

Transcranial magnetic resonance imaging-guided focused ultrasound in Parkinson's disease

Statement of the Swiss Neurology Society

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Patients with Parkinson's disease more and more frequently seek advice from their neurologists in private practice or hospitals about the emerging non-invasive treatment of transcranial magnetic resonance imaging-guided focused ultrasound (MRIgFUS). In the present commentary we provide information on behalf of the Swiss Neurology Society about the state of the art of this innovative procedure.

One of the major issues of medical treatment in progressive Parkinson's disease is the development of motor complications including ON/OFF fluctuations and troublesome dyskinesias. Motor complications are considered treatment refractory if they cannot be sufficiently controlled by adjustments of the medication. Today device-aided therapies such as deep brain stimulation (DBS), apomorphine pump, or the infusion therapy with L-Dopa/Carbidopa Intestinal Gel (Duodopa) are available when peroral medical strategies are exhausted. Another reason to think about stereotactical neurosurgery is tremor which may respond incompletely to medical treatment.

In the 50's and 60's stereotactical lesioning of globus pallidus internus (GPI, pallidotomy) and the ventral intermediate (VIM) nucleus of the thalamus (thalamotomy) was the mainstay of treatment for Parkinson's disease. After Levodopa became available, the need for surgical interventions initially greatly diminished. However, longterm motor complications of Levodopa led to their revival with the development of DBS in the 80's. DBS was approved by the FDA as early as 1982. In the following decades DBS proved not only to be effective in Parkinson's disease, but also in other movement disorders such as tremor and dystonia. Worldwide more than 100,000 patients (in Switzerland several hundreds) have been treated with DBS so far [1]. DBS is a stereotactical procedure in which basal ganglia nuclei, for instance, the subthalamic nucleus (STN) or GPI, are stimu-

lated with electric impulses delivered through implanted metal electrodes. The electrodes are connected to leads running subcutaneously from the impulse generators placed in the subclavical region. There are several advantages of DBS. Intraoperative testing allows optimal placement of the electrodes. Furthermore, stimulation parameters can be adjusted individually to achieve best clinical response. Finally, DBS is basically a reversible procedure. In contrast to the earlier thalamotomies and pallidotomies DBS does not produce permanent lesions. However, DBS is an intervention that requires open surgery with the known risk factors such as infections and haemorrhages (about 2%).

With the advent of precise stereotactical targeting the neuroanatomical knowledge of the pathophysiology of movement disorders has improved in recent years. Based on this progress the significance of functional neurosurgery has markedly increased and new techniques such as the MRIgFUS have emerged. MRIgFUS is a non-invasive procedure that ablates neural targets by ultrasound-controlled thermocoagulation (so-called sonication), thereby saving the surrounding brain tissue. The main advantage of MRIgFUS is that no open surgery of the skull is required. The most important disadvantage of MRIgFUS is its irreversible nature, similar to the older thalamo- and pallidotomies. Therefore, if side effects occur, they are permanent. However, MRIgFUS allows for testing to a certain extent for wanted effects (e.g., suppression of tremor) and unwanted side effects (dysarthria) by real time reversible inhibition of the target region. This is achieved by the application of lower energies, that is, of lower temperatures at about 50°C. Nonetheless, this procedure should be considered experimental at this stage. Lastly, it should be mentioned that MRIgFUS bears some risk of haemorrhage, although this complication is rare.

MRIgFUS proved to be a valuable and safe treatment in chronic pain as shown in phase I studies [2]. Furthermore, potential applications have been broadened to various movement disorders. Accordingly, two pilot studies have been recently published for essential tremor [3, 4]. In these two highly publicised but very small sample-sized open studies (including a total of 19 patients), tremor improved by 75 to 80% yet about a quarter of patients (5/19) exhibited persistent paraesthesias. So far, over 160 patients have been treated worldwide with MRIgFUS in the brain and preliminary results seem promising. However, for Parkinson's disease no published data is available yet. In Switzerland single centres offer the intervention for Parkinson's disease with the approval of Swissmedic and of the responsible ethic

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committees. Controlled longterm data on the efficacy and side effect profiles are not available and MRIGFUS has not been compared to other lesioning procedures such as gamma-knife or the older, but still used thermocoagulation. Additionally, it should be emphasised that experiences with earlier pallidotomies showed that bilateral interventions (often needed in Parkinson's disease) are associated with a high risk of permanent dysarthria and cognitive impairment. Furthermore, MRIGFUS has not yet been applied to STN, the most important target in Parkinson's disease. Finally, the costs are not covered by health care insurance.

Based on the current knowledge, MRIGFUS is still an experimental therapy. Therefore, from a neurological point of view, this intervention should only be applied if monitored with carefully controlled studies. Furthermore, the care by an interdisciplinary team is imperative, ensuring detailed examinations before and after the intervention.

At this stage, DBS remains the gold standard of functional neurosurgery for movement disorders. MRIGFUS in established targets should be considered as an alternative, if DBS is not an option for medical reasons or if the patient explicitly prefers an irreversible intervention. Controlled studies are needed to finally clarify the clinical value of MRIGFUS.

References

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