Case series

Endurance of short pulse width thalamic stimulation efficacy in intention tremor

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Short Title: Short pulse width for refractory essential tremor

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Keywords:

- Essential Tremor
- Ventral intermediate nucleus
- Deep Brain Stimulation
- Short pulse width
- Ataxia

Abstract

The benefit of short pulse width stimulation in patients suffering from Essential Tremor (ET) refractory to thalamic Deep Brain Stimulation remains controversial. Here we add to the minimal body of evidence available by reporting the effect of this type of stimulation in three patients with a persistent and severe intention tremor component despite iterative DBS setting adjustments. While a reduction of pulse width to 30 μs initially showed promise in these patients by improving tremor control and mitigating cerebellar side effects arguably by widening the therapeutic window, these benefits seemed to dissipate during early follow-up. Our experience supports the need for measuring longer-term outcomes when reporting the usefulness of this mode of stimulation in ET.

Introduction

Deep Brain Stimulation (DBS) in the thalamic Ventral Intermediate Nucleus (Vim)[1] or Posterior Subthalamic area (PSA) [2] is a validated treatment for medically refractory Essential Tremor (ET). Despite its general effectiveness, some implanted patients may experience a limited duration of benefit from stimulation. This seems to be more apparent amongst individuals experiencing prominent intention tremor [3], a symptom that can also be triggered by the stimulation itself [4]. Currently, very few strategies are available to tackle this issue. The most widely used approach being a recommendation that patients turn off the Implantable Pulse Generator (IPG) at night using their own programmer to prevent long-term loss-of-benefits [5]. The recent advent of a new generation of IPGs have enabled the delivery of pulse width shorter than 60 µs and several non-randomized clinical studies have explored the merits of this approach in essential tremor (ET) patients. These reports suggest that decreasing the pulse width in can lead to a larger therapeutic window [6] and a higher side effect threshold for provoking upper-limb cerebellar tremor [7]. Nevertheless, these findings were limited to recently implanted patients who were not experiencing DBS-refractory symptoms. Decreasing pulse width has also been explored in the management of Vim-DBS associated gait disorders [8]. Despite these encouraging findings, the value of short pulse width settings in the management of DBS-refractory intention tremor remains unexplored. Here we aim to share the potential merits, but also pitfalls of this approach by demonstrating our experience in three ET patients implanted unilaterally in the Vim who were suffering from severe disabling intention tremor unresponsive to conventional DBS despite extensive DBS parameters setting adjustments.

Material and Methods

Patients

Three patients with persistent and severe intention tremor despite extensive conventional DBS setting optimization were included. They underwent monopolar review of all DBS contacts, increasing the frequency of stimulation over 130 Hz and adapting the amplitude of stimulation accordingly. All three patients had previously been told to turn off their IPGs using the patient programmers to prevent early DBS tolerance. Relevant medical history was recorded, and the clinical characteristics of the tremor classified according to the latest consensus for the classification of tremor [9]. Medications were not modified during the assessment period.

Short Pulse Width stimulation

For patients 1 and 3 who were stimulated with an ACTIVA PC (Medtronic®) IPG that cannot deliver pulse widths shorter than 60 µs, we used the 8870 XBP Application Flashcard (Medtronic®) to implement the short pulse width stimulation functionality. For patient 2, the end of life ACTIVA PC (Medtronic®) device was replaced with a GEVIA RC (Boston Scientific®) IPG which has the capacity of delivering shorter pulse width stimulation [10].

Clinical Assessment

The therapeutic window was evaluated for every patient on the chronically used active contact(s) at 130 Hz for 30 and 60 µs pulse width. Stimulation was first turned off for 30 minutes, then the stimulation was recommenced with progressively increasing amplitudes with steps of 0.1-0.5 mA/V until the postural tremor intensity decreased to its lowest amplitude, thus defining the therapeutic threshold. Then, the amplitude was increased again until persistent side effects (upper limb intention tremor, dysarthria, paresthesia), occurred or worsened, defining the side effect threshold. The therapeutic window was defined as the difference in mA/V between the therapeutic and side effect thresholds. The optimal amplitude was chosen between the therapeutic and the side effect thresholds. The severity of tremor was assessed with the DBS turned off (i.e. at baseline) and for the optimal amplitude determined for both conditions using the Fahn-Tolosa-Marin Rating Scale (FTMRS) [11]. Ataxia was rated with the DBS turned off and at the optimal amplitude for both conditions using the Scale for the Assessment and Rating of Ataxia (SARA) [12]. After the assessment, the 30 µs stimulation was applied for all three patients. Patients were assessed at a planned follow-up consultation after one month to evaluate the longer-term effect of this therapy. The therapeutic threshold was recorded again at 60 µs pulse width during this consultation by the same clinician who evaluated the patients initially (V.D.).

Volume of Tissue Activated (VTA) modelling

Guide XT software (Boston Scientific®) was used to estimate the VTA with the DBS settings determined during the therapeutic window assessment (therapeutic and side effect thresholds) for the 30 µs and 60 µs pulse width in patients 1 and 2. Stimulation field models were constructed using a finite element model. This model was calculated assuming homogenous and isotropic tissue conductivity of 0.3S/mm, and neural activation threshold was based on myelinated axon models 5.7um in diameter, and oriented perpendicular to the lead orientation vector. The model also incorporated bulk tissue capacitance, an electrode electrolyte interface, and a tissue encapsulation

area [13]. Models similar to the one implemented here showed good reliability in predicting corticospinal tract activation when measured on electromyogram recordings [14].

Results

Patient clinical characteristics are summarized in Table 1. All patients fell within the definition of ET+ syndrome according to the latest consensus for the classification of tremor. All were suffering from severe intention tremor, that predated the DBS surgery and persisted despite more than a year of thalamic stimulation. The FTMRS ranged between 48 - 91 without stimulation. The SARA score was also high ranging from 8 to 21 in the off-stimulation condition (lower score denote better ataxia control). All patients were improved with DBS, demonstrating a reduction in the FTMRS of 8 to 19 points (lower scores denote better tremor control) with the 60 µs stimulation in comparison to the DBS-off condition while the SARA score increased slightly for patients 2 and 3.

Short Pulse Width (SPW) stimulation had greater effects on the tremor, in comparison to the 60 µs stimulation. Indeed, the FTMRS decreased further by 3, 19 and 7 points for patients 1, 2 and 3 respectively. The SARA score was also lower for all patients with SPW stimulation in comparison to both the off-stimulation condition and the 60 µs pulse width stimulation. The therapeutic window was larger for all patients with 30 µs pulse width in comparison to the usual 60 µs (2.2V, 0.3mA and 1.6V vs 0.8V, -0.5 mA and 1.3V for patient 1, 2, 3 respectively) (Table 1).

By modeling the VTAs (Figure1), we observed that despite an apparent better control of the tremor and the ataxia, the estimated VTA was smaller with 30 µs for both patients 1 and 2. The volume of stimulation included the Vim of the thalamus for patients 1 and 3 and the PSA for patient 2.

At the 1 month follow-up point, all patients required DBS setting adjustments with 30 µs pulse width stimulation. The therapeutic threshold at 60 µs was noted to be lower for every patient compared to the original threshold required for tremor control before going on SPW settings (Table1). Patient 1 no longer experienced the initial benefits of SPW, necessitating an increase in the frequency of stimulation, which did not correct the intention tremor. Patient 2 had a slight recurrence of upper limb ataxia and tremor after one month, leading to an increase in the frequency of stimulation to 180 Hz. While she was satisfied with her postural tremor control, the intention component remained disabling. Interestingly, she reported that her tremor was better controlled when she periodically cycled between two different programs, one with a pulse width of 60 µs, and one with a pulse width of 30 µs. Patient 3 did not tolerate the short pulse width stimulation in the long term because of a subjective sensation of fatigue. A 50 µs pulse width was trialed though her tremor control remained poor in the long term. She subsequently progressed to unilateral thalamotomy surgery.

Discussion

Here we report three ET+ syndrome patients with severe intention tremor components despite best efforts to optimize Vim DBS with conventional setting adjustments. Trialing short pulse width stimulation led to an improvement of tremor in 2 patients, with a clinical effect ranging from mild to substantial in the short term. This is in keeping with the hypothesis proposed by Groppa [4], which suggests that SPW stimulation is more selective of dentato- thalamic tract fibers, which are thought to be the anatomical substrate of therapeutic effects of Vim-DBS. Similarly, the cerebellar symptoms assessed using the SARA scale improved in all patients with 30 μs stimulation in comparison to both the off-DBS condition and the 60 μs pulse width stimulation. This may also be in keeping with the aforementioned hypothesis, suggesting that the cerebello-rubro-spinal system and the rubro-olivo-cerebellar system fibers, which might account for DBS-induced cerebellar side effects, are more likely to be stimulated with a large pulse width stimulation. Our additional observation that the VTA of the therapeutic and side effect thresholds determined were smaller with SPW stimulation suggests that the additional therapeutic effect observed at 30 μs is more likely driven by the nature of the stimulation and some relative selectivity for therapeutic associated neural elements rather than by the total volume activated. Furthermore, the therapeutic window was larger in the 30 μs pulse width condition in comparison to the 60 μs, confirming the previously reported finding [6,7].

Despite an initial improvement of the tremor in the 3 patients, all of them required DBS setting adjustments after one month of SPW stimulation due to either side effect emergence or relative loss of efficacy. This is contradictory to the more durable positive observations noted in Vim-DBS tremor cases where short pulse width settings have been employed to improve gait side effects [8], suggesting that these two cerebellar symptoms might respond differently to this type of stimulation. It is also interesting to note that the therapeutic threshold at 60 μs was lower for every patient after one month of 30 μs pulse width stimulation, and that cycling between two programs with two different pulse width seemed to benefit patient 2. This suggest that SPW stimulation might potentially reduce or temporarily reverse DBS tolerance in the same way as turning off stimulation to reduce the progressive loss of benefit over time.

To conclude, despite our limited number of cases, our series provides clues that SPW stimulation might be a valuable short-term therapeutic option in Essential Tremor patients with an intention tremor component refractory to classical DBS settings adjustments. However, longer term benefits may require cycling between settings, and SPW stimulation may be a valuable way of avoiding this. Larger cohorts as well as randomized and controlled studies are warranted to confirm or refute the

long-term effectiveness of SPW stimulation as well as variable pulse width program cycling stimulation on DBS induced intention tremor.

Statements

Acknowledgement

We thank the patients for their participation in this study.

Statement of Ethics

All procedures described in this case series were carried out under the institution's usual standard of clinical care, and no experimentation was performed. The patient provided written informed consent for use of clinical information and images for publication.

Disclosure Statement

T.W. received grant support from the Revue Neurologique, the APTES and the foundation Planiol organizations as well as travel funding from LVL medical. T.F. has received grant support from NIHR, John Black Charitable Foundation, Rosetrees Trust, Michael J Fox Foundation, and Cure Parkinson's Trust. He has received honoraria for speaking at meetings supported by Boston Scientific, BIAL, and Profile Pharma. He serves on advisory boards for BIAL, Oxford Biomedica, and Peptron. V.D. has received honoraria and travel expenses from Boston Scientific. NV has received unconditional educational grants from IPSEN and Biogen, travel grants from IPSEN, AbbVie and The International Parkinson's Disease and Movement Disorders Society, speaker's honorarium from AbbVie and STADA and served on advisory boards for Abbvie and Brittania. H.A. has received honoraria and travel expenses from Boston Scientific and BrainLab. P.L. and L.Z. have received honoraria and travel expenses from Medtronic and Boston Scientific for speaking at meetings.

Funding Sources

Thomas Wirth was funded by a grant from the APTES and the Fondation Planiol organizations for this work. Nirosen Vijiaratnam's research position is supported by a grant from the Janet Owen's charitable foundation.

Author Contributions

T.W.: writing of the first draft; V.D.: clinical assessment, A.dR.; F.F. : VTA modeling; N.V, H.A., L.Z., P.L., T.F.: critical review and revisions of the manuscript; all authors: participation in clinical care.

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Figure Legends

Table 1.

A] Clinical characteristics, DBS settings and clinical outcome of the 3 cases.

B] Therapeutic window and Volume of Tissue Activated assessment of the 3 cases.

Abbreviations: TW: therapeutic window, SET: side effect threshold, TT: therapeutic threshold, VTA: volume of tissue activated.

Figure 1.

VTA modelling with 60 us pulse width (A, C, E) and 30 us (B, D, F) for patient 1, 2 and 3 respectively. The Thalamus (Th) has been identified with the colour dark green, the subthalamic nucleus (STN) with the colour light green, the internal capsule (IC). Around the electrodes the VTA can be seen for the side effect threshold (colour red), and the therapeutic threshold (colour blue).