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Focused Ultrasound: Doing Damage So As To Heal

Innovative treatments that actually involve damaging certain parts of the brain may represent some patients' only chance for recovery.

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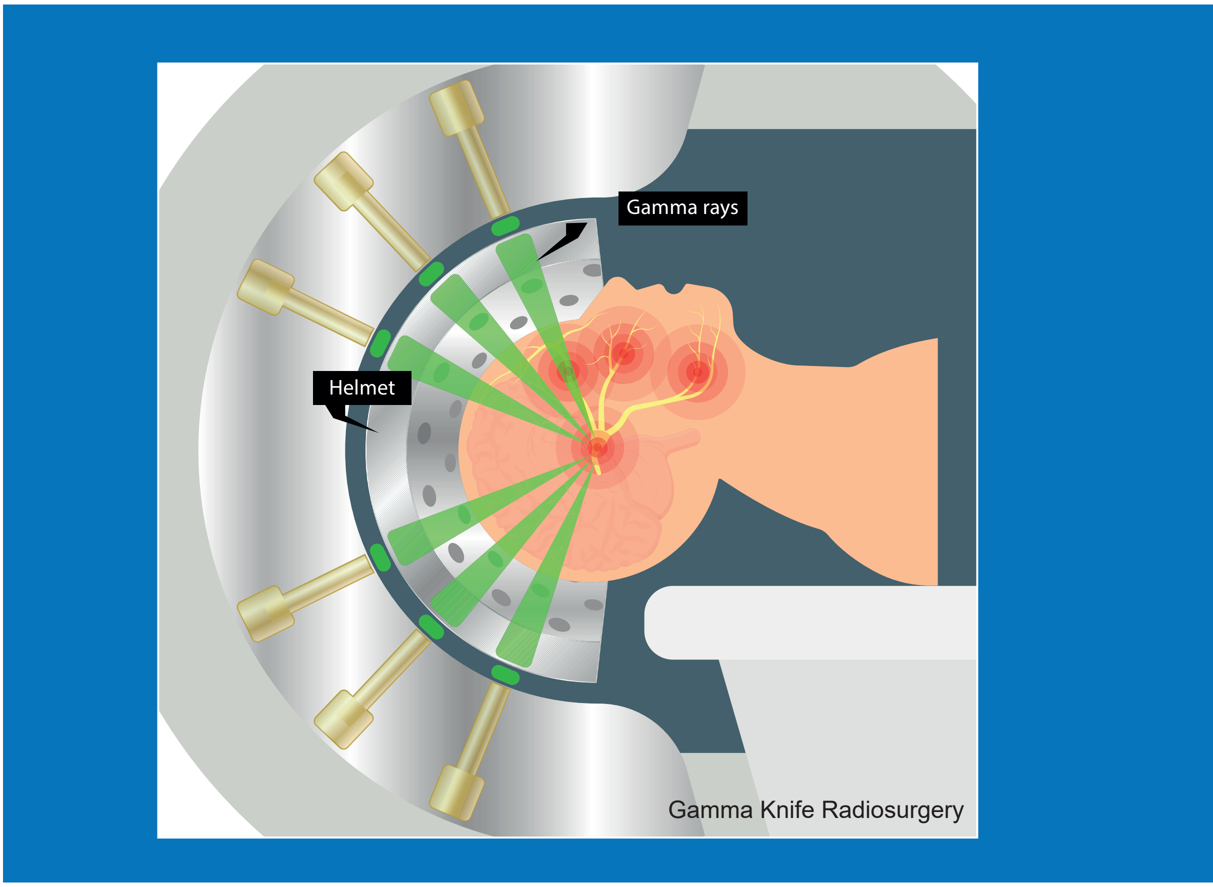

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Advances in technology develop in parallel to those in medicine, with the two fields propelling and inspiring each other. Consecutive innovations in the area of wireless networks, robotics, and miniaturization provide opportunities to implement new programs for advanced diagnostics and therapy, and biological discoveries redirect the interest of biotechnologists towards new areas, thus inspiring researchers to create tools that can be applied in patient care.

In daily clinical practice, we can observe a trend toward increasingly personalized therapies, with their simultaneous standardization and reproducibility, verifiable in terms of effects. In certain conditions, knowledge of a patient's genetic profile makes it possible to select a targeted therapy that may have better and longer-lasting effects. In turn, knowledge of the human body and numerous pathophysiological pathways underlying diseases makes it is possible to combine preparations with different mechanisms of action into a single drug, translating into significant benefits. For example, the dose of each component can be reduced, which lowers the risk of adverse reactions. In addition, this improves adherence to treatment, as patients are encouraged by a simpler regimen that involves taking one pill instead of several.

Treatment methods

Surgical fields of medicine also benefit greatly from technological advancement. Miniaturization of equipment and the development of powerful optical systems provide the basis for a growing number of minimally invasive procedures. This is especially a chronic when

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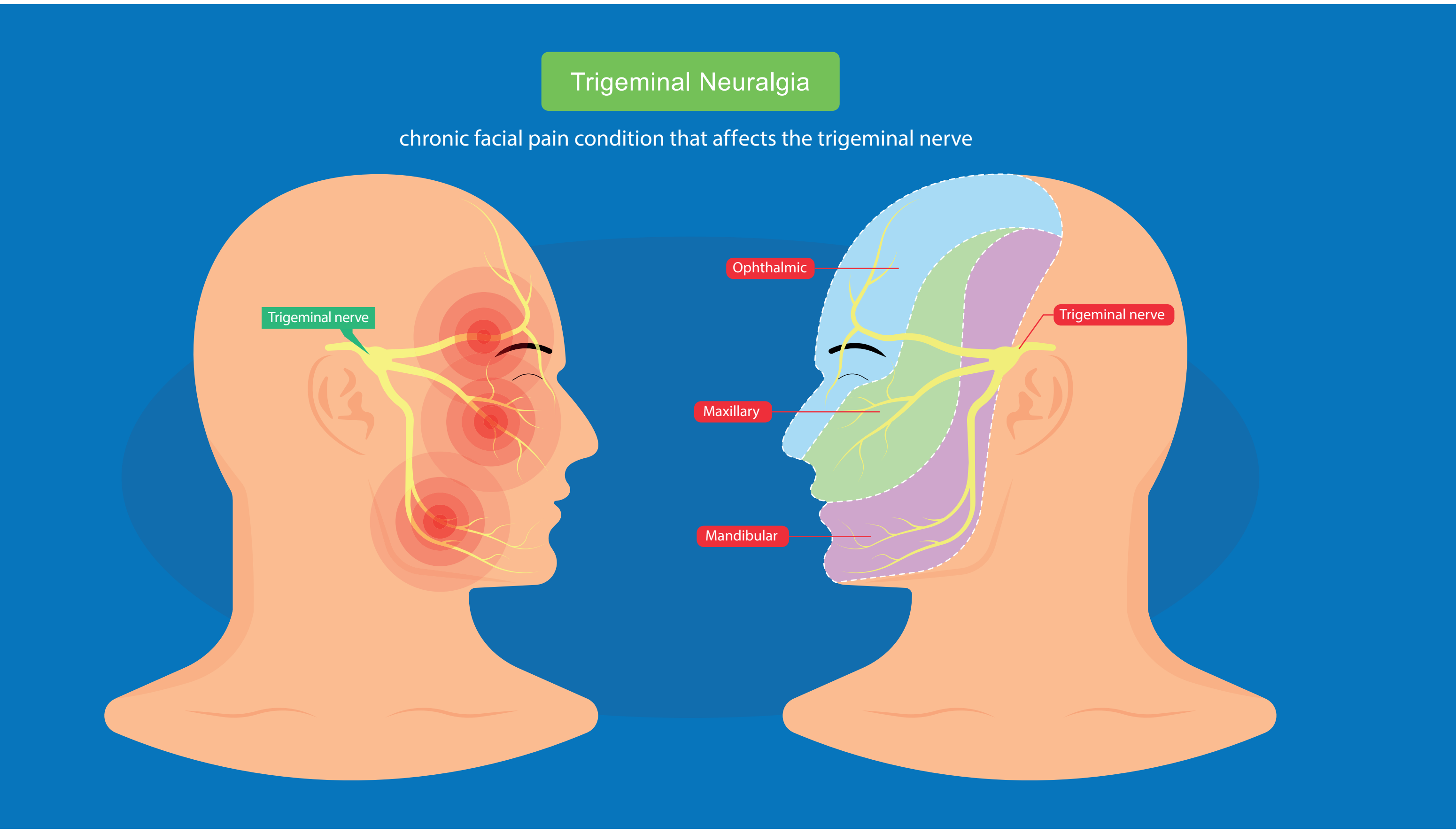

the prospect of undergoing an open surgery presents an insurmountable psychological barrier for many patients, causing them to opt out of treatment. A not insignificant role is also played by a shorter hospital stay, reduced recovery time, and reduced scarring after the surgery, which many patients find important.

In surgery, the most compelling procedures are those performed on the brain. In the common understanding, brain surgery continues to be shrouded in mystery – after all, it involves interventions in an organ that is crucial for the very essence of our human existence: our perceptions, thoughts, and feelings. Hence, the concept of "remote" treatment of brain diseases, without the need to penetrate its delicate structure, has been pursued for decades. The discovery of radioactivity, followed by the development of detailed brain imaging techniques, touched off the development of the extensive field of stereotactic radiosurgery, which occupies an important place in the treatment of central nervous system tumors thanks to such devices as the Cyber Knife and Gamma Knife (the use of gamma radiation to irradiate and destroy tumor cells with high precision). Over the past decade, another well-known physical phenomenon, namely ultrasound, has been investigated and developed rapidly for applications in functional neurosurgery.

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Functional neurosurgery is a branch of medicine that deals with the surgical treatment of primary disorders of the nervous system. It currently uses stereotactic techniques, which make it possible to stimulate or damage a specific target area in the brain after its precise identification. Long before the introduction of effective pharmacotherapy in the treatment of movement disorders, epilepsy, and certain psychiatric disorders, ablative brain surgery, which involves irreversibly damaging certain centers in the brain, was one of the basic methods offering a chance to reduce the symptoms of the disease.

In the 1950s, those techniques became marginalized as a result of the discovery of pharmacological agents that act on specific neuronal pathways. Another turning point in the treatment of movement disorders came in the 1990s with the introduction of deep brain stimulation (DBS), a procedure that involves the insertion of an electrode into a precisely defined area in the brain and its modulated stimulation, thus significantly reducing symptoms and improving the quality of life in patients with Parkinson's disease, among other disorders. DBS is a well-established procedure whose efficacy and safety have been confirmed over the years by many extensive publications.

Irreversible ablation

Ablative techniques, somewhat sidelined in the treatment of the disorders listed above for reasons related to their irreversibility, are experiencing a resurgence of interest among researchers and clinicians thanks to the use of focused ultrasound (FUS). The properties of high-intensity focused ultrasound (HIFU) have been known since the 1940s. In 1942, John G. Lynn and colleagues first used the thermoablative properties of HIFU (the ability to destroy cells using high temperature) on animals. They discovered that the successful destruction of target tissues depended on overcoming the strong resistance offered by the skull bones in the propagation of ultrasound. In the 1950s, the brothers William and Francis Fry first used FUS to treat patients with Parkinson's disease. As a result of the technological limitations of the transducers available at the time, the procedure could not be performed in a non-invasive manner. It involved performing a craniotomy (making a hole in the skull), which solved the problem of bone resistance. Nowadays, there are tools that make it possible to use FUS without classical surgical interventions in the patient's body. The procedure is also helped by magnetic resonance imaging (magnetic resonance-guided FUS, or MRgFUS) to pinpoint the area that should be thermoablated. The use of real-time MRI imaging improves the safety of the procedure. During the procedure, tissue temperature rises, which may lead to overheating, and MRI imaging acts as a thermometer.

The list of diseases that can be treated using FUS is constantly expanding. In addition to neurological disorders, this technique is used to treat uterine fibroids, cancerous bone metastases, prostate cancer, and benign prostatic hyperplasia. Among neurological disorders, FUS is most commonly used to treat essential tremor (ET). The disorder affects an estimated 5% of the population, which makes it the most common movement disorder affecting adults. It typically presents as a bilateral tremor of the upper limbs that worsens during movement. In a more advanced form, it can involve other parts of the body and also occur at rest. Essential tremor significantly reduces the quality of life for patients by making it a lot harder or sometimes impossible for them to perform daily activities. The condition has no identified cause. In nearly 50% of cases, it results from a genetic mutation. In such situations, it is called familial tremor. The absence of clear pathophysiology of the disease means there

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MRI-guided ablation of the ventral intermediate nucleus of the thalamus using a highly-focused ultrasound beam

is no causal treatment. The most important medications used to reduce the intensity of symptoms include beta-blockers, certain anti-epileptic drugs, and benzodiazepines. In some cases, if the symptoms cannot be controlled pharmacologically in an effective way, botulinum toxin is injected into the affected muscle groups. If there is still no satisfactory response to the therapy, this is an indication for neurosurgical treatment. The most commonly used procedure is DBS. Using methods that allow precise insertion of electrodes into a specific area of the brain, a mechanism is implanted that allows the stimulation or destruction of such brain regions as the ventral intermediate nucleus of the thalamus (VIM), which plays an important role in the pathophysiology of the disorder. In 2016, the US Food and Drug Administration (FDA) approved the use of MRgFUS to treat essential tremor. There are publications that confirm the efficacy of MRgFUS and, in certain clinical situations, compare it to that achieved by DBS.

The thalamic ventral intermediate nucleus is an attractive site in terms of surgical accessibility and susceptibility to MRgFUS damage – adequate depth and sufficient distance from the skull help limit interference and reflections of ultrasound waves from the bone. However, bilateral therapeutic VIM damage may lead to speech, motor, or cognitive deficits, usually of a transient nature.

Another group of patients in whom MRgFUS can be used are those suffering from Parkinson's disease and associated tremor.

Functional neurosurgery is also one of the methods used to treat some psychiatric diseases. Surgical procedures involving damaging specific structures in the brain were performed as early as the late nineteenth century to help patients with mania, dementia, and schizophrenia. One of the most infamous procedures in the history of psychosurgery is undoubtedly frontal lobotomy. Over time, it was regarded as unethical and unscientific, and for many years it cast a long shadow on the idea of surgical treatment of selected psychiatric disorders. The development of DBS in the late 1980s brought the attention of doctors back to the possibility of employing surgical procedures involving stimulating or damaging specific centers in the brain, for example in drug-resistant obsessive-compulsive disorder.

Focused ultrasound waves are also being explored for the surgical treatment of epilepsy. The use of such methods as DBS and Gamma Knife with good effects allows us to be optimistic about the results of therapies using MRgFUS.

A somewhat different issue related to FUS whose clinical usefulness is now under evaluation is the use of this method to create a temporary blood-brain barrier opening (BBBO). The procedure is expected to result in increased bioavailability of drugs and their easier penetration into the central nervous system. This problem poses a major challenge in immunotherapy and gene therapy, and its resolution would significantly improve the effects of the treatment of such diseases as malignant glioma, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease. It can also help personalize pharmacological treatment to an even greater extent and adjust the type of drug and its dosage to the needs of each patient.

Overall, modern minimally invasive neurosurgical techniques, including FUS, now provide important support in the treatment of diseases resistant to pharmacotherapy and offer a chance to reach areas of the brain where the surgeon's scalpel is not welcome. ■

Further reading:

MR-Guided Focused Ultrasound for Treatment of Tremor, https://my.clevelandclinic.org/health/treatments/21087-mr-guided-focused-ultrasound-for-treatment-of-tremor

Focused Ultrasound Opening Brain to Impossible Treatments, newsroom.uvahealth.com/2020/05/06/focused-ultrasound-opening-brain-to-impossible-treatments/