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Evolution of Movement Disorders Surgery Leading to Contemporary Focused Ultrasound Therapy for Tremor

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HISTORY OF MOVEMENT DISORDERS SURGERY

Gildenberg[1] describes five major epochs in the evolution of modern movement disorders surgery: the prestereotactic era before 1947, (2) the early stereotactic revolution between 1947 and 1969, (3) the latent period after the introduction of levodopa in the 1970s and 1980s, (4) the stereotactic revival of ablative surgery in the 1990s, and (5) the current modern period of deep brain stimulation. At present, with the advent of high-energy transcranial focused ultrasound, movement disorders surgery may be about to enter a sixth epoch. This article traces the historical progression of movement disorders surgery from early open craniotomy to the so-called incisionless image-guided ultrasound surgery that is now being developed to treat ET. It also describes relevant history of focused ultrasound and a few general principles that have allowed neurosurgeons to treat intractable tremor with acoustic ablation.

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The Prestereotactic Era

An early experimental understanding of motor systems began in the late 1800s, when Fritsch and Hitzig[2] conducted the first investigations into mammalian motor circuitry by applying local electrical stimulation to the cortical surface in dogs. Based on this pioneering work, Horsley, in 1909, resected a portion of the contralateral precentral gyrus in a 15-year-old boy for the treatment of postcarlatina hemiathetosis but acknowledged in later reports that these procedures often resulted in severe paralysis and paresis.[3,4] Hoping to alleviate tremor without weakness, Horsley and Clarke[3] attempted to target specific structures outside primary motor centers, for example, the deep cerebellar nuclei and other subcortical structures. They used the first skull-mounted stereotactic frame using external landmarks to guide slender probes and initiated the first use of discrete electrolytic lesions. The goal of these elegant preclinical investigations in the monkey was to find areas in the brain where small lesions could be accurately placed to control unwanted movements but not abolish movement altogether. This pioneering work in intracranial stereotaxy had to wait until the 1940s to finally be applied to human surgery (see later discussion).

Although Horsley and Clarke[3] laid the groundwork for an understanding of nonprimary motor areas in the brain, other investigators were beginning to study extracranial approaches to abnormal movements. As early as 1908, Foerster[5] reported posterior rhizotomy for control of spasticity and rigidity, leading others to try sympathetic ramisection and various ganglionectomies for similar indications throughout the 1920s and 1930s.[6,7] During this same period, surgical interest in open craniotomy for ablation of primary cortical structures continued despite permanent loss of function and high mortality. For example, Bucy and colleagues[8–10] continued to report their series treating athetosis and parkinsonism with ablation of both the supplementary and primary motor cortices despite accruing evidence from Meyers[11–13] and others that lesions confined strictly to the extrapyramidal system controlled tremor without weakness. Meyers reported excellent tremor control in a patient with hemiparkinsonism by resection of the contralateral caudate head through a transventricular approach, confirming that the basal ganglia is a viable extrapyramidal target for tremor. For other patients, Meyers also explored sectioning of the anterior internal capsule, ansa lenticularis (ansotomy), and internal pallidum. Despite the success of these transventricular extrapyramidal operations, postoperative mortality was never reduced less than 10%, deterring others from adopting similar free-hand transventricular approaches.[14] Nevertheless, Meyers' contributions clearly showed that basal ganglia lesions could effectively treat tremor without causing paralysis or coma. These decisive observations set the stage for future stereotactic surgical methods in targeting extrapyramidal subcortical structures for the treatment of refractory movement disorders.[14,15]

The Early Stereotactic Revolution

It was not until after 1947, when Spiegel and colleagues[16] described a procedure to ablate discrete targets in the human brain using a modification of the Horsley-Clarke frame, that the era of stereotactic surgery clinically emerged. The major advantage of their approach was the use of indirect internal landmarks based on ventricular encephalography to identify particular sites in the brain, making it possible to introduce a probe through a small burr hole to the intended target without the need for direct open visualization. The first stereotactic

operation was for the treatment of Huntington chorea in which alcohol injections were made into the pallidum and dorsomedian nucleus. Frame-based stereotaxy opened new doors for further exploration of other subcortical targets and ushered in a remarkably innovative period during which a variety of lesioning methods were explored, including chemical, cryo, thermal, physical, and ionizing energy methods.[17] Stereotaxy improved surgical safety, dramatically reducing the 10% to 15% mortality rates previously reported for open approaches to less than 1% by 1950.[18]

Target discovery was the major development of movement disorder surgery during this early exploratory period, and stereotactians focused predominantly on alleviating tremor and rigidity associated with Parkinson's disease. Based on Meyers' observations, several groups in the United States developed operations that lesioned the pallidum and/or its associated efferent tracts.[19–21] Other groups working in France[22,23] and Germany[24,25] found that lesion of the motor thalamus, the downstream target of the pallidum, produced complete arrest for virtually any type of tremor, including rest, intention, and postural types. Hassler and Riechert[24,26] refined the subnuclei nomenclature and boundaries of this part of the ventrolateral thalamus and, together with others, defined and demonstrated the small subnucleus they called the Vim nucleus (Vim) as the most effective antitremor target in the brain. This part of the thalamus links the deep cerebellar nuclei to the motor cortex and still remains the most common target used for the treatment of ET (see later discussion). The demonstrated safety of the stereotactic approach coupled with the discovery of symptom-specific targets set the stage for a short-lived heyday of stereotaxy during a golden period in the 1960s. Surgeons worldwide readily adopted the stereotactic methods as reflected in the large numbers of patients treated. By 1965, approximately 25,000 operations had been performed, and Spiegel[27,28] estimates that this number increased to approximately 37, 000 by 1969, the same year that Cotzias introduced levodopa.[29]

The Latent Period After the Introduction of Levodopa

During the early 1970s, levodopa advanced as the primary treatment method for disease, and the number of patients referred for surgery declined precipitously. This development, coupled with growing public discussions over psychiatric surgery,[30] led many surgeons to stereotactic interventions altogether by the early 1980s. Only a handful of centers maintained their stereotactic capability through this gloomy period,[31] treating a small number of refractory parkinsonian cases and other types of tremors. However, within a few years of its introduction, the enthusiasm for levodopa therapy was checked by the development of chronic drug-induced side effects. Severe peak-dose dyskinesia and end-dose freezing began to be widely reported in patients with long-term administration of levodopa.[32] Oddly, these so-called on-off effects would be the salvation of modern movement disorders surgery a few years later.

The Stereotactic Revival

In 1992, Laitinen[33,34] showed that the classic posteroventral pallidotomy not only controlled the cardinal motor manifestation of disease but most extraordinarily also abolished the effects of prolonged levodopa exposure.[35] The finding that an old ablative procedure treated not only the disease but also the problems associate with the side effects of the medicine to

treat the disease was something of a renaissance moment for movement disorders surgery. Laitinen's findings rekindled the movement disorders neurologist's interest in surgery. At present, the major indication and common time for a surgical referral in patients with Parkinson's disease occurs at the onset of uncontrolled and unpredictable effects.[36] In addition to Parkinson's disease, neurologists increasingly began to refer patients with dystonia[37,38] and the more-difficult-to-treat tremors including poststroke, multiple sclerosis, and ET.[39,40] This clinical revival of ablative stereotaxy came when deep brain stimulation (DBS) was beginning to gain recognition and, probably to a large extent, was one of the major drivers leading the remarkable success of the modern DBS.[41]

Modern Period of Deep Brain Stimulation

In general, contemporary targets for DBS for both movement disorders[42] and psychiatric indications[43] were derived from the same targets historically used for ablations. However, this recent period has also seen the discovery of novel targets for movement disorders surgery for Parkinson disease in the form of the subthalamic nucleus[44,45] and the pedunculopontine reticular formation.[46,47] Although the DBS mechanisms are incompletely understood, high frequency stimulation (>100 Hz) manifests functionally in the same way as a lesion. Neurosurgeons have, for some time, used intraoperative high-frequency stimulation at the intended target to predict whether a lesion would be effective.[48] The primary practical advantage of DBS over ablative procedures is usually said to be the ability to refine the physiologic postoperative response by changing electrical stimulation parameters. DBS is adjustable and reversible, whereas lesions are not. On the other hand, a well-placed lesion avoids implantation of hardware, concomitant risks of infection, and breakage that are associated with DBS.[49]

Several studies with class I level evidence confirmed the long-term control of the cardinal manifestations of essential and parkinsonian tremor,[36] and in 1997 and 2001, the US Food and Drug Administration approved DBS in the United States for ET and parkinsonian tremor, respectively. Despite its high cost, DBS has now virtually replaced lesion surgery as the dominant stereotactic surgical method in most movement disorders centers; this is in part because of better outcomes when examined head-to-head[50,51] and also because its seems that traditional radiofrequency lesion surgery carries a higher rate of complications.[52]

Despite several modern refinements in image guidance and target refinement, both conventional lesion surgery and DBS essentially rely on the same basic stereotactic principles introduced in the late 1940s. In particular, both require passage of probes through the skull and intervening brain to the desired target, and even though rates of complication in modern series are low, it may be possible to achieve substantially similar outcomes using completely noninvasive technology. High-energy transcranial focused ultrasound has emerged for the treatment of tremor, and a few proof-of-concept studies ablating the Vim nucleus for ET have been encouraging.

DEVELOPMENT OF INTRACRANIAL FOCUSED ULTRASOUND SURGERY

MR-guided focused ultrasound (MRgFUS) aims to efficiently transmit ultrasound through the intact skull without excessive bone heating, (2) monitor tissue thermal changes, (3) use

imaging to verify lesion location, and (4) confirm treatment efficacy through intraoperative clinical testing in an awake patient. Before its application in humans, MRgFUS was extensively safety tested in animal models, including rabbit[53] and primate.[54,55] MRgFUS accomplishes ultrasound delivery through an array of piezoelectric transducers (ie, a helmet containing approximately 1000 individual transducer elements). The transducers deliver a focused epicenter of high-frequency acoustic energy to a small volume of target tissue while avoiding significant bone heating by dispersing the incident acoustic energy over a large cranial surface. In addition, chilled degassed water runs between the transducer helmet and skull surface, actively cooling the scalp. The transducer array is paired to computed tomography (CT) software that corrects for variability in cortical bone thickness and acoustic impedance that can lead to focused ultrasound (FUS) wave distortion.[56] This computational ability is the key conceptual element allowing precise transcranial acoustic energy delivery. Small lesions are usually created for ablating most nuclear targets for movement disorders and chronic pain syndromes. However, larger volumes, such as tumors, require longer treatment times and multiple overlapping lesions.

MRgFUS incorporates tissue thermometry monitoring to precisely assess lesion shape and temperature increase. Several MR parameters are sensitive to changes in temperature, including T_1 and T_2 relaxation times, proton resonance shift, and diffusion.[57] The proton resonance shift method is the clinical standard for thermal monitoring and regulation. MR thermometry also detects pulses. Low intensity FUS heats focal zone tissue to a few degrees less than ablation thresholds, acting as a control for planned focal sites. MRgFUS offers the unique advantage of real time lesion localization using standard MR imaging T_1 and T_2 sequences.

The first human work in the development of MRgFUS was a clinical attempt by McDannold and colleagues[58] to treat brain tumors at the authors' institution. In this study, CT:betw dates, 3 patients were treated for recurrent glioblastoma, with deep-seated and centrally located foci. A system equipped with 670 kHz frequency transducers in a 1.5-T GE (Fairfield, CT) MR imaging scanner was used. Focal area and skull bone heating were measured independently, although not all heating at every focal lesion site was measured. No undesired focal thermal elevations were detected. However, this study was halted after a fourth patient who was treated with a lower-frequency version of the device died because of intracranial hemorrhage of unknown cause. In the last year, this trial has resumed with the 650-kHz MRgFUS system.[59]

The second study using MRgFUS in humans was designed to produce small, well-circumscribed lesions in the normal brain. Central thalamotomies to treat chronic neuropathic pain were performed by Jeanmonod and colleagues[60] at the University Children's Hospital in Zurich.[61] CT:betw dates, 11 patients received thermally ablative lesions in the central lateral thalamus at maximum temperatures of 51 C to 64 C during short sonications. T_2 and diffusion-weighted imaging was used to visualize induced lesions 2 days postoperatively. The study notes that lesions were not detected in the first 2 patients. After the procedure, patients were assessed for pain using a visual analog scale (VAS) rating of pain intensity and detailed questionnaire (9 patients). Six patients reported immediate pain relief after the procedure. Mean pain relief after 2 days was 71% (9 patients), after 3 months

was 49% (3 patients), and after 1 year was 60% (8 patients). VAS pain intensity mean scores were 60 at 3-month follow-up and 34 at 1-year follow-up. One patient experienced bleeding in the target region (8–10 mm diameter), leading to dysmetria and dysarthria that resolved within 1 year. No other significant adverse effects were reported.

Intracranial Focused Ultrasound: Proof of Concept Treating Essential Tremor

In 2009, the makers of the intracranial focused ultrasound system (InSightec, Inc, Tirat Carmel, Israel) partnered with Elias and colleagues[62] at the University of Virginia to plan for pilot clinical studies in the United States for an intracranial ultrasound procedure. ET was selected as the first treatment condition on which to focus because the clinical outcome (tremor severity) could be quantified objectively and because the historical success in treating the condition surgically had been well established.

ET is the most common movement disorder, affecting up to an estimated 4% of the general population.[63] Although the cause remains largely unknown, about half of all cases are familial, and transmission is most consistent with an autosomal dominant mechanism. No specific gene defect has yet been reported, but certain chromosomes have been implicated by linkage studies.[64,65] The tremor is postural, characterized by rhythmic oscillations (8–12 Hz) between opposing muscle groups and is exacerbated by movement.[66] ET progresses slowly over time and can lead to significant disability.[67] Although medical treatments are available to most patients, an estimated 25% to 30% of these patients cannot tolerate medication or become refractory to recommended treatment doses.[68] First-line oral medications typically include beta-blockers such as propranolol or anticonvulsants, particularly primidone. When the tremor progresses despite adequate oral therapy, surgical ablation or DBS of the Vim nucleus is indicated.

Three open-label clinical trials have illustrated the safety and efficacy of transcranial MRgFUS thalamotomy for refractive ET. Elias[62] evaluated 15 patients with severe, medication-refractory ET for unilateral treatment targeting the Vim nucleus of the thalamus. Patients were assessed post procedure for the safety and efficacy of tremor suppression using the Clinical Rating Scale for Tremor and the Quality of Life in Essential Tremor Questionnaire. All 15 patients reported significant improvement in their dominant hand tremor symptoms and quality of life scores 1-year post thalamotomy. Adverse effects of the treatment included transient cerebellar, motor, and speech abnormalities. Four patients reported persistent minor paresthesias after 12 months. T_2 and diffusion-weighted images were used to visualize acute lesions. Perilesional vasogenic edema was detected after 24 hours and 1 week but resolved within 1 month. At 3-month follow-up, punctate thalamic lesions were detectable in all cases and there was no evidence of hemorrhage on susceptible weighted images.

In Canada, Lipsman and colleagues[69] performed a separate proof-of-concept study in a small cohort of 4 patients with severe refractory ET. The study reported that initial clinical improvements in tremor appear at 50 C sonication, with tremor improvement after each cycle. The number of sonications delivered until tremor disappearance ranged from 12 to 29 over the course of 5 to 6 hours. At 1-month follow-up, reduction in the dominant arm tremor was 89% and reduction in motor-task impairment was 46%; at 3-month follow-up, these

were 81% and 40%, respectively. Two patients reported paresthesia development during the procedure, and another patient had paresthesia in the tips of the thumb and index finger at 3-month follow-up. One patient developed deep vein thrombosis in the lower limb approximately 1 week after therapy. No other adverse effects were reported.

At the Yonsei University College of Medicine in Seoul, Chang and colleagues[70] reported successful treatment of ET using MRgFUS. The study was conducted in 11 patients with medication refractory ET. Of the 11 patients, 8 completed treatments; 3 patients did not because of insufficient temperature levels. Treated patients reported immediate improvement in tremor symptoms, which lasted through the 6-month follow-up point. A few patients reported bouts of dizziness during treatment; 1 patient reported delayed postoperative balance. No patients reported permanent adverse events.

SUMMARY

Transcranial MRgFUS represents a significant milestone in the history of stereotactic ablative surgery and the development of ultrasound technology. MRgFUS has been evaluated in preclinical animal models and clinical studies and was determined to be safe and effective for Vim thalamotomy for up to 1 year in patients with ET. If the perceived safety profile of the procedure is realized following expanded clinical trials with longer follow-up, surgeons and clinicians may increasingly prefer MRgFUS as the initial treatment modality for patients with ET. Nevertheless, there are concerns that bilateral treatment may produce dysarthria, and no center has yet addressed the problem of continued tremor progression on the untreated side.

In addition to being noninvasive, MRgFUS has several other appealing features, including an instantaneous treatment effect that is free of ionizing radiation. In theory, the treatment could be repeated multiple times. Perhaps the most valuable aspect of the procedure is that MR guidance can provide real-time feedback to guide lesion position and size. Future directions using MRgFUS in movement disorders surgery will probably include explorations of other targets such as the pallidum and the subthalamic nucleus and its surrounding fiber tracts to treat levodopa induced dyskinesias and the primary dystonias. There are a large number of potential intracranial applications of the technology in addition to those of movement disorders. For instance, vascular, neuro-oncologic, and psychiatric indications are just now beginning to be explored. This elegant noninvasive technology will probably secure regulatory approval and clinical acceptance through strong evidence-based efforts gained in treating refractory ET. Ongoing refinements in computational and acoustic technology should allow high energy lesions or low-energy neuromodulation to be targeted to virtually any point in the neuroaxis, further opening wide vistas for human brain exploration.

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KEY POINTS

- Historically, patients with tremor of various causes, including essential tremor (ET), parkinsonian rest tremor, and action tremor, have been treated with stimulation or lesions placed in the ventrolateral thalamus.
- The most effective antitremor target in the brain may be the ventrointermedius (Vim) nucleus of the thalamus, a small subnucleus of the ventrolateral thalamus.
- It is now possible to create a lesion in the Vim nucleus using magnetic resonance (MR) imaging– guided high-energy focused ultrasound in a patient who is awake without a skin incision or craniotomy.