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Webinar EVER Pharma

The relevance of neurorehabilitation in acute and chronic stroke

June 29, 2021

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Webinar EVER Pharma (June 29, 2021)

The relevance of neurorehabilitation in acute and chronic stroke

Participants

Dafin F. Muresanu

President of the European Federation of NeuroRehabilitation Societies

Moderator

Valeria Caso

Stroke Unit, Santa Maria della Misericordia Hospital/ University of Perugia, Italy

Topic: Stroke rehabilitation in Europe: Still a long way to go

Sigrid Schwarz

Director of Early Rehabilitation Department and Neurorehabilitation Day Clinic, Tulln, Austria

Topic: Successful rehabilitation begins in the stroke unit

Andreas Winkler

Medical Director Klinik Pirawarth

Topic: How can we be more efficient in motor recovery after stroke?

Order of the webinar

Introduction

Dafin F. Muresanu

The invitation from Dr. Muresanu pronounced a very provocative and, at the same time, very informative program of this webinar, which is related to the relevance of neurorehabilitation in acute and sub-acute stroke. A stroke, being a devastating condition, requires many steps and efforts to improve patients' outcomes. Neurorehabilitation is one of the most needed assets in our armamentarium for the treatment of neurological disorders. It is probably true that there is no neurological condition that would not benefit from neurorehabilitation. Before introducing the speakers, Dr. Muresanu expressed his belief that we can still enhance stroke care by further refining our neurorehabilitation processes.

Stroke rehabilitation in Europe: Still a long way to go

Valeria Caso

Stroke rehabilitation has a long way to go compared to the progress made in acute stroke care. The main reason for concern for stroke specialists and patients worldwide is a perception, shared by many politicians and also administrative directors in healthcare systems, of a stroke as an elderly disease. This perception is false, as the current epidemiological data indicate that stroke affects also the working population in our societies. The stroke prevalence data show regional differences, with South-East Asia, East Asia, Oceania followed by Central and Eastern Europe and Central Asia leading the most affected regions. Especially there, stroke is a leading cause of disability in the working-age sections of society. Do resources and investments in healthcare match the impact of stroke on public health anywhere in the world? The answer is: No! Non-communicable diseases (NCDs) such as stroke, heart attacks, diabetes, and cancers account for 70% of global deaths and 58% of the burden of disability. At the same time, they attract only about 2% of global health care expenditures.[1] We are not prepared to meet the challenge of stroke internationally, in contrast to our declarations: UN declaration of 2011 on NCDs, WHO's Global Action Plan on prevention and control of NCDs, and Sustainable Development Goals of UN (post-2015), including good health and wellbeing. The current relevant goal for the year 2030 is to reduce by one-third premature mortality from NCDs through prevention and treatment supported with educational activities focused on mental health and wellbeing. Rehabilitation after stroke appears to be one of the components of the complex efforts aimed at reaching this ambitious goal (**Fig. 1**).

Fulfilling its practical mission, the European Stroke Organisation designed The Stroke Action Plan for Europe (SAP-E).[2] The Action Plan oversees a period between 2018 and 2030 and includes seven domains. These are primary prevention (new), organization of stroke services, management of acute stroke, secondary prevention with

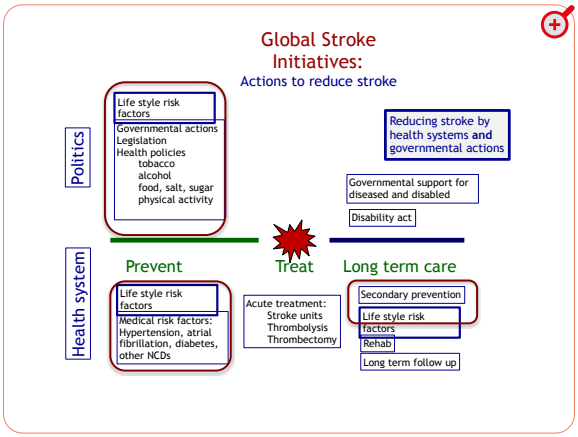

Fig. 1. The complex endeavor of reducing the global burden of stroke includes long-term care of affected patients

organized follow-up, rehabilitation, evaluation of stroke outcome with quality assessment, and life after stroke (new). The activities within these domains should lead to tangible clinical goals, including reduction of the absolute number of strokes in Europe by 10%, treating 90% or more stroke patients in the dedicated stroke units (first level of care), creating national plans for stroke encompassing the entire chain of care from primary prevention to life after stroke and, finally, the full implementation of national strategies for multi-sector public health interventions. This last target must entail promoting and facilitating a healthy lifestyle, reducing environmental (including air) pollution, and neutralizing the socioeconomic and educational factors that increase the risk of stroke. Neurorehabilitation services aim to counteract various disabilities inflicted by stroke. These more common disabilities include: motor impairments (50%-83%), cognitive impairments (50%), urinary incontinence (40%-50%), dysphagia (45%), language impairments (23%-36%), psychological disturbances (20%). The less obvious present themselves clinically as post-stroke seizures surfacing within five years (10%-11%), epilepsy occurring within five years span (2.5%), and neuropathic pain appearing within 1-year

post-stroke (8%). It is usual that after a stroke, many of these disabilities occur at the same time. Dr. Caso underlined motor and cognitive impairments as the most relevant disabilities for the working-age stroke patients, including those admitted to her stroke unit. She also pointed to one additional issue: adverse health effects of bed rest causing multi-organ deficits even in healthy individuals, not to mention in a stroke survivor.

Keeping these facts in mind, one can ask about the current state-of-the-art pertaining the stroke rehabilitation services in Europe? The Stroke Alliance For Europe (SAFE) and King's College (London) issued the Burden of Stroke in Europe (2017) report that showcased significant gaps between published evidence and clinical practice in this medical field.[3] Several indicators were necessary for enabling comparisons across countries and regions. The first postulates that patients are assessed within the first three days after admission for their rehabilitation needs and are provided with rehabilitation by a multidisciplinary team based on that assessment. The second indicator depicts early discharge of medically stable patients with mild-to-moderate stroke from acute care to inpatient rehabilitation unit or community and the third stipulates that patients are offered a review after the stroke for assessment of therapeutic and rehabilitation needs. Dr. Caso gave examples of the results of these analyses (**Fig. 2**).

The joint work of ESO and SAFE defines the following goals for stroke services to be accomplished by 2030: guaranteeing that at least 90% of the population have access to early rehabilitation within the stroke unit; providing early support discharge to at least 20% of stroke survivors in all countries; offering physical fitness programs to all stroke survivors living in the community; providing a documented plan for community rehabilitation and self-management support for all stroke patients with residual difficulties on discharge from hospital; ensuring that all stroke patients and carers have a review of the rehabilitation process and needs at three to six months after stroke and then annually.

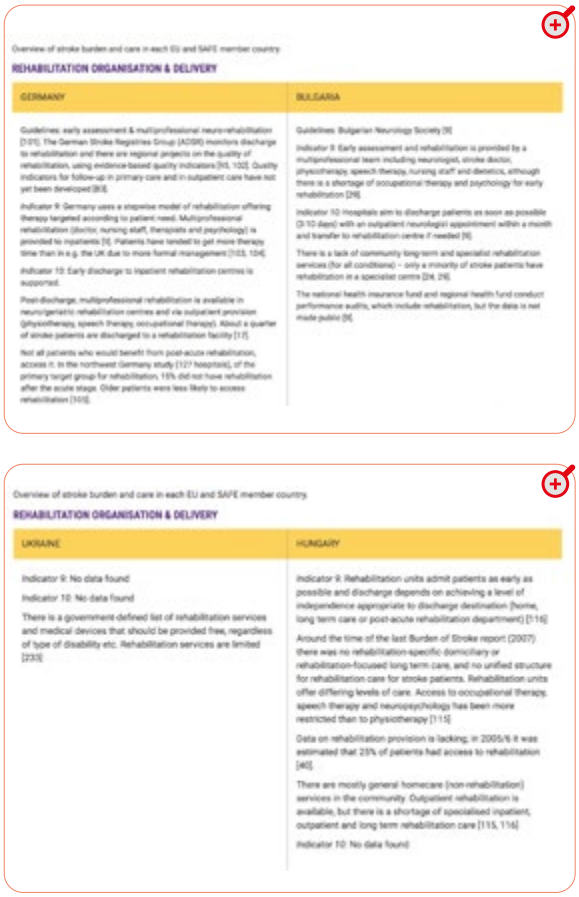

Fig. 2. The Burden of Stroke in Europe SAFE 2017 report identified significant gaps in rehabilitation services across Europe

One noteworthy example of a practical approach to managing the well-defined and understood issues of stroke care is the ESO-EAST project (established by the European Stroke Organisation in 2015) aimed at enhancing and accelerating stroke treatment through the implementation of evidence-based medicine. It is a comprehensive program focused on improving stroke care through cooperation with stroke professionals, societies, governments, and other stakeholders from 25 countries currently associated with this project (**Fig. 3**).

Dr. Caso concluded her lecture listing many synergies of the ESO-EAST with Stroke Action Plan for Europe. ESO invested its resources starting from 2015 to build a human infrastructure of stroke professionals with decision-making power. They were appointed National Coordinators (2016) responsible for facilitating stroke care improvement programs in their respective countries, with ESO-EAST support. ESO-EAST represents an infrastructure for SAP-E implementation in ESO-EAST countries. Personal overlap in the leadership of ESO-EAST and SAP-E helps in coordinated implementation of the plans. V. Caso, F. Pezzella, R. Mikulik, C. Tiu are simultaneously leaders in ESO-EAST and SAP-E Steering Committee. ESO-EAST obtained an IRENE COST grant, where SAP-E representatives have been already involved (including doctors: Caso, Mikulik, Pezzella, Tiu, Fischer, da Sousa). Finally, the IRENE Project supports SAP-E implementation. Customary declarations of progress require actionable and concrete projects, including delegating responsibilities and formulating plans with proper timelines. Only then, they have a chance to remain relevant and impact our clinical reality as expected. The efforts described here are backed up by the industry partners (including EVER Pharma and Boehringer Ingelheim) and are examples of such proactive and practical projects.

Fig. 3. The ESO-EAST project features synergies with SAP-E

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Successful rehabilitation begins in the stroke unit

Sigrid Schwarz

The general and strategic goals of stroke rehabilitation are closely related to development in the clinical setting of acute stroke care. Dr. Schwarz listed the key prerequisites for successful rehabilitation after stroke. Emergency stroke management in the stroke care unit sets the stage for early rehabilitation. During the first hours post-stroke, decisions for thrombolysis or thrombectomy have to be made and executed. Clinical assessment of a patient within the stroke care unit (NIHSS, Rankin Scale, lesion localisation) and general medical evaluation are the milestones preceding the very early rehabilitation. The initial action requires the definition of the clinical syndrome for each patient. It includes evaluation of sensorimotor problems, balance and hand coordination, dysphagia, communication, neuropsychological deficits, and cognition. In the next step, the evaluation of associated risks begins, including atrial fibrillation, diabetes, hypertonia, smoking, sedentary lifestyle, and nutrition. Very much related to the prospects of neurorehabilitation is a psychosocial assessment. It makes a difference if somebody lives alone or is supported by a loving family. The work status is relevant as even elderly patients are often involved in business-associated activities. The degree of social integration is also instrumental, as are the usual coping strategies and resilience of a patient; the rehabilitation plan evolves around these individual traits. Another part of the initial evaluation concerns the negative, prognostic factors assessment, including delirium (very early evaluation), cognitive deficits (MOCA), comorbidities (e.i. arthrosis), and incontinence. Dr. Schwarz stressed the significance of sleep disturbances (reported in up to 25% of stroke patients). These lower the quality of life and the cooperation within the rehabilitation program in a long-term perspective.

The international stroke rehabilitation guidelines (e.i. AHA/ASA, EUSI) recommend early rehabilitation under certain conditions. Early rehabilitation should be initiated early post-stroke and delivered by a multidisciplinary team in a dedicated hospital setting. The longer a patient awaits rehabilitation, the worse their prognostic factors are, additionally influenced by complications like aspiration pneumonia, thrombosis, exsikkosis, and decubitus.

Dr. Schwarz further discussed the pharmacological support for early rehabilitation. What options are available for enhancing acute rehabilitation apart from the first-line treatment, which is thrombolysis? The best possible treatment for diabetes, hypertonia, and hyperlipidemia is mandatory. Further on, plaque stabilization and prescribing SSRIs are recognized approaches for improved motor rehabilitation and post-stroke depression management, respectively. Proper fluid management is necessary for keeping patients well-watered. The direct pharmacological enhancement of neurorecovery and neuroplasticity is also possible, stated Dr. Schwarz. Cerebrolysin is an agent of interest in this context, where it was implicated (CARS trial, 2016) in the stimulation of the mechanisms of the brain's self-repair when used for the treatment of motor deficits after stroke.[1] The ECOMPASS study elucidated the mechanism of action by which Cerebrolysin modulated motor rehabilitation and indicated that, optimally, this pharmacological intervention should be applied together with a structured motor rehabilitation program.[2] Cerebrolysin enhanced the symmetric functional connectivity between the brain's hemispheres. This effect suggested modulation of network functions that underline the recovery processes, including those responsible for the hand motor functions (**Fig. 1**).

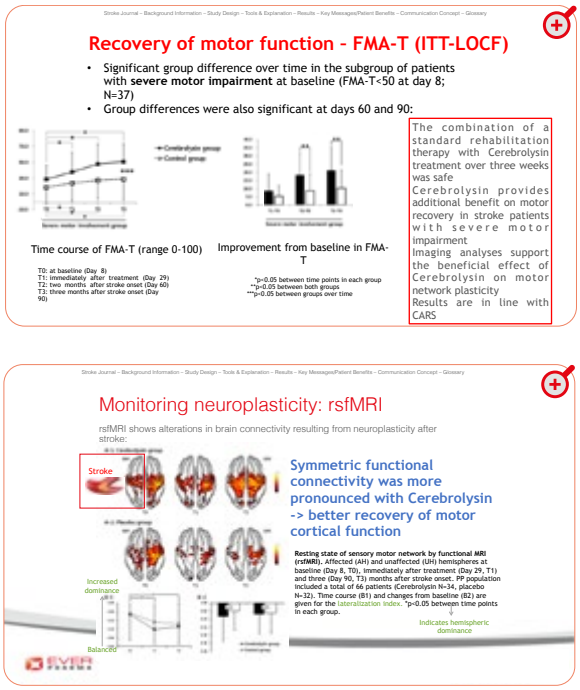

Fig. 1. The early motor rehabilitation in severe stroke patients receiving Cerebrolysin as an add-on to structured rehabilitation program

Of note, treatment with Cerebrolysin to support neurorehabilitation is recommended by several guidelines, including German Neurorehabilitation Society (DGNR) and Canadian (EBRSR) guidelines.[3,4]

The last section of Dr. Schwarz's lecture concerned conventional therapies. Early movement therapy provides rudimentary therapeutic input. Even passive movement, as well as correct positioning, is of significance for a patient. They can help to prevent spasticity and also provide physiological sensory stimulation. Stability in the vital signs is a prerequisite for rehabilitation, including early mobilization. Here, the ability to cope with verticalization and sitting position are required, but the clinical decision is always made individually for each patient. Also, dysphagia and speech therapies can be initiated quickly post-stroke. A new tool - Neuromuscular Electrical Stimulation

appears to effectively support the conventional dysphagia therapy, shortening the period necessary for the return of swallowing function. The Gugging Swallowing Screen (GUSS) should be conducted (within 24 hours post-stroke), as it supports the early dysphagia rehabilitation efforts. The GUSS helps in the assessment of the aspiration risk in these patients. Similarly, functional arm therapy can be started very early (from the first day on the stroke unit), concomitantly with continuous monitoring of blood pressure, heart rate, and oxygenation. The principles of the Constraint-Induced Motor Therapy (CIMT) can be subsequently applied (again for a fit patient able to cope with verticalization) for the paretic arm and hand (**Fig. 2**).

Another approach gaining ground in early stroke rehabilitation aims at rebalancing the brain networks. Non-invasive Brain Stimulation with rTMS (repetitive Transcranial Magnetic Stimulation) or tDCS (transcranial Direct Current Stimulation) can inhibit the hyperactive contralateral cortical regions or stimulate the hypoactive affected brain regions. Very early rehabilitation of stable patients includes occupational therapy for the improved activities of daily living (ADL). These rehabilitation measures can and should involve carers and family members, who can be supported initially in the clinic and then at home. The individual goals of rehabilitation must be oriented toward the participation and integration of a patient like: returning to work, caring for the family, performing leisure activities. Knowing the individual and meaningful goals of a patient and a carer allows for setting up realistic plans for rehabilitation in a long-term perspective.

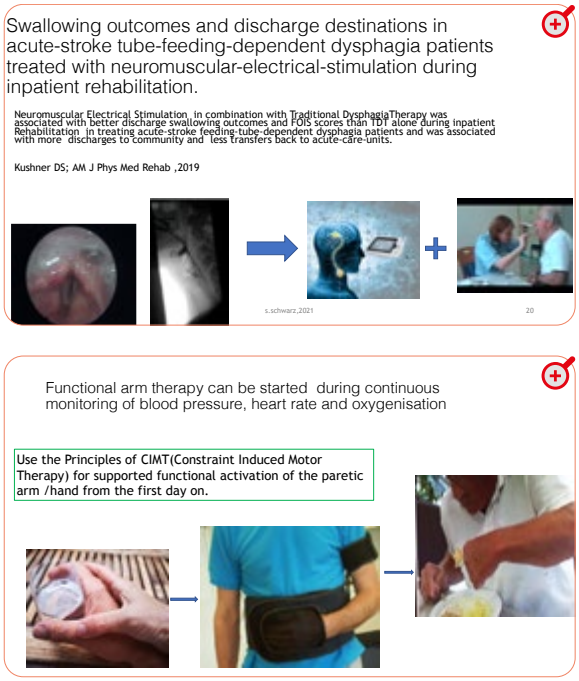

Fig. 2. Early rehabilitation of dysphagia and a paretic arm after stroke

Dr. Schwarz wrapped up her lecture with three take-home messages. Cognitive status, aphasia, the loss of bimanual hand function, and the loss of independent walking are central points in acute stroke rehabilitation. They need special attention and efforts during the structured rehabilitation program. In supporting these efforts, the pharmacological enhancement of neuroplasticity, using such agents as Cerebrolysin, should start within 1-week post-stroke, as recommended in the stroke management guidelines. Finally, the early rehabilitative assessment at the stroke care unit and the early start to rehabilitation are positive prognostic factors for long-term outcomes and were shown to improve self-esteem and quality of life post-stroke.

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How can we be more efficient in motor recovery after stroke?

Andreas Winkler

About 1000 patients are treated every year in the Clinic Bad Pirawarth, where Dr. Winkler is the Director and Head of the Department of Neurological Rehabilitation. The timing of therapeutic interventions in the clinic is sub-acute or chronic stroke. Although the clinic relies on tried and proven best standards in rehabilitation, they are also looking for new methods and explore new horizons in this evolving field of medicine and science. Dr. Winkler shared his practical experience with the audience while discussing some novel ideas for improving the rehabilitation processes, especially in the motor function rehabilitation domain. He started with the basics to define the targets for the therapeutic interventions. After a stroke, there is a period lasting for several weeks or months, called spontaneous or biological, or endogenous plasticity, initiated by the endogenous repair mechanisms triggered after stroke. In a practical sense, it was utilized in stroke rehabilitation already for hundreds of years. The neurological recovery usually depends on the spontaneous plasticity supplemented by intensive training/exercises supplied within a structured rehabilitation program. The concept of "recovery" is vital for understanding the neurorehabilitation goals. What is it? Recovery is defined as the individual's ability to perform movements using the same effectors and muscle activation patterns in the same manner as before the stroke. All other abilities acquired by a patient during the rehabilitation period are compensatory behavior. What we are looking for in the rehabilitation process is to promote the brain's neurorepair mechanisms, in the first place. The goal is to gain the restitution of functions. Nevertheless, this is not always possible due to various reasons concerning the difficulty to participate in the rehabilitation program or the nature/extent of the brain's lesion. That is why we often have to utilize the behavioral compensation leading to substitution of pre-stroke functions (**Fig. 1**).

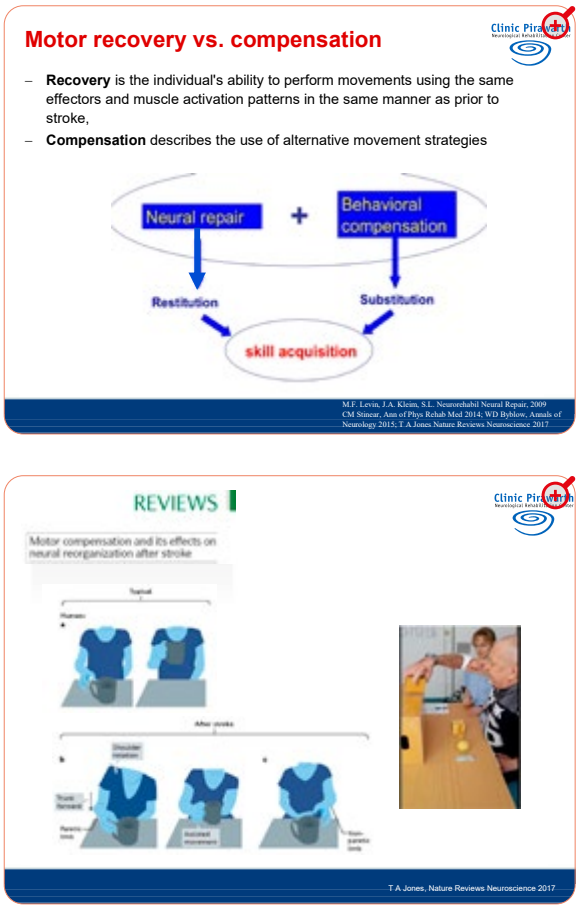

Fig. 1. The recovery vs compensation after stroke

Dr. Winkler used an example of hand movements to discuss the complexity of the motor rehabilitation process. There is always an interplay of strength/stability and control/precision in hand movement. A patient needs both to a different extent for power grip (more power needed), precision grip (increased need for precision), and individuation (selective movement of the fingers). This taxonomy of hand movements reflects the time course of rehabilitation. Precision is a function of the cortex. Stability and strength are more related to the subcortical structures involving the brain stem networks. Murata et al. (2008) investigated hand movement recovery in macaque monkeys.[1] The food gripping function was lost after induction of stroke and the monkeys that were trained during the rehabilitation period used compensatory grips. This behavior gradually shifted toward the natural/precision grips characteristic of healthy animals. In effect, the animals almost fully recovered their hand movement function. The control group, without training, could not fully recover and stagnated at the level of compensatory (alternative) grips. The conclusion was that spontaneous plasticity exists, but without training, it cannot be fully exploited for the recovery of lost functions. The time window of opportunity to effectively apply the training regimen varies between species. In a study using 2D kinematics, Cortes et al., (2017) showed that spontaneous motor improvement of the paretic arm lasted for about 5 weeks.[2] Any further motor improvement could be accounted for by the additional compensatory mechanisms, as these cannot be differentiated from the spontaneous recovery using the Fugl-Meyer, ARAT (Action Research Arm Test), AMD (Arm Motor Detection), and biceps strength scales. It seems, that the true motor recovery occurs within a very short time window after stroke: even in rehabilitation "time is brain" (**Fig. 2**).

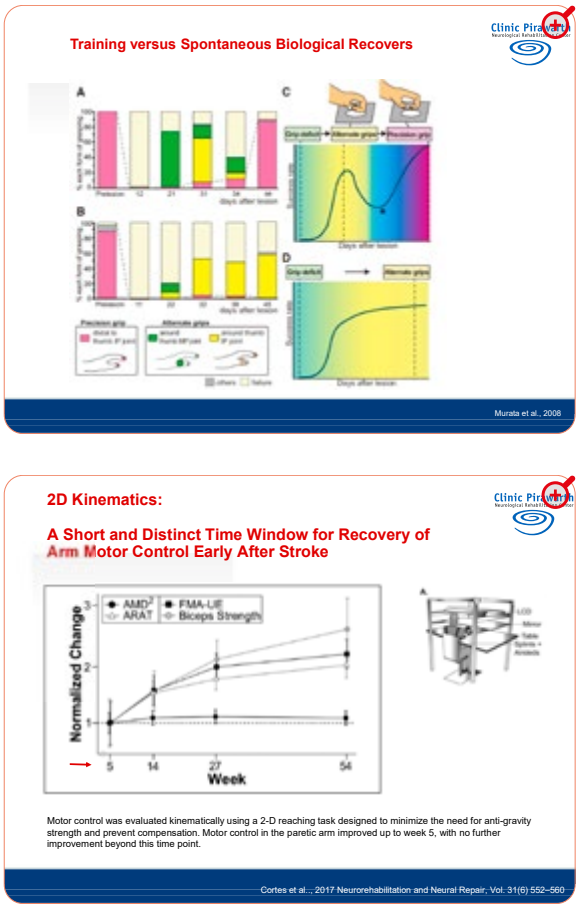

Fig. 2. "Time is brain": the spontaneous plasticity requires training for recovery of lost functions within the short sensitive recovery period post-stroke

Therefore, the valid question is: how can we intervene in this process? The accurate assessment of prognosis is the necessary first step. Especially the evaluation of lesions in the corticospinal tract (CST), which is vastly responsible for extremities movement, is of interest. The lateral CST is responsible for 90% of the direct synaptic connections between the cortex and the effector cells. The lesion size is not critical in comparison with its strategic location when predicting a deficit. The percentage of the lesion affecting the CST is relevant. This knowledge underlies the creation of the PREP score diagnostic tool. The intact CST determines the high SAFE (Shoulder Abduction and Finger Extension) score and predicts a favorable outcome leading to normal activity levels, as assessed by ARAT score. The Motor Evoked Potentials (MEPs) have a positive predictive value (about 70%) for recovery and could be induced in the motor cortex with non-invasive Transcranial

Magnetic Stimulation (TMS) technology. The presence of MEPs indicates chances for noticeable recovery in the absence of the clinical signs of functional CST.

Can we do better than that?, asked Dr. Winkler and explored the most current developments in this area. A new method for predicting recovery post-stroke is now available. It suggests, that the proportional recovery rule of 70% needs to be replaced by a model that uses several parameters (measured a few times during the sensitive recovery period) to calculate the outcome utilizing a mathematical function. These parameters include: subgroup assignment, probability, proportional recovery coefficient rk, time constant in weeks τk, and distribution of the initial FM-UE scores.[4] This Mixture Model can predict with very high accuracy (>80%) the outcome when applied within a short time after stroke. It identified three subgroups of patients that recover the upper extremity functions to a different extent: poor, moderate, and good recoverers. What is especially notable about this model is that it provides very high accuracy within four to five weeks.

The knowledge about the sensitive plasticity period and the availability of tools for precise prediction of the functional outcomes afford us a chance for developing novel therapeutic strategies in stroke rehabilitation. First of all, we should identify and eliminate treatments that suppress the endogenous plasticity mechanisms early post-stroke. Not only that - we should also try to find ways to induce plasticity in such a way that promotes neurological recovery while preventing maladaptation. (**Fig. 3**).

Several medications potentially could boost recovery post-stroke. However, mostly they gave disappointing results in the clinic. The DARS trial's results published in 2019 showed no effect of dopamine on motor recovery. The SSRIs were potential candidates, too, after the positive results of the FLAME study (2011). However, the most recent results (TALOS, 2017; FOCUS, 2018; and EFFECTS and AFFINITY, 2020 trials) were disappointing while confirming efficacy in post-stroke depression. Additionally, the studies uncovered some harmful effects of the treatment, making it difficult to expect positive clinical development in the future.

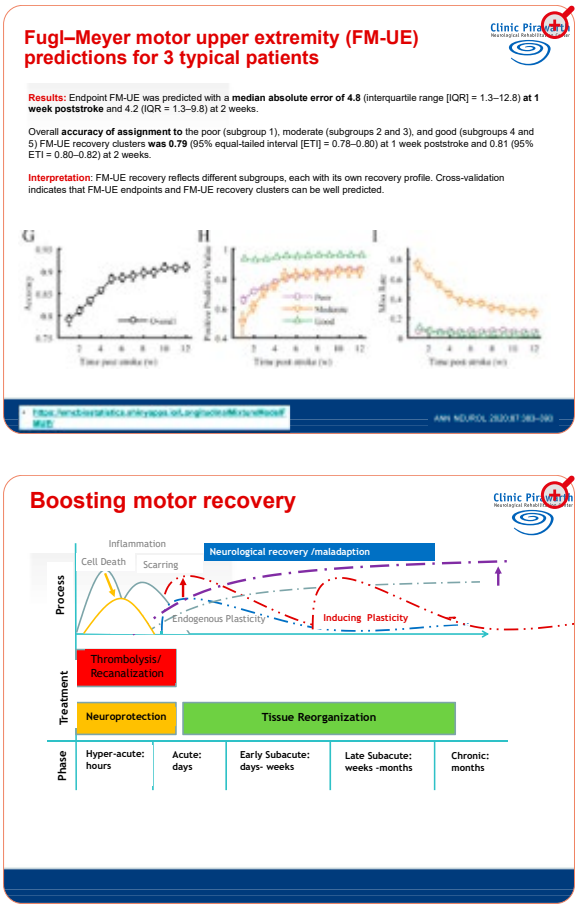

Fig. 3. The Mixture Model for predicting the recovery in stroke patients can work in synch with novel strategies for stimulating the endogenous recovery processes

Promising results were shown by the neuropeptide compound- Cerebrolysin, and Dr. Winkler's center is evaluating this agent in the framework designed for developing novel motor rehabilitation concepts. Cerebrolysin showed multimodal properties in pre-clinical trials. It mimics the activity of neurotrophic factors, and it enhances the levels of the endogenous BDNF (Brain-Derived Neurotrophic Factor) in both pre-clinical and clinical studies. It is worthwhile to recognize that BDNF is known to regulate synaptic plasticity in the brain. The CARS trial was a "game-changer" as we did not understand how to use Cerebrolysin in rehabilitation before the results of this trial were published.[5] The most relevant factors of clinical success discovered in this study were: 1) early administration of Cerebrolysin and 2) combining it with the structured motor rehabilitation program. The clinically significant effect of this combination treatment appeared very early in

the course of the study (2nd week of treatment) and allowed for 88% improvement in the FM-UE score relative to the control (rehabilitation-only, placebo) group. These results appear to be well-aligned with Cerebrolysin's mode of action elucidated earlier in the pre-clinical studies. The general outcome assessment with mRS confirmed the positive shift in the treatment group versus the control group (mRS 0-1; 42,3% vs 14,9% of patients at day 90). The recommendations of the Austrian (class 2 level B), German (1b when used within first three days post-stroke for 21 days), and Canadian (1a for motor function and 1b for ADL) guidelines for using Cerebrolysin in stroke rehabilitation followed this positive clinical development. The most recent recommendations based on the GRADE methodology from the European Academy of Neurology and the European Federation of Neurorehabilitation Societies mention only two EBM (evidence-based medicine)-verified agents for stroke rehabilitation: Citalopram (20 mg) and Cerebrolysin (30 ml, in moderate and severe cases).[6]

Considering the results of the whole clinical development program, we can appreciate that Cerebrolysin probably induces a favorable milieu for enhanced plasticity and motor recovery. This hypothesis was explored in pre-clinical and clinical studies. Recently, Steven Zeiler and coworkers from the Johns Hopkins University used a rodent stroke model for assessing Cerebrolysin's impact on the motor recovery of the arm.[7] In this model, Cerebrolysin prolonged the sensitive plasticity period when given early post-stroke. Of note, it allowed for recovery of the lost prehension function even after delayed motor training. It suggested, for the first time, the possibility of pharmacologically-induced extension of the spontaneous plasticity period after stroke. Newly published results of the ECOMPASS II trial further explored the mechanism of action of Cerebrolysin in stroke patients. This study extended the observations of the ECOMPASS trial (Chang et al., 2016) by analyzing a larger population of severely affected stroke patients (n=110).[8] The results pointed to the time-dependent efficacy of the intervention with Cerebrolysin when combined with motor rehabilitation. The fractional anisotropy index for white matter (obtained using DTI) suggested decreased degeneration in the Cerebrolysin group in comparison with the control group in the vital brain regions of the corpus callosum, CST, and capsula interna, when assessed at day 90 post-stroke. These results can also indicate a double mechanism of action for Cerebrolysin when administered early post-stroke. The first, relying on the preservation of the white matter, and the second, underlying stimulation of the synaptic plasticity post-stroke (**Fig. 4**

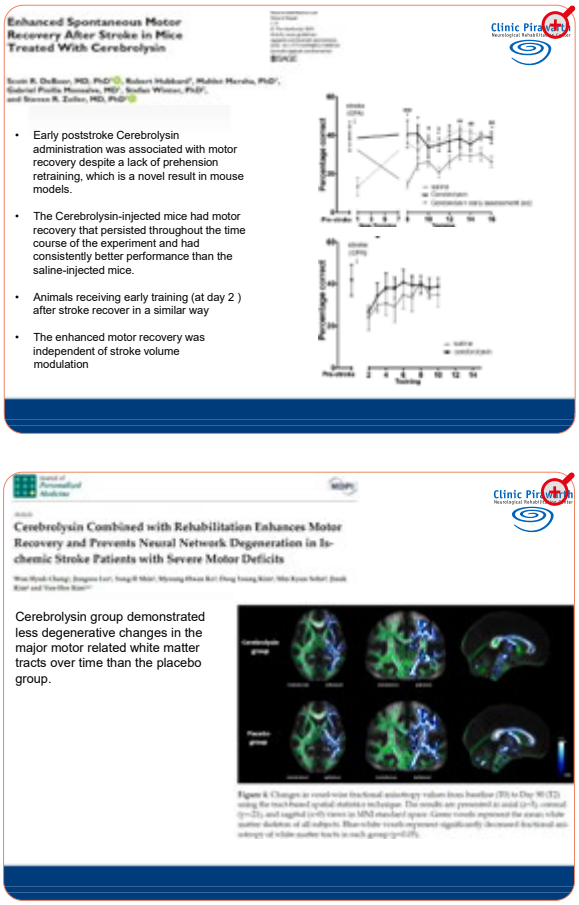

Fig. 4. Prolongation of the sensitive plasticity period and preservation of the brain structures with Cerebrolysin as relevant elements of Cerebrolysin's MoA

Lastly, Dr. Winkler introduced investigations based on the TMS (transcranial magnetic stimulation) and tDCS (transcranial direct current stimulation) methodology. These methods are used routinely in the clinical practice of clinic Bad Pirawarth in combination with classical neurorehabilitation therapy. Both methods allow for localized stimulation or inhibition of the cortical activity of interest. In this way, one can modulate the membrane potential of neurons and mimic the effects of long-term potentiation (LTP). Such an intervention causes increased susceptibility of the treated cortical regions for the therapeutic measure of choice. As shown earlier, the clinical effects of anodal tDCS depend on the BDNF.[9,10] The BDNF can be further stimulated by training or through the use of pharmacological intervention, as has been shown for Cerebrolysin (Alvarez et al., 2016). After a stroke, in subjects with more severe presentation and similarly, in its chronic phase, the levels of BDNF are diminished. Dr. Winkler is interested in designing the therapeutic strategy that combines all the various approaches described here to push the limits of the current neurorehabilitation standards. The goal is to combine early treatment, high intensity of task-specific training, tDCS, and Cerebrolysin (in the so-called triple-therapy approach). Stroke patients in their sub-acute phase are subjects of interest. The tested hypothesis states that the combined therapeutic approach would lead to improved outcomes through enhancing or stimulating late-stage endogenous plasticity processes post-stroke. A small exploratory trial included 44 moderate-to-severe subcortical ischemic stroke patients in their sub-acute phase, divided into three treatment groups.[11] Group A received the daily dose of the task-specific training (30 min/5 days weekly) for two weeks. Group B, received the same treatment as group A and additional sessions of tDCS (20 min/5 days weekly). Group C, received the same treatment as group B plus daily administration of 30 ml Cerebrolysin. The primary endpoint was the ARAT score at day 14 assessed as the percent of the proportional recovery. The results indicated a positive signal suggesting that the triple therapy approach has an advantage over the single (group A) and double (group B) treatment regimens. Based on this positive signal, the IMPULSE trial was initiated, and Dr. Winkler announced its recent start and inclusion of the first group of patients. The investigators aim to show that in 100 patients receiving the triple therapy, positive clinical outcome effects can be recorded within the 21 days of treatment in comparison with the patients receiving the conventional therapy plus placebo infusion and sham tDCS stimulation. The staged design of this trial allows for further expansion of the study population and the inclusion of additional treatment arms. This is planned after the confirmation of the positive signal obtained in the pilot phase (**Fig. 5**).

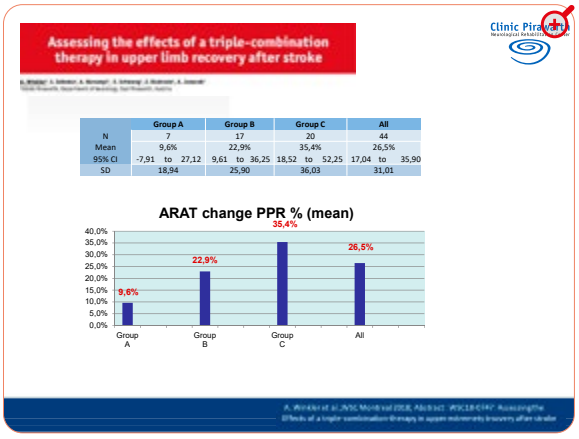

Fig. 5. The triple therapy concept currently tested in the Clinic Bad Pirawarth pushes the limits of the contemporary neurorehabilitation after stroke

Dr. Winkler concluded that in rehabilitation, we need an individualized, personalized multimodal approach to stroke patients as "one size does not fit everybody." Using Cerebrolysin for supporting motor recovery after stroke is the recommended EBM-based pharmacological approach, especially when practiced early - within 72 hours post-stroke.

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Panel discussion

Dafin F. Muresanu, Valeria Caso, Sigrid Schwarz, Andreas Winkler

Dr. Muresanu thanked the lecturers for their contribution to the webinar and underlined that the road to improved rehabilitation after stroke and neurorehabilitation generally is still long. However, we have reasons to be optimistic as new EBM data are published, and we start to appreciate the multimodal approaches that show to bring fruits in the clinical practice. This development is reflected in the recommendations for the treatment supporting stroke rehabilitation issued, among others, by EAN/EFNR and listing two agents: Cerebrolysin and Citalopram (20 mg).

The first question from Dr. Muresanu to Dr. Caso concerned the strategy to cope with the financial difficulties faced by many middle-to-low-income countries hampering their efforts in the effective organization of stroke rehabilitation. Dr. Caso indicated that the projects like ESO-EAST and the mission of ESO, in general, are to promote the implementation of stroke guidelines in all interested countries. The bottom line is that we have to do everything to secure their adoption. This work must proceed alongside the educational projects to get closer to the efficient Austrian or German rehabilitation model. The road leads through close cooperation between the reference centers and the partners in countries where such a need exists.

The question to Dr. Schwarz: Knowing that Dr. Schwarz is using Cerebrolysin in her rehabilitation practice, in line with the current Austrian guidelines, what is her experience with the treatment and remarks about its effects from the standpoint of everyday practice. Dr. Schwarz suggested that when properly used, Cerebrolysin represents a good treatment option in stroke rehabilitation. A standard operating procedure has been developed for Cerebrolysin in her clinic. It allows for using Cerebrolysin within the first week or up to 21 days. While using ARAT for routine arm function recovery assessment, Dr. Schwarz does not utilize the cognitive tests in her clinic. However, the impact of Cerebrolysin on cognition appears to help in the successful initiation of the rehabilitation.

The final question from Dr. Muresanu directed to Dr. Winkler, concerned the advantage of using tDCS together with Cerebrolysin and, additionally, what is the meaning of the 6 points difference in the ARAT score? Dr. Winkler answered that it is a convention used to describe the clinically meaningful change in the ARAT score (the 6 points difference). If it is of practical significance for a patient, is another question. Dr. Winkler's clinic initially tried to use tDCS without much interest in Cerebrolysin. Dr. Winkler tried Cerebrolysin treatment already 20 years ago but had no idea at this time how to use it and what to expect. The CARS trial delivered the argument that there must be a clinical effect of Cerebrolysin when the agent is administered very early after stroke. In the meantime, the tDCS' mode of action was elucidated and its link with Cerebrolysin was established. The seminal work of Brita Fritsch showed that BDNF is the vehicle of the clinical impact of tDCS. Other important works published afterward described a distinct connection between the neurotrophic factors and the mode of action of tDCS. It was then apparent to Dr. Winkler's team that combining tDCS and Cerebrolysin for supporting motor training is a well-grounded scientific idea. Apart from the discussed earlier effects of triple therapy, seen in the exploratory trial, this approach is now used routinely in the clinical practice of clinic Bad Pirawarth. The stroke patients improve beyond the typical recovery plateau when treated with this combination. Even in patients returning to the clinic after one year (chronic stroke), the benefits of re-treatment with triple therapy are noticeable. Although the treatment effect is evident, the investigators in the IMPULSE (which represents the proper multicenter, controlled, and randomized trial design) want to measure its size. Dr. Winkler expects to achieve the change in ARAT score bigger than 6 points, which should translate into noticeable functional benefits in hand movements. Such an improvement in hand

function should, as a consequence, support the activities of daily living that represent practically meaningful skills for stroke survivors.

The question addressed to the whole panel explored the timing and duration of Cerebrolysin treatment. Dr. Schwarz answered that the optimal treatment duration in her clinic is 21 days (meaning the recommended dose), provided it is possible due to the availability of a patient. The answer from Dr. Winkler confirmed this approach. Dr. Muresanu added that established treatment protocols are available for longer-term Cerebrolysin use. The concept of chronic intermittent treatment applies in this case. The pharmacological profile of Cerebrolysin emerging from the pre-clinical and clinical investigations and the long-term nature of the brain recovery processes seen in the clinical practice of rehabilitation determine the chronic therapeutic pathway. Dr. Muresanu's clinic employs, whenever possible, the repetitive cycles of Cerebrolysin treatment, depending on the individual situation of a patient. The long-term treatment schedule entails ten days-long treatment periods of 10 ml daily, every month or every other month.

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.

EVER Neuro Pharma GmbH
Oberburgau 3
4866 Unterach
Austria
www.everpharma.com

edited by: Pawel J. Ciesielczyk, PhD; EVER Neuro Pharma GmbH; made by Artists

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