Clinical Neurophysiology 129 (2018) 1628–1633

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Objective predictors of 'early tolerance' to ventral intermediate nucleus of thalamus deep brain stimulation in essential tremor patients

Shabbir Hussain Merchant [a,b,c,*], Sheng-Han Kuo [a], Yu Qiping [a], Linda Winfield [a], Guy McKhann [a], Sameer Sheth [a], Seth L. Pullman [a], Blair Ford [a]

[a] Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[b] Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institute of Health, Bethesda, MD, USA
[c] Department of Neurology, College of Medicine, Medical University of South Carolina, Charleston, SC, USA

ARTICLE INFO

Article history:
Accepted 4 May 2018
Available online 5 June 2018

Keywords:
Essential tremor
Early tolerance
Tremor habituation
Deep brain stimulation
Computerized spiral analysis

HIGHLIGHTS

- Spiral analysis identified differences in ET patients developing tolerance to DBS.
- Potential tolerance to Vim DBS in ET can be predicted pre-operatively.
- Objective kinematic testing can aid in pre-operative assessment of complex tremors.

ABSTRACT

Objective: To identify pre-operative clinical and computerized spiral analysis characteristics that may help ascertain which patients with Essential Tremor (ET) will exhibit 'early tolerance' to ventral intermediate nucleus of thalamus (Vim) deep brain stimulation (DBS).
Methods: Identification of comparative characteristics of defined cases of 'early tolerance' versus patients with sustained satisfactory response treated with Vim DBS surgery for medically-refractory ET, based on retrospective chart review by a clinician blinded to the findings of computerized spiral analysis.
Results: Statistically significant differences in two spiral analysis indices, SWVI and DoS, were found in the dominant upper limbs of patients who developed 'early tolerance', whereas the clinical characteristics were not significantly different.
Conclusion: Objective measurements of upper limb kinematics using graphonomic tests like spiral analysis should be considered in the pre-operative evaluation for DBS, especially in the setting of moderate-severe predominantly action and proximal postural tremors.
Significance: Ours is the first investigation looking into the pre-operative clinical and objective physiologic characteristics of the patients who develop 'early tolerance' to Vim DBS for the treatment of essential tremor. The study has significant implications for pre-operative evaluation and potential surgical target selection for the treatment of tremors.

1. Introduction

Essential tremor (ET), is the most common cause of adult onset tremors. The diagnosis is made clinically on the basis of chronic, disabling action tremors. The phenotype is variable and heterogeneous; some patients experience a gradual increase in severity and disability over the years, others developed generalized tremors, including legs, head, and voice; and some individuals evolve into a pancerebellar syndrome that includes limb dysmetria and gait ataxia. In accordance with the varied clinical presentation, the tremor may be generated by different pathophysiologic mechanisms, with important therapeutic and prognostic implications (Louis et al., 1998; Bain et al., 2000; Deuschl and Elble, 2000; Louis et al., 2000; Deuschl and Elble, 2009), and differing response to medication treatment and neurosurgical intervention (Gorman et al., 1986; Koller et al., 2000; Blomstedt et al., 2011).

Current pharmacologic treatment is helpful in only about half of the ET cases, and this may relate to different physiologic subtypes

* Corresponding author at: Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institute of Health, 10 Center Drive, Bldg. 10, Room 7D42, Bethesda, MD, USA. Fax: +1 301 480 2286.
E-mail addresses: shabbirhussain.merchant@nih.gov (S.H. Merchant), sk3295@cumc.columbia.edu (S.-H. Kuo), qy12@cumc.columbia.edu (Y. Qiping), lmw4@cumc.columbia.edu (L. Winfield), gm317@cumc.columbia.edu (G. McKhann), sas4451@cumc.columbia.edu (S. Sheth), sp31@cumc.columbia.edu (S.L. Pullman), bf25@cumc.columbia.edu (B. Ford).

https://doi.org/10.1016/j.clinph.2018.05.012
1388-2457/Published by Elsevier B.V. on behalf of International Federation of Clinical Neurophysiology.

(Sabra and Hallett, 1984; Deuschl et al., 1987; Koller et al., 2000; Deuschl et al., 2011). Deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (Vim) is an effective treatment for ET, particularly for medication-resistant disabling cases (Blomstedt et al., 2007; Baizabal-Carvallo et al., 2014). DBS has been shown to remain effective in long term follow-up studies; however, there may be loss of benefit over a long period of time in a subset of patients. Possible explanations for this include (i) disease progression and (ii) habituation to DBS, or tolerance, despite the absence of clinical progression, and repeated, optimal DBS programming (Springer et al., 2006; Barbe et al., 2011; Favilla et al., 2012). We have encountered recurrent tremor within weeks after DBS surgery, where excellent targeting and tremor control were noted intra-operatively. We have hypothesized that tremor recurrence/habituation may be predictable on the basis of pre-operative clinical and kinematic characteristics. In this study, we sought to identify and characterize if any pre-operative clinical and spiral drawing characteristics may help ascertain which ET patients will exhibit loss of efficacy or 'early tolerance' to Vim DBS.

2. Materials and methods

We reviewed all available charts of patients who had undergone thalamic Vim DBS surgery for ET over the last 15 years at Columbia University Medical Center and who had pre-operative computerized spiral analysis testing. Inclusion was based on availability of detailed pre-operative clinical, intra-operative, demographic, pre-operative spiral analysis and follow-up clinical and programming data at least for the first two years after DBS surgery. The study was conducted in accordance with the Institutional Review Board (IRB) of Columbia University Medical Center. Patients who were noted to have the clinical phenomenon of developing 'early tolerance' and those with sustained good response were identified by a movement disorder neurologist (BF) blinded to the spiral analysis findings. We defined those patients with 'early tolerance' as those who experienced (i) near-complete intra-operative tremor suppression (equivalent to a clinical score of 1 or less on a 5-point severity scale from 0 to 4 where 0 = normal, 1 = slight, intermittent, 2 = moderate amplitude, intermittent, 3 = marked amplitude and 4 = severe amplitude based on the Fahn-Tolosa-Marin (FTM) tremor rating scale as noted in the upper limbs with action and postural holding, and (ii) sub-optimal response post-operatively within the first two years characterized by the inability to maintain satisfactory tremor control in the performance of ADLs without experiencing adverse effects (paresthesias, disabling dysarthria or gait ataxia) from DBS programming.

General pre-operative characteristics of all cases were noted, including handedness, gender, age at time of surgery, presence or absence of limb dysmetria or gait ataxia prior to DBS surgery, head tremor, vocal tremor, presence of tremor with kinetic actions or posture-holding, clinical tremor rating score, and whether the DBS implant was unilateral or bilateral. The presence of ataxia was noted on the basis of clinical documentation of tandem gait difficulties, signs of cerebellar dysmetria or dysdiadochokinesia.

Implanted pulse generator programming data included changes in programming parameters: DBS lead voltage, frequency and pulse width. The changes in active lead configuration were also recorded.

Computerized spiral analysis testing involved drawing 10 spirals from each hand inside a 10 x 10 cm square box on 8.5 × 11-in. paper with a wireless inked pen placed on a graphics tablet (Intuos 2–4, Wacom Technology Corp, Vancouver, WA). Subjects were allowed to draw freely without any constraints, attachments, or traceable templates, and collection was standardized across all subjects. The tablet had a resolution of 2540 points/inch (accuracy of 0.005 in.), with 256 levels of measurable pressure acquiring data at 100 Hz. Quantification of handwritten spirals was as previously described and involved acquisition of data series consisting of time, x, y, and pressure axis values to unravel the spiral. Using these data points from kinematic, dynamic, and spatial attributes of spiral execution spiral indices were computed (Pullman, 1998; Rudzinska et al., 2007; Haubenberger et al., 2011; Hess and Pullman, 2012). All trials were performed in one session lasting about 15 min.

Two computerized spiral analysis indices were used as primary outcome measures in this study: (i) a measure of spiral loop-to-loop width variability index (SWVI) and (ii) an overall spiral degree of severity score (DoS). The means of 8 of the 10 trials (with the highest and lowest values removed) are used to calculate SWVI and DoS. SWVI is a unitless measure that highlights the fluctuations in spiral execution seen in patients with cerebellar dysfunction (Hess and Pullman, 2012). It is calculated as the coefficient of variation (ratio of the standard deviation to the mean) of the medians of spiral loop widths per angle over the 360° of each spiral loop and is independent of tremor. Higher SWVI scores are associated with greater degree of intention tremor and ataxia (Louis et al., 2012). DoS is a unitless continuous measure of overall spiral execution and spatial irregularity, derived from indices mostly related to drawing smoothness. DoS was designed as the computerized spiral analysis equivalent of the standard five-point (0–4) FTM clinical rating scale. The DoS index correlates with the neurologic exam and has been validated with clinical tremor scales (Elble et al., 2006; Saunders-Pullman et al., 2008; Louis et al., 2012). DoS was shown to have high sensitivity and specificity discerning early Parkinson disease (PD) subjects from normal controls, as well as being more revealing than the clinical exam elucidating pre-clinical spiral changes on clinically unaffected sides in PD (San Luciano et al., 2016).

3. Statistical analysis

Mann-Whitney test was used for comparing continuous data, and Fisher's exact test for categorical data between Groups 1 and 2. Non-parametric tests were chosen considering the small sample size and the lack of normal distribution of the data collected. Statistical analysis was performed using GraphPad Prism version 7.0. A probability value of <0.05 was considered to be statistically significant. Since all unilaterally operated cases were performed to improve the function of the dominant limb, spiral analysis data only from the dominant limb of patients were included in the final analysis. SWVI sensitivity and specificity calculations were performed using a cut-off value = 0.40, the median normal SWVI determined in a previous study investigating cerebellar dysfunction in ET (Louis et al., 2012).

4. Results

A total of 19 ET patients were identified as satisfying all inclusion criteria and were used in this study. Ten patients met the defined criteria for 'early tolerance' (Group 1) while 9 patients had a sustained good response at least for the first two years after surgery (Group 2).

4.1. Patient demographics and clinical characteristics

No significant differences were noted in patient age and sex at the time of DBS surgery between the two groups. 40% of Group 1 patients had unilateral DBS compared to 22% in Group 2. All unilateral DBS were implanted to improve the tremors in the dominant limb. All patients in both groups were initially programmed using