PAPER

Chronic spinal cord stimulation in medically intractable orthostatic tremor

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Background: Orthostatic tremor with its sense of unsteadiness when standing may have a devastating effect on affected persons. Currently, there are no other treatment options in those who do not respond or who do not tolerate medical treatment.

Objectives: To report on a pilot study on spinal cord stimulation in medically intractable orthostatic tremor.

Methods: Chronic spinal cord stimulation (SCS) was performed in two patients with medically-intractable orthostatic tremor via quadripolar plate electrodes implanted at the lower thoracic spine. The electrodes were connected to implantable pulse generators.

Results: Subjective and objective improvement of unsteadiness was achieved within a frequency range of 50 to 150 Hz, and occurred in the presence of stimulation-induced paraesthesia. With optimized stimulation settings polygraphic electromyogram (EMG) recordings continued to show the typical 14–16 Hz EMG activity. The beneficial effect of SCS was maintained at long-term follow-up.

Conclusions: The results of this pilot study indicate that SCS may be an option in patients with otherwise intractable orthostatic tremor.

Orthostatic tremor is a rare condition that was first described by Heilman¹ in 1984. It is characterised by an intense and disabling sensation of unsteadiness when standing quiet, accompanied by a 13–18-Hz tremor of the lower limbs.^{2–3} The tremor and the feeling of unsteadiness are relieved by walking, sitting or lying down. The ability to stand still without help may range between a few seconds and a few minutes depending on the severity of the condition. Although patients rarely fall down, the sensation of unsteadiness may have a devastating effect interfering markedly with quality of life.⁴ Electromyogram (EMG) recordings show a typical burst activation pattern with a high coherence between unilateral and contralateral muscles. The tremor can occur also in the upper limbs with sustained isometric contraction and in muscles of the trunk. It is thought that orthostatic tremor is driven by a central oscillator, but the pathophysiological mechanisms have not been definitely clarified.^{5–6} Medical treatment with a variety of drugs such as clonazepam, levodopa and primidone is considered to be the treatment of choice. A recent study,³ however, has shown that the overall response to medical treatment is poor. Thus far, there are no other therapeutical options in those patients with orthostatic tremor who do not benefit from medical treatment or who have side effects.

In the past few years, chronic neurostimulation techniques have proved to be beneficial in a variety of movement disorders.^{7–9} Current targets for deep-brain stimulation include the thalamus, subthalamic nucleus and pallidum. Spinal cord stimulation (SCS) is mainly used nowadays for the treatment of medically refractory pain,^{10–12} but it has been thought to be of interest for the treatment of tremors also.¹³ Here, we report on a pilot study on the use of SCS in otherwise intractable orthostatic tremor.

PATIENTS AND METHODS

Patients

Two patients with medically intractable orthostatic tremor were included in this prospective pilot study. Both patients

had the typical clinical picture of orthostatic tremor with characteristic EMG findings (described later). In the first patient, SCS was indicated also for treatment of neuropathic pain, whereas the second patient had no pain syndrome or sensory disturbances. Medical treatment, including primidone, clonazepam and levodopa, was either ineffective or not tolerated because of side effects in both patients. On inclusion in the study, no drug known to interfere with orthostatic tremor was taken. Magnetic resonance images of the brain and the cranium were normal. No evidence of psychological precipitants, somatisations or secondary gain was seen. Both patients gave informed consent for the study.

Patient 1, a 58-year-old woman, had a 10-year history of unsteadiness when standing quiet. In the further course, she was also diagnosed with diabetes, and she developed burning painful sensations of her feet and calves. She rated the maximal intensity of her pain as 8 on a Visual Analogue Scale ranging from 0 to 10. On presentation at our hospital she tolerated standing for about 2 min.

Since 8 years, patient 2, a 72-year-old man, had increasing instability on standing, which had resulted in an intense fear of falling. He left the house only with a walking frame with an integrated seat. When referred for consultation he almost completely avoided standing, which was possible for only 10 s. Medical history included arterial hypertension and compensated cardiac insufficiency.

Surface EMG recordings and measurement of outcome

Surface EMG activity was recorded with silver–silver chloride electrodes simultaneously from the vastus medialis, biceps femoris, tibialis anterior and gastrocnemius muscles while the patients were sitting and standing. EMG signals were amplified, band-passed filtered at 10–100 Hz, and digitised with a sampling rate of 1000 Hz. Recordings and analyses were made with Win Data supplied by Zebris (Isny,

Abbreviations: EMG, electromyogram; PSR, patient self-rating; SCS, spinal cord stimulation

Germany) and with DASyLab 5.6 supplied by DATALOG (Mönchengladbach, Germany). Tremor frequency was estimated by measuring interburst intervals and fast fourier transformation. The burst activation pattern occurred at a frequency of 15–16 Hz in patient 1 (fig 1) and at 14 Hz in patient 2.

Outcome was measured repeatedly by recording the time tolerated to stand still preoperatively, during the test stimulation trial, after implantation and programming of the implanted pulse generator, and on follow-up at 3 months and 1 year postoperatively. Patients were asked to stand with their feet apart without swaying from one leg to the other. The measurements were carried out in the late afternoon and they were repeated three times.

Surgery

Quadripolar plate electrodes (Symmix, Medtronic, Minneapolis, Minnesota, USA) were implanted via a unilateral limited laminotomy approach at D11/12 with the patients in the prone position under intravenous analgesia. Owing to the diamond-shaped configuration of the electrodes, bilateral dorsal column stimulation is possible. The electrodes were placed over the dorsal columns in the epidural space. Intraoperative electrical stimulation produced paraesthesias of both lower extremities without motor responses of trunk muscles. The electrodes were externalised for 5 and 10 days, respectively, to allow test stimulation and EMG recording with different stimulation settings. As both patients benefited from stimulation, the electrodes were connected to programmable impulse generators (Itrel III, Medtronic) that were implanted in a subcutaneous abdominal pouch in a second procedure under general

anaesthesia. The impulse generators were programmed and adjusted percutaneously to achieve maximal benefit targeting the symptom of unsteadiness.

RESULTS

Test stimulation and EMG studies

No adverse events were observed during or after the operative procedures. Test stimulation showed that the ability to stand still improved markedly in both patients (patient 1: from preoperative 120 (range 107–130) s to >180 s on three measurements; patient 2: preoperative 10 (range 8–12) s to 50 (range 30–62) s. Bipolar stimulation with 5 Hz and 10 Hz in patient 1 produced throbbing and humming sensations in both legs at a threshold of 1 V, but had no effect on the tremor, although at 3 V the feeling of unsteadiness increased. Stimulation at 50 Hz produced mild tingling sensations at 0.8 V, and improvement of the unsteadiness at 1.8 V. Subjective improvement of unsteadiness occurred only in the presence of stimulation-induced paraesthesias and was noted in a frequency range from 50 to 150 Hz. The maximum improvement at the lowest threshold for stimulation intensity was recorded with 100 Hz at 1 V. Higher frequencies of 500 and 1000 Hz were not effective.

With optimised stimulation settings resulting in almost complete disappearance of the feeling of unsteadiness and the patient being able to stand still for several minutes, EMG recordings continued to show the synchronous EMG activity of about 16 and 14 Hz in patients 1 and 2, respectively, typical of orthostatic tremor in both legs (fig 2). Amplitudes of the activity, however, were decreased by 52% (standard deviation (SD) 12%) on repeated measurements.

Figure 1 Polygraphic recording of knee angle and surface electromyogram (EMG) of antagonistic muscle pairs of the right thigh and lower leg in patient 1. After standing up from the sitting position (arrow), a burst EMG activity of 16 Hz typical of orthostatic tremor occurs in all four muscles. The inset zooms in on 1 s of EMG activity. Knee extension is shown by upward deflection of top trace. BF, biceps femoris; RF, rectus femoris; SO, soleus muscle; TA, anterior tibial.

Figure 2 Fast Fourier transformation (FFT) amplitude spectra of continuous electromyogram (EMG) recording of the vastus medialis muscle of patient 1 showing different settings of test stimulation. In this waterfall diagram of FFT amplitude spectra of continuous epochs of EMG recordings, the vastus medialis muscle shows a peak of 15 Hz muscle activity when the patient is standing. Electrical stimulation with impulses of 210 μ s duration and an intensity of 1.5 V at 50 Hz leads to a clearly visible reduction of tremor-associated EMG amplitude. Each switching of stimulation frequency is associated with an increase in EMG amplitude as during this brief time interval the electrical stimulation is paused. Each spectrum is derived from an epoch of 16.4 s of EMG recording; spectra are numbered in order of acquisition (z axis).

Clinical results

Both patients experienced marked improvement post-operatively and during follow-up. One year postoperatively, patient 1 was able to stand still for more than 5 min on three repeated measurements. Rating for the Visual Analogue Scale pain score was 2/10, also indicating marked improvement. Patient self-rating (PSR) of outcome regarding the unsteadiness was excellent (6 on a range from 0 to 6). The beneficial effect on orthostatic tremor was maintained at 3 years postoperatively (PSR 5), although the effect on pain was less stable. The ability to stand still in patient 2 increased from 10 to 102 s (range 80–114), at 1 year postoperatively (PSR 4). No further assessments were possible thereafter, as the patient had brain stem infarction and became severely disabled.

Chronic stimulation was carried out in bipolar mode with a pulse width of 210 μ s, at a frequency of 100 Hz with 1 V (patient 1), and at 110 Hz with 3.2 V (patient 2).

DISCUSSION

Studies on health-related quality of life have shown that orthostatic tremor has a marked effect on patients' state of well-being.⁴ Scores of patients with orthostatic tremor on the 36 item Short Form Questionnaire were markedly lower than in the general UK population and even lower than those found in patients having Parkinson's disease or multiple sclerosis. Also, higher depression scores were found in more than half of the patients with orthostatic tremor. Data on the clinical effects of drugs for treatment of orthostatic tremor are conflicting.^{3–6} Hence, the quest for alternative therapeutic options in orthostatic tremor has been considered worthwhile.⁶ The results of our pilot study indicate that chronic SCS may be an option in patients with otherwise intractable orthostatic tremor.

SCS has been used for more than three decades for treatment of various pain syndromes. Its application has been

expanded successfully also for ischaemia of the lower extremities and for angina pectoris. At this time, it remains unclear how SCS exactly works and different mechanisms probably operate simultaneously or sequentially.¹⁴ It is well known that orthostatic tremor is not modified by peripheral nerve stimulation,² and also magnetic stimulation over the lumbar spine did not have any effect.¹⁵ Chronic SCS, however, differs fundamentally from those stimulation techniques applied earlier in patients with orthostatic tremor.

The pathophysiological mechanisms underlying the development and manifestation of orthostatic tremor are unclear. Although the primary cause of orthostatic tremor remains unidentified, evidence suggests that various neuronal systems are affected, including the cerebellum, brain stem, striatum and thalamus, corticocortical pathways, and, in particular, the corticocerebellothalamic loop.^{3,5} The concept that orthostatic tremor is driven by a primary central generator has been accepted most widely, but it has also been suggested that the spinal cord may generate the 16-Hz tremor.¹⁶ Furthermore, orthostatic tremor has been thought to be the product of exaggerated activity of a physiological generator oscillating at approximately 16 Hz.¹⁷ Presumably, the generator of orthostatic tremor projects through the reticulospinal tract.⁵ Recently, a "double lesion" model has been suggested for orthostatic tremor to be manifested.³ According to this hypothesis, an abnormally active oscillator would have the key role, but orthostatic tremor would develop only if coupled with additional dysfunction at the level of the basal ganglia or the cerebellum, resulting in deficient control of the oscillator.

The therapeutic effect of SCS on orthostatic tremor in our study is presumably modulation of sensory input to the neuronal network subserving orthostatic tremor. The finding that the 16-Hz motor activity in the legs is still present indicates that SCS may have a more indirect modulatory influence on the activity of the primary oscillatory generator.

The improvement in unsteadiness along with reduction in the EMG amplitude, however, concurs with the hypothesis that the exaggerated sense of imbalance when standing still could be the actual core abnormality in patients with orthostatic tremor.¹⁷ Interestingly, in a previous study that showed small improvements in clinical parameters on blinded video rating after levodopa challenges in a group of patients with orthostatic tremor, the mean EMG frequency of tremor was also unchanged despite power analysis showing a clear reduction in the area under the curve.⁶ It is important to note, that there is a discrepancy between subjective and objective unsteadiness in orthostatic tremor, and that it has been postulated that the sense of instability in orthostatic tremor is related to "tremulous disruption" of proprioceptive afferent activity from the legs.¹⁸ Thus, SCS could also act by masking the pathological disruption to a certain extent and de-escalate activity in a reverberating vicious cycle. An alternative mechanism could be its effect on interneurons mediating either spinocerebellar input or projections to motor pathways and the reticulospinal tract.

The major problem with trials of new treatment in rare disorders such as orthostatic tremor is the small number of patients available. As with trials on medication, this is all the more true for the design of trials for alternative surgical options. Our findings also must be interpreted with caution in view of the lack of placebo control. As both patients perceived mild tingling sensation in their legs on effective stimulation, it was not possible to carry out placebo stimulation. Nevertheless, we think that SCS would probably not have such a marked and prolonged effect over years if it were attributable only to placebo effect. In conclusion, despite its limitations, our pilot study raises hope to provide a therapeutic option for patients with medically refractory orthostatic tremor. It will be necessary to confirm our results in a larger number of patients in a controlled study design.

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Competing interests: JKK is a consultant to Medtronic.

Informed consent was obtained from the patients described in this paper.

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