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A Commentary on the Lead Positioning for Deep Brain Stimulation in the Pedunculopontine Tegmental Nucleus in a Patient Affected by Multiple System Atrophy

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The case report by Acar et al. [1] recently published in *Stereotactic and Functional Neurosurgery*, as do other similar case reports [2, 3] populating the literature concerning deep brain stimulation (DBS) of the pedunculopontine tegmental nucleus (PPTg), demonstrates the growing interest of neurosurgeons in the use of new neurosurgical targets for the treatment of movement disorders in drug-resistant patients. Such an interest is especially prompted by the need to treat symptoms for which traditional stimulation of the subthalamic nucleus has given unsatisfactory results [4–6], such as gait freezing and postural instability. Undoubtedly, the efforts that several groups have devoted to this issue deserve to be appreciated. However, skepticism remains when observations are sporadic and carried out on a single case or on a few patients, who are often not affected by Parkinson's disease (PD) but rather by parkinsonian syndromes such as progressive supranuclear palsy and multiple system atrophy. The patient implanted in the PPTg by Acar et al. [1] suffered from multiple system atrophy. In this pathology, neither medical therapy nor neurosurgery of traditional targets improves motor signs; thus, the hope was that PPTg DBS would have a positive outcome, which did not occur. Although currently there is no convincing evidence to show that PPTg DBS may be of benefit in such parkinsonian syndromes, improper positioning of the stimulating leads in the PPTg may cause inconsistencies in the evaluation of clinical outcome.

We wish to point out that the axial slices of postoperative MRIs presented by Acar et al. [1] (fig. 1, 2) show a position of the stimulating tip that clearly differs from the region (fig. 3) that we targeted in the 27 patients so far implanted in our experience.

Identification of the position of the leads in the PPTg is problematic for a number of reasons that we extensively discussed in our recent review [6]. Briefly, the human brainstem has a high degree of variability from patient to patient; thus, the traditional stereotactic identification of a target based on ventriculography and evaluation of the Ca-Cp line cannot be adopted. Furthermore, the PPTg is only partly represented in the classic Schaltenbrand and Wahren's stereotactic atlas [7], while other reconstructions of the position of the PPTg [8] do not provide a detailed description of the structures surrounding the PPTg and extend the nucleus into the lower mesencephalon rather than below the pontomesencephalic junction. One way to overcome these limitations is to combine the axial plates reported in Paxinos and Huang's human brainstem atlas [9] with postoperative MRIs, in which the lead contacts may be appreciated. The lower and central portions of the PPTg, which are reported in Paxinos and Huang's plates, are useful for checking the spatial relationships between the discrete structures present in the targeted region and the location of the leads.

Fig. 1. Reconstruction of the lead positions according to Paxinos and Huang's atlas (slice +31 mm from the Obex) in the patient implanted by Acar et al. [1]. The leads appear to be medial to the caudal part of the PPTg. The absence of a reference scale in the MRIs does not allow a more accurate assessment. The vertical and horizontal white lines that we traced in the MRI slices represent the midline and the tegmental wall, respectively, which may be used as reference points. Paxinos and Huang's slices were overlapped on the MRI to verify the structures that were targeted. The black spots indicate the position of the leads, as can be inferred in the axial slice of Paxinos and Huang's atlas. A stochastic difference in the position of the leads can be appreciated in the antero-posterior direction. The contacts are outside of the posterior extension of the PPTg.

Fig. 2. Reconstruction of Paxinos and Huang's atlas (slice +33 mm from the Obex) of the lead positions in the patient implanted by Acar et al. [1]. The MRI axial slice is the same as that reported in figure 1. The lead tips are not within the PPTg but are close to its posterior extension. The projections on the two different atlas slices were included in order to take into account individual variability in the distance of the mesopontine junction from the Obex.

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Fig. 3. Reconstruction of the location of the lead tips in the PPTg in a representative patient in our series. The positions of the lead are more anterior and lateral with respect to the position of the leads in the patient described by Acar et al. [1] and analyzed in

figures 1 and 2. In this reconstruction, the relationship between the lead and the medial lemniscus can be clearly appreciated. The distances of the mesopontine junction (MPJ) and contact 0 from the Obex are reported. Note the reference scale in the axial MRI.

Thus, we overlapped two plates of Paxinos and Huang's atlas in which the PPTg is reported (inferior plate +31 mm and central plate +33 mm from the Obex) on the axial MRIs presented by Acar et al. [1] (fig. 1, 2) in order to compare the position of the leads between their patient and our patients (fig. 3). When comparing the figures it is quite evident that the position chosen by Acar et al. [1] for targeting the PPTg was more posterior and medial in comparison to the position in which the PPTg is reported in Paxinos and Huang's atlas (black dots in fig. 2). The artifact of the leads in Acar's axial slices appears to be closer to the posterior wall of the lower mesencephalic tegmentum, where other structures are likely to be stimulated, i.e. the superior cerebellar peduncle, the central tegmental tract, the nucleus laterodorsalis tegmentalis pars ventralis, and the mesencephalic nucleus and tract of the trigeminal nerve rather than the PPTg. Likely, the facial pain felt by the patient of Acar et al. [1] during the adjustment of stimulation parameters was due to the involvement of trigeminal struc-

tures. Moreover, the two leads show a stochastic variation in their positioning: the lead implanted on the right side is more anterior and more medial with respect to the lead positioned on the left side. In the sagittal view, the distal contact is close to the posterior surface of the inferior colliculus rather than being 6–7 mm in front of the ventricular floor line, as would be expected if it had been positioned in the site we use for the PPTg.

Anyhow, considering the limited number of patients implanted up to date in the PPTg and the scarce knowledge about the area of the PPTg in stereotactic human atlases, even implantations in sites surrounding the PPTg can provide data that might be useful for evaluating the role and effectiveness of the stimulation of brainstem structures. In this regard, the size of the lead, the extension of the electric field generated by the stimulation, and the degree of degeneration of brainstem nuclei in each patient must be taken into account when trying to explain the role of the implanted target or of structures close to it.

As far as microelectrode recordings are concerned, we do not believe that firing patterns recordable in the PPTg area may be indicative of the nucleus itself. The neuronal loss of brainstem neurons in multiple system atrophy, as well as in supranuclear palsy and PD, limits the expectation of reliable results and the presence of bursting neurons might not be ascribed to surviving neurons strictly confined to the PPTg nucleus. Recordings of somatosensory evoked potentials from the lead contacts when they cross the medial lemniscus before reaching the PPTg [5, 6] provide an index of the correct positioning of the implanted lead far more reliably than single unit recordings taken in a region where few surviving neurons are scattered.

We are also skeptical about the adoption of bilateral implantation since we reported that unilateral stimulation of the PPTg was sufficient to improve axial disorders and frozen gait in PD [5, 6], most likely due to bilateral interconnections of PPTg nuclei. Interestingly, in four patients affected by progressive supranuclear palsy, we obtained less encouraging results on motor signs in comparison to PD patients. This result may be in line with the lack of effect of PPTg DBS in the patient of Acar et al. [1], but the mismatch of the lead position does not allow us to determine anything more about this coincidence.

In conclusion, we believe that a standardized planning procedure should be adopted in order to obtain comparable results. Furthermore, an accurate selection of patients eligible for PPTg DBS and objective instrumental measurements for each aspect of motor control in a consistent number of patients are two crucial additional prerequisites that need to be met in order for any valid conclusions to be reached.

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