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Deep Brain Stimulation Leads to Long-term Improvement of Neuropathic Tremor due to Chronic Inflammatory Demyelinating Polyneuropathy: A Case Report

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Abstract

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a peripheral neuropathy caused by immune-mediated demyelination, causing tremors in 3.9%-58% of affected patients. This neuropathic tremor may persist after treatment and is known to be refractory to conventional medication. We present two cases of neuropathic tremor due to CIDP in which deep brain stimulation (DBS) over a long-term period led to marked improvement. Case 1: A 66-year-old woman presented with severe 2-3-Hz resting, postural, and kinetic tremors of both hands. The tremor was refractory to medication but improved well after bilateral VIM-DBS. However, 2 months after the procedure, the tremor worsened and was accompanied by sensory disturbance in the extremities. A diagnosis of CIDP was made, and treatment with corticosteroids and intravenous immunoglobulin achieved remission 6 months later. Although there was residual tremor after CIDP remission, it has been well controlled by DBS for the last 10 years. Case 2: A 56-year-old man presented with a 6-year history of CIDP after developing sensory dullness and tremors in the extremities. The CIDP had gone into remission 1 year previously and the sensory deficits had improved, but the tremors had gradually worsened: severe 8-12-Hz postural, kinetic, and resting tremors were present in both upper extremities. Right VIM-DBS was performed and the tremors on the left side showed marked improvement. Over the next 8 years, the tremors were well controlled and there were no relapses of CIDP. DBS may achieve long-term improvement of neuropathic tremor caused by CIDP if the CIDP is in remission.

Keywords: deep brain stimulation, stereotactic surgery, neuropathic tremor, chronic inflammatory demyelinating polyneuropathy, ventral intermediate nucleus

Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a neuropathy caused by immune-mediated demyelination. It typically presents as a progressive or relapsing symmetric sensory-motor polyneuropathy, including the proximal muscles. At least 50% of affected patients exhibit the typical CIDP phenotype, but there are various atypical variants.[1,2] CIDP is also known to cause tremor, but the incidence of such tremors remains unclear. Busby and Donaghy reported that 3.9% of patients with chronic dysimmune neuropathy - a concept broader than CIDP - had significant tremor.[3] Saifee et al. reported tremor in 15 out of 26 (58%) CIDP patients they examined. The tremor caused by CIDP often persists after treatment of the underlying neuropathy, and in most cases, it is refractory to tremor-specific medication.[4] We herein report two cases of CIDP-induced tremor that showed long-term improvement with deep brain stimulation (DBS).

Case Report

Case 1

A 66-year-old right-handed woman had been experienc-

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ing slight paresthesia in her peripheral extremities for 2 years and had developed persistent tremors in both hands 1 year before she consulted a neurologist at our institution. Physical examination revealed resting, postural, and kinetic tremors in both upper extremities, making eating difficult. There were no other neurological deficits in her sensory and motor systems. The tremors were characterized by a 2-3-Hz grasping and releasing movement (see Video 1, segment 1). Medications such as levodopa, atenolol, and clonazepam for 7 months were not effective; therefore, she was referred to our neurosurgical department. Although the etiology of the tremors remained unclear at this time despite examinations conducted in our neurological department, it significantly impacted her daily life; therefore, she opted for bilateral electrode implantation into the ventral intermediate nucleus (VIM) of the thalamus. The procedure was performed first on the left side, followed by the right side 6 months later. MRI was performed with a Leksell stereotactic frame placed on the patient, and the bilateral VIMs were targeted at the level of the anterior commissure (AC)-posterior commissure (PC) line, 25% of the AC-PC length anterior to the PC and 13.5 mm lateral to the midline. Microelectrode recording revealed oscillatory neuronal activities with frequencies similar to those of the arm tremor in bilateral VIMs. Test stimulation during the surgical procedure revealed that the tremor suppression effect was optimal 2.5 mm below the target on both sides and there were no side effects. Therefore, quadripolar electrodes (type 3387; Medtronic, Minneapolis, Minnesota, USA) were positioned at these points and connected to implantable pulse generators (Activa SC, Medtronic) in the bilateral subclavicular region. Monopolar stimulation using the most ventral or next-most ventral electrodes was effective on both sides, and the tremor was markedly improved. However, within the first 2 months after the procedure, the tremor worsened further and repeated DBS programming was not satisfactory. The patient also began to suffer severe numbness and weakness in both lower extremities and unsteadiness while walking. These symptoms were not related to DBS. Neurological examination demonstrated distal sensory loss and ataxia in both lower extremities and areflexia in all four extremities. A nerve conduction study showed severe demyelination changes in all four extremities. Biopsy of the left sural nerve also revealed demyelination. Based on these findings, a diagnosis of CIDP was made. The patient was treated with corticosteroids and intravenous immunoglobulin, which led to marked improvement of the sensory loss and ataxia. Mild-to-moderate tremor remained, and DBS was used for fine manual tasks (see Video 1, segment 2). During 10 years of follow-up, the patient has not shown relapse of CIDP, and her mild postural tremor has been effectively suppressed by VIM-DBS.

Case 2

A 56-year-old left-handed man with a medical history of hepatitis B, syphilis, and dyslipidemia presented with a 6-year history of tremor and numbness in the left hand. The numbness had spread to the extremities, and he had been diagnosed 1 year later as having CIDP based on neurological findings, a spinal fluid examination, and nerve conduction studies. Moreover, blood tests and bone marrow biopsy had shown monoclonal gammopathy of undetermined significance involving immunoglobulin G lambda. Although the patient achieved remission of CIDP after multiple courses of corticosteroids, intravenous immunoglobulin, and cyclosporine over a 4-year period, the tremor persisted in the limbs and gradually worsened over time. Medications such as levodopa, beta-blocker, trihexyphenidyl hydrochloride, and primidone for the tremor were not effective; therefore, he was referred to our institution for surgical intervention 1 year after completion of the CIDP treatment. He had no discernible sensory disturbance or motor weakness, but tendon reflexes were absent in all four extremities. He exhibited 8-12-Hz severe resting, postural, and kinetic tremors in both upper extremities (see Video 2, segment 1). He underwent unilateral stimulating electrode implantation into the right VIM using a Leksell stereotactic frame. MRI was performed with the frame fixed to the patient's head, and the right VIM was targeted at the level of the AC-PC line, 5 mm anterior to the PC and 13.5 mm lateral to the midline. Microelectrode recording confirmed positioning of the electrode in the VIM at the initial target site and oscillatory neuronal firing with a frequency similar to that of the tremor. The electrical stimulation suppressed the tremor successfully. A quadripolar electrode (type 3387; Medtronic) was then placed at this initial targeted location and connected to an implantable pulse generator (Activa SC, Medtronic) implanted in the subclavicular region. Monopolar stimulation using the most ventral and the next-most ventral electrodes was effective, and there were no side effects (see Video 2, segment 2). Postoperatively, the patient has been followed up for 8 years with no relapse of CIDP, and the tremor in the left hand has been well controlled.

Discussion

Tremor associated with peripheral neuropathy, including CIDP, is commonly referred to as neuropathic tremor. Neuropathic tremors occur in hereditary neuropathies such as Roussy-Levy syndrome and inflammatory neuropathies such as IgM paraproteinemic neuropathy, GBS, and CIDP.[4] Neuropathic tremors share similarities with essential tremors, as they are postural and kinetic, distal-predominant, and alike in amplitude and frequency. However, neuropathic tremor is often more irregular and jerkier than essential tremor and may also be manifested as resting tremor.[5] In Case 1, the tremor frequency was low, and in

both Cases 1 and 2, resting tremors were present. In addition, tremors of both patients were closely associated with the course of CIDP without any evidence of other neurological disorders and therefore were diagnosed as tremor caused by CIDP.

Although the literature on DBS for neuropathic tremor is limited, most studies have reported an improvement in tremor over a 1-2-year follow-up period.[6] Only two patients who underwent DBS for tremor due to CIDP have been reported. Patel et al. documented a case series of five patients, two of whom had CIDP, and suggested that the long-term efficacy of DBS might diminish over time (0.5-9 years) due to factors such as habituation and rebound.[7] One of these two CIDP patients underwent DBS 10 years after diagnosis, but the therapeutic effect was lost in 2 weeks. The other patient with a 10-year history of tremor, who was diagnosed as having CIDP due to exacerbated tremor and neuropathic symptoms, underwent DBS for residual tremor 1 year after plasmapheresis. However, the effect of DBS waned during 1 week after surgery. Unfortunately, the details of these cases after the efficacy of DBS had diminished were not described, and the mechanisms responsible for the attenuated efficacy remained unclear. Progression or recurrence of their CIDP disease status may have played a role, as seen in Case 1. Both patients demonstrated sustained and favorable outcomes of VIM-DBS over long-term periods (8 and 10 years) after the procedure. However, DBS may be less effective during the active phase of CIDP. In Case 1, VIM-DBS was initially quite successful in the early stage, but the tremor worsened with the progression of CIDP symptoms 2 months after surgery. The tremor was difficult to manage despite DBS reprogramming, and the remaining tremor was well controlled with VIM-DBS after treatment of the CIDP. Considering the improved symptoms in Case 1 after treatment of the CIDP, DBS might not have been necessary if the CIDP had been diagnosed and treated earlier. As shown in Case 2, it may be better to perform DBS after confirming remission of CIDP. However, determining the optimal timing of DBS for CIDP tremor is difficult because CIDP is reported to recur in 20%-35% of cases and is unpredictable.[2] Although CIDP did not relapse for 8 and 10 years after treatment in our present patients, it should be noted that CIDP can sometimes recur and the efficacy of DBS may be insufficient.

It remains unclear why peripheral neuropathy leads to tremor. Tremor can be classified into two main types on the basis of etiology: one results primarily from peripheral stretch-reflex oscillation and the other from central neural networks.[8] Tremors that exhibit changes in frequency due to factors such as mass loading are typically attributed to peripheral stretch-reflex oscillation.[8] Although we did not evaluate tremor frequency with mass loading in the present two cases, Saifee et al. found no significant changes in tremor frequency after mass loading in patients with neuropathic tremor.[4] Therefore, tremor due to peripheral neuropathy may arise via central mechanisms. Since VIM-DBS was effective in both cases, it is possible that - as in essential tremor - corticobulbocerebellothalamocortical loops are also involved in neuropathic tremor. This loop receives sensory information from the peripheral nerves,[8] and it is suspected that the distorted input due to CIDP causes dysfunction of the loop.[9] However, such a central mechanism alone does not explain the decreased efficacy of DBS in Case 1 when CIDP worsened. It has been hypothesized that neuropathic tremor occurs through a combination of central and peripheral mechanisms.[10] The peripheral mechanism includes altered spinal stretch-reflex arcs due to impaired or altered sensory input, inappropriate sensory input to the cerebellum leading to an imbalance between agonist and antagonist muscles, or exaggerated physiological tremor as a result of muscle weakness. Such peripheral mechanisms may be exacerbated during the active phase of CIDP, and DBS alone may not suppress the tremor effectively. Few studies[9,11] have assessed these mechanisms of neuropathic tremor, and further research is needed.

In conclusion, CIDP may produce tremor through central nervous system dysfunction, and DBS shows long-term efficacy for the control of such tremors. In addition, remission of CIDP may be an important requirement for a stable effect of DBS. If the tremor worsens during the postoperative course, the disease status of CIDP should be evaluated.

Supplementary Material

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Consent for Publication

All the participants have consented to the submission of the case report to the journal.

Author Contributions

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Conflicts of Interest Disclosure

All authors declare no conflict of interest.

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