Effects on cognition and quality of life with unilateral magnetic resonance–guided focused ultrasound thalamotomy for essential tremor

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OBJECTIVE Although neurosurgical procedures are effective treatments for controlling involuntary tremor in patients with essential tremor (ET), they can cause cognitive decline, which can affect quality of life (QOL). The purpose of this study is to assess the changes in the neuropsychological profile and QOL of patients following MR-guided focused ultrasound (MRgFUS) thalamotomy for ET.

METHODS The authors prospectively analyzed 20 patients with ET who underwent unilateral MRgFUS thalamotomy at their institute in the period from March 2012 to September 2014. Patients were regularly evaluated with the Clinical Rating Scale for Tremor (CRST), neuroimaging, and cognition and QOL measures. The Seoul Neuropsychological Screening Battery was used to assess cognitive function, and the Quality of Life in Essential Tremor Questionnaire (QUEST) was used to evaluate the postoperative change in QOL.

RESULTS The total CRST score improved by 67.3% (from 44.75 ± 9.57 to 14.65 ± 9.19 , $p < 0.001$) at 1 year following MRgFUS thalamotomy. Mean tremor scores improved by 68% in the hand contralateral to the thalamotomy, but there was no significant improvement in the ipsilateral hand. Although minimal cognitive decline was observed without statistical significance, memory function was much improved ($p = 0.031$). The total QUEST score also showed the same trend of improving (64.16 ± 17.75 vs 27.38 ± 13.96 , $p < 0.001$).

CONCLUSIONS The authors report that MRgFUS thalamotomy had beneficial effects in terms of not only tremor control but also safety for cognitive function and QOL. Acceptable postoperative changes in cognition and much-improved QOL positively support the clinical significance of MRgFUS thalamotomy as a new, favorable surgical treatment in patients with ET.

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KEY WORDS essential tremor; thalamotomy; cognition; memory; quality of life; focused ultrasound

STEREOTACTIC radiofrequency (RF) thalamotomy and thalamic deep brain stimulation (DBS) are well-known successful treatments to alleviate disabling tremor in patients with either essential tremor (ET) or Parkinson tremor.^{1,9,26,30,35,41} Despite their delivered improvement in tremor, these therapeutic modalities are often accompanied by adverse effects on speech or language. Recently, a meta-analysis demonstrated that speech difficulty occurred in 19.8% of patients after RF thalamotomy and 19.4% after DBS.³ In particular, pa-

tients treated bilaterally showed a 2- to 3-fold higher risk of a speech problem than unilaterally treated patients.³ Therefore, RF thalamic procedures to one side are frequently preferred, especially the left side given right-hand dominance. Moreover, some research has reported major concerns regarding other cognitive function changes following thalamic procedures. Because of the anatomical and functional relationships between the thalamus and cortex, in general, left-sided surgery is regarded as being associated with verbal fluency, verbal memory, and lan-

ABBREVIATIONS CRST = Clinical Rating Scale for Tremor; DBS = deep brain stimulation; ET = essential tremor; MCI = mild cognitive impairment; MRgFUS = MR-guided focused ultrasound; QOL = quality of life; QSI = QUEST summary index; QUEST = Quality of Life in Essential Tremor Questionnaire; RF = radiofrequency; SNSB-II = Seoul Neuropsychological Screening Battery II; Vim = ventral intermediate nucleus.

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guage, whereas right-sided surgery is associated with visual spatial demands.^{2,23,29,32} Many studies have reported that thalamotomy is associated with a risk of cognitive deterioration, especially score reductions in verbal fluency or verbal memory following left-sided procedures.^{34,40} With regard to ventral intermediate nucleus (Vim) DBS, verbal fluency could diminish relative to baseline in about 10% of patients, though overall cognitive function was stable due to compensation for improved visuomotor or verbal memory function.¹⁴ Although many studies on stereotactic surgeries for ET have demonstrated lower-than-expected postoperative cognitive impairment,^{21,34,40} it is still generally accepted that thalamic procedures, especially left-sided surgery, are risky to cognitive function.

Essential tremor is a distressful condition for patients because it restricts their behavior in performing even simple daily activities, such as writing, using chopsticks or a spoon, and drinking. Many studies have reported improved quality of life (QOL) after surgical treatment, either lesioning or DBS, mainly attributable to improvements in dominant hand tremor and the performance of daily activities.^{13,17,18,22} However, most of these findings neglect cognitive issues, and it would be difficult to assess whether outcome would be positive or negative when considering neuropsychological aspects.

Magnetic resonance-guided focused ultrasound (MRgFUS), a new stereotactic surgical technique, has become popular because of its noninvasiveness without scalp incision or craniotomy. Other major advantages include its clinical effectiveness in controlling tremor and its few side effects as a result of real-time monitoring.^{8,11,13} Its clinical applications have been expanding, from movement disorders such as ET or Parkinson disease to psychiatric diseases such as obsessive-compulsive disorder.^{8,11–13,16} Recently, Elias et al. reported some complications following unilateral MRgFUS thalamotomy for ET, including gait disturbance, paresthesia, contralateral weakness, dysarthria, and vertigo.¹³ Other studies have described similar adverse events related to MRgFUS thalamotomy in patients with ET or tremor-dominant Parkinson disease.^{8,11,42} However, not enough research has been focused on detailed cognitive issues. To our knowledge, this is the first study to evaluate pre- to postoperative changes in cognitive function and QOL in patients with ET who were managed with unilateral MRgFUS thalamotomy.

Methods

We prospectively evaluated comprehensive neuropsychological test batteries and measures of QOL in patients with ET who underwent unilateral thalamotomy with MRgFUS at Severance Hospital in the period from March 2012 to September 2014. Medically refractory ET was diagnosed by neurologists or neurosurgeons who specialize in movement disorders. All study participants were right-handed. We performed MRgFUS thalamotomy using the ExAblate 4000 device (ExAblate Neuro, InSightec Inc.) with direct targeting to the left Vim of the thalamus. The target coordinates were as follows: 14–15 mm lateral to the midline, 6–7 mm anterior to the posterior commissure,

and at the line of the intercommissural line. A detailed description of the conventional MRgFUS procedure is available in our previous study.¹¹

Patients were regularly evaluated with the Clinical Rating Scale for Tremor (CRST), neuroimaging, cognitive function assessment, and QOL measures. The CRST consists of 3 parts (A, B, and C), with higher scores indicating greater severity: part A quantifies the scores of resting, postural, and action tremor for 9 parts of the body; part B gives additional weight to action tremors of the upper extremities, such as writing, drawing, and pouring liquids; and part C evaluates global functional disability.³⁶ These scores were evaluated using videotaped neurological examinations at baseline and then 1 week, 1 month, 3 months, 6 months, and more than 1 year after MRgFUS thalamotomy. Three-tesla MRI was serially performed 1 day, 1 week, 1 month, 3 months, and 6 months, and 1 year after treatment.

The Seoul Neuropsychological Screening Battery II (SNSB-II) was used to assess cognitive function at baseline and more than 6 months following surgery, and it was evaluated by the same examiner who was blinded to the MRgFUS procedure. The battery included the following subsets of tests: 1) attention, 2) language and related functions, 3) visuospatial function, 4) verbal and visual memory, and 5) frontal/executive function. In the same interval, a QOL score was assessed using a reliable ET-specific measure, the Quality of Life in Essential Tremor Questionnaire (QUEST).³⁹ The QUEST consists of 30 items contributing to 5 subdomains, which were expressed as a percentage of the total score: 1) physical, 2) psychosocial, 3) communication, 4) hobbies/leisure, and 5) work/finances. The total score on the QUEST, or the QUEST summary index (QSI), indicated the mean score of the 5 subdomains, with a higher score interpreted as a worse perceived QOL. Sufficient information about the operation was provided to all participants, and written informed consent was obtained from all of them prior to the procedures. This study received full approval from the ethics committee of our institutional review board.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 23 (IBM Corp.). A paired t-test or Wilcoxon signed-rank test was chosen based on the normal distribution status to determine differences between preoperative and postoperative scores. Repeated-measures ANOVA was used to analyze serially measured data in the same subjects. Continuous variables were presented as the mean $\pm$ standard deviation and categorical variables as the frequency or percentage. Differences in demographics, clinical characteristics, and intraoperative findings were analyzed by selecting the t-test and Fisher's exact test that suited the situation. A p value < 0.05 was considered statistically significant.

Results

Data Related to Demographics and Sonication

A total of 20 patients with ET were enrolled in this study. They had a mean age of 64.1 years (range 47–77

years) with a male predominance (M/F 17:3). The mean age at disease onset was 42.9 ± 15.03 years (median 46.0 years), and all patients manifested their symptoms before 65 years of age. The average symptom duration was 21.2 years (range 5–54 years). The patients regularly took more than 2 medications for tremor control, including a beta-blocker or primidone, before surgery. During MRgFUS thalamotomy, patients underwent an average of 16.8 sessions of sonication (range 13–20 sessions) with various parameters, including mean maximal energy of $15,910 \pm 5702.7$ J and sonication power of 782.5 ± 152.4 W for 10–32 seconds. A maximal temperature rise up to 57.9°C on average was achieved.

Changes in the CRST

The part A score on the CRST showed 78.2% improvement (from 12.60 ± 3.80 to 2.75 ± 3.18 , $p < 0.001$), comparing the scores at baseline and the 1-year follow-up, and the part B score represented 68.2% improvement (from 19.35 ± 5.78 to 6.15 ± 5.60 , $p < 0.001$). Part C also improved by 55.1% (from 12.80 ± 3.17 to 5.75 ± 4.25 , $p < 0.001$; Fig. 1). Overall, the total CRST score remarkably improved by 67.3% (from 44.75 ± 9.57 to 14.65 ± 9.19 , $p < 0.001$) at 1 year after MRgFUS thalamotomy. Mean tremor scores improved by 68% (from 18.15 ± 3.96 to 5.80 ± 4.53 , $p < 0.001$) in the hand contralateral to the thalamotomy (right hand), whereas the ipsilateral hand (left hand) showed no significant difference in scores (from 10.10 ± 5.47 to 12.45 ± 7.14 , $p = 0.283$). When these results were verified with Bonferroni post hoc analysis with a significance level of 0.01 (0.05/5), improvements in total CRST scores were statistically significant at 1 month, 3 months, 6 months, and > 1 year ($p < 0.001$). Tremor scores in the left hand alone exhibited no significant improvement at the follow-up evaluations at 1 month ($p = 0.810$), 3 months ($p = 0.305$), 6 months ($p = 0.493$), and > 1 year ($p = 0.283$).

Neuropsychological Outcome

The mean psychometric results for all patients are shown in Table 1. Preoperative assessments showed that 9 (45%) of 20 patients already had various degrees of

cognitive impairment, including 6 patients with single-domain, nonamnesic, mild cognitive impairment (MCI) and 3 patients with multidomain amnesic MCI. Postoperatively, there were positive trends toward clinical improvement on the Korean version of the Boston Naming Test and visual memory functions, including immediate recall, delayed recall, and recognition ($p < 0.05$). Minimal declines in other areas of cognitive function were observed; however, these did not reach statistically significant results. When test results were classified by several domains (SNSB-II), we noted that memory function was much improved ($p = 0.031$) following MRgFUS thalamotomy (Fig. 2). When analyzing each individual's data, we found a total of 5 patients who exhibited a minor decline in verbal memory postoperatively. Four of these patients were among those who had preoperative MCI, and their verbal memory function became a little worse. Only 1 patient, a 61-year-old man, lost cognitive function in the fields of verbal memory and frontal/executive function. In contrast, the other 4 patients with MCI showed cognitive improvements, particularly in language, visual memory, or verbal memory. There were no statistically relevant factors related to cognitive changes after treatment.

Measurement of QOL

Postoperatively, the patients reported significant improvement in the overall QSI as compared with their preoperative state (64.16 ± 17.75 vs 27.38 ± 13.96 , $p < 0.001$). They represented balanced functional recovery in all domains after MRgFUS thalamotomy: physical (36.78 ± 16.29 vs 18.22 ± 8.45 , $p < 0.001$), social (66.55 ± 23.59 vs 30.12 ± 15.52 , $p < 0.001$), communication (80.00 ± 18.73 vs 34.66 ± 24.23 , $p < 0.001$), hobbies/leisure (74.34 ± 21.66 vs 30.00 ± 19.04 , $p < 0.001$), and work/finances (63.17 ± 22.36 vs 23.84 ± 13.12 , $p < 0.001$; Fig. 3).

Other Complications

Ten patients experienced mild headache, dizziness, or nausea during sonication. After treatment, 3 patients continued to complain of pain at the pin site due to stereotactic frame fixation, which easily resolved with pain

FIG. 1. Improvement in CRST after MRgFUS thalamotomy.

TABLE 1. Neuropsychological data between baseline and postoperative state

Factors	Baseline	FU (>6 mos)	p Value
K-MMSE	28.70 (1.45)	28.50 (1.28)	0.363
Attention			
Digit span (forward)	6.65 (1.23)	6.55 (1.32)	0.681
Digit span (backward)	4.25 (0.97)	4.15 (1.18)	0.713
Digit span (forward-backward)	2.40 (1.10)	2.40 (1.31)	0.707
Language & related function			
K-BNT	48.75 (5.57)	50.35 (5.14)	0.015
Repetition	14.80 (0.52)	15.00 (0.00)	0.102
Calculation	11.75 (0.64)	11.65 (0.75)	0.414
Visuospatial function			
RCFT	34.05 (1.54)	34.30 (1.58)	0.621
Verbal memory function (SVLT)			
Immediate recall	21.35 (4.97)	22.00 (5.67)	0.454
Delayed recall	6.35 (2.76)	6.15 (3.05)	0.750
Recognition	21.40 (2.56)	21.70 (2.00)	0.516
Visual memory function (RCFT)			
Immediate recall	19.30 (6.18)	22.05 (7.78)	0.049
Delayed recall	18.85 (5.31)	21.13 (7.25)	0.038
Recognition	20.50 (1.79)	21.45 (1.39)	0.028
Frontal executive function			
Contrasting program	19.95 (0.22)	19.95 (0.22)	>0.999
Go-no-go test	19.50 (2.24)	18.95 (4.25)	0.593
COWAT: animal	15.35 (2.87)	14.70 (3.11)	0.330
COWAT: supermarket	15.15 (5.06)	15.45 (3.61)	0.653
Phonemic generative naming	24.50 (9.25)	23.20 (8.29)	0.837
Word Stroop test	111.65 (0.75)	111.25 (2.69)	0.480
Color Stroop test	83.80 (21.69)	85.00 (24.48)	0.626

COWAT = Controlled Oral Word Association Test; FU = follow-up; K-BNT = Korean version of Boston Naming Test; K-MMSE = Korean version of Mini-Mental Status Examination; RCFT = Rey Complex Figure Test; SVLT = Seoul Verbal Learning Test.

Values are expressed as the mean (standard deviation).

killers and rest. Another patient suffered from a transient balance problem, possibly due to ultrasonic energy affecting the medial lemniscus; the patient completely recovered in 1 month with the use of an oral steroid. No significant aftereffects occurred during the entire follow-up period.

Discussion

Essential tremor is not a pure motor disease and is known to be associated with cognitive dysfunction, usually in the subtypes of attention, verbal fluency, and memory.^{4,5,15,28,33} Sánchez-Ferro et al. stated that patients with ET had impaired cognitive performance, predomi-

FIG. 2. Results for cognitive domains of the SNSB-II after MRgFUS thalamotomy for ET.

nantly in cognitive processing speed, even in nondementia cases.³³ Authors of some prospective studies have stated that patients with ET have an increased risk of dementia during the disease period.^{6,37} Therefore, when considering treatment for ET, one must remember that the goal of treatment is not only to improve tremor, but also to avoid cognitive decline after therapeutic intervention.

Magnetic resonance-guided FUS thalamotomy is an emerging technique for ET, but its effectiveness is comparable to that of other modalities, such as conventional lesioning methods (RF or Gamma Knife thalamotomy) or DBS.^{1,9,24,30,32} However, in terms of neuropsychologi-

FIG. 3. Changes in QUEST scores from baseline to follow-up.

cal effects, including cognition, there have been quite variable and controversial reports following these treatments.^{14,34,38,40} In patients with ET, it has been suggested that there are complex, widespread alterations of white matter fiber integrity in both motor and nonmotor networks.²⁵ Thus, theoretically, thalamic procedures can produce disruption in the neuroanatomical pathway connecting the prefrontal cortex and subcortical areas, resulting in frontal lobe dysfunction.²⁹ Moreover, thalamotomy usually seems to carry the risk of cognitive decline, possibly because of a decrease in thalamocortical drive.³⁴ Deep brain stimulation has been considered superior to thalamotomy in terms of cognitive function given the adjustability and reversibility of electrical stimulation. And certainly, there have been some studies with positive results of DBS in enhancing visuosperceptual or verbal memory function or in causing no significant effects on higher cognitive function even in the long term.^{14,19,38} However, DBS has also caused cognitive side effects, such as those related to language, visual memory, and verbal fluency.^{7,38} Interestingly, there has been a report of a subtle diminution in verbal memory in the DBS-on state versus the DBS-off state.²⁷

In the present study, we demonstrated that postoperative cognitive decline could be minimized by thalamic lesioning with MRgFUS. Only 5 patients manifested worsened cognitive function, but most of them (4 patients) already had cognitive impairment as a predisposing factor before surgery. This cognitive decline can be explained by the supposition that the disrupted neural pathway may have a significantly lower threshold for the alteration in neural process-related cognitive function. A study evaluating cognitive function after thalamic DBS revealed a similar result, that is, that preexisting dysfunction in verbal fluency may predispose to further decline after DBS.¹⁴ Conversely, some patients unexpectedly have improved cognition following MRgFUS thalamotomy. One possible explanation for this beneficial cognitive outcome with MRgFUS thalamotomy is appropriate control of the lesion size under real-time MR thermometry. As is well known, RF thalamotomy does not always guarantee the exact size in the optimal location in the thalamus. Hermann et al. showed that the mean size of lesions was larger in patients with Parkinson disease who suffered from aphasia after the surgical procedure.²⁰ Therefore, optimal control of the lesion size as well as the exact location in the thalamic target can guarantee surgical safety and cognitive benefits from MRgFUS thalamotomy.

We also suggest that some score gains in the cognitive function test may be attributable to a repetitive practice effect; however, it is generally not easy to accustom oneself to some examinations following only one experience. Actually, Fields et al. countered this possibility by explaining that the most substantial score gain occurred after a 9-month test-retest interval rather than a short 4-month interval in their clinical study of unilateral thalamic stimulation for ET.¹⁴ Instead, it could be a secondary effect of widening the scope of daily activities due to the improvement in movement.

When considering the impact of tremor control on patient satisfaction and QOL, many studies have suggested overly positive outcomes of surgical procedures.^{14,18,24,29,38}

Huss et al. demonstrated no difference in the change in reported QOL between bilateral Vim DBS and unilateral procedures, including DBS and MRgFUS thalamotomy.²² A randomized controlled study of MRgFUS thalamotomy described significant reductions of 46% in QUEST scores from baseline to 3 months after ablation as compared with a 3% reduction in the sham group.¹³ In particular, the authors found marked improvement in the psychosocial domain, which was one of the most important factors determining QOL in patients with ET.^{10,13} Therefore, tremor control and enhanced physical activities in daily living can result in better self-esteem and the restoration of social relationships and, consequently, great improvement in QOL. As observed in the present study, tolerable cognitive changes together with much improvement in QOL support MRgFUS thalamotomy as an acceptable treatment in terms of tremor control and safety apart from the neuropsychological impairment.

Study Limitations

The present study has several limitations. The small number of patients was a major shortcoming in analyzing the data. More clinical data are necessary to consolidate the results. In addition, we performed only left thalamotomy in all participants and thus could not compare the laterality effect of thalamotomy.

Conclusions

This study showed that MRgFUS thalamotomy has beneficial effects in reducing tremor and maintaining cognitive function in patients with ET. Although more long-term follow-up results are required to further solidify its effectiveness, MRgFUS thalamotomy can work as an emerging therapy to manage ET with cognitive stability as well as improved QOL.

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Disclosures

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Author Contributions

Conception and design: JW Chang. Acquisition of data: NY Jung, Park, WS Chang, HH Jung. Analysis and interpretation of data: NY Jung, Park, WS Chang, HH Jung. Drafting the article: NY Jung. Critically revising the article: all authors. Reviewed submitted version of manuscript: Park, WS Chang, HH Jung. Approved the final version of the manuscript on behalf of all authors: JW Chang. Study supervision: JW Chang.

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