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Research Submissions

Sustained Effectiveness of Occipital Nerve Stimulation in Drug-Resistant Chronic Cluster Headache

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Background.—Drug-resistant chronic cluster headache (drCCH) is a devastating condition for which various invasive therapeutic procedures have been tempted without any satisfactory effect. Recent studies suggest that occipital nerve stimulation (ONS) could be an efficient preventive treatment of drCCH.

Objective.—We conducted a prospective pilot trial of ONS in 8 subjects suffering from drCCH with encouraging results at 15 months. However, studies on a larger population with a longest follow-up were warranted.

Methods.—We recruited 15 patients with drCCH according to the previously published criteria of intractability. They were implanted with suboccipital stimulators on the side of their headache. Long-term follow-up was achieved by questionnaires administered during a headache consultation and/or by phone interviews.

Results.—Mean follow-up time post surgery is 36.82 months (range 11-64 months). One patient had an immediate post-operative infection of the material. Among the 14 remaining patients, 11 (ie, ~80%) have at least a 90% improvement with 60% becoming pain-free for prolonged periods. Two patients did not respond or described mild improvement. Intensity of residual attacks is not modified by ONS. Four patients (29%) were able to reduce their prophylaxis. The major technical problems were battery depletion due to the use of high current intensities (N = 9/14, 64%) and immediate or delayed material infection (N = 3/15, 20%). Significant electrode migration was only seen in 1 patient. Clinical peculiarities during the ONS follow-up period were side shift with infrequent contralateral attacks (N = 5/14, 36%), and/or isolated ipsilateral autonomic attacks without pain (N = 5/14, 36%). Two patients found ONS-related paresthesias unbearable: one had his stimulator removed, and the other switched it off although he was objectively ameliorated. Subjectively, 9 patients are very satisfied by ONS and 3 patients moderately satisfied. Effective stimulation parameters varied between patients.

Conclusions.—Our long-term follow-up confirms the efficacy of ONS in drCCH, which remains a safe and well-tolerated technique. The occurrence of contralateral attacks and isolated autonomic attacks in nearly 50% of ONS responders may have therapeutic and pathophysiological implications.

Key words: occipital nerve stimulation, drug-resistant, chronic cluster headache, neuromodulation

Abbreviations: drCCH drug-resistant chronic cluster headache, hDBS hypothalamic deep brain stimulation, MAF mean attack frequency, ONS occipital nerve stimulation

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INTRODUCTION

Cluster headache is considered as one of the most painful primary headaches. Approximately 10% of cluster headache are chronic (CCH[1]) producing recurrent attacks without remission periods exceeding 1 month. A small percentage of CCH become drug-resistant (drCCH), that is, become refractory to all available preventive pharmacotherapies.[2] Various novel invasive non-pharmacological procedures have been attempted in such patients over the last decade. Among them, deep brain stimulation of the ventroposterior hypothalamus (hDBS) gave the most encouraging results with an average improvement of 50% to 70% in attack frequency (see Magis and Schoenen[3] for review). However, hDBS is not a benign procedure, and in our series of 6 patients 1 patient died of an intracerebral hemorrhage along the electrode track.[4] Less risky methods were therefore proposed among which occipital nerve stimulation (ONS) seems to be the most promising one. As in other headache disorders, the main rationale for ONS in CCH is the anatomo-functional convergence of cervical (C2), somatic trigeminal and dural trigeminovascular afferents on second-order nociceptors in the trigeminocervical complex.[5]

In a previous prospective pilot study, we evaluated the therapeutic effect of ONS in 8 drCCH patients.[6] We found encouraging results after an average follow-up of 15 months, as 2 patients were pain-free, 3 patients had ±90% attack reduction, and another 2 patients had ±40% decrease in attack frequency. Similar results were simultaneously published by Burns et al in a series of 8 patients with a comparable follow-up duration.[7]

We have presently implanted and prospectively followed 15 drCCH patients, including the 8 patients cited before, and are to report our long-term evaluation over an up to 5 years follow-up.

METHODS

Patients.—Main patient characteristics are summarized in Table 1. We recruited 15 patients with side-locked drCCH attacks (1 female, mean age 47.6 ± 11.5 years). All patients fulfilled the previously published criteria of intractability.[2] Other criteria of eligibility were duration of the chronic phase of at least 2 years and absence of disabling organic or psychiatric disorder. Mean duration of the chronic phase at implantation was 7.07 ± 4.23 years (range 2-29 years). Eight patients had right- and 7 patients left-sided attacks. In 6 patients cluster headache was chronic from start on, while the other patients evolved from the episodic to the chronic form with time.

Patients were recruited in 2 waves between 2005 and 2009 and gave written informed consent. The study was approved by the local Ethics Committee of the Faculty of Medicine at Liège University.

Procedure.—The neurostimulator implantation was performed by the neurosurgeon (J. M. R.) in 2 steps. A paddle-style stimulating lead with 4 distal electrodes (Medtronic 3587A Resume II; Medtronic, Minneapolis, MN, USA) was first implanted subcutaneously on the side of the cluster headache according to the method described by Oh et al,[8] under general anesthesia (see Magis et al[6] for details). Hence, the neurosurgeon relied on anatomical landmarks but could not test the production of paresthesias peroperatively. After surgery, the lead was connected to an external battery which was switched on as soon as a typical cluster headache attack occurred. Three to 7 days later, an internal battery was implanted in the prepectoral region under brief general anesthesia (Medtronic 7425 Itrel 3; Medtronic). When the battery turned flat, it was replaced by a longer-lasting Medtronic Synergy stimulator, or by a rechargeable Medtronic Restore stimulator in patients using high current voltage for efficacy.

The stimulation parameters were adjusted to produce ascending paresthesias in the innervations' territory of the greater occipital nerve. The aim was to obtain the greatest possible spreading of paresthesias toward the parietal and frontal regions. In the second group of patients, we first chose the parameters which had been the most effective in the initial series of 5 patients, where after the stimulation parameters were adapted using a programming matrix (successive change of plot combination, stimulation voltage, frequency and pulse width) in case of poor efficacy. Each patient was allowed to switch on and off the stimulator, and to change the voltage with a remote control.

Table 1.—Clinical Characteristics of ONS-Treated Patients Including Treatment Outcome, Concomitant Drug Treatment, and Complications

Patients	Age (Years)	CH Side and Pattern	CCH Duration (Years)	Follow-Up Since Implantation (Months)	Attacks/Day Before ONS (Mean)	Attacks/Day at Last Follow-Up (Mean)	% Change in Attack Frequency After ONS	Intensity Before ONS (Mean/Attack)	Intensity at Last Follow-Up (Mean/Attack)	% Intensity Change in Residual Attacks
1	50	Right (e→c)	9	64	0.29	0.5	+72.4	2.2	0.9	–59
2	53	Right (e→c)	3	60	4.7	0.43	–90.8	1.6	3	+47
3	51	Left (e→c)	7	59	3.84	0	–100	2.6	NA	NA
4	37	Right (e→c)	4	53	1.16	0.1	–91.4	2.6	3.5	+36
5	57	Left (e→c)	4	38	0.16	0	–100	2.8	NA	NA
6	34	Right (c)	6	41	0.16	0	–100	3.0	NA	NA
7	63	Right (e→c)	5	40	1.00	0	–100	4.0	NA	NA
8	51	Left (e→c)	3	39.5	4.00	0	–100 (recent relapse)	2.1	1.5	–29
9	53	Right (c)	29	35	1.5	0.16	–89.3	2.6	3	+13
10	33	Left (e→c)	5	25	2.00	0	–100	4.0	NA	NA
11	46	Left (c)	2	21	0.57	0.5	–12.3	3.4	3.6	+6
12	34	Right (e→c)	8	NA	NA	NA	NA	NA	NA	NA
13	67	Right (c)	5	15	3.5	0	–100	4	NA	NA
14	55	Left (c)	2	14	5.5	0	–100	3.5	NA	NA
15	30	Left (c)	14	11	3.00	0	–100	3	NA	NA
Mean	**47.60**	—	**7.07**	**36.62**	**2.50**	**0.12**	**–94.6**	**3.60**	**3.00**	**+2.3**
SEM	9.55	—	4.23	15.18	1.00	0.16	—	0.48	0.00	—
Range	30-67	—	2-29	11-64	—	—	—	—	—	—

Patients	Preventive Therapy at Time of Implantation	Preventive Therapy at End of Follow-Up	Side Change After ONS	Non-Painful Autonomic Attacks After ONS	Relapse When Stimulator Off (+ Latency)	Subjective Satisfaction Level	Patient Would Recommend ONS to Others	Self-Reported Adverse Effects	Technical Problems	Comments
1	Verapamil 600 mg	Verapamil 600 mg	No	No	NA	0	No	Unbearable paresthesias	—	Explanted after 4 months' ONS
2	Verapamil 480 mg Melatonine 6 mg	Melatonine 3 mg	Yes (1 bout)	No	Yes (4 days)	2	Yes	Dysesthesias in the ear	Empty battery: ×3	—
3	Lithium carbonate 1200 mg Verapamil 720 mg	Lithium carbonate 200 mg Verapamil 240 mg	Yes (isolated attacks)	Yes	Yes (7 days)	2	Yes	None	Empty battery: ×4 Electrode migration: ×1	—
4	Verapamil 240 mg Lithium carbonate 800 mg	Verapamil 600 mg	No	No	No	2	No	Battery discomfort++	Empty battery: ×2	Improvement stable since 44 months' ONS Asked for explantation at month 49. State remains unchanged
5	(Methylprednisolone 4 mg for eczema) Verapamil 360 mg	(Methylprednisolone 4 mg for eczema) Verapamil 360 mg	Yes (1 bout)	Yes	Yes (hours)	2	Yes	None before infection	Delayed infection: explanted	—

Table 1.—*Continued*

Patients	Preventive Therapy at Time of Implantation	Preventive Therapy at End of Follow-Up	Side Change After ONS	Non-Painful Autonomic Attacks After ONS	Relapse When Stimulator Off (+ Latency)	Subjective Satisfaction Level	Patient Would Recommend ONS to Others	Self-Reported Adverse Effects	Technical Problems	Comments
6	Verapamil 240 mg Lithium carbonate 800 mg	Verapamil 720 mg Topiramate 50 mg Lithium carbonate 800 mg	No	No	No	2	Yes	Connecting wire discomfort; muscle contraction	None	Stimulator off after 37 months' ONS. No recurrence at 41 months
7	Methysergide 2 mg Lithium carbonate 800 mg	Verapamil 120 mg Lithium carbonate 800 mg	No	No	Yes (days)	1	Yes	Battery discomfort	Empty battery: ×3	Temporary recurrence when lithium dosage was decreased
8	Verapamil 240 mg Methylprednisolone 8 mg	None	Yes (1 isolated attack)	Yes	Never tried	1	Yes	Connecting wire discomfort	Empty battery: ×1	Recurrence 2 weeks before phone interview after total remission; battery OK
9	Verapamil 600 mg Lithium carbonate 1000 mg Methysergide 4 mg	Verapamil 600 mg Methysergide 8 mg	Yes (isolated attacks)	No	No	0	No	Unbearable paresthesias; connecting wire discomfort	None	Improvement stable after switching off stimulator at 3 months' ONS; considers stimulator explantation
10	Verapamil 360 mg	Verapamil 480 mg	No	Yes	Yes (1 day)	2	Yes	None	Empty battery: ×1	—
11	Verapamil 720 mg Lithium carbonate 2400 mg Gabapentine 900 mg Escitalopram 15 mg	Bupropion 150 mg Verapamil 480 mg Lithium carbonate 1200 mg Gabapentin 1200 mg Indometacine 75 mg Clomipramine 75 mg Duloxetine 60 mg	No	No	Yes (days)	2	No	None before infection	Delayed device infection: explanted	Patient also had ipsilateral neuropathic trigeminal pain
12	Methylprednisolone 8 mg	Methylprednisolone 8 mg	NA	NA	NA	NA	NA	NA	Immediate device infection: explanted	—
13	Verapamil 160 mg Lithium carbonate 750 mg	Verapamil 240 mg Lithium carbonate 750 mg Celecoxib 200 mg per 2 days Duloxetine 60 mg	No	No	Yes (days)	2	Yes	Diffuse headache on tilting his head	Empty battery: ×1	—
14	Methylprednisolone 16 mg Methysergide 2 mg Clomipramine 75 mg	Verapamil 360 mg Clomipramine 75 mg Lithium carbonate 1200 mg Melatonine 5 mg	No	Yes	No	2	Yes	None	Empty battery: ×1	—
15	Methysergide 4 mg Topiramate 100 mg Verapamil 720 mg	Verapamil 720 mg Gabapentin 1200 mg Lithium carbonate 800 mg	No	No	Yes (days)	1	Yes	None	Empty battery: ×1	Externalization of second stimulator needing reintervention
Mean	—	—	—	—	—	—	—	—	—	—
SEM	—	—	—	—	—	—	—	—	—	—
Range	—	—	—	—	—	—	—	—	—	—

e→c: evolved from an episodic to a chronic pattern; c: chronic since first attack.
Satisfaction level: 0 = none; 1 = moderate; 2 = high.
CH = cluster headache; CCH = chronic cluster headache; NA = not applicable; ONS = occipital nerve stimulation; SEM = standard error of the mean; — = not available.

Follow-Up.—Patients had to fill in a cluster headache paper diary for at least 1 month before and continuously after implantation. Attack occurrence, intensity (1—mild to 4—worst pain), associated autonomic signs, attack duration, acute therapy as well as clinical peculiarities such as side shifts, attack recurrence when stimulator off and side effects were recorded. Long-term follow-up was achieved by interviewing the patients during a headache consultation and/or over telephone calls. Mean daily attack frequency (MAF) was calculated retrospectively at every time point by averaging the number of attacks which had occurred since the last contact with the patient (consultation or phone call). If the battery turned out to be empty, we only considered the MAF during the period when the stimulation was active. Mean attack intensity was averaged by dividing the sum of intensities by the number of attacks. We also monitored the stimulation parameters used during the various follow-up periods.

Statistical Analysis.—We analyzed the change in average daily attack frequency and attack intensity before and after ONS using Wilcoxon's matched-pair test (Statistica 7.1 software; Statsoft, Naisons-Alfort, France, 2005). Statistical significance was set at $P < .05$.

RESULTS

One patient (number 13) had an infection of the implanted device within 15 days after surgery and was explanted. This subject was excluded from the trial.

Clinical characteristics, outcome, drug treatment, adverse events, and technical problems are summarized in Table 1.

Mean follow-up duration post surgery is now 36.82 months (range 11-64 months), whereas mean time with effective ONS (ie, with stimulator switched on) is 28.82 months (range 3-60 months). Among the 14 evaluable patients, 9 have been pain-free for long periods and are still asymptomatic at the time of this evaluation, except patient 8 who had recurrence of some attacks 2 weeks before he was contacted by phone (after a total remission without drug treatment for almost 2 years). Patient 8 is the only patient with a total remission of attacks who was able to interrupt drug treatment. Despite several attempts to suspend the pharmacological therapy, the other 8 patients all need preventive drugs to maintain remission, although number and/or dosages could be reduced in 4 of them after ONS (see Table 1). Three patients have a marked improvement in attack frequency exceeding or approaching 90%. Two patients had no (patient 1) or only minor improvement (patient 11). In the group of 14 patients, MAF was 2.24 before ONS and 0.12 after ONS ($P = .001$). Mean intensity of residual attacks is not improved by ONS (+2.3%; $P > .05$).

Outcome of attack frequency over time and corresponding stimulation protocols are sequentially shown in Table 2. In the 12 patients who have total or partial relief, the duration of ONS before obtaining at least 50% reduction in attack frequency varied between 2 and 10 months (mean 4.83 ± 2.5). The most effective stimulation parameters also vary between patients, although some common features can be recognized. For instance, using the battery itself as cathode (B+), which is only possible with the Itrel 3 stimulator, could be associated with a better outcome, as are tripolar and quadripolar stimulation combinations (0+1–2+, 0+2–3–, 1–2+3+, 0+1–2–3+. . .). At this stage of the follow-up, pulse width ranges from 330 to 450 μs, stimulation frequency from 45 to 130 Hz, and stimulus intensity from 3.1 to 10.5 V. Interestingly, occasional short-lasting relapses of attacks occurred in most improved patients, except one (patient 5), after several months' ONS under the same stimulation pattern. When such a relapse occurred, a slight modification of stimulation parameters or the addition of a second pattern of stimulation alternating with the previous one often sufficed to produce renewed improvement.

The major technical problems were battery depletion (N = 9/14, 64%) and immediate or delayed material infection (N = 3/15, 20%). Significant electrode migration was only seen in 1 patient. Clinical peculiarities during the ONS follow-up period were side shift with contralateral attacks (N = 5/14, 36%), occurring infrequently either isolated or in short bouts, and/or isolated ipsilateral autonomic attacks without pain (N = 5/14, 36%). The latter were not counted in the attack frequency analysis as they were not considered as disabling by the patients.

Table 2.—Sequential Change in Daily Attack Frequency and Corresponding Stimulation Protocols Over the Total Follow-Up Period

			Follow-Up Time (Months)												
			Baseline	1	2	3	6	±10	±13	±16	±18	±21	±30	±37	±45	±60
Patients	1	**Frequency**	0.29	0.9	0.5	—	—	—	—	—	—	—	—	—	—	—
		Stimulation pattern	—	0+2– 1.6-3 V 390 μs 50 Hz	B+3– 3 V 390 μs 50 Hz	—	—	—	—	—	—	—	—	—	—	—
	2	**Frequency**	4.7	5.1	5.4	5.4	5.4	2.0	2.0	5.3	2.5	2.5	3.5	2.5	2.0	0.43
		Stimulation pattern	—	0+3– 3.3 V 360 μs 50 Hz	B+3–/(2–) 3.15 V 420 μs 50 Hz	B+2– 3 V 450 μs 50 Hz	2–3– 3.7 V 360 μs 75 Hz	B+2–3– 5.8 V 450 μs 2.1 Hz	B+2–3– 5.8 V 450 μs 2.1 Hz	B+2–3– 5.8 V 450 μs 2.1 Hz	B+2– 2 V 270 μs 40 Hz	B+2– 7.5 V 300 μs 50 Hz	B+2– 7.5 V 300 μs 50 Hz	B+2– 4.7 V 300 μs 100 Hz	B+2– 4 V 390 μs 60 Hz	B+2– 4 V 390 μs 60 Hz
	3	**Frequency**	3.84	4.7	3.7	3.4	0.1	0.7	0.7	1.0	0.5	0	0.3	0	0	0
		Stimulation pattern	—	0+1–2+ 2.5 V 390 μs 45 Hz	B+2– 5.0 V 420 μs 50 Hz	B+2– 7.3 V 450 μs 60 Hz	B+1– 7.3 V 450 μs 60 Hz	0+1–2+ 9 V 450 μs 40 Hz	0+1–2+ 7.5 V 450 μs 40 Hz	0+1–2+ 8 V 450 μs 50 Hz	0+2–3+ 10.5 V 450 μs 50 Hz	0+1–2+ 10 V 450 μs 90 Hz	0+1–2+ 10 V 450 μs 90 Hz	A = 0+2–3+/ 10.5 V/ 450 μs/ 90 Hz B = 0+1–2+/ 10.5 V/ 210 μs/ 80 Hz	A = 0+2–3+/ 10.5 V/ 450 μs/ 90 Hz B = 0+1–2–3+/ 7 V/ 450 μs/ 80 Hz	A = 0+2–3+/ 10.5 V/ 450 μs/ 90 Hz B = 0+1–2–3+/ 7 V/ 450 μs/ 80 Hz
	4	**Frequency**	1.16	0.7	0.4	0.6	2.5	0	0	0	0	0.1	0.1	0.1	0.1	—
		Stimulation pattern	—	1+2–3+ 2.5-6 V 420 μs 50 Hz	B+2– 4 V 420 μs 50 Hz	2+3– 6.8 V 420 μs 50 Hz	1–2+ 5.2 V 360 μs 60 Hz	0+1–2+ 5.8 V 360 μs 50 Hz	0+1–2+ 5.8 V 360 μs 50 Hz	0+1–2+ 5.8 V 360 μs 50 Hz	0+1–2+ 5.8 V 360 μs 50 Hz	0+1–2+ 3.8 V 360 μs 50 Hz	0+1–2–3– 6 V 420 μs 70 Hz	0+1–2–3– 6 V 420 μs 70 Hz	0+1–2–3– 6 V 420 μs 70 Hz	—
	5	**Frequency**	0.16	0.5	0.8	0.9	0	0	0	0	0	0	0	0	—	—
		Stimulation pattern	—	B+2– 1.8 V 270 μs 40 Hz	B+2– 2.7 V 270 μs 40 Hz	B+2– 2.3 V 270 μs 40 Hz	B+2– 2.3 V 270 μs 40 Hz	B+2– 2.3 V 270 μs 40 Hz	B+2– 2.3 V 270 μs 40 Hz	B+2– 2.3 V 270 μs 40 Hz	B+2– 7 V 420 μs 60 Hz	B+2– 7 V 420 μs 60 Hz	B+2– 7 V 420 μs 60 Hz	B+2– 7 V 420 μs 60 Hz	—	—
	6	**Frequency**	0.16	0.3	0	0.3	0	0	0	0	0.7	0	0	0	0	—
		Stimulation pattern	—	B+2– 9.7 V 210 μs 50 Hz	B+2– 9.7 V 210 μs 50 Hz	B+2– 10.5 V 360 μs 50 Hz	B+3– 6.0 V 360 μs 100 Hz	B+3– 6.0 V 360 μs 100 Hz	B+3– 6 V 420 μs 125 Hz	B+3– 6 V 420 μs 125 Hz	B+3– 6 V 420 μs 125 Hz	B+3– 6 V 420 μs 125 Hz	B+2–3– 5.2 V 360 μs 130 Hz	B+3– 5.5 V 330 μs 90 Hz	B+3– 6.6 V 330 μs 60 Hz	—
	7	**Frequency**	1	0.3	0.1	0.4	0.1	0.1	0	0	0	0	0	0	0	—
		Stimulation pattern	—	B+2– 4 V 210 μs 35 Hz	B+3– 9 V 270 μs 50 Hz	B+3– 9 V 360 μs 90 Hz	B+3– 9 V 420 μs 125 Hz	1+2–3+ 4.5 V 420 μs 125 Hz	0+2–3– 8 V 420 μs 110 Hz	0+2–3– 8 V 420 μs 110 Hz	0+2–3– 8 V 420 μs 110 Hz	0+2–3– 8 V 420 μs 110 Hz	0+1–2–3– 6.5 V 360 μs 80 Hz	2 coupled programs alternating every week: A1 = 0–1+2–/5 V/420 μs/60 Hz A2 = 0+1+2–/6.5 V/390 μs/60 Hz B1 = 0–1–2+/7 V/450 μs/50 Hz B2 = 0+1–2–/6.5 V/450 μs/50 Hz		
	8	**Frequency**	4	3.3	3	1.5	4.2	3.5	3.5	7	7	1	0	0	—	—
		Stimulation pattern	—	1+2+3– 5.0 V 330 μs 100 Hz	B+2– 4.5 V 150 μs 45 Hz	0+1–2–3+ 10.5 V 99 μs 31 Hz Cycle mode	0+2–3+ 7.0 V 180-390 μs 55-65 Hz	B+1– 4.3 V 420 μs 130 Hz	B+1– 1.3 V 420 μs 130 Hz	0–1–2+3+ 3.8 V 420 μs 130 Hz	B+1–2–3– 3.5 V 420 μs 130 Hz	B+1–2–3– 0.6 V 420 μs 130 Hz	B+1–2–3– 0.6 V 420 μs 130 Hz	B+1–2–3– 0.6 V 420 μs 130 Hz	—	—

Table 2.—*Continued*

		Follow-Up Time (Months)												
		Baseline	1	2	3	6	±10	±13	±16	±18	±21	±30	±37	±45	±60
9	**Frequency**	1.5	0.3	0.1	0.2	—	—	—	—	—	—	—	(0.2)	—	—
	Stimulation pattern	—	0–1+2+3+ 8.8 V 330 μs 60 Hz	B+3– 6.8 V 390 μs 90 Hz	0+2–3+ 4.0 V 420 μs 110 Hz	—	—	—	—	—	—	—	Off	—	—
10	**Frequency**	2	0.1	0.2	0.3	0	0	0	0	0	0	—	—	—	—
	Stimulation pattern	—	0+1–2+ 1.6 V 210 μs 60 Hz	0+1–2+ 4-8.3 V 300 μs 60 Hz	0+1–2+ 4-8.3 V 300 μs 60 Hz	0+1–2+ 3.0 V 420 μs 90 Hz	0+1–2+ 3.0 V 420 μs 90 Hz	0+1–2+ 7.6 V 450 μs 90 Hz	A = 2+3–/ 2.0 V/ 150 μs/ 90 Hz B = 0+1–2+/ 7.9 V/ 450 μs/ 90 Hz	A = 2+3–/ 2.0 V/ 150 μs/ 90 Hz B = 0+1–2+/ 7.9 V/ 450 μs/ 90 Hz	A = 2+3–/ 2.0 V/ 150 μs/ 90 Hz B = 0+1–2+/ 7.9 V/ 450 μs/ 90 Hz	—	—	—	—
11	**Frequency**	0.6	0.5	0.5	0.3	0.4	0.4	0.4	0.4	0.4	0.5	—	—	—	—
	Stimulation pattern	—	B+0–1–2–3– 3.1 V 300 μs 50 Hz	B+0–1–2–3– 3.6 V 390 μs 70 Hz	B+0–1–2–3– 4 V 420 μs 60 Hz	0+1+2+3– 10.4 V 420 μs 60 Hz	0+1+2+3– 9.5 V 420 μs 70 Hz	0–1–2–3+ 5.8 V 420 μs 85 Hz	A = 0+1+2+3–/ 10.5 V/ 420 μs/ 55 Hz B = 0–1– 2–3+/ 10.5 V/ 440 μs/ 50 Hz or C = 0–3+/ 10.5 V/ 360 μs/ 60 Hz	A = 0+1+2+3–/10.5 V/ 420 μs/ 110 Hz B = 0–1– 2–3+/ 10.5 V/ 440 μs/ 110 Hz or C = 0–3+/10.5 V/ 360 μs/ 110 Hz	0–1–2–3+ 10.5 V 440 μs 110 Hz (B non- stop)	—	—	—	—
13	**Frequency**	3.5	0.3	0.1	0.1	0.1	0.1	0.1	0	—	—	—	—	—	—
	Stimulation pattern	—	0+1–2+3– 1.7 V 180 μs 75 Hz	0+1–2+3– 1.5 V 470 μs 75 Hz	0+1–2+3– 1.5 V 470 μs 75 Hz	0+1–2+3– 2.2 V 270 μs 75 Hz	0+1–2–3+ 2.4 V 270 μs 75 Hz	0–1+2–3– 3.3 V 330 μs 85 Hz	0–1–2+3+ 3.1 V 330 μs 130 Hz	—	—	—	—	—	—
14	**Frequency**	5.5	5.5	5.5	5.5	0	0	0	—	—	—	—	—	—	—
	Stimulation pattern	—	A = 0–1+2–3+/ 2.9 V/ 300 μs/ 60 Hz B = 0–1+2+3–/ 3.3 V/ 300 μs/ 60 Hz	A = 0–1+2–3+/ 2.9 V/ 300 μs/ 60 Hz B = 0–1+2+3–/ 3.3 V/ 300 μs/ 60 Hz	A = 0–1+2–3+/ 3 V/ 300 μs/ 30 Hz B = 0–1+2+3–/ 3.5 V/ 300 μs/ 30 Hz	A = 0–1+2–3+/ 3.7 V/ 360 μs/ 45 Hz B = 0–1+2+3–/ 3.6 V/ 300 μs/ 45 Hz	A = 0–1+2–3+/ 3.7 V/ 360 μs/ 45 Hz B = 0–1+2+3–/ 3.6 V/ 300 μs/ 45 Hz	A = 0–1+2–3+/3.7 V/ 360 μs/ 45 Hz B = 0–1+2+3–/ 3.6 V/ 300 μs/ 45 Hz	—	—	—	—	—	—	—
15	**Frequency**	3	0.4	0.4	0	1.5	0	—	—	—	—	—	—	—	—
	Stimulation pattern	—	0+1–2–3+ 4 V 300 μs 80 Hz	0–1–2+3+ 7.0 V 300 μs 80 Hz	0+3– 10.5 V 450 μs 130 Hz	A = 0+3–/ 10.5 V/ 450 μs/ 130 Hz B = 1–2+3+/ 8.0 V/ 360 μs/ 130 Hz	A = 0+3–/ 10.5 V/ 450 μs/ 130 Hz B = 1–2+3+/ 8.0 V/ 360 μs/ 130 Hz	—	—	—	—	—	—	—	—

Stimulation pattern: electrode plot combination, average voltage used, pulse width, stimulation frequency.
— = not available.

Recurrence or increase in frequency of attacks after stimulator arrest was reported by 8/11 improved patients (72%). Two patients (1 and 9) found the ONS-induced paresthesias unbearable.

Five patients had their stimulators removed. Patient 4 asked for explantation after 49 months' ONS although he had been significantly ameliorated during 44 months, because of intolerable local battery discomfort. At 53 months' follow-up, his clinical situation remains unchanged. Patient 1 required removal surgery because ONS lacked efficacy and was also poorly tolerated, and patients 5, 11, and 12 were explanted, respectively, because of delayed and immediate device infections. In patient 11, *Staphylococcus epidermidis* was identified as the causal agent.

Subjectively, 9 patients are at this stage very satisfied with ONS and 3 patients moderately satisfied. Ten patients would recommend ONS to other patients, while 4 other patients would not.

DISCUSSION

To the best of our knowledge, this is the study of ONS in drCCH with the longest follow-up. It confirms the published results after shorter observation periods,[6,7,9] showing that ONS is a valuable treatment option in drCCH, since 80% patients have at least a 90% improvement in attack frequency after a follow-up ranging from 11 to 64 months, with 60% of patients becoming pain-free for prolonged periods.

This outcome seems better than the results reported in other large studies. In Burns et al's trial,[9] where the mean follow-up time was twice smaller (17.5 months), 3/14 patients (21%) had an improvement exceeding 90%.[9] In another study,[10] 3/6 (50%) cluster headache patients had an excellent response to ONS. When compared to the responder rate in chronic migraine, ONS appears to be more effective in drCCH,[11] although more trials need to be performed in chronic migraine. In our series of drCCH patients, ONS has an efficacy close to that reported for hDBS where up to 70% of patients have marked improvement in attack frequency.[3] As in other studies,[9] we found no effect of ONS on intensity of persisting or breakthrough cluster headache attacks. Interestingly, there was no obvious difference in outcome between patients who evolved from an episodic to the chronic form of cluster headache and those who were chronic from start on.

Although the majority of patients have prolonged periods of total or subtotal attack remission, the long follow-up in our study clearly shows that the effect of ONS is only symptomatic and not sufficient by itself except in a single patient. In the other improved patients, the preventive drug treatment could not be interrupted, although it could be reduced in some. Also, breakthrough isolated attacks or bouts were common. In most patients, they were easily managed by modifying the stimulation parameters. Finally, in most patients who switched off their stimulator or had a flat battery of attacks recurred within hours or a few days. This would indicate that the beneficial effect on attack occurrence is due to a biological effect of the ONS, and not to the natural history of the disorder. As mentioned before,[5] it does not rule out, however, a placebo effect which is notoriously difficult to assess in ONS trials because of the presence of paresthesias. The fact that only 1 patient remained attack-free for a long period without preventive drug treatment suggests that neither ONS nor natural history were able to induce a total remission, and thus to transform the chronic into an episodic pattern of cluster headache. ONS has the advantage of providing substantial benefit to drCCH patients, but does not replace preventive drug treatment. It must be considered as an "add-on" minimally invasive non-pharmacological therapy that might make the former drCCH subjects more responsive to drug treatment.

To understand the mode of action by which ONS exerts its efficacy, we performed an 18-fluorodeoxyglucose positron emission tomography in 10 of the patients reported here (see Magis et al[12] for complete results). We found that ONS induced a progressive metabolic normalization in the so-called pain neuromatrix, which confirms that ONS would act through slow neuromodulatory processes.[6] In ONS responders, we also demonstrated a selective activation of the perigenual anterior cingulate cortex, a structure which is thought to be pivotal in the endogenous opioid system, suggesting that ONS could restore balance within dysfunctioning

pain control centers. Finally, we observed a persistent hypothalamic hypermetabolism ipsilateral to cluster headache. As the hypothalamus is believed to be involved in cluster headache pathophysiology, this is in line with our abovementioned clinical conclusion that ONS is nothing but a symptomatic treatment.

As for the peculiarities of the clinical course, the most remarkable is the occurrence of isolated nonpainful autonomic "attacks." The latter were reported before once[13] while they are not mentioned in the other large study.[9] They also support the argument that ONS does not silence the generator(s) of cluster headache attacks. In line with this concept is our finding of a persisting positron emission tomography hypermetabolism in the ipsilateral hypothalamus after 6 to 24 months of ONS despite clinical improvement.[12] Whether this persistent hypothalamic activation might be related to the persistence of autonomic attacks remains to be demonstrated. Attacks contralateral to the usually affected and implanted side occurred in a minority of our patients (36%), but only became disabling in 1 patient who had a prolonged bout. The cause of "sudden" side shift in some of our patients is unknown but this phenomenon is well known in the natural course of the disease. These attacks were easily managed both after short-term follow-up[6] and in the present long-term evaluation. Side shift of attacks is the reason why bilateral ONS electrodes are recommended in some studies.[7,9] Bilateral implantation is, however, likely to become the rule in future trials, given that transcutaneous leads are now available and make the procedure less invasive.

As far as stimulation parameters are concerned (Table 2), our patients needed on average relatively high current intensities to be relieved (on the whole follow-up time, mean 5.34 ± SD 2.05 V), leading to recurrent battery replacement. To our knowledge, there is only 1 other study reporting detailed stimulation parameters of the patients,[10] but a direct comparison appears difficult as the authors used a different stimulator (implantable Bion device), with a discontinuous stimulation and intensities reported in mA and not in V. These high current intensities might be explained by a larger distance between the stimulating electrode and the occipital nerve in some patients, as the neurosurgeon only relied on anatomical landmarks peroperatively.

Occipital nerve stimulation was associated with various complications. The most common one was repeated battery replacement which had to be performed up to twice per year in 1 patient. The rapid emptying of batteries was undoubtedly due to the high stimulation voltage that was necessary in most patients. Battery replacement can now be avoided by using available rechargeable batteries, which was done in some of our patients. Significant lead migration needing surgery occurred in only 1 patient while it was a frequent complication in other studies.[9,14] This difference could be either related to the fact that paddle style lead is less susceptible to be dislocated than the transcutaneous leads, or related to the surgical method under general anesthesia. It has recently been suggested that the latter might improve ONS outcome.[15] A serious complication in our study was device infection which occurred in 3 patients leading to explantation of the material. While the early infection in patient 12 might have been favored by an insufficient hygiene and home care, there is no good explanation for the late device infections. Infection is, however, a well-known complication of implanted stimulators and leads. For instance, in a large review of cardiac pacemakers,[16] the 3-year infectious complication rate ranged from 0.5% to 12.6%. Finally, the unbearable paresthesias were unfortunately unpredictable. Actually, they did not appear immediately when stimulator was switched on but after several weeks, and were mainly due to the permanent quality of the stimulation.

CONCLUSIONS

This long-term follow-up of 15 chronic cluster headache patients resistant to drug treatment confirms that ONS is a useful therapy that generates sustained disability reduction. It does, however, not induce complete remission of the disorder and preventive pharmacological treatment remains necessary to maintain the long-term benefit. Stimulation parameters have to be adjusted frequently to control breakthrough attacks or bouts. ONS is overall well tolerated, but infection of the device may lead in

some patients to explantation. Some patients do not tolerate the ONS-induced paresthesias, especially when the clinical improvement is not overwhelming. Given the high current intensities necessary for effective ONS, batteries have to be replaced frequently or rechargeable batteries should be recommended. Taken together, ONS is a safer neurostimulation method in drCCH than hDBS and has on the long term a comparable efficacy. It should therefore be considered before hDBS for drCCH patients.

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