Brain Stimulation 12 (2019) 1304–1306

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Posterior subthalamic area deep brain stimulation for treatment of tremor and dystonia in Wilson's disease

Keywords:
Deep brain stimulation
DBS
Wilson's disease
Posterior subthalamic area
Tremor
Dystonia

Dear Sirs,

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism associated with *ATP7B* gene mutations. In this condition, copper accumulates in various tissues especially the brain, and liver. The resulting cellular dysfunction commonly manifests as ataxia, tremor, dystonia and parkinsonism. Whilst copper chelation therapies, including trientene and penicillamine, are well-established disease-modifying treatments, up to 50% of patients have persistent neurological symptoms despite optimal non-surgical therapy [1]. Brain lesioning [2] and deep brain stimulation (DBS) [3,4] have been occasionally used but this is not established treatment and there is no consensus on the optimal target. Reported surgical targets include the Vim/Voa thalamic nuclei for tremor [2,3] and globus pallidus interna (GPi) for hemiballismus and axial dystonia [4]. Although the subthalamic nucleus (STN) has been targeted for dystonia control [5,6] we could not, at the time of writing, find any published articles on its use in WD. Indeed, there is an ongoing trial seeking to determine whether the STN or the GPi is a better target for stimulation in patients with WD [7].

Recently, there has been increasing interest in targeting the posterior subthalamic area (PSA). This region contains and is close to structures involved in movement control control such as the STN, caudal zona incerta (cZI), pallidothalamic tracts and the prelemniscal radiation (RaPRL). cZI and RaPRL stimulation have been shown to be very effective in tremor control [8] whereas lesioning or stimulating the RaPRL reduces dystonia [9,10]. Since both the cZI and RaPRL are located within the PSA, posterior subthalamic area deep brain stimulation (PSA-DBS) could conceivably control both tremor and dystonia.

We present a patient with Wilson's disease whose major problems were severe arm tremors and left arm dystonia. The patient underwent bilateral PSA-DBS with excellent results. The patient gave informed consent for the use of his case and images in this publication.

Case report

A South African man first experienced tremor interspersed with left-sided chorea in late adolescence. The abnormal movements progressed and his speech became slurred by the age of 26. A diagnosis of Wilson's disease (WD) was made on the basis of clinical and investigative findings (choreoathetosis, dystonia, tremor, deranged liver function tests, Kayser-Fleischer rings, serum ceruloplasmin concentrations less than 0.2g/l and urinary copper excretion greater than 100 μg/24 hours). Liver biopsies or genetic tests were not carried out as the clinico-biochemical picture was considered sufficiently diagnostic of Wilson's disease. Conventional management with D-penicillamine and trientine (sequentially) improved the biochemical features but not the movement disorder and he was referred for deep brain stimulation in 2016. On presentation, he had severe bilateral action and postural arm tremor (worse on the left) and marked action-induced dystonia of the left arm and leg. The tremor significantly affected his ability to write, clean, dress or feed himself whilst the dystonia affected his gait. The preoperative Fahn-Tolosa-Marin tremor score (FTMTS) was 87/144 with the right and left arm tremor sub-scores being 13/28 and 26/28 respectively. The Burke-Fahn-Marsden dystonia score (BFMDS) was 48/150 (movement scale 29/120; disability scale 19/30).

MRI brain demonstrated severe atrophy of the lentiform nuclei, diencephalon and upper midbrain with abnormal signal in the dorsal mesencephalon, the dorsal pons and both superior cerebellar peduncles.

We considered performing either GPi-DBS or bilateral PSA-DBS but chose the latter as the major portion of the his disability was tremor rather than dystonia. Additionally, marked atrophy of the lentiform nuclei precluded confident identification of the GPi. The PSA target was the mesencephalic white matter just lateral to the equator of the red nucleus and posteromedial to the subthalamic nucleus. Intraoperative macrostimulation was used to locate the area in the PSA associated with maximum tremor reduction and no side effects. Microelectrode recording did not prove useful in this case. Medtronic 3389 electrodes were placed in the target before being connected to an Activa PC neurostimulator (Medtronic, Minneapolis). Intraoperative MRI scans confirmed correct electrode placement (Fig. 1). The effect of surgery was immediate and profound. He was able to drink from a cup without spilling,

https://doi.org/10.1016/j.brs.2019.05.014

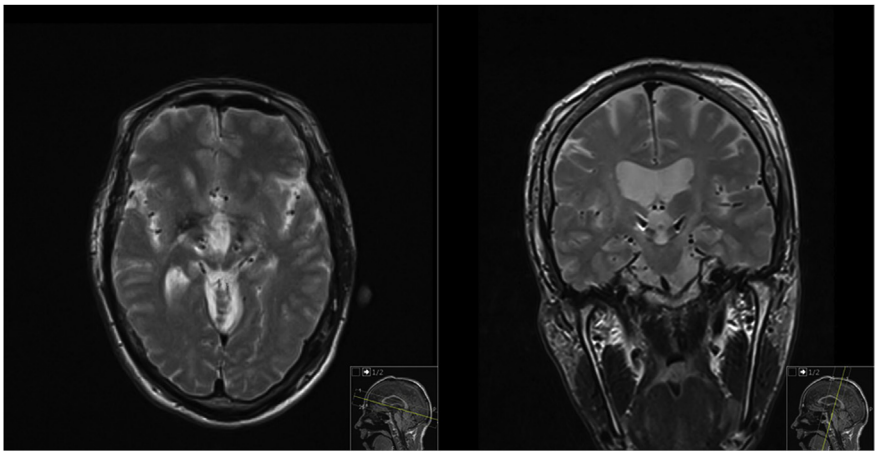

Fig. 1. Axial and coronal T2-weighted MRI scans showing the location of the active DBS contact.

use cutlery and write comprehensibly soon after surgery. He was discharged two-days after surgery. DBS programming commenced three-weeks later.

Tremor suppression was achieved early and at low amplitudes (1.8V) but control of his dystonia took almost one year and only at higher stimulation amplitudes and pulse widths. At the 2-year follow-up, the FTMTS was 4/144 (right and left arm tremor sub-scores of 0/24 and 4/24) with the neurostimulator ON and 74/144 (right and left arm sub-scores of 24 and 28) with the device OFF. There was significant reduction of his left arm dystonia. He reported improvement in his ability to write, feed and clean himself (BFM score 15/150; movement scale 10/120, disability scale 5/30). The final stimulation parameters were case (+) 0 negative; 3V, 60 μs, 120Hz on the left and case (+) 4 negative; 5V, 180 μs, 120Hz on the right. The x/y/z coordinates of the active contacts relative to the mid-commissural point was +10.60mm/-6.32mm/-5.04mm on the right and −10.80mm/-7.04mm/-3.65mm on the left. The patient continues on copper chelation therapy. His movement disorders remain very well controlled nearly 3-years after surgery.

Conclusions

Although PSA-DBS has been shown to be very effective in tremor control, there are few studies on its use to control dystonia, especial non-PD dystonia and none for WD. We present the first reported case of PSA-DBS in Wilson's disease and show that it is very effective in controlling both the tremor and dystonia of WD. Further work needs to be done to define the exact substrate stimulated and whether the STN, PSA or GPi are better DBS targets in WD.

Authors' roles

HLL was responsible for the overall conception of the study, writing, acquisition and analysis of data and revision of the manuscript for intellectual content. SKA, AM and GG were involved in the writing, acquisition and analysis of data.

Funding source

None.

Disclosures and declarations of interest

None.

Acknowledgement

We thank Sr J Foley and Mr A Taqvi for their help in completing this article.

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19 April 2019
Available online 21 May 2019