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Chronic high frequency stimulation of the posteromedial hypothalamus in facial pain syndromes and behaviour disorders

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Summary

Chronic high frequency stimulation (HFS) of the posteromedial hypothalamus (PMH) has been the first direct therapeutic application of functional neuroimaging data in a restorative reversible procedure for the treatment of an otherwise refractory neurological condition; in fact, the target coordinates for the stereotactic implantation of the electrodes have been provided by positron emission tomography (PET) studies, which were performed during cluster headache attacks. HFS of PMH produced a significant and marked reduction of pain attacks in patients with chronic cluster headache (CCH) and in one patient with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). The episodes of violent behaviour and psychomotor agitation during the attacks of CCH supported the idea that the posteromedial hypothalamus could be also involved in the control of aggressiveness; this has been previously suggested, in the seventies, by the results obtained in Sano's hypothalamotomies for the treatment of abnormal aggression and disruptive behaviour. On the basis of these considerations, we have performed HFS of the PMH and controlled successfully violent and disruptive behaviour in patients refractory to the conventional sedative drugs. Finally, we also tested the same procedure in three patients with refractory atypical facial pain, but unfortunately, they did not respond to this treatment.

Keywords: Neuromodulation; posteromedian hypothalamus; cluster headache; high-frequency stimulation.

Introduction

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies recently demonstrated hypothalamic structural asymmetry and ipsilateral activation of the postero-inferior hypothalamic gray matter during the attacks of chronic cluster headache (CCH) [7, 15, 16].

Based on these neuroimaging data, electrical high frequency stimulation (HFS) of this distinct brain structure was carried out by deep brain stimulation (DBS) electrodes stereotactically implanted within the posterior hypothalamus itself. DBS induced a remission of the pain bouts and also of the autonomic dysfunction in patients with cluster headache. This was the first direct therapeutic application of functional neuroimaging data in a restorative reversible approach for the treatment of an otherwise refractory condition [4]. Moreover, CCH is the only facial pain syndrome in which violent behaviour and psychomotor agitation can develop during the pain attacks [13, 24]. These observations support the notion that focal inhibition of the posteromedial hypothalamus could explain the results obtained in the seventies in Sano's hypothalamotomies for the treatment of abnormal aggression and disruptive behaviour [19, 22]. Subsequently, the indications for chronic hypothalamic stimulation have been extended to the treatment of severe behavioural disorders unresponsive to medical treatment.

In this chapter, we report results, problems and technical suggestions collected during five years of experience in the implantation of hypothalamic electrodes for the treatment of CCH or refractory severe aggressive and disruptive behaviour. The same procedure has been carried out in other intractable facial pain syndromes including SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), and atypical facial pain. The common factor in this heterogeneous clinical series is the selected target for high frequency electrical stimulation, namely the posteromedial hypothalamus.

Patients

Chronic cluster headache (CCH)

Sixteen patients, who fulfilled the International Headache Society criteria for the diagnosis of CCH, were included in this study [8]. Fourteen

were males and two females. All suffered from CCH for at least one year; two had CCH at onset, and in the remainder, the chronic form evolved from episodic CH. The medical treatment for these patients before referral to neurosurgery consisted of a regimen of the following drugs, provided as a single treatment or in combinations: corticosteroids, lithium, methysergide, ergotamine, calcium channel blockers, beta-blocking agents, tricyclic antidepressants, melatonin, and non steroidal anti-inflammatory drugs. All patients were hospitalized on various occasions, during which pain attacks were witnessed and assessed; cycles of high dose intravenous dexamethasone (12–20 mg/day or more) were administered, and two-to-four infiltrations of the ipsilateral sphenopalatine ganglion with a preparation containing triamcinolone acetonide (40 mg), bupivacaine (1%), carbocain (2%), and adrenalin (0.0001%) were given, without benefit. Patients eligible for DBS had normal neurological examination and brain MRI. They were also psychologically stable. Before surgery, all patients were in poor condition: one had attempted suicide on two occasions because of refractory pain, another had severe steroid myopathy and coronary artery disease contraindicating the use of triptan, and a third patient had severe steroid-myopathy and was unable to walk upstairs, but improved after steroid withdrawal. The patients were unable to work and their quality of life was severely affected. In 13 patients, the pain attacks were strictly unilateral. Patients 1, 9, and 13 (18.7%) had a history of attacks that affected each side alternately. Patient 1 received implants on both sides on separate occasions [10]. Patients 9 and 13 each received one implant on the most affected side (>95% of attacks). A month after implantation on the left side, patient 7 developed uncontrollable CH attacks on the right side, and subsequently received a right sided implant. The clinical results in terms of reduction of the frequency of attacks in CCH patients are reported in Fig. 1.

All patients were also informed of the classic surgical procedures that were available in our Institute for the treatment of the intractable CH namely open microvascular decompression, lesion of the fifth nerve in the cerebellopontine angle, and percutaneous microcompression or radiofrequency (RF) trigeminal rhizotomy [9, 14]. The first patient of the series was successfully treated in July 2000 and was reported in 2001 [10]. The patients' age at the time of surgery, in the whole series, ranged from 24 to 70 years (mean 46 years).

SUNCT

A 66-year old female patient had a 14 years history of short-lasting (2–20 seconds), severe, ''piercing and burning'' pain episodes in the right labial commissure, sometimes radiating to the jaw, ear, and occipital region. The attacks were strictly unilateral with no side shift, and were always accompanied by ipsilateral eyelid edema, eye reddening, unilateral nasal obstruction, and profuse lacrimation. Attacks were triggered by talking, chewing, face washing, teeth brushing, neck movements, or face touching, and often occurred for more than 100 times a day (mean 70; maximum 300). In the 2 years preceding the implantation, the patient experienced more than a thousand attacks per month. CT, MRI, and MR angiography of the brain were normal with no vascular ectasia observed at the cerebellopontine angle. A diagnosis of SUNCT namely short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing was made. The patient was treated with carbamazepine (1200 mg/day), gabapentin (2400 mg/day), oral and intravenous valproate (1500 mg/day), lamotrigine (300 mg/day), topiramate (200 mg/day), indomethacin (oral 200 mg/day; intramuscular up to 150 mg/day) ketorolac, coricosteroids (methylprednisolone, prednisone), and tramadol with only minimal symptom control. Cardiac status and age contraindicated the use of verapamil. In July 2003, after Ethical Committee approval and the patient's informed consent, the electrode implantation in the ipsilateral posterior hypothalamus was performed. This case has been extensively reported by the neurologists of our Institution [10].

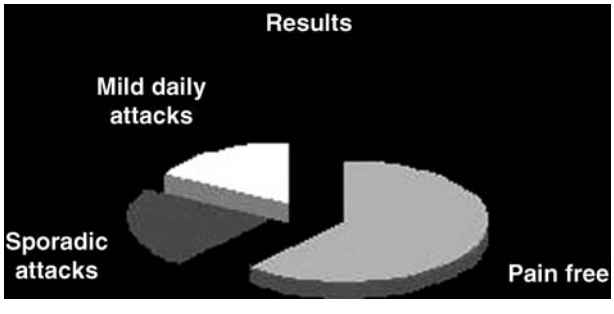

Fig. 1. Long-term results of deep brain stimulation of the posterior hypothalamus in chronic cluster headache patients

Atypical facial pain

Three patients with atypical facial pain were treated by DBS of the ipsilateral posteromedial hypothalamus.

The first patient was a 47 male with a diagnosis of an expanding right posterior mandibular carcinoma. In August 2002, a radical transmandibular tumour resection was performed. A few days after surgery hypoesthesia and burning pain developed in the II and III right trigeminal branches that progressively increased; drug therapy with carbamazepine (1000 mg), non steroidal anti-inflammatory drugs, local anesthetics, and opioids were ineffective. After a few months, the burning pain was severe, continuous, with spontaneous paroxysms several times a day. After six months, this condition was severe and the patient's quality of life (QOL) worsened dramatically. The neurological examination showed only moderate right hypoesthesia in the area innervated by the third trigeminal branch. Radiotherapy was not performed and at two years of follow up, no tumour recurrence was detected.

The second patient was a 52 year old female who had a 3 years history of facial pain. The symptoms appeared after a minor dental procedure and were described as a continuous disabling burning pain, localized to the area innervated by the II and III right trigeminal branches. Daily activities (i.e. talking, eating) were severely compromised. Attacks of exceptionally severe paroxysmal pain were also reported. Carbamazepine, lamotrigine and phenytoin at full dosages were ineffective. MRI ruled out any abnormalities and a diagnosis of atypical facial pain was made.

The third patient was a 55 year old male with a diagnosis of nasopharyngeal carcinoma. He underwent radiotherapy and few months later developed a continuous severe burning right facial pain more intense in the area innervated by the 1st and 2nd divisions of the trigeminal nerve. Paroxysmal pain was provoked by peripheral stimuli and was resistant to any kind of analgesic drug including opioids. Cerebral CT and MRI were performed after radiotherapy and showed disappearance of the tumor and ruled out any other pathology.

Disruptive behaviour

Two patients with learning disabilities affected by medically intractable impulsive and violent behaviour, as described elsewhere [2], were treated by DBS of the posteromedial hypothalamus [5].

The first patient was a 36 years old male who had suffered birth anoxia and developed progressive mental and motor retardation and myoclonic epilepsy from early childhood. At the age of 16, the cognitive impairment was found to be severe and precluded any psychometric assessment. His behaviour was impulsive, violent, and self-destructive. The medical treatment included neuroleptic (chlorpromazine 200–400 mg, thioridazine 100–300 mg, clotiapine 100–200 mg), and antiepileptic (carbamazepine 800–1200 mg,

clonazepam 6–12 mg) medication. Cerebral MRI showed mild T1 and T2 signal alteration of the basal frontal cortex. In the last two years, the patient became more aggressive and the episodes of rage increased in frequency. A severe cervical dystonia (anterocollis) also began to develop. The blood tests suggested hepatotoxicity from high-dose medication.

The second patient was a 37 year old male with congenital toxoplasmosis which resulted in labiopalatoschisis, chorioretinitis, and moderate oligophrenia. Since early childhood, the patient exhibited aggression against objects and people. The violent behaviour worsened in his teens and admission at a psychiatric institution was required when he was seventeen years old. In-patient psychiatric care was required for a long time after many attempts at community living failed. His aggressive behaviour did not allow any psychometric analysis. Occupational and sedative drug therapy including high-dosage neuroleptic, antiepileptic drugs, and benzodiazepines did not control his aggression. The neurological examination showed only mild weakness of the right leg. Cerebral CT and MRI appeared normal. After 20 years of being drug resistant with daily aggressive episodes, DBS of the posterior hypothalamus was considered.

Surgical procedure

The stereotactic implantation was performed with the Leksell frame (Eleckta, Stockholm, Sweden) under local anesthesia. When sedation was required, low doses of midazolam (0.05–0.1 mg/kg) or propofol (0.5–1 mg/kg) were used. General anesthesia was offered only in the two patients who were affected by behavioural disorders. Perioperative antibiotics were administrated to all patients. A preoperative MRI (brain axial volumetric fast spin echo inverson recovery and T2 images) was used to obtain high definition images for the precise determination of both anterior and posterior commissures and midbrain structures below the commissural plane such as the mammillary bodies and the red nucleus. MR images were fused with 2 mm thick CT slices that were obtained under sterotactic conditions by using an automated technique that is based on a mutual-information algorithm (Frame-link 4.0, Sofamor Danek Steathstation, Medtronic, Minneapolis, MN). The workstation also provided stereotactic coordinates of the target: 3 mm behind the midcommissural point, 5 mm below this point, and 2 mm lateral from the midline. The target planning that was based exclusively on the midcommisural point caused electrode misplacement in one patient as previously reported [4]. This kind of error is due to the anatomical individual variability of the angle between the brainstem and the commissural plane [35]. To correct this possible error, we introduced a third anatomical landmark, which allowed the final target registration. We called this landmark ''interpeduncular nucleus'' or ''interpeduncular point'' and it is placed in the apex of the interpeduncular cistern 8 mm below the commissural plane at the level of the maximum diameter of the mammillary bodies (Fig. 2). The Y value of the definitive target (anteroposterior coordinate to the midcommissural point in the classical midcommissural reference system) was corrected in our patients and the definitive target coordinate was chosen 2 mm posterior to the interpeduncular point instead of 3 mm posterior to the midcommissural point.

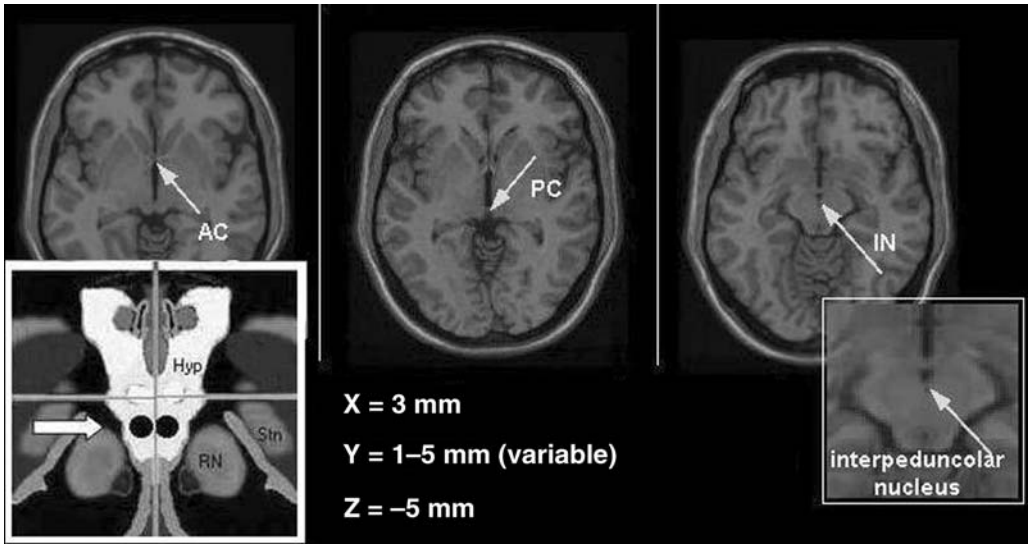

Fig. 2. The three reference points which are used to calculate and standardize the stereotactic coordinates of the target. *AC* Anterior commissure, *PC* posterior commissure, *IN* interpeduncular nucleus. *Left box* Axial slice (5 mm below the commissural plane) of the stereotactic atlas registered to the AC-PC midpoint; the black circles represent the target on both sides, *X* lateral coordinate to the commissural line, *Y* anteroposterior coordinate to the midcommissural point which varies between 1 and 5 mm according to the interpeduncular nucleus coordinates, *Z* the millimiters below the commissural plane

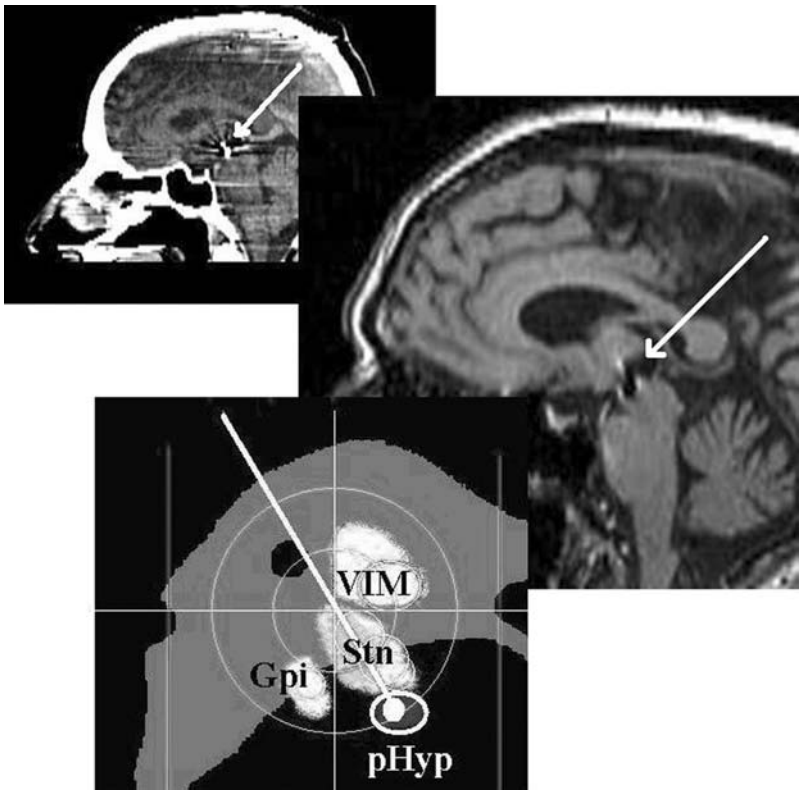

Fig. 3. Sagittal CT and MRI slices showing the active contact of the electrode stimulating the posteromedial hypothalamus (*white arrows*). The inferior box shows the target on the ventriculogram registered to the bicommissural system

A rigid cannula was inserted through a 3 mm, coronal, paramedian twist-drill hole and placed up to 10 mm from the target. This cannula was used both as a guide for microrecording (Lead Point, Medtronic) and for the placement of the definitive electrode (Quad 3389; Medtronic) [3]. Macrostimulation was carried out in patients operated under local anesthesia (1–7 V, 60 μsec, 180 Hz). All patients, subjected to stimulus intensities higher than 4 V, showed conjugated ocular deviation that was followed by verbal reports of a repeated severe negative affective experience described as: ''I feel very close to death''. No pupillary reaction or cardiovascular effects were evoked. When other side effects were ruled out at the standard parameters stimulation, the guiding cannula was removed and the electrode secured to the skull with microplates. A single unit recordings were performed at the target chosen for stereotactic implantation of the stimulating lead in two patients. Microrecordings began as soon as the microelectrode (9013-S-0842 microTargeting^{R} electrode, Medtronic Inc., Minneapolis, TN, USA) reached the presumed coordinates of the target, and were performed by means of a *Medtronic Leadpoint*^{TM} system (Medtronic Inc., Memphis, TN, USA). The response properties of the isolated neurons were obtained with the patients being fully awake.

Post-operative stereotactic CT was performed to exclude any complications and was merged with the pre-operative MRI to confirm the correct electrode placement [5] (Fig. 3). Unilateral or bilateral implantable pulse generator (IPG) (Medtronic, inc.) was then placed in the subclavicular area and connected to the brain electrode for chronic continuous electrical stimulation. During the period 1–7 days after surgery, an additional MRI study was repeated in order to ensure the electrode's position. Unilateral or bilateral continuous bipolar and then monopolar (case positive) 180 Hz, 0.5 V, 60 μsec stimulation was started using the deepest contact in the target. Voltage was gradually increased up to the therapeutic effect. No side effects developed at the therapeutic levels of electrical stimulation.

Results

Chronic cluster headache

The results of DBS on CCH patients in this study are shown in Figs. 1 and 4. Two patients (Nos. 1 and 7) had bilateral electrodes placement, one patient (No. 4) required electrode replacement after 9 months and the

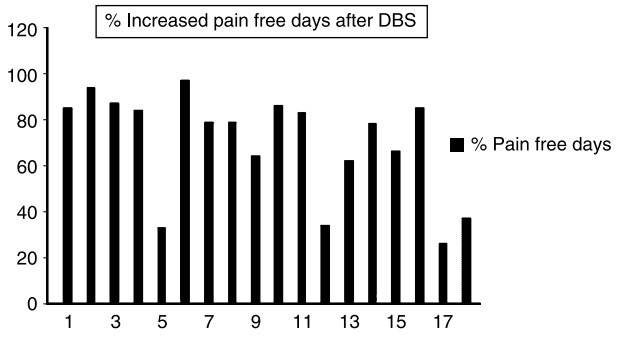

Fig. 4. Increase of number of days free from pain attacks (ordinates) in 18 patients (abscissas) after deep brain stimulation of the posteromedial hypothalamus

other patient (No. 1) one year after the second procedure due to cranial migration of the electrode. A total of 20 electrode implantations were carried out. Unilateral or bilateral continuous unipolar stimulation was administered with the following parameters: frequency 180 Hz, pulse width 60 μsec, amplitude 0.6–3.3 V (mean 2.4). All patients with CCH achieved pain relief as a result of the long term, high frequency, hypothalamic DBS which continued to the follow-up evaluation. The decrease in the frequency of attacks was never immediate but it occurred between 1 and 86 days (mean 42 days). Moreover, the maximum improvement of the pain in terms of intensity and frequency of the CH episodes was achieved progressively in the next one to five months. Abolition of pain or major improvements occurred in 13 patients: 10 patients had a complete and persistent pain-free state, and three patients (7, 11, and 13) had almost complete pain relief, although sporadic attacks still occurred. It should be noted that the drugs were completely ineffective before the surgical procedure. For the remaining three (16.7%) patients (Nos. 4, 10, and 16) the CH attacks continued. In patient 4, the attacks were reduced from seven per day to one every two days; he requires verapamil as well as methysergide for prophylaxis. In patient 10, the attacks have been reduced in intensity from excruciating to mild and the duration from 90 to 15 minutes; he injects sumatriptan (which is effective) for only about 10% of the attacks. In patient 16, the attacks have been reduced from five to one per day after 20 days of stimulation. In patient 3, it proved necessary to add long-term prophylactic medication in order to keep this patient free of attacks.

In four cases in whom the stimulation was turned off to allow cardiological or MR evaluation, the pain attacks recurred after few days and disappeared few hours after reactivation of the IPG. When hardware failure occurred, pain attacks recurred; following the repair, the IPG was switched on and the CCH attacks improved after a few days. At last follow up, on 16 CH patients, the percentage of total number of days free from pain was 71%. No major adverse effects of high-frequency hypothalamic stimulation have been reported or observed during the ongoing chronic stimulation. Oculomotor or affective responses were frequently observed in our patients particularly when the stimulation amplitude was higher than 4 V. A postoperative asymptomatic complication occurred in one case; the CT showed a mild hemorrhage in the posterior wall of the third ventricle. There were no other acute complications resulting from the implantation procedure. There was no clinical evidence of autonomic effects of hypothalamic stimulation during either acute operative electrical stimulation or chronic therapeutic stimulation. Twenty-four hours of continuous monitoring of the arterial blood pressure, in four patients evaluated before and after surgery, revealed only asymptomatic orthostatic hypotension triggered by the electrical stimulation. There were no tolerance phenomena.

SUNCT

After 15 days of bipolar stimulation offered no improvement, unipolar stimulation was started (180 Hz, 60 μsec). The pain attacks subsided after 1 month of stimulation at 0.9 V but reappeared at month 4; the amplitude was gradually increased to 1.8 V, and again the attacks subsided. After one pain-free month, in month 8, the stimulator was turned off with the patient being unaware of it; she remained pain-free for the next 3 months; in month 11, the attacks gradually reappeared and persisted, and, hence, the stimulator was turned on again at 0.9 V. In month 13, the attacks gradually reappeared and the amplitude was progressively increased to 1.8 V and the attacks disappeared. Fifteen months after surgery, the patient started experiencing sporadic attacks, and lamotrigine was given at 100 mg/day; the attacks then subsided. The patient remained unaware of the stimulation status for 8 months. Stimulation was always well tolerated; however, when amplitude was increased up to 1.4 V difficulties in conjugate eye movements appeared and subsided few minutes to few hours later. Blood pressure, heart rate, electrocardiogram, hormone levels, temperature, sleep-waking cycle, body weight, and behaviour remained normal from implantation to the latest checkup.

Atypical facial pain

After surgery, the three patients had no reduction in pain. The stimulation parameters were the same as for CCH and SUNCT patients (180 Hz, 60 μsec, mean voltage 1.3). After four months of continuous stimulation (6, 8, and 10 months, respectively) the continuous pain was the same as preoperatively. Increase of amplitude did not offer any pain relief. Amplitude higher than 3 V induced dizziness and oculomotor symptoms in all cases. Bipolar stimulation did not offer any improvement. When the IPG was switched off with the patient being unaware of it, the episodes of paroxysmal pain were described by the patient as being slightly more intense than those that occurred during stimulation.

Disruptive and aggressive behaviour

HFS of the posteromedial hypothalamus offered consistent improvement of disruptive behaviour in both patients at last follow-up.

Case 1

After two weeks from the beginning of stimulation, neuroleptic medication was withdrawn; at that time the patient appeared much more calm and more cooperative. Few weeks later, he was able to stand and walk and to interact easily with the examiners. One year later, the therapeutic effect of stimulation was still present at the same parameters (180 Hz, 60 μsec, 1 V) without any side effects. The patient regained a normal circadian rhythm, and had complete resolution of his disruptive behaviour. Therefore, he was able to provide for his self-care, underwent rehabilitation and became ambulatory; the dystonic neck posture also improved slightly. The patient's relationships with his family members and his social activities improved greatly. The frequency of epileptic seizures was reduced from 7–10 to 4–7 per day. At the follow up of 18 months, the results were stable.

Case 2

One month after the beginning of stimulation (180 Hz, 60 μsec, 1 V), the aggressive behaviour completely disappeared and the neuroleptic medication was reduced. After 3 months, no behavioural changes were observed; increase of stimulation amplitude was done (180 Hz, 60 μsec, 1.5 V) with no side effects. Three months later, the psychiatric condition was stable and the patient was then transferred to an occupational therapy center. After 15 months of DBS, the aggressive behaviour remains well controlled.

Microrecording

Two cells were recorded with a mean firing discharge rate of 14.35 and 24.77 Hz, respectively. Both neurons generated isolated action potentials during most of recordings. The inter-spike interval histograms (ISIHs) have shown the highest concentrations of intervals in the 10–15 ms range, and the percentage of ISI shorter than 5 ms. In one patient during surgery, it was possible to deliver somatic stimulation to the face, and to record the evoked firing discharge. Postoperative data analysis of the spontaneous and evoked neural discharge was performed by the Spike 2 analysis package (Cambridge Electronic Design, Cambridge, UK). Single unit events were identified, and confirmed as arising from a single neuron, using template-matching spike sorting software. This recorded neuronal activity around our target is of uncertain origin as it does not correlate with any previously anatomically described central gray matter focus; we could only confirm that neurons are present on this target.

Finally, the postoperative fused CT-MR images and controls showed the correct placement of the electrodes in all cases confirming that the ''interpeduncular nucleus'' or ''interpeduncular point'' is more strictly related to our target than the conventional midcommissural point (Fig. 3).

Discussion

The hypothalamus is a core structure of the limbic system that connects two large limbic domains: the mesial temporal structures and the orbito-frontal cortex [23]. The hypothalamus is a central component of the Papez circuit; it is connected with the hippocampus, amygdala, and limbic thalamus on one side via the mamillary bodies and the fornix and on the other side via the cingulate gyrus and the entorhinal cortex. The connection with hippocampus, amygdala, cingulate gyrus, and the entorhinal cortex could explain the role of hypothalamus in learning, memory, emotions, motivation, affiliative behaviour, and autonomic and endocrine functions [17]. The alleged activation of hypothalamus during CCH attacks is considered the origin of some other symptoms which often appear during the attack itself such as abrupt rise of the arterial pressure, psychomotor agitation, hypersexuality, hyperphagia, insomnia, aggression and focal vasomotor alterations. These observations and the results obtained in our series of patients suggest that the posterior hypothalamus is a major part of a neural network, which controls different interlaced

functions. These data suggest that hypothalamic stimulation could potentially have future applications such as in the treatment of severe sleeping disorders, malignant arterial hypertension, and eating disorders; notably, the patients submitted to hypothalamic stimulation showed increase of sleeping time, normalization of arterial blood pressure and significant weight loss. Unfortunately, current pathophysiological findings are insufficient for drawing any conclusions about the mechanisms of hypothalamic HFS; moreover, certain proposed applications, nowadays, seem too distant from becoming a sound scientific proposal. Nevertheless, the analysis of our patients allows a few solid remarks and considerations.

First, chronic neurostimulation of the posterior hypothalamus did not produce any behavioural effects in CCH patients while it produced cessation of disruptive behaviour in the two cases of severe refractory aggressiveness [4, 5, 12]. In other words, neurostimulation of the same target induced different effects in different brains in different clinical conditions [1, 6]. Similar observations were reported in Sano's series; this included patients with facial pain and psychiatric conditions who benefited by RF lesions in the same target, namely the posteromedial hypothalamus [20]. In accordance with Sano's series, one of the two reported psychiatric patients had a 50% decrease in the frequency of drug refractory multifocal epileptic seizures; it should be noted that the considerable amount of neuroleptics that were administered before the stimulation could facilitate the development of multifocal epileptic seizures. Secondly, neuropathic facial pain was completely unaffected by HFS of the posteromedial hypothalamus. This data suggests that the pathophysiological mechanisms giving rise to continuous pain of the face due to fifth nerve lesions does not involve the hypothalamus. Similarly in the Sano's series, patients affected by neuropathic facial pain had poor results after radiofrequency (RF) hypothalamotomy [19]. Thirdly, the involvement of the autonomic system has been confirmed in our patients by the dramatic and sudden disappearance of the neurovegetative dysfunction associated with CH [5, 21]. HFS of the PMH did not produce clinically relevant modifications in the blood pressure profile and in cardiac activity in any of the treated patients. More refined investigational instruments revealed only a delay in orthostatic pressure adjustments.

In conclusion, our data suggests that HFS of the PMH interacts with the mechanisms involved in episodic facial pain, behavioural disease, and neurovegetative system regulation. Future HFS of this target could be considered in the treatment of diseases which show, on imaging, hypothalamic activation. Considering the large number of involved functions, the target volume is small and the stereotactic procedure has to be very precise. This statement applies to all stereotactic procedures, but because of the potentially misleading anatomical variability of the PMH, any targeting error may result in clinical failure requiring reposition of the electrode [5]. Moreover, a recent report of a fatal outcome indicates that the procedure is not entirely free of risks [21]. The reversibility of the procedure and the absence of side effects during chronic continuous and even bilateral PMH DBS should be stressed; this made this technique ethically acceptable in these otherwise untreatable patients whose quality of life consistently improved by this neuromodulation technique. The potential therapeutic role of stimulation of this distinct brain structure is probably greater than it has been previously thought.

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