Parkinsonism and Related Disorders 60 (2019) 173–175

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

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

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Dentate nucleus stimulation in a patient with cerebellar ataxia and tremor after cerebellar stroke: A long-term follow-up

ARTICLE INFO

Keywords:
Ataxia
Cerebellum
Deep brain stimulation
Dentate nucleus

Cerebellar modulation has emerged as a promise therapy in the movement disorders field, as cerebellum pathways present connections with critical cortical areas. We have previously reported the short-term outcome in a patient with unilateral cerebellar stroke who improved the ataxia after cerebellar neuromodulation [1,2]. The rational hypothesis lies on the fact that unilateral chronic cerebellar ischemic lesions were linked with a decrease in intracortical inhibition in the contralateral motor cortex, culminating to inter-hemispheric asymmetry in cortical excitability, which could contribute to the motor impairment [3]. Then, modulating the healthy dentate nucleus could increase contralateral intracortical facilitation, restoring cortical excitability symmetry (Fig. 1) [2]. We report here the 4-year results of this patient using a single-blinded evaluation.

A 53-year-old female patient underwent a resection of acoustic neuroma, complicated by stroke of the right cerebellar hemisphere. Due to the refractoriness of her ataxia, we conducted double-blind trial of 1 Hz, transcranial magnetic stimulation (TMS) to the left ("healthy") dentate nucleus (DN). Based on her clear response to TMS, after consent of the patient, she underwent DBS of the left DN. A double-blind assessment 12 months after surgery showed tremor improvement by 37% and ataxia by 33%. Motor cortex excitability showed restoration of the asymmetry between both hemispheres during on-condition (supplementary file 1). Details about the procedure have been described [1,2].

Four years after surgery, the patient (unware to DBS status) was assessed during on-stimulation (1.9 mA, 60 μs, 20 Hz) and 30 minutes after the DBS has been switched off. The tremor continued to further improve (Fahn, Tolosa, Marin Tremor Rating Scale [FTMRS] baseline = 38, after = 19/144 [50% reduction]) and the ataxia improvement stabilized (scale for the assessment and rating of ataxia [SARA] baseline = 25, after = 17/40 [33% reduction]) in the on-stimulation (video, supplementary file 2). When the DBS was switched off, the patient spontaneously reported worsening the symptoms, and the SARA worsened to 30/40 (supplementary file 3). No adverse events were reported. The patient's global impression of change was 6 (moderately improved).

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2018.10.001.

The present case is the first prospective long-term report of DN-DBS in a patient with cerebellar stroke assessed in a blinded fashion. The findings suggest an initial and sustained benefit in tremor and ataxia of unilateral DN-DBS along with long-term safety and a good tolerability profile.

To date, only few studies have been designed to assess the effects of cerebellar modulation. A recent study showed that stimulation of dentate nucleus in rats with cortical stroke was associated with motor recovery, probably via intensification of perilesional excitability [4]. Two trials reported improvement in posture and gait in patients with cerebellar ataxia due to stroke after repetitive-TMS stimulation [4]. In regard to cerebellar DBS, there is no study focusing exclusively in ataxia outcomes.

In addition to the evidence that cerebellar modulation could restore the altered cortical excitability asymmetry seen between both motor cortices after a chronic cerebellar stroke, structural changes in brain blood flow and metabolism can also be involved in the pathophysiology [4]. Patients with spinocerebellar degeneration showed increased brain blood flow in the cerebellum, putamen, and pons after sessions of cerebellar TMS. A reduction in cerebellar metabolism after 5 sessions of cerebellar TBS in parkinsonian patients was observed through positron emission tomography imaging [5].

Despite the consistent result described in the present case, and a reasonable explanation for the improvement, at least in part, based on the restored cortical excitability, the hypothesis on why cerebellar stimulation could change motor symptoms after cerebellar lesions is still theoretical. This is the index case, and larger prospective studies are obviously necessary. The best target into the cerebellum (DN or the dentate-rubro-thalamic tracts or both), the stimulation parameters, and

https://doi.org/10.1016/j.parkreldis.2018.10.001
Received 22 July 2018; Received in revised form 21 September 2018; Accepted 1 October 2018

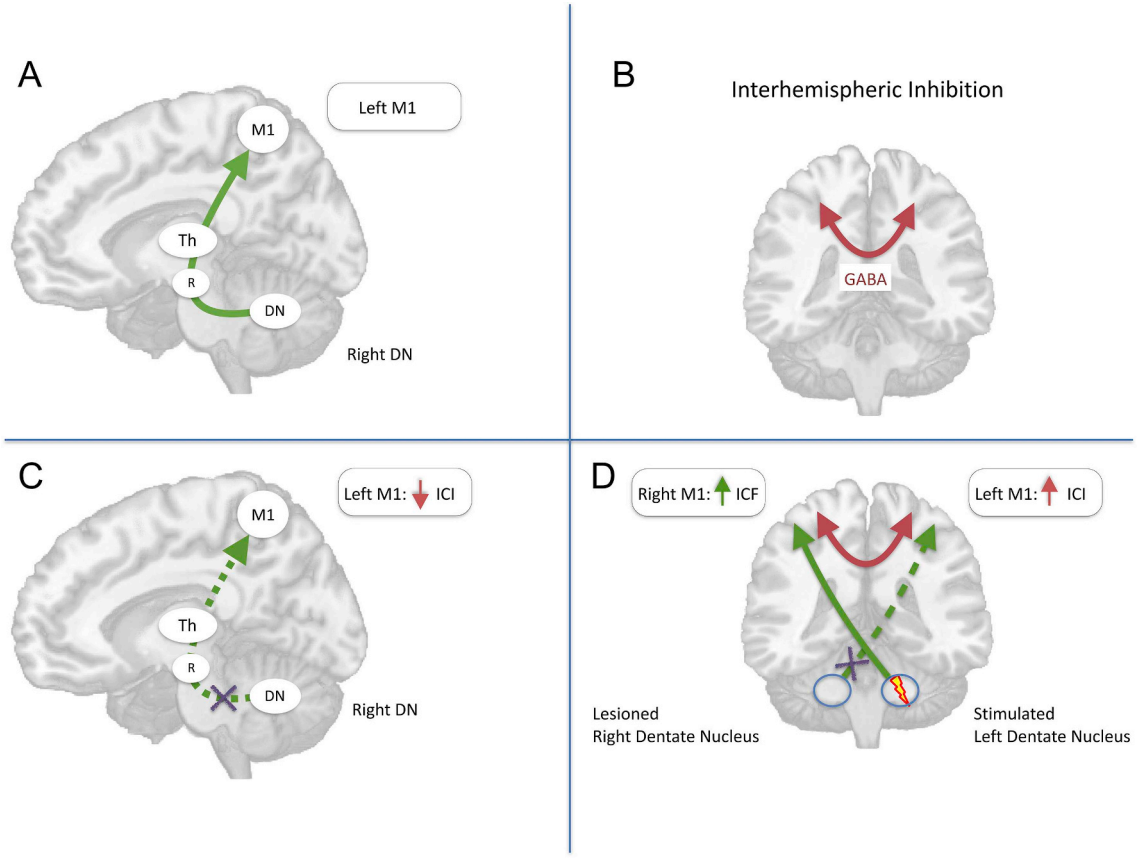

Fig. 1. Representation of the physiology of cerebellar cortical pathway and the effect of the dentate-deep brain stimulation after unilateral lesion of the cerebellum. Legend. Panel A displays the excitatory cerebellum-cortico pathway passing through the rubro nucleus and thalamus. There is an ICI between both M1 cortices that is related to preserving the integrity of limbs coordination (panel B). Panel C shows a progression of changes in intracortical motor function over time following a contralateral cerebellar lesion leading toward progressive disinhibition of the primary motor cortex (the ICI of contralesional M1 decreases). Panel D shows the restoration of the interhemispheric asymmetry after DBS of the left DN (ICF of the ipsilesional M1 and ICI of the contralesional M1 both increase). DN = Dentate Nucleus, R = Rubro Nucleus, Th = Thalamus, M1 = Motor Cortex, ICI = Intracortical Inhibition, ICF = Intracortical Facilitation, Green arrow = Excitatory projection, Red arrow = Inhibitory projection (adapted from Teixeira et al., 2015). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the baseline clinical characteristics predictive of response should be further explored. Interestingly, during the off-stimulation in the last follow-up (4 years) the SARA worsened when compared to the pre-operative score, i.e., after the stimulation has been switched off, the worsening of symptoms exceeded the baseline levels, probably reflecting a rebound phenomena. Defining whether the sudden interruption of stimulation affects the cerebellar-cortical circuitry and whether these rebound symptoms also occur when stimulation is tapered off slowly could help explain the mechanism behind the effects of cerebellar modulation.

Continuous progress in our understanding of brain pathology, connectivity and biomarkers will certainly contribute to the field of movement disorders research, especially regarding new brain targets for neuromodulation. We showed that DN-DBS improved tremor and ataxia in a single patient with cerebellar stroke, and this effect is sustainable over time. The study protocol was safe and well tolerated. Additional comprehensive studies are required to bring evidences for its application in clinical practice.

Conflicts of interest

The authors report no conflict of interest involved in this article.

Funding sources for study

This project was funded by the Pain Center, University of São Paulo.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2018.10.001.

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