**Dystonia as Complication of Thalamic Neurosurgery**

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# Abstract

## *Background.* Thalamotomy and deep brain stimulation of the ventralis intermedius nucleus are effective symptomatic treatments for tremor, irrespective of the underlying diagnosis.

## *Methods and Results.* Herein we describe six tremor patients (2 Parkinson’s disease, 1 dystonic tremor, 2 Essential tremor plus dystonia, 1 Essential tremor plus ataxia) who underwent thalamic neurosurgery and acutely or sub-acutely developed dystonia that was permanent in three cases and could not be managed with any adjustments in the stimulation settings. Tremor response was excellent. We argue that thalamic procedures disrupted either or both the cerebello-thalamic and the cortico-striato-pallido-thalamo-cortical loop resulting in an increase of the thalamo-cortical outflow and subsequent change in the clinical picture from tremor to dystonia.

## *Conclusion*. Thalamic neurosurgery might be rarely complicated by dystonia. Why some patients are more prone to develop this adverse event is still unknown and possibly related to intrinsic factors, which certainly need further studies.

# Introduction

Thalamotomy and deep brain stimulation (DBS) of the ventralis intermedius (Vim) nucleus of the thalamus are effective symptomatic treatments for tremor irrespective of the underlying tremor diagnosis, i.e. essential tremor (ET), Parkinson's disease (PD) and dystonic tremor [1]. The long-term efficacy is good, although loss of benefit can occur due to habituation and/or disease progression [1-2]. The adverse effect profile of both is acceptable overall, particularly for DBS as adjusting stimulation settings can lessen common issues such as balance and speech problems [2].

Here, we describe six patients who underwent thalamic procedures for tremor in three centers and acutely or sub-acutely developed dystonia contralateral to the targeted hemisphere. We also provide possible pathophysiological explanations to explain this interesting and rare phenomenon.

# Case reports

Patient 1. A 50-year-old, right-handed Indian man with a diagnosis of PD complained of left hand tremor and stiffness for 10 years. Due to the disabling and drug-resistant tremor (Video 1, segment 1), he underwent right Vim DBS (3387 lead connected to an Activa SC implantable pulse generator – IPG – by Medtronic, Minneapolis, MN, USA). Post-operative brain MRI confirmed satisfactory electrode location (Figure 1A). The tremor was abolished immediately after electrode insertion in absence of any acute adverse events. However, within a few days the patient developed a sustained dystonia of left hand and foot (Video 1, segment 2). One month post surgery he still had no tremor but the ipsilateral hemidystonia persisted (Video 1, segment 3). No additional neurological signs suggesting damage of the cortico-spinal tracts were observed. Stimulation was started with the most proximal contact in the attempt to reduce dystonia by stimulating the ventral lateral anterior portion of the thalamus, which is closest to ventralis oralis posterior (Vop) nucleus [3]. Finally, stimulation was turned off due to lack of benefit after several unsuccessful programming sessions. Levodopa was discontinued and he became bradykinetic confirming a diagnosis of PD with probable dystonic tremor at onset and hemidystonia triggered by the introduction of the thalamic electrode. A year later, the patient developed generalized levodopa-induced dyskinesias and underwent bilateral DBS of the globus pallidus pars interna (GPi) with significant improvement of dyskinesia and only partial improvement of hemidystonia. Further symptomatic management was also achieved with injections of botulinum neurotoxin (BoNT) in left hand and foot.

Patient 2. A 57-year-old, left-handed, woman with a diagnosis of tremor-dominant PD complained of left hand rest and kinetic tremor for 7 years. Tremor was partially levodopa-responsive but she remained disabled as kinetic tremor affected her dominant side (Video 2, segment 1). Right subthalamic nucleus (STN) DBS (3387 lead connected with an Activa PC IPG) improved tremor but induced left-hand cramping (Video 2, segment 2). Any stimulation reprogramming resulted in further worsening of the dystonia, thus STN stimulation was finally switched off with subsequent worsening of tremor and resolution of spasms. Six years later, she was implanted with right Vim DBS (3387 lead connected with an Activa SC IPG) (Figure 1B). Vim stimulation was effective on tremor but induced task-specific hand dystonia (Video 2, segment 3). Again stimulation was turned off with resolution of dystonia. After reviewing the clinical history (particularly the lack of bradykinesia and rigidity), the initial diagnosis of PD was reconsidered and dystonic tremor was the final diagnosis. Nuclear imaging of the dopaminergic pathway was not available.

Patient 3. A 55-year-old man with tremor-dominant PD with off medication dystonia underwent right-sided radiofrequency thalamotomy due to disabling left hand kinetic tremor (Video 3, segment 1). He had paraplegia due to a previous spinal trauma and given the presence of infected pressure holes, often causing sepsis, DBS was not considered a good option for such a patient.

Tremor improved right after surgery but left arm dystonic posturing slowly developed over a 3-month period (Video 3, segment 2). Brain MRI showed a lesion limited to the Vim thalamus (Figure 1C). No additional neurological signs suggesting damage of the cortico-spinal tracts were observed. The patient is currently managed with high doses of BoNT injections with partial benefit, particularly alleviating his pain.

Patient 4. A 76-year-old man with an 8-year history of alcohol-responsive postural and action tremor consistent with ET was referred as a surgical candidate for bilateral Vim DBS. In hindsight, he had very subtle right foot posturing prior to surgery and a possible increased blinking rate (i.e., ET plus dystonic signs) (Video 4, segment 1). After initial improvement, he developed progressive right foot dystonia, neck stiffness with jaw-opening dystonia and blepharospasm over a 1-year period, not alleviated by any stimulation adjustments nor by turning off the stimulation for several minutes (Video 4, segment 2). No additional neurological signs suggesting damage of the cortico-spinal tracts were observed. In view of the persistent tremor and worsening of dystonia, bilateral Gpi DBS was performed at age 81 (Figure 1D). After intensive programming, his tremor was well controlled with partial improvement of right leg dystonia, dysarthria, oromandibular dystonia and blepharospasm.

Patient 5. A 66-year-old man with a 20-year history of action tremor in the upper limbs and a diagnosis of ET underwent bilateral Vim DBS (directional lead 6171 connected to Infinity IPG, Abbott Inc, Plano, TX, USA) (Video 5, segment 1). Prior to surgery, he had very mild dystonic posturing of the right hand characterized by finger extension and wrist flexion, when outstretching the upper limbs (i.e., ET plus dystonic posturing).

The most ventral contacts of the electrodes were positioned in the Zona Incerta (ZI) (Figure 1E). Despite full control of tremor on both sides, dystonic movements in the right arm appeared right after the first programming (Video 5, segment 2) and decreased when the intensity of stimulation on left Vim was reduced from 3.2 to 2.8 mA. At this DBS setting he had satisfactory control of action tremor with mild dystonic movements not interfering with activities.

Patient 6. A 63-year-old woman diagnosed with tremor of the head, vocal cord and limbs (more severe in the upper limbs) obtained excellent tremor control after bilateral Vim/ZI DBS (directional lead 6171 connected to Infinity IPG) (Figure 1F). Before DBS, she had some difficulty with tandem gait and a slightly wide base when walking (i.e., ET plus ataxic signs). After surgery, prior to turning DBS on, a mild inclination of the head to the left was apparent. The best effect on tremor was obtained with the stimulation of the first (on ZI) and third (on Vim) contact. However, stimulation with the most distal contact in ZI worsened balance. One month following her first DBS programming session, a mild dystonic posturing of both hands was evident with stimulation of both hemipsheres, especially with increased intensity of stimulation (Video 6, segment 1). Significant improvement of dystonic posturing was achieved by using the most distal contacts located in ZI (Video 6, segment 2).

# Discussion

Despite different clinical presentations, the patients described here share common features: an excellent tremor response after a thalamic procedure, the relatively rapid development or worsening of dystonia after surgery, the presence of subtle to evident dystonic signs before surgery (in all patients but number 6), and non contributory brain MRI.

In patient 1 the tremor completely and permanently resolved with right Vim lead insertion but left hemidystonia occurred. In patient 2 focal dystonia was induced by Vim stimulation and, despite intensive reprogramming satisfactory control of tremor without dystonia was impossible. Patient 3 developed permanent dystonia as a result of radiofrequency thalamotomy. Patient 4 progressively developed generalized disabling dystonia after bilateral Vim DBS that required Gpi DBS as rescue therapy. Patients 5 and 6 presented with mild to moderate dystonia after Vim DBS, manageable with changes in stimulation settings (reduction of amplitude of stimulation in case 5 and switch from Vim to ZI stimulation in case 6).

There are few patients reported who presented with a thalamic-induced or aggravated dystonia. Sydow and colleagues reported four ET patients who developed stimulation-induced dystonia during a Vim DBS programming session [4]. Hedera et al described two dystonic patients whose limb dystonia worsened following unilateral Vim DBS [5]. Similarly to our patients 5 and 6, in these patients optimizing DBS settings resolved the dystonia. By contrast, there are no reported cases of permanent dystonia triggered by lead insertion or thalamotomy (like our patients 1, 3 and 4). We are aware of similar other unpublished cases (personal communication of Prof. Deuschl in Kiel, Germany and Prof. Krack in Grenoble, France).

Both focal and hemidystonia have been described after isolated lesions involving the postero-lateral portion of the thalamus in previously healthy individuals [6]. The pathogenesis of thalamic dystonia is not completely known but may result from dysfunction of the cerebello-thalamic pathway. Alternatively, a disruption of the cortico-striato-pallido-thalamo-cortical loop may disinhibit the ventrolateral nucleus producing increasing thalamo-cortical drive [6].

The role of the cerebellum in the pathophysiology of dystonia is the focus of recent research [7]. Argyelan et al. demonstrated a reduced integrity of cerebello-thalamo-cortical fiber tracts, likely developmental in origin, in both manifesting and clinically non-manifesting *TOR1A* mutation carriers [8]. In these subjects, reductions in cerebello-thalamic connectivity correlated with increased motor activation responses, consistent with loss of inhibition at the cortical level [8].

Although all our patients had an action tremor, they had different clinical presentations (Table 1). In hindsight, patients 1 had dystonic tremor followed by PD, while patient 2 had dystonic tremor mistaken for PD. Patient 3 had tremor-dominant PD also characterized by off medication dystonia. Patient 4’s presentation was consistent with long-lasting ET plus soft dystonic signs. Patient 5’s diagnosis is consistent with ET plus dystonic posturing, while patient 6 presented with ET plus ataxic features [9].

We argue that dystonia can be a rare and disabling complication of thalamic surgery and it is probably more frequent in patients with pre-existing dystonic features. Similarly to observations in post-stroke patients, thalamic procedures can disrupt either or both the cerebello-thalamic and the cortico-striato-pallido-thalamo-cortical loop resulting in an increased thalamo-cortical outflow causing a different movement disorders [6]. The effect may be specific to the thalamus, as switching the stimulation from Vim to ZI in patient 6 improved the dystonia. As highlighted by Argyelan et al. our patients might have been predisposed to development of dystonia after Vim DBS because of intrinsic unknown factors [8].

Indeed, the main challenge to our hypothesis that thalamic surgery either triggered or unmasked dystonia in our patients is that thalamic procedures are an effective and safe treatment for dystonic tremor [10]. Our observation that thalamic procedures themselves can cause dystonia is therefore important, but puzzling.

Our report has practical implications. Vim DBS and thalamotomy are considered as effective, symptomatic treatments for tremor irrespective of the underlying diagnosis. Our patients had a negative outcome after thalamic procedures with permanent dystonia in patients 1, 3 and 4 possibly because of altered neural circuits that led to a switch from tremor to dystonia. It is possible that this phenomenon may be more prevalent but underreported in the literature because of the known publication bias of not reporting negative outcomes. Therefore some tremulous patients may not benefit from thalamic procedures because of risk of developing or aggravation of pre-existing dystonia and may be considered for other surgical targets (i.e., GPi, the thalamic ventralis oralis anterior and posterior or STN) [11]. The description of other similar cases may shed light on the intrinsic factors associated with that risk. To date, there are no randomized prospective trials comparing Vim and GPi in dystonic tremor, in our patients Vim was chosen in such patients because tremor was the most disabling symptom, in keeping with previous observation in dystonia patients carrying both Vim and GPi electrodes [5]

There are a number of limitations with our paper including differences in neurosurgical procedures between centers, the lack of neuroimaging investigating the dopaminergic pathways in patient 2, and the variable inter-rater reliability of the detection of soft neurological signs using videos [12]. Finally, thalamic surgery clearly led to the dystonia in patients 1, 3 and 4, however for remaining patients alternative hypotheses should be made. In fact, we cannot exclude the possibility of cortico-spinal side effect due to the spread of current in cases with stimulation-induced dystonia (patients 2, 5 and 6).

In conclusions, we have reported six patients who developed dystonia after thalamic procedures for tremor, complication that was permanent in three of them, a circumstance never reported before. Indeed, such new phenomenon appears to be rare as we were able to collect six cases in three large DBS centers. However, we suspect that this unexplained adverse event may be more prevalent as it probably is underreported in the literature. It is likely that thalamic procedures altered neural circuits resulting in unexpected dystonia in our patients. Further studies are warranted to clarify the intrinsic factors possibly predicting the development of dystonia after thalamic procedures.

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1. Research project: A. Conception, B. Organization, C. Execution;

2. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

MP: 1B, 1C, 2A

VP: 1C, 2A

FM: 1C,2B

MA: 1C,2B

DAO: 1C,2B

RPM: 1C, 2B

TA: 2B

EP: 2B

MH: 2B

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AML: 2B

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**Conflict of interest related to research covered in this article**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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**Figure legend**

**Figure 1.** A) Patient 1’s T2w brain MRI showing the thalamic electrode position (white arrow). Later on, the patients underwent bilateral GPi DBS. B) Patient 2’s T2w brain MRI showing the thalamic electrode position (white arrow). C) Patient 3’s T2w brain MRI showing a right-sided radiofrequency thalamotomy. D) Patient 4’s T2w brain MRI showing bilateral Vim DBS as well as bilateral Gpi DBS (white dots). E) Patient 5’s T2w brain MRI resonance image with superimposed post-operative CT showing bilateral Vim/ZI DBS at the Vim level (white dots). F) Patient 6’s postoperative CT fused to T2w brain MRI image showing bilateral Vim/ZI DBS (white dots).

# Video legends

## Video 1 - Patient 1.

## Segment 1. L­evodopa challenge before surgery. Left hand kinetic tremor is evident OFF medication as well as hypomimia. After a challenge with levodopa 150 mg left hand tremor improves but dystonic posture appears.

## Segment 2. Video from the Emergency department seven days after surgery showing left hand fixed dystonia (DBS off).

## Segment 3. First programming session one month after surgery off stimulation and off medication. The patient presents with left hemidystonia with toes curling during walking. Patient has no spasticity, weakness or other pyramidal signs.

## Video 2 - Patient 2.

## Segment 1. Baseline evaluation before surgery: left hand rest tremor and reduced left arm movements during walking are evident.

## Segment 2. Right STN DBS effectively controls tremor but induces disabling task-specific cramping with left shoulder elevation.

## Segment 3. Patient with both Vim and STN DBS stimulation off: left hand rest tremor with no dystonia is shown. After turning right Vim DBS on (case+2- 2.5V/60μs/130Hz) tremor subsides but painful, task-associated dystonia with shoulder elevation is evident. Rest tremor is slightly present in the right hand as well.

## Video 3 - Patient 3.

## Segment 1. Levodopa challenge before surgery: left hand kinetic tremor and dystonic posturing as well as hypomimia are evident OFF medication. Levodopa challenge with 150 mg does not improve tremor.

## Segment 2. Patient is seen after right thalamotomy while on levodopa: he presents left hand dystonia and levodopa-induced dyskinesias involving his trunk and neck.

## Video 4 - Patient 4.

## Segment 1. Upper limbs postural tremor is shown with worsening in the bat-wing position. Kinetic tremor is also present. .

## Segment 2. Post-operative condition with DBS on (4.5V/90μs/150Hz, 4.4V/90 μs/150Hz) is characterized by laryngeal, jaw and right foot dystonia. An improvement of tremor (left>right) is also noticeable. Left foot drop is secondary to an incidental peroneal nerve palsy.

## Video 5 - Patient 5.

## Segment 1. Upper limbs rest and postural tremor (right>left) is seen during the preoperative assessment.

## Segment 2. After surgery the patient has a dramatic improvement of tremor with dystonic posturing of right arm (case+ 2(a,b,c)-/2 mA/90 μs/130 Hz).

## Video 6 - Patient 6.

## Segment 1. Dystonic posturing of the upper limbs (left>right) is evident during Vim stimulation (case+ 3(a,b,c)-/1.8 mA/60μs/130Hz).

Segment 2. Improvement of dystonic posturing of the upper limbs with preserved benefit on the tremor is seen with ZI stimulation (case+ 1(a,b,c)-/1.8 mA/60μs/130Hz). Finally the patient was managed with Vim stimulation as her balance was worse with ZI stimulation and she had little disability from the mild dystonic posturing of the hands.