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Scientific Symposium EVER

Immediate neurorecovery treatment improves longterm outcome

Official Symposium of the
5th European Stroke Organisation Conference (ESOC 2019)
22-24 May, 2019 | Milan, Italy

Program of the symposium

Immediate neurorecovery treatment improves longterm outcome

Thursday, 23th May 2019, 12:45-14:15 (Auditorium)
Chairman: Dafin Muresanu, Romania

Welcome speech

Dafin Muresanu

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

Doctor Muresanu greeted the audience of the EVER symposium indicating that neurologists should commit more to rehabilitation of their patients. This is particularly relevant now, when the important new data are being published about the endogenous mechanisms of recovery from neurological disorders, like stroke and TBI. We have better chances right now to knowingly and precisely support, enhance and prolong the spontaneous recovery by various interventions, including pharmacological approaches. This symposium, which is dedicated to neurorehabilitation, will review the current knowledge and new therapeutic approaches in this fast developing field.

Cerebrolysin - challenges & perspectives in neurorecovery

Michael Brainin

Department of Neurosciences and Preventive Medicine, Danube University Krems, Austria

ABSTRACT:

Neuroprotection and Neurorepair after Stroke: Overview of Recently Published Cerebrolysin Studies.

Cerebrolysin is a neuropeptide preparation with neurotrophic factor-like effects and has shown to promote recovery after brain injury. Its pre-clinical profile promises wide applications due to multi-target effects. Currently, Cerebrolysin is used for treatment of cerebral ischemia and neurodegeneration. In a stroke, early clinical trials were performed mostly in mildly affected stroke populations which usually have a favorable prognosis. Due to this selection, a floor or ceiling effect of recovery measures in the mild cases did not allow to show a statistical benefit among treatment groups at the chosen study endpoints in time. More detailed subgroup analyses of more severely affected patients reveal a strikingly positive effect for enhanced recovery. Based on the findings from several studies it became evident that the effect sizes of Cerebrolysin were increasing with stroke severity. Other controlled studies showed that Cerebrolysin can be safely used in combination with thrombolysis. More recently, Cerebrolysin has been tested not only for neuroprotection but also for its neurorecovery potential. Recent trials showed a beneficial effect for functional recovery when combined with neurorehabilitation versus neurorehabilitation alone. Also when using this combined or ragmatic approach for neurorecovery, beneficial effects are most clearly demonstrated in moderately to severely affected patients. This gives a lead to the planning of a more rigorous study design in the future. Moreover, in all studies Cerebrolysin was applied safely and was well tolerated.

Dr. Brainin, the current President of the World Stroke Organization, began his lecture with an overview of the knowledge about physiopathology of the ischemic stroke. He directed the attention of the audience to the concept of the penumbra and showed how it can be rescued through timely intervention leading to reperfusion. Acknowledging the success of this acute treatment milestone is important as a backdrop for discussing alternative treatment approaches. To date, as many as 1026 experimental studies and 114 clinical trials (including 912 experimental drugs) failed to provide measurable clinical benefits after ischemic stroke. This unfortunate experience called for the revision of standards for conducting the experimental assessment of candidate drugs. Sometimes, failure leads to progress. This issue has been addressed by STAIR (Stroke Therapy Academic Industry Roundtable) criteria for conducting the experimental studies in stroke. Among the major issues, approached by STAIR, were: choice of animal models, insufficient experimental rigor and wrong timing. Also, our ability to better understand the physiopathology of stroke led us to reject the one-dimensional study designs. Directed at one particular component of a heterogenous and constantly changing ischemic brain environment, they were inadequate and had to fail. One needs a multi-dimensional approach in order to influence the complex biology of ischemic damage. A new era for studying the neuroprotection and neurorecovery had begun which promised to re-ignite stroke research. One additional reason for optimism was the advent of the sophisticated imaging technology in experimental studies, which allows us to guide our investigations in a way formerly unattainable. For example, the alternative approach to neuroprotection, which is neurorepair, can be assessed more precisely. Clearly, processes of neurorepair post-stroke extend beyond the therapeutic window of neuroprotection, and are active when the damage is already present. Neurorehabilitation and targeted pharmacotherapies that stimulate natural processes of neurogenesis and neurorepair may provide the much-needed new impulse in stroke research (**Fig. 1**).

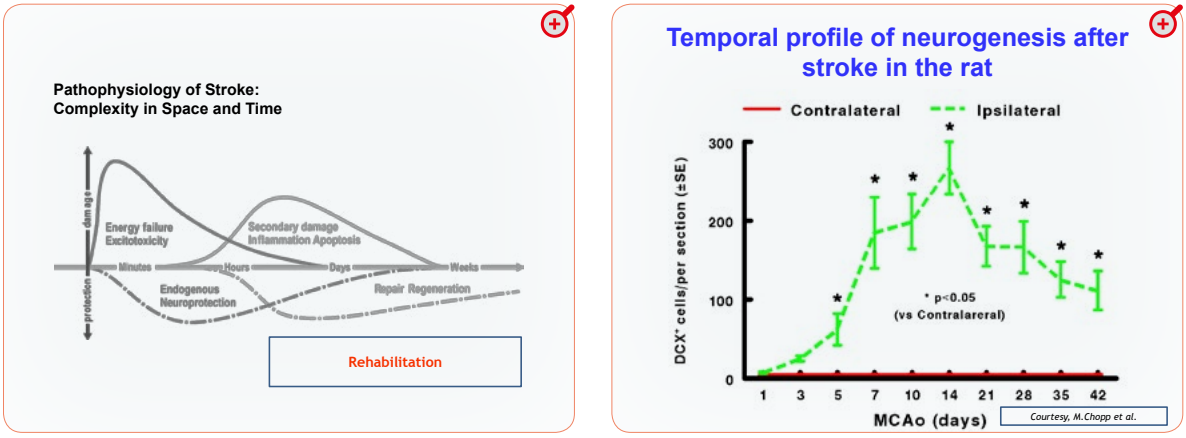


Fig. 1 The recovery from stroke is extended in time and offers opportunities for therapeutic stimulation of natural neurorepair processes

This quest is already underway. Among the recognized agents and methods studied in the context of neurorecovery are stem cells, natural and synthetic biologicals (HGF), extracts from the brain (Cerebrolysin), anti-inflammatory cytokines (TNF alpha, IL10), and reduction of toll-like receptor signaling (DAMPs). To this category belong also some already registered drugs, enhancers of motor recovery, like SSRIs (antidepressants), dopaminergic drugs (L-Dopa) and biologicals (Cerebrolysin).

One of the emerging topics in the field is the enhancement of early mobilization (EM) by Cerebrolysin treatment. This concept is based on the assumption that positive clinical effects of EM are mediated by mechanisms of spontaneous recovery. The same mechanisms were earlier shown to be stimulated by Cerebrolysin.

The clinical data show that treatment with Cerebrolysin might promote early recovery after ischemic stroke. It has also promising impact on patients presenting with severe neurological deficits. The largest to date study, CASTA, performed in over a thousand patients, showed that Cerebrolysin improves recovery of the more severely affected subgroup (with NIHSS>12). These results allowed for the formulation of the efficacy hypothesis that needed to be confirmed in future RCTs. Another interesting set of data came from smaller RCT investigating the combination of Cerebrolysin and rt-PA. The treatment combination was safe and we observed the steeper and faster recovery of patients in the initial period after stroke in comparison with the control, rt-PA only group (**Fig. 2**).

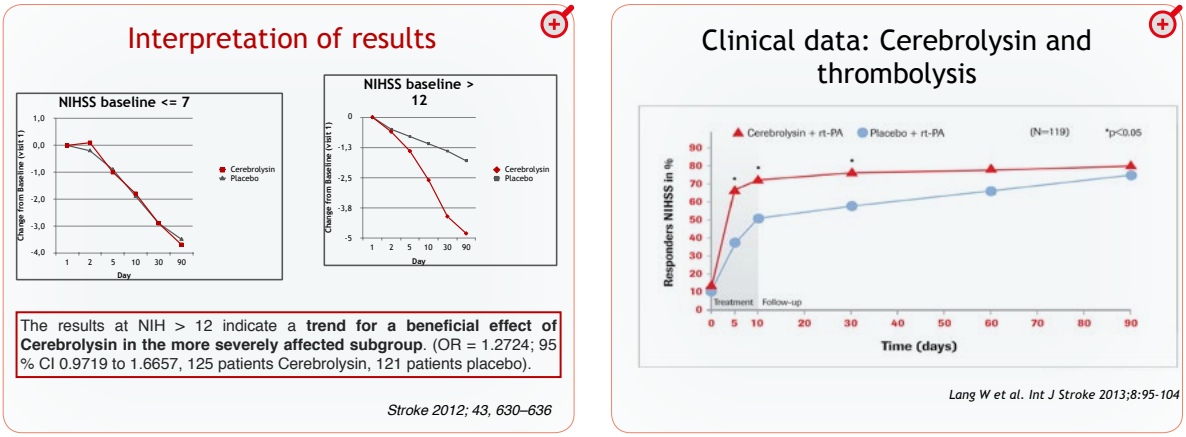


Fig. 2 The results of the early acute clinical trials indicated that Cerebrolysin speed up recovery early after stroke

One of the oldest studies, performed by the group of Ladurner on 146 patients, investigated a high dose of Cerebrolysin (50 ml) applied for 21 days. The results at the time were considered strikingly positive and indicated significant improvement ($p<0.05$) of motor functions (measured with the Canadian Neurological Scale, Section A1; a standard before NIHSS) and significant improvement ($p<0.001$) of activities of daily living (Barthel Index) in the right-sided subgroup of patients. Additionally, cognitive performance was investigated and here the results also favored Cerebrolysin treatment significantly ($p<0.05$ in MMSE, SST). Cerebrolysin was well tolerated, with no reported difference to placebo with respect to nature and frequency of AEs. A newer study, corresponding directly to the new era of neurorecovery oriented trials, ECOMPASS (from Korea), investigated 70 extremely well-documented stroke patients participating in a rehabilitation program focused on motor rehabilitation. The patients were concomitantly treated with 30 ml daily dosage of Cerebrolysin (from day 8 after stroke, and for 21 days). Again, the more severely impaired stroke patients (like in previous trials) reacted significantly better to combination Cerebrolysin and motor rehabilitation in comparison with the control group (rehabilitation alone). Recovery of motor function, as measured with Fugl-Meyer Assessment (FMA), was significantly improved in upper limbs. The study provided an interesting insight into the neuroplasticity processes underpinning the treatment. By employing resting-state functional MRI (rsfMRI) analysis, the researchers were able to show improved recovery of motor cortical function suggesting a synergistic positive effect of motor rehabilitation and Cerebrolysin on the endogenous neuroplasticity and neurorecovery after stroke (**Fig. 3**).

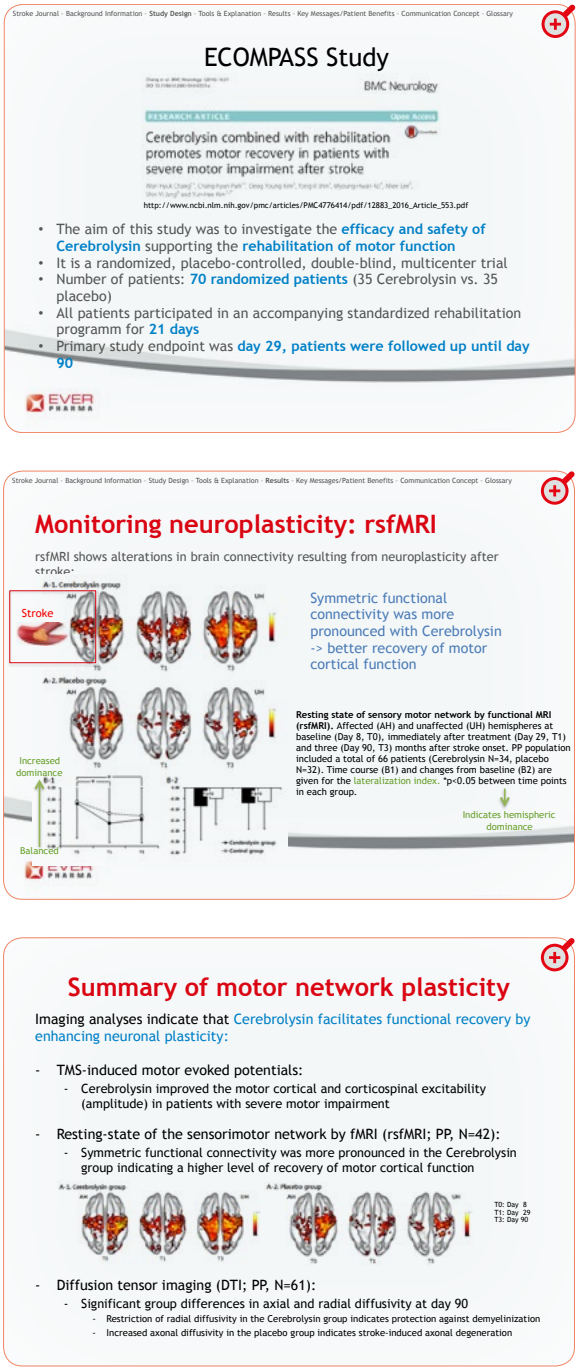


Fig. 3 The results of ECOMPASS trial showed how Cerebrolysin impacts neural plasticity after stroke, leading to improved recovery of motor functions

Ultimately, the CARS study performed by Professor Muresanu and coworkers confirmed and extended the findings of previous investigations. Also here, the stroke patients were treated with Cerebrolysin in the combination with motor rehabilitation. The primary outcome measure, in this case, was the action research arm test (ARAT) score allowing to focus on upper limb motor recovery as indicative for the overall stroke recovery. This study was later repeated (CARS II) by another group. The meta-analysis of the results from both CARS trials showed the significant advantage of Cerebrolysin treated group in the primary outcome measure as well as in the several other clinical outcome assessment scales (e.g. NIHSS, mRS). The CARS trials confirmed that severely affected patients benefit most from the treatment with Cerebrolysin and that this benefit is most prominent in the early recovery phase.

Dr. Brainin indicated that these and other results show the need for re-organization of stroke rehabilitation. The biological processes of recovery should be our therapeutic target. To see rehabilitation as unified process cannot be defined in an institutional way. We have to stick to the physiopathology of the recovery processes when we want to understand what is going on. Also, the need to start rehabilitation earlier (early mobilization), than currently practiced, appears justified and is under ongoing investigation. Finally, longer rehabilitation is needed due to the dynamics of chronic stroke. Neurorehabilitation should be viewed as a continuous, long process starting in the acute treatment unit. Dr. Brainin concluded that this apparent change in the treatment paradigm, which was the subject of his talk, is yet to be reflected in the organization of stroke care.

The chairman of the symposium, Dr. Muresanu, commented on the lecture indicating that it highlighted an issue of the alignment of the design of a clinical study with the mechanism of action of the investigated agent. The second take-home message is to combine pharmacological intervention with the stroke rehabilitation program in order to achieve an improved outcome.

Innovative treatment options reducing the risk of post-stroke dementia

Leonardo Pantoni

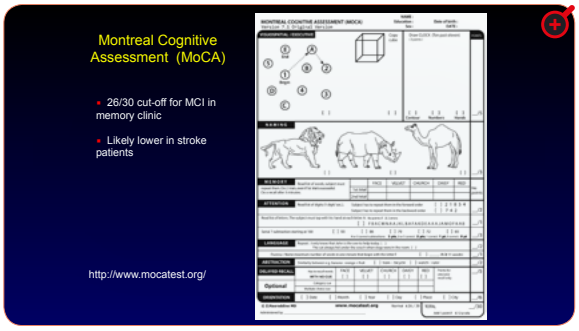
Department of Biomedical and Clinical Sciences,
University of Milan, Italy

ABSTRACT:

The current focus of stroke clinicians and researchers is mainly on the acute phase of the disease. While this is greatly justified by the recent improvement in acute stroke treatment strategies and on the potential of these treatments, one should not forget that the greatest burden of stroke remains in the chronic phase that lasts much longer than the brief acute phase and involves patients, their families, and the entire society. Among the heaviest consequences of stroke are the cognitive and behavioral sequelae. It is now well documented that about a third of stroke patients are found with dementia some time after stroke, and another quarter by milder cognitive deficit. We need to recognize cognitive deficits in stroke patients since the acute phase by measuring cognition together with other neurological functions. The implementation of neuropsychological measures in stroke units will also help to recognize and target those patients who are already cognitively impaired before stroke and therefore need to be directed to more specific pathways, for example in terms of rehabilitation. Finally, symptomatic treatments of stroke-related cognitive impairment are badly needed to reduce the burden of stroke consequences.

Dr. Pantoni invited the audience to the talk about vascular cognitive impairment, the seriously neglected part of stroke care. There are no standard treatment regimens available, there is no defined treatment window for such patients, there are no approved drugs for vascular cognitive impairment. One of the major challenges of stroke care is to change this situation and Dr. Pantoni wanted to share his view about the development in this field.

The risk of dementia after stroke is double that of healthy people after the age of 65 and its frequency is between 15 and 25%. Additionally, the more time elapses after stroke, the higher is the probability of dementia. In order to properly tackle this problem, we have to start with an accurate diagnosis of post-stroke dementia and post-stroke mild cognitive impairment. One of the key diagnostic issues is the choice of neuropsychological tests, as these are usually incompatible with the acute stroke unit environment. There is currently no consensus about the choice of the test as there is no consensus about the optimal timing of the test. In practice, the evaluation almost never is being performed on the stroke unit. Dr. Pantoni submitted that in spite of the intensive care related obstacles characteristic for stroke unit, the evaluation of stroke patients is possible and feasible, and it should be attempted. He is using the Montreal Cognitive Assessment (MoCA) test, a task which takes approximately 15 min to complete. Dr. Pantoni's research showed that the MoCA baseline score and severity of leukoaraiosis are independent predictors of post-stroke cognitive impairment. (**Fig. 1**).



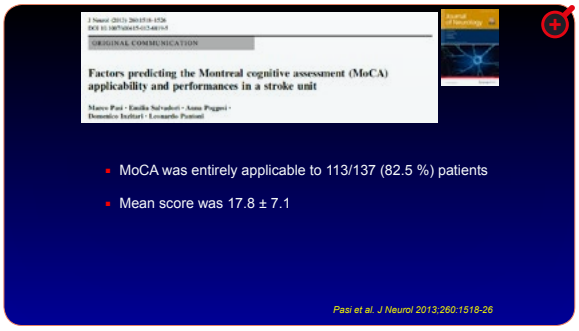


Fig. 1 MoCA test can be used for evaluation of majority of stroke patients already in the stroke unit

The continuation of this diagnostic work has been conducted at The Luigi Sacco Hospital Stroke Unit and VAC-COG Clinic in Milan. The results of these one-year-long investigations confirmed the high prevalence of cognitive impairment in stroke patients before (about 40%) and after the stroke onset (35%) when evaluated 3-4 months later. Additionally, the study found that another simple cognitive test, the Clock Drawing Test, is an independent predictor of post-stroke cognitive decline. Why is it important to establish the standards of cognitive evaluation of stroke patients? One recovery-related reason is that the adherence of patients to often complex and long-lasting therapeutic processes (therefore, their success or failure) depends on their cooperation. Unfortunately, currently, the patient's cooperation is mainly evaluated from the standpoint of their physical abilities, while cognitive abilities remain neglected. This should be changed to enable a more comprehensive approach to rehabilitation. More clinical studies are needed than currently ongoing, indicated Dr. Pantoni.

Regarding the trials evaluating the already existing neurological treatments, Dr. Pantoni mentioned the ARTEMIDA trial as well as Cochrane Review of trials assessing the Cerebrolysin treatment of post-stroke vascular dementia. The results from these studies indicated the improvement of cognitive performance of stroke patients suffering from vascular dementia. The treatment is possible, but we need to administer therapies in the right way. Dr. Pantoni finished his lecture with the take-home message that stroke specialists should be more involved in the cognitive arena in order to increase chances for new standards of clinical practice to emerge which would be much needed.

The importance of early mobilization and rehabilitation after stroke

Katharina Stibrant Sunnerhagen

Department of Clinical Neuroscience,
University of Gothenburg, Sweden

ABSTRACT:

The efficacy of the comprehensive stroke unit has been shown. This includes the part of mobilization and getting people out of bed. In this talk, the negative effects of bed rest will be presented as well as how early rehabilitation in the comprehensive stroke unit can be performed. The plasticity of the brain will be discussed. The importance of considering timing, dosing and content of the rehabilitation intervention will be highlighted. In the end, the talk will touch upon the possible use of drugs and/or devices to enhance the rehabilitation efforts.

Dr. Sunnerhagen's lecture was centered upon early mobilization (EM) and rehabilitation after stroke, and she remarked right from the beginning that this topic is underrepresented during ESOC 2019. She also promised the audience that this mistake will be corrected next year when the conference takes place in Vienna.

What determines neurorehabilitation is plasticity. The term refers generally to the brain's ability to reorganize neural pathways throughout a person's lifespan, as a result of experience. This learning process causes changes in the structure of neurons with the increase in the number of synapses.

It is a firmly established knowledge that animals after ischemic stroke can recover motor functions of their impaired limb when given the right incentive to train it (for example, their favorite food located in such a way that the animal must repeatedly use the impaired limb to reach out for it). When planning the therapies on our patients (including rehabilitation), we must take the results of basic research, coming from animal models, into account. There are three steps to rehabilitation. In the first step, ideally, a patient should be evaluated from the standpoint of his metabolic and his brain's plasticity status right after stroke. In this process, biomarkers would be important to better understand the genetic determinants of recovery of a patient. In the next step, we should consider means to stimulate natural plasticity processes in the brain and in the spinal cord. We can think about growth factors and certain stimulatory agents. Finally, we should make a decision about the training for selection and targeted stabilization of the new neural connections (the repetition is a key factor in the stabilization process). Neurorehabilitation should start immediately after stroke and our ability to induce it early was shown to have long-lasting effects. For example, it was shown that early mobilization and good control of blood pressure in the stroke unit are the strongest predictors of good outcome after stroke (**Fig. 1**).

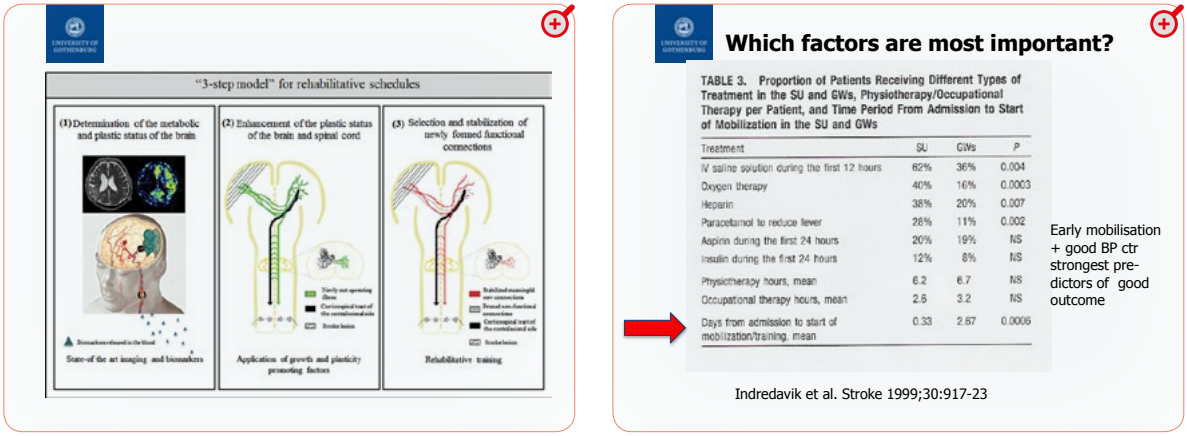


Fig. 1 Neurorehabilitation is closely associated with the brain plasticity and must be properly planned and initiated early, already in the stroke unit

Why is EM so effective? Physiological effects of bed rest in healthy subjects were extensively studied by NASA in order to prepare astronauts for space expeditions to the Moon. The students who volunteered for the study were put in beds for three weeks and their physiological parameters were closely monitored. This groundbreaking study showed that bed rest has profoundly negative effects on our key physiological parameters, including: loss of muscular strength and endurance, loss of muscle mass, bone resorption (from 2nd day), impaired lipid profile (from 3rd day), insulin sensitivity (from 3rd day), amino acid-induced protein anabolism, lower basal metabolic rate, increased diuresis, increased natriuresis, autonomic dysfunction, orthostatic hypotension, constipation, infectious complications, DVT and pressure sores, decline of cardiac fitness (within few days). The follow-up study conducted 40 years later illustrated the effectiveness of using oxygen by the subjects (VO2 max parameter). During the 40 years, this parameter declined as much as during the 3 weeks of bed rest period studied in 1968 (**Fig. 2**), which shows how physiologically abnormal bed rest is.

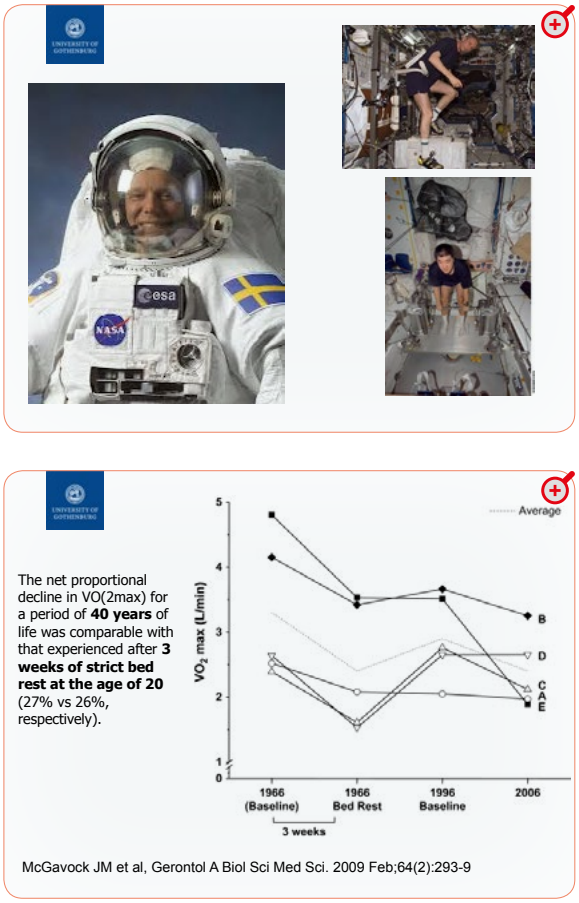
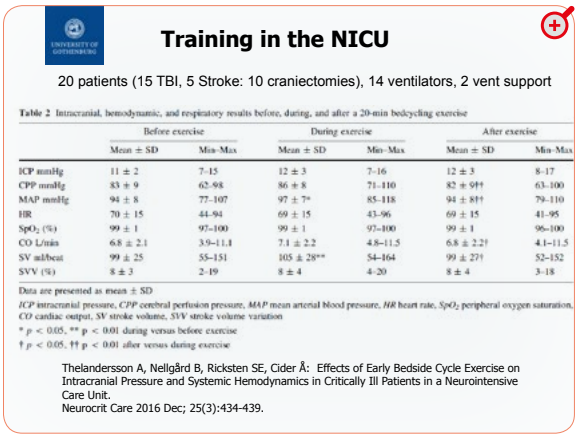


Fig. 2 The studies performed by NASA help us to understand serious negative health effects of immobilization in stroke patients

To prevent such drastic loss of vital parameters in their astronauts, NASA equips their space ships with all kinds of training equipment. These effects were seen in healthy young individuals. We can safely assume that bed rest of older stroke victims leads to even more serious health consequences. In fact, not surprisingly, it is being held responsible for 50% of deaths after stroke. Early mobilization can be done in many different ways, for example, using the bed cycle. This kind of equipment is used in the stroke unit and neurointensive care unit (NICU) at the University of Gothenburg. Recently, a study evaluating the safety of this exercise in mostly comatose, very ill patients was performed by Dr. Sunnerhagen and coworkers. The study showed that the exercise was safe and feasible in even the most seriously affected patient population (**Fig. 3**).



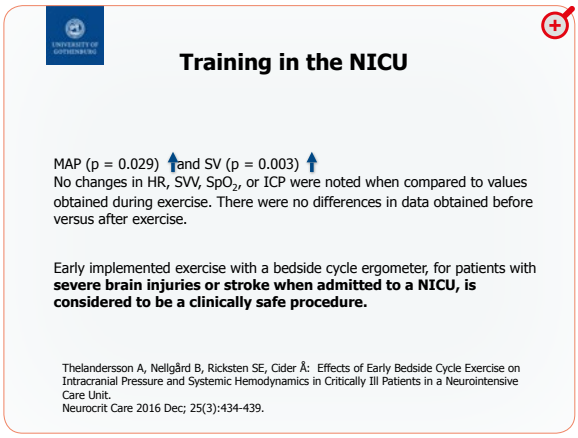


Fig. 3 Early mobility in the NICU is safe and feasible and can be administered for even the most severely affected patients

Early mobilization is safe for stroke patients and should be considered as an integral part of the stroke unit. In approaching EM for your patients, please observe the symptoms, do not force patients, use it not too often (evaluate the right dosage), and use common sense reacting appropriately to patients' feedback.

On top of early mobilization, use of certain drugs can help in the recovery process. Dr. Sunnerhagen is involved in the evaluation of SSRIs (antidepressants) as potential helper therapies after stroke. The Swedish study (EFFECTS) will include 1500 patients and the results will be presented during the next ESO Conference in Vienna. It is a part of the international effort to evaluate efficacy (mRS at 6 months, effects on cognitive and motor functions) and safety of SSRIs in the stroke patients (FOCUS, AFFINITY and EFFECTS studies). The results of the largest of these trials, FOCUS, have already been published and showed no positive effects of the treatment while presenting some safety issues (e.g. pro-epileptic activity).

Another aspect of successful stroke care is the avoidance of drugs that may reduce brain plasticity and recovery, like benzodiazepam, neuroleptic drugs, and anti-epileptic drugs. The stimulating/inhibiting technologies, like rTMS (repetitive Transcranial Magnetic Stimulation) and tDCS (transcranial Direct Current Stimulation) are promising approaches showing some actual effects in patients with aphasia and motor function or even depression. The open question remains if all these methods can be used together and if they provide synergistic treatment effects?

Dr. Sunnerhagen summarized her lecture saying that the brain is plastic and this valuable natural feature is subject to modification by drugs that may enhance plasticity. Such drugs, in combination with more training, might increase function. The motor training was already shown to increase dendritic growth after stroke. Devices and drugs in combination with more targeted and intense training might be the way forward.

New hope for chronic stroke patients – The IMPULSE study

Andreas Winkler

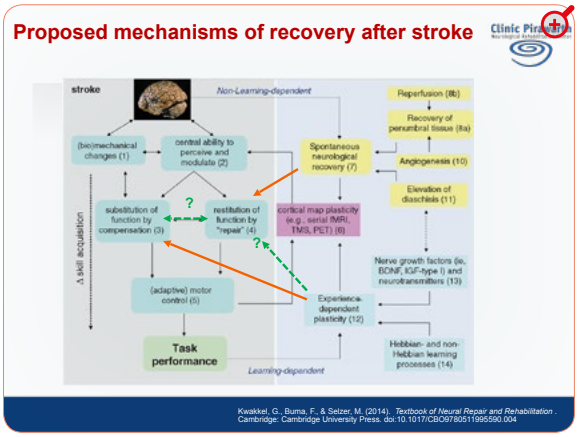
Department of Neurological Rehabilitation,
Clinic Pirawarth, Austria

ABSTRACT:

Study protocol, rationale and design of the IMPULSE study - a prospective, multicenter, randomized, double-blind study on the stIMulation of brain Plasticity to improve Upper Limb recovery after StrokE

Following a stroke, the initial recovery process follows the resolution of reversible pathophysiological events and later on functional improvement occurs as the neural networks within the brain undergo changes in response to various stimuli. Up to 85% of motor improvement in patients with mild to moderate impairment is seen within the first 8 weeks after stroke. This functional gain is attributed to an early, but relatively short, "sensitive period" post-stroke, which represents an environment of heightened plasticity. Animal studies suggest that both, recurrent stroke and pharmacological interventions can induce or extend this sensitive period, which correlates with the levels of the neurotrophin BDNF that has been implicated in the modulation of synaptic function and plasticity. We hypothesize in this prospective, multicenter, randomized, double-blind study that the combination of the neuropeptide preparation Cerebrolysin and neurostimulation (tDCS) re-induces a milieu of heightened neuroplasticity in subacute and chronic stroke patients who have an unexploited potential for functional recovery. The study will be performed at seven Austrian stroke centres, the first patient will be recruited in early summer 2019, more than 200 patients are planned to take part in the trial. The IMPULSEstudy is part of the VascAge-C Program, a publically funded research program with partners from science/industry, promoting research and deeper insights on the effects of ageing on the vascular system.

The call of Dr. Sunnerhagen for combination therapies in neurorehabilitation was answered by Dr. Winkler, who presented to the audience the concept of the IMPULSE study. He began with the rationale for the study which essentially defines its design and the treatment protocol. In general terms, the stroke recovery can be seen as the competition of two processes: compensation and true recovery of lost functions. In our current rehabilitation practice, we normally see compensation. We do not know how compensation and true restoration of lost function interact. Is compensation negatively affecting real recovery? What we know for sure is that experience based plasticity helps to achieve compensation. When we look at the time scale of post-stroke recovery, we immediately notice that the enhanced plasticity period lasts for several weeks. 85% of motor recovery happens in this period (lasting up to 8 weeks post-stroke). Hence our understanding of how important this period is and that we should concentrate on it in our rehabilitation efforts. In the chronic phase, in contrast to the short-lived enhanced plasticity phase, there is currently no much we can do in terms of stimulation of the spontaneous, endogenous recovery processes (**Fig. 1**).



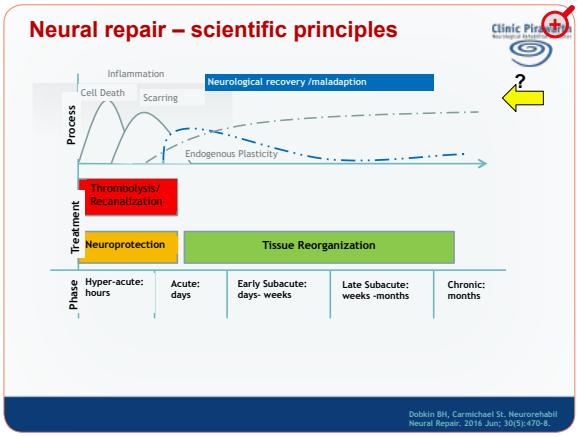
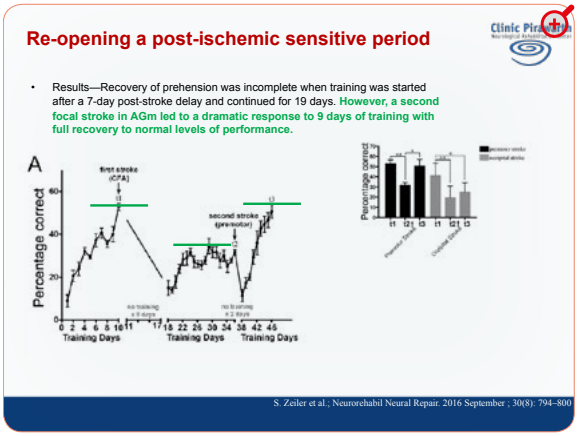


Fig. 1 The scientific principles of compensation and true recovery after stroke

To date, the only trial documenting enhancement of plasticity in the early recovery period was the CARS trial. It assessed a combination of motor rehabilitation and pharmacological treatment with Cerebrolysin. We need more data in this respect. We also need to see, if the same can be done in the chronic phase - can we re-induce the plasticity and prolong our ability to stimulate neurorecovery long after the onset of stroke?

Certainly, we can do it in animal models, what has recently been shown by Steven Zeiler and coworkers from Johns Hopkins University. They confirmed that an enhanced plasticity period can be re-induced when a second stroke is applied and followed immediately by motor training (**Fig. 2a**).

Although this approach cannot be replicated in human patients, we can think about any other safe way to re-induce plasticity after stroke. One particular strategy emerged recently and led to current concept of the IMPULSE trial. In a lately published study by Carmichael group from UCLA, it was shown that treatment that enhances neuronal excitability enhances also motor performance after stroke. Knowing that the CREB transcription factor signaling mediates neuronal excitability, the researchers have been able to show that increased levels of CREB led to enhanced motor recovery. Moreover, the inhibition of the endogenous CREB singling pathway prevented the motor recovery of animals (**Fig. 2b**).



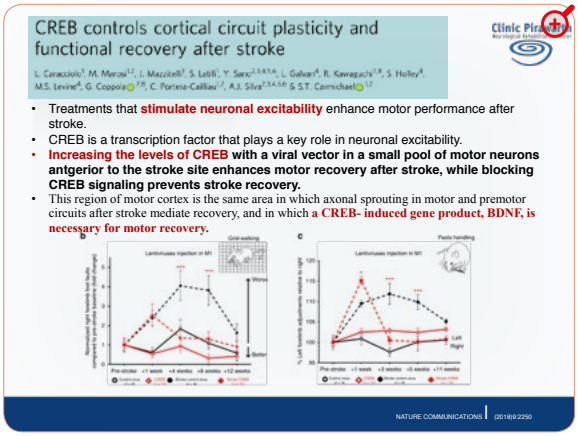


Fig. 2a

Fig. 2b

The experimental models of stroke show that it is possible to enhance plasticity processes after stroke

Thanks to this excellent research, we know the molecular mechanisms that can be utilized for the stimulation of enhanced plasticity period post-stroke. But how can we target them safely? The transcranial Direct Current Stimulation (tDCS) is one method shown to enhance cortical excitability and to temporary improve motor recovery post-stroke. It was also shown that tDCS works through the brain-derived neurotrophic factor (BDNF) dependent long-term potentiation (LTP) mechanism. Consequently, blocking the BDNF pathway prevents tDCS-dependent motor recovery. BDNF is known to be involved in synaptic plasticity and other recovery-related processes. The fact that expression of BDNF is controlled by CREB singling, as described earlier, creates a convincing scientific rationale for using tDCS as a proper tool for specific stimulation of the plasticity processes. Looking at BDNF from the clinical perspective, several studies found that the serum levels of BDNF are suppressed in more severely affected stroke patients and in chronic stroke patients.

All these data helped researchers in formulating the hypothesis that a combination of tDCS with a neurotrophic factor treatment and with motor rehabilitation could result in synergistic action leading to stimulation of neural plasticity and improved motor recovery of post-acute stroke patients. As we remember, Cerebrolysin is a safe agent used for the treatment of stroke, exhibiting neurotrophic properties, and additionally also enhancing the levels of BDNF. Its physiological relevance, as well as the reported to date clinical properties justify its use in the combination trial. This is, in summary, the scientific rationale for the IMPULSE study. Dr. Winkler pointed out that this rationale was already pre-tested by his group in an exploratory trial with 35 chronic stroke patients (>4 weeks after stroke). The results showed that upper limb motor recovery was much more effective in combination with tDCS (double the proportional recovery of motor rehabilitation alone) and Cerebrolysin (triple the proportional recovery of motor rehabilitation alone). The treatment with a combination of motor rehabilitation, tDCS and Cerebrolysin was safe and feasible (**Fig. 3**).

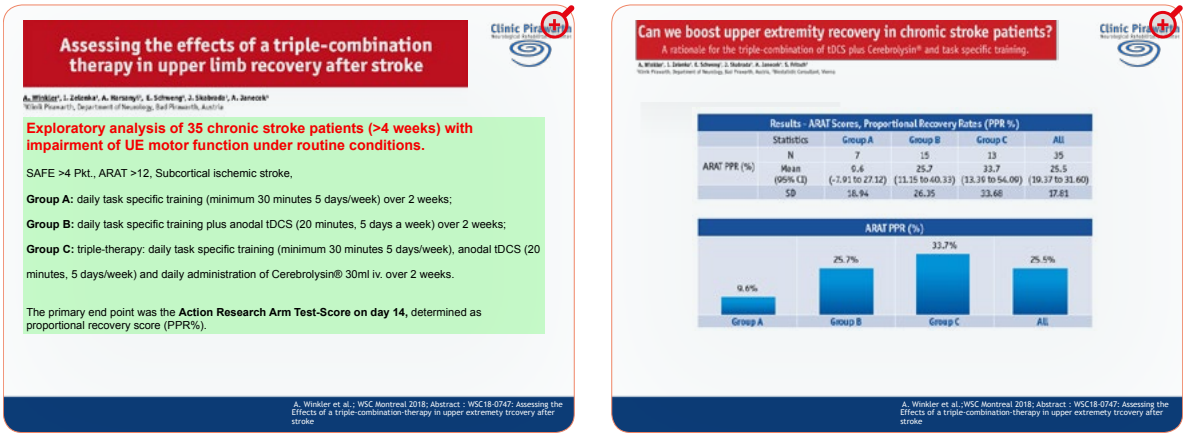
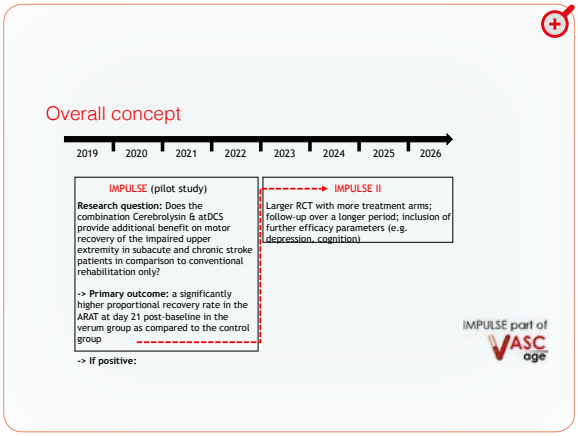
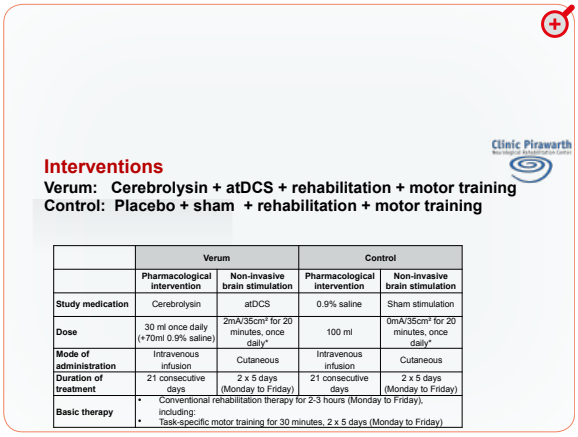


Fig. 3 The exploratory trial of triple combination (motor rehabilitation, tDCS and Cerebrolysin) treatment of chronic stroke patients

IMPULSE is a prospective, multi-center, randomized, double-blind study on the stIMulation of brain **P**lasticity to improve **U**pper **L**imb recovery after **S**trokE. This is a publicly founded trial and part of the Austrian VASCage program for studying vascular aging. The trial is designed in two phases and if the pilot shows positive results, the second, much larger and longer lasting trial, will be initiated (Phase II). The population of the pilot study is 90 patients (from 7 Austrian centers) and recruited 8 weeks to 12 months after a first-ever ischemic stroke. The study will begin in October this year and the results are expected within the next two years. At the end of his talk, Dr. Winkler elaborated on the inclusion criteria and described details of interventions (**Fig. 4**).





	Verum		Control	
	Pharmacological intervention	Non-invasive brain stimulation	Pharmacological intervention	Non-invasive brain stimulation
Study medication	Cerebrolysin	atDCS	0.9% saline	Sham stimulation
Dose	30 ml once daily (+70ml 0.9% saline)	2mA/35cm² for 20 minutes, once daily*	100 ml	0mA/35cm² for 20 minutes, once daily*
Mode of administration	Intravenous infusion	Cutaneous	Intravenous infusion	Cutaneous
Duration of treatment	21 consecutive days	2 x 5 days (Monday to Friday)	21 consecutive days	2 x 5 days (Monday to Friday)
Basic therapy	• Conventional rehabilitation therapy for 2-3 hours (Monday to Friday), including: • Task-specific motor training for 30 minutes, 2 x 5 days (Monday to Friday)			

Fig. 4 The IMPULSE study design and interventions of the pilot part (phase I)

Dr. Muresanu closed the session by thanking the lecturers for the interesting talks and expressing hope that in the near future more similar combination trials will be performed. This should allow us to progress toward the creation of more effective rehabilitation regimens for our stroke patients.

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type – Post-apoplectic complications – Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. 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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