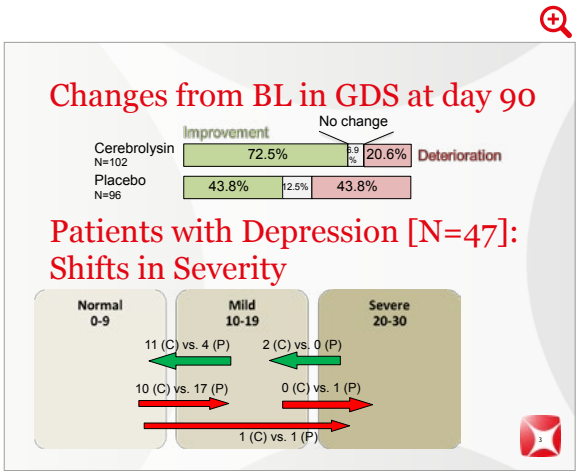
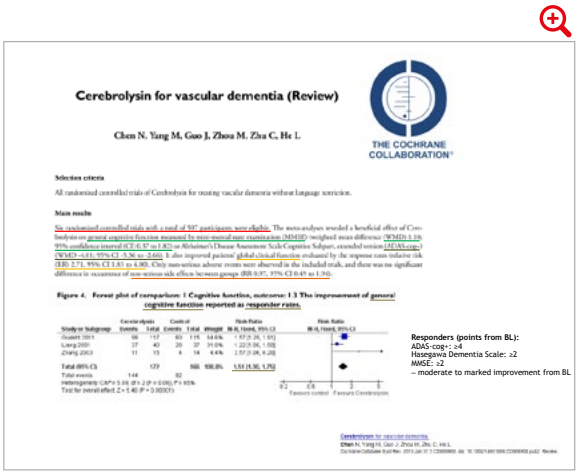


Fig. 1. The CARS trial results point to anti-depressive potential of Cerebrolysin



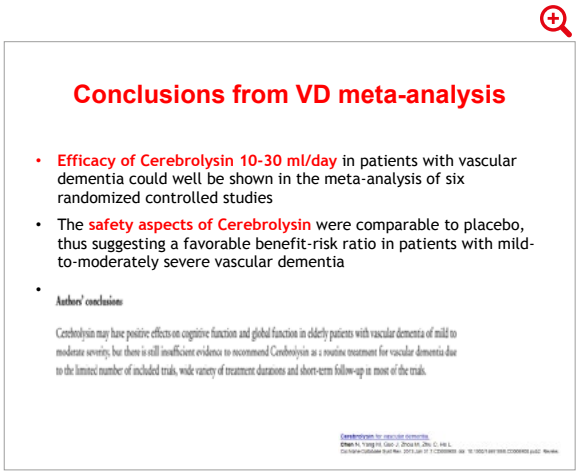


Fig. 2. Meta-analysis of Cerebrolysin treatment of VaD patients

The focus should be also on post-stroke cognitive impairment, mostly associated with vascular disease, which may be the only preventable dementia of late life. About 10% of patients will develop dementia after their first stroke, while recurrent strokes evoke dementia in about 30% incidence rate. Additionally, one in ten patients suffer from pre-stroke dementia. In this context, it should be mentioned that Cerebrolysin improves cognitive parameters in vascular dementia **(Fig. 2)** and Alzheimer's disease patients.

Among key benefits of Cerebrolysin treatment of dementia are:

- **combination of symptomatic with long-term treatment effect**
- **lower doses (10-30 ml) improve cognitive functions at early AD stages**
- **higher doses (60 ml) improve behavioral symptoms at late AD stages**
- **Cerebrolysin is as effective as ChEI**
- **Cerebrolysin is safe and well tolerated also in combination with CHEI**
- **Cerebrolysin is safe and effective treatment for mild-to-moderate forms of dementia (VaD and AD)**
- **Cerebrolysin is effective in in-patients and out-patients**
- **injectables, like Cerebrolysin, have better compliance than oral drugs**

Fig. 3. Evolution of stroke care toward wellbeing

Regarding the outcome after stroke, it is important to focus more on the patient's individual handicaps, and this can be achieved by using PROMs (Patient Related Outcome Measures). Traditionally, medical professionals focus on impairment (neurological deficits, measured with NIHSS) and disability (measured with mRS), but the patient's perspective about the perceived individual value of the treatment and about the ensuing handicap are the most important and often neglected parameters. Utilizing PROMs can support healthcare institutions in improving patient's care experience, health outcomes and the value of offered treatments. The idea behind PROMs is to engage with patients instead of treating them as passive entities, to prioritize value over quality of care and of long-term outcome over clinical processes. PROMs can guide medical professionals in understanding stroke patient's needs and priorities in life, which is what matters most to patients, carers, families and populations **(Fig. 3)**.

Outcomes are results people care about when seeking treatment, including functional improvement and the ability to live normal, productive lives.

Post-Stroke Spasticity – Current treatments and new opportunities

Romil M. Martinez

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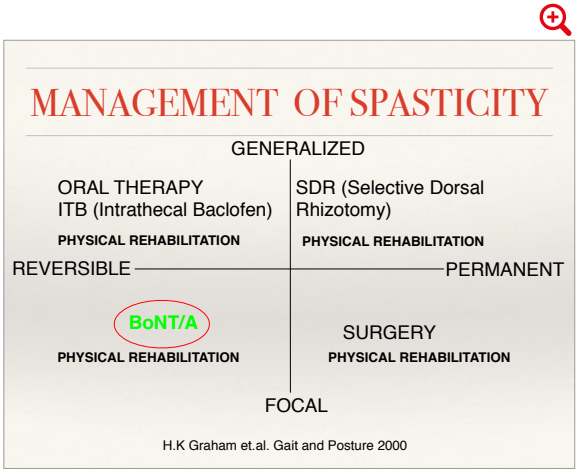
ABSTRACT:

Spasticity which is considered to be one of the main complications after stroke has a prevalance rate of 30% among stroke survivors. We still have to come to terms of consensus definition of spasticity because of its complexity. However such phenomena maybe described as an upper motor neuron syndrome caused by damage to parts of the brain that sends messages for GABA to be released, which increases excitatory impulses. Available treatment for spasticity includes the use of oral medications such as Baclofen, Tizanidine, and Dantrolene; chemodenervation using Botulinum Toxin A; intrathecal Baclofen; neurosurgical procedures and physical rehabilitation using modalities and therapeutic exercises. In relation to this, we conducted a retrospective study in the Department of Rehabilitation Medicine of Amang Rodriguez Memorial Medical Center on stroke survivors who received Cerebrolysin 10ml/ampule intramuscularly given for 30 days and stroke survivors who did not receive Cerebrolysin. Outcome measures using Rankin Handicap Scale, Modified Ashworth Scale, and Manual Muscle Testing were analyzed between the two groups. Results showed a significant decrease in spasticity, increase in the MMT scores and improvement in Rankin Scale in the Cerebrolysin group. In conclusion, Cerbrolysin (IM) treatment over 30 days is safe and may have a significant effect in reducing spasticity, increasing motor recovery and function among post-stroke patients in an out-patient rehabilitation setting.

The lecture of Dr. Martinez focused on post-stroke spasticity caused by GABA-deficiencies and an excess of excitatory impulses. Intrathecal treatment with baclofen (GABA B receptor agonist) and nipecotic acid (GABA uptake inhibitor) provides a significant suppression of spasticity, rigidity, H-reflex or motor evoked potentials. Dr. Martinez referred to the earlier lecture of Prof. Bornstein and said that self-perception of stroke patients plays an important role in recognizing spasticity. The management of spasticity was summarized **(Fig. 1)**, and Dr. Martinez reviewed major pharmacological agents, like botulinum toxin, as well as electrotherapy, exercises and stretching. Just like the treatment of stroke, treatment of spasticity is a multidisciplinary challenge.



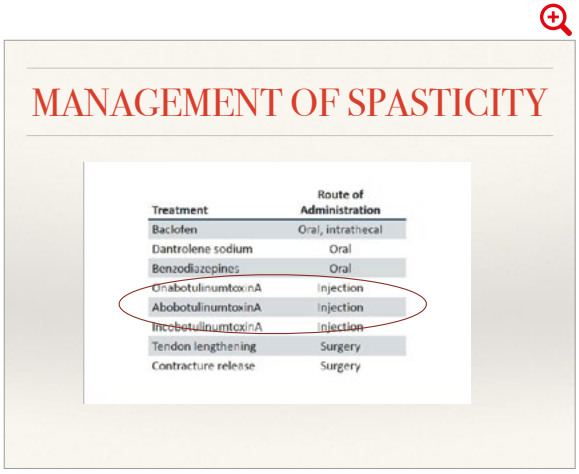
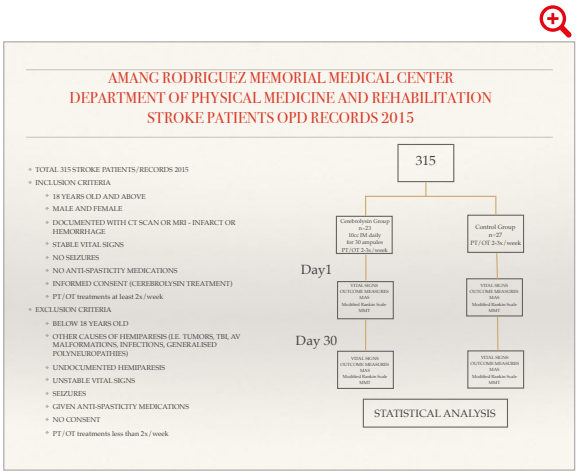


Fig. 1. The management of spasticity

Finally, Dr. Martinez presented the results of a study in which he was one of main investigators, titled: A RETROSPECTIVE STUDY ON THE EFFECT OF INTRAMUSCULAR CEREBROLYSIN ON POST STROKE FILIPINOS IN AN OUT-PATIENT REHABILITATION SETTING.

The inclusion and exclusion criteria and study design were discussed **(Fig. 2)**.

Cerebrolysin was administered intramuscularly into deltoid, biceps, quadriceps, gluteus max in 10 ml daily for 30 days. The study used the Modified Ashworth Scale for the impairment and Rankin Handicap Scale for disability endpoints as well as the Manual Muscle Test (MMT). For all the tested muscle groups, in upper and lower extremities, the treatment with Cerebrolysin resulted in a significant decrease in spasticity during the study observation time. The MMT scores indicated that



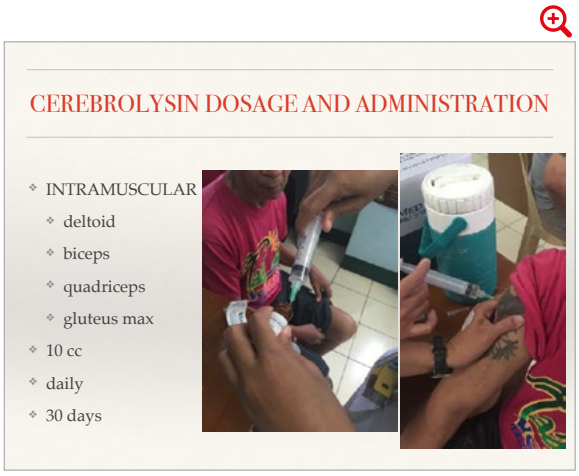
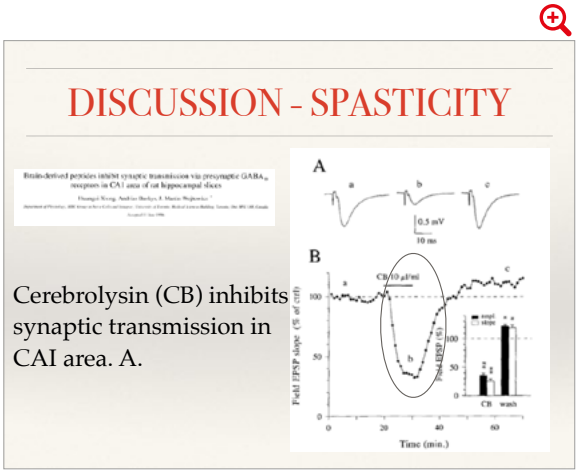


Fig. 2. The design parameters of the retrospective study evaluating the effect of Cerebrolysin on spasticity during rehabilitation after stroke



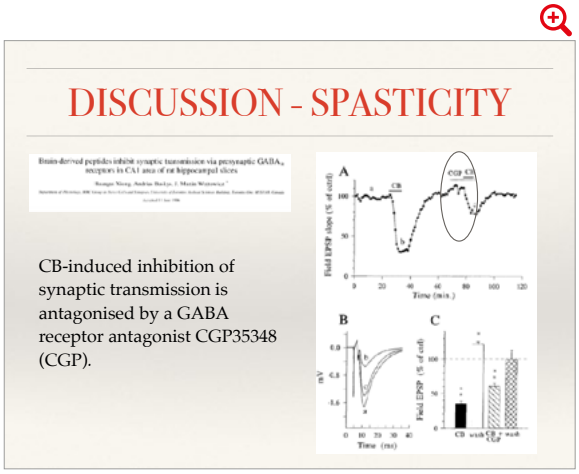


Fig. 3. The potential mechanism of action of Cerebrolysin in post-stroke spasticity

Cerebrolysin enhanced motor recovery in the majority of muscle groups. The Ranking Scale scores did not show any differences between Cerebrolysin and placebo groups.

The potential mode of action for reduction of spasticity was discussed as well **(Fig. 3)** and Dr. Martinez mentioned that Cerebrolysin (CB) inhibits synaptic transmission in the CAI area A. Additionally, CB-induced inhibition of synaptic transmission is antagonized by a GABA receptor antagonist CGP35348 (CGP).

In conclusion, Cerebrolysin (IM) treatment over 30 days was safe and may have a significant effect on reducing spasticity, increasing motor recovery and function among post-stroke patients in an out-patient rehabilitation setting. Dr. Martinez illustrated the talk with case documentation of patients treated with Cerebrolysin and recommended that further studies with improved methodology i.e. randomized controlled trial, increased sample size and more reliable, valid and responsive outcome measures should be considered.

Rehabilitation in low and middle income countries – Status quo and perspectives

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ABSTRACT:

Stroke is the second most common cause of death worldwide and the third most common cause of long term adult disability in developed countries. Age specific mortality rates for both stroke types, ischemic and hemorrhagic, are greater overall in low-income to middle-income countries (LMIC), than in high income countries. Stroke victims are considerably younger in LMICs and suffer more often from hemorrhagic than ischemic stroke. Prevention of stroke is of course the ideal scenario but with more than 15 million strokes every year worldwide, acute treatment and rehabilitation should also be optimized. In recent years, significant advances have been made in the understanding of stroke pathophysiology, diagnosis, prevention and treatment. Intravenous application of tPA within the first 4,5h of stroke significantly reduces stroke morbidity and mechanical thrombectomy with new generation stent-retriever devices have been recently proven to contribute substantially to a favorable outcome. However, a significant number of stroke victims, especially in Vietnam, do not arrive at the hospital in time for tPA treatment; partly, due to geographical reasons as well as shortcomings in the availability of emergency services and rescue supply chains. In general, LMIC Rehabilitation facilities are lacking, there are scarce ambulatory rehab services and virtually no specialized rehabilitation-therapists (one for all). The current burden for stroke patients in LMICs is shifted towards the caregivers and families.

Therefore, it is of vital importance to establish evidence based rehabilitation guidance programs at the community level for stroke recovery, especially in LMICs, countries with lack of post-acute rehabilitation facilities. With the AVANT-Program (Austrian Vietnamese Advancement Neurorehabilitation Treatment) we provide a community based, training program, teaching basic, video guided principles of motor recovery, which can be easily adapted by general practitioners, therapists and caregivers. During the course of the AVANT-Program more than 30 therapists from Vietnamese stroke centers attend a 3 week rehab-training-program in Austria. Over the next three years, Vietnamese trainees will pass on their skills to their colleagues by giving more than 70 educational courses at 64 Central hospitals in Vietnam. The final goal is to provide practical and theoretical support and empowerment for caregivers and families of Vietnamese stroke patients.

The burden of stroke is not distributed equally between countries which is the reason why international programs, like AVANT, are needed to change or improve standards in clinical practice. More than 80% of the world`s population live in over 100 developing countries and we observe a fast epidemiologic transition from infectious to chronic non-communicable diseases. Stroke causes 6 million deaths each year, with the greatest burden in LMIC (low, middle income countries) where it affects people at younger ages with poor control of risk factors. Globally, the WHO estimates that about 1 billion people live with disabilities. Of these, 80% live in low/middle-income countries with inadequate access to health and rehabilitation services. Neurological disorders are among the leading causes of disabilities: stroke – in LMIC accounts for 86% of global stroke deaths; TBI, mainly caused by road traffic accidents and falls, shows similar figures. **Altogether, 3% of people with chronic disabilities worldwide receive rehabilitation in their lifetime, but 60% of developing countries have no or insufficient rehabilitation services.** When available, they are usually located in urban centers, often inaccessible for many patients due to costs and distance. Even when available, a lack of a well structured neurorehabilitation facilities exist and healthcare systems cannot provide comprehensive rehabilitation services. Physicians with expertise in neurorehabilitation training are relatively uncommon. Therapists usually have variable levels of training ("one for all"). OT, ST, neuropsychologists, Rehab-nurses are usually missing.

In Vietnam, stroke is the leading cause of death, with 230,000 cases annually accounting for 110,000 deaths and 1.7 disability-adjusted life years (DALYs) lost. Many complications are preventable using simple, inexpensive interventions, but many hospitals lack access to evidence-based standards of care due to workforce and capacity constraints. Patients are generally discharged within one week of admission. Most (75%) return home to their provinces, where few healthcare resources are available. 62% of caregivers have low education level (less then 9 years of schooling).

Fig. 1. The AVANT Program is sponsored by EVER Pharma GmbH

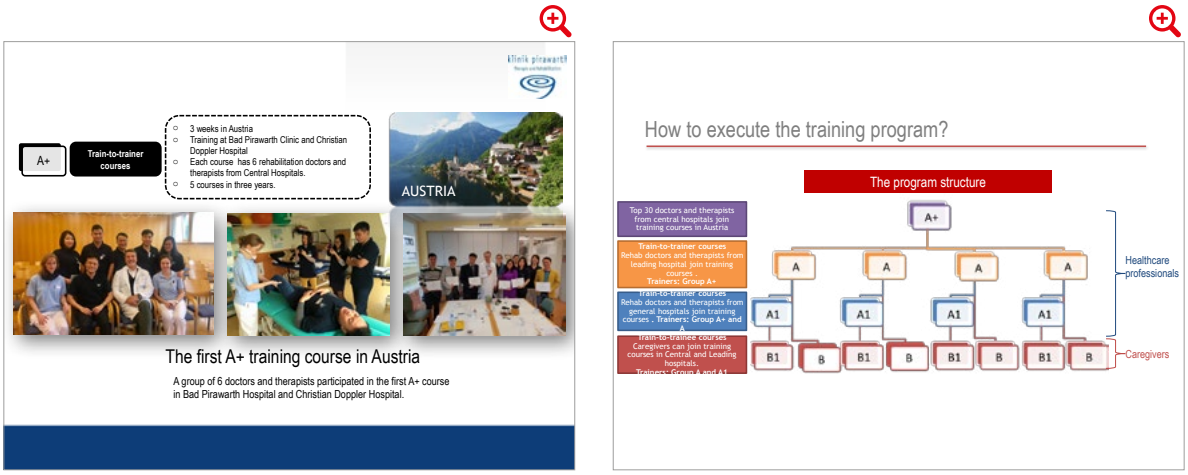

Fig. 2. The goals and the milestones of the AVANT program

66% have an income less than US$ 250. 80% of stroke patients were discharged without receiving physiotherapy. Specific occupational (OT) or speech therapy (ST) cannot be offered. Insufficient support or education for caregivers exist. Also, information is insufficient how to avoid stroke recurrences (incl. pharmacological support, risk factor management).

In this context the AVANT program aims at standardization and systemization of neurorehabilitation practices in Vietnam (Fig. 1). Prof. Winkler thanked EVER Pharma GmbH for the sponsorship and the conceptual support for this program which is officially endorsed by the Vietnamese Ministry of Health.

In AVANT's initial step, EVER Pharma GmbH, in cooperation with Austrian rehabilitation centers, developed specific material (video, booklet with pictures) for rehabilitation experts and caregivers in Vietnam – this material shows basic routines and enables caregivers and patients to exercise and do simple task-oriented training in the absence of professional rehabilitation infrastructure.

The second step aims to introduce the Vietnamese doctors and therapists to structure and practice of the Austrian rehabilitation system. This exchange program lasts 3 weeks, includes hospitation in acute care and in a rehabilitation facility focused on stroke patients. The goal is to train at least 30 Vietnamese specialists within 2 years (2017-2018). These Austrian-trained specialists become the main coaches in Vietnam and cascade their knowledge down to the level of caregivers. The final goal is that all regions in Vietnam have access to knowledge and experience via the AVANT Program. Many partner hospitals in Vietnam already participate in this program and more than 70 workshops will be implemented within the next 3 years. After three years, the program expects to deliver: 100 classes for healthcare professionals yielding 3000 trained doctors and therapists as well as over 100 classes for caregivers with 10.000 – 20.000 caregivers trained, focusing on the prevention of post-stroke consequences and improvement of motor recovery. A scientific evaluation of the AVANT with quality improvement projects, as known from acute stroke therapy areas (stroke registries), are in the development phase.

Dr. Winkler mentioned at the end that the AVANT program is available not only for Vietnam and that rehabilitation physicians in all countries can adjust the content and structure, in order to create their own concepts which optimally respond to local rehabilitation needs.

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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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