NEUROLOGIA I NEUROCHIRURGIA POLSKA 48 (2014) 292–295

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Case report

Deep brain stimulation in the treatment of Holmes tremor – A long-term case observation

Natalia Grabska [a,*], Monika Rudzińska [b], Małgorzata Dec-Ćwiek [a], Marcin Tutaj [c], Wojciech Pietraszko [d], Michał Michalski [a], Andrzej Szczudlik [a]

[a] Department of Neurology, Jagiellonian University Medical College, Krakow, Poland
[b] Department of Neurology, Medical University of Silesia, Katowice, Poland
[c] Medtronic, Poland
[d] Department of Neurosurgery, Jagiellonian University Medical College, Poland

ARTICLE INFO

Article history:
Received 9 April 2014
Accepted 17 June 2014
Available online 27 June 2014

Keywords:
Holmes tremor
Deep brain stimulation
Ventralis oralis anterior
Zona incerta

ABSTRACT

We present the patient with Holmes tremor secondary to the infarction of thalamus, successfully treated with the deep brain stimulation (DBS) of the area between ventralis oralis anterior and zona incerta for a long time, in whom the severe tremor reappeared after removal of the DBS lead. This is the first presentation of the effective DBS on this location. Our case does not support the hypothesis that the DBS treatment could lead to sustained relief of symptoms after cessation of stimulation.

Holmes tremor (HT), also known as 'rubral tremor' or 'midbrain tremor', is a rare movement disorder causes by the lesion in different regions of the brainstem, cerebellum or thalamus, that follows the dysfunction of the cerebello-rubro-thalamic tract and/or nigrostriatal pathway and leads to severe, low frequency (<4.5 Hz), resting, intention and/or postural tremor. The onset of tremor is usually delayed, from 4 weeks to 2 years after lesion [1]. Pharmacological treatment in many cases is not effective, and therefore surgical procedures, deep brain stimulation (DBS) of thalamic nuclei, usually the ventral intermedius nucleus (Vim), or ablative therapies e.g. thalamotomy, are offered to patients. We report a case of HT due to ischemic stroke of the thalamus, successfully treated by the DBS of the area between ventralis oralis anterior nuclei (Voa) and zona incerta (ZI) with a long follow-up period (more than 4 years) and with temporary reappearance of tremor after the DBS removal due to infection of the skin on the head around the place where the electrode was inserted.

1. Case report

A 45-year-old female was admitted to the Outpatient Movement Disorder Clinic of the Department of Neurology,

* *Corresponding author at*: Department of Neurology, University Hospital, Jagiellonian University Medical College, ul. Botaniczna 3, 31-503 Krakow, Poland. Tel.: +48 124248600; fax: +48 124248626.
E-mail address: nath87@wp.pl (N. Grabska).

http://dx.doi.org/10.1016/j.pjnns.2014.06.002

University Hospital in Cracow in April 2004 because of severe tremor of the right limbs. At the age of 15 she had developed suddenly right hemiparesis and aphasia. Computed tomography showed an infarct of the left thalamus. Paresis disappeared completely within several months and she was been able to speak normally. Within 4 weeks after the ischemic episode, tremor of right limbs gradually appeared and remained severe and unchanged for the next years. She had difficulties during eating, drinking and precise movements of her right arm. Tremor exacerbated by emotional stress or voluntary movements and persisted during sleep. She had no history of using neuroleptics or other tremor-inducing drugs prior to and after the thalamus infarct. The family and social history were unremarkable.

Neurological examination revealed severe, disabling unilateral resting, postural and kinetic tremor affecting right limbs, mainly the upper limb, greater proximally than distally. The amplitude was moderate at resting tremor and extremely high in kinetic and intentional tremor. The severity of tremor assessed with the Fahn–Tolosa–Marin Tremor Rating Scale (FTMTRS) was scored on 42 points [2]. The patient also had a slight ataxia in the same arm.

Magnetic resonance imaging showed small (<1 cm), lacunar infarct in the upper–posterior–lateral part of the left thalamus, ranging to the Vim nucleus. DaTSCAN test (^{123}I-ioflupan) showed a normal presynaptic dopamine reuptake in the putamen and caudate nucleus on both sides. Accelerometric and electromyographic studies demonstrated an alternating activity of the flexor and extensor muscle in the right arm. The rhythm of resting, postural and intention tremor was periodically irregular with a frequency of approximately 4.5 Hz. The amplitude of tremor increased during postural and voluntary movements. Pharmacological treatment with neuroleptics (haloperidol), anticholinergics (trihexyphenidyl, biperiden), benzodiazepine (diazepam), amantadine and levodopa did not relieve the tremor.

In April 2009, the patient underwent stereotactic surgery and a four-contact DBS lead (Medtronic, Inc., Model 3387) was implanted into the area between Voa nucleus and ZI, and connected to single-channel implantable pulse generator (IPG, Medtronic, Inc., Model Soletra). The choice of this particular target for DBS was based on the best reduction of the tremor during the operation. The procedure was performed in a local anesthesia with a temporary analgesia. The stereotactic frame (RM frame) was positioned and computed tomography scan was obtained, the computed tomographic and MRI scans were fused and stereotactic targeting was carried out with a use of PraezisPlus software. The trajectory of five microelectrodes was planned at the front of the stroke area (central microelectrode: 14 mm lateral to the anterior commissural–posterior commissural (AC–PC) line, 8 mm anterior to PC, on the level of AC–PC line). Detailed microelectrode recording confirmed location of the thalamus (−6 to +2 mm) as well as ZI (+3 to 4 mm) and subthalamus (STN) (to +5 mm). Macrostimulation of the three microelectrodes: central, medial and posterior was performed. The best result of tremor relief was obtained with a central microelectrode activation, placed 3 mm below the AC–PC line, where final electrode (Medtronic 3389) was inserted. The optimal clinical effect was obtained with DBS parameters as follows: C+, 0 − (ZI), 2 − (Voa/Vop), 1.8 V, 185 Hz, 60 μs.

The adjustment of stimulation settings included decreasing the voltage to 1.3 V. After 6 months of stimulation, the severity of tremor assessed with the FTMTRS was significantly reduced to the score of 11. The reduction was prominent mostly for postural tremor of the right upper limb. The severity of task-specific tremor (e.g. during writing and in daily tasks, like using cutlery) was just slightly reduced. Tremor of the lower right limb and ataxia in the upper one did not change. Twenty-four months after the surgery, the patient presented with similar tremor severity to that observed at the assessment after 6 months and because of that, the voltage was increased to 1.8 V. At follow-up after 36 months, the patient's condition was stable, the clinical status and the FTMTRS score were unchanged. The parameters settings were as previously.

Four years after the DBS implantation, in June 2013, the patient developed an infection of the skin on the head around the place where the electrode was inserted. Two-month treatment with antibiotics according to antibiogram was ineffective, therefore the decision of the explantation of DBS system was made. Involuntary movements of the right arm reappeared immediately, with a severity similar to presented before the DBS lead implantation (FTMTRS score = 42) with no other abnormalities in the neurological examination. The severity of tremor did not change during the 6-month follow-up.

2. Discussion

Our case illustrates the effectiveness of DBS in a new, previously not reported location of the Voa/ZI border with a long-term follow-up and no persisted effect of tremor suppression after the removal of the DBS lead, indicating that 4 years of stimulation could not be sufficient to produce neuroplastic changes in this case.

The publications discussed location and the effectiveness of the surgical treatment of HT are limited. We found only 19 published HT cases treated by the DBS implanted mostly in the Vim nucleus, including four cases with a long-term observation (over 30 months) [3–7]. Vim stimulation, in some cases, was insufficient and dysarthria as a side effect after bilateral DBS was frequently observed. The effect of DBS location in different thalamic nuclei, globus pallidus internus (GPi) or ZI on HT severity was similar [4,8–10]. The positive effect of Voa or ZI stimulation was described in three papers, but no case of the stimulation of the area between Voa and ZI was published as yet. Foote et al. [8,9] reported three cases with a posttraumatic HT, successfully treated with the use of two stimulators implanted in different locations on one side: one in Vim and the second in the junction of Voa and ventral oralis posterior nucleus (Vop). The improvement of tremor was greater when two leads were used in parallel. A case of a post-stroke HT successfully treated with GPi DBS and no excessive benefits after the additional stimulation of the Vim and Voa was reported by Lim et al. [10]. Plaha et al. reported high-frequency DBS of ZI is effective in suppressing resting and kinetic tremor, located in the distal as well as proximal muscles [4].

The role of ZI in connecting the nigrostriatal pathway and the cerebello-thalamo-cortical loop has not been clearly demonstrated in human. According to studies based on

researches made on animals, it is known that ZI receives afferents from different parts of the brain like GPi, substantia nigra pars reticulata (SNpr), cerebellum, motor cortex [11,12] and sends efferents to ventro-lateral nucleus of thalamus, cerebellum, inferior olive, SNpr, GPi and as well as to the cerebral cortex [13–15]. Its role in connecting the nigrostriatal pathway and cerebello-thalamo-cortical loop is essential. Because it seems that, both loops are involved in the pathogenesis of HT, DBS of the ZI could be effective in the control of this involuntary movements [4]. Stimulation of the area between Voa and ZI in our patient was not totally effective and the tremor of the lower extremity persisted. Although different combinations of the electrode location were checked, none of them improved tremor of lower extremities. Our goal in this case was to position the electrode at a location where stimulation would reduce tremor primarily of the upper extremity, because this right limb tremor was most debilitating. The patient did not agree to undergo implantation of another DBS lead, in a different target, so we could not check the effectiveness of parallel stimulation. Our long-term observation supports the view that stimulation of a part of the thalamus other than Vim is equally effective in the treatment of HT.

Mechanisms of HT are complex and heterogeneity of its pathophysiology is speculated [16]. Gajos et al. [16] showed that impairment of nigrostriatal pathway is not necessary and damage of cerebello-thalamic pathway is sufficient to HT development. In our patient lesion of the posterior–lateral part of left thalamus indicated damage of the Vim nucleus of the thalamus which provided activation from the nucleus dentatus. To evaluate presynaptic dopaminergic striatal denervation the SPECT examination was performed but radiotracker uptake was symmetrical. Morerover our patient did not respond to the treatment with levodopa what proved that there were no changes in the nigrostriatal area. It is controversial whether the dopaminergic neurotransmission in the nigrostriatal area is necessary or not in HT etiology. Our results are consistent with a study described by Gajos et al., indicating plurality of pathophysiological mechanisms underlying HT.

Our case does not support the view that the long-lasting stimulation cause persistent suppression of the tremor after the DBS lead removal. Sustained or transient relief of motor symptoms after cessation of prolonged DBS was reported in patients with dystonia [17,18]. So far, only three cases with HT were described, confirming persistent effect of DBS in this kind of tremor [5,6]. Castrop et al. [6] reported two patients with HT after hemorrhagic lesion of mesencephalon effectively treated by Vim stimulation for 7 and 6 years and a 1-year follow-up of sustained suppression of the tremor when stimulation was turned off. Similar outcome was presented by Diederich et al. [5] who observed persisted effect of DBS in one patient with HT after battery failure. Based on this reports, the hypothesis that the longitudinal Vim stimulation leads to neuroplastic reorganization and results in a persistent tremor suppression might be made. The lack of suppression in our case could be related to the shorter time of stimulation (4 years) or to the very long (30 years) period of tremor before the DBS lead was implanted, leading to sustained changes in the neuronal loops, not so easy to reverse.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

[1] Deuschl G, Bain P, Brin M, Scientific Committee. Consensus statement of the Movement Disorder Society on Tremor. Mov Disord 1998;13:2–23.
[2] Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, editors. Parkinson's disease and movement disorders. 2nd ed. Baltimore: Urban & Schwarzenberg; 1993. p. 271–80.
[3] Peker S, Isik U, Akgun Y, Ozek M. Deep brain stimulation for Holmes' tremor related to thalamic abscess. Childs Nerv Syst 2008;24:1057–62.
[4] Plaha P, Khan S, Gill SS. Bilateral stimulation of the caudal zona incerta nucleus for tremor control. J Neurol Neurosurg Psychiatry 2008;79:504–13.
[5] Diederich NJ, Verhagen ML, Bakay RA, Alesch F. Ventral intermediate thalamic stimulation in complex tremor syndromes. Stereotact Funct Neurosurg 2008;86:167–72.
[6] Castrop F, Jochim A, Berends LP, Haslinger B. Sustained suppression of Holmes tremor after cessation of thalamic stimulation. Mov Disord 2013;28:1456–7.
[7] Follett MA, Torres-Russotto D, Follett KA. Bilateral deep brain stimulation of the ventral intermediate nucleus of the thalamus for posttraumatic midbrain tremor. Neuromodulation 2014;17(3):289–91.
[8] Foote KD, Okun MS. Ventralis intermedius plus ventralis oralis anterior and posterior deep brain stimulation for posttraumatic holmes tremor: two leads may be better than one: technical note. Neurosurgery 2005;56(ONS Suppl. 2). ONS-445.
[9] Foote KD, Seignourel P, Fernandez HH, Romrell J, Whidden E, Jacobson C, et al. Dual electrode thalamic deep brain stimulation for the treatment of posttraumatic and multiple sclerosis tremor. Neurosurg 2006;58(4 (Suppl. 2)):280–6.
[10] Lim DA, Khandhar SM, Heath S, Ostrem JL, Ringel N, Starr P. Multiple target deep brain stimulation for multiple sclerosis related and poststroke Holmes' tremor. Stereotact Funct Neurosurg 2007;85(4):144–9.
[11] Mitrofanis J. Some certainty for the ''zone of uncertainty''? Exploring the function of the zona incerta. Neuroscience 2005;130:1–15.
[12] Mitrofanis J, Mikuletic L. Organisation of the cortical projection to the zona incerta of the thalamus. J Comp Neurol 1999;412:173–85.

[13] Heise CE, Mitrofanis J. Evidence for a glutamatergic projection from the zona incerta to the basal ganglia of rats. J Comp Neurol 2004;468:482–95.
[14] Bartho P, Freund TF, Acsady L. Selective GABAergic innervations of thalamic nuclei from zona incerta. Eur J Neurosci 2002;16:999–1014.
[15] Lin CS, Nicolelis MA, Schneider JS, Chapin JK. A major direct GABAergic pathway from zona incerta to neocortex. Science 1990;248:1553–6.
[16] Gajos A, Bogucki A, Schinwelski M, Sołtan W, Rudzińska M, Budrewicz S, et al. The clinical and neuroimaging studies in Holmes tremor. Acta Neurol Scand 2010;122:360–6.
[17] Hebb MO, Chiasson P, Lang AE. Sustained relief of dystonia following cessation of deep brain stimulation. Mov Disord 2007;22:1958–62.
[18] Cheung T, Zhang C, Rudolph J, Alterman RL, Tagliati M. Sustained relief of generalized dystonia despite prolonged interruption of deep brain stimulation. Mov Disord 2013;28:1431–4.