Voice Tremor in Patients With Essential Tremor: Effects of Deep Brain Stimulation of Caudal Zona Incerta

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Summary: Objectives. The present study aimed at evaluating the effect of deep brain stimulation (DBS) of the caudal zona incerta (cZi) on voice tremor in patients with essential tremor (ET).

Study Design. This is a prospective nonrandomized design with consecutive patients.

Methods. Twenty-six patients operated with cZi DBS were evaluated under two conditions: without stimulation (Stim OFF) and with stimulation (Stim ON). Voice tremor was assessed on the basis of recordings of sustained vowel productions using a four-point rating scale in a blinded and randomized procedure. Averaged values of multiple assessments for each stimulus were used in statistical testing. The group of patients with voice tremor in Stim OFF was analyzed separately from the group of patients without voice tremor.

Results. Voice tremor was significantly reduced on stimulation compared with off for the subgroup with initial voice tremor. Voice tremor prevalence was found to be 50% (13 patients). Individual differences in voice tremor outcome were noticeable. Six of the patients with voice tremor at baseline improved substantially by cZi DBS treatment.

Conclusions. On the group level, voice tremor in patients with ET was found to reduce when stimulating the cZi. Bilateral stimulation was indicated to be more effective in reducing voice tremor than unilateral stimulation. However, individual voice tremor outcomes suggest that not all patients benefit from cZi DBS. Severity of voice tremor at baseline may not be a good predictor of voice tremor outcome after cZi DBS. Patients should be informed before surgery regarding individual differences in response to DBS treatment.

Key Words: Essential tremor–DBS–cZi–Voice tremor–Perceptual evaluation.

INTRODUCTION

Essential tremor (ET) is one of the most common adult-onset motor disorders.[1] The overall disease prevalence has been estimated to 0.9%, rising to 4.6% in the population aged >65 years.[2]

The pathophysiology is not clearly understood. Although the basal ganglia-thalamic pathway of tremor is of importance in Parkinsonian tremor, the cerebello-thalamocortical pathway is heavily implicated in the generation of ET, and dysfunction of a brainstem nuclei or degenerative changes of the cerebellum have been suggested as the cause of ET.[3]

Because there are no biomarkers or pathologic markers for ET, the diagnosis is based on clinical evaluation,[1,4] and rating scales are used to assess the degree of tremor in different parts of the body.[5]

ET is a postural-action-kinetic tremor, usually bilateral, with a frequency of 7–12 Hz, and the condition is mainly characterized by tremor occurring during voluntary movements of the arms and sometimes of the head or legs.[1] Components of the speech mechanism can also be affected, including the respiratory muscles, the larynx, and the musculature within the vocal tract,[6-8] resulting in rhythmic fluctuations in loudness and/or pitch during phonation, which is perceived as a voice that sounds tremulous and shaky.[9,10] Severe voice tremor can pose a considerable handicap to the patient, not least from a social perspective.

Estimates of the prevalence of voice tremor in patients with ET vary, ranging between 18 and 30%[7] up to as much as 62%.[11] The large differences in prevalence estimates may be due to the heterogeneity of the disorder and the method being used by the examiner.[10] Voice tremor typically emerges at a later stage of the disease.[10,12]

About 50% of the patients will respond well to pharmacologic treatment, mainly beta blockers.[13,14] In the remaining patients, surgical intervention might provide an option.

Stereotactic functional neurosurgery has a long history of lesional procedures for tremor. However, these have, at least in the Western world, today been largely replaced with deep brain stimulation (DBS). In DBS, electrodes connected to a neuropacemaker are surgically implanted in different targets in the thalamus and the basal ganglia. It was first introduced as a therapy for tremor in 1997 in the ventral intermediate nucleus of the thalamus (Vim; Figure 1) by Benabid et al.[15] Vim DBS of the thalamus was approved by the US Food and Drug Administration in 1997 as a treatment for ET and is today the treatment of choice for patients with medication-resistant ET.[16,17]

Extensive research has demonstrated that DBS targeting the Vim is effective in reducing overall tremor.[18,19] However, not all patients respond well to Vim DBS, and stimulation-induced adverse effects such as dysarthria, disturbance of gait/balance, and paresthesias are relatively common,[13,18] especially so in patients receiving bilateral stimulation.[16,20,21] Another concern regarding Vim DBS is that the treatment effect seems to be diminishing over time.[22–24]

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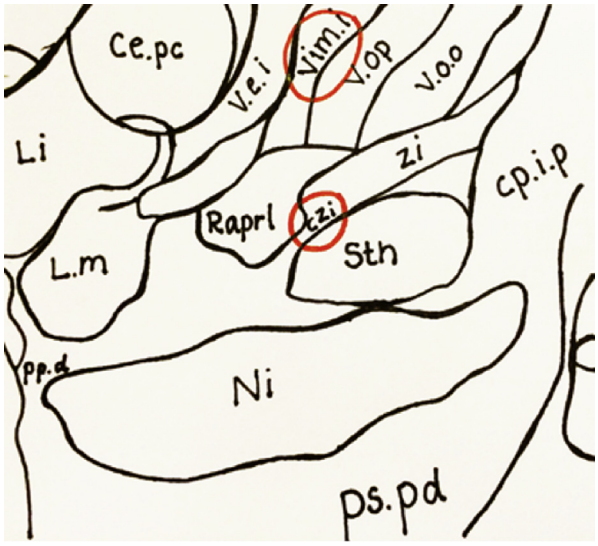

FIGURE 1. An illustration of DBS targets for the treatment of essential tremor: the ventral intermediate nucleus of the thalamus (Vim) and the caudal zona incerta (cZi).

Because of these relative shortcomings, alternative targets for DBS have been explored. Most interest has been focused on the posterior subthalamic area, including the caudal zona incerta (cZi; Figure 1), a target previously used for subthalamotomies during the lesional era.[25–29] Recent reports suggest that the effect of cZi DBS on tremor compares favorably with Vim DBS, although adverse events have been limited.[20,29–32]

Voice tremor outcome is routinely assessed as part of both the established essential tremor rating scale (ETRS,[33] item 3) and the recently proposed TRG essential tremor rating assessment scale (item 1[34]). However, few studies have included voice tremor in their reporting of DBS outcomes for patients with ET. Regarding Vim DBS, Deuschl et al[13] concluded, in their review, that bilateral DBS appears to be more effective (mean ETRS voice item of 1.47 off stimulation; 0.3 on stimulation) than unilateral DBS (mean ETRS voice item of 1.07 off stimulation; 0.78 on stimulation) for voice tremor but also more likely to cause adverse effects.

To date, there are no studies specifically aimed at voice tremor outcomes in cZi DBS for ET, but two recent reports have suggested a positive effect. Fytagoridis et al[35] found that voice tremor was marginally reduced with stimulation of the cZi in a cohort of 18 patients with low voice tremor scores at baseline. Plaha et al[29] found that voice tremor scores improved by 33% with bilateral cZi DBS in a similar cohort of patients. In both reported studies, as common in clinical evaluations, the assessments were nonrandomized and nonblinded. Additionally, assessments were obtained using rating scales and performed once, a method liable to low interrater agreement and reliability.[36] Because of the small number of studies reporting specifically on voice tremor outcomes and the difficulty in estimating the stability of the assessments made in the ones that do, the literature currently does not afford conclusions to be drawn regarding the effects of cZi DBS on voice tremor.

The primary aim of this study was to provide a blinded quantitative evaluation of the effect of cZi DBS on voice tremor in patients with ET. A secondary aim was to investigate the presence of perceptually perceived voice tremor in this group of patients.

METHODS

Participants

Twenty-six patients (14 men, 12 women) diagnosed with ET and operated with cZi DBS were included in this study. An overview of the patients is presented in Table 1. The patients were asked to give their written informed consent before recording. The diagnosis of ET was made by a movement disorder neurologist, and all DBS procedures were performed at Umeå University hospital by the same neurosurgeon. The study has been approved by the Regional Ethical Review Board (Dnr: 2012-364-31M).

Speech material

The evaluation of voice tremor was performed on sustained vowels[37] produced by patients under two conditions: without stimulation (Stim OFF) and with stimulation (Stim ON). Recordings were made in a quiet environment in the patients' homes, approximately 15 minutes after DBS had been switched on or off. Patients were instructed to produce a sustained vowel for as long as possible using his or her "comfortable everyday pitch and loudness levels." The front open vowel [a] was used to capture the effects of jaw tremor in addition to laryngeal tremor and tremor affecting respiration. The task was repeated two times per condition (Stim OFF/Stim ON), for a total of four recordings per patient. All recordings were made using a free-field, head-mounted microphone placed approximately 4 cm from the corner of the mouth.

An interval of 3 seconds was extracted from each vowel for auditory-perceptual analysis. First, the beginning and end times of each produced vowel were marked manually. Then, the interval was extracted, beginning 1 second into the marked vowel, using a computer program within the *Praat* software package.[38]

Auditory-perceptual evaluation

The produced vowels were rated perceptually multiple times by the first author (P.H.) and the second author (L.S.) in a blinded and randomized procedure. Voice tremor was defined as rhythmic fluctuations in pitch or loudness of the voice. For each produced vowel, an auditory-perceptual rating of voice tremor was made using a four-point rating scale (0 = absent, 1 = mild voice tremor, 2 = moderate voice tremor, and 3 = severe voice tremor). The recordings were presented through headphones in random order, using the *Alvin* stimulus presentation software package.[39] Thus, the raters were at all times blinded to patient identity and condition when assessing the vowels.

The 104 (26 × 4) recordings were rated seven times by each rater (randomized in seven blocks), resulting in a total of 14 ratings of each recording. The raters underwent a joint rating session using reference stimuli at the onset of the perceptual analysis stage of the study, aimed at reaching consensus concerning the rating scale, and strengthen the reliability of the