

[CASE REPORT]

Magnetic Resonance Imaging-guided Focused Ultrasound Thalamotomy for Parkinson's Disease

Hisashi Ito¹, Shigeru Fukutake¹, Kazuaki Yamamoto², Toshio Yamaguchi³,
Takaomi Taira⁴ and Tetsumasa Kamei¹

Abstract:

Thalamotomy is effective in treating refractory tremor in Parkinson's disease (PD). We herein report a PD patient who underwent left ventral intermediate nucleus and ventro oralis posterior nucleus thalamotomy using magnetic resonance imaging-guided focused ultrasound (MRgFUS). Right-side resting tremor and rigidity were abolished immediately following the ultrasound energy delivery. In addition, left-side resting tremor and rigidity also improved. No adverse events occurred during the procedure. We observed the exacerbation of bradykinesia, which might have been caused by edema around the target. This is the first report of thalamotomy using MRgFUS for PD patient from Japan. Further investigations concerning the efficacy and safety of this procedure are necessary.

Key words: Parkinson's disease, MRI guided focused ultrasound, thalamotomy, ventral intermediate nucleus, ventro oralis posterior nucleus

(Intern Med 57: 1027-1031, 2018)

(DOI: 10.2169/internalmedicine.9586-17)

Introduction

Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder presenting with multiple motor and non-motor symptoms. Resting tremor is the most identifiable sign of PD, and it can occur in postural or kinetic forms, interfering with daily activities and being a source of social embarrassment. The primary therapeutic targets of current medications are bradykinesia, gait disturbance, and rigidity (1). Surgical intervention via deep brain stimulation (DBS) of the ventral intermediate nucleus (Vim), globus pallidus internus (Gpi), and subthalamic nucleus is a therapeutic option for PD, especially in advanced-stage patients or for medication-refractory patients. However, these treatments are invasive and extremely expensive. Magnetic resonance imaging (MRI)-guided focused ultrasound (MRgFUS) is a new technology that enables minimum intracranial focal ablation. Previous reports on the efficacy and safety of MRgFUS thalamotomy for essential tremor (ET) led to its

Food and Drug Administration (FDA) approval (2). While MRgFUS thalamotomy has not yet been approved for use in treating PD, several reports concerning MRgFUS treatment for PD have been published, as shown in Table 1 (3-6).

We herein report a 73-year-old Japanese PD patient who underwent left Vim and ventro oralis posterior nucleus (Vop) thalamotomy using MRgFUS.

Case Report

A right-handed 73-year-old man developed left hand resting tremor at 68 years of age. He was diagnosed with PD according to the UK Parkinson's Disease Society Brain Bank Criteria and started treatment with anti-Parkinsonian agents. At 73 years of age, we evaluated him as grade 2.5 on the Hoehn-Yahr scale and prescribed 300 mg of levodopa with benserazide. He had been annoyed by refractory tremor in the extremities and right-hand disability; however, we could not increase the dose of levodopa because of drug-induced hallucinations. We were unable to use dopamine ag-

¹Department of Neurology, Shonan Fujisawa Tokushukai Hospital, Japan, ²Department of Neurosurgery, Shonan Kamakura General Hospital, Japan, ³Research Institute of Diagnostic Imaging, Shin-Yurigaoka General Hospital, Japan and ⁴Department of Neurosurgery, Tokyo Women's Medical University, Japan

Received: May 29, 2017; Accepted: August 22, 2017; Advance Publication by J-STAGE: December 21, 2017

Correspondence to Dr. Hisashi Ito, hisashi.ito@tokushukai.jp

Table 1. Characteristics of PD Patients who Underwent MRgFUS Treatment.

Reference	Patients (numbers)	Follow-up (months)	Main symptoms	Target	Outcomes		Adverse events
					UPDRS	Others	
(3)	13	3	tremor akinesia	PTT	45.7% reduction (part III)	none	
(4)	7	3 to 12	tremor	Vim	49.7% reduction (total)	Tremor disappeared in 4 patients during follow-up	DP: vertigo (n=4), headache (n=3), dizziness (n=2), lip paresthesia (n=1) AP: gait ataxia (n=1), unsteady feeling (n=1), hypogeusia (n=1)
(5)	1	6	LID	Gpi	60.0% reduction (part III) (on medication)	70% reduction of UdysRS	not described
(6)	9*	6	tremor	Vim	46.2% reduction (part II)	Tremor disappeared in 7 patients during follow-up	DP***: vertigo (n=14), headache (n=11), dizziness (n=4), nausea (n=3), burning scalp sensation (n=3), vomiting (n=2), lip paresthesia (n=2) AP***: gait ataxia (n=5), unsteady feeling (n=4), taste disturbances (n=4), asthenia (n=4), hand ataxia (n=3)

LID: levodopa-induced dyskinesia, PTT: pallidothalamic tract, UdysRS: Unified Dyskinesia Rating Scale, DP: during the procedure, AP: after the procedure

* Seven of the nine patients in (6) were also reported in (4).

*** Including the data of 18 ET patients and 3 ET-PD patients who underwent Vim thalamotomy

onists (pramipexole and ropinirole), monoamine oxidase (MAO)-B inhibitor, or catechol-O-methyltransferase (COMT) inhibitor because of daytime sleepiness and hallucination. Furthermore, he was concerned about the invasiveness of DBS and refused it. His Mini-Mental State Examination was 25/30, and he was not demented. The skull density ratio (the mean value for the ratio of Hounsfield units of marrow and cortical bone, which reflects the amount of ultrasound energy that can penetrate the skull effectively) (7) was 0.42 (exclusion criteria: ≤ 0.30).

In April 2017, we scheduled MRgFUS thalamotomy, which has been approved by the Review Board of Tokushukai Medical Alliance for PD patients suffering from medication-resistant tremor and who have refused other procedures involving DBS. The patient provided his written informed consent in accordance with the Declaration of Helsinki before treatment commenced.

MRgFUS ultrasonic bursts (sonications) were performed using a 1.5-Tesla MRI (Signa HDx, GE Healthcare, Milwaukee, USA) and a focused ultrasound system (Exablate 4000[®], InSightec, Tirat Carmel, Israel), which received regulatory approval for ET in December 2016 in Japan. The day before thalamotomy, we performed T1- and T2-weighted MRI to plan the procedure. Based on the patient's preference, we selected the left Vim and Vop as the target. We chose the target for Vim at a point 7.5 mm anterior to the posterior commissure (PC) and 16.5 mm lateral from the midline, and 1.5 mm above the anterior commissure (AC)-PC line. The Vop is located immediately anterior to the Vim (Fig. 1).

On the day of the procedure, we shaved his head completely and placed a stereotactic frame. We attached the head to a helmet with 1,024 ultrasonic transducers. A silicone membrane tightly sealed the space between his head and the transducer, enabling us to surround the head with chilled and degassed water and thereby preventing excessive scalp heating and minimizing acoustic reflection. We gradually increased the total energy of the sonications by either increasing the intensity or extending the sonication duration. We finished the sonications when an adequate reduction in both tremor and rigidity were observed. Right-side resting tremor and rigidity were abolished immediately following 10 sonications with an average maximum sonication time of 13.0 ± 3.4 seconds (range 10-17 seconds). The mean energy reached $5,382.7 \pm 3,639.2$ J (range 1,977-10,086 J) with a mean maximum temperature of 53.3 ± 6.9 °C (range 45-64 °C). In addition, his left-side resting tremor and rigidity also improved. No adverse events occurred during sonications. Bradykinesia was exacerbated after thalamotomy; however, we did not observe any right-sided weakness, pathological reflex, or ataxia.

As we confirmed an edematous lesion around the target, we administered 30 mg of prednisolone for 5 days followed by 15 mg for 2 days, which improved his bradykinesia within 2 weeks from the procedure (Fig. 2). We administered the Movement Disorder Society-Sponsored Revision of

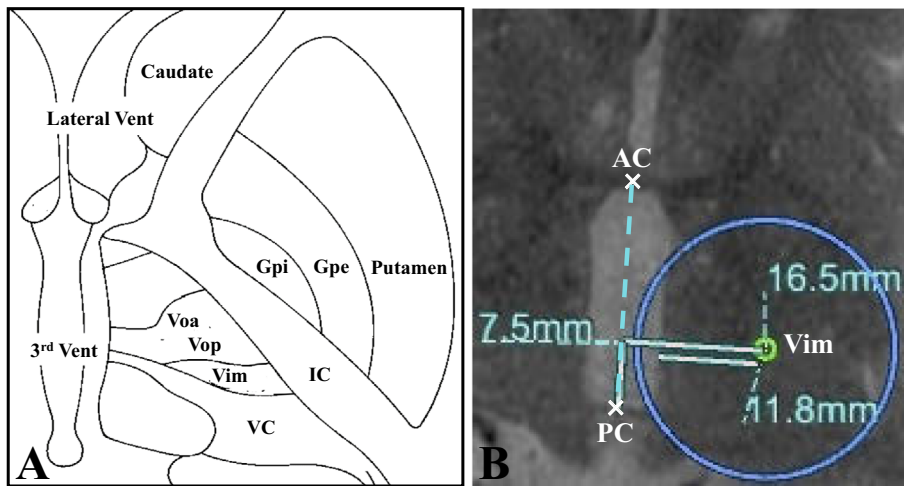


Figure 1. Anatomical structure of the thalamus and basal ganglia (A) and the MR image used for planning the procedure. Vent: ventricle, Voa: ventral oralis anterior nucleus, Vop: ventral oralis posteriornucleus, Vim: ventral intermediate nucleus, VC: ventral caudalis nucleus, IC: internal capsule, Gpi: globus pallidus internus, Gpe: globus pallidus externus

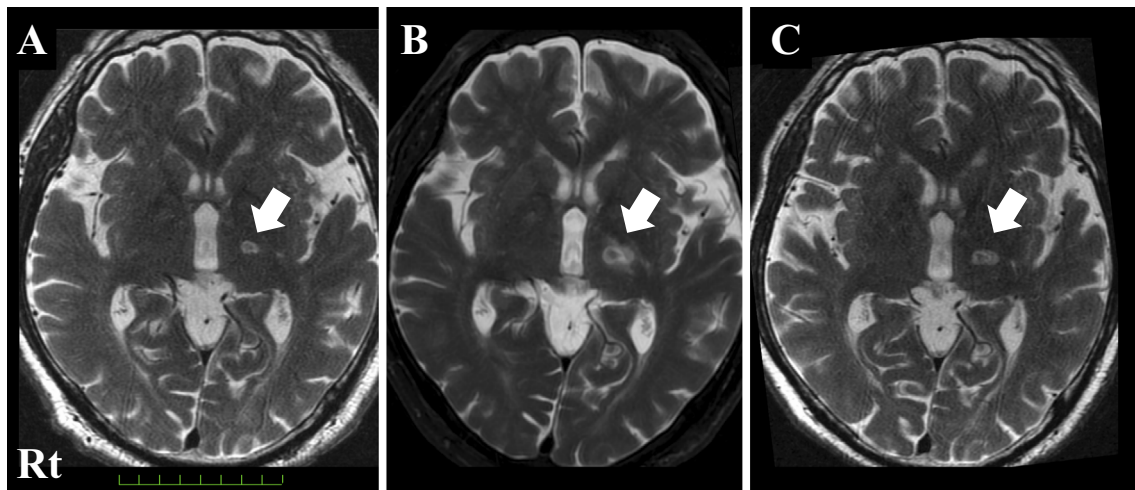


Figure 2. T2-weighted MR image of the brain showing the coagulated lesion (white arrow, A: immediately after thalamotomy, B: 7 days after thalamotomy, C: 1 month after thalamotomy). The hypointense zone at the center was considered to indicate microbleeding. Surrounding edema was obvious at seven days after thalamotomy (B), but it improved after the administration of corticosteroid (C).

the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-Part III at baseline and 4 and 9 weeks after thalamotomy. The total score and the scores of items 3 (rigidity), 17 (rest tremor amplitude), and 18 (constancy of rest tremor) decreased from baseline. Neither tremor nor rigidity were exacerbated, despite reducing the dose of levodopa. However, the scores of items 5 (left hand movements) and 9 (arising from chair) increased after the procedure (Table 2).

Discussion

The therapeutic use of focused ultrasound started in the 1950s. In those days, a craniotomy was essential to provide an acoustic window (8); however, we can now perform this

procedure without any incisions or burr holes due to technical advances. Furthermore, we can monitor the location and the temperature of the targeted lesion in real time. Table 3 summarizes the features of the current radiological or neurosurgical approaches (9). MRgFUS thalamotomy is characterized by minimum invasiveness, no exposure to radiation, and an immediate therapeutic effect. The common sonication-related adverse events include vertigo or dizziness, headache, and nausea. Gait disturbance (including an unsteady feeling in walking) and paresthesia are typical adverse events reported to last after thalamotomy (2, 4, 6). These events have been reported to persist in 9% and 14% at 12 months, respectively (2). However, Zaaroor et al. found that no adverse event lasted beyond three months (6).

Table 2. The Changes in the UPDRS Part III Score and Levodopa Dose.

		Baseline	After 4 weeks	After 9 weeks
	MDS-UPDRS part III			
	Total score	39	19	20
1	Speech	2	1	1
2	Facial expression	2	2	3
3	Rigidity - neck	1	0	0
	- RUE	2	0	0
	- RLE	0	0	0
	- LUE	1	0	0
	- LLE	0	0	0
4	Finger tapping - Right	1	0	1
	- Left	1	1	0
5	Hand movements - Right	1	1	1
	- Left	1	2	2
6	Pronation-Supination movements of hands - Right	1	1	1
	- Left	2	2	1
7	Toe tapping - Right	1	0	0
	- Left	1	0	0
8	Leg agility - Right	0	0	0
	- Left	0	0	0
9	Arising from chair	0	3	1
10	Gait	1	0	1
11	Freezing of gait	0	0	0
12	Postural stability	0	0	1
13	Posture	1	1	1
14	Global spontaneity of movement	1	1	2
15	Postural tremor of the hands - Right	1	0	0
	- Left	1	1	1
16	Kinetic tremor of the hands - Right	2	0	0
	- Left	2	1	1
17	Rest tremor amplitude - RUE	3	0	0
	- RLE	2	0	0
	- LUE	3	1	1
	- LLE	2	0	0
	- Lip/Jaw	0	0	0
18	Constancy of rest tremor	3	1	1
	L-dopa	300mg	300mg	250mg

RUE: right upper extremity, RLE: right lower extremity, LUE: left upper extremity, LLE: left lower extremity

Our patient experienced an exacerbation of bradykinesia, which led to a deterioration in the hand movements and ability to rise from a chair. Edema surrounding the target lesion might have resulted in the impairment of the decreased dopaminergic neurons from the substantia nigra to striatum. While an increasing trend in the exacerbation of bradykinesia was noted, whether it will be transient or permanent remains to be seen.

Resting tremor is a major symptom of PD, and it usually improves with dopaminergic therapy. However, the responsiveness of resting tremor to medication is often of a lesser extent than bradykinesia and rigidity (1). There have been several reports on the clinical efficacy and safety of Vim thalamotomy using MRgFUS for medication refractory tremor in ET and PD (2, 4, 6). The Vim has been regarded as a generator of tremor because of its rhythmic neural ac-

tivity related to contralateral tremor (10). In addition, connections with the Vim, primary motor cortex, and dentate nucleus were suggested to correlate with tremor (11). We therefore selected the Vim as the therapeutic target for tremor. In addition, we added the Vop because rigidity was considered to be associated with the pallidal-Vo complex, the combination of the ventral oralis anterior nucleus (Voa) plus Vop (10).

Our patient also showed improvement in left-side resting tremor and rigidity. Anecdotal evidence exists concerning the therapeutic effects of unilateral Vim thalamotomy on ipsilateral tremor in PD patients (12, 13); however, the reason for this effect has yet to be clearly explained. This is the first experience of Vim plus Vop thalamotomy for a PD patient using MRgFUS in Japan. Although the reason for the effect is unclear, not only contralateral but also ipsilateral

Table 3. The Features of the Current Radiological and Neurosurgical Treatments in Functional Neurosurgery (9).

	RF-thermo coagulation	γ -knife	DBS	MRgFUS
Hair shaving	slight	none	partial	complete
Incision / Burr hole	must	none	must	none
Device implantation	no	no	yes	no
Radiation	low (X-ray, CT)	high	low (X-ray, CT)	low (screening CT)
General anesthesia	no	no	yes*	no
Therapeutic duration	1hr	1hr	2~4hrs	4hrs
Efficacy onset	immediate	delayed up to 1 year	adjustable	immediate
Bilateral procedure	impossible	impossible	possible	possible
post-treatment MRI	possible	possible	impossible	possible
Hemorrhagic complications	possible	almost none	possible	possible
Infection	possible	none	possible	none
Long-term data	yes	yes	yes	unknown

* For implantation of pulse generator

tremor and rigidity improved. The long-term efficacy and safety of MRgFUS thalamotomy for PD patients is still unclear, and we must investigate the exacerbation of bradykinesia after the procedure. In addition, we must explore the adverse events, including gait and sensory disturbances. However, these findings overall suggest that MRgFUS thalamotomy may become a viable therapeutic option for PD patients with medication-resistant symptoms who refuse other neuroradiological or neurosurgical procedures.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Mr. Yoshiaki Murayama (Clinical Research Center, Shonan Fujisawa Tokushukai Hospital, Japan) for his great contributions to the MRgFUS treatment.

References

- Sung YH, Chung SJ, Kim SR, Lee MC. Factors predicting response to dopaminergic treatment for resting tremor of Parkinson's disease. *Mov Disord* **23**: 137-140, 2008.
- Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. *N Engl J Med* **375**: 730-739, 2016.
- Magara A, Bühler R, Moser D, Kowalski M, Pourtehrani P, Jeanmonod D. First experience with MR-guided focused ultrasound in the treatment of Parkinson's disease. *J Ther Ultrasound* **2**: 11, 2014.
- Schlesinger I, Eran A, Sinai A, et al. MRI guided focused ultrasound thalamotomy for moderate-to-severe tremor in Parkinson's disease. *Parkinsons Dis* **2015**: 219149, 2015.
- Na YC, Chang WS, Jung HH, Kweon EJ, Chang JW. Unilateral magnetic resonance-guided focused ultrasound pallidotomy for Parkinson disease. *Neurology* **85**: 549-551, 2015.
- Zaaroor M, Sinai A, Goldsher D, Eran A, Nassar M, Schlesinger I. Magnetic resonance-guided focused ultrasound thalamotomy for tremor: a report of 30 Parkinson's disease and essential tremor cases. *J Neurosurg* **128**: 202-210, 2018.
- Chang WS, Jung HH, Zadicario E, et al. Factors associated with successful magnetic resonance-guided focused ultrasound treatment: efficiency of acoustic energy delivery through the skull. *J Neurosurg* **124**: 411-416, 2016.
- Meyers R, Fry WJ, Fry FJ, Dreyer LL, Schultz DF, Noyes RF. Early experiences with ultrasonic irradiation of the pallidofugal and nigral complexes in hyperkinetic and hypertonic disorders. *J Neurosurg* **16**: 32-54, 1959.
- Rohani M, Fasano A. Focused ultrasound for essential tremor: review of the evidence and discussion of current hurdles. *Tremor and other hyperkinetic movements. Tremor Other Hyperkinet Mov (NY)* **7**: 462, 2017.
- Narabayashi H, Yokochi F, Nakajima Y. Levodopa-induced dyskinesia and thalamotomy. *J Neurol Neurosurg Psychiatry* **47**: 831-839, 1984.
- Zhang JR, Feng T, Hou YN, Chan P, Wu T. Functional connectivity of Vim nucleus in tremor- and akinetic-/rigid-dominant Parkinson's disease. *CNS Neurosci Ther* **22**: 378-386, 2016.
- Diederich N, Goetz CG, Stebbins GT, et al. Blinded evaluation confirms long-term asymmetric effect of unilateral thalamotomy or subthalamotomy on tremor in Parkinson's disease. *Neurology* **42**: 1311-1314, 1992.
- Franzini A, Marchetti M, Brait L, et al. Deep brain stimulation and frameless stereotactic radiosurgery in the treatment of bilateral parkinsonian tremor: target selection and case report of two patients. *Acta Neurochir (Wien)* **153**: 1069-1075, 2011.

The Internal Medicine is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).