Programme & abstracts

New evidence for Multi-modal Treatment Concepts in Post-Stroke Recovery

Thursday, 17 May 2018, 12:45-14:15
(Meeting Hall E1)

Chairman: Wolf-Dieter Heiss, Germany
New evidence for Multi-modal Treatment Concepts in Post-Stroke Recovery

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- Neuroprotection and Neurorepair after Stroke: Example Cerebrolysin
  Michael Brainin, Austria

- Noninvasive Brain Stimulation & multi-modal treatment concepts
  Andreas Winkler, Austria

- Anticorrelated processes in neurobiology - possible consequences for neurorehabilitation strategies
  Dafin Muresanu, Romania

- New evidence from a recent meta-analysis in acute ischemic Stroke
  Natan Bornstein, Israel
Neuroprotection and Neurorepair after Stroke: Example Cerebrolysin

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

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In stroke survivors, motor impairment is a leading cause of chronic disability in activities of daily living with 80% experiencing hemiparesis of the contralateral upper limb. While 4 out of 5 stroke patients will be able to walk independently, only 2 out of 5 with upper limb paresis regain functional use. Most troublesome symptoms of upper extremity motor impairment compromise paresis, flaccid or spastic changes in muscle tone, joint laxity, impaired motor control and loss of selective finger movements. These impairments interfere with everyday activities such as reaching, grasping and picking up and holding on to objects. Rehabilitation training is the most effective way to enhance motor recovery in stroke patients and to minimize impairments. Task specific training is still the gold standard for post-stroke rehabilitation, but effect sizes studied recently in patients with upper extremity impairment (UE) in the subacute stages after stroke were rather small. Special concerns regard stroke patients with more severe initial impairments who in general will not show the same degree of proportional recovery compared to stroke survivors with mild or medium impairment. A multimodal approach in upper extremity rehabilitation combining synergistic effects of different treatment modalities might therefore be beneficial. Transcranial direct current stimulation (tDCS) is a promising new technique to optimize the effect of task specific training in the context of UE motor recovery. tDCS is a convenient and safe rehabilitation method as it allows modulations in brain plasticity through direct stimulation of the cortex. Cerebrolysin is a neuropeptide preparation with neuroprotective and neurorestorative effects which has shown to support upper extremity motor recovery. Combining tDCS with Cerebrolysin and task specific training might theoretically exhibit synergetic effects in UE motor recovery. In a retrospective analysis we studied stroke patients under routine conditions with moderate to severe impairment of UE motor function.
(SAFE-Score > 4 pts.; ARAT-Score >12 pts.). Eligible patients were stratified into three groups: group one received a triple-therapy consisting of daily task oriented training (TOT, 30 minutes 5 days/week), anodal tDCS (20minutes, 5 days/week) plus daily administration of Cerebrolysin 30ml iv. Group two received a combination of TOT plus anodal tDCS, patients in group three were treated as usual by TOT. After two weeks of treatment we assessed differences in functional UE recovery between treatment groups by measuring changes in proportional recovery using the ARAT-Score. To our knowledge, the effects of the combination of these potentially synergetic acting therapeutic modalities on functional UE recovery have never been studied before.

Your notes

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From neurobiology to evidence based medicine concepts in neurorehabilitation after stroke

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Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes. Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone. Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data show that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization-related complications cause over 50% of stroke patients’ deaths, rehabilitation plays an important role in stroke care. It is increasingly evident that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke. The results of recently published large and well-controlled clinical studies show a positive effect of Cerebrolysin on neurological recovery after acute ischemic stroke. The newly published CARS study assessed the efficacy and safety of Cerebrolysin in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper-limb motor functions. Cerebrolysin was administered for 21 days, starting within 48-72 hours after ischemic stroke. The study showed a statistically significant group difference in the upper-limb motor function (ARAT) at day 90 – primary end point. Cerebrolysin was also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with
Cerebrolysin showed less depressive symptoms and better quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of Cerebrolysin. Analysis of the safety parameters did not show any clinically statistical significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach. Furthermore, CARS 1 and CARS 2 meta-analysis provides evidence that Cerebrolysin has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary meta-analytic results were statistically significant.
New evidence from a recent meta-analysis in acute ischemic Stroke

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This meta-analysis combines the results of nine ischemic stroke trials, assessing efficacy of Cerebrolysin on global neurological improvement during early post-stroke period. Cerebrolysin is a parenterally administered neuropeptide preparation approved for treatment of stroke. Design: All included studies had a prospective, randomized, double-blind, placebo-controlled design. The patients were treated with 30-50 ml Cerebrolysin once daily for 10-21 days, with treatment initiation within 72 hours after onset of ischemic stroke. Data Sources: For five studies original analysis data were available for meta-analysis (individual patient data analysis), for four studies aggregate data were used. Study Selection: The combination by meta-analytic procedures was pre-planned and the methods of synthesis were pre-defined under blinded conditions. Search deadline for the present meta-analysis was December 31st, 2016. Results: The nonparametric Mann-Whitney (MW) effect size for NIHSS on day 30 (or 21), combining the results of nine randomized, controlled trials by means of the robust Wei-Lachin Pooling Procedure [MERT], indicated superiority of Cerebrolysin as compared with placebo (MW 0.60, P<0.0001, N=1879). The combined number-needed-to-treat (NNT) for clinically relevant changes in early NIHSS was 7.7 (95% CI 5.2 to 15.0). The additional full scale ordinal analysis of mRS at day 90 in moderate to severe patients resulted in MW 0.61 with statistical significance in favour of Cerebrolysin (95% CI 0.52 to 0.69, P = 0.0118, N = 314). Safety aspects were comparable to placebo. Conclusion: Our meta-analysis confirms previous evidence that Cerebrolysin has a beneficial effect on early global neurological deficits in patients with acute ischemic stroke.
Reconnecting Neurons.
Empowering for Life.

SMALL MOMENT. BIG DIFFERENCE.
Last month, Paul was suffering from cognitive and motor impairment.
Today, he’s making his next big move.

Improvement of motor functions
Early recovery after stroke
Regain full independence
Increase quality of life

Muresanu, et al., 2016

ABBREVIATED PRESCRIBING INFORMATION: Name of the medicinal product: Cerebrolysin® - Solution for injection. Qua-
litative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cere-
brolysin® concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic
indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer’s
type - Post-apoplectic complications - Cranio-cerebral trauma; post-operative trauma, cerebral contusion or concussion.
Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing
More information about pharmaceutical form, posology and method of administration, special warnings and precau-
tions 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, pharmaco-
kinetic 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.