Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study

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Summary

Background **Drug-resistant chronic cluster headache (drCCH) is a devastating disorder for which various destructive procedures have been tried unsuccessfully. Occipital nerve stimulation (ONS) is a new, safe strategy for intractable headaches. We undertook a prospective pilot trial of ONS in drCCH to assess clinical efficacy and pain perception.**

Methods **Eight patients with drCCH had a suboccipital neurostimulator implanted on the side of the headache and were asked to record details of frequency, intensity, and symptomatic treatment for their attacks in a diary before and after continuous ONS. To detect changes in cephalic and extracephalic pain processing we measured electrical and pressure pain thresholds and the nociceptive blink reflex.**

Findings **Two patients were pain free after a follow-up of 16 and 22 months; one of them still had occasional autonomic attacks. Three patients had around a 90% reduction in attack frequency. Two patients, one of whom had had the implant for only 3 months, had improvement of around 40%. Mean follow-up was 15·1 months (SD 9·5, range 3–22). Intensity of attacks tends to decrease earlier than frequency during ONS and, on average, is improved by 50% in remaining attacks. All but one patient were able to substantially reduce their preventive drug treatment. Interruption of ONS by switching off the stimulator or because of an empty battery was followed within days by recurrence and increase of attacks in all improved patients. ONS did not significantly modify pain thresholds. The amplitude of the nociceptive blink reflex increased with longer durations of ONS. There were no serious adverse events.**

Interpretation **ONS could be an efficient treatment for drCCH and could be safer than deep hypothalamic stimulation. The delay of 2 months or more between implantation and significant clinical improvement suggests that the procedure acts via slow neuromodulatory processes at the level of upper brain stem or diencephalic centres.**

Introduction

Cluster headache is thought to be the most painful primary headache disorder. It is part of the so-called trigeminal autonomic cephalalgias.[1] The episodic form of the disorder (International Classification of Headache Disorders, second edition [ICHD-II] 3.1.1)[2] is characterised by attacks of unilateral periorbital pain associated with ipsilateral autonomic signs occurring in bouts (clusters) of weeks or months, separated by headache-free intervals of variable length (months or years). About 10% of patients with cluster headache[3] either have from onset or develop a chronic form of the disorder in which attacks persist for more than 1 year without remissions or with remissions lasting less than 1 month (ICHD-II 3.1.2).[2] Effective acute treatments for cluster headache attacks are injectable or intranasal triptans, or oxygen inhalation, whereas steroids, verapamil, methysergide, and lithium carbonate are the most efficient preventive therapies.[4]

Although precise figures are missing, about 1% of patients with chronic cluster headache are expected to become refractory to medical treatment and fulfil proposed criteria for intractable headaches.[5] Although patients with drug-resistant chronic cluster headaches (drCCH) may still have some relief with attack treatments, the disorder can be substantially disabling and some patients may become suicidal. Hence, various surgical procedures that target the trigeminal nerve or the cranial parasympathetic outflow have been tried in such patients. Examples include radiofrequency lesions, glycerol injections or balloon compressions of the Gasserian ganglion, gamma knife surgery or root section of the trigeminal nerve, trigeminal tractotomy, lesions of the nervus intermedius or greater superficial petrosal nerve, blockade or radiofrequency lesions of the pterygopalatine ganglion, and microvascular decompression of the trigeminal nerve combined with nervus intermedius section.[4] None of these procedures has been satisfactory for the long term and many have produced serious complications such as permanent neurological deficits with corneal anaesthesia leading to visual loss and anaesthesia dolorosa, or even death. Moreover, despite complete sectioning of the trigeminal nerve, persistence of cluster headache attacks was reported in one patient.[6] More recently, hypothalamic neurostimulation with deep-brain electrodes was shown to be effective in drCCH[7] and criteria for the selection of these patients for deep-brain stimulation were proposed.[8] In our series of five patients treated with hypothalamic stimulation, one patient unfortunately had a lethal treatment-related cerebral haemorrhage,[9] which confirms that deep-brain stimulation is not free from risk.

Suboccipital injections of steroids or local anaesthetics are thought to be useful in the management of patients with cluster headache.[10,11] We have shown their efficacy in a placebo-controlled trial.[12] Along the same line, peripheral stimulation of the greater occipital nerve (ONS) has been tried with some success in intractable

headaches, including chronic cluster headache and migraine.[13–15] The rationale for ONS is multifaceted. Peripheral neurostimulation is a non-destructive way for pain control and can be effective in other pain disorders such as neuropathic pain.[16] Convergence of cervical, somatic trigeminal, and dural trigeminovascular afferents on second order nociceptors in the brain stem is well documented.[17] Up to now, two patients with drCCH have been abstracted for whom ONS was helpful.[18] The same group reported on one patient with pain relief but who had persistent autonomic attacks after ONS.[19]

In light of our previous experience with both suboccipital steroid injections and deep hypothalamic stimulation, we decided to undertake a pilot study of ONS in patients with drCCH and to gather information about its mode of action by assessing pain thresholds and the nociception-specific blink reflex. We report here on eight patients after a maximum follow-up of 22 months.

Methods

Patients

We recruited eight patients with drCCH (seven men and one woman, mean age 45·3 years SD 9·7 years). Inclusion criteria were: chronic cluster headache for at least 2 years; four or more attacks per week by history; side-locked attacks from the beginning of the disease; no associated disabling organic or psychiatric disorder; and resistance to drug treatment. Resistance to drug treatment was defined as the lack of persistent improvement or intolerance after appropriate regimens of all of the following preventive oral drugs as single and as double or triple combinations: methylprednisolone (≥64 mg/day for ≥4 weeks), verapamil (≥720 mg/day for ≥12 weeks), lithium carbonate (up to a serum concentration 0·8–1 mmol/L for ≥16 weeks), indometacin (150 mg/day for 2 weeks), methysergide (4–6 mg/day for ≥4 weeks), and valproic acid and topiramate (both in six patients, one or the other in two patients, respectively at ≥1000 mg/day and ≥150 mg/day for ≥8 weeks), and at least one of melatonin (≥9 mg nocte), ergotamine tartrate (1–2 mg nocte), clomipramine (50–100 mg/day), gabapentin (800–1200 mg/day), or amitriptyline (75–100 mg/day). All patients had also received on the pain side one or several suboccipital injections of a mixture of 2 mL of long-acting and rapid-acting betamethasone combined with 0·5 mL lidocaine 2%[12] without long-lasting benefit, and two of them had also received pterygopalatine ganglion blocks. The various treatments were applied by neurologists during at least 2 years before enrolment and during the waiting time before the procedure attempts to optimise the preventive treatment were made in all patients—eg, by increasing the dose of drugs like verapamil, adding another drug, or doing another suboccipital infiltration.

Patients were recruited in two waves and gave written informed consent. Approval of the ethics committee of the faculty of medicine at Liège University was initially obtained for five patients. As results were encouraging after the follow-up analysis at 16 months, we requested ethics committee approval for a protocol amendment allowing us to recruit supplementary patients. Three patients were thus recruited in a second wave 18 months after the first patients received their implant.

Procedures

The surgical part was divided in two steps separated by a 3 day hospital stay on the neurosurgery ward. In the first step, a paddle-style stimulating lead with four distal electrodes, labelled 0–3 towards the tip (Medtronic 3587A Resume II, Medtronic, Minneapolis, USA), was implanted subcutaneously on the side of the cluster headache via a retromastoid C1–2–3 approach, according to the method described by Oh and co-workers[13] and under general anaesthesia. The lead localisation was determined by classic anatomical landmarks, but could not be tested preoperatively for the production of paraesthesias. After surgery, the implanted lead was connected to an external stimulator, which was switched on as soon as a typical cluster headache attack occurred. The stimulation parameters were chosen to obtain paraesthesias in the innervation territory of the greater occipital nerve. About 3 days later, an internal stimulator (Medtronic 7425 Itrel 3, Medtronic, Minneapolis, USA) was implanted subcutaneously under brief general anaesthesia in the prepectoral region of the chest. When the battery was empty, it was replaced by a longer lasting Medtronic Synergy stimulator.

During follow-up, because of lack of effect or paraesthesias, the stimulation parameters were adapted by two investigators (DM and JS) with a programming matrix: electrode plot combination, stimulation voltage, frequency, and pulse width were successively modified if needed. In the last three treated patients, the stimulation programme that was the most effective in the first series of five patients was chosen. Each patient was allowed to switch the stimulator on or off and to modify the stimulation voltage via a remote control system.

The patients had to fill in dedicated cluster headache paper diaries for at least 1 month before and without time limit after the implantation, recording attack occurrence, intensity (rated from 1–the mildest to 4–the worst pain), presence of ipsilateral autonomic signs (tearing, conjunctival injection, rhinorrhoea, ptosis), and acute treatment (subcutaneous sumatriptan 6 mg recommended as first choice or oxygen inhalation or analgesics). The patients were examined regularly in our headache clinic at short time intervals (2–3 week) during the first 3 months and at longer intervals (2–4 months) thereafter. At each visit the cluster headache diaries were collected and the stimulation parameters checked and, if necessary, modified. Extra visits or phone calls were scheduled on request, which is a general policy for all our patients with cluster headache.

Because the precise mechanisms by which ONS decreases pain are not known, we also did

electrophysiological and algometric measures on attack and healthy sides before and 1 week and 1 month after implantation with the stimulator switched on and off. We measured electrical perception and pain thresholds in increasing and decreasing steps of 0·2 mA intensity over the supraorbital nerve in the forehead with a custom-built, high-density current concentric electrode,[20] and over the sural nerve at the ankle with a standard surface electrode (Grass S88 stimulator, Grass Medical, MA, USA).

After the supraorbital stimulation, which is thought to chiefly activate trigeminal Aδ afferents, we recorded the nociception-specific blink reflex (nsBR) with surface electrodes placed over both orbicularis oculi muscles using a CED device (Cambridge Electronic Design, Cambridge, UK). The stimulus intensity for the nsBR recording was set at 1·5 times the individual pain threshold. Five rectified electromyographic responses, separated by 15–17 s intervals, were averaged offline and the area under the curve was measured (Signal software version 3.05, CED). Habituation of the nsBR was determined on five successive blocks of five responses (interblock interval 2 min) as the percentage change of the area under the curve between blocks 5 and 1. Because of the ONS stimulus artifacts, nsBR recordings were done only with the stimulator switched off.

Pressure pain thresholds were determined with a Somedic algometer over the anterior temple, anterior forearm (10 cm proximal to the wrist), and inner part of the calcaneal (achilles) tendon just above its insertion on the calcaneum. Six measures separated by 20 s intervals were averaged for each location.

Statistical analysis

Weekly and daily attack frequencies were calculated from the patients' diaries and mean intensity per attack was computed. Attack rates per person-month were calculated by counting the total number of attacks in all patients and dividing them by the summed total time in months each participant was in the study. The attack rate ratio was obtained by dividing the attack rate per person-month after ONS by the rate before ONS. We analysed

Patients	Age (years), sex	Disease duration (years)	Chronic phase duration (years)	Side	Follow-up after implantation (months)	MAF before ONS	MAF after ONS	MIA before ONS	MIA after ONS	Preventive therapy before and after ONS (daily doses)	Efficient stimulation parameters*	R/A when stimulator off	Adverse effects and clinical peculiarities
1	45, M	19	9	R	22·0	2·03	3·5	2·22	0·94	Verapamil (before and after: 600 mg)	NA	NA	Lack of efficacy after 4 months, paraesthesias felt unbearable, stimulator turned off
2	49, F	13	3	R	22·0	32·9	2·5	1·64	1	Verapamil (before: 480 mg; after: 120 mg Melatonin (before : 6 mg; after: 3 mg)	B+2–7·5 V 50 Hz 300 µs	YES	Empty battery replacement at 20 months
3	46, M	16	7	L	22·0	26·88	0	2·55	0	Verapamil (before: 720 mg; after: 600 mg) Lithium carbonate (before : 2000 mg; after: 800 mg)	0+1–2 +10·0 V 90 Hz 450 µs	YES	Persistent autonomic attacks after 1 month; transient side-shift of attacks at 7 months; empty battery replacement at 11 months; one battery switch-off by interference
4	32, M	4	4	R	22·0	8·12	0·47	2·6	3	Verapamil (before: 240 mg; after : 720 mg) Lithium carbonate (before : 800 mg; after: 0)	0+1–2+5·8 V 50 Hz 360 µs	YES	Empty battery replacement at 10 months, mild thoracic discomfort with safety belt
5	52, M	12·5	4	L	18·5	1·12	0	2·8	0	Verapamil (before : 360 mg; after: 0)	B+1–2·4 V 40 Hz 270 µs	YES	Transient side shift at 6 months; slight electrode migration at 12 months; no surgery needed–no loss of effect
6	60, M	16	5	R	4·0	7	0·21	4	2	Methysergide (before: 2 mg; after: 0) Lithium (before: 800mg; after: 0) Verapamil (after: 240 mg)	B+2– 6·0 V 100 Hz 360 µs	YES	Supportable chest tingling, empty battery replacement at 4 months
7	31, M	15	6	R	4·0	1·12	0·21	3	2	Verapamil (before: 720 mg; after: 720 mg) Lithium carbonate (before: 1000 mg; after: 200 mg)	B+3– 8·3 V 90 Hz 360 µs	YES	None
8	47, M	12	3	L	3·0	28	17	2·11	1·5	Verapamil (before: 840 mg; after 480 mg)	B+2– 6·0 V 50 Hz 270 µs	NA	Lead displacement after fall

MAF=mean attack frequency per week. MIA=mean intensity per attack. R/A=recurrence/aggravation. M=male. F=female. L=left. R=right. NA=not applicable. *Electrode plot combination, voltage, frequency, and pulse width.

Table 1: **Synopsis of clinical data**

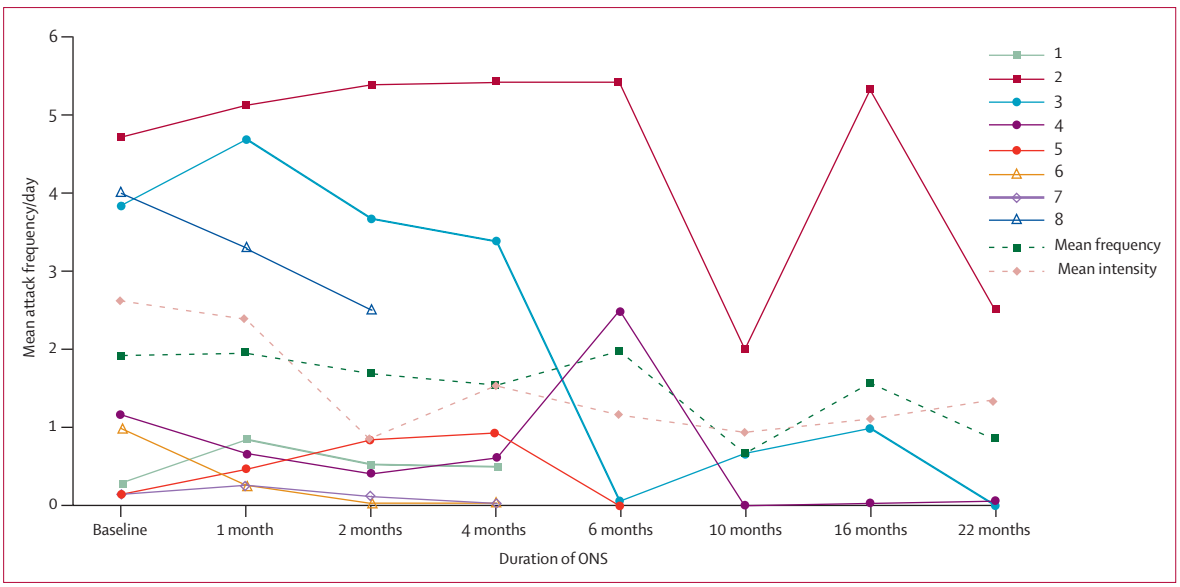

Figure: **Change of mean daily attack frequency in individual patients and in the total group of eight patients after various durations of ONS**
Filled symbols represent the first series of patients with a follow-up of 18·5–22 months. Open symbols represent the second series of three patients with a follow-up of 2–4 months. Pink dashed line represents average change in mean intensity per attack.

change in monthly attack frequency before and after ONS as well as electrophysiological and algometric data for statistical significance ($p<0·05$) using Wilcoxon's signed rank test for paired variables and the Statistica 7.1 software (StatSoft France, 2005). The analysis of electrophysical and algometric data was undertaken on measurements obtained in six patients for whom there were no missing values at any time.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In all implanted patients the disease started as episodic cluster headache before developing to the chronic form. Mean disease duration was 13·6 years (SD 3·4) and mean duration of the chronic phase was 5·1 years (SD 1·7). Three patients had left-sided and five had right-sided attacks (table 1). Mean duration of follow-up is presently 15·1 months (SD 9·5, range 3–22). Weekly frequency of cluster headache attacks before ONS was on average 13·4 (SD 11·9); after ONS it was 2·8 (SD 3·5), a reduction of 79·9%. If patient 8, who only had the implanted device for 3 months, is omitted from the analysis, the reduction in attack frequency after ONS is 93·2%.

Attack rate per person-month was 57·4 at baseline (459 attacks for a total person-time of 8 months). It dropped to 28·8 after ONS (2942 attacks for a total person-time of 102 months) producing an attack rate ratio of 0·5. On average the ONS to baseline attack ratio per month was 0·65 (SD 0·37, 95% CI 0·40–0·90); it was 0·45 (0·23, 0·28–0·62) when patient 1 in whom the neurostimulation was interrupted was excluded from the analysis. Over the total ONS period, mean monthly attack frequency was 29 (27·9, 95% CI 9·7–48), ie, an average reduction of monthly attacks compared with baseline of –28·4 (23·2, 95% CI –12·4 to –44·4; p=0·03).

Mean attack intensity before ONS was 2·62 (0·49); mean intensity of remaining attacks during ONS was 1·47 (0·85), ie, reduced by 44%. All patients used subcutaneous sumatriptan or oxygen inhalation, or both, for symptomatic attack treatment. A decrease in attack intensity occurred early after the start of the neurostimulation, in general before a clear reduction in attack frequency; it reached its maximum at 2 months of ONS (figure).

The first patient decided to switch off his stimulator 4 months after implantation because the treatment was ineffective and caused unbearable paraesthesias. When his data were treated as last values carried forward, mean attack frequency and intensity up to 22 months of ONS for the whole patient group decreased; we decided therefore to include only the values obtained during the 4 months of ONS in the final analysis.

Patient 2 had no improvement up to month 9 after which her attack frequency dropped by 57% for 5 months. Frequency returned to baseline values at month 16 when she became depressed because of family problems and developed daily analgesic consumption. At month 18, her attack frequency dropped again to 2·5 per day until her battery ran flat (figure).

Patient 3, after improving from four severe attacks per day to two mild attacks per month after 6 months of ONS,

	Before ONS	1 week post-ONS	1 month post-ONS
1st block AUC			
Pain side stimulated			
Ipsilateral response	0·49 (0·33)	0·76 (0·54)	0·84 (0·38)*
Contralateral response	0·38 (0·25)	0·47 (0·44)	0·61 (0·40)
Healthy side stimulated			
Ipsilateral response	0·49 (0·41)	0·51 (0·41)	0·91 (0·55)*
Contralateral response	0·31 (0·25)	0·44 (0·32)	0·66 (0·39)*
Average AUC of 5 blocks			
Pain side stimulated			
Ipsilateral response	0·44 (0·33)	0·67 (0·49)	0·63 (0·29)†
Contralateral response	0·35 (0·26)	0·42 (0·41)	0·49 (0·29)*
Healthy side stimulated			
Ipsilateral response	0·45 (0·25)	0·55 (0·34)*	0·80 (0·28)†
Contralateral response	0·30 (0·17)	0·48 (0·29) †	0·56 (0·21)*

Data are mean (SD). AUC=area under curve. *p<0·05. †p<0·1.

Table 2: **Area under the curve of the nociception-specific blink reflex (μVxms) before and after 1 week or 1 month of ONS**

became attack-free at 19 months. After 1 month, he had a 3 week period of isolated painless autonomic attacks and at 7 months his attacks shifted side for 1 month.

In patient 4, frequency decreased from 1·16 attack per day to 1–2 attacks per month at follow-up of 22 months. Patient 5 became totally pain free 5 months after implantation. A month later, attacks developed on the opposite (right) side, but disappeared within 72 h after a suboccipital steroid injection. He was still attack-free at 22 months.

As far as the three more recently implanted patients are concerned, patients 6 and 7 became transiently pain-free after 2 months of ONS; at 4 months they were having fewer than one attack per month. Patient 8, despite a follow-up of only 3 months, has already had his attack frequency and intensity improved by around 30%, which allowed him to decrease the daily dose of verapamil from 840 mg to 480 mg.

All the other patients who responded to ONS were able to substantially reduce their preventive drug treatment, with patient 5 being able to stop it completely (table 1). ONS had no effect on the efficacy of acute treatments such as sumatriptan injections. However, as it decreased intensity, several patients reported that with ONS they used oxygen inhalation again for the less severe attacks, which they had abandoned before ONS because of lack of effectiveness.

To verify that clinical improvement was treatment related, we switched off transiently the stimulator in all ONS responders; severe attacks recurred within 1–4 days in all of them. Moreover, patients 2, 3, 4, and 6 noticed the spontaneous disappearance of occipital paraesthesias related to the ONS. This was due to an empty battery and also followed rapidly by recurrence (patient 3) or increase in frequency or intensity of attacks (patients 2, 4, and 6). After battery replacement, all these patients recovered their previous state of improvement (table 1). Patient 3 additionally had an accidental stimulator switch off due to external interferences at 7 months, which was immediately followed by a transient aggravation of attack frequency.

In the first series of five patients we tried several different parameters during the initial 4 months after surgery because no specific recommendations were available and there was no significant effect on attack frequency (figure 1). Intuitively, the electrode combination that produced the most extensive paraesthesias in the territory of the greater occipital nerve was chosen in every patient. A bipolar setup using the battery itself as an anode and plots 1, 2, or 3 as cathodes seemed to be most effective. When battery power was lost, however, as in patients 3 and 4, the initially implanted Itrel 3 stimulator (Medtronic) was replaced by a Synergy device (Medtronic), which has a longer power duration but which cannot be used as an anode. In those patients, including most recently in patient 6, the bipolar plot combination was replaced by a tripolar one (plot 1 as cathode flanked by plots 0 and 2 as anodes). In our group of patients, mean voltage is 6·36 V (range 2·4–10), mean stimulation frequency 66 Hz (range 40–100), and mean pulse duration 364 μs (range 270–450). All patients use continuous stimulation (table 1).

There were no serious adverse effects. Immediately after surgery, all patients had some local discomfort or pain for a week or two. In some, slight neck stiffness persisted for several months. All patients, except patient 1, habituated rapidly to the stimulation-induced paraesthesias, although some turned off the stimulator during the night for a few weeks after surgery. The lead and the stimulator were explanted 12 months after surgery in patient 1 on his request. As mentioned, attacks recurred on the opposite side in two patients who were pain-free after ONS. Fortunately, these attacks disappeared after suboccipital injections of steroids and have not recurred since. Four patients needed replacement of an empty battery after an average of 11·5 months of ONS (range 4–20). A transient disappearance of paraesthesias in patient 5 was due to a slight lead displacement and was corrected by adjusting the stimulation parameters. Patient 8 had a slight electrode displacement after an accidental fall. This was followed immediately by a reduction in extent of occipital paraesthesias, which was not corrected by increasing stimulation intensity. A surgical revision of the lead location is planned if attack frequency does not improve further. Finally, the external interference that accidentally switched off the stimulator in patient 3 was attributed to magnetic fields transiently produced at his working place.

When questioned, all patients, except patient 1, felt that ONS had greatly improved their quality of life and that they would recommend it to others. At this stage, these feelings were also expressed by the more recently implanted patients.

There were no significant differences in cephalic or extracephalic pressure and electrical pain thresholds between baseline, 1 week after ONS or 1 month after

ONS, neither on the cluster side nor on the healthy side. By contrast, the area under the curve of the nsBR recorded with the stimulator off was increased after ONS (table 2). For the area under the curve of the first block of five averaged responses, the increase reached the level of statistical significance after 1 month of ONS when stimulation and recording were on the pain side (p=0·03) and when stimulation was on the healthy side and recording on the healthy (p=0·04) or pain side (p=0·03). Regarding the mean area under the curve of five blocks of five responses, the post-ONS increase was significant after 1 week for recordings on the stimulated healthy side (p=0·04) and after 1 month for recordings on the contralateral side after stimulation of the cluster side (p=0·04) or the healthy side (p=0·04). For other nsBR amplitude increases after ONS there were only statistical trends (p<0·1; table 2). Habituation of the nsBR between the first and the fifth block of averagings was normal at any time and with any stimulation-recording combination (mean 25%, range 13–40%).

Discussion

This prospective study shows that ONS could be an effective treatment for drCCH for a follow-up of up to 22 months. The findings accord with previous published case reports[15,18] and extend the potential therapeutic spectrum of ONS, which has up to now mainly been used in so-called occipital neuralgia,[21–24] and in chronic migraine.[14,15,25] Overall attack rate per person-month decreased by 50%, which may seem modest considering that it is the threshold at which medical treatments in headache are deemed to be effective. One has to take into account, however, that the patients recruited here were drug-resistant and fulfilled all criteria for intractability of headache[5] as they had no satisfactory response to an adequate regimen of at least four different classes of conventional drugs for cluster headache, including verapamil, lithium, and methysergide. All of them also received at some time in their disease course steroids at an adequate dose and for sufficient time. Despite transient partial improvement in four patients, all abandoned this treatment because of non-lasting efficacy and life-threatening side-effects with escalation of doses. Moreover, the attack-rate ratio per person-month is associated with the mean change occurring over the whole treatment period—ie, it includes the first postoperative months during which ONS has not yet reached full efficacy. When we compared pretreatment baseline with the last month of treatment, as done in most other therapeutic trials in headache, the decrease in attack frequency was 79·9%.

The efficacy of ONS in drCCH is similar to that reported for deep-brain neurostimulation (DBS) of the ventroposterior hypothalamus, despite some differences in speed of action and, possibly, robustness of remission. Although in the present study four of five patients with a long follow-up (18·5–22 months) are pain-free (n=2) or almost pain-free (≥90% reduction of attack frequency; n=3), the corresponding figures in our previous pilot study of hypothalamic DBS were three out of four effectively implanted patients.[9] For comparison, in the hitherto largest series of hypothalamic DBS in drCCH, 13 of 16 patients showed substantial improvement—ie, were pain free or almost pain free after a follow-up of up to 23 months.[7] The two patients who became attack free during hypothalamic DBS in our previous study[9] were able to completely stop their preventive drug treatment for cluster headache, which was also the case in most, although not all, of Leone and colleagues' patients.[7] In the present study, only one patient out of eight was able to stop preventive drugs after ONS.

Another difference between hypothalamic DBS and ONS in drCCH may be speed of action. Most patients who respond to hypothalamic DBS do so within days or weeks, although the optimum effect, and thus disappearance of attacks, might take several months and might need multiple adjustments of stimulation parameters.[7,9] During ONS a clear reduction of attack frequency seems to take several months. This misled us to judge the treatment to be disappointing in an abstracted preliminary report on the first five treated patients, although four of them were satisfied overall and were willing to continue the trial.[26] The more rapid effect of ONS on the intensity of cluster headache attacks shown in our study might explain this apparent discrepancy. As a matter of fact, the absence of previous experience or guidelines for the choice of ONS stimulation parameters has probably caused a delay of several months to search for the best stimulation protocol. The faster efficacy obtained in the second series of three patients, two of whom have less than one attack per month after 4 months of ONS, favours such an explanation. Patient 1, who dropped out after 4 months and has now been explanted, must be regarded as a failure of ONS, but suboptimum stimulus parameters and an initial effect on attack intensity alone (improved by 58%) might explain this failure. Lastly, like in our study of hypothalamic DBS,[9] the response to suboccipital infiltrations of steroids and local anaesthetics[12] was not predictive for the therapeutic effects, as none of the patients had long-lasting remissions, albeit short-lived improvement occurred in some of them.

Contrary to hypothalamic DBS, which produces no perceivable symptoms or signs, the paraesthesias associated with ONS preclude an adequate placebo control. Because of the rapid recurrence or aggravation of attacks in all patients with improvement when the stimulator was purposely or accidentally turned off, or when the battery ran out of power, it is likely that the clinical improvement observed here is due to the neurostimulation per se and not to the natural history of the disorder. A placebo effect cannot be excluded, but it would be expected to occur more rapidly and to be less progressive than that observed.

In ONS done for occipital neuralgia or chronic migraine various relatively moderate adverse effects have been reported, such as infection, allergy, cervical pain, or electrode migration necessitating reintervention.[21–23,25,27] In our series of eight patients, the most cumbersome side-effects were the local paraesthesias, which it took most patients a few weeks to habituate to. One patient who had no improvement from the stimulation still found them unbearable after several months of ONS. Besides some transient local neck discomfort, there was a mild lead displacement in one patient, which did not require another surgical procedure. Such a side-effect profile contrasts with the serious, though infrequent, risk of intracerebral haemorrhage due to the lead implantation for hypothalamic DBS. Although the overall risk of cerebral haemorrhage, which is most often small and non-disabling, is estimated at 1–2% for DBS, it could be higher for hypothalamic DBS; in our series of five implanted patients one had a lethal haemorrhage,[9] and in another group of 16 patients, there was one minor haemorrhage.[7]

Two other adverse events reported in our study can also be encountered during the natural history of cluster headache:[1,3] autonomic attacks without pain and side shift of otherwise typical attacks. Autonomic attacks persisted for some time in one patient despite the disappearance of all painful attacks. This finding was also reported in another drCCH patient treated with ONS.[19] Two of our patients, in whom the attacks completely disappeared on the side of the ONS, presented for the first time with attacks on the other side. Fortunately, these attacks were rapidly prevented by suboccipital infiltrations of steroids.[12] Side shift requiring bilateral electrode implantation was also reported in a patient after hypothalamic DBS.[28] The risk for the occurrence of intractable attacks on the opposite side have led some to propose ab-initio bilateral implantation of suboccipital electrodes (Goadsby PJ, University College London, UK, personal communication). There is, however, no information about the overall prevalence of side shift after neurostimulation, nor on the intractability of side-shifted attacks. Moreover, if needed—ie, in theory if the attacks on the opposite side fulfil the criteria for intractability[8]—a suboccipital lead can be implanted contralaterally in a second step.

Finally, four patients needed a replacement of their battery because of power loss, one as soon as 4 months after initial surgery, the others between 10 and 22 months. There is no doubt that this rather rapid loss of power is due to the high voltage needed to effectively stimulate the greater occipital nerve and to effectively produce paraesthesias in the innervation territory of the greater occipital nerve, which is not in anatomical contact with the electrode.

The mechanisms by which ONS can improve drCCH are not known. ONS could induce changes segmentally in the trigeminal system or suprasegmentally in centres relevant for cluster headache pathogenesis or implicated in endogenous pain control. The lack of ONS-induced changes in pain thresholds argues against a general non-specific analgesic effect. There is ample experimental evidence that C2 afferents converge in nucleus trigeminalis caudalis on second order nociceptors with dural afferents from the trigeminovascular sytem and with somatic trigeminal afferents.[17,29–31] In human beings, repetitive transcutaneous electrical stimulation is known to differentially modulate pain perception in the long term depending on the stimulation frequency used. It induces homotopic hyperalgesia at high stimulation frequencies (100 Hz), an occurrence attributed to long-term potentiation and blocked by the NMDA receptor antagonist ketamine, but decreases pain perception when low frequency stimulations (1 Hz) are used, which is thought to be associated with long-term depression.[32] Such plastic changes at the level of nucleus trigeminalis caudalis are unlikely to be relevant for the clinical effect of ONS in drCCH. First, the average ONS stimulation rate of 66 Hz would induce long-term potentiation, and thus hyperalgesia, rather than long-term depression and hypoalgesia. Second, several of our patients reported that an increase in ONS voltage during a cluster-headache attack had no beneficial effect on pain, an observation also made by patients treated with hypothalamic DBS.[7] This finding seems to be different for ONS in chronic migraine for which the headache is reported to be directly dependent on the stimulation intensity and related paraesthesias.[14] A durable increase in excitability of the interneurons in the trigeminal nucleus caudalis that mediate the nsBR could, nevertheless, be responsible for its amplitude increase after ONS. A plastic change induced by the neurostimulation might explain why, even with the stimulator switched off, the nsBR amplitude tends to augment with increasing duration of ONS and slightly more so on the pain side—ie, the stimulated side (table 2). Of note, we have reported a similar nsBR increase after 1 month of hypothalamic DBS[9] and the latter was in a PET study associated with activation of several structures of the pain processing network including the trigeminal nucleus and ganglion.[33] By contrast, an anaesthetic block of the greater occipital nerve decreases the nsBR amplitude.[34] Whether the ONS-induced increase of nsBR is due to segmental or to suprasegmental changes is unclear.

A more likely explanation for the therapeutic effect of ONS in drCCH is the induction of slow neuromodulatory changes in centres belonging to the pain matrix or playing a pathogenic role in the disorder. For instance, in a functional imaging study of ONS in chronic migraine, activity of an area in the dorsal rostral pons, known to be activated during migraine attacks, was modulated proportionally to the pain, whereas activity in the left pulvinar was correlated with ONS-induced paraesthesias.[14] Such slow plastic changes might explain why the therapeutic effect after ONS takes some time to appear, but they seem to be more rapidly reversible. Recurrence or aggravation of attack frequency occurred within a few days in our study when the stimulation was suspended.

To conclude, our study indicates that ONS could be an efficient preventive treatment in medication-resistant chronic cluster headache, a most distressing and disabling disorder. ONS is well tolerated and a safe alternative to hypothalamic DBS. With an optimum stimulation protocol, significant improvement in attack frequency takes at least 2 months, but reduction in attack intensity could appear earlier. Rapid recurrence after stimulation arrest suggests that ONS does not induce definitive long-lasting remissions. Nonetheless, slow plastic changes in central pain processing structures could be responsible for its therapeutic effects, whereas a long-term excitability increase at the level of the spinal trigeminal nucleus could explain the increased amplitude of the nociceptive blink reflex.

Contributors

JS participated in the design, recruitment, and clinical follow-up of patients. DM participated in the clinical follow-up of patients and wrote the manuscript with JS. J-MR participated in the surgical implantation of leads and stimulators. MB, DM, MA, and VDP did the electrophysiological and algometric recordings and MB and DM analysed the recordings.

Conflicts of interest

We have no conflicts of interest.

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