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ONS and DBS for the Treatment of Chronic Cluster Headache

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Abstract

Research focus: Chronic cluster headache (CCH) is a pathological entity leading to a severe degree of disability. It is characterized by pain attacks occurring daily or spaced out by remission periods of <1 month, contrarily to the episodic form. When the condition results to be refractory to conservative treatments (both prophylactic and abortive treatments) and when such condition is present for at least 2 years, surgical treatment is suggested.

Research methods: We here report our institutional experience with regard to both occipital nerve stimulation (ONS) and deep brain stimulation (DBS) for the treatment of the disease.

Results/findings of the research: 15 out of 28 (65%) patients submitted to ONS had $\geq 50\%$ reduction in 32 headache number per day and were considered responders; 12 out of 17 patients (70%) submitted to phyp DBS showed long-last improvement.

Main conclusions and recommendations: Although no valid predictive factor is available at the moment, due to the lack of prospective and randomized studies, both procedures seem to constitute safe and valid treatments for such disabling condition.

Keywords: cluster headache, occipital nerve stimulation, deep brain stimulation, hypothalamus

1. Introduction

Cluster headache (CH) is characterized by severe strictly unilateral headaches lasting 15–180 minutes, and accompanied by autonomic signs (rhinorrhea, lacrimation, and conjunctival injection). CH appears most commonly in its episodic form (pain bouts occurring from once every day to eight times a day, with pain periods lasting about 1–2 months). The chronic form of CH (CCH) is instead characterized by pain attacks which recur over >1 year without remission periods or with remission periods lasting <1 month [1]. Some patients affected from the chronic form become drug-resistant, with subsequent severe disability in activity of daily life. In the past, different ablative surgical procedures have been employed, but with overall poor results due to the high incidence of adverse events [2]. For more than a decade, deep brain stimulation of the posterior hypothalamic region (pHyp) has been employed to treat such patients at several centers, with encouraging results [3]. In the past years, however, a less invasive procedure, occipital nerve stimulation (ONS), has been effective as well [4–7]. Such procedure is now currently proposed as first-line surgical treatment, before the employment of deep brain stimulation (DBS). At present, no prospective randomized controlled trial is available for either procedure, although one such study is ongoing at present with regard to ONS [8]. It is thus not possible at the moment to draw any certain conclusion about the predictive factors which could influence the outcome in both procedures, but results available to date are encouraging. Correct selection criteria, however, appear of utmost importance to maximize results.

1.1. Occipital nerve stimulation

The rationale for the employment of electrical current applied to the great occipital nerve to treat headache relies on the evidence of convergence of trigeminal and cervical afferents on second-order neurons located on the so-called trigeminocervical complex (neural columns extending from the trigeminal nucleus caudalis to the C2 spinal segment) [9]; furthermore, steroids injected into the suboccipital region were able to improve some types of headaches, including CH [10]. Several reports suggest that ONS is an effective procedure for drug-resistant chronic CH patients [4–7]. We began to use this surgical procedure in 2004 at our Institution, proposing it before the more invasive DBS.

2. Materials and methods

Inclusion criteria for ONS at our Institution were drug-resistant CCH, that is daily or almost daily attacks in the past year and resistance to all known prophylactic drugs for such condition, including verapamil, lithium carbonate, methysergide, valproate, topiramate, gabapentin, melatonin, pizotifen, indomethacin, and others including sphenopalatine ganglion blockade [11, 12]. Long-term steroid cycles were also used in all patients at the expense of development of well-known related side effects (arterial hypertension, peptic ulcers, bone fractures, weight increase, insomnia, psychosis, glaucoma, and skin eruptions). Although we think successful

occipital nerve blockade was one of the factors which initially encouraged the use of the procedure in CH, it was not used as a selection criterion at our center (and the same applies to external ONS trial) due to the uncertainty with regard to its predictive positive effect.

Twenty-eight patients satisfied the criteria underwent ONS system implantation at our Institute from March 2004 to February 2013. They included 23 men and 5 women. The mean age at operation was 43 years, the mean duration of chronic CH was 6.6 years (range: 1–27), and the mean number of attacks per day was 5.4 (range: 2–10) (Table 1). All patients had normal neurological examination and normal cerebral MRI; psychiatric and psychological evaluations were negative in all cases. The five women included were not pregnant. All patients gave written informed consent to the procedure.

Pt. No	AGE	GENDER	DURATION OF CHRONIC CH (years)	No OF ATTACKS PER DAY	FOLLOW UP	RESPONDERS (Y/ N)	IMPROVEMENT (%)	TIME TO IMPROVEMENT (weeks)	MEDTRONIK=M; SAINT JUDE=SJ	BILATERAL STIMULATION	STEROIDS AFTER ONS	EMPTY BATTERY	ADVERSE EVENTS
1	56	M	4	4	NA	NA	NA	NA	M	N	NA	NA	-
2	69	M	4	2	NA	NA	NA	NA	M	N	NA	NA	-
3	24	M	1	4	NA	NA	NA	NA	M	N	NA	NA	-
4	27	M	3	6	NA	NA	NA	NA	M	N	NA	NA	-
5	45	F	5	5	NA	NA	NA	NA	M	N	NA	NA	-
6	56	M	3	5	8,6	N	NO	-	M	N	Y	N*	-
7	44	M	9	4	8,0	Y	EPISODIC CH SPORADIC	12	M	Y	N	Yes (1)	electrode migration
8	53	M	18	3	9,4	Y	HEADACHES SPORADIC	14	M	Y	N	Yes (1)	-
9	53	M	3	4	7,8	Y	HEADACHES	18	M	Y	N	Yes (1)	wire decubitus
10	37	F	5	6	8,3	Y	EPISODIC CH	9	M	Y	N	Yes (2)	-
11	43	M	5	6	8,1	N	NO	-	M	Y	Y	Yes (1)	electrode migration
12	33	M	7	3	10,3	N	NO	-	M	N	Y	Yes (2)	-
13	33	M	10	4	7,1	Y	SPORADIC HEADACHES	32	M	Y	N	Yes (1)	-
14	31	M	11	3	7,0	Y	SPORADIC HEADACHES	12	M→SJ	Y	N	Yes (2)	electrode migration
15	53	M	11	7	6,9	N	NO	-	M	Y	Y	N*	-
16	48	M	3	8	6,6	Y	SPORADIC HEADACHES	2	M→SJ	Y	Y	Yes (2)	wire decubitus
17	38	M	2	8	6,5	N	NO	-	M	Y	Y	Yes (1)	-
18	33	F	3	8	6,4	Y	SPORADIC HEADACHES	9	M	Y	N	Yes (2)	-
19	35	M	4	4	6,1	N	NO	-	M	Y	Y	Yes (1)	-
20	33	M	4	10	5,7	N	NO	-	M	Y	N	N	electrode migration
21	49	M	10	6	5,5	Y	SPORADIC HEADACHES	8	M	Y	N	N	-
22	54	M	27	6	4,5	Y	SPORADIC HEADACHES	1	M	Y	N	N	-
23	30	M	4	7	5,1	Y	EPISODIC CH	37	M	Y	N	Yes (1)	electrode migration
24	53	M	2	7	5,1	Y	SPORADIC HEADACHES	3	M	N	N	N	-
25	29	M	10	8	4,5	N	NO	-	M	Y	Y	N	electrode migration
26	44	M	10	4	3,0	Y	SPORADIC HEADACHES	9	SJ	N	N	Yes (2)	-
27	53	M	5	6	3,0	Y	SPORADIC HEADACHES	21	SJ	Y	N	Yes (2)	electrode plus wire malfunctioning
28	50	M	3	3	2,8	Y	HEADACHES	60	SJ	Y	N	Yes (1)	-
43			6,6	5,4	5,2			6,7					

Table 1. Clinical and outcome features in ONS patients

The first five implanted patients received ONS for less than 6 months with poor results, so we decided to offer them hypothalamic stimulation; at that time, it was shown that in neurovascular headaches ONS was only effective at short-term follow-up [13]. These five patients are not considered in the analysis.

3. Surgery

The ONS surgical procedure varies from center to center. We here describe the procedure employed at our Institution, taking into account the validity and safety of other methodologies. Ours has also been described in a previous report [14]. The patient is placed in a prone position, and the Mayfield head holder system is used to fix the head. Bony prominences must be padded to prevent postoperative lesions of nondependent skin and nerves. The head is positioned in line with the neck and posterior thoracic region and chest to avoid skin creases and curvatures, which could be cumbersome and lengthen the procedure. The Mayfield head holder is positioned in the parietal region bilaterally so as not to interfere with the leads' positioning. We always perform bilateral ONS to anticipate eventual side shift of symptomatology. Quadripolar bilateral electrodes or one longer octopolar electrode is employed. A vertical skin incision is made in the posterior cervical region in the midline from 1 cm above to 1 cm below the external occipital protuberance (EOP). The greater occipital nerve (GON) is usually present about 4 cm lateral to the midline turning in a slight mediolateral direction before dividing into a medial and a lateral branch about 1 cm above the EOP (**Figure 1**). Two symmetric vertical incisions are then made 7 cm lateral to the EOP bilaterally. The cervical fascia located superficial to the trapezius and splenius capitis muscles is exposed after blunt dissection of subcutaneous tissue in the region.



Figure 1. Preoperative GON localization.

A Tuohy needle is then inserted from each lateral incision to the midline incision, allowing the insertion of the electrode after the removal of the stylet. The wires connected to the electrodes are then tunneled together in a caudal direction along the occipital and neck midline until about the middle dorsal level.

We do not use anchorage devices but in the cervical region we fix both electrodes to the underlying fascia with nonresorbable stitches to prevent their caudal dislodgement; and relief loops are made at both this site and at more subcutaneous caudal sites during tunneling passages to prevent excessive discomfort to the patient, and possible leads' fracture. For the same purpose (avoid excessive strain on the system), we use 95 cm length connection wires. We create a little subcutaneous pocket at the level of the connectors (whenever present) between main leads and connection cables to avoid possible skin erosions underlying them. Another incision is made in the midline at the lumbar level and, at this point, the two connection cables diverge on each side to the site of the subcutaneous pockets where internal pulse generators (IPGs) will be located.

One or two IPGs (Solettra, Medtronic, Libra, St Jude, Activa PC, Medtronic, Libra xp, St Jude) can be used. Of course, we leave the connection cables and the IPGs in site, when it becomes necessary to convert ONS into hypothalamic deep brain stimulation. Subcutaneous pockets for IPGs are made approximately 4 cm above the iliac crest at the level of the external oblique muscle, paying attention not to jeopardize the latter muscle and not to cause excessive bleeding and postoperative pain.

In the postoperative period, all patients underwent plain cranial radiographies to verify the adequate leads' positioning, and IPGs were switched on, progressively increasing voltage or current intensity until adequate paresthesia coverage was reached in the somatic GON territory.

4. Results

Following implant, we turned on IPGs after a median of 3.3 days (range: 0–14 days) because of the lack of attacks in such postoperative period. Stimulation was started once attacks reappeared and improvement occurred after a median of 6.7 weeks (range: 1–37 weeks; **Table 1**).

All patients perceived paresthesias in somatic areas innervated by the occipital nerve. Stimulation parameters were set according to the patient's tolerability. When induced perceived paresthesia became unbearable for the patient at some time after activation the amplitude was reduced accordingly. No specific stimulation pattern was found to be predictive of long-term efficacy; in fact, many stimulation adjustments were necessary to achieve optimal results.

After a median follow-up of 5.2 years (range: 2.8–10), 15 (65%) patients had $\geq 50\%$ reduction in headache number per day (responders). Eleven (47%) responders have a stable condition with only sporadic attacks; in three other patients, chronic CH turned into episodic CH; the remaining responder had a 60% reduction in headache number per day (**Table 1**).

Eight (34.7%) patients were nonresponders. Five of these showed a $\geq 50\%$ reduction in headache number per day in the first months after implant: in four patients the initial improvement lasted up to 12 months after ONS; in the remaining patient such improvement lasted 48 months.

After ONS 15 (65%) patients stopped steroidal treatment while the remaining eight received short-term steroid courses. All patients needed to maintain prophylactic treatment for CH.

5. Discussion

As stated above, at long follow-up examinations, our results show that ONS is able to produce long-lasting improvement in a large number of patients (65%); more importantly, in 47% of patients a stable condition with sporadic attacks is reported.

It is well known that a placebo effect cannot be excluded in CH patients [15], and it is not possible to rule out that the improvement observed is part of the natural course of the disease; furthermore, for long-term observational purposes, blinding in such cases is not possible because paresthesias are necessary to achieve positive results. Anyway, two elements point to a real effectiveness of ONS: the long-term follow-up of the present series (and of other series reported in literature) and the relapse of symptoms at battery's exhaustion.

Several studies report different long-term outcomes. In the study of Magis et al. [5] of 2011, responders' rate was as high as 78.6% (11 of 14 patients) after a mean follow-up of 36.8 months. The same author recently published a very long term follow-up extension of such study including 10 patients [7]; of these, four (40%) evolved to an episodic form and six (60%) remained chronic but with a reduction of about 70%. Fontaine et al. [6] reported a responders' rate of 76.9% (11 of 13 patients) after a mean follow-up of 14.6 months and Muller et al. [4] reported a responders' rate of 90% (9 of 10 patients) after a mean follow-up of 12 months. A lower percentage of responders, 35.7% (5 of 14 patients), after a median follow-up of 17.5 months has been reported in another study [16]. Such differences in outcome could most probably reflect differences in follow-up lengths (given the substantial standardization of the procedure). Note that in our study five patients became resistant after several months of improvement; one patient became resistant to ONS after a 4-year improvement. Our experience thus witnesses the possibility of developing tolerance to ONS, but unfortunately we did not find any significant factor which could be considered a reliable predictor of tolerance or unresponsiveness.

All the patients considered responders in our series could stop steroid therapy and only one third of them needed steroids for short periods. It is worth noticing that the daily Sumatriptan injection consumption was markedly reduced after ONS. It is well known that the prolonged use of these drugs can lead to life-threatening side effects, and in fact this is actually considered among selection criteria for ONS in drug-resistant chronic CH patients.

Empty batteries were the most common AE (adverse event) (and it is in the existent literature). This is due to the high voltage or current intensity necessary to obtain satisfactory results; anyway, in long-term responders, we have begun to implant rechargeable IPGs in such patients.

The exact mechanisms underlying the beneficial effects of ONS in drCCH patients are still under investigation; the co-presence of trigeminal and cervical somatic input to second-order

neurons located in the so-called trigeminocervical complex, extending from the trigeminal nucleus caudalis to the C2 cervical nuclear complex, could explain the role of modulating the myelomere C2 in the beneficial effect of ONS [17]; Magis et al. [18] in 2011 investigated the FDG-PET modifications in 10 patients submitted to ONS after a minimum of 6-month follow-up. In CCH patients at baseline (compared to healthy subjects), hypermetabolism was noticed in the ipsilateral hypothalamus, midbrain, and ipsilateral lower pons. In all patients, this picture normalized after ONS, and the hypothalamus was the only exception. It was also noticed that the metabolism of perigenual anterior cingulate cortex (PACC) was hyperactive in ONS responders compared to nonresponders. The authors thus hypothesized the pure symptomatic role of ONS in CCH patients (given the lack of changes in the hypothalamus), a slow neuromodulatory role of ONS on the “pain neuromatrix” (also involving the pACC), and, as such, a specific analgesic effect acting at central dysfunctional pain control centers.

6. pHyp DBS

Two main original observations initially led to the identification of the posterior hypothalamus as having a pivotal role in the genesis of cluster headache: its activation, as revealed in brain PET studies, during CH attacks [19], and the evidence of an increased neuronal density at this site measured with voxel-based MRI morphometry [20]. Furthermore, CH attacks often recur following a certain circadian rhythm and cluster periods occur circannually. So, it was initially hypothesized that hypothalamic “biologic clocks” may be involved in the pathogenesis of CH [21]. The aim of the stereotactic procedure (pHyp DBS) performed at our Institute was thus to inhibit the posterior hypothalamic neuronal pools, thought to be responsible (when hyperactive) for the disease. Several institutional experiences have been reported since our initial observations, and overall results are encouraging. To date, pHyp DBS is offered to patients not responding to ONS, since the first obviously constitutes a more risky and invasive surgical procedure.

7. Materials and methods

Selection criteria for pHyp DBS are quite uniform among all centers employing such technique; at our Institution, we use the following criteria: (1) the presence of diagnostic criteria for CCH according to the International Headache Society [1]; (2) inadequate relief from prophylactic therapy, including verapamil, lithium, sodium valproate, methysergide, topiramate, gabapentin, nonsteroidal anti-inflammatory drugs such as indomethacin, and corticosteroids; (3) CCH lasting at least 2 years; (4) unsatisfactory relief from abortive therapy, including oxygen, Sumatriptan, and opioids; and (5) failure of occipital nerve stimulation therapy for at least 1 year.

At our Institution, 19 patients satisfying such criteria (15 men; mean age at surgery: 42 years; mean duration of CCH: 3 years) underwent pHyp DBS. Psychiatric and neuropsychological

examinations were normal in all of them. All patients gave written informed consent for the procedure.

8. Surgery

Brain MRI images, obtained preoperatively, were transferred to the operating room workstation (StealthStation; Medtronic Sofamor Danek, Memphis, TN). After positioning of the stereotactic frame around the patient's head, computed tomographic (CT) scans were taken. MRI and CT images were then merged using the Framelink 4.0 software (Medtronic). From the resulting three-dimensional reconstruction, the exact position of the anterior commissure-posterior commissure line and the coordinates of the target were derived. pHyp region's coordinates were 3 mm behind the midcommissural point (Y), 5 mm below the midcommissural point (Z), and 2 mm lateral to the midline. A 7 mm hand-driven burr hole is then made at 3 cm lateral to the scalp midline and about 2 cm anterior to the coronal suture; after coagulation of the dura mater a rigid cannula is inserted to within 10 mm of the target; the quadripolar electrode was then inserted to the target. We usually perform intraoperative stimulation (beginning at 60 μ s, 180 Hz, up to 7 V) to verify tolerability and side effects. Amplitudes above 4 V usually produced ipsilateral eye version with consequent diplopia. Throughout the procedure, pupils, heart rate, blood pressure, electroencephalogram, body temperature, and respiratory function were monitored. Cerebral CT was performed immediately after implant; MRI was performed within 48 hours after surgery and merged with postoperative CT scan to accurately verify the position of electrode's contacts (**Figures 2 and 3**). Postoperatively, patients were left without active stimulation till insurgence of CH attacks; they were not provided prophylactic medication in the meantime.

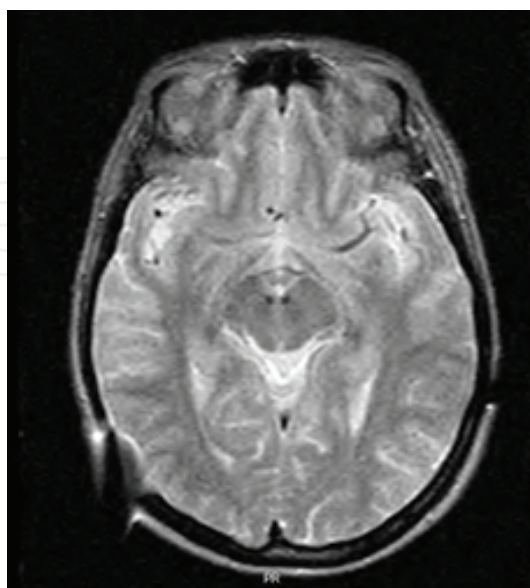


Figure 2. Postoperative MRI showing bilateral pHyp electrodes' tips localization in a CCH patient.

Hospitalization lasted about 10–20 days in order to allow for monitoring of CH attacks, blood pressure, heart rate and function, temperature, sleep-wake cycle, body weight, electrolyte balance, and hormone levels. These variables were checked at regular intervals after discharge.

Patients also kept a diary reporting headache attacks, drug use, and adverse events. Parameters' settings (in particular amplitude and current intensity) were then programmed taking into account the minimum level providing efficacy or the maximum level tolerated.

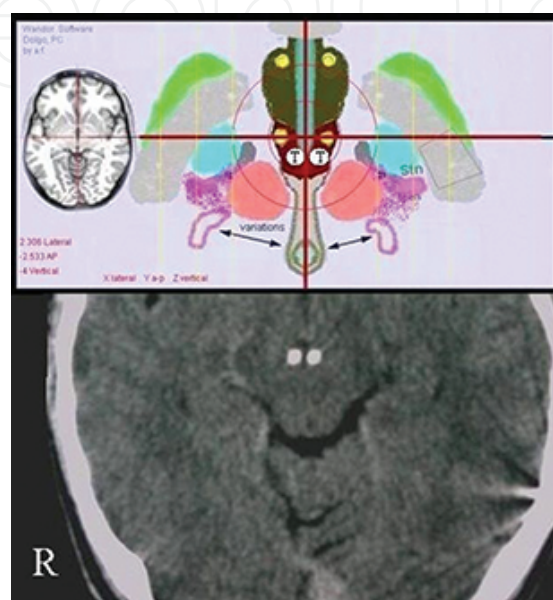


Figure 3. Upper: our institutional localization system applied to posterior hypothalamic region. Lower: Postoperative MRI-CT merged image showing the localization of bilateral posterior hypothalamic electrodes.

9. Results

Outcomes relating to our series and related details can be more systematically found by Leone [21] (**Table 2**). Briefly, the median follow-up was 8.7 years; one of our patients died of septic shock caused by *Legionella* infection. He was, however, free of CH bouts. Due to the infection, the entire DBS system was removed from another patient. In the remaining 17 patients, 6 (35%) subsequently had fewer than one attack every 3 months; in 5 of them, the IPG had been off (unactivated) for a median of 3 years, after a median of 6.4 years of active stimulation with continuous improvement. Another 6 patients (35%) did not experience daily attacks, instead suffering from attacks lasting from 2 to 5 months, followed by remission lasting from 5 to 10 months.

Five of 17 patients (30%) were not responders despite experiencing daily CH attacks after an initial improvement period. After DBS implantation, patients remained unstimulated for a median of two days (range: 0–12 days), given the lack of pain bouts in this period. Stimulation was initiated once pain attacks reappeared; improvement occurred 2–16 weeks later. As for ONS, several parameter adjustments were necessary to optimize clinical results.

Patient no./side	Age at operation (y)	Sex	Chronic for (y) a	Follow-up (y)	Headache response: current and (headache status in 2006)	Current stimulation status	Time to response after stimulation (d)	Prophylaxis	Amplitude (V)	Adverse events
1 L	39	M	4	12	Recurrence in periods (painfree)	off	30	Verapamil		
1 R	40			11	Recurrence in periods (painfree)	on	1		1.6	Right: electrode displaced; electrode replaced. Pulse generator infection; replaced
2 L	50	M	4	11	Almost painfree (pain-free)	off	72	Methysergide		
3 L	63	F	7	11	Almost painfree (pain-free)	Off	32	Verapamil		
4 R	52	M	5	10	Recurrence in periods (1 attack every 2 d)	on	42	Methysergide plus Verapamil	2.6	Electrode mal-positioned; repositioned
5 L	30	M	2	10	Almost painfree (pain-free)	off	22	None		
6 L	45	M	2	NA	NA (pain-free)	NA	43	None		
7 L	27	F	1	9	Tolerance on both sides (sporadic attacks)	OFF	38	Verapamil		Reduced right arm strength. Electrode (right) displacement after trauma; infection after electrode replacement. One seizure 24 h after replacement
7 R				9			32			
8 R	25	M	1	9	Almost painfree (pain-free)	OFF	44	None		
9 R	47	M	3	8	Recurrence in periods	ON	23	Lithium	2.0	

					(painfree)					
10 L	43	M	10	8	Almost painfree (1 mild attack per day)	ON	56	Verapamil	2.6	Subtle transient asymptomatic hemorrhage in third ventricle
11 R	49	M	1	8	Recurrence in periods (sporadic attacks)	ON	37	Verapamil	2.6	
12 L	36	M	3	8	Recurrence in periods (painfree)	ON	62	Topiramate plus lamotrigine	4.5	
13 L	24	M	1	8	Tolerance on both sides (Sporadic attacks)	OFF	40	Verapamil		
13 R	26			7						
14 R	50	M	1	8	Tolerance (painfree)	ON	48	Lamotrigine plus prednisolone	4.6	
15 R	57	M	4	8	Almost painfree (pain-free)	OFF	86	None		
16 L	70	M	4	7	No (improvement (1 attack per day)	OFF	b	Ergotamine		
17	39	F	2	NA	NA	removed	NA	None	NA	Electrode infection and transient hemiparesis; electrode removed
18 L	28	M	3	6	30–40% reduction in headache frequency and intensity on both sides	on	95	Verapamil plus amitriptyline	1.0	
18 R						on			3.5	Electrode infection (right) and transient hemiparesis
19 L	45	F	5	6	Recurrence	on	72	Verapamil	2.7	

					e in periods					
Mean	42		3	8.7			47		2.8	

Table 2. Clinical and outcome features in DBS patients.

10. Discussion

Our experience has shown that hypothalamic stimulation produces long-lasting improvement in a high proportion of patients (70%). Stimulation seems to be tolerated for years after implantation. It is worth noticing that in some patients, after several years of stimulation, a persistent, almost pain-free, condition could be maintained in off stimulation conditions. Bilateral chronic CH seems to predict poor response to hypothalamic stimulation. After a median of almost 9 years (range: 6–12 years), 70% of our patients were improved: six patients (35%) were in a persistent almost pain-free state, and in six patients (35%), CCH condition turned into episodic CH. In most patients, prophylactic drugs were required to maintain improvement, whereas they were ineffective before surgery. High-dose steroids led to some relief, although accompanied by adverse effects. The 12 improved patients discontinued steroid therapy. When the stimulator was switched off (condition blinded to the patient), the crises returned and the same thing occurred when the stimulator batteries ran down. After IPGs replacement, these patients improved again. Worsening of attacks also occurred after electrode displacement in two patients. Taking into account these findings, a placebo effect seems unlikely. So far, over 50 chronic drug-resistant CH patients are documented to have received hypothalamic stimulation; marked improvements have occurred in 50–100% of cases (with a median follow-up of 15.8 months) (range: 12–33 months) [22–25].

It is noteworthy that in five of six of our persistently almost pain-free patients, this state is now maintained even though the stimulator has been off for several years. It should thus be proposed that after a long period of stimulation (median 6.4 years), in long-term responsive patients turning off stimulation should be tried. In five cases, headache frequency did not worsen. Such patients could tolerate a low-frequency attack (which was much better than the previous situation of intractable attacks several times daily), which also responded promptly to Sumatriptan injection.

This was not the case in the early years after implantation, when in all cases attacks reappeared when the stimulator was turned off. In six patients, the condition reverted to episodic CH but the patient needed to continue stimulation. The outcomes in these two subgroups suggest that years of continuous hypothalamic stimulation can change the course of the illness. Five of our patients (30%) were not responders. Patients without response to hypothalamic stimulation have been reported by other authors [22–25], but no reliable predictive factor is available so far. Four (80%) of our unsuccessful cases had bilateral CH, and three developed tolerance to hypothalamic stimulation after 1–2 years of improvement.

These observations suggest that bilateral CH predicts poor response to hypothalamic stimulation. As far as coordinates are concerned, Seijo et al. [26] modified them to avoid the lateral ventricle wall, also extending the stimulated brain area to the lateral hypothalamus implicated in pain modulation. The good results in this small series are encouraging, but longer follow-up is required. Our experience is that small changes in contacts and electrode position do not have influence on therapeutic response.

11. Conclusions

ONS and pHyp DBS should be proposed to drug-refractory CCH patients according to the above-mentioned criteria; a randomized trial is actually ongoing to determine the effectiveness of ONS in such patients [8], but, to date, no prospective and randomized trial is available for both procedures to determine eventual positive or negative predictive factors in the outcome of the disease; thus, our observations could be still considered useful until new findings will come.

The role of a pure symptomatic role of ONS seems to be a likely observation, whereas long-term effectiveness of pHyp DBS, especially considering patients with positive results despite off-stimulation condition, suggests a possible role in plastic neuronal changes induced by such procedure. Prospective and randomized studies are, of course, necessary, to date, to clarify the issue of nonresponder patients, thus refining the selection criteria and improving outcome in more carefully selected drug-resistant CCH patients.

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