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Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action

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Summary

We enrolled six patients suffering from refractory chronic cluster headache in a pilot trial of neurostimulation of the ipsilateral ventroposterior hypothalamus using the stereotactic coordinates published previously. After the varying durations needed to determine optimal stimulation parameters and a mean follow-up of 14.5 months, the clinical outcome is excellent in three patients (two are pain-free; one has fewer than three attacks per month), but unsatisfactory in one patient, who only has had transient remissions. Mean voltage is 3.28 V, diplopia being the major factor limiting its increase. When the stimulator was switched off in one pain-free patient, attacks resumed after 3 months until it was turned on again. In one patient the implantation procedure had to be interrupted because of a panic attack with autonomic disturbances. Another patient died from an intracerebral haemorrhage that developed along the lead tract several hours after surgery; there were no other vascular changes on post-mortem examination. After 1 month, the hypothalamic stimulation induced resistance against the attack-triggering agent nitroglycerin and tended to increase pain thresholds at extracephalic, but not at cephalic, sites. It had no detectable effect on neurohypophyseal hormones or melatonin excretion. We conclude that hypothalamic stimulation has remarkable efficacy in most, but not all, patients with treatment-resistant chronic cluster headache. Its efficacy is not due to a simple analgesic effect or to hormonal changes. Intracerebral haemorrhage cannot be neglected in the risk evaluation of the procedure. Whether it might be more prevalent than in deep-brain stimulation for movement disorders remains to be determined.

Keywords: hypothalamus; neurostimulation; cluster headache; algometry; nitroglycerin

Abbreviations: BiFR = biceps femoris flexion reflex; CCH = chronic cluster headache; DBS = deep-brain stimulation; nBR = nociceptive blink reflex

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Introduction

The prevalence of cluster headache, the most intense primary headache, is around 1 in 500 persons, predominantly males (Russell, 2004). One in 10 subjects presents the chronic form (CCH), in which remissions are absent for at least 1 year or last less than 2 weeks (International Classification of Headache Disorders, ICHD-I 3.1.3; 1998) or less than 1 month (International Classification of Headache Disorders, ICHD-II 3.1.2; 2004). A small proportion of CCH subjects are resistant to medical therapy and thus dramatically disabled. Traumatic procedures, such as radiofrequency trigeminal rhizotomy, Gasserian ganglion glycerol injection or compression, greater superficial petrosal nerve section or Janetta's microvascular decompression of the trigeminal nerve, have been used in refractory CCH without lasting success (Bahra and Goadsby, 2004).

Recently, deep-brain stimulation (DBS) of the ventroposterior hypothalamus was claimed to provide for the first time spectacular and lasting relief in such patients (Leone *et al*., 2001, 2004*a*; Franzini *et al*., 2003). This area of the brain was targeted for stereotactic neurostimulation because

it is metabolically activated on the side of nitroglycerin-induced (May *et al*., 1998) or spontaneous (Sprenger *et al*., 2004) cluster headache attacks and contains an increased amount of tissue (May *et al*., 1999). Activations in a similar region may, however, occur as a secondary phenomenon after nociceptive stimulation in the face (Kupers *et al*., 2004) or peripheral limbs (Petrovic *et al*., 2004). That the ventroposterior hypothalamus is a primary generator of cluster headache attacks is thus not definitively demonstrated (Schoenen, 1998). It could be a relay in the pain-controlling network that is activated by the trigeminal nociceptive input and produces a non-specific generalized analgesia after neurostimulation, as shown in animals (Rhodes and Liebeskind, 1978) and humans (Hosobuchi, 1986).

Besides the fact that the favourable results obtained by the Italian group need to be confirmed, the therapeutic application of functional neurosurgery in cluster headache presents several interrelated difficulties. By contrast with subthalamic nucleus stimulation in Parkinson's disease, there is no physiological or clinical marker to confirm the accurate positioning of the stimulating electrode in the posterior hypothalamus. While it is easy to test a patient with a stable and permanent clinical syndrome, such as in Parkinson's disease, assessing treatment effects may cause problems in cluster headache, in which attacks are transient and fluctuate over time. It is thus important to verify if the effect of neurostimulation in CCH is symptomatic and short-lasting or inducing a stable remission phase.

We decided therefore to perform a pilot study of hypothalamic DBS in refractory CCH patients and to monitor, besides the effect on headache attacks, the following variables: neuronal activity at the implantation site, changes in pain thresholds at cephalic and extracephalic sites, neurohypophyseal hormones, propensity to trigger attacks by sublingual nitroglycerin, and relapse of attacks after turning off the stimulator in certain patients.

Material and methods

Patients

We obtained approval from the Ethics Committee of the University of Liège Faculty of Medecine to recruit six patients fulfilling the following inclusion criteria: male or female subjects aged 25–55 years suffering from chronic cluster headache (ICHD-I code 3.1.3) for at least 2 years, with four or more disabling side-locked attacks per week, resistance or intolerance to adequate trials of steroids, verapamil, methysergide, lithium and/or ergotamine (noctem for prevention of nocturnal attacks), and no other disabling medical or psychiatric disorders. Written informed consent was obtained from each patient for all procedures described below. Four patients consented to undergo a nitroglycerin provocation test. One patient accepted that, after a pain-free period of 3 months, the stimulator would be turned off until recurrence of an attack.

Neurostimulation

The stimulating lead (Medtronic 3389-40, with four distal electrodes labelled 0–3 towards the tip) was implanted according to the stereotactic parameters published by Leone and colleagues (Leone *et al*., 2001): $y = 6$ mm behind the midcommissural point, $x = 2$ mm lateral to the midline and $z = 8$ mm below the commissural plane. Before implantation of the quadrifilar stimulating lead, microelectrode cell recordings were performed (Medtronic 9013-S-0841) starting 10 mm above the theoretical target and at each subsequent mm up to the target. Recordings were collected with a Medtronic Leadpoint® device. Thereafter, 180 Hz stimulation was administered at the theoretical target and 2 mm above and below at intensities up to 4 mA to check for adverse reactions. After surgery, the lead was connected to an external stimulator, which was switched on (frequency 180 Hz, intensity 1–3 V, pulse width 60 μs) as soon as the patient presented an attack. If necessary, the stimulation parameters were adjusted over the succeeding days, before the stimulator (Soletra® Medtronic) was subcutaneously implanted in the subclavicular region.

Clinical evaluation

The patients recorded attack frequency, intensity, autonomic symptoms and adverse events on paper diaries for at least 1 month before the procedure and without interruption after implantation.

In the four patients who consented, a nitroglycerin provocation test (1.2 mg sublingual) was performed before implantation and, if spontaneous attacks had disappeared, after 1 week and 1 month of neurostimulation.

Electrophysiological and algometric studies

We studied two nociceptive reflexes before and 1 week and 1 month after neurostimulation: the nociceptive blink reflex (nBR) obtained by supraorbital stimulation with a concentric high-density current electrode (Kaube *et al*., 2000) and the biceps femoris flexion reflex (BiFR) elicited by electrical stimulation with a standard electrode of the sural nerve at the ankle (Sandrini *et al*., 1993). Perception and pain thresholds were determined in each location bilaterally with an ascending and a descending sequence of 0.2 mA intensity steps. The stimulus intensity was set at 1.5 times the individual pain threshold. We measured the area under the curve of five averaged rectified EMG responses and compared the baseline recording performed several days before the procedure with those obtained 1 week and 1 month after turning on the neurostimulator. For the nBR, orbicularis oculi EMG was recorded on both sides.

Pressure pain thresholds were determined with a Somedic algometer bilaterally over the temple, extensor muscles of the upper forearm and lateral aspect of heel. The mean of three consecutive measurements separated by at least 1 min was taken into account at each site.

Endocrine studies

Urinary excretion of melatonin was measured on samples obtained during three different time epochs: 7 p.m. to 11 p.m., 11 p.m. to 7 a.m., and 7 a.m. to 11 a.m. The total 24 h urinary excretion of cortisol was also determined. These tests were performed before implantation and after 1 week of neurostimulation. Plasma oxytocin and vasopressin were measured at baseline, at 10 min intervals during electrode implantation and after switching on the stimulator for the first time.

Statistics

Student's paired *t* tests and analysis of variance were used to compare the electrophysiological and hormonal results before and during hypothalamic stimulation.

Results

Clinical results

While waiting for ethics committee approval, we assigned 12 candidate patients with an IHS diagnosis of refractory chronic cluster headache from the entire country to a waiting list. After the first visit and changes in drug therapy made in some of them, nine patients went into remission and one was lost to follow-up.

We finally enrolled for the intervention two patients from the waiting list and four other patients recruited over a 6-month period. One of these six patients was not implanted because of an adverse effect during electrode implantation. The demographics and clinical characteristics are shown in Table 1. There were five men and one woman. Mean age was 46.7 ± 7 years, mean duration of the disorder 6.7 ± 2.8 years and mean duration of the chronic phase 4.5 ± 2.6 years. Daily attack frequency ranged from 1 to 7. All patients were resistant to available preventive treatments, including to changes made during the 1- to 3-month waiting time before the operation.

At present, among the five patients who were implanted and stimulated two are totally pain-free, one has relief with fewer than three attacks per month and one has had transient remissions; none of them is taking prophylactic medications. All patients improved within 2 weeks after the operation, but improvement was definitive in only two patients. One patient died shortly after implantation. The average follow-up time is 14.5 ± 1.5 months.

After initial relief allowing the interruption of prophylactic medications, patient 1 returned to several months of almost daily attacks despite several stimulation adjustments and had to resume drug prophylaxis. With an unusual bipolar plot combination (electrodes 1–2 as cathodes, 3 as anode) he became pain-free for more than 5 months. Recently he had recurrence of daily attacks, but preferred to postpone prophylactic drug treatment until further stimulation protocols had been explored. Patient 2 became pain-free after 8 months of relief. The hypothalamic DBS in patient 3 reduced attacks to two or three per month, which were effectively treated with injectable sumatriptan. After 8 months of relief, attack frequency increased to several per week and stimulation parameters had to be adjusted; after 1 month he switched back to one or two attacks per month without need for prophylaxis. Patient 4 became pain-free after some weeks of neurostimulation; after 9 months he consented to have his stimulator turned off and remained pain-free for 3 months. Thereafter almost daily cluster headache attacks resumed and the stimulator was switched on again. As soon as the previous stimulation voltage of 3.3 V was reached, he became pain-free again. The mean voltage used in our patients was 3.28 ± 1.02.

Sublingual nitroglycerin induced attacks in three out of four patients before implantation, in two out of four after 1 week and in none out of three after 1 month of stimulation.

Adverse effects

All patients complained of diplopia and dizziness when high stimulus intensities were reached (above 1.5 V). The oculomotor disturbances were the main limiting factor in increasing stimulus voltage; when mild, they usually disappeared after 24–48 h. The patients described above had no other adverse events.

During the implantation procedure, patient 5 had a panic sensation with polypnoea, tachycardia and moderate hypertension. After the recording electrode had been taken out and the operation interrupted, his vital parameters returned rapidly to normal.

Patient 6 had an unremarkable implantation except for moderate hypertension (160/120 mmHg) and occurrence of an attack that had to be treated with 1 mg intravenous

Table 1 *Demographics, clinical features and outcome of enrolled patients*

Patient	Age (years), sex	Disease duration (years)	Duration of chronic phase (years)	Attack frequency (per day) and side	Follow-up (months)	Outcome	Stimulation parameters
1 (BD)	45, M	3	2	2–7, L	17	Unstable for 7 months Pain-free for 5 months Recent relapse	Bipolar (1−, 2−, 3+), 4.5 V, 185 Hz, 90 μs
2 (FE)	34, M	10	5	1–3, L	15	Relief for 8 months Pain-free for the last 5 months	Monopolar (0−) 3.3 V, 185 Hz, 60 μs
3 (BA)	46, M	6	5	4–5, L	14	Relief for 8 months Relapse Relief for the last 4 months	Monopolar (3−), 2 V, 185 Hz, 90 μs
4 (FC)	51, M	4	2	1–4, R	12	Pain-free for 9 months Pain-free for 3 months Relapse Pain-free for the last 3 months	Monopolar (0−), 3.3 V, 185 Hz, 60 μs Stimulator OFF Stimulator ON
5 (CM)	53, M	8	4	3–4, R	–	Panic and vegetative dysfunction during procedure	Not implanted
6 (BV)	51, F	9	9	1–3, L (3 suicidal att.)	–	Died from ic haemorrhage	Not stimulated

F = female; M = male; L = left; R = right.

dihydroergotamine. Five hours later, while still in the intensive care unit, she became comatose with bilateral mydriasis and a CT scan showed a massive left intracerebral haemorrhage with ventricular inundation (Fig. 1A). On digitized angiography there was a saccular aneurysm in the supracavernous portion of the left carotid artery (Fig. 1C). She was artificially ventilated and remained in deep coma until her death 3 days later. On autopsy, the stimulating electrodes were correctly positioned. There was a massive deep haemorrhage in the left hemisphere along the lead body tract with blood suffusion into the ventricular system and along the implantation trajectory up to the left cortical surface (Fig. 1B). Besides the haemorrhage, no vascular or inflammatory lesions were found on histopathological examination.

Electrophysiological and algometric results

During intraoperative microelectrode recordings no specific neuronal activity similar to that found in DBS of the subthalamic nucleus or globus pallidus was identified. In two patients we recorded bursts of action potentials that were synchronous with heart beats.

The results of electrophysiological and algometric measurements are summarized in Table 2. The supraorbital electrical pain threshold was on average significantly decreased after 1 week ($P = 0.001$), but not after 1 month of neurostimulation on the side of the cluster headache attacks. By contrast, pain thresholds at the level of the sural nerve tended on average to be higher compared with baseline after 1 month of neurostimulation, a difference which was significant only on the healthy side ($P = 0.04$) (Fig. 2A).

Pressure pain thresholds were clearly lower over the temple than over extracephalic sites. During neurostimulation there was no significant change in cephalic thresholds, which contrasted with a uniform tendency for extracephalic thresholds to increase over time with neurostimulation. This trend, however, reached the level of significance only 1 month after implantation at the forearm on the side of cluster headache attacks ($P = 0.05$) and at the heel on the non-painful side ($P = 0.01$) (Fig. 2B).

There was overall no significant change in response areas of nociceptive blink and biceps femoris flexion reflexes on either side of the body. The only exception was a significant increase in ipsilateral nBR response area after supraorbital stimulation on the cluster side after 1 month of neurostimulation compared with the preimplantation recording ($P = 0.04$). This was in line with two out of three other nBR response area measurements at month 1, which also tended to increase and contrasted with the decrease in BiFR response areas (Table 2).

Endocrine tests

Decreased nocturnal urinary excretion of melatonin was found at baseline in two implanted patients. This did not change after 1 week of hypothalamic stimulation. There were no

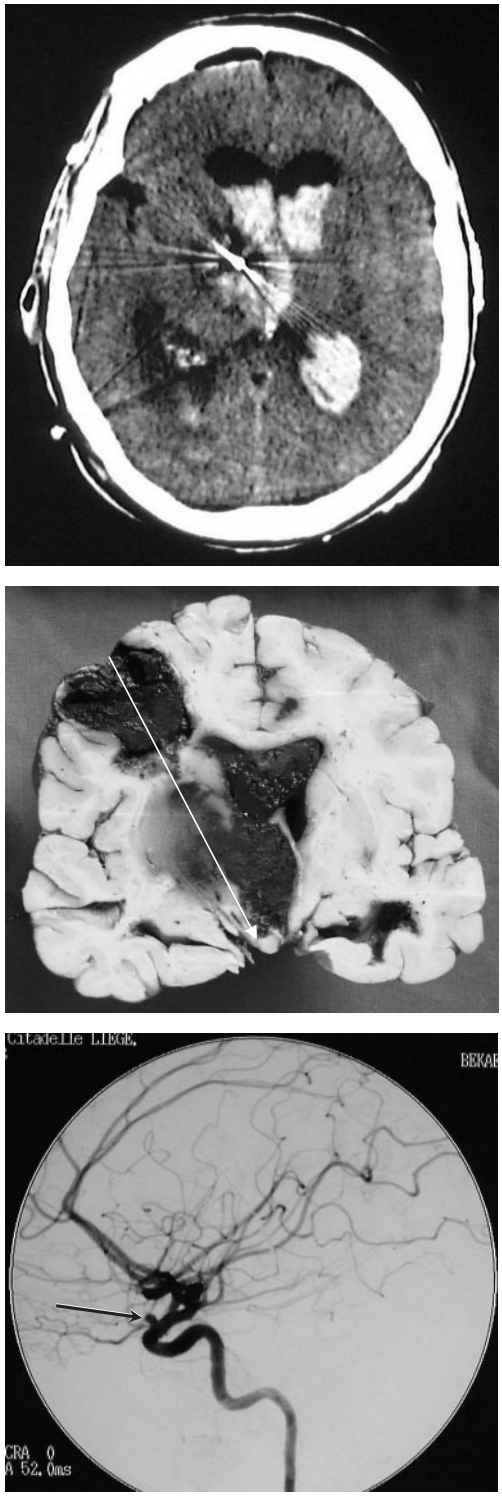

Fig. 1 Patient 6. (**A**) CT scan 6 h after electrode implantation showing left deep intracerebral haemorrhage around the electrode artefact and blood in both lateral ventricles. (**B**) Coronal section of formalin-fixed brain at the level of the posterior hypothalamus. Note swollen left hemisphere, basal ganglia haemorrhage, intraventricular blood and a superficial haematoma at the entry site of electrode implantation. The arrow indicates the approximate position of the stimulating electrode. (**C**) Digitized angiography 18 h after electrode implantation, showing a saccular aneurysm of the supracavernous portion of the left carotid artery (arrow).

Table 2 *Synopsis of algometric and electrophysiological recordings before and 1 week and 1 month after hypothalamic neurostimulation*

Recordings	Time of recording		
	Before	1 week DBS	1 month DBS
Electrical pain threshold (mA): mean ± SEM			
Supraorbital			
Cluster side	3.35 ± 0.45	2.06 ± 0.26*	3.00 ± 0.53
Healthy side	3.75 ± 1.63	2.93 ± 1.04	3.17 ± 0.71
Ankle			
Cluster side	12.3 ± 4.35	12.25 ± 5.38	13.0 ± 1.67
Healthy side	11.0 ± 4.0	10.63 ± 4.63	11.83 ± 1.78*
Pressure pain threshold (kPa): mean ± SEM			
Temple			
Cluster side	389 ± 128	380 ± 212	396 ± 183
Healthy side	411 ± 116	362 ± 139	418 ± 155
Forearm			
Cluster side	844 ± 344	880 ± 481	948 ± 406*
Healthy side	855 ± 287	853 ± 368	933 ± 458
Heel			
Cluster side	832 ± 315	873 ± 350	934 ± 441
Healthy side	854 ± 381	941 ± 447	986 ± 451*
nBR response area (mVxms): mean ± SEM			
Stimulation cluster side			
Ipsilateral R2	0.69 ± 0.37	0.75 ± 0.53	1.15 ± 0.48*
Contralateral	0.57 ± 0.40	0.57 ± 0.36	0.67 ± 0.30
Stimulation healthy side			
Ipsilateral R2	0.87 ± 0.32	0.77 ± 0.53	0.87 ± 0.06
Contralateral R2	0.55 ± 0.33	0.55 ± 0.43	0.69 ± 0.29
BiFR response area (mVxms): mean ± SEM			
Stimulation cluster side			
Ipsilateral FR	0.83 ± 0.79	0.40 ± 0.39	0.69 ± 0.40
Stimulation healthy side			
Ipsilateral FR	0.47 ± 0.43	0.49 ± 0.41	0.40 ± 0.35

FR = flexion reflex.

other hormonal abnormalities or changes during implantation or after 1 week of stimulation.

Discussion

This pilot study confirms that hypothalamic DBS with the same devices as used in movement disorders is an effective treatment in refractory chronic cluster headache, as first shown by Leone and colleagues (Leone *et al*., 2001). After a mean follow-up of 14.5 months, two out of four stimulated patients are lastingly pain-free, one has a spectacular reduction in attack frequency and the fourth has periodic but non-lasting remissions. None of them is taking preventive drug treatment. The electrode implantation itself delayed an attack for no more than 48 h. All patients had some rapid relief after turning on the stimulator. In two of them it took nonetheless repeated adjustments of stimulation parameters over several months to obtain stable and satisfactory relief. These results are similar to those obtained by the Italian researchers, who also report delays of several months before achieving optimal relief and need for prophylactic treatment in some patients (Franzini *et al*., 2003). We show in addition that, after 1 month of stimulation, nitroglycerin, a classical trigger (Bogucki, 1990), was unable to provoke an attack in patients who were pain-free. This suggests that, within this time period, the hypothalamic stimulation had induced rather stable remission and was providing resistance to an attack trigger. This can be compared with spontaneous remissions in the episodic form of cluster headache, during which alcohol, for instance (another well-known trigger during a bout), becomes ineffective. Attacks recur nonetheless at varying delays after switching off the stimulator, as illustrated in one of our patients and in a bilaterally implanted patient of Leone and colleagues (Leone *et al*., 2004*a*), demonstrating that the hypothalamic neurostimulation does not cure the disorder, but that it is able to induce remission of several months.

It must be pointed out that the stereotactic coordinates used in our study were those published initially by Leone and colleagues (Leone *et al*., 2001). After the first two patients, the Italian group used different coordinates, positioning the electrode 3 mm higher and 3 mm more rostrally (Franzini *et al*., 2003). Comparing globally the results in our small series with those presented by Leone in 14 patients (M. Leone, personal communication), the change in the stereotactic target does not greatly modify efficacy. It might, however, explain why we had to use on average higher stimulation voltages (mean 3.28 ± 1.02 versus 2.0 ± 0.98V) and induced more severe oculomotor disturbances. The latter are due to the short distance between the stimulation electrode and the rostral mesencephalic oculomotor centres. The precise nucleus to be targeted for effective neurostimulation in cluster headache therefore remains to be determined. The microelectrode recordings obtained in our study were not able to identify specific neuronal discharge patterns. The burst activity synchronous with heart rhythm that was recorded in two patients was probably triggered by pulsatility of neighbouring arteries.

Hypothalamic stimulation is a well tolerated treatment with only reversible oculomotor side-effects in the majority of patients. It is not, however, a benign and atraumatic procedure. In our small series, the electrode implantation had to be interrupted in one patient because of a panic attack associated with autonomic disturbances. A possible causal relationship with the procedure cannot be ruled out, although the patient appeared excessively anxious and stressed already before the operation. The lethal outcome of our last implanted patient is of greater concern. There is little doubt that the massive intracerebral and intraventricular haemorrhage was a consequence of the lead implantation. As this patient had been using narcotics daily for more than a year, vasculopathy was suspected as a possible favouring factor, but this was ruled out by the histological examination of the brain. Intracranial haemorrhage is a known, albeit rare, complication of electrode implantation for DBS in movement disorders, in which its incidence varies between 5% (Deep-Brain Stimulation for Parkinson's Disease Study Group, 2001) and 1% (Benabid *et al*., 2003; Binder *et al*., 2003; Lyons *et al*., 2004).

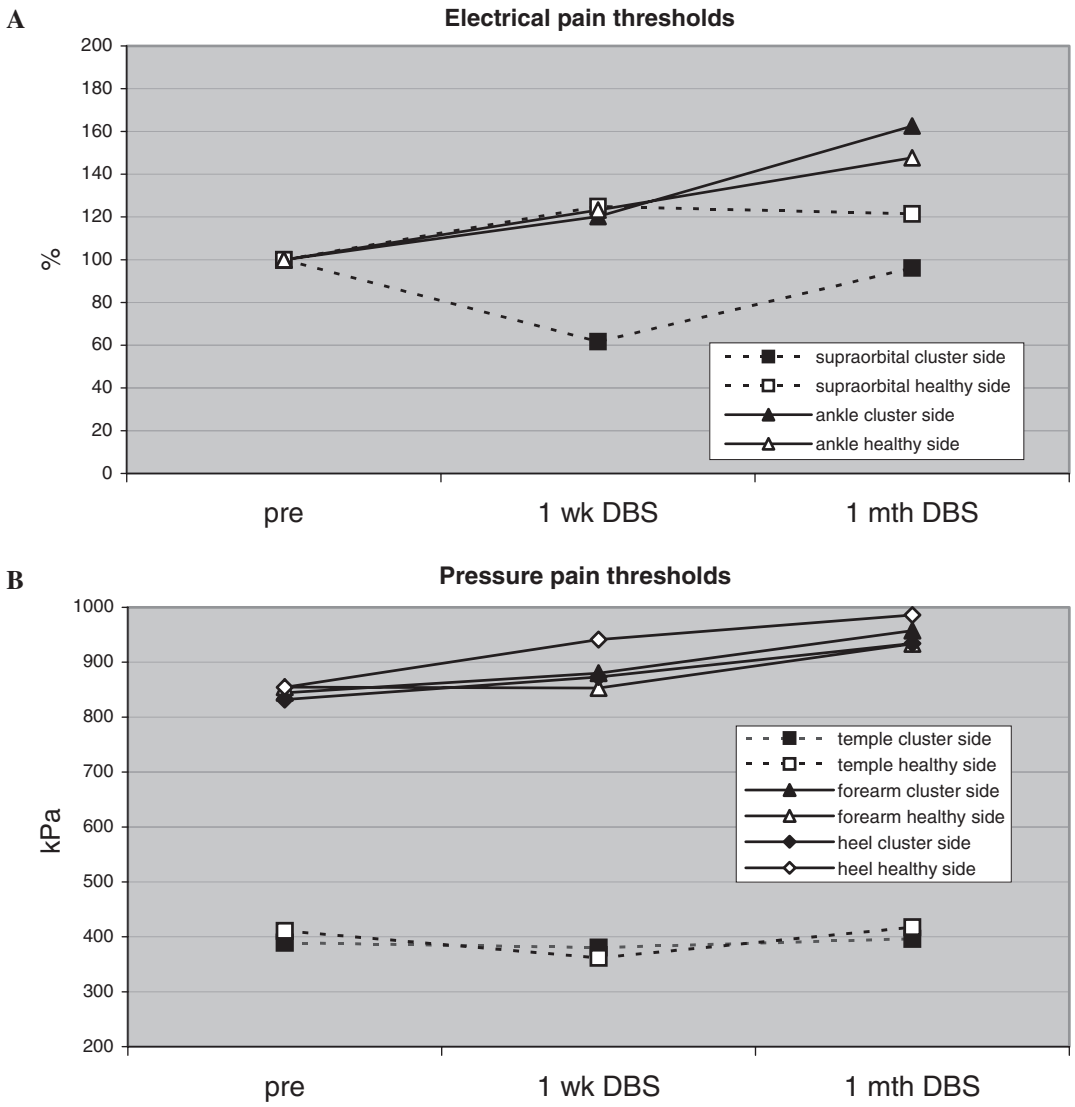

Fig. 2 Algometric measures. (**A**) Electrical pain thresholds over supraorbital and sural nerves: percentage change after 1 week and 1 month of hypothalamic stimulation relative to preimplantation measures. During stimulation, thresholds increased over the sural nerve on both sides of the body, but transiently decreased over the supraorbital nerve on the pain side (for statistical differences see Table 2). (**B**) Pressure pain thresholds over bilateral temples, finger extensors and heels: percentage change after 1 week and 1 month of hypothalamic stimulation relative to preimplantation measures. During stimulation, thresholds tended to increase uniformly at extracephalic sites, but they did not change in the face (for statistical differences see Table 2).

If cluster headache cases are pooled with all patients who underwent DBS in our centre ($n = 51$), the overall prevalence of clinically significant haemorrhage is 2%, similar to that in other groups. It is not clear if the haemorrhagic risk is increased for implantations in the ventroposterior hypothalamic area compared with basal ganglia or thalamic sites or for microelectrode-guided DBS. With the latter method the incidence of haematoma ranged in one study from 0% per lead for thalamic DBS to 6.7% for globus pallidus stimulation (Binder *et al*., 2003). A small haemorrhage without any clinical consequence was detected on CT scanning in one of the patients of Leone and colleagues who had been implanted for refractory cluster headache (M. Leone, personal communication).

A supracavernous carotid aneurysm was detected in this patient on digital angiography during work-up for her neurological deterioration, although a magnetic resonance angiography performed 1 year earlier had been considered normal by the physicians who referred her to our centre. Symptomatic cluster headache is indeed known to occur with paracavernous midline lesions (Sjaastad, 1988). It has been reported with various vascular lesions, such as intracavernous pseudoaneurysm (Koenigsberg *et al*., 1994), carotid artery dissection (Frigerio *et al*., 2003), thrombotic aneurysm of the posterior communicating artery (McBeath and Nanda, 2000) and aneurysm of the vertebral artery (West and Todman, 1991). Although up to now small supracavernous carotid aneurysms have not been associated with

cluster-like headache, the unruptured aneurysm in our patient was located on the side of the attacks and a causal relationship with the headache cannot be ruled out. This observation underscores the need for strict selection criteria when considering refractory CCH patients for deep hypothalamic stimulation (Leone *et al*., 2004*b*).

The mode of action of hypothalamic neurostimulation in cluster headache is unknown. Activation of various central structures belonging to the pain network was reported recently (May and Leone, 2003), which could be in line with the observations of general analgesia observed after hypothalamic stimulation in animals (Rhodes and Liebeskind, 1978) or humans (Hosobuchi, 1986). Albeit limited in number, our algometric measures tend to confirm that peripheral hypoalgesia occurs after neurostimulation of the ventroposterior hypothalamus. Because of the large standard deviations in our small sample, the tendency for an increase in electrical and pressure pain thresholds, though uniform, is significant only in a few peripheral sites. By contrast, there is a trend for pain threshold decreases at cephalic sites and for an increase in the response area of the nociceptive blink reflex. These data need to be confirmed on larger samples, but, taken together, they suggest that the therapeutic effect of hypothalamic neurostimulation in cluster headache is not due to a reduction of pain perception or sensitivity in the trigeminal system. Finally, according to our results, hypothalamic implantation and stimulation do not induce marked hormonal changes, nor do they normalize within 1 week the abnormal excretion pattern of melatonin which is well documented in cluster headache (Chazot *et al*., 1994; Leone *et al*., 1995).

To summarize, this small pilot study confirms that stimulation of the ventroposterior hypothalamus with deep electrodes is an effective treatment in refractory chronic cluster headache. Optimal efficacy is not reached before several months because multiple adjustments of the stimulation parameters are necessary and voltage increase is limited by oculomotor side-effects. Turning off the stimulator is followed by recurrence of attacks after several months in patients in whom continuous stimulation provided resistance to the attack-triggering agent nitroglycerin. The effects of hypothalamic neurostimulation in cluster headache cannot be explained by a decrease in pain processing in the trigeminal system, but it may induce hypoalgesia at extracephalic sites. It has no effect on neurohypophyseal hormones or on the circadian rhythm of melatonin excretion. It is well tolerated, but has, like implantation of deep electrodes in other sites, the potential risk of provoking a cerebral haemorrhage.

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