

Thalamic Deep Brain Stimulation for Refractory Atypical Tremor after Encephalitis of Unknown Etiology: A Case Report

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Abstract

Tremor associated with encephalitis is usually transient and rarely becomes chronic and refractory. Treatment for such tremor using deep brain stimulation (DBS) has not yet been reported. We report an uncommon case of chronic tremor after encephalitis of unknown etiology and its outcome treated with thalamic DBS. A 47-year-old man presented with a 6-month history of medically refractory tremor after non-infectious and probable autoimmune encephalitis. The patient showed an atypical mixture of resting, postural, kinetic, and intention tremor. The tremor significantly disabled the patient's activities of daily life (ADL). The patient underwent bilateral thalamic DBS surgery. DBS leads were placed to cross the border between the ventralis oralis posterior (Vop) nucleus and ventralis intermedialis (Vim) nucleus of the thalamus. Stimulation of both the Vop and Vim using the bipolar contacts controlled the mixed occurrence of tremor. The ADL and performance scores on The Essential Tremor Rating Assessment Scale (TETRAS) improved from 47 to 0 and from 44 to 9, respectively. The therapeutic effects have lasted for 24 months. Administration of combined Vop and Vim DBS may control uncommon tremor of atypical etiology and phenomenology.

Keywords: tremor, encephalitis, deep brain stimulation, ventral intermediate nucleus, ventral posterior oralis nucleus, thalamus, case report

Introduction

Thalamic surgery for tremor has been revisited due to recent advances in thalamotomy and deep brain stimulation (DBS) for essential tremor and Parkinsonian tremor.^{1–4)} Thalamic surgery is also used for the treatment of uncommon tremor syndromes, such as Holmes and cerebellar tremors, due to traumatic

brain injury, multiple sclerosis, and stroke.^{5–7)} While thalamic surgery is an established treatment for these representative types of tremor, it is unknown whether this conventional treatment can be applied to atypical tremor cases.

Tremor associated with encephalitis rarely becomes chronic and refractory,^{8,9)} and its surgical treatment has not been reported in detail.¹⁰⁾ Herein, the authors report a patient who, after encephalitis of unknown etiology, suffered severe chronic tremor of the head and limbs. The patient presented an atypical mixture of resting, postural, and action tremors and underwent bilateral thalamic DBS. This report aims to describe unique aspects of the tremor syndrome,

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which neither corresponded to a common etiology nor an exclusive phenomenology, but clinically responded well to thalamic DBS targeting the ventralis oralis posterior (Vop) and ventralis intermediate (Vim) nuclei.

Case Presentation

A 47-year-old right-handed Japanese man presented with a 6-month history of severe tremor of the head and limbs. He was referred to us for the medical management of undiagnosed encephalitis and refractory tremor. His medical history was unremarkable. Eight months prior to the referral, the patient was found in a comatose state. A detailed neurological examination was not available at the onset of this case. The head computed tomography revealed diffuse cerebral edema with no signs of stroke. His complete blood cell count, biochemistry findings, and thyroid function test results were normal; the cerebrospinal fluid was aseptic, the polymerase chain reaction test for herpes simplex virus was negative, and the serum antibodies for voltage-gated sodium channels and paraneoplastic antigens were negative. The patient was diagnosed with non-infectious and probable autoimmune encephalitis, and he was administered high-dose methylprednisolone and intravenous immunoglobulin therapy. One month later, the patient awakened and exhibited tremor of the head and limbs. The tremor restricted the most activities of daily life (ADL) including bathing, dressing, transferring, toileting, and eating. The patient needed complete assistance to engage in these ADLs. The patient had also difficulties in speech and gait. Clonazepam, flunitrazepam, propranolol, trihexyphenidyl, and zonisamide were ineffective in reducing tremor.

On examination, the patient had a resting tremor of the head and all limbs and postural and kinetic tremors were observed bilaterally in his hands. Intention tremor was worse on the right side (Video; Video is available online.). The resting tremor in both legs was mild. The ADL and performance scores on The Essential Tremor Rating Assessment Scale (TETRAS) were 47 and 44, respectively. Besides tremor, the patient had dysarthria and disturbances of gait and balance. The T1- and T2-weighted magnetic resonance (MR) images did not show apparent brain lesions, although there were slightly hyperintense spot in the right dentate gyrus, and hyperintense spots in the left thalamus, and bilateral subcortical white matter on T2-weighted MR images (Figs. 1A–1C). The tremor of the present case seemed to be similar to Holmes tremor; however, the activation of tremor by posture was not compatible with the typical

presentation of Holmes tremor.¹¹⁾ Therefore, the present tremor was considered to be atypical.

The patient and his family consented to him undergoing bilateral thalamic DBS surgery. The target was placed slightly posterior to the Vop/Vim border on the plane of the anterior and posterior commissure (AC–PC) line at 13.5 mm from the midline and 6 mm anterior to the PC. As the AC–PC distance was 23 mm, this target was placed slightly anterior¹²⁾ to the standard target for the Vim^{13,14)} (Table 1). The trajectory was moderately leaned forward to cross the border between the Vop and Vim (Vop/Vim). The arrayed microelectrodes recorded spiking activity from the tremor and kinesthetic cells in the Vop and Vim (Fig. 1D). Their ventral border was also estimated from the microelectrode recording. Accordingly, the DBS leads (model 3387; Medtronic, Minneapolis, MN, USA) were implanted bilaterally as they crossed the Vop/Vim border (Figs. 2A–2C). The leads were connected to internal pulse generators (Activa SC, Medtronic) via extension cables. Lead-DBS (<https://www.lead-dbs.org/>) was used to localize and nonlinearly warp the electrodes to the MNI ICBM 2009b Nonlinear Asymmetric space.¹⁵⁾ On the DISTAL (DBS Intrinsic Template AtlAs) atlas,¹⁶⁾ the contacts #2 and #1 were localized within the Vop and Vim, respectively (Fig. 2D). Stimulation of the contact #2 or #1 in each lead suppressed tremor. The final stimulation parameters were 130 Hz, 60 μ sec, and 2.0 volts in the bipolar configuration, using the contact #2 as a cathode and #1 as an anode, bilaterally (Table 1). The volume of activated tissue¹⁷⁾ adequately covered the Vop/Vim border (Fig. 2D). With this stimulation, the occurrence of resting, postural, kinetic and intention tremors was suppressed (Video). The patient could independently eat, walk with assistance from a walker, and maintain hygiene. In addition, minimum assistance was required for transfer. The postoperative ADL and performance scores on TETRAS were 0 and 9, respectively. The patient used the DBS during daytime and had the device turned off before sleep. The therapeutic effects of DBS have lasted for 24 months with no further adjustments of the stimulation parameters.

Discussion

The present case is unique given the rare etiology of chronic tremor syndrome. Most tremor seen in patients with infectious and autoimmune encephalitis^{8,9,18)} is transient, self-limiting, and subsides with treatment of the underlying disorders. To review cases of atypical chronic tremor after encephalitis, a literature search on MEDLINE was completed

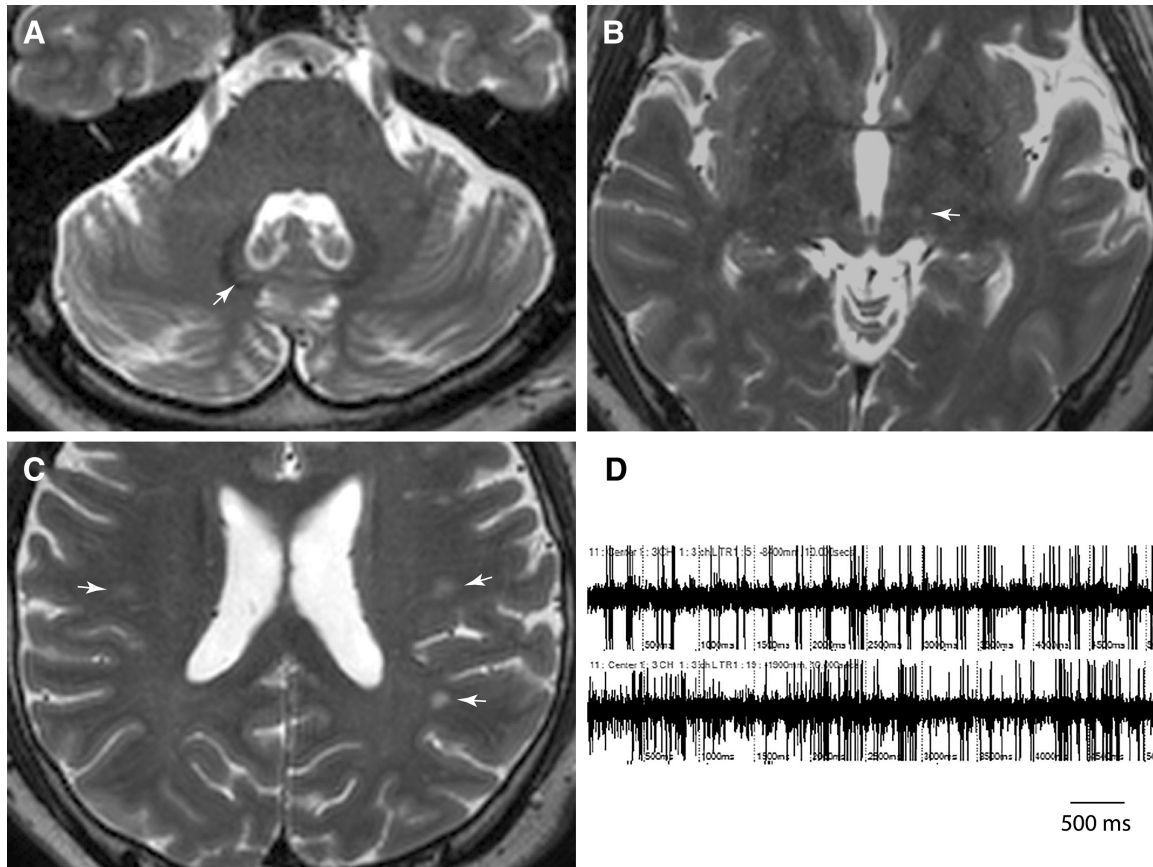


Fig. 1 (A–C) T2-weighted MR images of the cerebellum, thalamus, and cerebrum. A slightly hyperintense spot is seen in the right dentate gyrus (arrow, A). Hyperintense spots are also seen in the left thalamus (arrow, B), and bilateral subcortical white matter (arrows, C). (D) Microelectrode recordings in the ventral tier of the thalamus showing activity of the rhythmic tremor cells (top) and random burst cells (bottom) responding to kinetic motions. MR: magnetic resonance.

Table 1 Coordinates for target, active contact, angle of DBS lead, and stimulation parameters

Side	Target coordinates			Active contact coordinates			Angle of lead (degree)		Stimulation parameters			
	X	Y	Z	Contact	X	Y	Z	ML	AP	Frequency (Hz)	Pulse width (µsec)	Amplitude (V)
Right	13.5	6	0	1 (Anode)	13.7	7.9	2.2	19.9	56.4	130	60	2.0
				2 (Cathode)	14.5	9.3	4.2					
Left	13.5	6	0	1 (Anode)	13.8	7.2	1.7	22.8	58.2	130	60	2.0
				2 (Cathode)	14.3	8.6	3.5					

Coordinates are shown with distance (mm) from the midline (X), anterior to the PC (Y), and above the AC-PC plane (Z). AC: anterior commissure, AP: anteroposterior angle from the AC-PC plane, DBS: deep brain stimulation, ML: mediolateral angle from the median sagittal plane, PC: posterior commissure.

using the title/abstract-tagged keywords “tremor AND encephalitis.” After the screening, the search results based on the title, abstract, and full-text assessment, we identified four medically treated cases with tremor lasting more than 6 months after

the onset of encephalitis^{19–21)} and one chronic post-encephalitic tremor case treated with gamma knife¹⁰⁾ with no clinical details. There were no other surgically treated corresponding cases found in the literature.

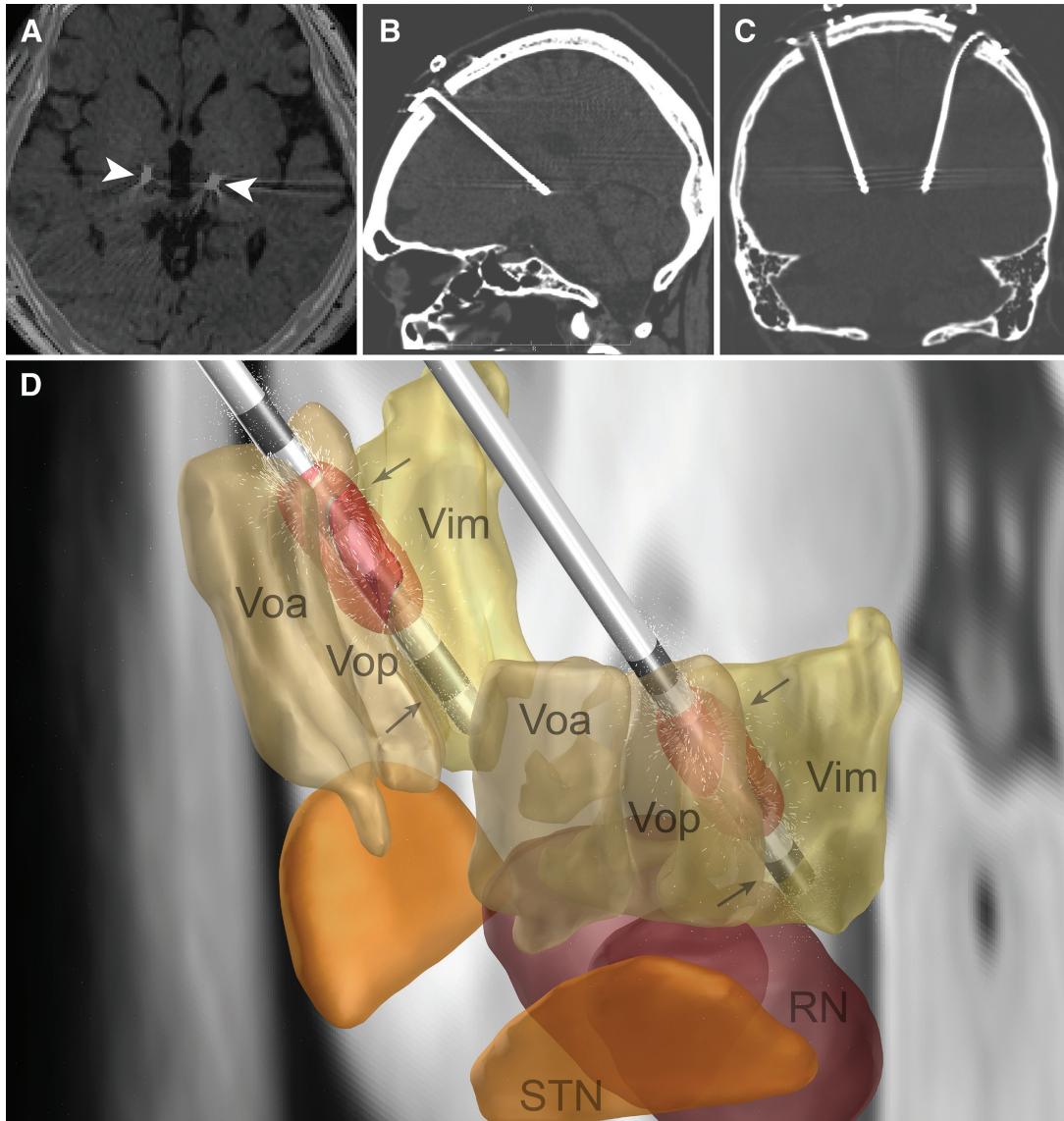


Fig. 2 (A) Bilateral thalamic DBS electrodes (arrowheads) are shown on postoperative computed tomography fused with T1-weighted MR image. Sagittal (B) and coronal (C) images of the DBS leads. (D) Reconstruction of DBS leads in the nucleus Vop and nucleus Vim of the thalamus. The DBS leads go through the border (arrows) between the Vop and Vim. The volume of activated tissue by bipolar stimulation is shown around a cathode of contact #2 and an anode of contact #1 (red). RN: red nucleus, STN: subthalamic nucleus, Vim: ventralis intermedius, Voa: ventralis oralis anterior, Vop: ventralis oralis posterior.

The phenomenology of the tremor is also unique in the present case. The mixed presentation of resting and kinetic tremor in the present case is similar to that of Holmes tremor¹¹⁾; however, the presence of a postural tremor is not compatible with the typical presentation of Holmes tremor.¹¹⁾ The radiological investigation reveals the several hyperintense lesions on MR T2-weighted images (Figs. 1A–1C). Those lesions may be encephalopathic or non-specific. The appearance of the T2-weighted slightly hyperintense spot in the right dentate gyrus

differs from apparent pathogenic lesions in the triangle of Guillain and Mollaret as often observed in patients with Holmes tremor²²⁾ and cerebellar tremor.²³⁾ Therefore, an exclusive phenomenological classification of the present case is rather difficult. The pathological significance of the hyperintense spots in the dentate, thalamus, and subcortical white matter in the present case is unknown. It is assumed that the mixed types of tremor in the present case may have resulted from radiologically obscure lesions in the basal ganglia and cerebellar pathways.

A surgical strategy for this case was adopted from that of Holmes tremor,⁵⁻⁷⁾ given the similar presence of a mixed presentation of basal ganglia and cerebellar tremor.¹¹⁾ Holmes tremor is often treated with multiple stereotactic targets within the striato-pallidal and cerebellar pathways.⁵⁻⁷⁾ The ventral oralis anterior (Voa) and Vop of the thalamus, those receive the striato-pallidal projection,²⁴⁾ are co-stimulated with the Vim.^{25,26)} Alternatively, the posterior subthalamic area (PSA), which carries cerebellar outflows within the prelemniscal radiation and the caudal zona incerta,^{24,27,28)} can be targeted with Voa/Vop^{29,30)} sometimes using a single trajectory.³⁰⁻³²⁾ In the present case, bilateral insertion of the DBS electrodes was necessary to control bilateral and axial tremor symptoms. Therefore, a single trajectory for multiple targets was preferred. Targeting the Vop and Vim and placing the DBS lead across the Vop/Vim border can be a simple and safe trajectory to stimulate both the striato-pallidal and cerebellar pathways, although its validation is limited by a single-case observation.

Conclusion

Tremor after encephalitis of unknown etiology may become chronic, and its presentation may not correspond to typical phenomenology. By adjusting the lead trajectory and target coordinates, single-lead Vop/Vim DBS can modulate both basal ganglia and cerebellar pathways and may control uncommon tremor of atypical etiology and phenomenology.

Statement of Ethics

This case report complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The institutional review board of Tazuke Kofukai Medical Research Institute and Kitano Hospital approved the study (reference number S18-01-014). Information revealing the subject's identity is to be avoided. Written informed consent was obtained from the patient and his family. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Authors' Contributions

Yusuke Nakajima: Investigation, Resources, Writing—Original Draft, Daisuke Kambe: Methodology, Data Curation, Software, Visualization, Hiroki Toda: Conceptualization, Methodology, Validation, Writing—Review and Editing, Visualization, Project administration, Funding acquisition, Namiko Nishida: Resources, Shigeto Nagao: Resources, Nobukatsu Sawamoto: Conceptualization, Writing—Review and Editing, Supervision, Ryosuke Okumura: Resources, Methodology, Data Curation, Visualization, Akihiko Ozaki: Resources, Supervision, Koichi Iwasaki: Supervision.

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Conflicts of Interest Disclosure

None of the authors have any conflict of interest to disclose regarding the publication of this article.

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