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MRI-guided focused ultrasound (MRgFUS) in the treatment of movement disorders

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Movement disorders such as essential tremor and Parkinson disease are steadily on the rise worldwide and can significantly reduce quality of life. Medication is often associated with severe side effects and not always effective. For many tremor patients, interventional procedures such as MRI-guided focused ultrasound (MRgFUS) offer a new and effective treatment option.

Essential tremor

With a prevalence of 0.4% to 5.6% in people 40 years and older, essential tremor is one of the most common movement disorders. In most cases, the disease progresses slowly and in mild stages affects mainly the upper extremity; as the disease worsens, the lower extremity, voice, and trunk may also become afflicted. This is characterized by postural and intention tremor that often makes many everyday actions impossible, depending on the severity. Almost all tremor patients suffer from restrictions in their social life, and in about 25% of patients the tremor necessitates a change in occupation or even early retirement. The precise pathophysiologic origin of the disease is not fully known, but a dysfunction in both the midbrain, cerebellum, thalamus, and the network of these structures has been suggested.

Parkinson disease

This disease is characterized by progressive degeneration of dopaminergic neurons in the substantia nigra and other nuclear regions. The typical symptoms of the disease, such as akinesia, tremor and rigor, are caused by the resulting dysfunction of the basal ganglia loops and other pathways. Despite the best possible medication, in advanced stages of the disease the tremor can be so severe that it markedly impairs the quality of life (tremor-dominant type).

Therapeutic options to date

Essential tremor can be treated with any of a number of medications. The beta-blocker propranolol and the anticonvulsants primidone and topiramate are considered first-line agents. However, the side effects of drug treatment are common and have up to 30% of patients discontinuing their treatment. For example, treatment with propranolol may result in bradycardia, syncope and fatigue. Possible side effects when taking primidone include nausea; dizziness; fatigue; ataxia; and depression. Moreover, if the tremor is severe, drug treatment often does not effectively control symptoms.

Treatment of tremor-dominant Parkinson disease can be challenging. The first line of treatment is levodopa and other dopaminergic drugs such as dopamine agonists. Drug selection is based on individual patient characteristics such as age; tremor severity; tremor response to levodopa; cognitive status; and other factors. Selected patients may benefit from treatment with

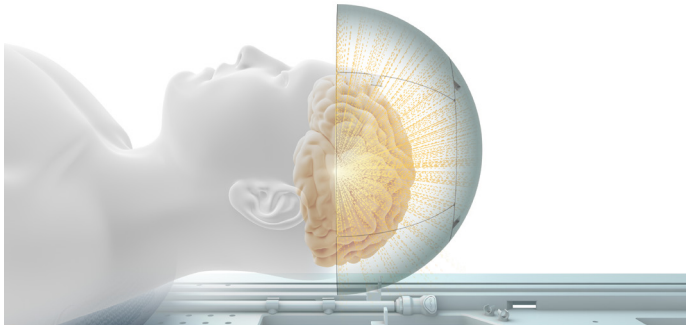
anticholinergics, e.g., trihexyphenidyl; clozapine, a neuroleptic; clonazepam, a benzodiazepine; or propranolol, a beta-blocker. Side effects limiting further dose increase or a good effect on tremor may be seen with any medication. For levodopa, these include postural hypotension, confusion, or hallucinations, and for dopamine agonists, they include dizziness; sleep attacks; fatigue; and impulse control disorders. Side effects of second-line therapeutics include memory impairment and hallucinations for anticholinergics, agranulocytosis and hypotension for clozapine, and sedation and memory impairment for clonazepam. Second-line therapeutics, in particular, are useful only in selected patients.

In Germany, standard treatment may take two avenues - medication or deep brain stimulation (THS). This involves stereotactic placement of stimulation leads into specific nuclear regions of the brain. Tremor is treated by high-frequency stimulation (around 130 Hz) either in the ventral intermedius nucleus (VIM) of thalamus (in essential tremor and Parkinson disease) or in the subthalamic nucleus (STN, in Parkinson disease). The region to be targeted is determined by the individual characteristics of each patient. The high-frequency stimulation is provided by a subcutaneous pulse generator, usually implanted below the clavicle, and transmitted via subcutaneous extensions to the tip of the leads in the brain.

This procedure, although invasive, usually provides good outcomes. Bilateral implantation reduces tremor in both sides of the body by approximately 80%. The long-term effect over more than 15 years has been well documented in many studies. By increasing the intensity of stimulation to compensate for disease progression, younger patients in particular can benefit from deep brain stimulation. However, for some patients this procedure is not an option. For example, blood vessels in the planned passage of the lead may make DBS too risky. Anticoagulants may also interfere with surgery. Moreover, patients biologically older than 75 years run a higher risk of surgery due to the invasiveness of the procedure. Potential side effects such as bleeding, infection, and hardware problems affect less than 2% of patients, but represent important risks that must be considered in the decision-making process by both the physician and the patient regarding the indication of this procedure.

MRgFUS – a new modality

MRI-guided focused ultrasound is a thermal and less invasive procedure than deep brain stimulation. It does not require open surgery on the patient's skull. During MRgFUS, the patient's head is fitted with a cap containing more than 1000 ultrasound sources. When these numerous waves are focused in one point, the targeted tissue heats up. Adjacent brain tissue is spared as much as possible. In order to monitor the highly accurate focusing of the ultrasound waves, and thus the local heating, continuous MRI thermography is performed to control the temperature both in the targeted region and its surroundings.



The ultrasound waves are generated by more than 1000 ultrasound transmitters, focused at the point target with millimeter precision, and resulting in heating and necrosis of the region of interest in the brain. During this procedure, the scalp is permanently cooled by water.

Since the ultrasound sources can be controlled individually, the focal depth can be set between 5 cm and 22 cm and the cylindrical focus can vary between 2x2x4 millimeters and 10x10x3 millimeters in the brain region so treated.

In the targeted region, the ultrasound energy is converted into thermal energy, resulting in temperatures exceeding 60 degrees Celsius, which causes protein denaturation and coagulation necrosis in the targeted region. Exact monitoring and pinpoint focusing allow the adjacent structures to be spared in this procedure.

MRgFUS workflow

The skull must first be scanned by computed tomography (CT) so that the permeability of the skull to ultrasound waves can be calculated to ensure that the temperature reached during treatment will be adequate. In addition, MRI of the brain is required to identify the target region prior to treatment. In order to improve the effect and reduce side effects, MRI 'fiber tracking' is now employed routinely to visualize the relevant fiber tracts. Fiber tracking refers to the visualization of fiber bundles connecting functional centers in the brain. Treatment centers using this modality for target planning were able to significantly improve their outcomes. The patient's scalp must be shaved prior to treatment to avoid skin burns from trapped air bubbles and to identify possible scars on the scalp hidden under the hair. For the treatment, the patient's head is secured in a stereotactic frame under local anesthesia. In addition, a rubber membrane allowing continuous water cooling of the head must be put in place. The patient is then positioned on the MRI couch with the cap containing the ultrasound sources positioned above the patient's head.

During treatment, the patient is fully conscious while vital signs are monitored. Medication against nausea and restlessness can be administered as a supportive measure. Treatment is applied in 3 phases under continuous neurological monitoring:

Phase 1: Here, it is first checked to see if the selected target area matches the actual heated brain tissue at low energy input.

Phase 2: This is followed by a temperature increase to 47–52°C to verify that this is the optimum target point. At these temperatures, there is a reversible loss of function of the affected cells, so that both the effect and the side effects can be identified.

Phase 3: The actual thermal ablation takes place using 500–1,000 watts of sonic energy, creating a temperature of 57–63 degrees Celsius in the target region. This may also result in a brief sensation of pressure in the skull.

All in all, the treatment, including fixation of the frame and positioning on the MRI couch, takes about three hours. The crucial treatment step, thermal ablation in phase 3, takes only 15-25 seconds and is usually repeated. The effect of treatment is immediate, so patients can experience the success right away. MRgFUS treatment is multidisciplinary with the participation of neurosurgery, neurology, anesthesiology, and neuroradiology.

Clinical application of MRgFUS

At present, MRgFUS is routinely applied unilaterally, so that tremor is reduced on only one side of the body. The effect on arm tremor is comparable to deep brain stimulation (approximately 80-90% reduction in tremor). More than 10,000 patients worldwide have

been treated with this procedure. Long-term data over 5 years has shown a sustained therapeutic effect. Current trials are studying bilateral applications. In general, side effects are rare, usually mild, and remit within a few months after MRgFUS treatment. There are no side effects such as bleeding and brain infection, as the skull does not have to be opened. MRgFUS is a good treatment option for patients with essential tremor or tremor-dominant Parkinson disease in whom the tremor is mostly unilateral, who are older and whose disease progresses slowly. If the ongoing trials prove that bilateral MRgFUS treatment is useful, this could result in a paradigm shift in the future. On the whole, optimal treatment should be selected for each patient on an individual basis and involve a multidisciplinary team.

The future of MRgFUS

MRI-guided focused ultrasound is an innovative modality with few side effects and is well established in the treatment of tremor. The German Neurological Society (DGN) and its partner organizations from Austria and Switzerland recommend this treatment in their guidelines for the treatment of essential tremor (ET). Recent studies have also demonstrated a good risk-benefit ratio for Parkinson disease patients with marked unilateral symptoms such as rigor and akinesia, and in patients with fluctuating effects. Current studies are investigating the optimal target (subthalamotomy versus pallidotomy), bilateral application, and long-term effect. The outcomes of these studies will provide further insight into which type of treatment should be primarily recommended for patients with advanced Parkinson disease. At present, MRgFUS in patients with fluctuating effects in Parkinson disease and markedly unilateral symptoms offers another effective modality that can be addressed in individual patient counseling - apart from pump therapy and deep brain stimulation - if the best possible medication is not effective enough.

In addition to MRgFUS treatment of tremor and Parkinson disease, patients with (focal) dystonia, dementia, epilepsy, and neuropathic pain syndrome are also treated, primarily as part of clinical trials. Preliminary study outcomes for the treatment of focal dystonia have demonstrated a positive effect of MRgFUS treatment. Additional study findings will allow a better classification of the therapeutic effects in the above diseases.

Treatment steps in MRgFUS

Treatment involving an invasive procedure generally requires detailed information of the patient and completion of the necessary prior examinations to identify any potential risks. The first step should be a consultation with the neurologist to discuss possible treatment options (further optimization of drug therapy, deep brain stimulation, MRgFUS, possibly other treatment options). This should be followed by contacting a specialized center offering MRgFUS treatment. In Germany, the procedure is currently being performed at the University Medical Centers in Bonn and Kiel. This therapeutic modality will also be offered at the Paracelsus-Elena Klinik in Kassel sometime in the first quarter of 2023. Taking into account the characteristics of each patient and performing the necessary prior examinations (MRI of the brain; CT of the skull; coagulation tests; detailed examination with disease-specific scales; possibly further examinations), MRgFUS is a promising approach with lasting therapeutic success.

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