Concurrent excitatory and inhibitory effects of high frequency stimulation: an oculomotor study

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Objective: To describe a reversible neurological condition resembling a crossed midbrain syndrome resulting from high frequency stimulation (HFS) in the midbrain.

Methods: Postoperative evaluation of quadripolar electrodes implanted in the area of the subthalamic nucleus of 25 patients with Parkinson's disease (PD) successfully treated by HFS.

Results: Four of the 25 patients experienced reversible acute diplopia, with dystonic posture and tremor in the contralateral upper limb when the white matter between the red nucleus and the substantia nigra was stimulated. The motor signs resembled those caused by lesions of the red nucleus. The ipsilateral resting eye position was "in and down" (three patients) or "in" (one patient). Enophthalmos was seen. Abduction was impaired and vertical eye movements were limited, but adduction was spared. The movements of the contralateral eye were normal. The ocular signs could be best explained by sustained hyperactivity of the extrinsic oculomotor nerve. Simultaneous tonic contraction of the superior rectus, the inferior rectus, and inferior oblique may cause the enophthalmos and partial limitation of upward and downward eye movements. Antagonist tonic contraction of the ipsilateral medial rectus severely impairs abduction.

Conclusion: This crossed midbrain syndrome, possibly resulting from simultaneous activation of oculomotor nerve and lesion-like inhibition of the red nucleus suggests that high frequency stimulation has opposite effects on grey and white matter.

Over the past decade, deep brain stimulation has progressively replaced ablative surgery to alleviate motor impairment in Parkinson's disease. Three targets are commonly used: the lateral thalamus, the globus pallidus internus, and the subthalamic nucleus. High frequency stimulation (HFS) has been considered to improve motor disability by inactivating neural structures, because the effects found so far resemble those obtained by destruction of brain tissue.

The accuracy with which electrodes are implanted in target tissue is increased by the use of quadripolar electrodes (Medtronic, Minneapolis, MN, USA) with four independent contacts that can be used for stimulation. Postoperatively, the four contacts of both electrodes are evaluated individually with a standardised protocol to identify the most effective site of stimulation.

In four of our first 25 patients treated by bilateral subthalamic HFS, stimulation through the deepest contact induced a neurological condition consisting of diplopia with displacement of the ipsilateral eye and tremor in the contralateral upper limb. As the effects of HFS are reproducible and immediately reversible, it was possible to analyze the pathophysiology of this syndrome by videotaping the patients while current of different voltages was applied through the contact producing the syndrome.

METHODS

Surgical procedure

The quadripolar electrodes were implanted as previously described. The contacts of the electrodes (1 mm diameter, 1.5 mm long) are arranged linearly every 0.5 mm over a distance of 7.5 mm (Model 3387.28R, Medtronic Inc, MN, USA). They are numbered 0 to 3 from the bottom up. Each contact can be activated independently by a subclavicular pulse generator (Itrell II, Medtronic Inc, MN, USA) through a subcutaneous cable. The parameters, amplitude (V), frequency (Hz), and pulse width (μm), are programmed by telemetry.

After surgery, the most effective site of stimulation and current parameters were determined. Both the beneficial or adverse effects of stimulation were carefully analyzed. Each contact of the electrode was routinely tested 12 hours after withdrawal of levodopa and dopamine agonists. A monopolar current from the pulse generator (anode) to the contact (cathode) was progressively applied with a frequency of 130 Hz and a pulse width of 60 μs. Amplitude was increased stepwise from 0 to 5 V, by increments of 0.1 V, with a 5–10 minute plateau after every additional 0.5 V. A brief neurological evaluation, including the unified Parkinson's disease rating scale (UPDRS)-part III; cerebellar, motor, and cranial nerve function, and vigilance, was performed at each plateau. Stimulation was stopped immediately if the patient reported an adverse effect, such as muscle spasm, paraesthesia, dizziness, or motor or psychic inhibition.

Patient selection and study design

The clinical profile and the parameters of stimulation are given in table 1. Four patients reported binocular diplopia during postoperative assessment when stimulation was applied through the most caudal of the electrode contacts, except for one (table 2). As the diplopia was tolerable and totally reversible after cessation of stimulation, all patients consented to repeat the experience 1 month after surgery, in a videotaped session, and to undergo a neuro-opthalmic evaluation, including the unified Parkinson's disease rating scale (UPDRS)-part III; cerebellar, motor, and cranial nerve function, and vigilance, was performed at each plateau. Stimulation was stopped immediately if the patient reported an adverse effect, such as muscle spasm, paraesthesia, dizziness, or motor or psychic inhibition.

Abbreviations: HFS, high frequency stimulation; PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale; AC, anterior commissure; PC, posterior commissure; rMLF, rostral interstitial nucleus of the medial longitudinal fascicle; INC, interstitial nucleus of Cajal
examination. As a new reversible adverse effect of therapy was involved, we did not require approval of the local ethics committee.

Contact localisation

The position of the contacts of the electrodes was determined on reformatted axial volumetric T1 weighted MR sections obtained during the postoperative evaluation. The MR slices where the contacts were visible were projected onto homologous sections in the Schaltenbrand and Wahren atlas to precisely localise the centre of the contact.

Evaluation of diplopia

Conditions

Stimulation was repeated through every diplopia inducing contact of the electrode at increasing amplitudes (1, 1.5, 2, or 3 V), with a frequency of 130 Hz and a pulse width of 60 µs. The session was videotaped in the morning after a 12 hour period of drug withdrawal. In addition, in patients 1 and 3, current was also applied with a frequency of 2 Hz, an amplitude of 3 V , and a pulse width of 60 µs.

Study of eye movements, intraocular pressure, and pupil diameter

Neuro-ophthalmic examinations were performed by the ophthalmologist (DM) before stimulation. At baseline and after each stimulation plateau, pupil diameter and motility were assessed. These measurements were performed both in the dark and under normal lighting conditions. Pupil diameter was measured in each patient with a millimetric scale. Intraocular pressure was also measured by Goldmann tonometry. Ocular movements were quantified at baseline and after each stimulation with the Lancaster red-green test, a variant of the red glass test. The amplitude of each movement was recorded according to a standardised schema.

Analysis of saccades

In addition, a study of reflexive visually guided vertical and horizontal eye saccades was performed in patient 3. The other patients declined to participate in the saccade analysis. Horizontal head movements were measured by a rotary potentiometer mounted on a lightweight soft helmet worn by the patient. The helmet was connected to a metallic frame fixed to the chair above the patient’s head by carbon fibre rods and a hinge. This system, by virtue of its universal joints, did not hamper horizontal angular head movement and had a resolution of 0.5°. Movements of both eyes were recorded simultaneously with an infrared eye tracker mounted on eyeglasses (IRIS; Skalar Medical, Delft, The Netherlands). The spatial resolution was 0.1°. The patient was instructed to fix on a central point that was illuminated for 2.5 to 3.5 seconds, then to make a saccade towards a 15° lateral target that appeared randomly to the right or left, up or down, 200 ms after the extinction of the central fixation point. Visual cues were presented at a distance of 1.2 cm with red light emitting diodes embedded in a curved ramp. Data were sampled at a frequency of 500 Hz and stored for off line analysis.

Table 1 Clinical characteristics of patients and high frequency stimulation parameters

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age/sex</th>
<th>Disease duration (y)</th>
<th>UPDRS-III off/on stimulation*</th>
<th>Optimal improvement of motor disability</th>
<th>Contact (left/right)</th>
<th>Voltage (left/right)</th>
<th>Diplopia inducing contact (left/right)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44/M</td>
<td>12</td>
<td>57/13</td>
<td>3/1</td>
<td>3.0/3.0</td>
<td>0/none</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>64/M</td>
<td>9</td>
<td>58/18</td>
<td>2–31/3</td>
<td>2.5/2.8</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>52/M</td>
<td>12</td>
<td>53/11</td>
<td>3/3</td>
<td>2.4/2.4</td>
<td>0/0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>59/M</td>
<td>14</td>
<td>47/11</td>
<td>3/3</td>
<td>3.1/3.1</td>
<td>0/0</td>
<td></td>
</tr>
</tbody>
</table>

*Stimulation parameters used for optimal treatment of parkinsonian motor disability. 11 The electrodes contained four discrete stimulation contacts numbered 0 to 3 (from most distal to most proximal); †parallel monopolar stimulation from two adjacent contacts.

Table 2 Effects of midbrain stimulation on diplopia-inducing contacts

<table>
<thead>
<tr>
<th>Patients</th>
<th>Side</th>
<th>Ipsilateral eye</th>
<th>Contralateral hand</th>
<th>Other signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Palpebral fissure</td>
<td>Enophthalmia</td>
<td>Primary position</td>
</tr>
<tr>
<td>1</td>
<td>Left</td>
<td>Unchanged</td>
<td>Present</td>
<td>Down and in</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>Reduced</td>
<td>Present</td>
<td>Down and in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>Enlarged</td>
<td>Present</td>
<td>In</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>Reduced</td>
<td>None</td>
<td>In</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>Reduced</td>
<td>Present</td>
<td>Down and in</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>Reduced</td>
<td>Present</td>
<td>Down and in</td>
</tr>
</tbody>
</table>

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To detect a potential torsion nystagmus, we performed an image by image study of the videotapes, using a conjunctive vessel as a marker in each patient.

RESULTS
Effects of high frequency stimulation on dystonia and tremor
A mild dystonic posture of the hand or the wrist was noted contralateral to the side of stimulation, regardless of the amplitude. The abnormal posture varied among patients: all had dorsiflexion of the wrist and flexion of the metacarpophalangeal and proximal interphalangeal joints, combined in two patients with abduction and extension of the interphalangeal joints of the fifth finger. The lower limb was never involved. The dystonic posture was associated in all patients with a fine, rapid, irregular, rest and postural tremor of the hand and forearm. A proximal component, consisting of tremor of the elbow and the shoulder, was found during finger to nose movements in two patients when the current reached 3 V. No tremor was seen in the lower limb contralateral to the side of the stimulation, although patient 2 reported a feeling of “internal” tremor in the thigh. No abnormal postures or movements were seen in the upper or lower limbs ipsilateral to stimulation. When a 2 Hz current was applied, patient 3 reported hearing a rhythmic clicking with a 2 Hz frequency. We did not see visible palatal tremor in this patient.

Effects of high frequency stimulation on eye movements
Primary position
When current (1 to 3 V, 130 Hz, 60 µs) was applied through contact 0 (right electrode in patient 1, both electrodes in patients 2, 3, and 4), binocular diplopia with limb tremor contralateral to the side of stimulation was seen in the four patients within less than 1 second. The eye ipsilateral to stimulation presented a sustained backward and medial tonic movement resulting in enophthalmos and convergent position. When current was applied to the left midbrain, the left eye rotated counterclockwise (from the patients’ perspective), then slightly downward and inward, then remained in the “in” or “in and down” position, whereas stimulation of the right midbrain caused clockwise rotation of the right eye (fig 1). No torsion nystagmus was detected when the videotapes were analysed image by image. Eyelid retraction was seen in patient 3. The eye was turned inward in patient 3 (left and right contacts), downward and inward in patients 1, 2, and 4. Diplopia was present as long as the stimulation was maintained. An increase in voltage resulted in greater deviation of the eye and globe retraction. Primary gaze eye position in patient 3 before and after stimulation through the deepest contact of the right electrode is shown in figure 1. When a 2 Hz current was applied, patients 1 and 3 described oscillopsia with a 2 Hz frequency. However, no rapid movement of the eyeball was visible. When current was slowly increased to 3.5 V through the right electrode in patient 3, a backward and leftward tilt of head and neck appeared.

When the current was turned off or applied through any of the other contacts, including contact 2 that improved motor disability (table 1), none of the patients had visual symptoms, and ocular position, motility, pupil size, and function remained normal. Intraocular pressure was within normal limits at baseline and did not increase during stimulation.

Eye movements
During voluntary, pursuit, and oculocephalic reflexive movements, abduction of the affected eye was limited at 1.5 V and impossible at 3 V. Similarly, upward and downward movements were partial at 1.5 V and totally restricted at 3 V. Figure 2 shows the trajectory of the eye when a 3 V current was applied through the deepest contact of the left electrode in patient 1. An example of the progressive limitation of ocular movements with increasing voltage, visible on the Lancaster test, is presented in figure 3. A compensatory increase in the movement of the contralateral eye was seen on the Lancaster test (not shown). All the above signs and symptoms resolved completely when stimulation was stopped.

The position at rest, saccadic and pursuit motility, and oculocephalic reflexes of the contralateral eye were clinically normal. Pupil diameter and motility were similar before and after stimulation.
during stimulation, in all the patients, regardless of the intensity of the stimulation.

**Saccadic eye movements**
Study of vertical and horizontal saccades in patient 3 indicated a monocular voltage dependent restriction of abduction and of upward and downward vertical movements of the ipsilateral eye (fig 4). The amplitude of the saccades of the contralateral eye was slightly increased during stimulation (compensation). Blinking was frequent at 1.5 V and constant at 2 V. The blinking artifact was visible on the recordings of contralateral eye movements, but was limited on the recordings of the ipsilateral eye.

The image by image study of the videotape sequence did not show any torsion nystagmus.

**Localisation of contacts inducing diplopia**
The seven diplopia inducing contacts were located in the junction between the substantia nigra and the anterodorsal part of the red nucleus where the oculomotor nerve emerges ventral and medial to the STN. The right contact of patient 3 was the most medial (fig 5).

**DISCUSSION**
In four patients with Parkinson’s disease treated by continuous high frequency stimulation of the subthalamic nucleus through quadripolar electrodes, application of current through a non-therapeutic contact, located between the substantia nigra and the red nucleus where the oculomotor nerve emerges, consistently elicited contralateral upper limb tremor and ipsilateral voltage dependent diplopia reminiscent of a crossed midbrain syndrome.

**Clinical interpretation**

**Tremor and dystonic posture**
The fine, rapid, distal irregular tremor in the contralateral upper limb, both resting and postural, is reminiscent of the tremor that Benedikt first ascribed to lesions in the region of the red nucleus.13 “Midbrain tremor” has since been described after tumoral, infectious, post-traumatic, or inflammatory lesions in this area, presumably resulting in damage to the cerebellothalamocortical and dentatorubro-olivary pathways.14 More recently, dystonic hand postures have been associated with lesions in the contralateral mesencephalon including the ventromedial and caudal part of the red nucleus. Thus, HFS through a contact in the region of the contralateral red nucleus seems to reproduce the tremor and dystonic hand postures caused by lesions in the same area. In addition, the rhythmic clicking heard by patient 2 when stimulated at 2 Hz resembles the sound accompanying palatal tremor that results from lesions in the midbrain tegmentum.15 The contacts of the electrode were located in the white matter between the red nucleus, the subthalamic nucleus, and the substantia nigra. The fact that a midbrain tremor was seen, and was pronounced at higher current amplitudes, suggests that stimulation impinged upon the red nucleus.

**Oculomotor symptoms**
The ocular symptoms in the four patients cannot be ascribed to any known movement disorder. The spontaneous eye position in adduction and the limitation of abduction are suggestive of palsy of the lateral rectus (sixth nerve palsy), pseudoabducens palsy, convergence spasm, conjugated gaze palsy, or hypercontraction of the medial rectus. The fibres of the sixth nerve are probably unimpaired, however, as they emerge at the bulbopontine junction, far from the site of stimulation. In addition, vertical movements were also restricted following stimulation through a contact in the region of the red nucleus.
affected and a visible movement of adduction of the eye was seen, suggesting that contraction of the medial rectus predominated over the lateral rectus. Because the contralateral eye was not convergent, convergence spasm can be ruled out.

This eye movement disorder may be of supranuclear origin, as lesions of the rostral interstitial nucleus of the medial longitudinal fascicle (rMLF), and lesion or stimulation of the interstitial nucleus of Cajal (INC), both located within the rostral midbrain, may cause diplopia and ocular torsion. However, we did not find any torsional nystagmus on the videotapes or restriction of contralateral eye movements in our patients that would suggest involvement of the rMLF. Furthermore, the rMLF lies dorsomedial to the red nucleus, far from the contact of the electrode. The fact that stimulation of the adjacent contact, which is 0.5 mm rostral to the diplopia inducing contact, does not elicit a diplopia suggests that the current acts very locally. The backward and leftward deviation of the head and neck seen with high voltage stimulation in patient 3 differs from the ocular tilt reaction caused by lesions or stimulation of the midbrain, as there was no skew deviation, vertical divergence of the eye, or involvement of both eyes. It is possible that in patient 3 the high voltage stimulation spread to the INC. It is also possible that the patient tried to compensate for diplopia by moving the head. Pseudoabducens palsy caused by lesions near the midbrain-diencephalic junction would associate upgaze palsy and convergence retractive nystagmus, which was not the case in our patients. The absence of vestibulo-ocular reflexes in patient 3 differs from the “down and in” position seen in other patients, possibly because of the more medial and rostral placement of the electrode contact in the oculomotor fascicles. Clockwise and counterclockwise rotations of the eye, which were seen with right and left stimulation, respectively, can be explained by hyperactivity of the inferior oblique muscle.

The “in” position of the eye and the eyelid retraction seen in patient 3 was different from the “down and in” position seen in other patients, possibly because of the more medial and anterior position of the electrode contact, which would result in stimulation of the medial fibres of levator palpebrae not the lateral fibres of inferior oblique muscle.

When oculomotor nerve fibres, including pupil fibres from the Edinger-Westphal nucleus are stimulated, miosis can occur. No changes in the pupil were found, however, in our patients. Anatomical studies of fascicles in the oculomotor complex show that pupil fibres follow a route medial and dorsal to fibres innervating the inferior rectus, levator palpebrae, medial rectus, and superior rectus in the ventral midbrain tegmentum. All diplopia inducing contacts were predominantly lateral, stimulation would spare the pupillary fibres but not the others.

Pathophysiological consequences

The mechanism of high frequency deep brain stimulation is poorly understood. Because of the similarity between the
effects of lesions and high frequency stimulation in the ventral thalamus and the subthalamic nucleus, it has been thought to inhibit neuronal activity. However, lesions and high frequency stimulation do not always produce the same effects. In the present study, signs suggestive of neuroinhibition (contralateral “midbrain tremor”) and of neural activation (the ipsilateral hyperactivity of oculomotor nerve) may be explained by the fact that the area affected by stimulation included both the red nucleus and the myelinated passing fibres of the oculomotor nerve. The occasional adverse effects of thalamic HFS, that are not found after thalamotomy, might be similarly explained. In this case, when voltage is increased, the area affected extends beyond the VIM and causes contralateral tonic contraction of the upper limb, probably as a result of activation of the adjacent myelinated corticospinal fibres. If this area is affected during thalamotomy, monoparesis or paralysis occurs. This differential effect may explain the few discrepancies between the results of lesioning procedures and stimulation in the globus pallidus. This nucleus, unlike the ventral intermediolateralis and subthalamic nucleus, is characterised by a high density of myelinated fibres. Hence, the similarity between the effects of pallidal stimulation and pallidotomy (dyskinesia suppression) suggests that high frequency stimulation is inhibitory, whereas the effects that differ from those of pallidotomy (worsening of parkinsonian signs and the suppression of the levodopa beneficial antiparkinsonian effects) may imply an activation of afferent and efferent fibres within the nucleus.

Our results, therefore, suggest that high frequency stimulation had differential effects on the passing fibres and the adjacent nucleus that were excitatory on the first and inhibitory on the second. The oculomotor fibres are excitatory on extrinsic eye muscles, explaining why stimulation causes contraction of these muscles. As for the adjacent nucleus, high frequency stimulation may either activate an inhibitory structure or inactivate an excitatory structure. Benazzouz et al have proposed that high frequency stimulation might block depolarisation of the output neurons in the nucleus. The mechanism remains to be elucidated.

In conclusion, we have presented a neurological condition resembling a crossed midbrain syndrome, which results from high frequency stimulation of the red nucleus and the passing fibres of the third nerve. The results show for the first time that high frequency stimulation can be either excitatory or inhibitory, depending on the target tissue.

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References