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Scientific Symposium EVER
Stroke Recovery – Pharmacological Treatment Concepts in the acute and sub-acute phase

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Program of the symposium

Stroke Recovery – Pharmacological Treatment Concepts in the acute and sub-acute phase

Thursday, 18 May 2017, 12:15-13:45 (Meeting Hall I)
Chairmen: Michael Chopp, USA & Michael Brainin, Austria

New rigorous preclinical trials of Cerebrolysin for stroke

Michael Chopp

Vice Chairman, Dept. of Neurology, Zoltan J Kovacs Chair of Neuroscience Research, and Scientific Director, Neurosciences Institute Henry Ford Hospital, Detroit, Michigan, USA

ABSTRACT:

Cerebrolysin has potent protective and restorative therapeutic effects for the treatments of stroke, traumatic brain injury (TBI) and neurodegenerative diseases. Here, I will summarize our recent data on prospective, double blinded placebo controlled preclinical studies, performed under rigorous clinical trial conditions for the treatment of embolic stroke. A clinically relevant model of embolic stroke is induced in rat by placement of a preformed clot at the origin of the middle cerebral artery. Outcomes of dose-response and therapeutic window studies demonstrating highly efficacious therapeutic benefit of Cerebrolysin will be presented. In addition, I will provide new insight into the multiple mechanisms of therapeutic action of Cerebrolysin. Data will be shown that Cerebrolysin evokes expression of Angiopoietin 1 (Ang1), which promotes blood brain barrier integrity, is anti-inflammatory and mediates axonal outgrowth. Importantly, Cerebrolysin also upregulates the expression of the developmental morphogen Sonic Hedgehog (Shh) which stimulates cellular expression of specific sets of microRNAs (miRs). miRs are small non-coding RNAs which can simultaneously post-transcriptionally regulate the translation of many genes. Shh up regulates cellular expression of a specific group of miRs, the miR-17-92 cluster. This cluster of miRs, has potent anti-inflammatory effects as well as promotes axonal outgrowth. Thus, we demonstrate that Cerebrolysin has multifactorial neurovascular remodeling effects on tissue which drives neurological recovery, data on which are evident in our rigorously controlled preclinical stroke studies. These data strongly support translation of Cerebrolysin therapy from the laboratory to the stroke patient.

Dr. Chopp introduced his lecture dividing it into two sections. First, he talked about major scientific arguments that can influence the use of Cerebrolysin in clinical practice as well as the understanding of the molecular mechanisms by which Cerebrolysin exerts its clinical actions. Second, he turned attention of the audience to field of microRNAs (miRs), the molecules regulating the expression of genes.

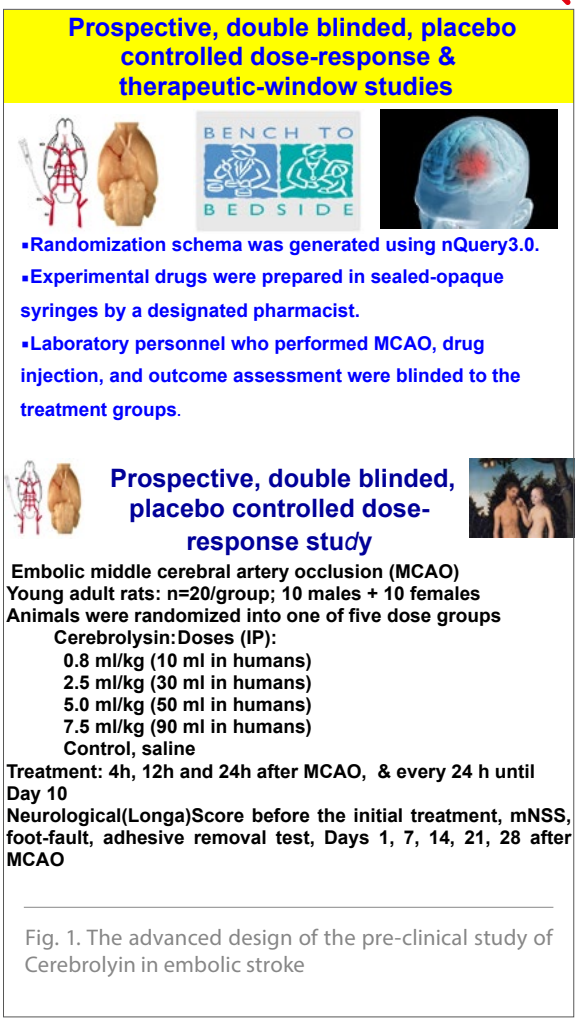

Fig. 1. The advanced design of the pre-clinical study of Cerebrolyin in embolic stroke

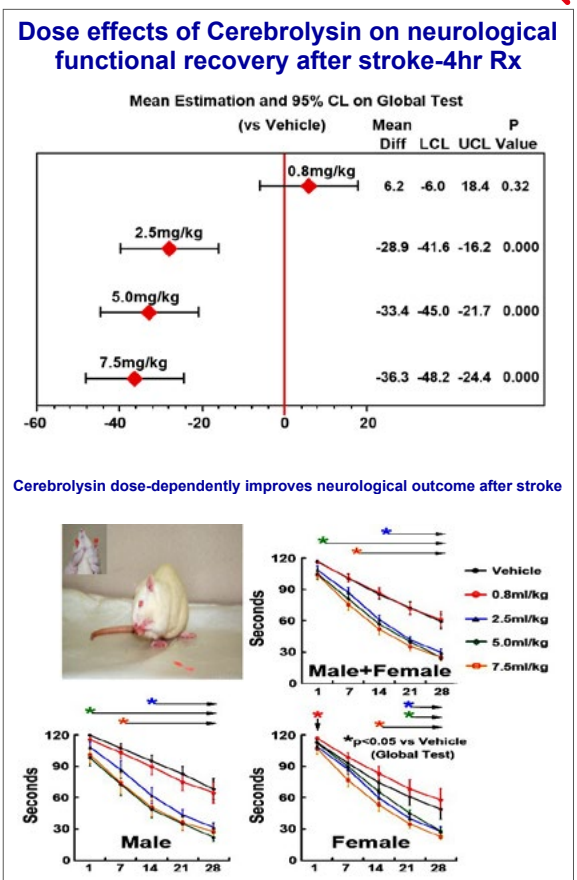

Fig. 2. The combined neurological outcomes - the results of pre-clinical study with Cerebrolysin in the rat embolic stroke model

Historically, there was a failure in translational studies in neurology. Among many methodological problems explaining this situation, one particular problem appears to be the lack of scientific rigor of the pre-clinical studies. In order to address this matter, Dr. Chopp and EVER Pharma decided to apply very rigorous study design closely resembling that of the most advanced prospective, randomized, double blind, placebo controlled clinical trials, in order to investigate dose response and the therapeutic window of Cerebrolysin **(Fig. 1)**.

The combined neurological outcomes were analyzed as a global score, which was the end point of the study **(Fig. 2)**. This statistical concept was taken directly from the pivotal NINDS tPA trial, with results published in 1995. There was a clear dose response effect of Cerebrolysin with all but the lowest dosage. One of the essential points of the study was looking into the differences between sexes, because this reflects also the clinical and biological reality of our patients. The levels of the inflicted injury as well as the response to the injury differed significantly between males and females in this study.

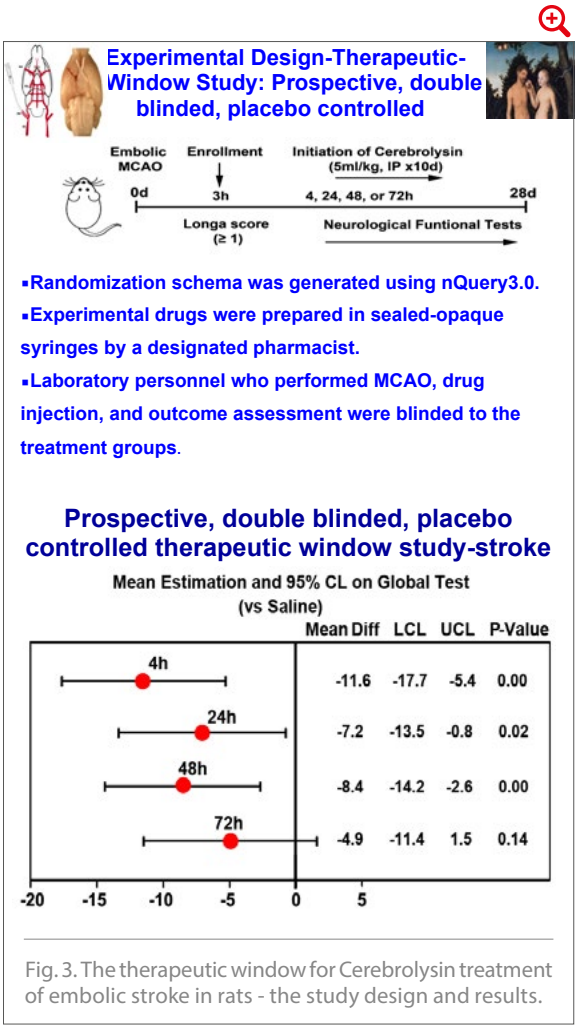

Fig. 3. The therapeutic window for Cerebrolysin treatment of embolic stroke in rats - the study design and results.

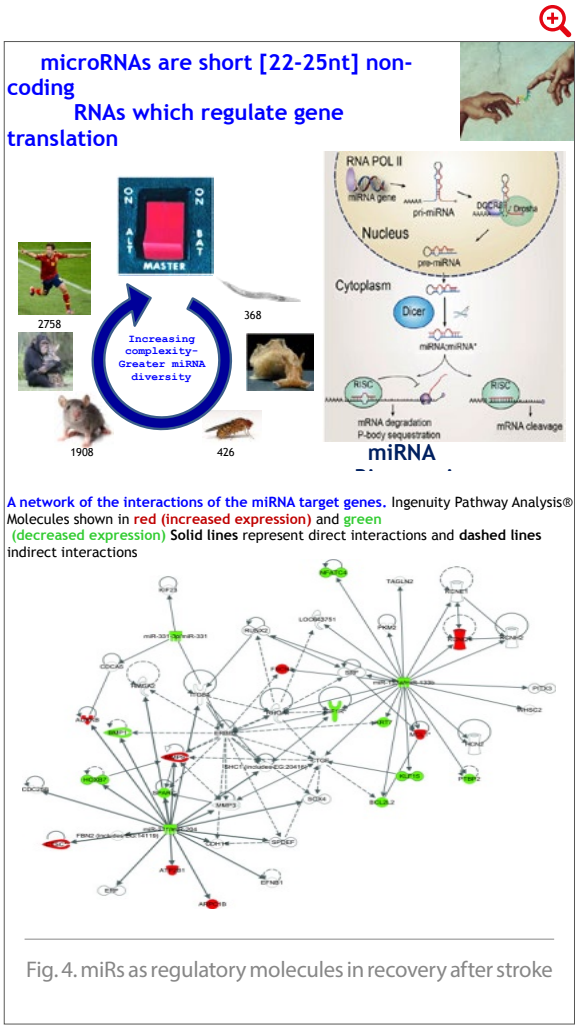

Fig. 4. miRs as regulatory molecules in recovery after stroke

The therapeutic window part of the study was performed according to similar design, with additional treatment time points **(Fig. 3)**. It was shown that 4 hours to 48 hours time window provides substantial treatment benefits in global neurological outcome. Summarizing the results of this study, Dr. Chopp underlined that Cerebrolysin demonstrated clear dose response and time window related efficacy as measured with global neurological outcome.

Next, Dr. Chopp turned to discussing the mechanism of action of Cerebrolysin. What it primarily does is the stimulation of the endogenous restorative responses, with a major component of this action localized to microvasculature. This includes stimulation of expression of important molecules, like vascular endothelial growth factor (VEGF) and angiopoietin 1 (ANG1). ANG1 plays important role in controlling the function of the blood brain barrier, which is vital for the recovery from stroke. Additionally, it was shown to stimulate neurite outgrowth. Related to this topic is a question of the role of miRS in regulation of the recovery processes post-stroke **(Fig. 4)**.

Dr. Chopp and his team have found out that Cerebrolysin turns on some of the very important (for post-stroke recovery) miRS populations. They established that Cerebrolysin stimulates morphogens important for the recovery processes, like Sonic Hedgehog (Shh). In turn, Shh switches on some important clusters of miRS **(Fig. 5)**, which drive plasticity processes post-stroke.

The interplay between Shh and microRNAs is an emerging topic in science and drug development. miRS act at the translational level in the process of genes expression and can simultaneously switch off and on the synthesis of various families of proteins, adding a separate level of control and complexity in regulating biological process.

Dr. Chopp finished his lecture by underlining that successful translation of research results into the clinic requires rigorous approach in study design and execution already at the early pre-clinical stage. Cerebrolysin has been successfully tested according to this principle. Moreover, the emerging research data help explaining Cerebrolysin mode of action and therefore can be useful in fine tuning the clinical protocols employing this complex drug.

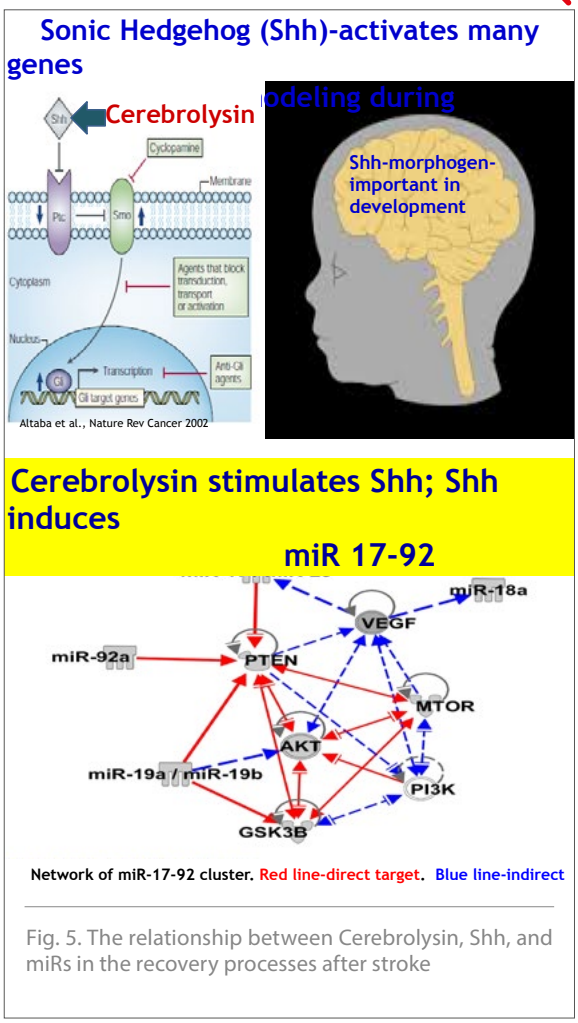

Fig. 5. The relationship between Cerebrolysin, Shh, and miRs in the recovery processes after stroke

Cerebrolysin's evidence in acute stroke - a clinical review

Milan Vosko

Dept. of Neurology 2, Kepler University Clinic, Linz, Austria

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 in stroke patients. Additional efforts have been directed at developing drugs with a neuroprotective and neurorestorative effect and some promising advances have been made in recent years. 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 favor of Cerebrolysin in patients with NIHSS>12. Combination of Cerebrolysin with thrombolysis (Lang et al., 2005) found in patients additionally treated with Cerebrolysin earlier recovery seen on the NIHSS compared to placebo treated patients. Although this difference did not persist until 90 days endpoint, the Cerebrolysin-induced earlier recovery of stroke patients can positively affect early mobilization. CARS trial showed a significant beneficial effect on function and global outcome in early rehabilitation in stroke patients as well as safety comparable to placebo. Experimental studies (Chopp et al.) prove the mechanism of action through the sonic hedgehog signaling pathways mediating Cerebrolysin enhanced neurogenesis and white matter remodeling. Controlled registries have shown to offer a reliable scientific evidence of real life acute stroke treatment (SITS-MOST). The ongoing CREGS-S registry trial is registering worldwide acute stroke patients treated with Cerebrolysin.

Dr. Vosko presented an overview of clinical results for Cerebrolysin in stroke. He represents the stroke unit from Linz in Austria where thrombolysis (30% of stroke patients) and thrombectomy are routinely performed procedures. However, thrombolysis and thrombectomy is not all we can do to help stroke patients. The major problem with stroke is that it is a heterogenous disease **(Fig. 1)**.

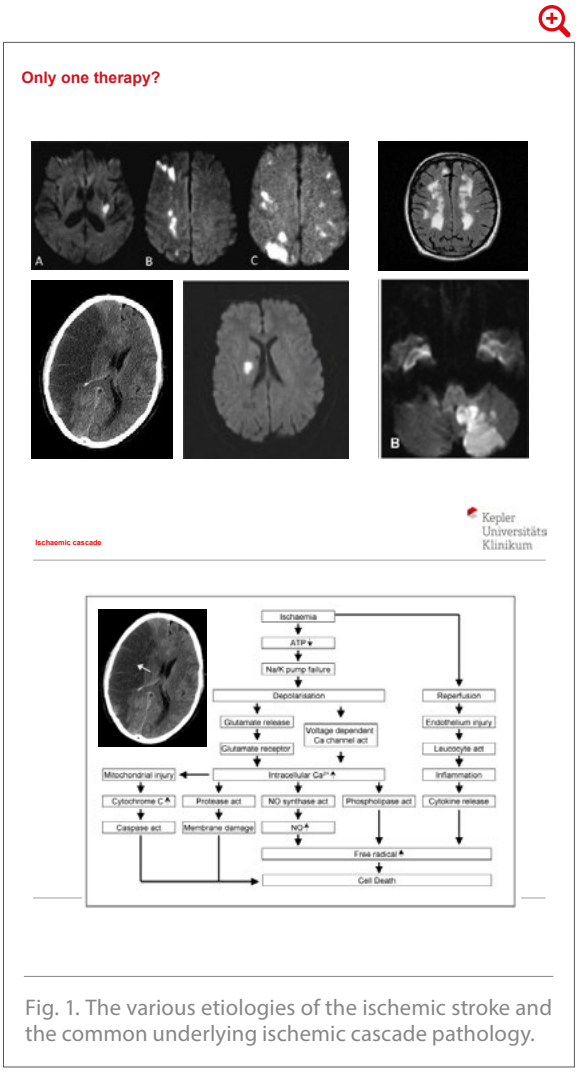

Fig. 1. The various etiologies of the ischemic stroke and the common underlying ischemic cascade pathology.

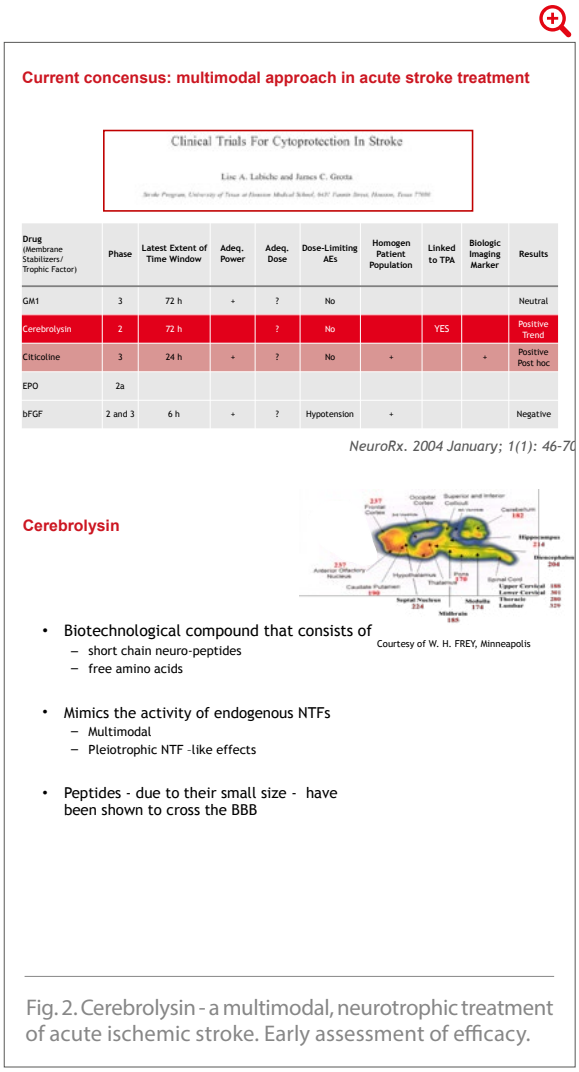

Fig. 2. Cerebrolysin - a multimodal, neurotrophic treatment of acute ischemic stroke. Early assessment of efficacy.

Thrombolysis and thrombectomy are helping from 5% to 30% of all ischemic stroke patients and we have to find the way to help the remaining patients, too. A comprehensive approach is needed that would support the current standard. Addressing the ischemic pathology but also stimulation of endogenous restorative processes seems to be a logical thing to do. In fact, the proper target for a supporting therapy in stroke appears to be the neurovascular unit, not just neurons. In spite of the slow development in the field of supporting neuroprotective therapies in recent years, it seems that there is still hope for establishing new treatments. In our thinking about any stroke treatment, we should remember about the phases of stroke. Fast action in the acute period is the key to success. Then, comes the possibility to quickly apply other therapies, like Cerebrolysin **(Fig. 2)**.

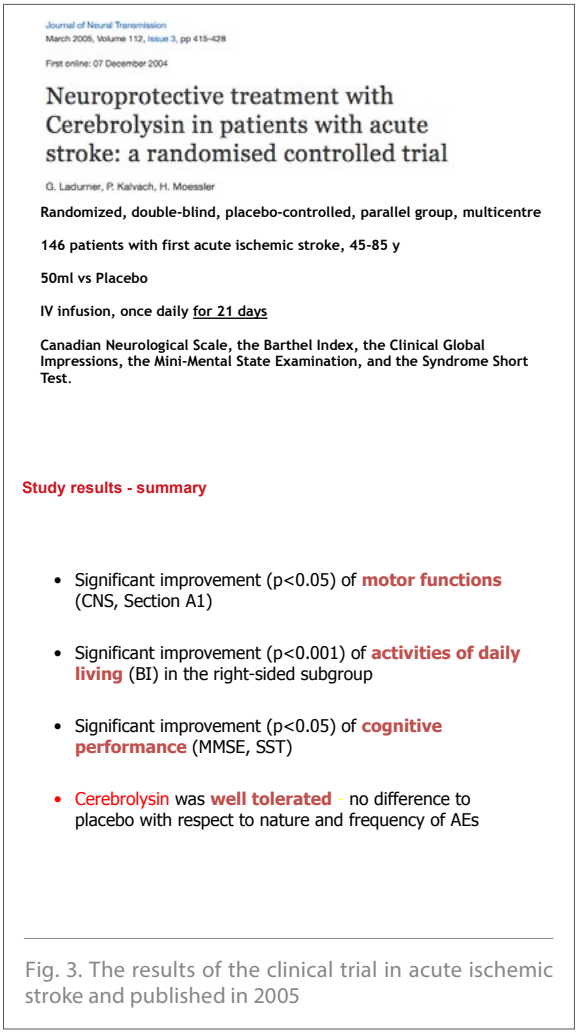

Fig. 3. The results of the clinical trial in acute ischemic stroke and published in 2005

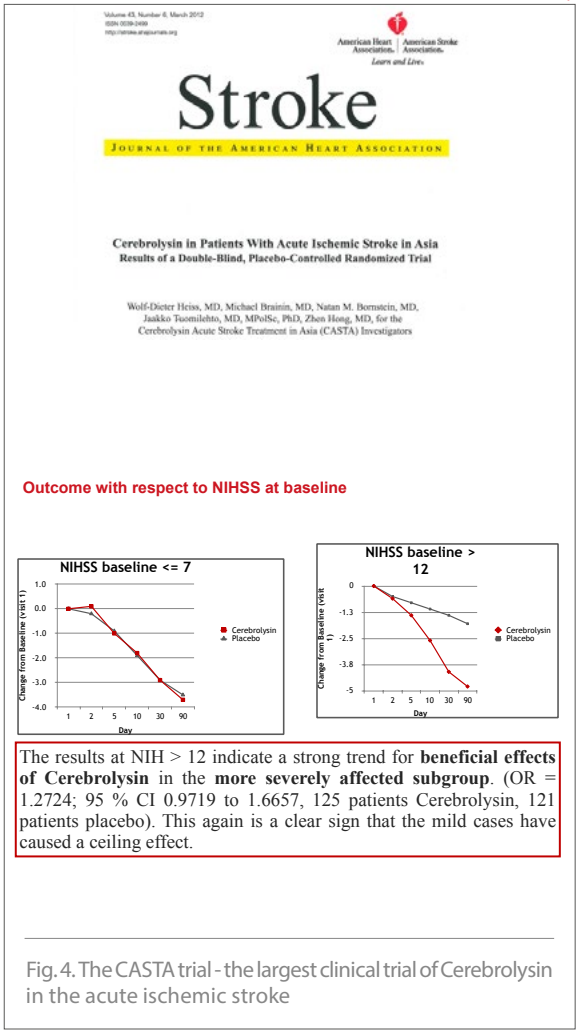

Fig. 4. The CASTA trial - the largest clinical trial of Cerebrolysin in the acute ischemic stroke

Experimentally, Cerebrolysin showed positive effect on apoptosis (downregulation), neurogenesis and neural maturation. How this mechanisms translate into the clinic? asked Dr. Vosko. The first results discussed were of the study performed by the group of Prof. Ladurner **(Fig. 3)**.

This trial gave first positive results for Cerebrolysin treatment of stroke in the randomized, placebo controlled, double blind, multi center, and parallel groups design. The recovery domains affected were motor functions, activities of daily living and cognitive performance. The safety of the treatment was very good. Next discussed trial, the CASTA-trial, was the largest performed trial of the Cerebrolysin treatment of acute ischemic stroke **(Fig. 4)**.

This trial has shown positive trend in global endpoint (combination of Modified Rankin scale, Barthel Index, and NIH Stoke Scale scores). Clearly, too mild stroke patients were included in the trial and they recovered fast by themselves masking, too great extent, the therapeutic effect of Cerebrolysin. In the more severely affected patients, with NIHSS at admission 12 or higher, there was a much stronger trend toward improvement in the Cerebrolysin group.

The CERE-LYSE trial was performed, among other centers, in the stroke center of Dr. Vosko. This trial investigated safety and efficacy of the combination rtPA and Cerebrolysin **(Fig. 5)**.

The treatment time was only 10 days, and Dr. Vosko suggested that we have learned important things from this trial. At the endpoint of day 90 the study was neutral. However, when we look at the differences between the groups (rtPA + placebo and rtPA + Cerebrolysin) at earlier time points, we can see that there is a highly significant positive response in the combination group, in comparison with the control group. One conclusion is that the treatment time was probably too short. However, the positive short term effect of the combination with Cerebrolysin is important in the acute setting. For example, during this early period a decision must be made about admission of a patient to a rehabilitation center. The response of a patient to Cerebrolysin can indicate the readiness of a patient for rehabilitation. The general idea of acute therapy is to start early an intensive treatment in order to achieve a better outcome as early as possible, so the patient can be accepted to a rehabilitation center as soon as he/she is ready for this intensive and very demanding therapeutic phase.

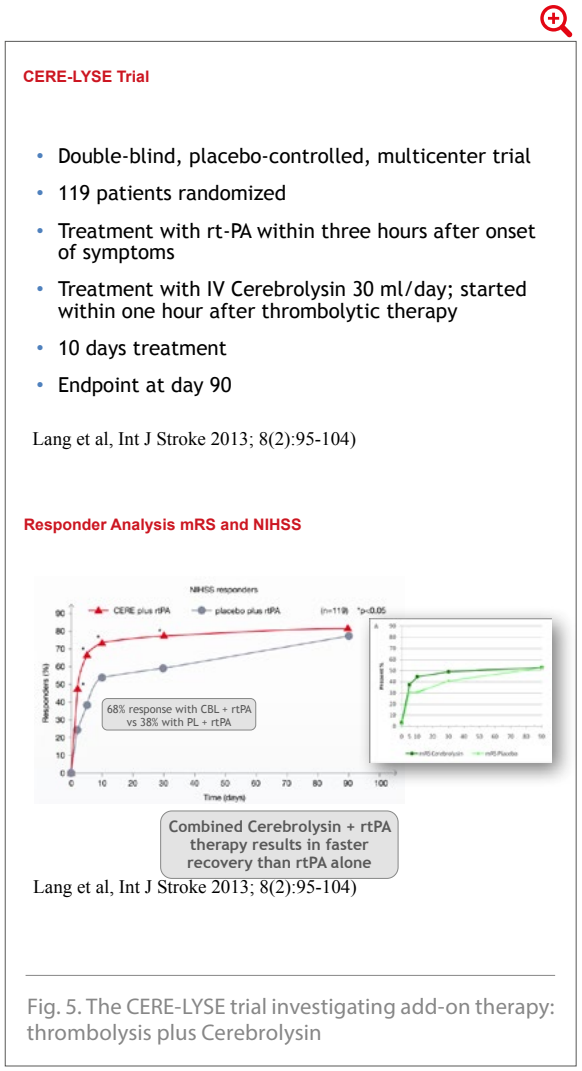

Fig. 5. The CERE-LYSE trial investigating add-on therapy: thrombolysis plus Cerebrolysin

Dr. Vosko went on to mention the recent trial in which Cerebrolysin was used as add-on to active rehabilitation program of the paretic arm (see the lecture of Prof. Muresanu). The treatment duration was 21 days and a significant benefit of the combination treatment was recorded.

Dr. Vosko concluded that the Cerebrolysin trials were important for our better understanding of the optimal application of this drug in stroke patients. Another way to optimize the therapy, which is already in clinical use, is to utilize registries, like CREG-S which is running already in its 2.0 iteration.

Challenges & Opportunities in Motor Recovery

Dafin Muresanu, MD, PhD, Professor

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

ABSTRACT:

Nowadays, it is still difficult to find the correct therapeutic approach for brain protection and recovery in stroke, especially because we do not fully understand all of the endogenous neurobiological processes, the complete nature of the pathophysiological mechanisms and the links between these two categories. Endogenous neurobiological processes, such as neurotrophicity, neuroprotection, neuroplasticity and neurogenesis, are central to protection and recovery and represent the background of endogenous defense activity (EDA). Stroke pathological cascades contain a limited number of pathophysiological processes. It is characterized mainly by excitotoxicity, oxidative stress, inflammation, apoptotic-like processes and important metabolic disturbances. Pathophysiological processes share some common mechanisms with EDA (e.g. excitotoxicity and neurotrophicity together with neuroplasticity have, as a common important driver, the NMDAR activity; inflammation has an important contribution for neuroregeneration, stimulating neuroplasticity, via trophic factors). Postlesional brain regulation is currently better understood. Every lesion in the nervous system triggers in the first minute an endogenous neuroprotective reaction. An endogenous repair process, combining neuroplasticity and neurogenesis follow this as a second answer. All these processes are initiated and regulated by endogenous biological molecules. The biological reality of the nervous system is far more complex. In fact, there is an endogenous holistic process of neuroprotection and neurorecovery that should be approached therapeutically in an integrated way. The current tendency to exclusively frame drug activity in terms of single mechanisms and single focus effect might distract from other paradigms with greater explanatory power and hinder the development of more effective treatment strategies. A change of concept is required in pharmacological brain protection and recovery in stroke therapy. This presentation briefly reviews the current and future considerations in this therapeutic strategy, including an integrated pharmacological approach, focusing on drugs with multimodal activity rather than single mechanism drugs, which usually are chemical drugs. In line with this strategy the current presentation will also highlight the result of CARS Trial, one of the latest double blind placebo randomized controlled trial in the field.

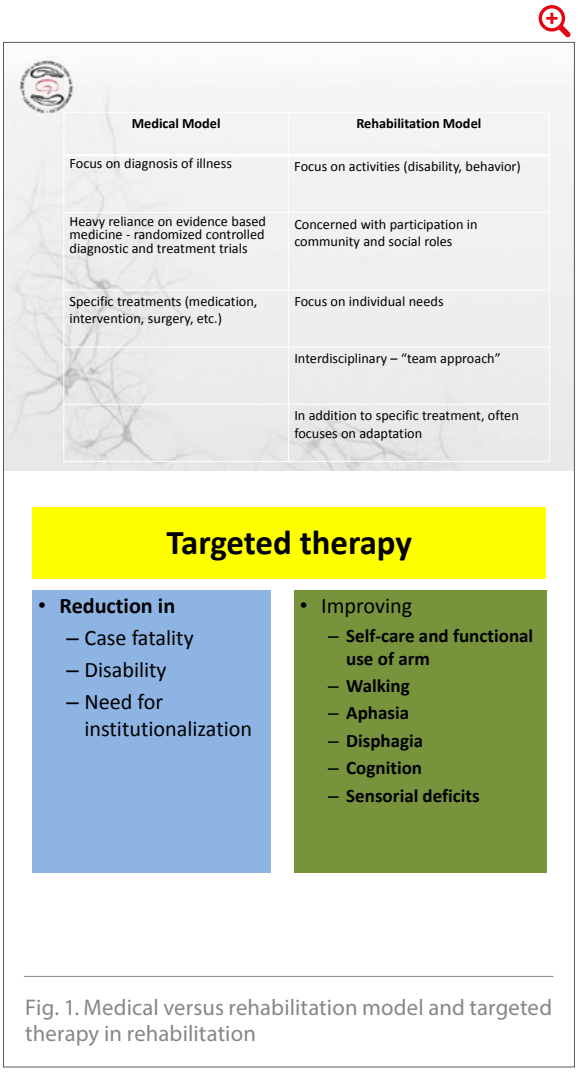

Fig. 1. Medical versus rehabilitation model and targeted therapy in rehabilitation

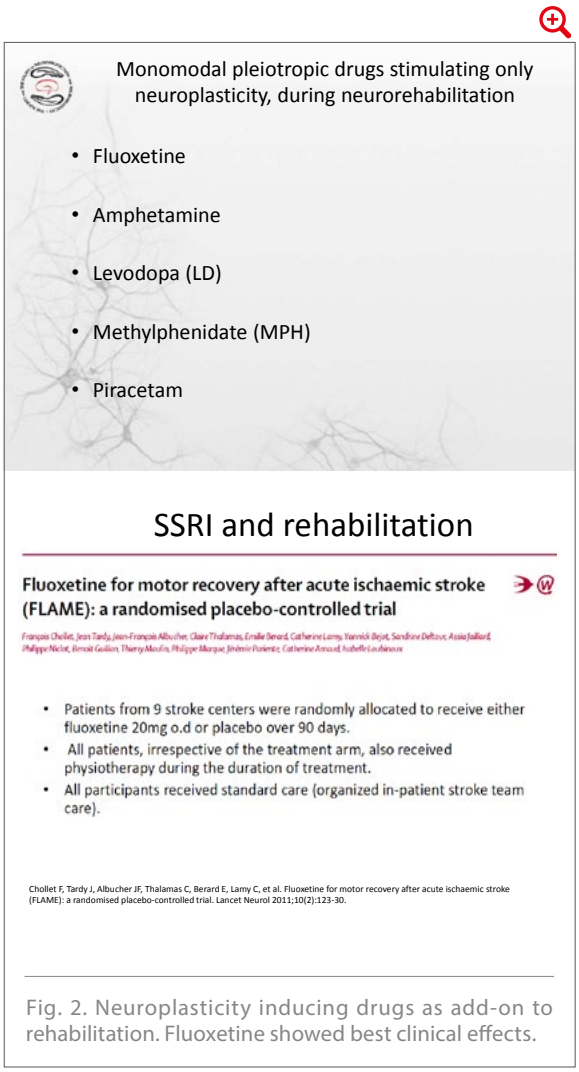

Fig. 2. Neuroplasticity inducing drugs as add-on to rehabilitation. Fluoxetine showed best clinical effects.

Prof. Muresanu began his lecture by stating that rehabilitation is rather a complicated process of recovery where we have to balance the limits of disability and a biological reserve. There are currently two models employed in the treatment of stroke: the medical model and the rehabilitation model **(Fig. 1)**.

One of the major current goals is to bring the complex rehabilitation model closer to the rigorous requirements of the medical model. Prof. Muresanu went on to outline the conceptual status of rehabilitation as part of the comprehensive therapy of stroke, its relation to organized stroke care, acute phase interventions, duration and also idea of targeted therapy as the most useful approach in the rehabilitation process. Acute rehabilitation, including early mobilization is important part of the recovery, in most cases. However, very intensive mobilization within first 24 hours is currently not recommended.

The pharmacological support of the rehabilitation is considered as important field of development with some promising results coming from recently performed trials. Among agents stimulating neuroplasticity, fluoxetine showed the most interesting results **(Fig. 2)**.

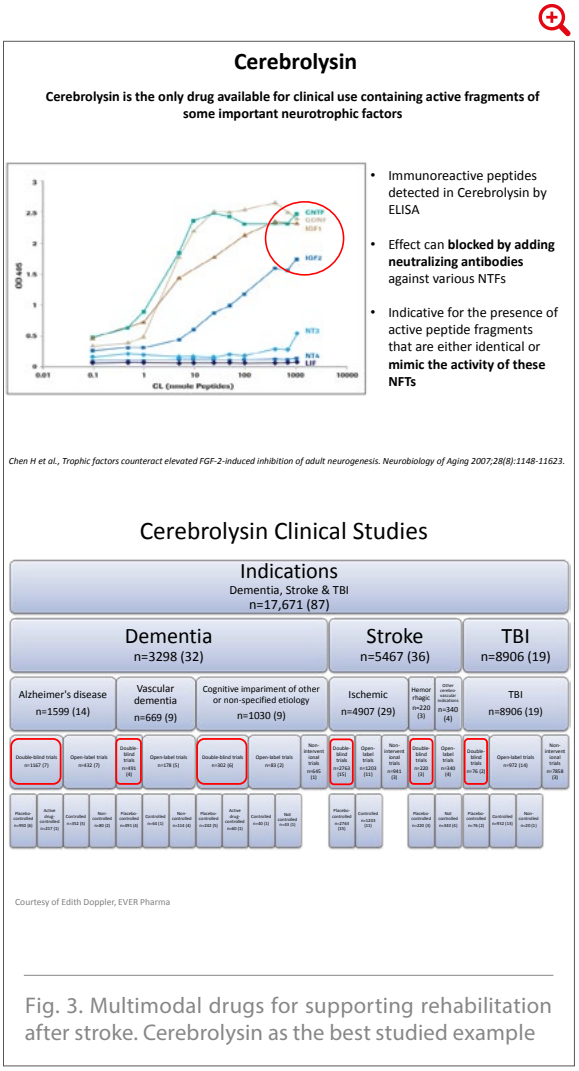

Fig. 3. Multimodal drugs for supporting rehabilitation after stroke. Cerebrolysin as the best studied example

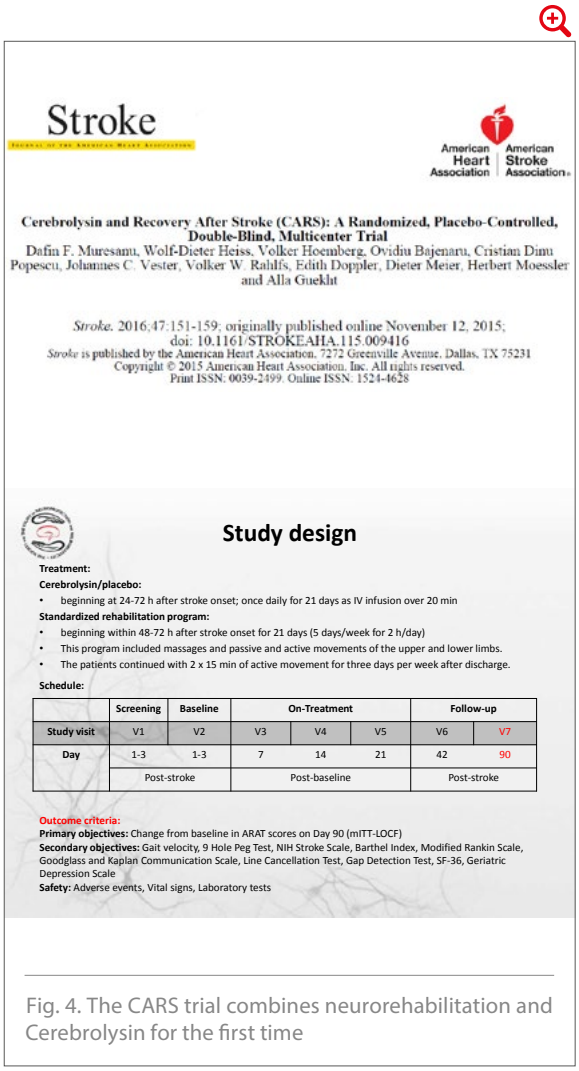

Fig. 4. The CARS trial combines neurorehabilitation and Cerebrolysin for the first time

Another promising group of treatments in supporting rehabilitation are multimodal drugs that act at the level of the endogenous recovery mechanisms **(Fig. 3)**.

The early trials with Cerebrolysin were dedicated to protection in the acute phase of stroke, hence their duration was usually 10 days an there was no concomitant structured rehabilitation applied. The most recent trial, CARS, addressed this situation by applying the design which combined pharmacological intervention with Cerebrolysin and structured neurorehabilitation of the affected arm **(Fig. 4)**.

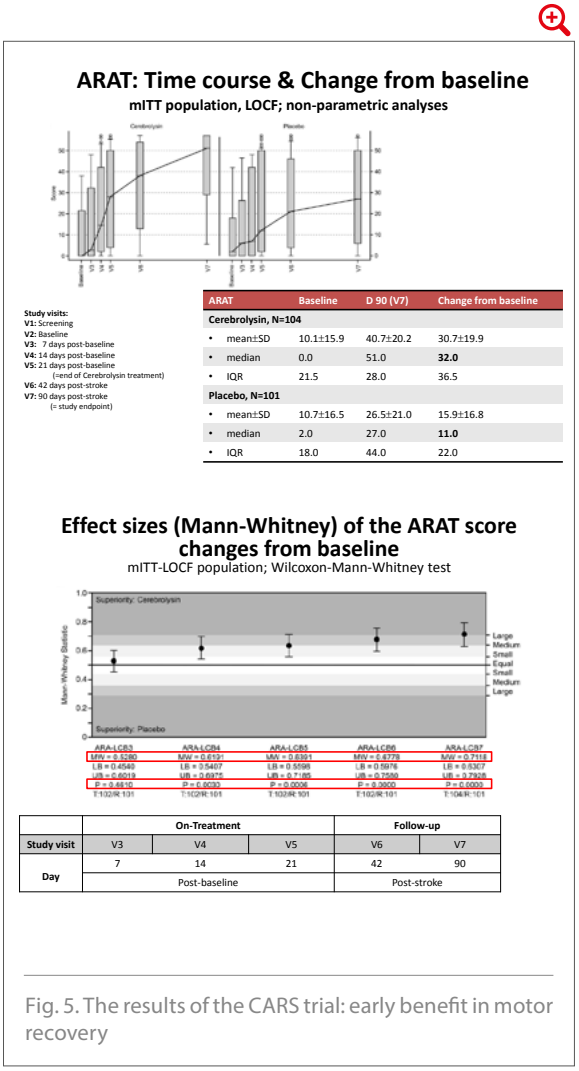

Fig. 5. The results of the CARS trial: early benefit in motor recovery

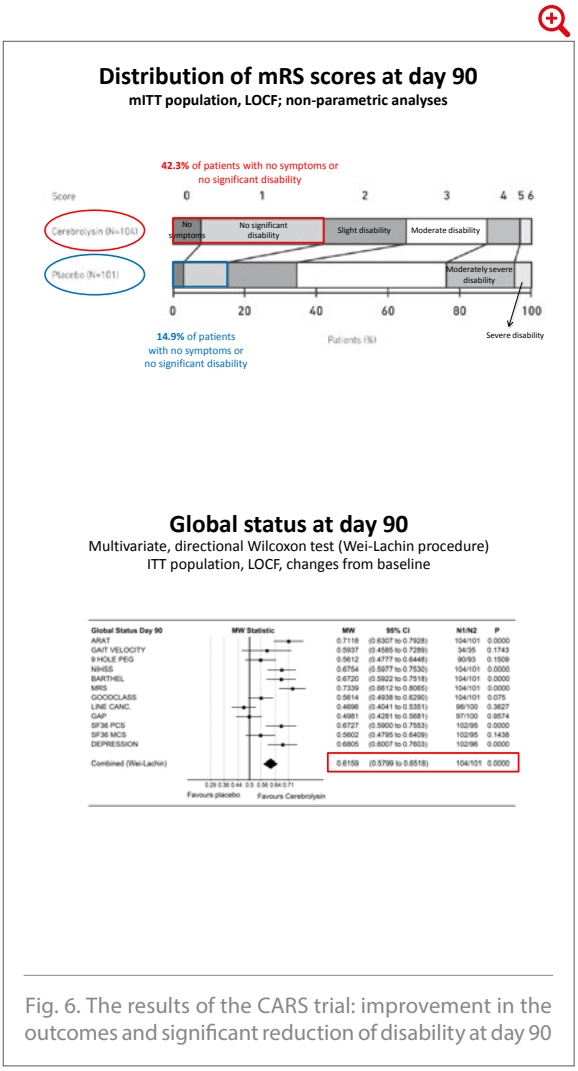

Fig. 6. The results of the CARS trial: improvement in the outcomes and significant reduction of disability at day 90

It was previously shown that the upper limb recovery is more difficult than the recovery of the lower limb. On the other side, recovery of the upper limb is highly desired from the rehabilitation standpoint because it enhances the recovery of other important functions like cognitive and activities of daily living. This clearly supports overall rehabilitation process. The specific measure of upper limb recovery, the ARAT (Action Research Arm Test) score, was chosen as the primary endpoint in this study. The results of CARS were positive and there was statistically significant advantage of the combination group versus rehabilitation only group in the primary endpoint analysis **(Fig. 5)**.

The early treatment effect detected already after 14 days of treatment/rehabilitation is especially important as it leads to reduction of various serious complications post-stroke. The modified Rankin scale score and the final multivariate analysis of several (12) employed neurological outcome assessment tools provided evidence for strong therapeutic effect of the combination Cerebrolysin with motor rehabilitation of the paretic arm **(Fig. 6)**.

No safety problems were detected, as expected in the case of this well studied drug. Concluding his lecture, Prof. Muresanu indicated that the concept of pharmacological support of neuroprotection and neurorehabilitation is valid, but we should preferably address it from the standpoint of the multimodal therapies, correct dosage and proper duration of the treatment. Additionally, the therapeutic decisions in the rehabilitation after stroke should be highly individualized.

Stroke and Cognition

Michael Brainin

Danube University Krems, Krems, Austria

ABSTRACT:

Dementia following stroke is a frequent finding and affects one out of ten patients. More frequently, a decline in cognitive function occurs that does not reach dementia levels but significantly impedes everyday function due to impairment mostly of executive domains without affecting memory functions. Such dysexecutive syndromes are very frequent and can occur immediately following stroke but most often in time-delayed fashion following some weeks or even months after stroke. Most often the caregivers notice such changes once the patient has been discharged home. The pathophysiology of this process is not easily understood and molecular changes and predisposing factors are currently being investigated. Previous randomized trials aiming at promoting recovery after stroke such as with levodopa, natural biologicals (Cerebrolysin) or SSRI's have been successful in showing improvement of motor recovery. A recent study showed that Cerebrolysin promotes arm recovery following stroke (CARS Study). Also for Cerebrolysin, cognitive data are scarce, but a Cochrane analysis has shown some effects on vascular dementia patients with significantly improved outcomes. It is quite plausible that a multimodal acting biological drug such as Cerebrolysin stands up better to rigorous testing for complex endpoints such a cognition. Up to now, for prevention or treatment of dysexecutive syndromes following stroke no proven drug treatment exists. Single or combined drug interventions tested up to now were based mostly on secondary outcome analyses and included antihypertensive drugs which showed only a modest effect on cognition in general and no consistent effect was shown for lipid lowering drugs. Combination of antiplatelet drugs have been tested in the SPS3 trial but showed no effect on cognitive outcomes. Life-style interventions include studies of a Mediterranean diet with extra virgin olive oil and nuts but while stroke occurrence can be reduced, no data on post-stroke cognition exist. The same applies for physical exercise programs which show good effects on physical fitness but less studies are performed using endpoints reflecting the preservation of cognitive function following stroke. Multi-domain intervention studies are much more likely to be effective on cognition because they perform multiple risk factor management with lifestyle adaptation including diet changes with increase of drug compliance and adherence. Intensifying these interventions and to monitor them is crucial. In the first comprehensive multi-domain intervention trial (ASPIS) the primary endpoint was a significant change of the z-score of 5 neuropsychological domains. While the overall result was neutral, a signal for change of dysexecutive function was seen and follow-up studies might have to consider this finding. In the future, there is a need for including cognitive outcome measurements in all trials targeting the brain, to consider larger sample sizes, to harmonize assessment strategies, to focus on a high risk population, and to include biomarkers and imaging data for confirmatory analyses. Overall, it is crucial to aim for intervention intensities that create significant group differences and to continue to study the protective effects with multimodal drugs that already have shown a significant potential for motor recovery.

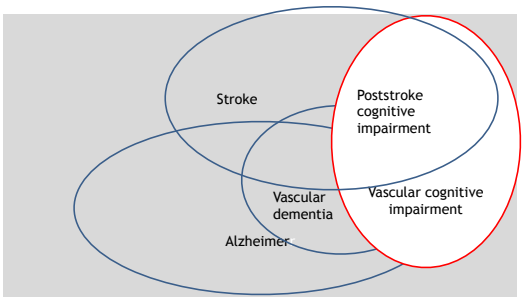

Fig. 1. Post-stroke cognitive impairment - a definition

The lecture of Prof. Brainin addressed still unsolved issue of post-stroke cognitive impairment. We know that cognitive impairment after stroke can progress to dementia, but not in all cases. The definition of cognitive impairment is itself a difficult matter, mainly due to different criteria used to asses it across clinical trials. One common aspect of post-stroke cognitive impairment is lack of involvement of memory deficit whereas executive functions appear to be most affected. This indicates different kind of impairment in comparison with Alzheimer's disease (AD) or prodromal AD. It seems that post-stroke cognitive impairment is a separate disease entity **(Fig. 1)**.

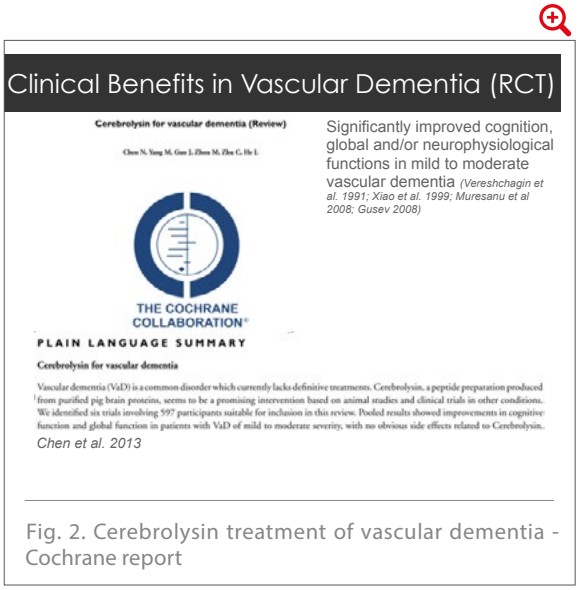

Fig. 2. Cerebrolysin treatment of vascular dementia - Cochrane report

The persistent glia activation was linked with the cognitive decline post-stroke and this appears as independent process from the amyloid accumulation. It rises a question which medications should be used to treat this disease? In the clinical practice, there are many drugs used during rehabilitation after stroke, but they are used for motor rehabilitation. There are no drugs used for prevention of cognitive decline. Blood pressure lowering appears to have some slight positive effect. Interestingly, Cerebrolysin was shown to have positive treatment effect on vascular dementia **(Fig. 2)**. This is not that surprising if we take into account all the clinical experience with this drug, although majority of stroke data relates to motor recovery, said Prof. Brainin. Mediterranean diet was shown to be single most important measure to prevent stroke. Fitness training after stroke appears to also have positive impact on cognitive fitness of stroke patients. However the most interesting thing appears to be multi-domain interventions. This paradigm was establish in the FINGER study **(Fig.3)**.

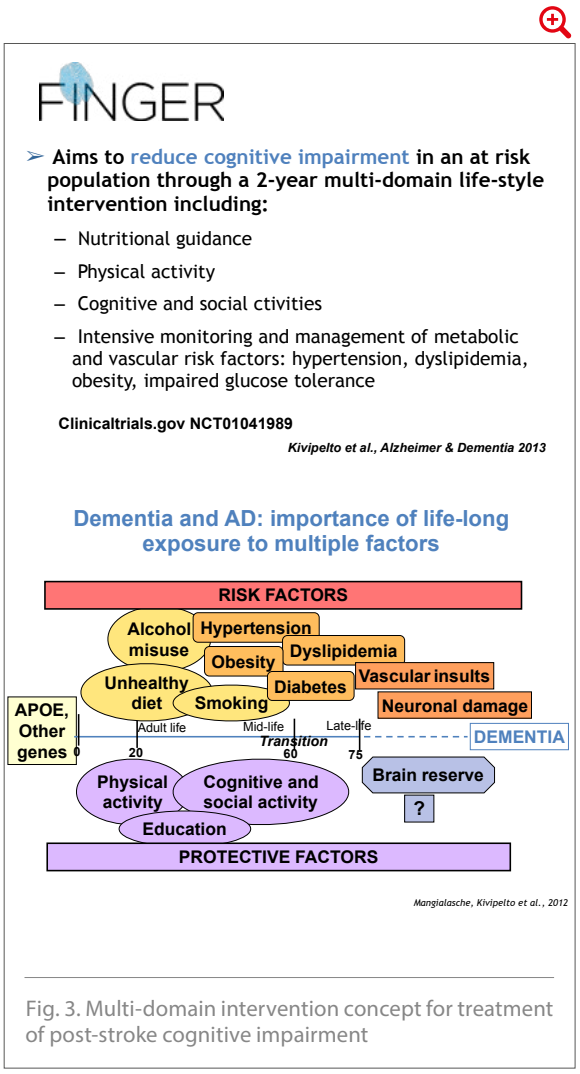

Fig. 3. Multi-domain intervention concept for treatment of post-stroke cognitive impairment

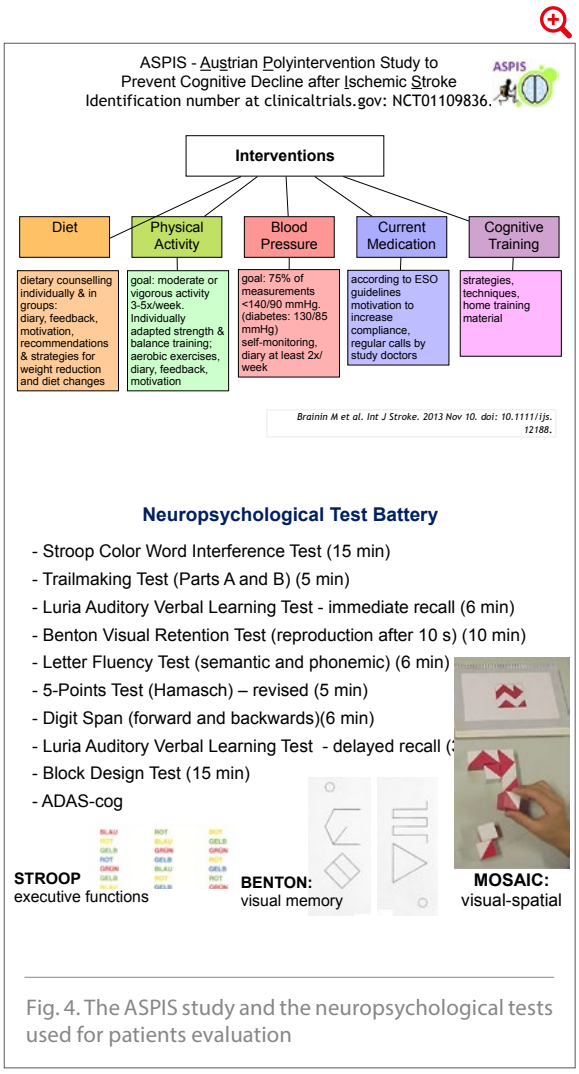

Fig. 4. The ASPIS study and the neuropsychological tests used for patients evaluation

Prof. Brainin was one of the investigators in the study in which the investigators tried to replicate the concept of the multi-domain interventions learned from the FINGER study in the stroke population. The ASPIS - Austrian Polyintervention Study to Prevent Cognitive Decline after Ischemic Stroke (identification number at clinicaltrials.gov: NCT01109836) was very intense study involving many resources and high number of patients **(Fig. 4)**.

The overall study results were neutral. However, there was a strong signal of the impaired executive functions **(Fig. 5)**. This convinces us to repeat this trial with strong focus on executive functions, said Prof. Brainin.

The general idea of multi-domain intervention is compatible with pharmacotherapy utilizing a multimodal drug like Cerebrolysin, which showed already interesting efficacy signals in vascular dementia, as mentioned earlier.

Prof. Brainin concluded his lecture with some recommendations for future studies, including harmonization of cognitive outcome measures for RCTs, increasing the sample size, testing more severely affected patients, and the suggestion that the follow up period should be longer (above 2 years) than usually seen in former trials. Biomarkers and imaging are needed, as well as interventions that make difference from the statistical point of view.

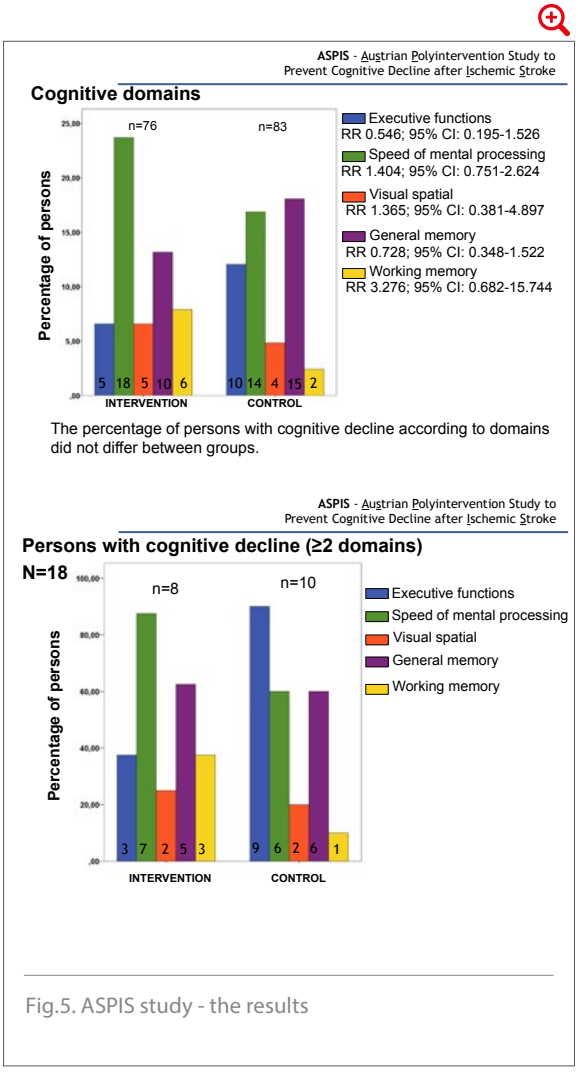

Fig.5. ASPIS study - the results

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EVER PHARMA

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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