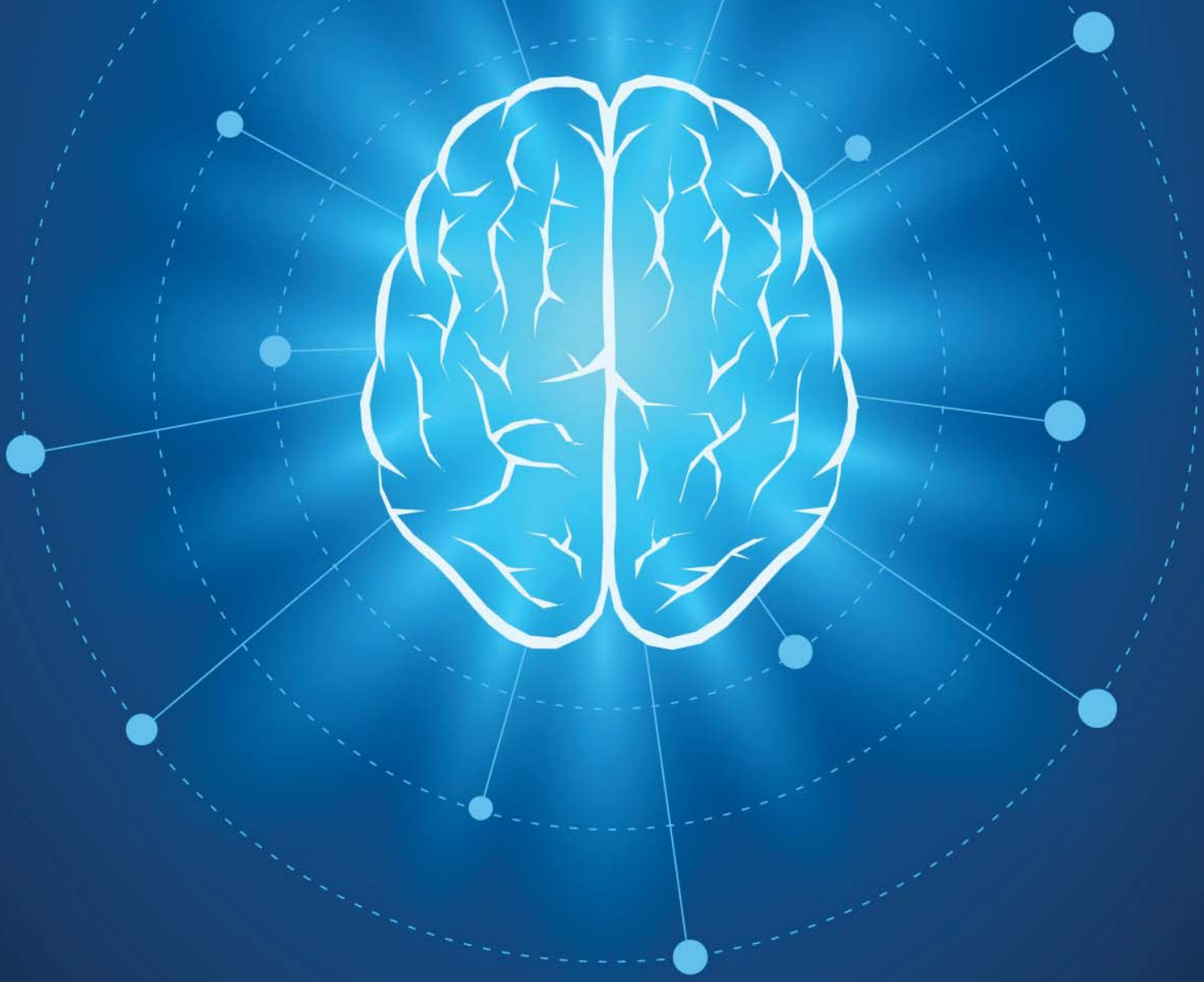
FUS THERAPY: Treatment of The Future

Using focused ultrasound and MRI instead of invasive surgery, doctors have succeeded in stopping tremors associated with ***PARKINSON'S DISEASE.***

BY RHONA LEWIS



In November 2013, at Rambam Health Care Campus, 73-year-old Sami Zangi, who suffered from ET (essential tremor, a neurological disorder that causes terrible trembling), became the first patient in Israel to undergo the surgical removal of deep-seated brain tissue through an intact skull. The innovative therapy was made possible by bringing together focused ultrasound ablation (scarring) and MRI (magnetic resonance imaging) technologies. It's less than a year and a half later, and thanks to this innovative technique, 33 additional ET and Parkinson's disease patients are now tremor free.

In this first-ever procedure, Zangi spent three hours wide awake inside an MRI machine, communicating with and monitored by senior neurologist Dr. Ilana Schlesinger, head of the Movement Disorders and Parkinson's Center, while Professor Menashe Zaaroor, director of the department of neurosurgery, used a computer mouse to direct 1,000 ultrasonic beams to the focal point on the thalamus, a mass of gray matter situated toward the back of the forebrain. It relays sensory impulses and motor signals to the cerebral cortex — the brain's outer layer of tissue. Essential tremor is caused by the neurons in the thalamus becoming overactive and firing in symmetry at several cycles per second. Making a lesion in the thalamus interrupts the circuit by cutting the neural pathway that causes the tremor — rather like cutting a wire.

This technology of applying ultrasound waves for noninvasive surgery was developed in Israel in 1999 by InSightec. "Since I didn't invent the technology, but just happened to be in the right place at the right time, I can boast about how wonderful it is," says Dr. Schlesinger with a warm laugh.

How Focused Ultrasound and Magnetic Resonance Imaging Work in Tandem

Focused ultrasound (FUS) provides the energy to treat tissue deep in the body precisely and noninvasively. Magnetic resonance imaging (MRI) first identifies and targets the tissue to be treated. Then it guides and controls the treatment in real time. Finally, it confirms the effectiveness of the treatment. "It's like using a magnifying glass to focus beams of sunlight on a single point to burn a hole in a piece of paper," says Dr. Schlesinger. "The ultrasound machine emits sound waves that warm up the tissues. (These sound waves are on a different wavelength from the high-frequency sound waves that you're familiar with and are used to create an image of some part of the inside of the body.) The patient wears a special helmet on his shaven head that directs multiple beams of ultrasound onto a target deep in the body," she explains. Depending on the design of the lens and the ultrasound parameters, the target can be as small as 1x1.5mm or as large as 10x16mm in diameter. While the commercial use of FUS in the brain is approved in Europe and Israel, approval is still pending in the United States.

Treating the Tremor

"Many people get so used to a tremor that they don't even go to a doctor to try and alleviate their suffering," says Dr. Schlesinger. "As the person gets older, the tremor worsens. But often, with simple medication, the tremor can be stopped."

Treatment of essential tremor for medicine-resistant patients involves an invasive surgical procedure known as deep brain stimulation. The procedure means inserting two electrodes deep in the two sides of the brain and a pacemaker in the chest. Not surprisingly, many potential patients are reluctant to undergo surgery. With the new available technology, the patient lies awake in the MRI machine for four hours while a lesion is made using FUS. "Treatment is carried out gradually, and since the patient is awake, we are able to monitor his functions in real time," says Dr. Schlesinger.

"Treating the right side of the brain stops the tremor in the left side of the body and vice versa," says Dr. Schlesinger. Adverse effects, like an unsteady gait or a disturbance in the sense of taste, disappear within two weeks to two months. "At this time, we aren't treating both sides of the brain. The reason for this is that, in the past, tremors were treated by creating lesions in both sides of the brain by using a device to mechanically warm up the affected area. Some patients found that they couldn't swallow or walk properly after the surgery," explains Dr. Schlesinger.

The technology is used to treat both essential tremor and Parkinson's disease. "Most of our patients have remained tremor-free," says Dr. Schlesinger. "Although in some Parkinson's patients, the tremor has returned, but not as severely as before."

And what does the future hold? "We hope to use FUS to treat epilepsy and brain cancer," says Dr. Schlesinger. "Pray that I get the funding to carry out the research," she instructs me.

Ultrasound for Soft Tissue Tumors and Bone Metastases

Pejman Ghanouni, M.D., PhD, an Assistant Professor of Radiology at Stanford University in Palo Alto, California, has been using MR imaging-guided focused ultrasound to combat a range of tumors. "We use MRI guided focused ultrasound to successfully treat uterine fibroids, essential tremor, prostate cancer, soft tissue tumors and vascular malformations located in the extremities," says Dr. Ghanouni. "MRI combined with FUS provides a non-invasive and elegant way to treat these pathologies," he explains. "With MR imaging, I can easily see the target for the focused ultrasound beam; during treatment I can verify the effect in real time using MRI-derived temperature maps at the target; and immediately afterward, I can validate the effects of the treatment."

In addition to the list of applications above, Dr. Ghanouni uses MRI

guided focused ultrasound to treat bone metastases. Cancer cells can break away from a tumor and travel through the bloodstream or lymph vessels to other areas of the body. This is called metastasis. Although the cancer cells can spread to nearly all tissues of the body, they often settle in the bones. Says Dr. Ghanouni, "Bone metastases are the most common cause of the pain associated with cancer."

Dr. Pejman Ghanouni

"Currently, radiation is the standard treatment for painful bone metastases. While about two-thirds of patients will find partial or complete relief from pain after radiation, a good percentage do not respond or have residual or recurrent pain," he says. "These patients are offered more radiation (which is usually less effective than the primary radiation treatment and is only possible if patients have not reached their radiation toxicity limits with the first treatment), or narcotics (which come with their own unpleasant side effects). MRI-guided FUS has proven to be an effective alternative for patients who do not respond to radiation. This is a single outpatient treatment (as opposed to the usual regime of 10 radiation treatments), and is effective in 80 to 90 percent of my patients," according to Dr. Ghanouni. "Although there may be a slight increase in pain from the initial swelling after treatment, within three to seven days, the relief is there — and it can hold up for years," says Dr. Ghanouni.

After cancer has spread to the bones or to other sites in the body, cure is more difficult. However, the cancer can still be treated to shrink, stop, or slow its growth. Even if a cure is no longer possible, treating the painful bone metastases can improve quality of life. "These patients, like one woman who could keep smiling and joking despite the pain of her pelvic metastasis, are inspirational. It's very gratifying to have this impact on their lives," says Dr. Ghanouni.

What Are We Hoping For?

Hamodia talked to Jessica Foley, Ph.D., chief scientific officer and Susan Klees, director of communications of the Focused Ultrasound Foundation, a Virginia-based organization that is expanding and promoting the use of ultrasound to treat a wide range of clinical disorders including Parkinson's disease, pain, and tumors of the prostate, brain and others to hear about current clinical trials and what we can hope for.

Mechanical Tissue Destruction: Pre-clinical work is being carried out at the Universities of Michigan and Washington using the mechanical effects of focused ultrasound to disrupt cells without heating. By applying high energy levels of ultrasound, bubbles of gas are generated in tissue. "Think of popping open a bottle of champagne," says Dr. Foley. The collapse of these bubbles, called cavitation, generates enough force to destroy cell membranes or liquefy cells. Once mechanical tissue destruction has demonstrated through research to be safe and effective, treatment of larger, more solid tumors like those in the prostate gland or liver may be easier and faster.

Blood-Brain Barrier Disruption: "The blood-brain barrier is a protective layer of tightly joined cells that line the blood vessels of the brain to prevent harmful toxins from entering. Unfortunately, it also prevents the delivery of beneficial drugs to diseased brain targets. Focused ultrasound can vibrate microbubbles that have been injected systemically to temporarily loosen the lining of the blood vessels, thus allowing drugs to pass through," says Dr. Foley. A clinical trial at Sunnybrook Health Sciences Centre in Toronto showed that FUS can open the blood-brain barrier and enhance delivery of chemotherapy. Once the clinical trials are behind us, FUS could be used to treat brain tumors, Alzheimer's disease and epilepsy.

Targeted Drug Delivery: While this treatment is still in the pre-clinical area, the scope is promising. Drugs can be loaded into carriers (microbubbles) and injected into the bloodstream. Because the drug is encapsulated, it can circulate harmlessly throughout the body without harming any tissue. When ultrasound is focused on the targeted area, the carriers release the drug which is then quickly absorbed by the surrounding tissue. *Voilà!* The drug is delivered in high concentrations to precisely where you want it.

Amplification of Cancer Biomarkers: Still in the pre-clinical stages, this treatment offers hope to anyone tracking the progress of a tumor. Tumors release biomarkers into the bloodstream, usually in very small quantities. Low-frequency focused ultrasound can cause the tumor to release more biomarkers and aid in diagnosing cancer. How? If a potential tumor site has been identified, FUS could be used to determine whether there really is a tumor or not. It could be used instead of biopsy to confirm a cancer diagnosis. Depending on the type of biomarker picked up, FUS could help determine the most effective treatment course for a patient. Finally, after treatment of a known tumor, FUS could be used to check if the treatment worked. ■

HEALING STORIES

From Rambam Health Care Campus

A 67-year-old jeweler who was suffering from Parkinson's was forced to abandon his craft as the tremor increased to a point when he could no longer work. After we treated him, the first thing he did when he got home was create a bracelet for Dr. Schlesinger. A year after the procedure, he is still working successfully.

An airline purser, who was particularly charming and well-liked, developed Parkinson's. As the disease progressed and the tremor became more disruptive, he gave up his job and became a recluse to the point that he refused to leave the house. His wife brought him to the hospital for a consultation. After undergoing treatment he was able to return to being his old outgoing self.

A woman in her seventies had been suffering from a tremor to the point that she could no longer eat and drink. Particularly difficult for her was that she had to give up her dream of learning German because she couldn't write. After undergoing treatment, she not only began to eat and drink normally, she also returned to her language classes.

From the University of Maryland

Suffering from Parkinson's disease, Kimberly Spletter, 50, could no longer ride her bike, care for her grandson or dance at a wedding. The medication taken to control PD led to dyskinesia (involuntary, erratic movements of the face, arms and legs). Referred to the University of Maryland, Kimberly chose to be one of the first patients to undergo Focused Ultrasound Ablation with MRI. After the treatment, during which she was awake, Kimberly walked unaided to a recovery room. These days, Kimberly helps others overcome the symptoms of PD by teaching a spin (cycling) class called "Pedaling for Parkinson's."

From the Stanford University Medical Center

When a rancher from northern California arrived for a consultation with Dr. Ghanouni, he could barely sit due to a tumor in his right buttock. Radiation and medication hadn't helped to alleviate his pain. A week after one MRgFUS treatment, however, the rancher's pain had been cut to half; within a month, it was hardly noticeable. When Dr. Ghanouni tried to reach him in a follow-up call, his wife told him that her husband was horseback riding in the mountains. The rancher later told Dr. Ghanouni that he'd worn out his horse to the point that he had to dismount and lead him.