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Anatomo-clinical correlation of intraoperative stimulation-induced side-effects during HF-DBS of the subthalamic nucleus

F. Tamma[1] (✉) · E. Caputo[1] · V. Chiesa[1] · M. Egidi[2] M. Locatelli[2] · P. Rampini[2] · C. Cinnante[3] A. Pesenti[3] · A. Priori[3]

[1] Department of Neurology, Ospedale San Paolo, Via di Rudinì 8, I-20142, Milan, Italy
[2] Department of Neurosurgery, IRCCS Ospedale Maggiore Policlinico, Milan, Italy
[3] Department of Neurology, IRCCS Ospedale Maggiore Policlinico, Milan, Italy

Abstract The efficacy of deep brain stimulation of the subthalamic nucleus (STN) is dependent on the accuracy of targeting. In order to reduce the number of passes and, consequently, the duration of surgery and risk of bleeding, we have set up a new method based on direct magnetic resonance imaging (MRI) localisation of the STN. This procedure allows a short duration of the neurophysiological session (one or two initial tracks). Whenever a supplementary track is needed, the stimulation-induced side effects are analysed to choose from one of the remaining holes in Ben's gun. A good knowledge of anatomical structures surrounding the STN is mandatory to relate side effects to the actual position of the track. In our series of 11 patients (22 sides, 37 tracks), the most common and reproducible side effects were those characterised by motor, sensorial, oculomotor and vegetative signs and symptoms. Moreover, the therapeutic window (distance between the current intensity needed to obtain the best clinical effect and the intensity capable to induce side effects) predicted clinical efficacy in the long-term, and contributed to the choice of which among the examined tracks had to be implanted with the chronic macroelectrode.

The efficacy of high frequency deep brain stimulation (HF-DBS) of the subthalamic nucleus (STN) for the treatment of advanced Parkinson's disease (PD) is strictly dependent on the precision of reaching the target. This concept was well clear to the first authors when they proposed a multitrack approach to determine target location in DBS [1]. Afterwards, several authors have replicated their good clinical results. Various different strategies have been developed to reach the target, generally with a multiple simultaneous or independent trajectories approach to cover with both recording and stimulation a wider area. Recently a review on STN-implanted patients suggested that the higher the number of microelectrode passes, the higher the risk of intracranial bleeding during DBS maneuvers [2].

In order to improve the risk-benefit ratio, we proposed a novel technique guided by magnetic resonance imaging (MRI) and based on multiple sequential image fusion (MuSIF), which allows a direct localisation of the subthalamic nucleus [3]. In our experience, the high targeting precision reached by this technique made it possible to reduce the number of intraoperative tracks. We present our DBS method and discuss how the analysis of stimulation-induced side effects evoked during the initial neurophysiological session (one or two tracks) can help address a supplementary track, if needed, and limit the total number of passes.

Twelve consecutive PD patients were selected for bilateral STN implantation of electrodes. The operative session was started after a navigation session in which the stereotactic coordinates were obtained by means of the fusion of stereotactic computed tomography (CT) and frameless MRI data. Through a burr hole located 2 cm anteriorly to the coronal suture, one microelectrode inserted into the central hole of the Ben's gun was advanced with a micrometric drive towards the target (patients 1–7). For patients 8–12, two parallel microelectrodes were simultaneously inserted into the brain. The Ben's gun has 5 holes 2.0 mm apart from each other and arranged in a cross-fashion. Recording and then semi-microstimulation were performed at several levels with a coaxial electrode starting 6 mm before and ending 6 mm after the theoretical target. The results were collected and then discussed during a brain storm session. If the required criteria were satisfied, i.e. recording and stimulation data met our standard, the chronic macroelectrode was implanted; otherwise a new neurophysiological session was started with a supplementary track.

Position of chronic electrodes was regularly checked a few days after stimulators implantation, by means of a postoperative MR image, which was eventually compared with the preoperative MR image. The electrode was visualised as a 1.5-mm diameter artefact which is an acceptable size to reliably indicate the electrode's actual position. We have arbitrarily subdivided the STN into nine regions: 1 central and 8 peripheral (Fig. 1). All the electrodes were classified as central (C), anteromedial (AM), anterior (A), anterolateral (AL), lateral (L), posterolateral (PL), posterior (P), posteromedial (PM), or medial (M), according to the position of the artefact.

We analysed the side effects evoked by intraoperative semi-microstimulation at 5 levels (-2, -1, 0, +1, +2; level 0 was the target), thereby covering a 4-mm area along the trajectory of each track.

The therapeutic window for each side effect was considered, i.e. the ratio between the current intensity needed for eliciting the side effect and the current intensity required at the same level to obtain the maximum clinical effect.

At the 3-month follow-up, all patients benefited from chronic stimulation as shown by improvement of the UPDRS III score in med-off conditions and reduction in off-time and dyskinesia scores and levodopa equivalent daily dose (LEDD). The first patient did not undergo postoperative MRI and was not enrolled in this study. In the remaining consecutive 11 patients (22 sides), we used 37 passes with a mean of 1.7 per side. No intracranial bleeding occurred during the procedures.

In the 12 patients (24 sides), the central track was accepted for definitive implantation in 20 sides (83.3%). In 6 sides,

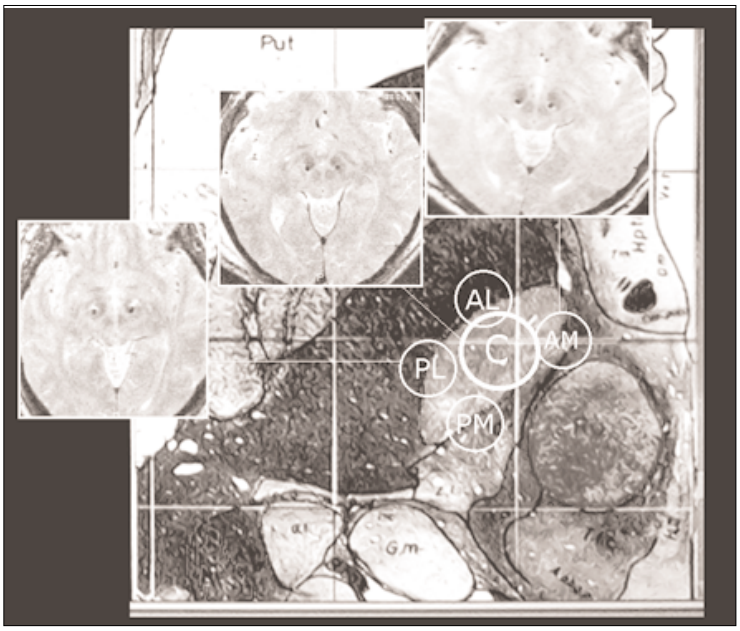

Fig. 1 The position of the definitive electrocatheter as visualised on MRI is then reported onto the Schaltenbrandt Atlas axial view of the subthalamic area. Each circle corresponds to a discrete part of this area

in which clinical and neurophysiological results were mildly consistent with our criteria, a supplementary trajectory was explored and eventually chosen for definitive implantation in 2 sides. The side effects evoked during stimulation addressed the choice of which of the available holes in the gun had to be used and consequently the orientation of the additional track. We never needed a fourth pass.

The most common side effects elicited during the 37 tracks stimulation were pyramidal, sensorial, oculomotor and vegetative. Unspecific side effects, like chest constriction, malaise and dizziness, were hardly related to specific structures, so they were not useful to locate the position of the track.

Motor contractions in the contralateral hemibody were due to stimulation of the corticobulbar and corticospinal tracts. They were frequent (30 tracks, 81%), particularly in C and AL regions, but not in M and PM regions. They were time-locked to stimulation and of paramount importance for the definition of the therapeutic window. We presumed that horizontal gaze deviation can be considered to be a motor side effect deriving from stimulation of the corticofugal pathways which traverse the anterior limb of the internal capsule. Moreover we considered both reduced ipsilateral gaze and contralateral gaze deviations to be part of the same phenomenon, since they were evoked at the same level and since the latter comes out as the current intensity is increased.

Sensorial side effects were perceived by the patient as paraesthesic sensations and were due to stimulation of the medial lemniscus fibres. They were fairly common (12 tracks, 32.5%; persistent in 6 of 12) and more frequent in M and PM regions and at lower levels.

Oculomotor side effects were quite uncommon (9 tracks, 24%), exclusive of C, M and AM regions. They were due to stimulation of the third nerve (adduction or reduced abduction, elevation of superior eyelid in ipsilateral eye) or of the rostral interstitial nucleus (oblique, i.e. lateral and upward, gaze deviation).

Vegetative side effects (nausea, heat sensation, sweating, bradycardia, observed in 15 tracks, 40.5%) were frequent in the anteromedial area and less common in C region. They were not reproducible in the long-term stimulation.

Discussion

In order to reduce the risk of bleeding, we used only one or two trajectories during the initial neurophysiological session of STN surgery. Stimulation-induced side effects are a reliable and reproducible tool for determining the actual localisation of the trajectories. Therefore, if a supplementary trajectory is needed, the analysis of side effects can help in deciding which one among the available holes in the Ben's gun has to be used. Moreover, the ratio of side effects to clinical effects (therapeutic window) is important in deciding where to implant the definitive electrode. It is a marker of the distance between the tip of the electrode and the structure which is responsible for that side effect. The lower is the value of the therapeutic window, the nearer is the tip of the electrode to structures other than STN. The amplitude of the therapeutic window predicts the safety of increasing current intensity in the long term.

References

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