Spark Waves® in Neurodegenerative Diseases- Concept for the Treatment of Alzheimer's and Parkinson's Disease.

(Mar 5, 2020)

Introduction

The use of non-invasive brain therapies has become a hot topic recently. Alzheimer's and Parkinson's are major medical challenges in the context of our ageing society. The available treatments are limited, and such patients are therefore very important candidates to benefit from the clinical utility of new additional therapies.

Clinical Background

Alzheimer's disease (AD) is recognized by the World Health Organization as a global public health priority. Despite large gains in our understanding of AD pathogenesis and how the disease is conceptualized since Alois Alzheimer reported the first case in 1907 there are still no disease-modifying treatments. [1] This neurodegenerative disorder is characterized by various pathological processes including regionally specific and sequential brain atrophy, amyloid plaques, neurofibrillary tangles, synaptic dysfunction and neuronal cell death. [2] AD has an apparent multifactorial ethology encompassing nutritional, genetic, and environmental risk factors, none of which is sufficient to account for all cases and convergence of these factors may be required for clinical manifestation. [3]

Parkinson's disease (PD) is the most common movement disorder and represents the second most common degenerative disease of the central nervous system. PD affects 1–2 per 1000 of the population at any time. PD prevalence is increasing with age and PD affects 1 % of the population above 60 years. The main neuropathological finding is α-synuclein-containing Lewy bodies and loss of dopaminergic neurons in the substantia nigra, manifesting as reduced facilitation of voluntary movements. With progression of PD, Lewy body pathology spreads to neocortical and cortical regions. PD is regarded as a movement disorder with three cardinal signs: tremor, rigidity and bradykinesia. [4]

Non-invasive Brain Stimulation with ESWT - State-of-the Art

The overall positive effect of low-energy ESWT stimulation on the brain has already been demonstrated in preclinical studies with animal models. The stimulation of neuronal stem cells by ESWT leads to improved cerebral blood flow and neuronal function, and Spark wave Therapy protects from neuronal degeneration after CNS / brain injury. [5–8]

Feasibility, safety and efficacy of non-invasive brain stimulation in humans by ESWT was initially demonstrated by pioneering case reports of Lohse-Busch *et al*. in 2014 and Werner *et al*. in 2016 who reported clinical improvement of coma remission scales in patients suffering from unresponsive wakefulness syndrome or chronic disorders of consciousness. [9–11]
Recently, a large multicentric sham-controlled CE-approval study about Transcranial Pulse Stimulation (TPS) in Alzheimer`s disease was published by Beisteiner et al. in 2019. [12] Efficacy of TPS for dose dependent neuromodulation was demonstrated *in vivo* and neuropsychological scores of Alzheimer`s patients (CERAD corrected total score - CTS) improved significantly after TPS treatment. Improvement sustained up to three months and correlated with an upregulation of the memory network (fMRI data). [12] Data from simulations, laboratory and in vivo animal measurements indicated broad safety ranges - even high energy levels did not induce any haemorrhage or brain injury. The therapy was well tolerated by the patients and no major side effects occurred. [12]
In this publication, the TPS is referred to as ultrashort ultrasound pulses which basically reflect the characteristics of shock waves. Advantages of the new TPS (= ESWT) technology over the previously used regular ultrasound technology include a deeper skull penetration depth, the absence of secondary stimulation maxima which may occur due to interaction of reflections or standing waves with long train sonication and there is no heating of the cerebral tissue. [12]

The precise cellular mechanism of action about how these therapies stimulate the neurons and improve their plasticity and survival is still to be investigated. Several principles have been proposed and preclinical data has shown that the mechanical stimulation leads to the enhanced expression and release of relevant growth-associated factors such as brain-derived neurotrophic factor (BNDF), glial cell line-derived neurotrophic factor (GDNF) and vascular endothelial growth factor (VEGF), for example. This stimulates proliferation and differentiation of neuronal stem cells as well as it improves the blood circulation and constitution of the cerebral tissue. It is also likely that an increased permeability of the blood-brain barrier and of the cell membranes leads to an improved pharmaceutical supply and transfection of the affected areas. [5–8,12,13]

Outlook

State-of-the-art clinical research shows that non-invasive brain stimulation techniques like TPS / ESWT have great potential to act as independent adjunct therapies in the treatment of severe neurodegenerative diseases such as Alzheimer`s and Parkinson`s and encourages a broader investigation in clinical neuroscientific application.

References

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