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RESEARCH

# Unilateral deep brain stimulation (DBS) of nucleus ventralis intermedius thalami (Vim) for the treatment of post-traumatic tremor in children: a multicentre experience

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## Abstract

**Purpose** Deep brain stimulation (DBS) of nucleus ventralis intermedius thalami (Vim) is a validated technique for the treatment of essential tremor (ET) in adults. Conversely, its use for post traumatic tremor (PTT) and in paediatric patients is still debated. We evaluated the efficacy of Vim-DBS for lesional tremor in three paediatric patients with drug-resistant post-traumatic unilateral tremor.

**Methods** We retrospectively collected data regarding three patients with unilateral tremor due to severe head injury, with no MRI evidence of basal ganglia lesions. The three patients underwent stereotactic frame-based robot-assisted DBS of Vim contralateral to the tremor side.

**Results** Mean follow-up was 48 months (range: 36–60 months). Tremor was reduced in all patients with a better control of voluntary movements and improvement of functional status (mean FIM scale improvement + 7 points). No surgical complications occurred.

**Conclusion** Unilateral contralateral DBS of Vim could be efficacious in post-traumatic tremor, even in paediatric patients and should be offered in PTT drug-resistant patients.

**Keywords** Post traumatic tremor · Paediatric · Deep brain stimulation · Nucleus ventralis intermedius thalami

## Introduction

Post-traumatic tremor (PTT) is defined as a secondary movement disorder (SMD) that occurs in about 5% patients who have suffered a severe head injury, after a mean latency between 2 weeks and 2 years [1–5]. Clinical features of

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PTT resemble Holmes tremor and include resting, postural, kinetic and intentional tremors, mostly involving the upper limbs [1, 2]. The neurophysiological basis of PTT relies on impaired midbrain and cerebello-thalamic tracts, likewise Holmes tremor which is due to isolated midbrain dysfunction frequently caused by vascular malformations like AVMs and cavernomas [3, 4].

Pharmacological treatment of PTT is difficult since most of the available drugs (propranolol, L-dopa, carbidopa, carbamazepine, clonazepam, trihexyphenidyl, glutethimide, isoniazid, valproic acid, phenytoin, anticholinergics), along with botulinum toxins, provide limited benefit [2, 3, 6–15]. Stereotactic thermal lesion of the ventrolateral thalamus was used to treat patients in 1984 with encouraging results when Bullard et al. performed stereotaxic thalamotomies on 11 patients. All patients benefited from the approach in the immediate and long-term post-operative period [16]. However, thermal lesions of the ventrolateral thalamus carried a high morbidity as up to 63% of the patients had permanent definitive motor and/or sensitive impairments [2].

Due to this high morbidity rate, almost all stereotactic lesional procedures have been replaced by the deep brain stimulation (DBS) due to its reversible and adjustable nature and lower fatality rates [17, 18]. In 2008, Schuurman et al. compared DBS and thalamotomy with long-term follow-ups (5 years) in patients with essential tremor (ET) and tremor caused by Parkinson's disease (PD) and multiple sclerosis (MS) [19]. The authors concluded that thalamic stimulation is preferable over thalamotomy to improve functional abilities. For ET, surgical outcomes proved satisfactory and morbidity rates lowered after DBS-Vim, compared to thalamotomy [19]. The most common and efficacious target of DBS for ET is the anterior margin of the Vim, also known as ventralis oralis anterior (Voa) part/zona incerta (ZI) [20–23]. Specific Vim coordinates for indirect targeting are $X = 10.5$ mm lateral to the lateral ventricular wall and no more than 14 mm lateral from midline, $Y = 25\%$ of the anterior commissure to posterior commissure (AC-PC) distance posterior to the mid commissural point and $Z =$ AC-PC plane [24]. The Vim-Voa has been targeted for other movement disorders accompanied by tremor, such as refractory PD [25], PTT [26–28] and dystonic tremor [29]; even surgical results are not always encouraging [1, 16, 26–28]. Herein, we present the case series of three children that received DBS of Vim contralateral to PTT.

## Materials and methods

We collected data on three paediatric patients (two females, mean age 12 years; one male, age 16) with unilateral PTT resulting from severe traumatic brain injury (TBI) who received unilateral DBS of Vim-Voa extended to zona incerta at the Neurosurgery Department of Meyer Paediatric Hospital (Florence, Italy) between 2016 and 2019. Previous TBI was medically treated in intensive care in different hospitals and did not require any emergent neurosurgical procedure. Subsequent MRI assessments ruled out any traumatic brain lesions. All patients developed a progressive and worsening PTT which was unresponsive to different drugs in various combinations (trihexyphenidyl, clonazepam, propranolol) and to botulinum toxin injection. Patients' characteristics and surgical results are summarised in Tables 1, 2 and 3.

Based on this data and a multidisciplinary work-up, unilateral DBS of Vim-Voa-zona incerta, contralateral to the tremor, was offered according to the ethical regulations of the hospital. The study was approved by the Local Ethical Committee. Patients' parents gave a signed informed consent for the surgical procedure and expected outcome. Patients' neurological status was assessed with the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), the Melbourne Assessment of Unilateral Upper Limb Function and the Quality of Upper Extremity Skills Test (QUEST). Patients' Quality of Life (QoL) was assessed with the Functional Independence Measure (FIM) Scale. Patients' tremors were classified before and after surgery, according to the

**Table 1** Patients' characteristics

| PT | *S* | Age at Trauma (years) | Trauma-PTT (months) | Age at surgery (years) | Trauma surgery (years) | F-UP (months) | SITE | Coordinates | PARAMETERS (at last follow up) | Therapy |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 6.00 | 10.00 | 14.97 | 8.98 | 48 | Left | $X+14.0$;<br>$Y-4.2$;<br>$Z-3.8$ | 5.5 V<br>120 ms<br>110 Hz | Triesifenidile<br>Clonazepam<br>Propranolol |
| 2 | M | 9.24 | 1.00 | 16.86 | 7.63 | 60 | Right | $X-9.5$<br>$Y-6.7$<br>$Z-3.65$ | 3.4 V<br>90 ms<br>130 Hz | Triesifenidile<br>Pimozide<br>Propranolol<br>Tetrabenazine |
| 3 | F | 7.94 | 2.00 | 9.63 | 1.69 | 36 | Left | $X-13.5$<br>$Y-1.8$<br>$Z-4.1$ | 3.5 V<br>60 ms<br>130 Hz | Triesifenidile |

**Table 2** Patients' neurological and functional scores

| PT | PRE-OP SCORE | QOL PRE (FIM scale) | POST-OP SCORE | SCORE pre-post | QoL POST (FIM scale) | FIM pre-post |
|---|---|---|---|---|---|---|
| 1 | Marsden 59.5 | 47 | Marsden 53.5 | Marsden − 6 | 54 | +7 |
| 2 | Marsden 27 Melbourne 80 QUEST 83.02 | 93 | Marsden 26.5 Melbourne 89 QUEST 88.25 | Marsden − 0,5 Melbourne +9 Quest +5.23 | 99 | +6 |
| 3 | Melbourne 72 | 105 | Melbourne 81 | Melbourne +9 | 113 | +8 |

Rojas-Medina et al. scale [18], which consists in four grades of severity (0 = no tremor; 1 = mild tremor, 0–2 cm amplitude; 2 = moderate tremor, 2–5 cm amplitude; 3 = marked tremor, 5–10 cm amplitude; 4 = severe tremor, more than 10 cm amplitude); the overall postoperative improvement was classified on a five-point scale (0 = minimal or no change; I = mild improvement; II = moderate improvement; III = marked improvement; IV = excellent, no tremor).

All patients underwent frame-based (Leksell-G, Elekta®, Sweden) DBS of Voa-Vim contralateral to the tremor by stereotactic robotic technique (Neuromate Neuroinspire®, Renishaw-Mayfield SA, Nyon, Switzerland). T1W-3D gadolinium-enhanced and T2-3D MRI sequences were scanned after the Leksell stereotactic frame was positioned with the patient under general anaesthesia. The Vim-Voa was targeted by positioning one avascular trajectory with three tracks using a software tool coupled with the robotic system (Neuroinspire®, Renishaw-Mayfield SA, Nyon, Switzerland). A 14-mm frontal burr hole was performed, and three microelectrodes (Model 22675L, FHC® Bowdoin, USA) were introduced along parallel paths to provide neural activity registration and optimise the target positioning. The definitive stimulating electrode catheter (Model 3387, Medtronic® Inc. Minneapolis, USA) was implanted along the trajectory (with the most suggestive electrical pattern). During the same surgical procedure, an Implantable Pulse Generator (IPG) (Activa RC, Medtronic® Inc. Minneapolis, USA) was placed in the subclavicular region in two patients (patients 2 and 3) and in a subcutaneous abdominal pocket connected subcutaneously to the DBS electrode with a lead extension in the youngest patient (patient 1). A postoperative head CT scan was merged with the preoperative MRI to verify the correct position of the electrode and rule out any surgical complication. Two weeks after surgery, a monopolar stimulation (battery positive/electrode contact 0 negative) commenced and progressively increased to maximise clinical effect to none or acceptable side effects.

**Table 3** Patients' tremor assessment and results according to Rojas-Medina et al.'s score [18]

| Case | Follow-up | Tremor score | Improvement |
|---|---|---|---|
| 1 | Pre-op | 4/4 | |
| | At 12 months | 3/3 | I |
| | At 24 months | 3/3 | Stable |
| 2 | Pre-op | 4/4 | |
| | At 12 months | 3/3 | I |
| | At 60 months | 2/2 | II |
| 3 | Pre-op | 3/4 | |
| | At 12 months | 2/3 | I |
| | At 36 months | 0/1 | III |

## Results

Patients' characteristics are summarised in Table 1. Patients' neurological and functional scores are shown in Table 2. Patients' tremor assessment is shown in Table 3.

No surgical morbidity occurred. The early postoperative head CT scan merged to the preoperative MRI planned targets showed an optimal position of the electrode and ruled out any haemorrhagic complications. None of the patients experienced permanent or disabling side effects due to the stimulation. After a mean follow-up of 48 months (range 24–60 months), the tremor had significantly improved, and all patients reported a better control of movement. According to patients and caregivers, the mean improvement at the FIM scale was + 7 points. The BFMDRS (patients 1 and 2) and Melbourne Assessment (case 2 and 3) showed concordant improvement in neurological conditions.

### Patient 1

A previously healthy 6-year-old girl was involved in a road accident causing a severe TBI. The trauma was complicated by diffuse brain oedema requiring neuroprotection. The patient recovered from a comatose state after 3 months and developed post-traumatic epilepsy treated which required multidrug therapy (valproic acid, phenobarbital and phenytoin). After 10 months, she manifested a high-frequency tremor involving the upper and lower right limb, triggered by voluntary movements. This condition was associated with mild spastic quadriparesis that was more severe on the left. She was diagnosed as PTT and started on trihexyphenidyl (12 mg/die) and treated with injections of botulinum toxin at

the flexor's muscles of the hand (50 UI) and gastrocnemius (150 UI). Trihexyphenidyl failed in controlling the PTT and was replaced by clonazepam, for drowsiness, hyposthenia and sialorrhea. Walking with support was not possible due to global hyposthenia and uncertain balance. Clonazepam was then stopped and replaced by propranolol (20 mgx2/die), which was in turn stopped after 9 years as not effective.

After multidisciplinary case discussions, unilateral DBS of left Vim was offered to the patient's parents and performed when she was 15 years old (9 years after TBI). In the same surgical session, one electrode was implanted into the left Vim-Voa with the stereotactic robot (Fig. 1) and connected to IPG placed into a subcutaneous pocket in the subclavian region.

Two weeks after surgery, DBS was started with 1.5 V, 90 µs, 130 Hz parameters with no remarkable side effects. At the 2-month follow-up, the tremor movements of the right arm improved, and the patient was able to stand and walk without aid. Voluntary movements of the left side were improved overall but still impaired by intentional long-range myoclonus at the upper right limb. Four months after DBS, the voltage was ramped up to 5.5 V, resulting in further improvement in voluntary movements and balance control (other parameters of the stimulation were unchanged). At last follow-up after surgery, her neurological status was stationary and the mild improvement in tremor was maintained.

## Patient 2

A 9-year-old boy was involved in a domestic accident resulting in small intraparenchymal left frontal and right thalamic haemorrhages. During follow-up, he developed a left spastic hemiparesis with voluntary tremor, diagnosed as PTT, especially triggered by voluntary movement of the left upper limb. Mild cognitive impairment was also present. To control the PTT, various pharmacological therapies were performed over a 7-year period of trihexyphenidyl, pimozide, propranolol and tetrabenazine with no improvement. The MRI documented post traumatic lesions in the frontal lobes and corpus callosum, with hemosiderin deposits in the right internal capsule. The preoperative evaluation of QUEST was 83.02. At the age of 16 years and 10 months, a right Vim-Voa DBS was performed (Fig. 2) with a progressive increase of voltage stimulation up to 3.4 V, duration 90 ms, frequency 130 Hz. At last follow-up, the QUEST recorded a slight improvement settling at 88.25 while the tremor assessment showed moderate improvement.

## Patient 3

A previously healthy 8-year-old girl was involved in a road accident with severe TBI. After the trauma, she developed spastic quadriplegia, dysphagia and unresponsive wakefulness syndrome that recovered after 2 months. Her gait was ataxic, with oscillatory movements on all planes, and difficulties in changing direction; in addition, intentional wide-ranging tremor on the right arm and dysarthric speech were present. Trihexyphenidyl at 12 mg per did not control tremor. At 9 years and 8 months, a DBS procedure at the level of left Vim-Voa was performed (Fig. 3).

Stimulation parameters were progressively increased up to 3.5 V, duration 60 µs, frequency 130 Hz. The DBS

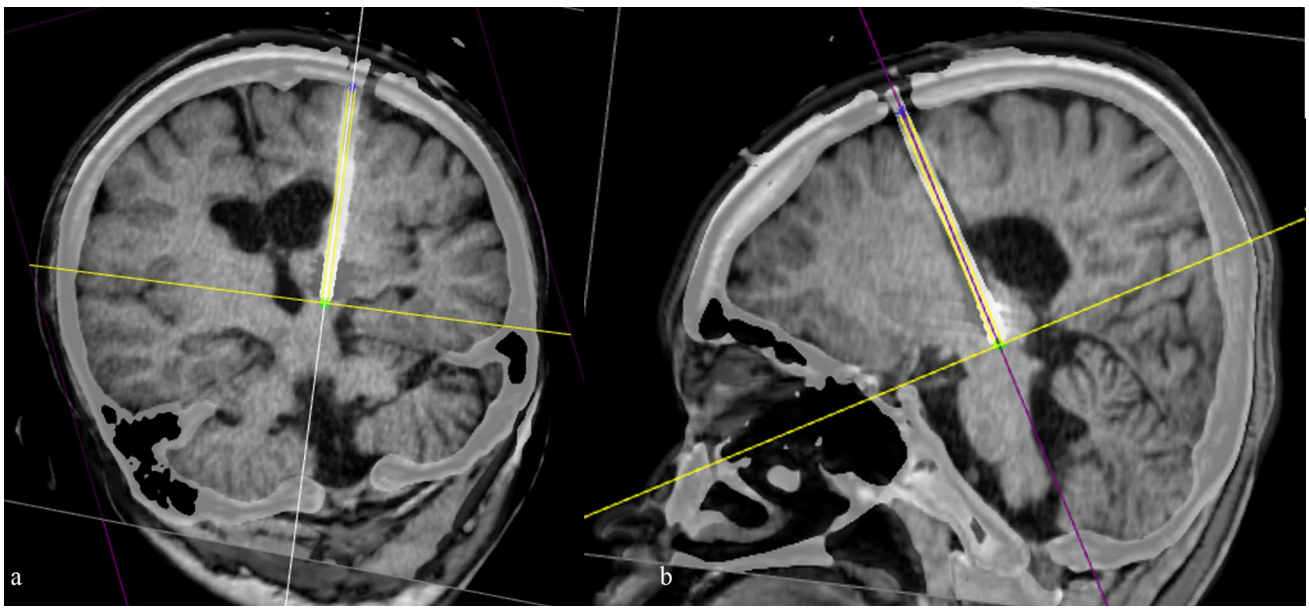


**Fig. 1** T1-weighted MRI coronal (**a**) and sagittal (**b**) sections representing the trajectory plans of patient no. 1

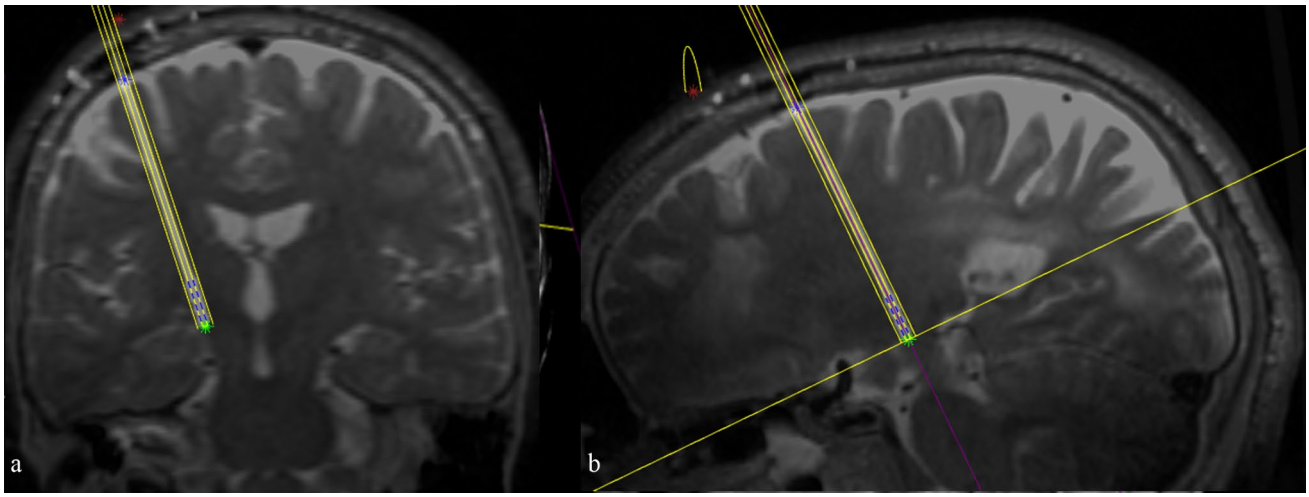


**Fig. 2** T2-weighted MRI coronal (**a**) and sagittal (**b**) sections representing the trajectory plans of patient no. 2

resulted in clinical improvement of her gait. Although the dyskinetic component still negatively affected the movement of the upper limb, a functional improvement was reported; pointing and reaching are more fluid, and grasping and releasing objects was possible. At the last follow up, tremor assessment recorded a marked improvement.

## Discussion

PTT is the most frequent movement disorder secondary to cranioencephalic trauma in the adult population and can be persistent and disabling, but little is known regarding the prevalence and prognosis of PTT in the paediatric age. In 1992, Johnson and Hall published a survey of 289 severely head-injured children and estimated that PTT tremor was present in at least 45%, transient in 54% and permanent in 36% [30]. Probably, this questionnaire-based prevalence was overestimated, and since then, only a few case reports have been published.

As also reported in the adult population [31], in our three paediatric patients, PTT followed severe or severe/moderate brain injury. TC scan at the time of the trauma showed focal and diffuse post-traumatic lesions, diffuse axonal injury damage (DAI) and brain oedema. In all patients, therefore, there were diffuse axonal injuries that might explain the heterogeneity of the neurological post-traumatic disorders and identify a "connectomic" cause of PTT, namely an injury

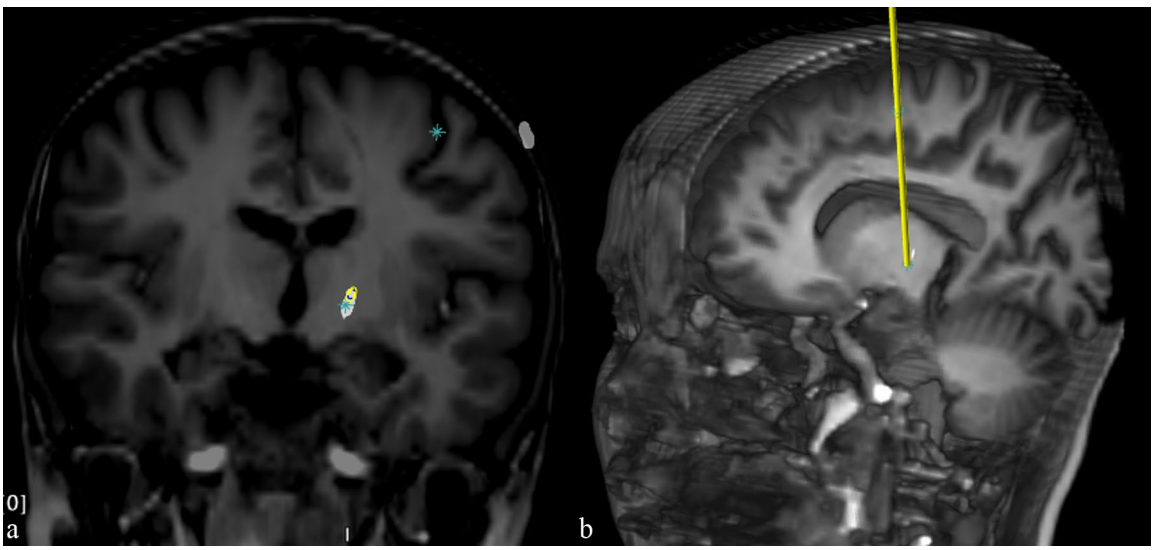


**Fig. 3** T1-weighted MRI coronal section (**a**) and 3D sagittal reconstruction (**b**) representing the trajectory plan of patient no. 3

to the dentato-thalamic tract, dentato-rubro-thalamic tract, pallido-thalamic tracts and their respective cortical M1 and SMA projections [32, 33].

According to this pathophysiological hypothesis, in the adult population, the best results of DBS in the treatment of tremor have been described when Vim, VOP-VOA, ZI and GPI are stimulated [1, 18, 34–36].

MRI fails to identify thalamic nuclei, in particular Vim and VOP and VOA, located anteromedially to the Vim, so the target is normally reached based on the anterior–posterior commissure plane and adjusted according to the adjacent structures detected by the stereotactic MRI, in particular the adjacent internal capsule. We targeted the selected nuclei by stereotactic robotic technique (Neuromate Neuroinspire®, Renishaw-Mayfield SA, Nyon, Switzerland), adjusted according to the anatomical structures detected by stereotactic MRI. In our three patients, the main variability of the sagittal and lateral localization of the selected target in respect to the bicommissural plane (9.5 to 14 mm lateral, 4.1 to 6.7 mm posterior to the midcommissural point) was determined by the different anatomical reliefs detected by MRI, while the depth with respect to the bicommissural plane was more constant among the three patients ($Z-3.8$ to 4.1 mm), to reach the ZI.

Although there is no typical pattern of neurophysiological firing to detect the thalamic nuclei, in particular Vim, VOP and VOA, we refined our target by using semi-microrecording to probe whether firing activity was present. In all three patients, however, we could not record any specific firing such as tremor cells activity, probably due to previous traumatic lesions and general anaesthesia.

Given that PTT, as probably other forms of tremor, is sustained by a "connectomic injury", it is possible that the future targeting may be checked by MR-DTI, as suggested by Middlebrooks et al. [32].

Since all our patients were operated under general anaesthesia, it was impossible to verify efficacy of intraoperative stimulation on tremor, or the side effects caused by the stimulation of the neighbouring structures, in particular the ventro-lateral nuclei of the thalamus and the internal capsule.

In our patients, the clinical outcome was in line with the current literature describing promising results of thalamus DBS treatment for PTT [31]. The efficacy of targeting the lower part of the thalamus for deep stimulation was similar to that described by other authors [1, 3, 17, 18, 37, 38]. It was previously reported that the stimulation of the lower part of the Vim was more effective in the distal component of the tremor, whereas its proximal component was specifically reduced by stimulation of the upper part. Moreover, the stimulation of the middle part of the Vim demonstrated a good suppression of both distal and proximal components of tremor in one patient with intractable PTT [3].

The strategy of targeting both Vim and Voa had been previously described as more successful in the treatment of posttraumatic Holmes tremor, even though an alternative explanation for the success of this technique may simply be related to increasing the effective volume of tissue activation (VTA) [34]. Vim was the DBS preferred target for lesional tremor in a systematic review with a 71.4% rate of median improvement [35]. In the aforementioned case series [34], Vim-VOA-ZI DBS proved safe and effective for PTT treatment, with improvement in the patients' neurological and functional status, as also confirmed in literature suggesting that DBS is a treatment option for paediatric patients with medically refractory neurological disorders [39].

In our patients, the best results at the 24–60 months follow-up do not correlate with the severity of the previous brain injury, with the age at trauma, or with the stereotactic coordinates in relation to the bicommissural plane, probably due to the anatomical variability and in relation to the previous brain injury. There might be a correlation with the time of surgery after onset of PTT; however, as we achieved the best results (marked improvement) in patient 3, who was operated 20 months after the onset of PTT, moderate improvement in patient 2 operated after 7 years and mild improvement in patient 1 operated 9 after years. A larger number of observations are needed to establish whether early surgery from the onset of PTT may correlate with the best clinical control of tremor.

Some biases of this study are related to the mid-term follow up, with lack of long-term outcome information and the unavoidable co-occurrence of neurological abnormalities —such as spastic hemiparesis, dystonic movements and neurobehavioural deterioration—that makes the PTT assessment itself challenging.

## Conclusion

DBS of Vim-Voa for secondary tremors like PTT may be efficacious in the paediatric population. Due to damage that can occur to neural pathways, ET is often offered as the safer alternative. However, DBS should be offered to patients not responding to pharmacological therapy, given its low morbidity and invasiveness. Longer follow-ups and larger cohorts are needed to further confirm the efficacy of VIM-VOA-ZI DBS to treat PTT, its relationship to the time of surgery, and the best strategy to reach the most effective target.

**Acronyms** DBS: Deep brain stimulation; Vim: Nucleus ventralis intermedius thalami; ET: Essential tremor; PTT: Post traumatic tremor; SMD: Secondary movement disorder; PD: Parkinson's disease; MS: Multiple sclerosis tremor; VOA: Ventralis oralis anterior; ZI: Zona incerta; GPi: Globus pallidus internus; IPG: Implantable pulse generator; BFMDRS: Burke-Fahn-Marsden Dystonia Rating

Scale; QUEST: Quality of Upper Extremity Skills Test; QoL: Quality of life; FIM: Functional independence measure; DT: Dystonic tremor; VOP: Ventro-oralis posterior

**Author contribution** Conceptualization: Peraio, Giordano. Methodology: Peraio, Giordano, Araceli, Scalise. Formal analysis and investigation: Mantovani, Mongardi, Fino, Formica, Piccinini, Battini. Writing - original draft preparation: Mantovani, Araceli, Mongardi. Writing - review and editing: Araceli, Noris, Di Rita, Lenge, Fino, Melani, Scalise, Cavallo, Guerrini. Supervision: Giordano, Cavallo, Guerrini.

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**Data availability** Data are available from corresponding author upon reasonable request.

## Declarations

**Ethical standard** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Local Ethical Committee.

**Consent to participate** Patients' parents gave a fully signed informed consent about the surgical procedure and expected outcome.

**Conflict of interest** The authors declare no competing interests.

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