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The 23rd International Mondsee Medical Meeting

Salzburg, Austria,
September 16th, 2016
Wyndham Grand Salzburg Conference Centre

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Program of the symposium

September 16th, 2016 (Friday)

Keynote speaker

Session 1: Advances in acute care of stroke
Chair: Michael Brainin & Eugen Trinka

Session 2: Advances in the Treatment of Complications after Stroke
Chair: Erich Schmutzhard & Jan Sobesky

Session 3: Advances in Neurorehabilitation after Stroke
Chair: Valeria Caso & Johannes Thome

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Keynote speaker

Stroke Care in Europe – Disparities and Strategies for Harmonization

Valeria Caso

Stroke Unit, Department of Vascular and Cardiovascular Medicine
Santa Maria della Misericordia Hospital, University of Perugia, Perugia, Italy

Prof. Valeria Caso was introduced by a chairman of the session Prof. Michael Brainin, who said that, as a President of the European Stroke Organisation, Prof. Caso is extremely well informed in the topic of differences in the standards of stroke care between particular European countries. There is a dramatic change in the epidemiology of stroke occurring globally over the last 40 years, said Prof. Caso. The picture of 1990 indicated that the incidence of stroke is much lower in Western Europe than in the developing countries. Both external factors may play significant role (like pollution) and also different standards of care. Jumping to 2010, we can see that the incidence rate increased in the low income countries and went down in the high income countries, in comparison with 1990. The growing frustration about inability to effectively tackle the stroke care led to conviction that stroke therapy is a certain pathway filled with well controlled procedures rather than one particular treatment. Similar situation concerns the mortality rate globally between 1990 and 2010, with the exception that it decreased in both Western and Eastern Europe (decrease of 37% vs 20 % respectively). The age-adjusted prevalence of stroke has exploded in high income countries. With time passing, there are more and more people living with the burden of stroke, especially in high income countries, although this phenomenon is also present in lower income countries. This is why a need for properly organized care and rehabilitation of stroke victims becomes extremely important. The DALY lost factor describing live with the disease is decreasing, but only in high income countries. Various preventive measures in place are to be credited for this positive trend. The worldwide stroke epidemic is on increase (Fig. 1) and the

Worldwide stroke epidemic continues to increase

1990-2010

- **25%** in strokes in people 20-64 years
- **113%** in stroke prevalence
- **70%** in the number of strokes each year
- **36%** in the number of deaths from stroke
- **31%** in DALYs (Disability Adjusted Life Years)
- **16%** in the global incidence of HS

In most LMIC mortality from stroke greater than that from IHD
>60% of all strokes occur in people younger than 75 yr
(68% in LMIC and 50% in HIC)

New GBD 2013 Stroke burden estimates

Estimates of the burden	Absolute numbers (millions)		
	1990	2005	2013
Incident strokes	6.2	8.4	10.3
Prevalent strokes	14.0	22.4	25.7
Fatal strokes	4.6	5.7	6.4
DALYs lost	90.1	107.7	112.9

Fig. 1. The global burden of stroke

most important change throughout the years is the fact that stroke cannot be considered anymore the old age disease because there is a 25% increase in the incidence in the age span of 20 to 64. The estimates for 2013 (Fig. 1) do not show any improvement. One additional important factor to consider is that the stroke is the second most prevalent cause of dementia. Finally, among the leading causes of the burden of the disease, stroke is predicted to move from 6th to 4th place until 2030. This means that we are witnessing the global pandemic of stroke and we have to act now to minimize its negative impact on our societies. This led to initiative by World Stroke Organisation called Global Action Plan which aims at decreasing the number of premature death by cerebrovascular diseased by 25% in 2025. The reason is that stroke is preventable disease and we can do much more in the education for stroke prevention.

Further on, Prof. Caso discussed best standards of stroke treatment and the issue of their widespread application. Stroke units, thrombolysis and thrombectomy are the leading modern standards of treatment as are various procedures for prevention and treatment of post-stroke complications. One of the most basic assumptions is therefore development of stroke units and there are several steps possible to reach this goal in all hospitals which still lack such facility or which would like to improve its quality. These are specified in the WSO's Global Stroke Services Guidelines and Action Plan. The European Stroke Organisation is actively involved in facilitating the move from the minimal health care system to the essential stroke system especially in the countries with large discrepancies in the stroke treatment standards. This ambitious program, called ESO-EAST, is supported by unlimited grants from EVER Pharma and Boehringer Ingelheim and is operating in the Eastern Europe and beyond (Fig. 2). Harmonization

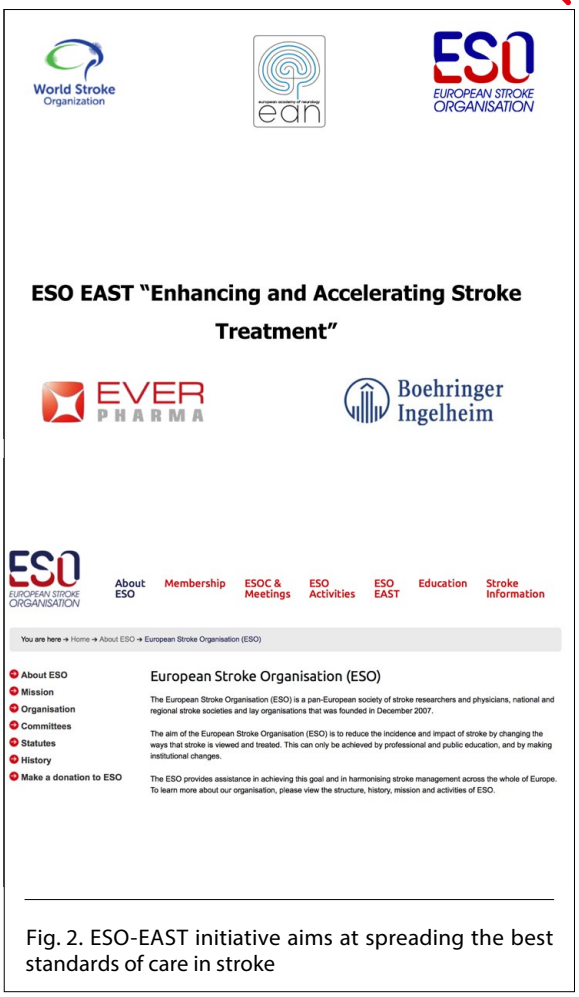

Fig. 2. ESO-EAST initiative aims at spreading the best standards of care in stroke

of stroke care all over Europe is the main mission of the program. Prof. Caso invited the audience to participate in the ESO-EAST mentioning that the project is progressing with active mailing list and quality registry (RES.Q) as well as the active support of World Health Organization. Prof. Caso encouraged the participants to actively support the quality registry in stroke and explained the importance of this project within the ESO-EAST program.

Emerging new roles for neurologists in the treatment of patients with aneurysmatic subarachnoid hemorrhage

Erich Schmutzhard

Department of Neurology, NICU, Medical University Innsbruck, Austria

The lecture of Prof. Schmutzhard concerned a highly specific subject of aneurysmatic subarachnoid hemorrhage (aSAH) discussed in the context of intensive care. The lecture was divided in three sections starting from characterization of aSAH, role of emergency specialists, and the significance of the neurointensive care in managing aSAH cases and improving the long-term outcome after aSAH. The recently published review on aSAH (Fig. 1) gave as an update on the aSAH. Similarly to the stroke units based care established for the ischemic stroke patients, a dedicated intensive care units were shown to improve survivability and long term outcomes of aSAH patients. Only 15% of all aneurysms can be secured in time (stabilization and prevention of re-bleeding), while the remaining majority of cases are emergency medicine and also the post-intervention critical care which are the key for optimal neurorehabilitation. The ischemic lesions after aSAH are very common and lead to a widespread secondary damage in the brain. However, the vasospasms are only one of many causes of ischemic damage collateral to aSAH, noted Prof. Schmutzhard. There are several phases of the spontaneous aSAH (Fig. 2). After stabilization and prevention of re-bleeding, the multimodal monitoring is essential for increasing survival and decreasing morbidity among aSAH patients. Then comes the control of intracranial pressure, prevention and detection of the ischemic

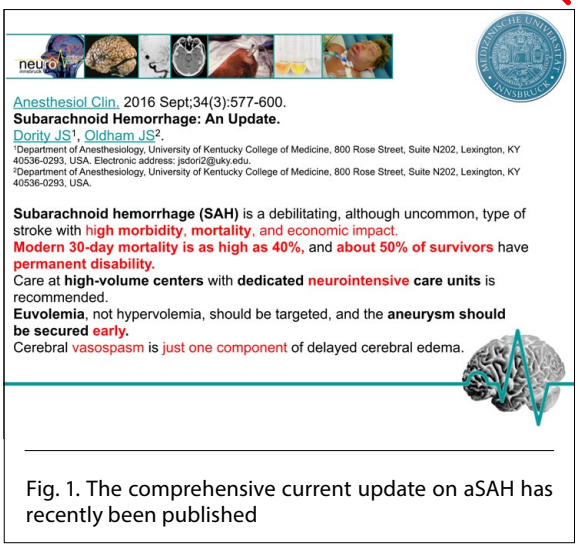

Fig. 1. The comprehensive current update on aSAH has recently been published

neurological deficits, and identification and treatment of medical/neuro/ICU complications. With the progress in the emergency medicine and multimodal neuromonitoring there are many more possibilities of intervention than in the past. However, tissue oxygen level must be always considered a necessary prerequisite in decision making process, said Prof. Schmutzhard. Also acute use of beta blockers to diminish the emergency cardiac consequences of so called sympathetic storm, has been repeatedly shown to improve outcomes of aSAH patients. The imaging (CT, angiography) helps in defining the aneurysm

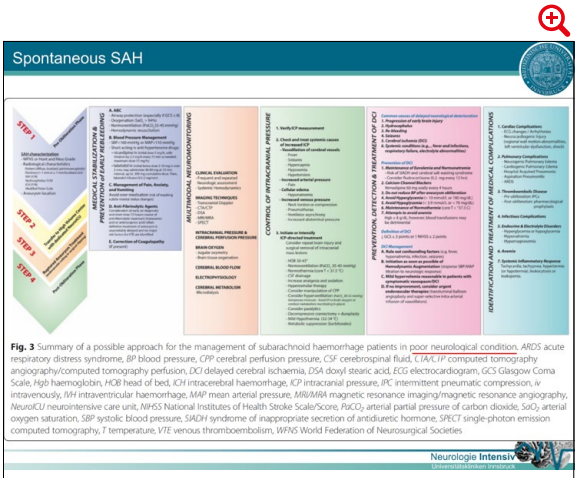

Fig. 2. Subarachnoid hemorrhage (SAH) requires fast cardiopulmonary and cerebral stabilisation

and inform decisions regarding obliteration, with coiling procedures being preferrable in comparison to clipping, in Prof. Schmutzhard's institution. Hydrocephalus ICP, vasospams with delayed cerebral ischemia, epileptic seizures, and complications related to management of an aneurysm are main neurological complications in aSAH patients. An interesting and very important aspect of ischemic complications is its immunological origin.The mechanical damage to endothelial structures leads to immunological response and consequently to emergence of neumerous micro-thrombi. These thrombi embolize leading to widespread secondary ischemic strokes around the affected brain area. Concerning hypertention, hypervolemia and hemodilution procedures, Prof. Schmutzhard provided a word of caution about the potential adverse effects of these procedures on already severely compromised cardiac functions. Apart from unintended aggravation of cardiac problems, we must avoid highly probable metabolic crises, for example due to hypoglycemia. As recently concluded by joined American and European consensus, the High Volume Centers (defined as more than 40 cases per year) with dedicated facilities and procedures are highly effective in decreasing mortality and morbidity of aSAH patients. Prof. Schmutzhard suggested that existence of such a center in his institution, in Innsbruck (about 120 cases per year), can be credited for notable success of managing aSAH with current mortality rate of around 10% (down from 34% in 2005 and from 22% in 2010). Finally, concerning neuroprotection approaches for aSAH, the current knowledge indicates that modulation of neuroinflammation apears as a very promising target for pharmacotherapy. Inhibition of cortical spreading depolarization and cortical spreading ischemia is the issue which is still not fully understood. Using proper sedative agents, like ketamine, appears to help in minimizing the deleterious impact of this phenomenon. Use of some promising agents like magnesium and statins did provide limited benefits, as did non-pharmacological neuroprotective interventions like ischemic preconditioning and partial aortic occlusion. Cerebrolysin appears as an interesting option for aSAH patients and should be further studied as it showed a positive impact on the volume of hemorrhage as well as good safety profile in these patients. The current standard of care indicates that various invasive multimodal neuromonitoring procedures are effective and efficacious methods of treatment (Fig. 3).

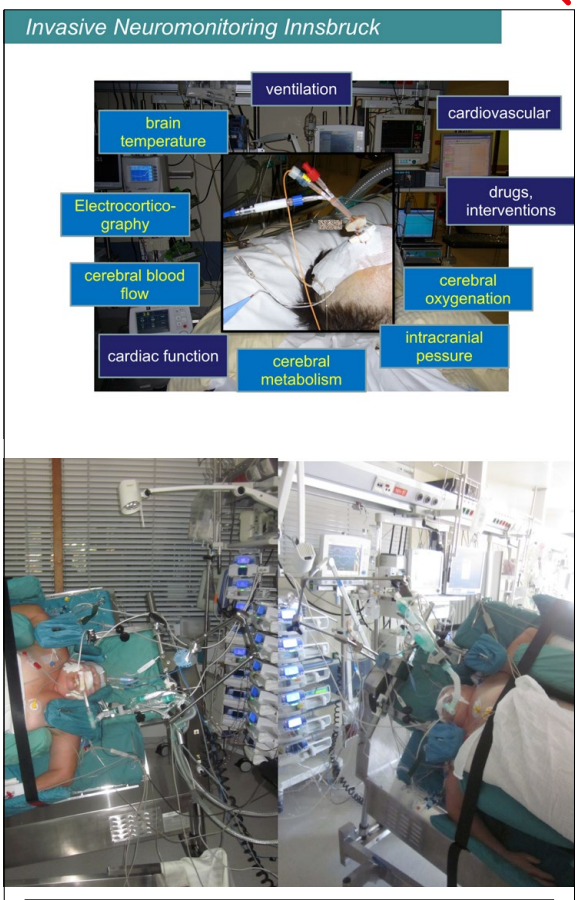

Fig. 3. The intensive neuro- and systemic critical care management of SAH patients at Innsbruck, Austria

The relevance of modern registry trials – CREGS-S

Milan R. Vosko

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The relevance of modern registry trials as seen from the clinical point of view was the subject of Dr. Vosko's lecture. The etiologies of ischemic stroke are very different (Fig. 1). This is why there is no one, and there cannot be one medication to treat the ischemic stroke. This is also probable explanation why so many clinical trials gave disappointing results: they focused on analyzing the effect of one medication at a time. We have to apply modern, complex therapeutic approach and we should also think about neurorecovery at the very beginning of the acute treatment. We should also keep in mind that deleterious effects of the ischemic cascade pertain to the whole complexity of the brain tissue, including damage to blood vessels and its link to hemorrhages; not only to neurons. One of the problems of past clinical trials was their poor design. However, with improving knowledge and understanding of the complexity of stroke trials comes a trade off related to optimal selection criteria of a patient population. This can often lead to difficulties in recruitment, under-powering, and bias in the selection of patients in otherwise promising clinical trials design. One good remedy for these issues are registry trials. When analyzing past trials' results, one can notice that Cerebrolysin, a neurotrophic compound, stands out as showing positive trends in clinical outcomes. Dr. Vosko summarized shortly the mechanism of action of Cerebrolysin indicating that both neuroprotective (anti-apoptotic) and neurorestorative properties have been well documented for this agent across various pre-clinical models of stroke and other neurological disorders. Probably the most prominent data came from the laboratory of Prof. Michael Chopp, from the Henry Ford Hospital in Detroit. He has shown that Cerebrolysin stimulates sonic hedgehog (Shh) signaling pathway which is one of the key drivers of natural recovery processes after ischemic stroke. Can this interesting facts be translated into clinic? asked Dr. Vosko. To answer this question, Dr. Vosko overviewed clinical trials testing the safety and efficacy of Cerebrolysin in the ischemic stroke patients. The trial performed by Prof. Ladurner's group and published in 2005 (Fig. 2) has shown significant improvement of

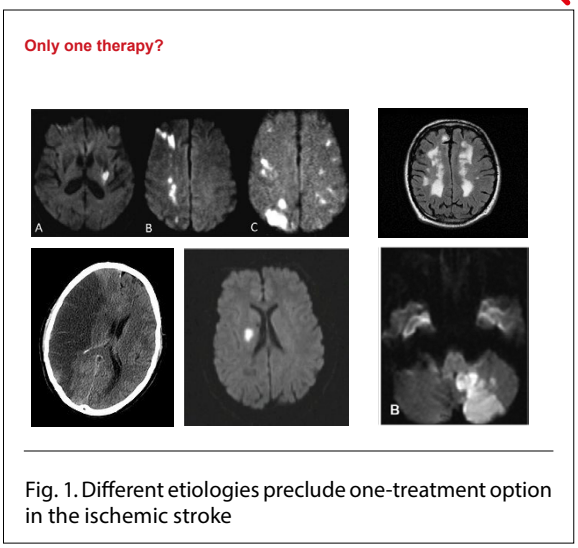

Fig. 1. Different etiologies preclude one-treatment option in the ischemic stroke

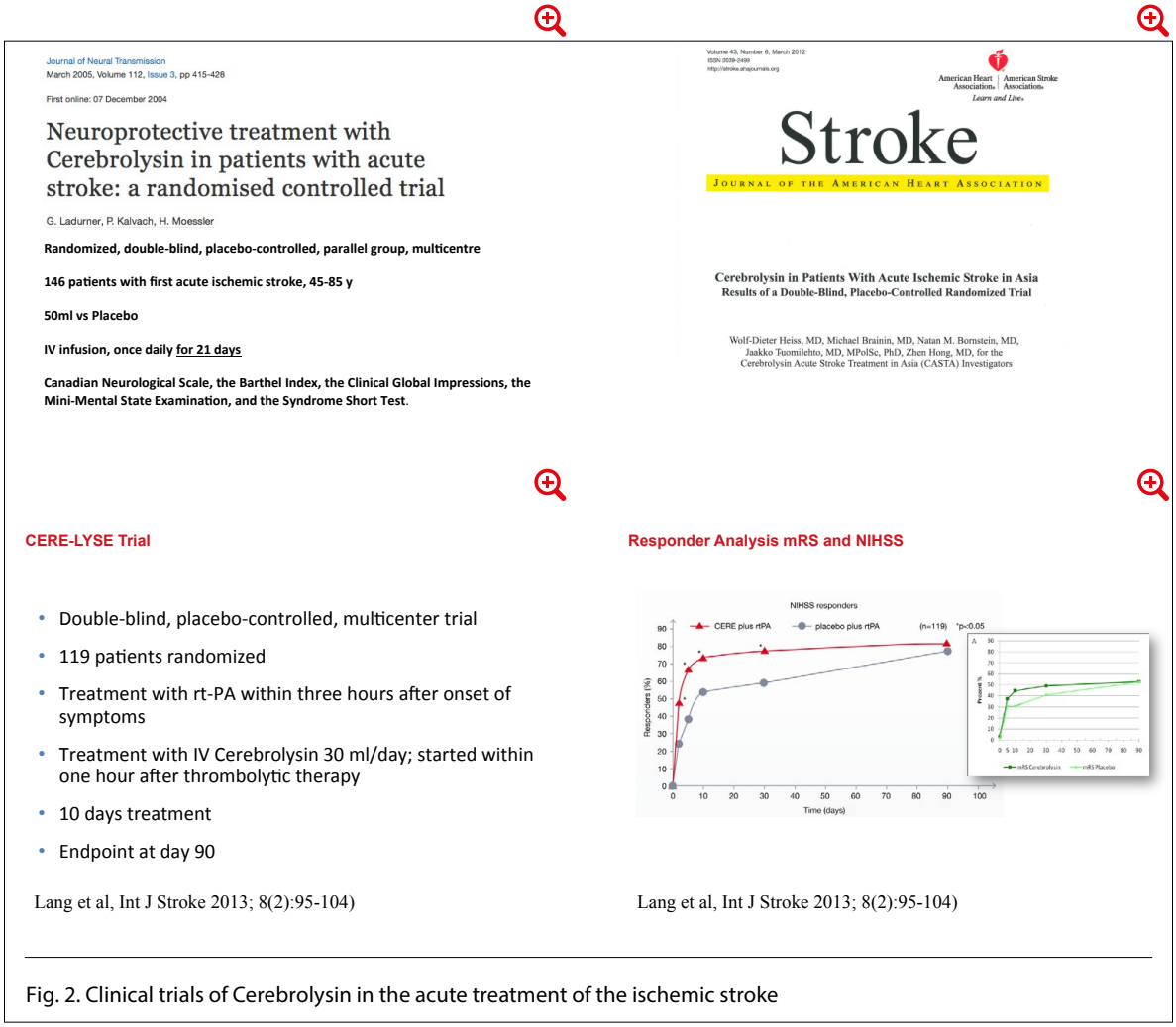

Fig. 2. Clinical trials of Cerebrolysin in the acute treatment of the ischemic stroke

motor functions, activities of daily living and cognitive functions as well as good safety profile of the drug. The biggest trial to date was so called CASTA trial (Fig. 2). This trial missed the significance in the endpoint due to inclusion of too mild stroke cases with average NIHSS of 9; while the benchmark thrombolysis trials indicated that the optimal severity level should lay between NIHSS 12 and 16. Nevertheless, in the subgroup of patients with more severe stroke (NIHSS>12), Cerebrolysin significantly improved survival as well as benefit in clinical outcomes. Another trial, so called CERE-LYSE trial, tested combination of Cerebrolysin with thrombolysis (Fig. 2). Dr. Vosko's stroke unit participated in this trial. The patients were treated with systemic thrombolysis and either with Cerebrolysin or saline (control group). The short-term outcome was significantly positive for the Cerebrolysin group as the response measured in NIHSS was much higher in the combination group in comparison with thrombolysis alone. However, at the endpoint of 90 days this advantage was no longer visible. We could conclude that probably the treatment was too short (only 10 days) and we have to think how we can better desing the future trial with Cerberolysin. The level of evidence for Cerebrolysin in stroke can be currently described as level 2b, according to American Heart Association guidelines criteria, said Dr. Vosko. The important question, however, is how to deliver more convincing clinical data for such an agent like Cerebrolysin which is already used in the clinical practice of stroke? There is a case for alternative strategies. It relates to the fact that RCTs can be slow to complete due to involved resources and very high costs. Also smaller RCTs may not give the whole picture (e.g. ECASS trials did not evaluate older patients), and adjustment for covariates remains desirable in RCTs. Additionally, for every active RCT center, there may be many other offering routine care according to local protocols. In fact, we can use registries as well-controlled, high quality alternatives to RCTs. It was shown that modern registries (e.g.

SITS registry) deliver similar if not identical quality clinical data as conventional RCTs. In this way, the findings established through rigorous, costly, and time-consuming thrombolysis RCTs have been fully confirmed. Additionally, the registries have capacity to answer many questions which RCTs cannot, as they are performed in real-life clinical situations, indicated Dr. Vosko. For example SITS registry provided evidence that stroke patients over 80 years old benefit from thrombolytic treatment. However, the most important prerequisite for successful registry study is proper matching of the patients groups. The so called propensity matching score is a method of choice here. The matching panel is blinded to clinical assessment and the final selection of target population is done after enrollment is completed. The CREGS-S study is an example of the registry performed using this well established methodology, including the proven platform of SITS registry (Fig. 3). Dr. Vosko's stroke unit is actively participating in this project, with 25 patients already enrolled. The study runs in 12 countries with 1200 patients already registered with the final study population goal of about 2500. Dr. Vosko shortly introduced the audience to the usage of SITS registry as a platform for CREGS-S saying that active data collection takes only about 5 min. This shows how user friendly and time/cost effective this study is. Finally, the objective and independent outcome measurement is assured by simple video recording the mRS interview using a portable camera. The independent, blinded (without knowledge of the treatment, or the study center, and patients data) raters stationed in the UK perform the assessment based on the internet-uploaded video. Dr. Vosko summarized his lecture saying that while RCTs are necessary, we need also registries like CREGS-S which can be valuable in fine-tuning current standards of stroke care.

Fig. 3. The modern registry in stroke: CREGS-S

Challenges in the treatment concept of spinal cord ischemia

Johannes Sebastian Mutzenbach

Department of Neurology, Christian Doppler Medical Centre, Paracelsus Medical University Salzburg, Salzburg, Austria

The spinal cord ischemia (SCI) is a disorder caused by variety of pathologies, stated Dr. Mutzenbach. He went on to overview potential causes of SCI and added that it is a very rare phenomenon accounting for 1-2% of all vascular neurological disorders (Fig. 1). The most frequent type of SCI is actually cryptogenic, as for up to 30% of patients the etiology will remain unclear. Besides of that, the most frequent appear to be atherosclerosis background and aortic surgery. The severity can vary, and while many patients make some functional recovery, permanent and disabling neurological deficits remain in most cases (Fig. 1). There are 2 main types of spinal cord ischemia: radicular artery territory infarct (unilateral or bilateral infarcts of territories supplied by the anterior or posterior spinal artery), and extensive spinal cord hypoperfusion (central and transverse infarcts). The peak incidence occurs in 6th and 7th decade with usually abrupt onset, but the progress may extend over several minutes or even a few hours (clinical nadir within 1 hour). In 80% of cases, there are no changes in ASIA (American Spinal Injury Association impairment scale) score after 12 month. The fatality rate during hospital stay varies from 10 to 23% with greatest risk being cardiac arrest and acute aortic rupture or dissection, and high cervical lesions. The clinical presentation is complex, with the severity varying widely, from minor weakness in the legs to tetraplegia. Back or neck pain is noted in 70% of patients, typically occurring at the level of the lesion. The

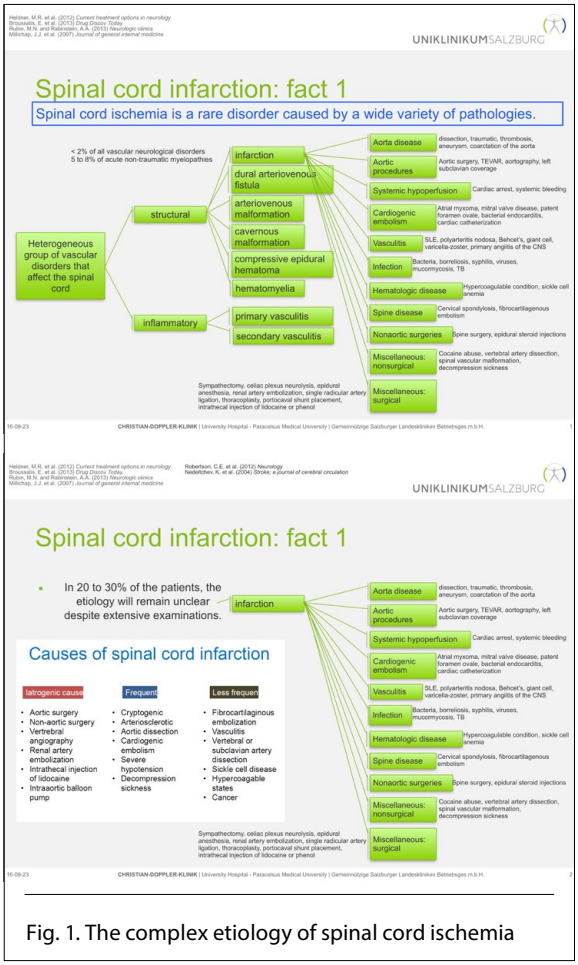

Fig. 1. The complex etiology of spinal cord ischemia

neurological presentation is primarily defined by the vascular territory involved. The prognosis of SCI is generally bad. Up to 60% of patients remain

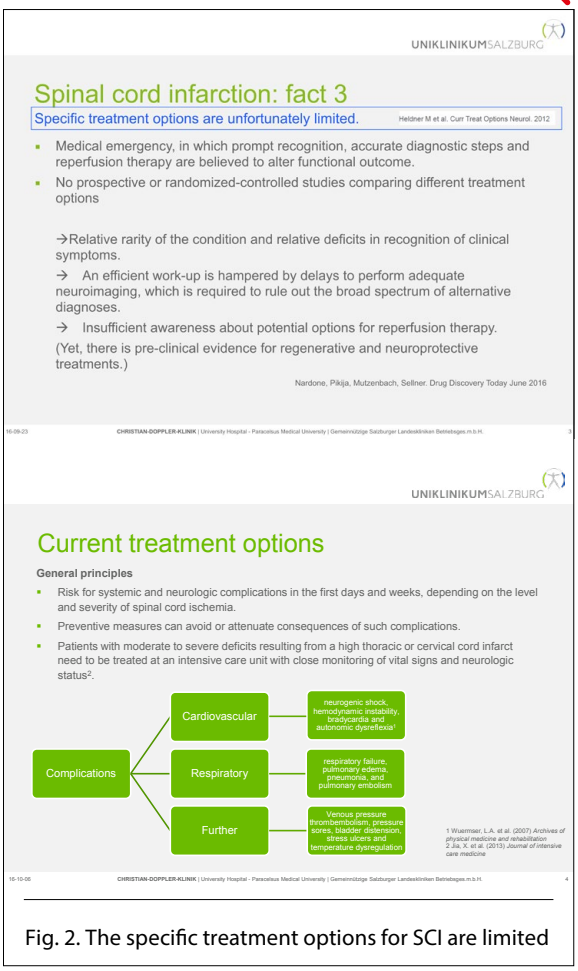

Fig. 2. The specific treatment options for SCI are limited

wheelchair bound. Nevertheless, there are some good results in long-term follow up studies. The specific treatment options are very limited (Fig. 2). Like in the ischemic stroke, the medical emergency is vital, in which prompt recognition, accurate diagnostic steps and reperfusion therapy are believed to alter functional outcome. There are no prospective or randomized-controlled studies reported comparing different treatment options. This can be attributed to rarity of the condition and relative deficits in recognition of clinical symptoms. An efficient work-up is hampered by delays to perform adequate neuroimaging, which is required to rule out the broad spectrum of alternative diagnoses, which Dr. Mutzenbach called "diagnostic dillemmas", which are related to factors like vascular anatomy, clinical presentation (syndrome, time course), varying location, inconsistent imaging and rare causes. There is insufficient awareness about potential options for reperfusion therapy. Yet, there is some pre-clinical evidence for regenerative and neuroprotective treatments. Regarding imaging, MRI is very useful with detection of T2-lesion in 70% of cases. The DWI (diffusion weighted imaging) is more sensitive but technically challenging, normalizes after 1 week while the contrast enhancement after 3-4 days. There is a concomitant vertebral body infarction in 35% of cases. The current treatment options must be considered in the context of potential complications, and there are many of them (Fig. 2). Therefore, it is better to treat these patients in the emergency unit. The therapeutic dilemmas relate to factors like broad range of causes, limited awareness for the condition, requirement for MRI, time window for reperfusion therapy as well as the fact that there is absolute contraindication of rt-PA in some cases (like in aortic dissection), and there are no viable concepts for acute care. One approved treatment option is aortic surgery and thoracic endovascular repair (TEVAR). For many cases of non-surgical spinal infarction the antiplatelet therapy is available. Also thrombolysis is being used for some cases. Importantly, there are no clinical trials published and the treatment remains experimental. Also cortison appears as an option in some cases. Regarding the emerging treatment options, we are talking about phase after thrombolytic window which can span from hours to days and weeks after SCI. The major targets appear to be stimulation of neurogenesis and attenuation of inflamation wich leads to apoptosis. The spinal cord protection startegies were by Dr. Mutzenbach (Fig. 3). Among them, hypothermia and hyperbaric oxygen therapy are of growing importance. Finally, there are some neuroregenerative strategies, with Cerebrolysin as a very good, well researched option (Fig. 3). Dr. Mutzenbach confirmed that all patients with SCI admitted to his institution are treated with Cerebrolysin at least over 21 days, with a 50 ml daily dosage. The multimodal approach combining broad armamentarium of procedures and treatments appears to be the optimal way in management of SCI.

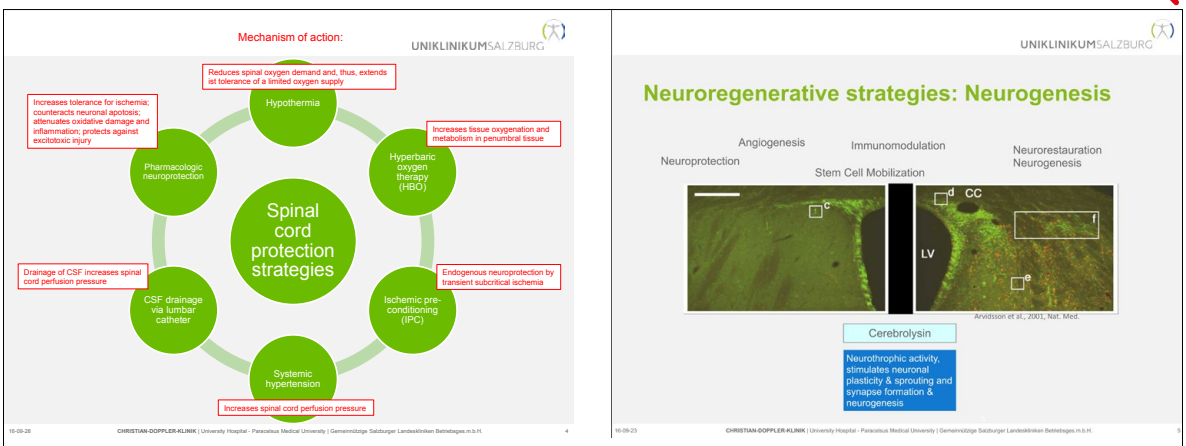

Fig. 3. The emerging treatment options for SCI

Challenges & Opportunities in Motor Recovery

Dafin F. Muresanu

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For years, we have been using inadequate pharmacological approach to brain protection and recovery due to the lack of knowledge about biological processes underlying recovery after stroke, stated Dr. Muresanu.[1-3] These suppressing or stimulating strategies employed monomodal acting molecules targeting pathophysiological mechanisms considered in isolation from the complex biological reality. Numerous inconsistencies in the clinical trials' design contributed to the unfavorably complex picture of clinical development in the field. This resulted in a virtual failure of all so called neuroprotective trials. However, we are now ready for a paradigm shift in the stroke therapy, said Dr. Muresanu. At the core of the new approach lays the knowledge about endogenous functional modulation within the central nervous system. There are three major modulation levels observed: cellular, circuitries, and dynamic network level. The brain after ischemia must be analyzed from the standpoint of imbalances observed at all three modulatory levels. These imbalances were poorly understood and barely taken into account in majority of stroke trials. In the future, the existing and potential neuromodulatory approaches should be regarded as treatments of choice for stroke patients. This is also the reason why using multimodal pharmacological agents, like those based on neurotrophic factors activity, makes biological and therapeutic sense (Fig. 1).

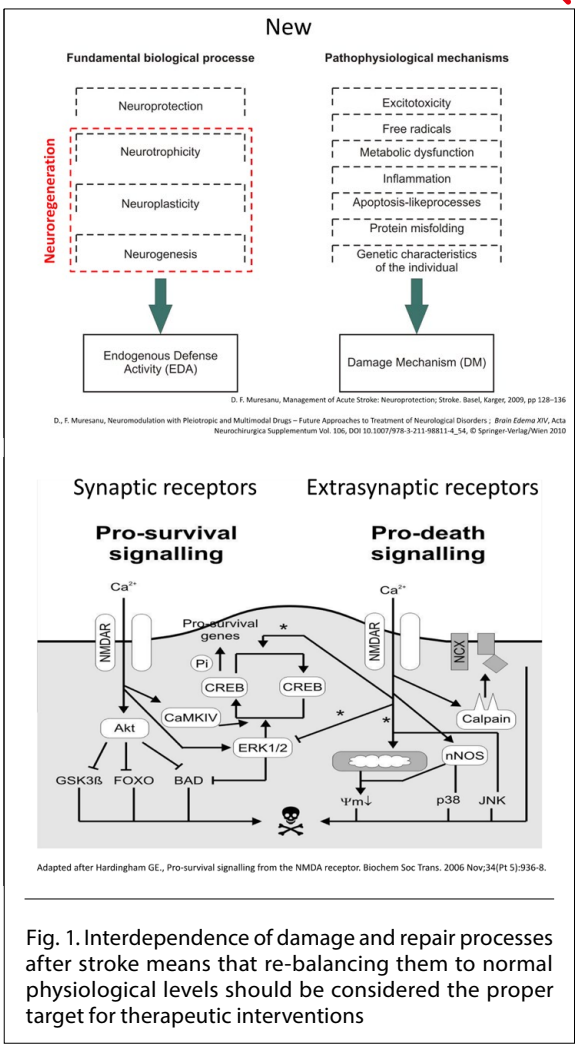
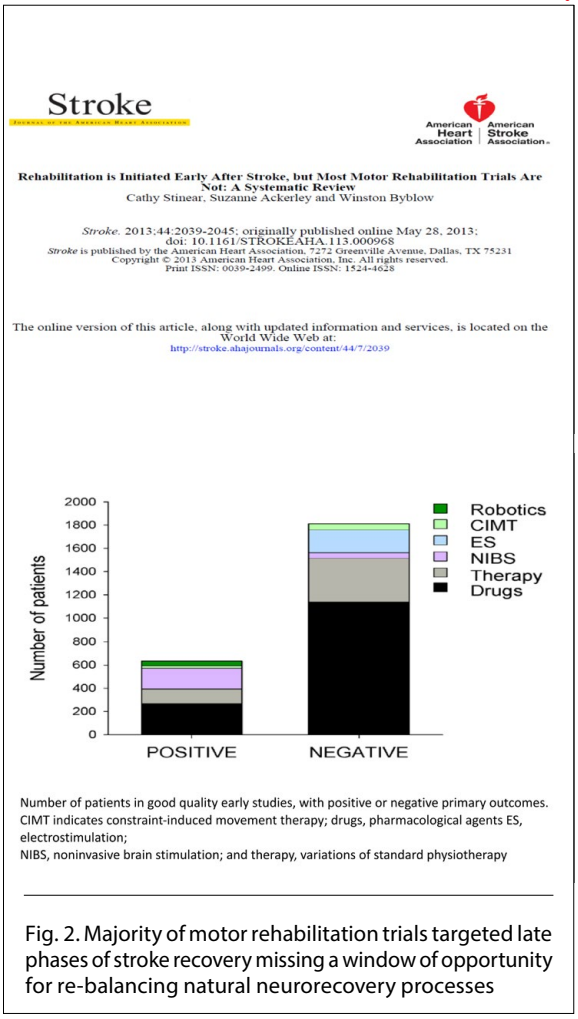


Fig. 1. Interdependence of damage and repair processes after stroke means that re-balancing them to normal physiological levels should be considered the proper target for therapeutic interventions

In real life clinical situation we need to consider proper (scientifically informed) matching between distinct elements and phases of rehabilitation, on one side, and pharmacological multimodal intervention, on the other side. This also concerns the timing of motor rehabilitation. For example, the analysis of already published trials[4] indicates that in a vast majority of cases rehabilitation was initiated late post stroke (Fig. 2). Consequently, majority of these trials missed important therapeutic window in which endogenous processes of neurorecovery are most active.



Number of patients in good quality early studies, with positive or negative primary outcomes. CIMT indicates constraint-induced movement therapy; drugs, pharmacological agents ES, electrostimulation;
NIBS, noninvasive brain stimulation; and therapy, variations of standard physiotherapy

Fig. 2. Majority of motor rehabilitation trials targeted late phases of stroke recovery missing a window of opportunity for re-balancing natural neurorecovery processes

Among these trials, only 12 included pharmacological support of rehabilitation. Dr. Muresanu mentioned the results of the most prominent combination trials with fluoxetine, amphetamine, levodopa, methylphenidate and piracetam as add on to motor rehabilitation. Among them, the fluoxetine showed some interesting results which are being now assessed in an ongoing, large scale rehabilitation trial.

In the last part of his lecture, Dr. Muresanu discussed recently published results of the CARS trial in which he was the principal investigator (Fig. 3). This trial focused on early rehabilitation of impairment of upper extremities as a particularly challenging (and more difficult than rehabilitation of lower extremities) and, at the same time, desirable therapeutic goal.[5]

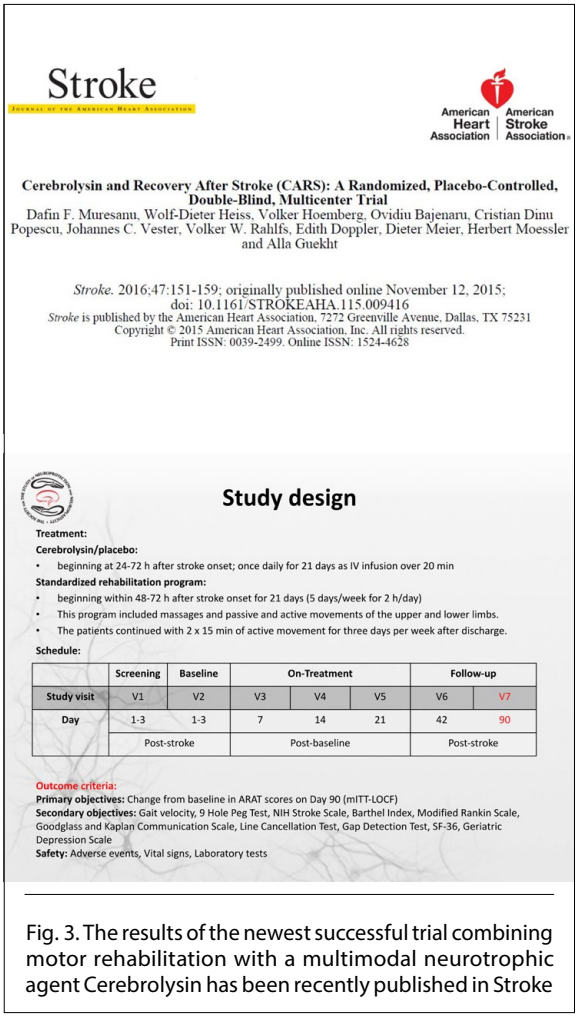


Fig. 3. The results of the newest successful trial combining motor rehabilitation with a multimodal neurotrophic agent Cerebrolysin has been recently published in Stroke

The primary endpoint of this study was an outcome in motor function of an affected arm measured with ARAT (Action Research Arm Test) score at day 90. The ARAT is a complex and reliable measure of arm function rehabilitation. After discussing the methodological prerequisites and the key elements of the study design, Dr. Muresanu outlined major results of the study. In the primary endpoint, there was a statistically significant improvement of arm motor function in the Cerebrolysin group in comparison with placebo (Fig. 4).

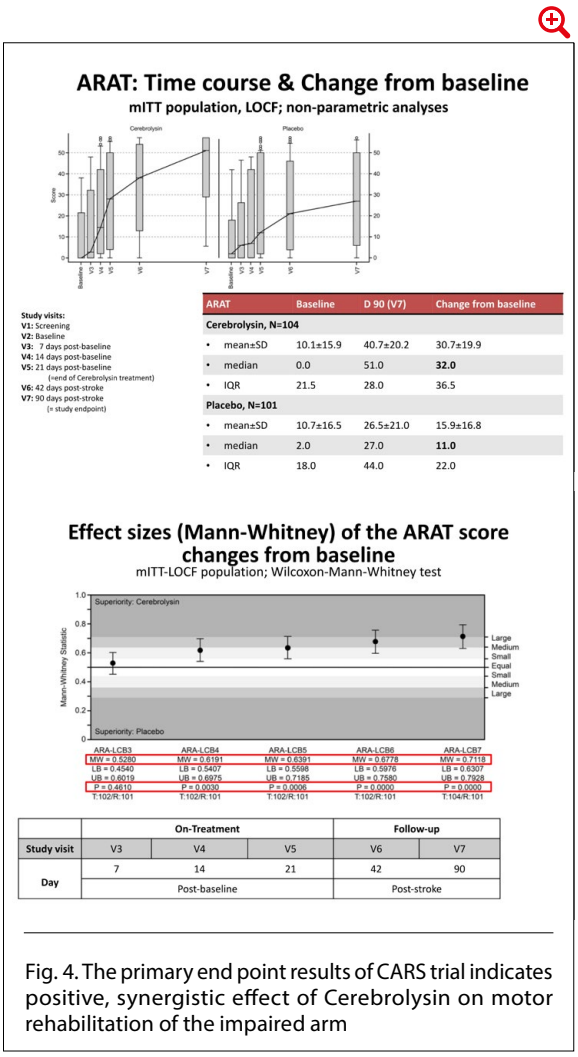


Fig. 4. The primary end point results of CARS trial indicates positive, synergistic effect of Cerebrolysin on motor rehabilitation of the impaired arm

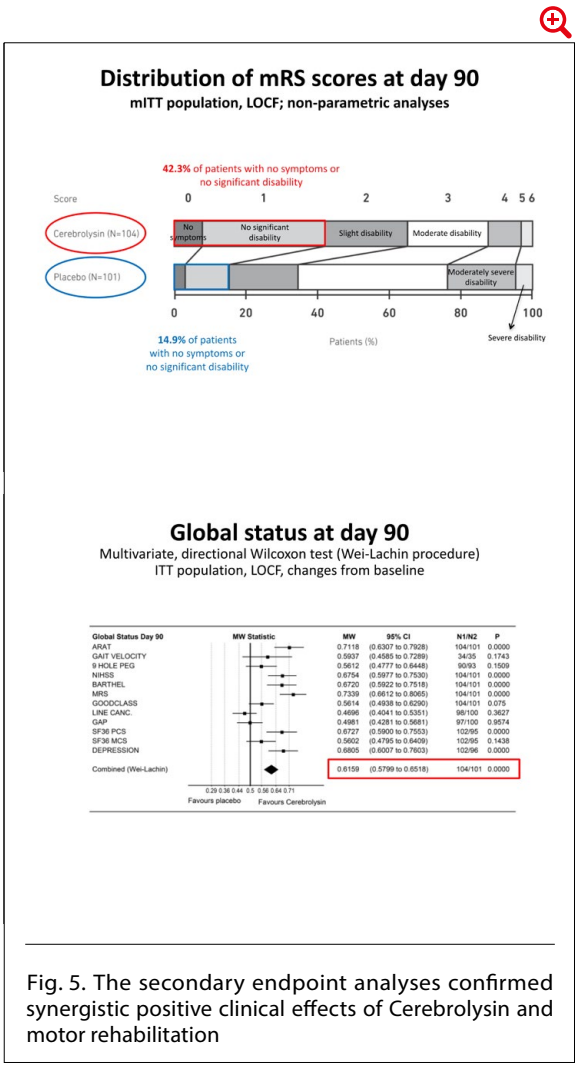


Fig. 5. The secondary endpoint analyses confirmed synergistic positive clinical effects of Cerebrolysin and motor rehabilitation

Importantly, the significant improvement has been observed already after 14 days of treatment. This early response can positively impact many aspects of recovery and rehabilitation downstream, including improved cognitive performance, said Dr. Muresanu. Also the distribution of the modified Rankin Scale scores indicated highly positive treatment effects of combination rehabilitation therapy with Cerebrolysin. Together with other various secondary endpoints, with 6 out of 12 showing statistically significant improvement in the Cerebrolysin group, the CARS trial results confirm earlier clinical findings with Cerebrolysin and reinforce the rationale for employing multimodal therapeutic agents in the early support of stroke rehabilitation (Fig. 5).

Summarizing the results, Dr. Muresanu indicated that Cerebrolysin had a positive influence on the patient's condition during stroke recovery in terms of the motor function of the paretic side, related neurological deficits, activities of daily living, the quality of life, and depression. Treatment with Cerebrolysin has shown a fast initial improvement in the ARAT; the time course revealed a constant growth of the effect size, which reached a maximum on day 90. The beneficial effects of Cerebrolysin were stable over a long period: the distribution of mRS scores were in favor of Cerebrolysin at day 90, and the results of sensitivity analyses (observed cases; stratifications for age, gender, baseline ARAT score and site; ARAT values >0 at baseline) were consistent with

the results of the primary analysis. The safety of the treatment was also confirmed and did not differ from other trials with Cerebrolysin. Dr. Muresanu finished his lecture by suggesting that the new concept of pharmacological support of neurorehabilitation with multimodal agents makes therapeutic sense and that the results of the new rehabilitation trials, including CARS, open the doors for future successful development in the organized stroke care.

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The role of BDNF in post stroke complications

Anton Alvarez

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The most important point about stroke is to reduce disability after it happened, said Dr. Alvarez. He drew the picture of various disabilities after brain injuries as well as reminded the audience that we are talking here about neurovascular continuum of cerebrovascular disorders (Fig. 1). At the cellular and tissue level, we can see the basis of this continuum, which is the neurovascular unit. The neurovascular unit integrates vascular and neural cells and molecular mediators, and constitutes the essential network element in the regulation of endogenous processes of neural plasticity and brain repair. The neurotrophic factors such as brain derived neurotrophic factor (BDNF) and vascular endothelial growth factor's (VEGF) are key modulators of neurovascular unit functions, like angiogenesis and neurogenesis, that are essential for neurorestoration after stroke. And this is the reason why this lecture is dedicated to the role of BDNF in recovery processes after brain injuries. After stroke, both BDNF and VEGF promote neurogenesis. They also play a mediatory role between endothelial cells and neural stem cells, in effect promoting both angiogenesis and neurogenesis after stroke. BDNF is a 13 kDa dimeric protein widely expressed in the adult brain that is produced from its precursor protein (proBDNF). The Val/Met substitution in the gene ecoding BDNF has been linked to many neurological disorders (including stroke, TBI, and dementia). Dr. Alvarez went on to outline details of the neurotrophic signaling pathway and indicated that proBDNF has capacity for triggering apoptotic processes. It is therefore important that the mature BDNF is enhanced and promoted by potential pharmacological

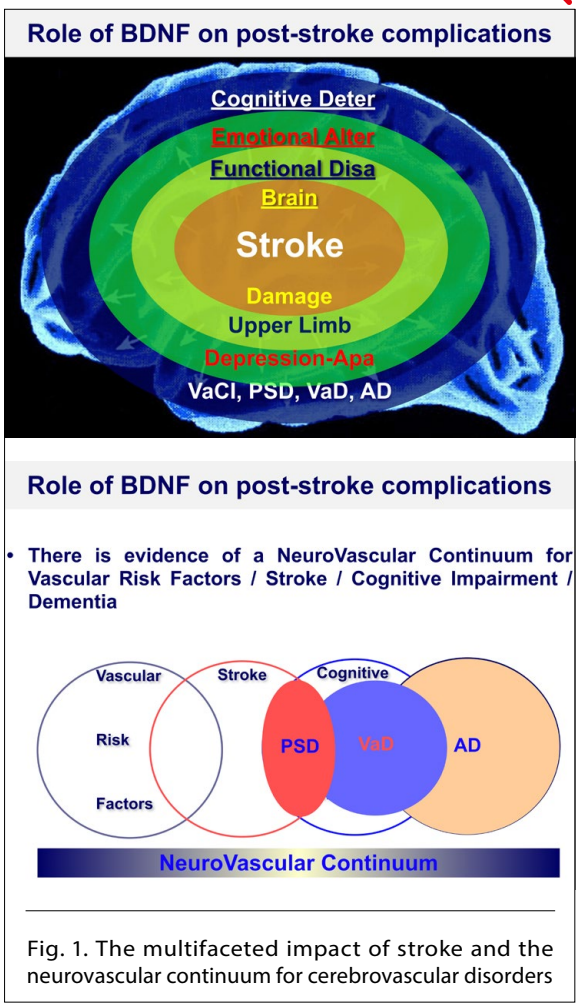


Fig. 1. The multifaceted impact of stroke and the neurovascular continuum for cerebrovascular disorders

approaches. One of the most important elements of BDNF signaling is activation of PI3K/Akt kinase pathway leading to increased synaptic plasticity, neurogenesis and anti-apoptotic, pro-survival cellular regulation. Additionally, the same pathway may block GSK-3beta kinase which is involved in the amyloid precursor protein (APP) maturation. In this way BDNF is capable of reducing the deposition of beta-amyloid plaques. This was indeed confirmed in animal models of Alzheimer's disease (AD) and in patients suffering from this disorder. The phosphorylation of Tau which enhances neurodegeneration in the brain can also be decreased in the same way in AD. The inhibition of apoptotic processes, prevention of damage to mitochondria as well as decreasing the glutamate related cytotoxicity were also linked to BDNF signaling pathway. All these mechanisms have a potential to affect recovery processes after stroke (Fig. 2). First, BDNF can reduce risk of stroke and also brain damage associated with stroke. The lower serum level of BDNF has been linked with increased cumulative incidence of stroke and TIA. At the same time, higher levels of BDNF were associated with better visual memory and lower level of white matter hyperintensity. Improvement of functional recovery and prognosis were also associated with higher levels of circulating BDNF. Also poor recovery of upper limb motor function in stroke patients correlates with Val/Met substitution which leads to decreased production of BDNF. There is also evidence of BDNF involvement in prevention or improvement of post-stroke depression. The reduced serum levels of BDNF were found to be a predictive factor for post-stroke depression. BDNF can also counteract the cognitive deficits in stroke patients. Aerobic exercises during rehabilitation enhance both the levels of BDNF and cognitive functions. Having all this in mind, how can we increase BDNF levels in stroke patients? asked Dr. Alvarez. First option is the early mobilization and aerobic exercise. Dietary approaches, including alpha-linolenic acid were shown to enhance the release of BDNF. The repetitive transcranial magnetic stimulation (rTMS) was shown to enhance levels of BDNF. The multisensorial stimulation, like social interactions, were neuroprotective and at same time stimulated production of BDNF in animal models of stroke. Progesteron plus vitamin D were also capable of neuroprotective effcts after stroke, which were mediated through BDNF signaling pathway. Angiotensin II receptors blockers (ARB) were shown to stimulate expression of BDNF and angiogenesis, at the same time. Use of the selective serotonin uptake inhibitors (SSRI) in stroke patients was associated with both improved outcomes and enhanced levels of BDNF. The last example of BDNF enhancing treatments listed by Dr. Alvarez is Cerebrolysin. The results published by Dr. Alvarez's group, just one week before this conference, showed that Cerebrolysin enhances serum BDNF levels in patients suffering from Alzheimer's disease. This action occured in synergy with donepezil when both treatments were combined. This observation correlated with improved cognitive performance of AD patients. Dr. Alvarez summerized shortly the clinical evidence for efficacy of Cerebrolysin in stroke and hypothetized that majority if not all clinical effects of Cerebrolysin can be explained by its known neurorestorative properties which overlap with the role of BDNF in the regulation of natural recovery processes after stroke. Interestingly,

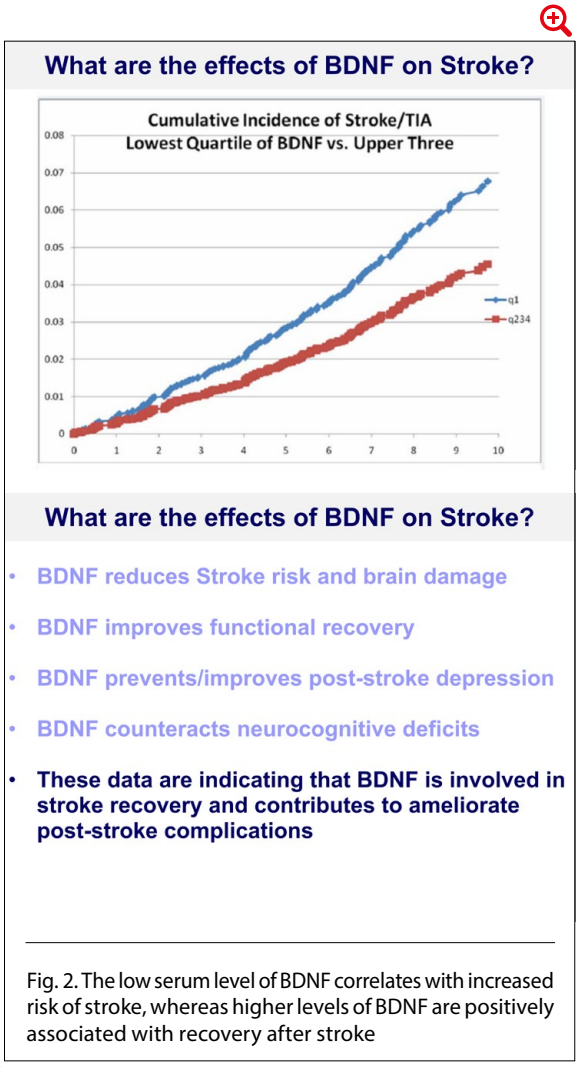


Fig. 2. The low serum level of BDNF correlates with increased risk of stroke, whereas higher levels of BDNF are positively associated with recovery after stroke

anti-depressive action observed in Cerebrolysin treated stroke patients was also evident in AD patients and correlated with increased serum levels of BDNF. At the end of his lecture, Dr. Alvarez summarized known therapeutic options for enhancing BDNF levels in patients suffering from stroke (Fig. 3).

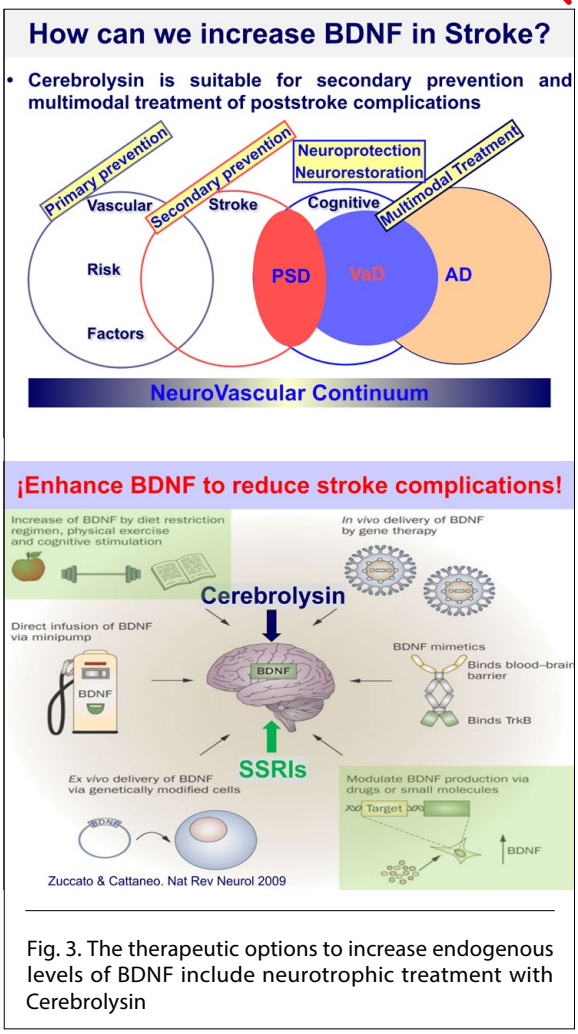


Fig. 3. The therapeutic options to increase endogenous levels of BDNF include neurotrophic treatment with Cerebrolysin

Cerebrovascular diseases and Cognitive Decline

Michael Brainin

Center Clinical Neurosciences, Danube University Krems, Austria

Prof. Brainin divided his lecture into four sections: stroke and cognitive impairment – actualization of the problem; statistics and risk factors; clinical features, prognosis; and new research data. It is well known that 1 patient in 10 already has dementia when stroke occurs, that 1 patient in 10 will develop dementia after a first-ever stroke, and that 1 in 3 patients will develop dementia with stroke recurrence. Post-stroke cognitive impairment can result from different factors, like multiinfarct dementia, strategic infarct dementia (e.g. related to left thalamus infarct), mixed dementia, and delayed onset dementia/ impairment. The last one is most important, according to Prof. Brainin, because there is a window of opportunity for treatment, as we know some of the risk factors for the delayed dementia. The known neuropathological changes correlating with development of dementia are numerous: lacunar infarcts, microinfarcts, white matter changes, hippocampal atrophy and sclerosis, and overlap with AD pathology (amyloid plaques, neurofibrillary tangles) (Fig. 1). The issue with post-stroke dementia is closely related to the facts discussed earlier by Prof. Caso: the increasing prevalence of stroke means increasing rates of dementia among stroke survivors, said Prof. Brainin. The accumulation of risk factors actually means not the sum of all the factors. It means multiplication of the causative mechanisms of cognitive impairment. One positive conclusion out of this is that identification and

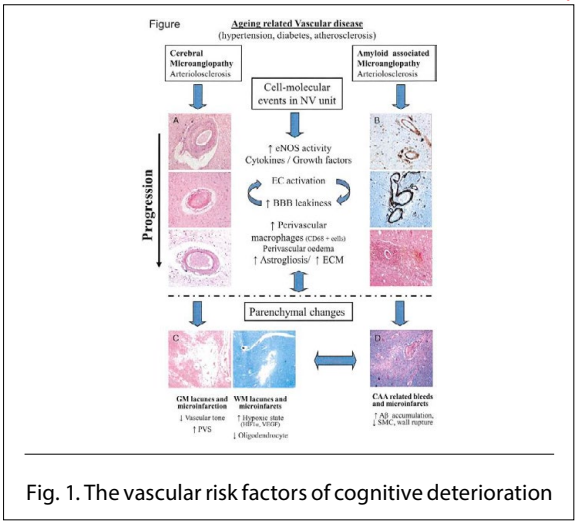


Fig. 1. The vascular risk factors of cognitive deterioration

effective treatment of these mechanisms can lead to reversion of the cognitive decline trend of the same magnitude. This is why the lifestyle modification has such a tremendous effect on stroke prevention. However, when we consider the clinical picture, we don't always talk about dementia. It can be something less pronounced including, primarily, behavioural disturbances (dysexecutive syndrome, spatial, language, orientation), and later memory decline becomes visible. Especially the disexecutive syndrome prevention should be in our focus when we talk about post-stroke cognitive impairment. Prof. Brainin mentioned in this context some clinical benefits of Cerebrolysin treatment of vascular dementia summarized in the Cochrane review.

He also mentioned CREGS registry (see Dr. Vosko's lecture) and noted that it involves evaluation of cognitive endpoints (Fig. 2).

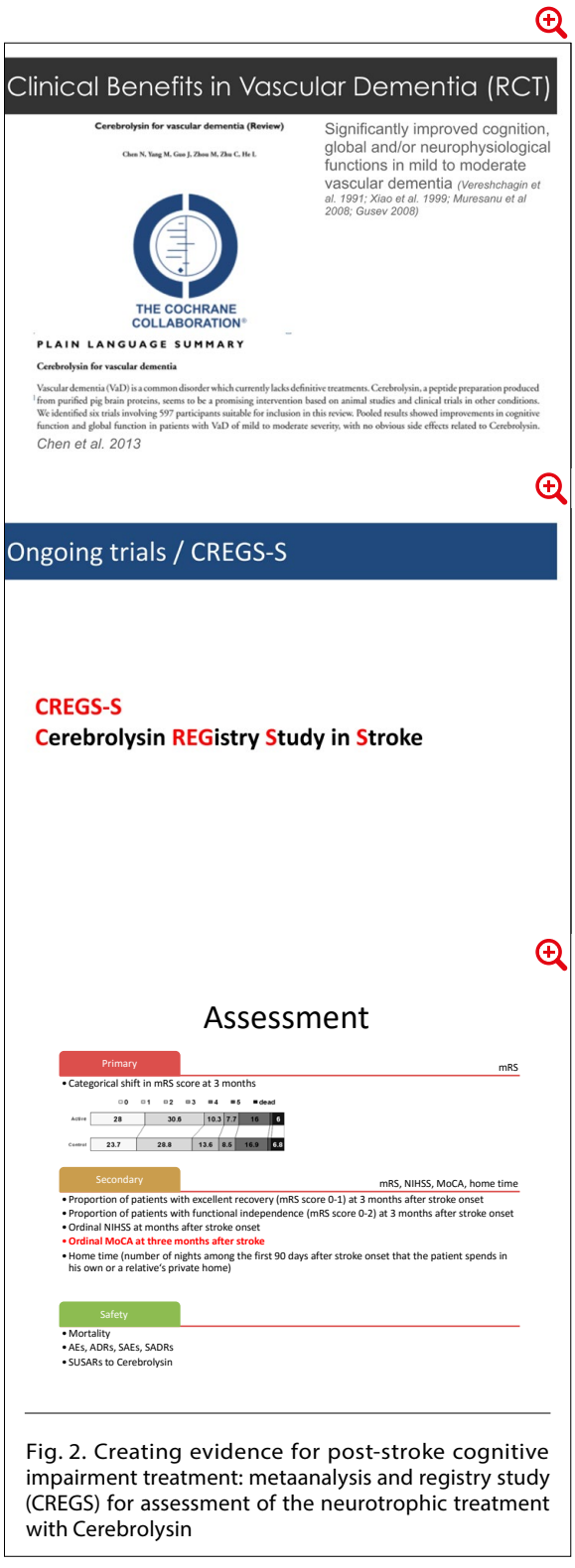


Fig. 2. Creating evidence for post-stroke cognitive impairment treatment: metaanalysis and registry study (CREGS) for assessment of the neurotrophic treatment with Cerebrolysin

Finally, Prof. Brainin overviewed briefly the most recent research data. Lowering the blood pressure has no preventive effect, similarly to antithrombotics. It is very difficult to motivate patients to stay physically active and therefore the potential impact on cognitive impairment is difficult to assess. The Mediterranean diet was shown to significantly prevent strokes and obviously has great significance in preventing cognitive impairment related to stroke prevalence data mentioned earlier. Prof. Brainin added that single domain interventions practiced in the past proved absolutely useless. Instead, what is needed now are multi-domain interventions. This was a goal for ASPIS polyintervention study conducted by group of Prof. Brainin. It confrmed that disexecutive functions should be our prominent target in treatment of cognitive impairment in stroke patients (Fig. 3).

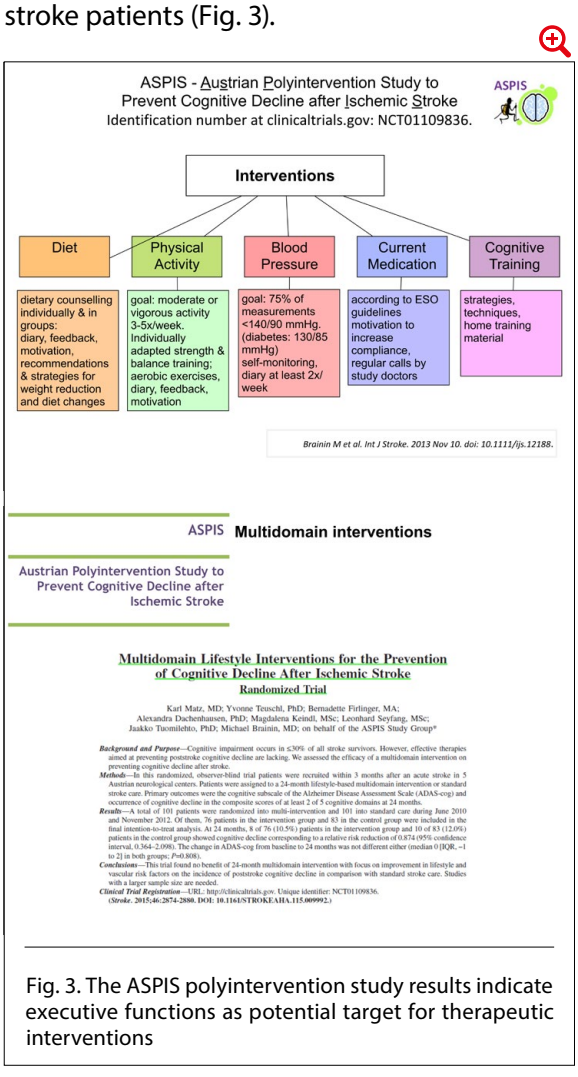
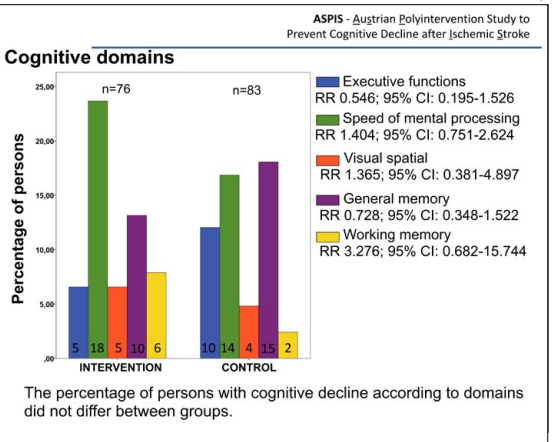


Fig. 3. The ASPIS polyintervention study results indicate executive functions as potential target for therapeutic interventions



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Vascular Epilepsy Syndrome, its Treatment and Prevention

Eugen Trinka

Department of Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria

Prof. Trinka started the lecture by indicating that he will be talking mainly about the relationship between seizures and stroke. His comprehensive talk was divided in a few sections: general remarks, case vignette, seizures and stroke, and finally risk factors and causes of vascular precursor epilepsy. Vascular epilepsy syndromes are a heterogeneous group of disorders including such as: post-ischemic-stroke seizures and epilepsy, prestroke seizures, seizures/epilepsy due to cavernomas, seizures/epilepsy due to arterivenous malformations, seizures/epilepsy due to subarachnoidal bleeding or intracerebral hematoma, seizures/epilepsy due to sinus or cortical venous thrombosis, seizures/epilepsy due to subdural hematoma. The etiology is always an implication for physiopathology, and this is key consideration for the treatment setup. Prof. Trinka summerized the newest data on etiology of seizures (Fig. 1). The major point to consider is that whenever a patient has a seizure, it is not a diagnosis. It is a symptom of an underlying disease. In all cases of seizures, whether they are provoked by or heralding stroke, one need to perform a thorough examination and complete vascular workout (Fig. 2). If a patient has early seizures after stroke, these correlate with increased mortality at both short-term and long-term observation time. At the same time, seizures after stroke are indicators of higher severity of stroke. Accordingly, also the outcomes are adversely affected by seizures, including the increased hospital stay. Seizures

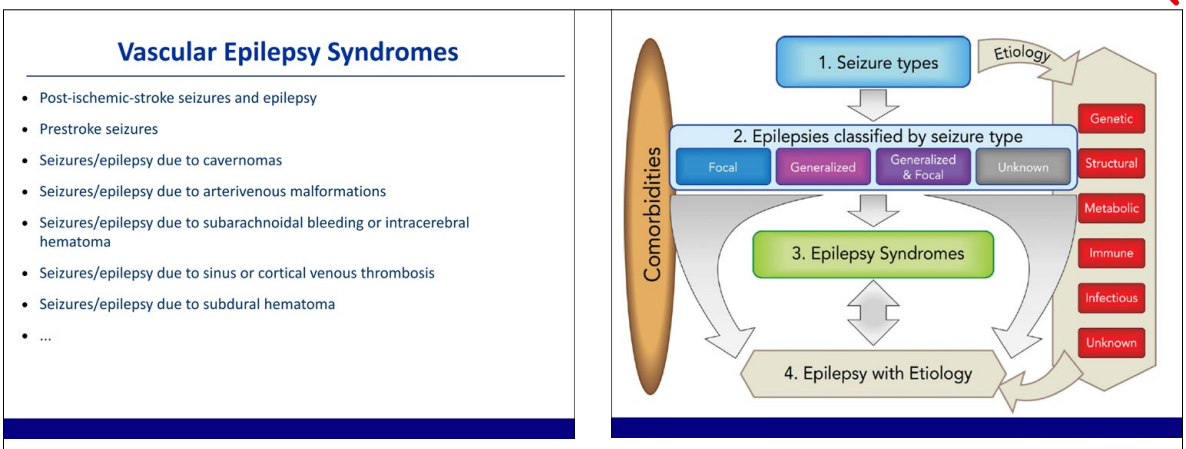

Fig. 1. The new classification system of seizures

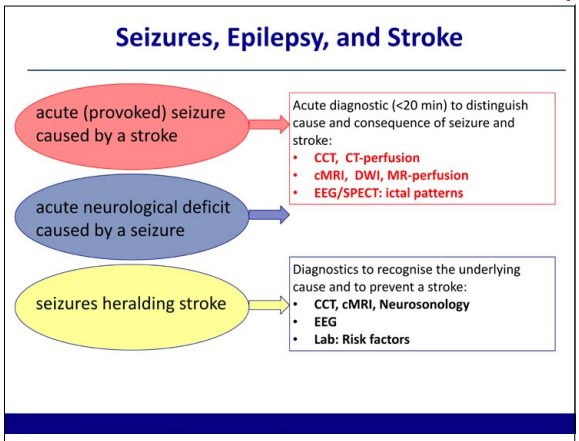

Fig. 2. The relationships between stroke and epilepsy

occurring during the acute phase of stroke are also independent predictors of cognitive decline (with hazard ratio close to 4.0). Next, Prof. Trinka discussed seizures heralding strokes (epilepsia praecursiva). Historically, this type of seizures were ascribed to atherosclerotic background. Later on, the cerebral amyloid angiopathy was also implicated. The heralding seizures were subsequently classified as belonging to following three categories: 1) late onset seizures after age 60 years, 2) seizures as the first sign of a cerebral or systemic insult, and 3) seizures preceding the full clinical manifestation of a cerebral/systemic insult, disorder that is known to increase the risk of developing epilepsy, but which at the time of the epileptic event is not definitively demonstrated. This is a retrospective evaluation, however with significance for the clinical practice.The vascular origin of heralding strokes was further detailed. Subcortical small vessel disease was shown to lead to disruption of cortico-subcortical circuits altering the balance between excitability and inhibitory pathways. Neurovascular unit dysfunction with altered integrity of blood–brain barrier causes subsequent disruption of cerebral metabolism and/or perfusion. Finally, cerebral amyloid angiopathy (beta-amyloid in media and adventitia of small- and mid-sized arteries of the cortex and the leptomeninges) leads to stenosis of the vessel lumen, with subsequent fibrinoid necrosis and microaneurysms. Regarding the risk factors, there is a significant overlap between ischemic stroke risk factors and heralding seizures. The serum lipids profile (as related to atherosclerosis) has also been implicated as a significant risk factor. Interestingly the resent evaluations indicate that statins, age older than 85, obesity and hypercholesterinaemia are all protective factors against seizures. Concluding his lecture, Prof. Trinka said that prestroke seizures and vascular precursor epilepsy are a clinically retrospectively defined entity. It is also clear that the definition of prestroke seizures has to be refined. Importantly, the newly diagnosed seizures after the age of 35 need a thorough cardiovascular workup. Without that, we can miss the underlying disease and cannot react accordingly to minimize risk factors. The causes of seizures can be: (a) small vessel disease and (b) cerebral amyloid angiopathy, but pathophysiology is currently poorly understood. There appears to be a strong genetic contribution and finally the enzyme inducing AEDs may contribute to cerebrovascular risk factors.

Post-Stroke Depression – The Psychiatrist's Perspective

Johannes Thome

Clinic and Policlinic for Psychiatry and Psychotherapy, University of Rostock, Rostock, Germany

Prof. Thome started his lecture by mentioning what a few other speakers did before about increasing life expectancy and prevalence of stroke globally. What this means is that also psychiatric problems, and specifically depression, is a growing global burden, too. A patient with dementia can be happy, the quality of life can also be good when there is a proper support in place; and if the physical symptoms are not too bad. However, if the same patient suffers from depression, and his emotions will not function, the quality of life is going to be lost. This is also true even in the case when there is no cognitive decline at all. All the cognitive functions cannot help, if you are sad, depressed and you cannot enjoy life anymore. The point is that depressive symptoms are at least as important in the stroke research and clinic as cognitive problems, said Prof. Thome. Among different disorders, stroke appears as the most frequent trigger of depression (Fig. 1). However, depression leads to stroke as well (Fig. 2). Apart from depression, stroke victims can experience a cluster of different symptoms, like manic symptoms (<1%), post-stroke emotional incontinence (11-27%), personality changes; apathy (20-40%), generalized anxiety disorder, panic attacks (5-30%), PTSD (post-traumatic stress-disorder), high mortality and co-morbidity with post-stroke depression (PSD). Major risk factors of PSD are: physical impairment after stroke, severity of stroke, cognitive impairment, female sex, social isolation / lack of social support, pre-morbid alcohol abuse (men), preexisting depression, and genetic associations. However, the localization of the stroke doesn't seem to be related to onset of depression. The important question is if the PSD is reactive or organic. It seems that it is more than reactive as stroke patients exhibit a higher rate of depression when compared to orthopedic patients with similar disability. Equally, the patients with anosognosia (no awareness of disorder and disability) can suffer from PSD. The fact that PSD has to great extent organic character means that it is amenable to pharmacotherapy and, as a supporting approach, the psychotherapy. Interestingly, treatment with antidepressants was shown to increase survival rate after stroke. It was also shown that SSRI treatment is helpful in

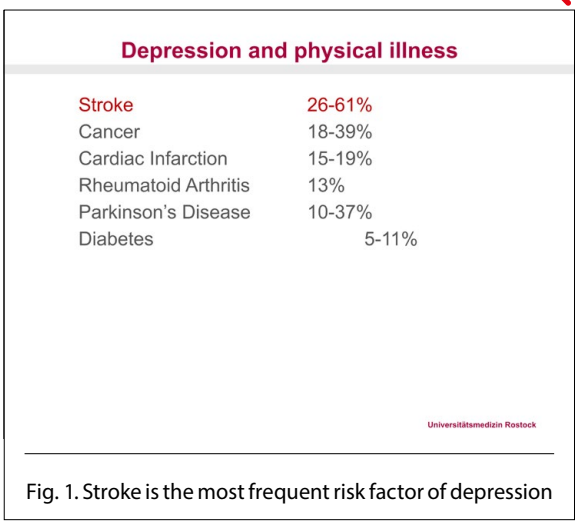

Fig. 1. Stroke is the most frequent risk factor of depression

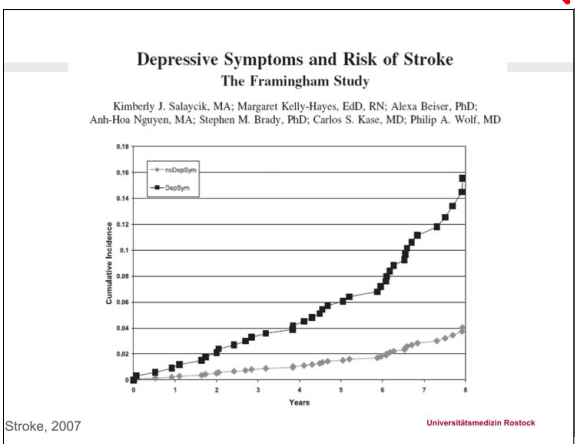

Fig. 2. Depression leads to deterioration of quality of life after stroke, but also leads to more strokes

motor function rehabilitation (Fig. 3). Prof. Thome mentioned also Cerebrolysin as a viable option for treatment of PSD. He referred to CARS study results and the lecture of Prof. Muresanu (Fig. 3). The Geriatric Depression Scale was employed as one of 12 different outcome measures. There was a significant therapeutic effect of Cerebrolysin on decreasing depression symptoms in the treated patients. It must be noted however, that depression is underrated among stroke specialists and the integration of the depression diagnosis and management within stroke units is not yet solved.

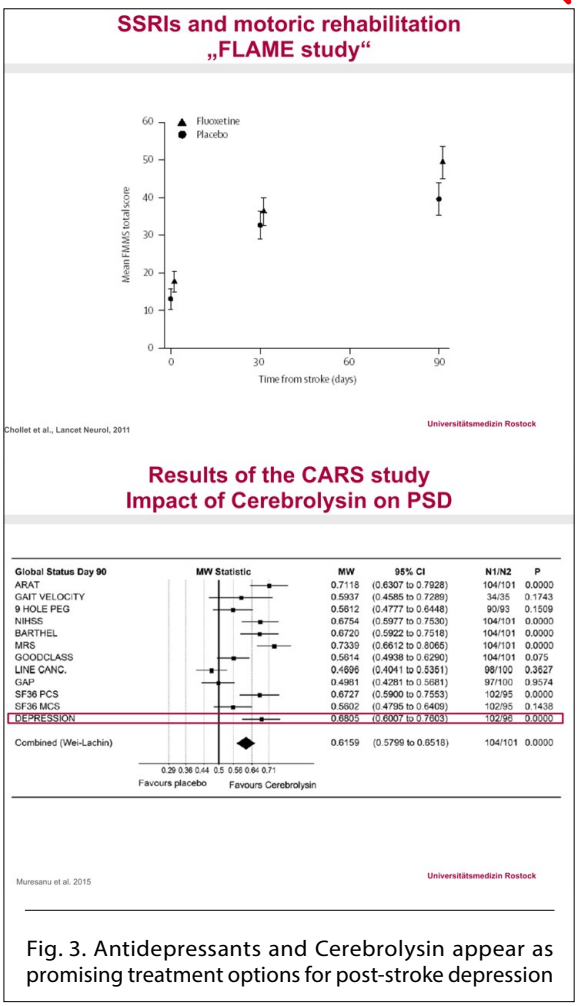

Fig. 3. Antidepressants and Cerebrolysin appear as promising treatment options for post-stroke depression

The role of imaging in Stroke Rehabilitation

Jan Sobesky

Dept. of Neurology, Charité Berlin & Centre for Stroke Research Berlin (CSB), Berlin, Germany

One of the important tasks of neuroimaging is to help in understanding the clinical trials results, like these obtained in the CARS trial and measured with mRS, said Prof. Sobesky. He divided his lecture into three parts: imaging tools, acute ischemic damage, and recovery and plasticity. What are the major techniques that we have to examine the brain. There are three major approaches: computer tomography (CT), positron emission tomography (PET), and magnetic resonance imaging (MRI). With very expensive, albeit very specific, PET we can trace almost any biological substance in the body. With that comes ability to assess tissue viability, and activity or level of metabolism in the brain. More important and commonly used is MRI. The speed of assessment in acute stroke cases is very high, which is a valuable advantage. Where the CT cannot provide answer for hours, with diffusion weighted imaging we have it done in a few minutes. MRI has good resolution, but microinfarcts escape detection. This problem can be addressed with stronger magnetic field applied (up to 7 Tesla). However, this is very expensive and difficult to perform. Apart from morphology assessment, MRI serves us well in determination of perfusion and connection between different areas of the brain (fiber tracts) after stroke. The functional MRI (fMRI) helps us to detects brain functions in a non-invasive manner (in contrast to PET). The resting state MRI is a quite new technique, which we don't fully understand yet. In the brain that is not active, there are certain connections and certain oscillations between different areas which cannot be traced just by perfusion. By performing very complex mathematical analysis, the resting state MRI tells us which regions of the brain are functionally connected. This helps in identification of brain's functional networks and therefore allows for detection of their disturbances. This technique explains well why some relatively small lesions have strong impact on certain functions underlying mood, depression, cognition etc. There are good reasons to combine PET and MRI and such new facilities are already being tried in clinical practice. The fusion images coming from such techniques give us rich and concomitant information about relationships between morphological changes and intensity of the metabolism in the brain. Prof. Sobesky went on to describe the application of the aforementioned techniques to the analysis of the acute ischemic damage. The PET analysis of penumbra and non-penumbra situation shows how we can facilitate the decision making process about thrombolysis (Fig. 1). The diffusion/perfusion MRI mismatch (DWI/PWI) is however much more practical in the clinical setting than PET analysis (Fig. 1). Finally, Prof. Sobesky overviewed application of various imaging techniques for analysis of the recovery processes after stroke. Focal lesions leading to widespread and distant damages or functional abnormalities as well as localization of distant and long-lasting inflammatory processes can be appropriately assessed. Very interesting case of activation studies came recently from publication of Prof. Heiss. The treatment of aphasia with repetitive transcranial magnetic stimulation (rTMS) led to deactivation of hyperactivated/suppressing hemisphere. This therapeutic process was finely

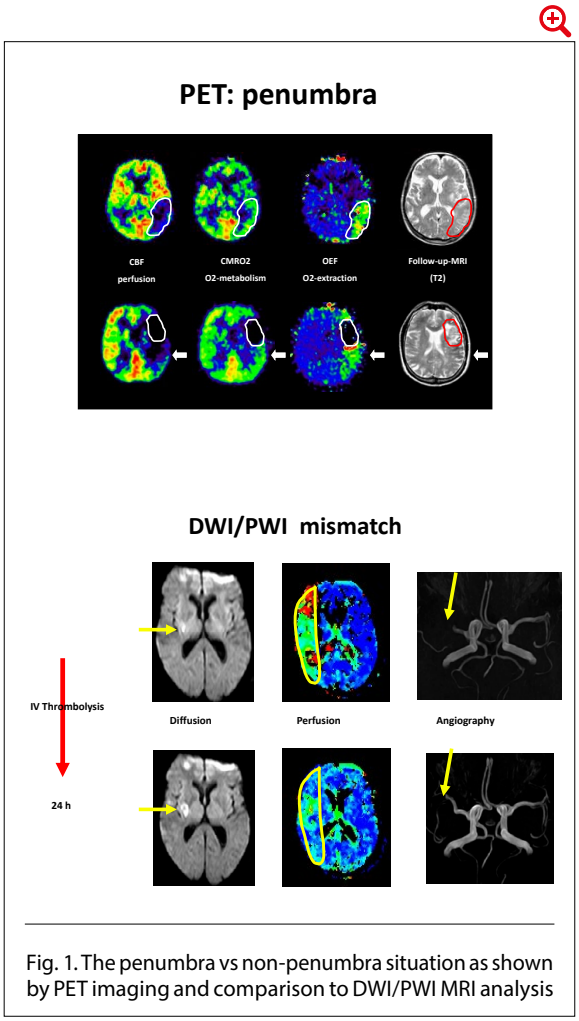

Fig. 1. The penumbra vs non-penumbra situation as shown by PET imaging and comparison to DWI/PWI MRI analysis

illustrated by PET imaging analysis (Fig. 2). Good imaging leads therapy in rehabilitation process, underlined Prof. Sobesky. The last part of the lecture related to a recently published results of ECOMPASS (Effects of Cerebrolysin On Motor recovery in Patients with Subacute Stroke) study. This study also used modern imaging techniques for interpretation of the results of the applied therapy. Patients with moderate to severe motor deficits benefited from the treatment as assessed with Fugl-Meyer Assessment. The investigators correlated these results with neuroimaging. In the resting state functional MRI imaging, we could see that combination treatment Cerebrolysin plus

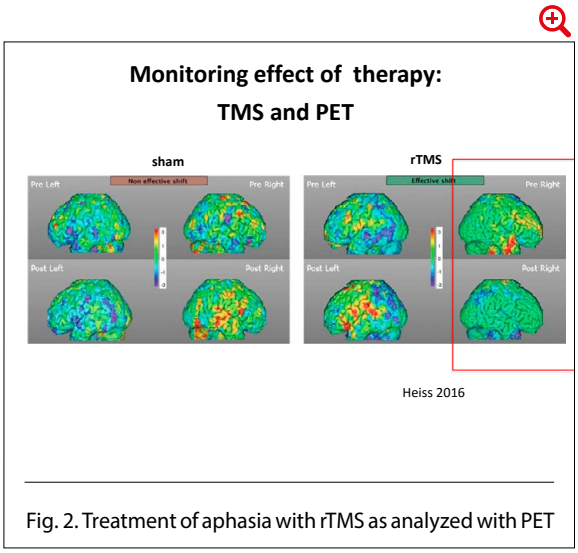

Fig. 2. Treatment of aphasia with rTMS as analyzed with PET

motor rehabilitation leads to reactivation of the affected brain regions whereas in the placebo group (without Cerebrolysin) this reactivation is not present (Fig. 3). This pilot study is a good example of the utility of modern imaging technology for the evaluation of treatment effects and for better understanding of mechanisms through which therapy works in stroke patients.

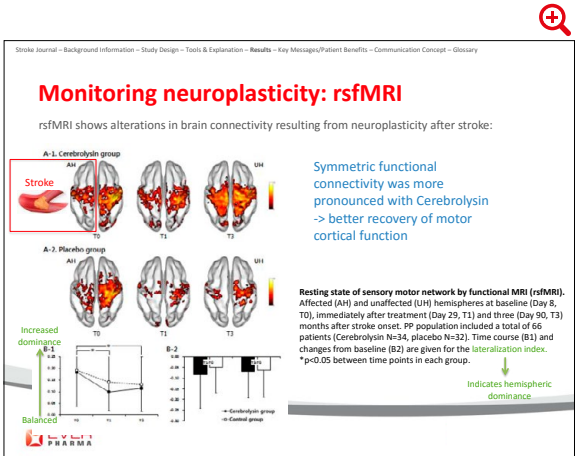

Fig. 3. The ECOMPASS trial showed positive correlation between the therapeutic effect of Cerebrolysin on motor function rehabilitation and activation of the affected brain regions as analyzed by rsfMRI

Post-Stroke Spasticity – Current Treatments and new Opportunities

Romil M. Martinez

Amang Rodriguez Memorial Medical Center, Philippines

Dr. Martinez presented the results of the retrospective study in rehabilitation performed recently in his department: "A retrospective study on the effect of intramuscular cerebrolysin on post stroke filipinos in an out patient rehabilitation setting." The study protocol was shortly presented (Fig. 1). Dr. Martinez noted that patients were admitted to rehabilitation relatively late, between 4 and 7 month post-stroke.

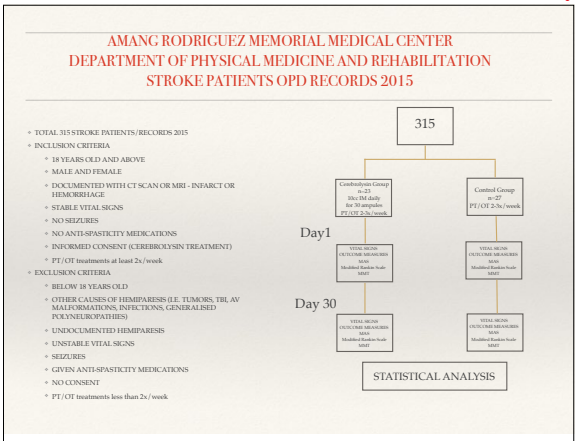

Fig. 1. Methodology of the stroke rehabilitation study with Cerebrolysin performed in Amang Rodriguez University Hospital

No significant differences in all relevant demographic profiles were seen when compared between Cerebrolysin and control group. Similar situation was seen in the vital signs. However, there was a significant increase in mean diastole pressure (mm Hg) from day 1 to day 30 in the Cerebrolysin group (71.52+9.47 vs 78.04+3.61, 0.006). Moreover, there was a significant increase in mean pulse rate (bpm) from day 1 to day 30 in the Cerebrolysin group (75.39+10.30 vs 82.30+8.81, 0.020). There was also a significant increase in the temperature in the Control group from day 1 to day 30. Additionally, the data shows that when the mean difference between the groups where compared in terms of vital signs, there was no significant difference between the two study groups. Dr. Martinez referred to published formerly and updated in 2013 standards in the evaluation of rehabilitation effects on stroke patients (Fig. 2). These served also as guidelines for the evaluation of the outcomes in the presented study which employed: Modified

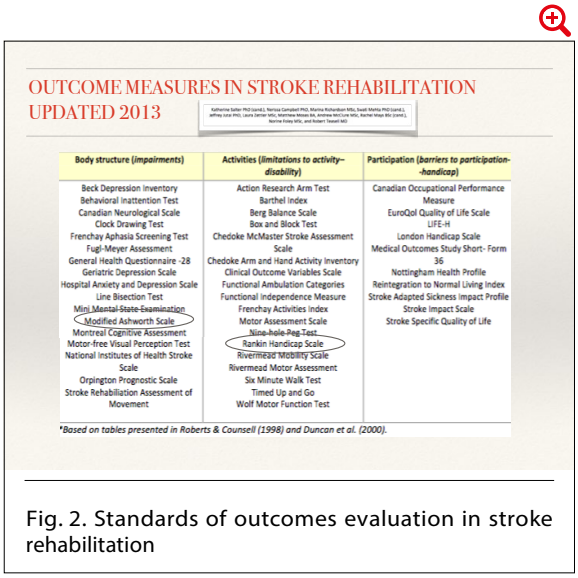

Fig. 2. Standards of outcomes evaluation in stroke rehabilitation

Ashworth Scale (MAS), Modified Rankin Scale (MRS) and the Manual Muscle Test (MMT).

After a short outline of methodology used for assessment of rehabilitation success in the discussed study, Dr. Martinez summarized its results. There was no significant difference in the spasticity between groups at day 1 (p-values above 0.05). However, there was significant difference in the spasticity between groups at day 30 in following motor domains: pectoralis, biceps, wrist and finger flexors, hamstrings, tibialis posterior (TP), gastrocnemius. At day 30, spasticity was less pronounced in the Cerebrolysin group when compared with the control in the pectoralis (1.48+0.67 vs 2.63+0.63), biceps (1.74+0.62 vs 2.93+0.73), wrist (1.57+0.73 vs 2.56+0.75) and finger (2.00+0.74 vs 2.52+0.85) flexors, hamstrings (0.78+0.80 vs 2.04+0.85), TP (1.57+0.79 vs 3.15+0.53), gastrocnemius (1.57+0.73 vs 3.00+0.55). Less spasticity in the Cerebrolysin group, in comparison with the control group, was consistently detected in both lower and upper extremities. There was no significant difference in the MMT and Rankin scale between groups at day 1 (p-values above 0.05). At day 30, MMT was better in the Cerebrolysin group compared to the Control group. No significant difference was observed at day 30 on Rankin scale between the groups (Fig. 3).

Discussing the results of the presented study, Dr. Martinez paid special attention to spasticity, which is experienced by about 60% of stroke survivors, and interpreted the positive Cerebrolysin-induced effects within the context of its known mechanism of action (Fig. 4). Muscle tone—the state of muscle contraction—is controlled by two factors: inhibitory (relaxing) signals combing down from the brain into the spinal cord, causing the release of a chemical, GABA, which make the muscles relax, and excitatory stimulating signals coming from the muscles into the spinal

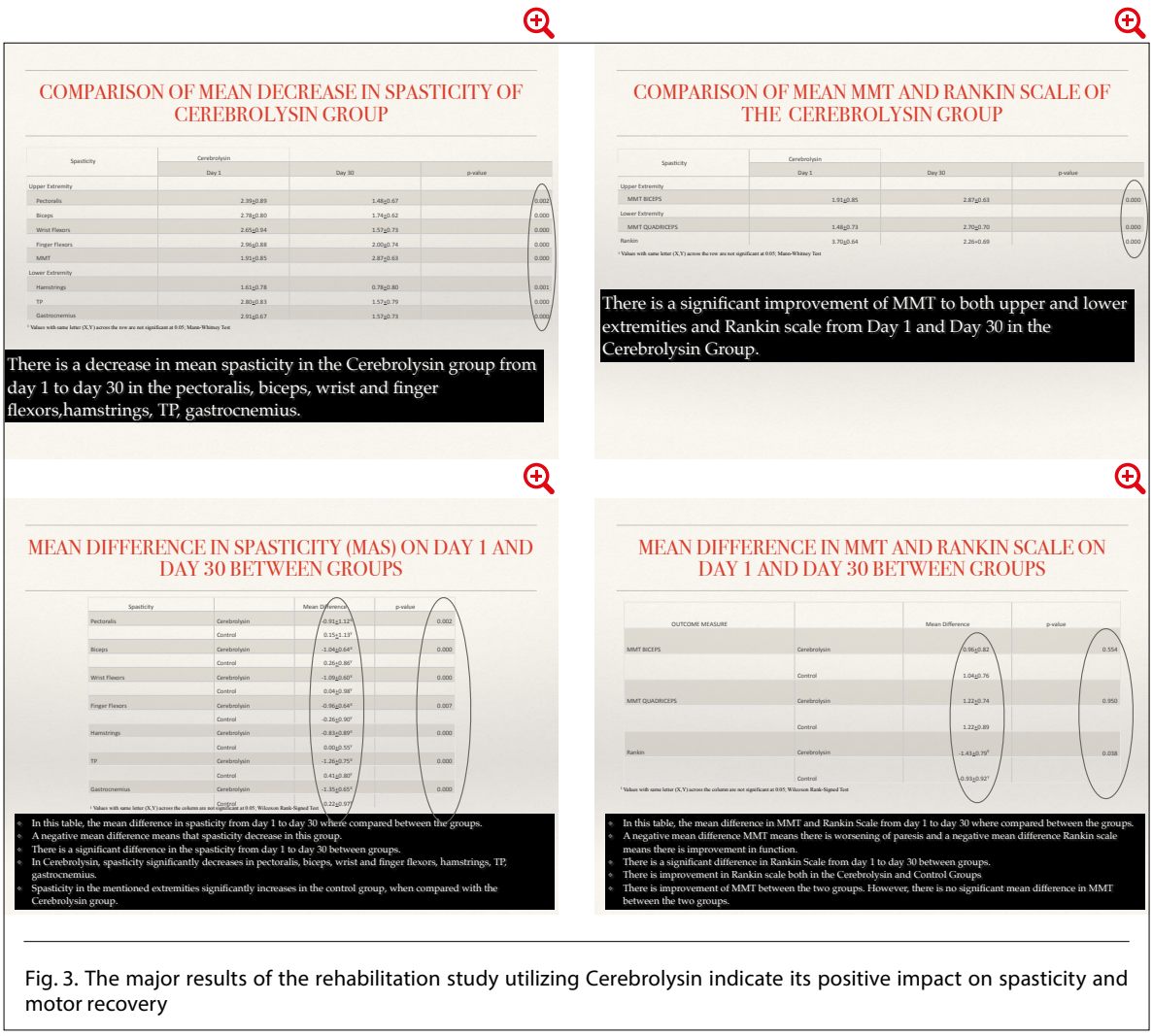

Fig. 3. The major results of the rehabilitation study utilizing Cerebrolysin indicate its positive impact on spasticity and motor recovery

cord, telling them to contract (tighten). If the balance between those two is normal, muscle tone is normal. Spasticity is caused by damage to parts of the brain that send the messages for GABA to be released. The damage may occur anywhere along the pathway, from the brain to the brainstem to the spinal cord. The end result is the same: deficiency of GABA and a relative excess of excitatory impulses. Intrathecal treatment with baclofen ($GABA_B$ receptor agonist) and nipecotic acid (GABA uptake inhibitor) provided a significant suppression of spasticity, rigidity, H-reflex or motor evoked potentials. In the study published in 1996, Cerebrolysin has been shown to inhibit synaptic transmission via presynaptic $GABA_B$ receptors (Fig. 4) showing its activity as a GABA agonist. Additionally, Cerebrolysin has been shown to stimulate important neurotrophic factors, like angiopoietin 1 (Ang1) and vascular endothelial growth factor (VEGF) in the brain's vasculature (Fig. 4). This vasculature stabilizing agents are also important for neurite outgrowth and contribute to overall recovery from stroke in animal models. Cerebrolysin also stimulates the production and action of sonic hedgehog (Shh) signal transduction pathway which is implicated in both development of central nervous system and concerted expression of genes underlying natural, spontaneous recovery from stroke (Fig. 4). All these and other factors may play important role in the observed therapeutic effects of Cerebrolysin in the rehabilitation of motor functions and spasticity in stroke patients.

Concluding his lecture, Dr. Martinez indicated that intramuscular treatment with Cerebrolysin over 30 days is safe and may have a significant effect on reducing spasticity, increasing motor recovery and improving function among post-stroke patients in an out-patient rehabilitation setting. Further studies with improvements in methodology i.e. employing a randomized controlled trial protocol, increasing sample size and using more reliable, valid and responsive outcome measures should be considered.

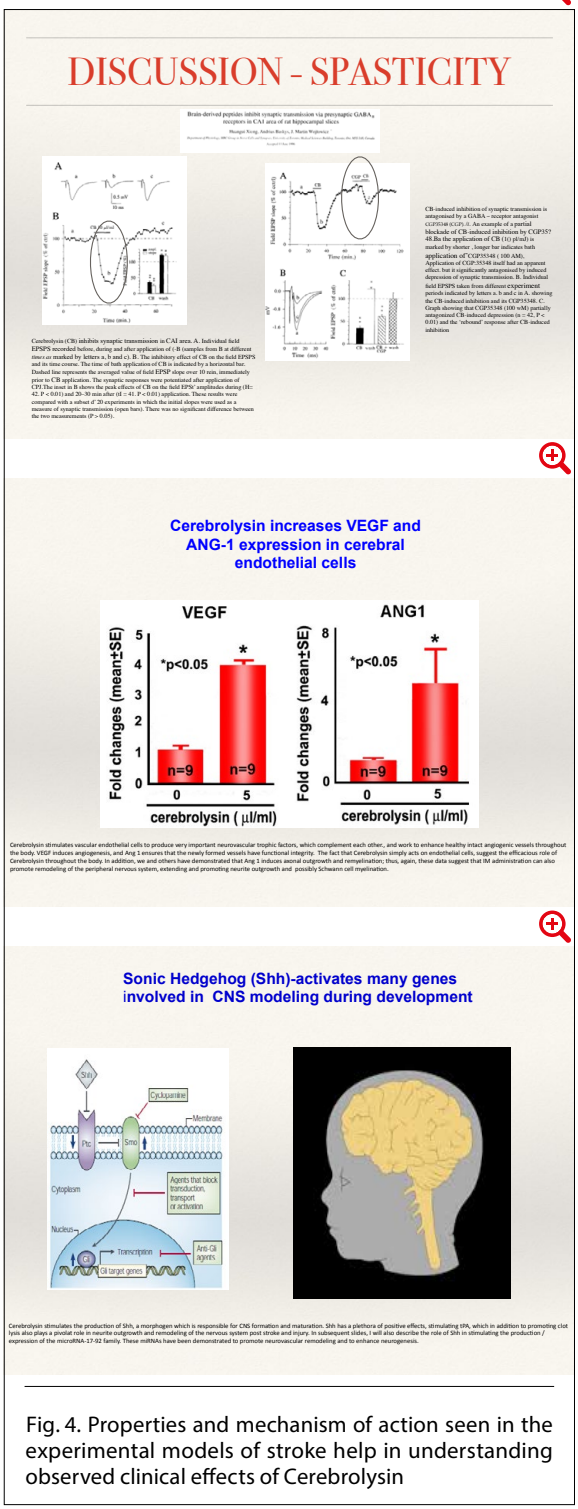

Fig. 4. Properties and mechanism of action seen in the experimental models of stroke help in understanding observed clinical effects of Cerebrolysin

Rehabilitation in low and middle income countries – Status Quo and Perspectives

Andreas Winkler

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Prof. Winkler began his lecture by outlining the role rehabilitation plays in the overall scheme of integrated stroke management. The leading idea behind the lecture was juxtaposing Western stroke management standards with those practiced in middle and low income countries, with special attention to Vietnam (Fig. 1). In these countries the role of caregiver is much more important than in high income countries because of the fact that the access to rehabilitation services is much more difficult, if not impossible in many cases. Prof. Winkler presented a broad epidemiological picture of global burden of stroke referring to data discussed extensively earlier by Prof. Caso in her key note lecture. About 3% of people with chronic disabilites worldwide receive rehabilitation in their lifetime, while for example in Austria every patient has the right to be rehabilitated. While 60% of developing countries have no rehabilitation services, when they are available it happens usually in urban centers, inaccessible to many due to costs and geographic distance. Even when rehabilitation services are available, there is a lack of a well structured neurorehabilitation system; the health care system is unable to provide the comprehensive rehabilitation services. The needed specialists with expertise in neurorehabilitation training are uncommon. The therapists usually have variable levels of training (one specialist for all tasks; lack of specialization). The occupational therapists, speech and swallowing therapists, neuropsychologists, rehab-nurses are usually not present for a patient. This is why the initiatives

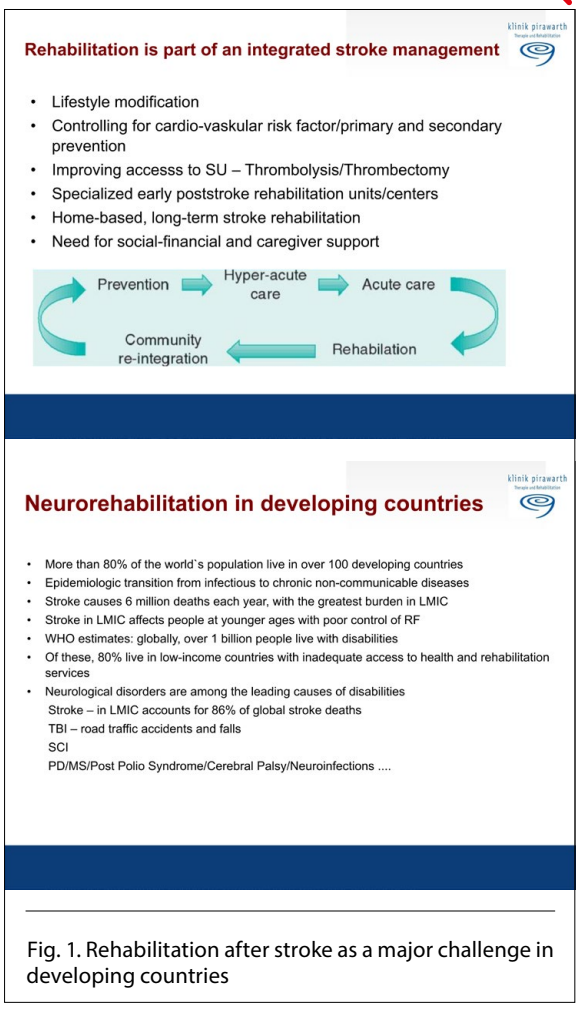

Fig. 1. Rehabilitation after stroke as a major challenge in developing countries

aimed at bringing well working standards to developing countries make a lot of sense, said Prof. Winkler. One good example of such an

initiative is the AVANT Program supported by EVER Pharma (Fig. 2). The details of this initiative were formulated from analyzing the differences between standards of rehabilitation practiced in Austria and in Vietnam. Moreover, it was refined taking into account very practical considerations and after looking for pivotal elements identified during practical visits and discussions of Austrian rehabilitation specialists in Vietnam health care centers, in which Prof. Winkler actively participated. The AVANT program uses multimedia environment for educational purposes and it is three-steps-stratified program. It also includes direct exchange of experiences and discussions between specialists from both countries.

Fig. 2. The AVANT program aims at reducing the burden of stroke in Vietnam

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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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