Magnetic Resonance-Guided Focused Ultrasound Thalamotomy to Treat Essential Tremor in Nonagenarians

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Keywords

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Abstract

Essential tremor (ET) is a disabling movement disorder that is most prevalent among the elderly. While deep brain stimulation surgery targeting the ventral intermediate nucleus of the thalamus is commonly used to treat ET, the most elderly patients or those with multiple medical comorbidities may not qualify as surgical candidates. Magnetic resonance-guided focused ultrasound (MRgFUS) constitutes a less invasive modality that may be used to perform thalamotomy without the need for a burr hole craniotomy. Here, we report on 2 patients over the age of 90 years who benefited significantly from MRgFUS thalamotomy to relieve their symptoms and improve their quality of life. The procedure was well tolerated and performed safely in both patients. We conclude that age should not be a limiting factor in the treatment of patients with MRgFUS.

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Introduction

Essential tremor (ET) is a common movement disorder with an estimated prevalence of approximately 4.6% among individuals over the age of 65 years [1]. The disorder is characterized by a kinetic tremor with a frequency of 4–12 Hz that most commonly affects the hands but may also involve the head, trunk, and voice [2]. The incidence of ET increases dramatically with age, and the prevalence among those aged >95 years was estimated to be as high as 21.7% in a multiethnic, community-based, epidemiological study [3]. The disorder is progressive and associated with a high degree of functional disability, which has been correlated with co-morbid depression and anxiety [4]. Some patients may eventually avoid public places and social interaction due to embarrassment, leading to high incidences of depression and poor quality of life [5]. Early loss of independence, inability to perform basic activities of daily living, such as feeding and dressing oneself, and social isolation can severely impact the lives of elderly patients with ET.

While pharmacotherapy is the first-line therapy for ET, up to 25–55% of the patients will show no response [2], and thus surgical intervention may be the only option for relief of symptoms. Surgical interventions for ET include radiofrequency ablation thalamotomy, and deep brain stimulation (DBS) targeting the ventral intermediate (VIM) nucleus of the thalamus. Thalamic DBS has previously been shown to have a significant impact on the disability and quality of life in patients with ET [6]. However, not all patients may qualify as surgical candidates, especially among the elderly, and brain atrophy may also complicate the placement of DBS electrodes. Alternatives to DBS surgery include radiofrequency ablation and less invasive procedures such as gamma knife radiosurgery [7], and more recently, magnetic resonance-guided focused ultrasound (MRgFUS) [8]. Gamma knife and MRgFUS may be advantageous for treating high-risk patients, as they do not require intracranial access.

One disadvantage of gamma knife thalamotomy is delayed therapeutic effect, and as a result, side effects may arise in a delayed fashion without the opportunity to intervene. MRgFUS provides an immediate clinical response, and clinical assessments can be performed throughout the procedure to screen for side effects after each sonication. Hence, MRgFUS may be ideally suited for treating patients with ET who prefer less invasive options. Here, we describe 2 patients with ET over the age of 90 years who experienced significant tremor relief after MRgFUS thalamotomy.

Case Report

Patient A

The patient was a 93-year-old, right-handed male who had developed kinetic tremor in his upper extremities in his 50s, which progressively worsened over time. The tremor began in his dominant hand, but progressed to involve his left hand as well. At the time of treatment, both upper extremities were severely affected. Of note, the patient's mother had suffered from a similar condition, suggesting a familial etiology. His quality of life was severely impaired: his handwriting became illegible, and he could not bring a cup to his mouth without spilling, requiring him to sip through a straw.

At the time of screening, the patient had severe tremor in the right arm and hand, marked tremor in the left arm and hand, and moderate tremor in the bilateral lower extremities. Tremor severity was evaluated preoperatively and at each follow-up point using the Clinical Rating Scale for Tremor (CRST) [9]. The treated hand score was extracted from the CRST total score by adding the scores of the dominant hand tremor portion of part A and the dominant hand scores of Part B of the CRST.

Prior to intervention, the patient's skull density ratio was calculated as 0.65, indicating increased likelihood of favorable energy transfer through the skull [10]. MRgFUS thalamotomy was performed as previously described targeting VIM (Fig. 1) [11]. A total of 13 sonications were performed, achieving a maximum temperature of 59 °C and a maximum energy of 18,302 J. The total duration of the procedure was approximately 1 h and 20 min. The patient demonstrated an immediate clinical improvement, and at 1 week of follow-up, his CRST total score was reduced by 66%, while his treated hand score was reduced by 95% compared to baseline.

Immediate side effects experienced by this patient following treatment included mild gait instability and mild weakness of the right lower extremity. These side effects completely resolved by the time of his 1-month follow-up. After 3 months, the patient's CRST total score was reduced by 58%, and his treated hand score was reduced by 59% compared to baseline. He demonstrated stable improvement at 1 year with a 52% reduction in the CRST total score and a 64% reduction in the treated hand score compared to baseline. The patient continued to have good tremor control at the time of his last follow-up, 2 years after his procedure. Of note, the patient had been an avid bird watcher, and the improvement in his tremor enabled him to hold his binoculars up to his eyes, which he had not been able to do independently for many years.

Patient B

A 93-year-old-female was referred for evaluation for ET, initially diagnosed at 53 years of age. She was affected by bilateral upper extremity tremor, head tremor, and voice tremor, which caused her significant disability. Her handwriting was illegible, and she was not able to perform essential activities of daily living, such as dressing and feeding herself. At the time of screening, she scored 81 of a possible 144 on the CRST. Her tremors were extremely bothersome and disturbing to her despite taking maximal doses of primidone and propranolol.

When she was initially evaluated for consideration for surgical treatment of her tremor, she was also found to have motor features suggestive of comorbid Parkinson's disease (PD), such as resting tremor, bradykinesia, and bilateral rigidity, thus fulfilling the current diagnostic criteria for "PD with antecedent ET" [12]. Nevertheless, a diagnosis of PD could not explain all characteristics of her disorder. Her prominent bilateral hand tremor became progressively severe with any posture, and she demonstrated moderate head and voice tremor. The patient was started on levodopa, which helped improve her mobility, and she was deemed to be an appropriate candidate for thalamotomy. Due to her medical comorbidities, which included atrial fibrillation requiring chronic anticoagulation, MRgFUS thalamotomy was recommended.

The patient's skull density ratio was calculated as 0.45. She received a total of ten sonications, reaching a maximum temperature of 60 °C and a maximum energy of 15,150 J. The total duration of the procedure was 2.5 h. At one week of follow-up after treatment, the patient was found to have grade 4/5 weakness in the right leg, which caused her to drag her foot slightly while walking; however, this resolved by the time of her 1-month follow-up, and she did not develop any additional side effects thereafter. At the time of her last follow-up visit, her CRST total score was reduced by 32%, and her treated hand score was reduced by 57%. She became capable of feeding and dressing herself, which she had not been able to do for many years.

Fig. 1. Post-procedure MRI demonstrating lesions in the left thalamus for Patient A (left) and Patient B (right).

Unfortunately, the patient expired 1 day prior to her scheduled 6-month follow-up appointment due to a medical condition unrelated to her treatment. Correspondence from the patient's family informing the treating team of her passing expressed gratitude for the immense improvement in the patient's quality of life up until the time of her passing.

Both patients experienced immediate improvement following MRgFUS thalamotomy. The lesions produced from MRgFUS as seen on MRI are shown in Figure 1. The change in the treated hand score for both patients from the time of screening to 3 months of follow-up is depicted in Figure 2a, and the change in the CRST total score is illustrated in Figure 2b. Unfortunately, Patient B passed away before the 6-month follow-up point; however, Patient A was followed for up to 1 year. The extended treated hand score and CRST total score are displayed in Figure 2c.

Quality of life for both patients was evaluated using the Quality of Life in Essential Tremor Questionnaire (QUEST) [13]. Patient A completed assessments at screening and at 12 months of follow-up, while Patient B completed the assessment at screening and 3 months of follow-up. After the procedure, Patient A's QUEST summary index (QSI) improved by 24%, while Patient B's QSI improved by 15%. While the change in QSI for these 2 patients is lower compared to previous reports [8], due to factors related to the patients' advanced age, minimal to no improvement occurred in the subscales of work/finances or hobbies/leisure, and Patient B did not report a net improvement in the physical subscale due to factors related to her co-morbid PD (Fig. 2d).

Discussion

While the incidence of ET increases with age [12], and the highest rates of the disorder are found among those of advanced age [3], surgical options for these patients may be limited. Indeed, many patients and families may be reluctant to pursue invasive procedures due to surgical risks and potential hardware infections. Additionally,

some physicians may be more cautious and reluctant to treat as age constitutes a significant factor in morbidity and mortality, retaining this patient population from potentially effective treatment. Other factors to consider include economic burden on healthcare systems and the elective nature of procedure.

MRgFUS thalamotomy allows for immediate tremor relief in the contralateral limb, which restores the ability to perform essential activities of daily living, leading to improved quality of life. Unlike gamma knife thalamotomy, the effects of the treatment are seen immediately, and the patient may be screened for side effects during the procedure to optimize the size and location of the lesion. These features of MRgFUS are advantageous for the care of elderly patients suffering from ET. For patients with poor health whose life expectancy may be uncertain, the ability to provide immediate and sustained tremor relief can improve the quality of life even in the setting of end-of-life care, as demonstrated in the case of Patient B. Furthermore, MRgFUS thalamotomy may be performed as an outpatient procedure, avoiding the need for hospitalization, which is required for DBS surgery and radiofrequency ablation.

The most common side effects after MRgFUS thalamotomy include balance disturbance and mild weakness of the contralateral lower limb [8]. Additionally, patients may experience mild sensory loss in the contralateral hand and mouth area [8]. These side effects tend to be mild and largely resolve within 3 months. The region of optimal therapeutic benefit for MRgFUS thalamotomy has been localized to the border between the VIM nucleus of the thalamus and the ventral caudal nucleus of the thalamus, which is not significantly dif-

Fig. 2. Clinical outcome after MRgFUS thalamotomy. **a** Line plot demonstrating improvement (reduction) in the treated hand score over 3 months of follow-up for Patient A (blue) and Patient B (red). **b** Line plot demonstrating improvement (reduction) in the CRST total score over 3 months of follow-up for Patient A (blue) and Patient B (red). **c** Line plot depicting 1-year outcomes for Patient A: CRST total score (purple) and treated hand score (green). **d** Bar graph illustrating the change in QUEST subscores for Patient A (blue) and Patient B (red).

ferent from the region corresponding to the highest risk of ataxia and dysmetria [14]. This finding may explain why gait disturbance after MRgFUS is the most common side effect and often occurs in the setting of optimal clinical response.

MRgFUS thalamotomy may also be advantageous for treating tremor-dominant PD in elderly patients. Patients with ET may have an increased risk of developing Parkinsonian features compared to the general population [12]. Comorbid PD and ET is exemplified in the case of Patient

B in the present report. A multicenter, randomized pilot trial of MRgFUS thalamotomy for tremor-dominant PD found a significant improvement in tremor improvement following active treatment compared to sham treatment, despite a prominent placebo effect, which is common among PD patients [15].

In conclusion, MRgFUS thalamotomy may serve as an ideal intervention for treating tremor in elderly and fragile patients. Further studies are needed to compare quality-of-life improvements and the incidence of side

effects in the most elderly patients compared to younger populations. As life expectancy is increasing, the elderly and nonagenarian patient populations are growing, and there is an increased need to find suitable treatment options [16].

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Statement of Ethics

This case report was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients and/or next-of-kin gave permission for their stories to be included in this case report.

Disclosure Statement

The authors report no conflict of interests other than serving as consultants for the company that manufactures the MRgFUS device.

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Author Contributions

Michelle Paff, Alexandre Boutet, and Clemens Neudorfer were responsible for data collection, production of figures, and composition of the manuscript. Gavin J.B. Elias, Jürgen Germann, and Aaron Loh contributed by critically reviewing and revising the manuscript. Alfonso Fasano, Walter Kucharczyk, Michael L. Schwartz, and Andres M. Lozano were the treating physicians for these patients. They supervised the construction of the manuscript and approved the final submission.

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