Long-term follow-up of bilateral hypothalamic stimulation for intractable cluster headache

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Summary
We provide a detailed case history of the first patient to receive bilateral hypothalamic stimulation to control severe bilateral chronic intractable cluster headaches initially occurring mostly on the left. These attacks were accompanied by life-threatening hypertensive crises and a grave deterioration in the patient’s psychological state. Destructive surgery to the left trigeminal was absolutely contraindicated. Electrode implantation and continuous stimulation of the left posterior inferior hypothalamus resolved the left attacks. After four destructive operations on the right trigeminal, right side attacks recurred. Electrode implantation (with continuous stimulation) to the right resulted in immediate resolution of the right side pain and the hypertensive crises. On several occasions, both known and unknown to the patient, the stimulators were turned off: in all cases, crises reappeared and in all instances disappeared relatively quickly after turning stimulation back on. Pain crises have never reappeared when ipsilateral stimulation is ongoing. The only side effects were observed during long-term bilateral stimulation, consisting of transient vertigo and bradycardia. After 42 months (left) and 31 months (right) of follow-up, the patient remains crisis free without the need for pharmacological prophylaxis.

Keywords: cluster headache; treatment; deep brain stimulation; pathophysiology, head pain

Abbreviation: CH = cluster headache.


Introduction
Cluster headache (CH) is a primary headache syndrome characterized by strictly unilateral head pain attacks accompanied by ipsilateral autonomic facial phenomena (Headache Sublissification Committee of the International Headache Society, 2004). The pain may be the most severe known to humans. The attacks are relatively short lived and in the episodic form occur daily for some weeks followed by a period of remission. In the chronic form, attacks occur on a daily basis without significant periods of remission. When chronic CH is unresponsive to medical treatments, it is a major problem and surgical options have to be considered (O’Brien et al., 1999). The trigeminal nerve and cranial parasympathetic nerves on the affected side have been targeted, with inconsistent results (Ekbom and Solomon, 2000). The most widely used surgical procedure for intractable chronic CH is radiofrequency thermocoagulation of the trigeminal ganglion. This procedure is often effective initially (Jarrar et al., 2003). However, the headache may recur, in which case a repeat procedure may be useful. Possible sequelae are corneal analgesia with markedly increased susceptibility to corneal infection, corneal opacification and anaesthesia dolorosa (Matharu and Goadsby, 2002; Jarrar et al., 2003).

Lack of understanding of the causes of CH has impeded the development of new therapeutic options (Goadsby, 2002; May and Leone, 2003). However, in recent years, neuroimaging has expanded our understanding of the pathophysiology of the condition. PET has revealed activation of the ipsilateral posterior inferior hypothalamic grey matter during CH attacks (May et al., 1998; Sprenger et al., 2004), and voxel-based morphometric MRI has documented alteration of the same area (May et al., 1999), strongly suggesting that the CH generator is located there (May et al., 1998). By analogy with the use of electrode stimulation for intractable movement disorders (Benabid et al., 1996), we reasoned that stereotactic stimulation of this area might interfere with this generator and relieve intractable forms of CH (Leone et al., 2001).

The first patient in whom we tried this approach had suffered intractable bilateral chronic CH for 5 years and had an
absolute contraindication for left side trigeminal surgery (Attanasio et al., 2000; Leone et al., 2001). The patient’s left side attacks disappeared after electrode implantation and continuous stimulation of the left posterior inferior hypothalamus (Leone et al., 2001). Unfortunately, the attacks on the right side worsened following the successful treatment on the left, and it became necessary, as explained below, to implant an electrode on the right. We report in detail the history of this first patient with bilateral hypothalamic implantation and stimulation, after 42 months of follow-up for the left, and 31 months for the right.

**Case history**

Our patient is a 39 year-old male who had suffered from bilateral chronic intractable CHs since 1995, most of which were on the right. Extensive investigations, including cerebral MRI, MR angiography and catheter angiography, excluded other conditions (Attanasio et al., 2000; Leone et al., 2001). The attacks were accompanied by life-threatening hypertensive crises with systolic pressure up to 260 mmHg and diastolic pressure reaching 160 mmHg, and conspicuous oculo-facial phenomena (Attanasio et al., 2000) (Fig. 1A). Underlying causes of the hypertension were ruled out by appropriate investigations (Attanasio et al., 2000). The patient received two balloon compressions and two percutaneous thermal rhizotomies: only after the last thermal rhizotomy (March 2000) did the right side CH attacks disappear (Attanasio et al., 2000). However, the patient then developed intractable right side anaesthesia dolorosa consisting of severe stabbing/burning pain episodes of a few seconds in duration occurring numerous times a day. This pain, mainly felt in the district of the second trigeminal branch but also in the districts of the other two branches, was triggered by chewing, light touching and speaking. Antiepileptics and numerous other drugs were tried (e.g. carbamazepine, lamotrigine, gabapentin, phenytoin, steroids and phenothiazine), with no benefit.

Soon after the disappearance of the right side CH attacks, those on the left worsened markedly, with about eight drug-refractory pain episodes occurring per day. The patient was blind in the right eye following vitreous humor haemorrhage induced by a hypertensive crisis; left eye vision was compromised for the same reason. Therefore, left trigeminal surgery was absolutely contraindicated as any corneal sequelae could have rendered the patient completely blind. At this point, we proposed an electrode implant, which we carried out in July 2000 after ethical committee approval and the patient’s informed consent (Leone et al., 2001). Stereotactic coordinates were derived from the voxel-based morphometry MRI study (May et al., 1999; Leone et al., 2001). The operation was performed, under local anaesthesia using a CRW (Cosman–Roberts–Wells) frame; the electrode (Medtronic 3089, MN) was inserted at coordinates 6 mm posterior to the anterior commissure–posterior commissure midpoint, 2 mm left of the midline, and 8 mm below the commissural plane (May et al., 1999; Leone et al., 2001). Intraoperative electrical stimulation induced no side effects. The permanent generator (Soletra, Medtronic, MN), embedded in a subclavicular pocket, was connected by subcutaneous tunnelization (Leone et al., 2001). Implantation alone did not affect the crises, and 2 days after the operation the electrode was turned on. Bipolar stimulation at high and low frequency (5 days at 60 Hz and 5 days at 180 Hz) had no effect, so continuous unipolar stimulation was tried initially at low frequency, but after 7 days there was no change. The frequency was then increased to 180 Hz, with pulse width 60 μs, and the amplitude was gradually increased to 3.0 V. After 7 days at these stimulation parameters, the left side attacks gradually disappeared without the use of pharmacological prophylaxis (Leone et al., 2001).

During August 2000, the stimulator was switched off twice, unknown to the patient, during emergency operations on the left eye requiring general anaesthesia (see Table 1); each time
the attacks reappeared soon after and disappeared again when
the stimulator was turned back on (Leone et al., 2001).

In December 2000, 9 months after the last operation on the
right trigeminal, the patient’s right sided CH attacks recurred.
The attacks lasted 30 min to 4 h, occurred up to eight times a
day, were associated with striking oculo-facial phenomena
(Fig. 1B) and, like those on the left, were refractory to all
medication (Attanasio et al., 2000) [subcutaneous sumatriptan
6 mg, indomethacin 50 mg intramuscularly (i.m.) and intra-
venously (i.v.), ergot derivatives, clonidine i.v., valproic i.v.,
various non-steroidal anti-inflammatory drugs (NSADs) i.m.,
dexamethasone i.v. up to 16 mg per attack, and oxygen
(Dodick and Capobianco, 2001)]. During these attacks, the
patient became extremely agitated and the associated intract-
able hypertensive crises remained life-threatening.

A further operation on the right trigeminal was ruled out as
unlikely to be useful, since the CH attacks had recurred not-
withstanding persistent deep anaesthesia. At this point, the
patient was receiving continuous deep brain stimulation on
the left side, which had produced complete control of the left
CH attacks with no significant side effects. We proposed a
similar approach to the intractable right side attacks. After
ethical approval and informed consent, an electrode was
implanted in May 2001. We targeted the same hypothalamic
area on the right as the previous implant on the left (May et al.,
1999; Leone M et al., 2001). The position of the electrode was
verified by postoperative MRI (Fig. 2). The detailed descrip-
tion of the surgical procedure has been reported elsewhere
(Leone et al., 2001).

Stimulation began immediately in view of the life-threatening
hypertensive crises which occurred in association with the
several times daily attacks. We adopted the parameters that
were successful on the left (180 Hz and 60 μs pulse width) except
that amplitude was somewhat lower (0.5 V); at the same time, the
amplitude on the left was reduced from 3 to 1 V in order to be
cautious. The following day, the right side CH crises and the
severe hypertension episodes disappeared completely. For the
first time in years, the patient started sleeping normally at night,
probably because the nocturnal CH crises had disappeared, but it
is also possible that stimulation restored normal sleep–waking
rhythms.

After 4 months of continuous bilateral hypothalamic sti-
mulation, and freedom from all CH attacks, the patient de-
veloped vertigo and bradycardia (42 per min); before the
implants, heart rate had been 48–52/min in relation to the

Table 1. Time relationships between switching off/on the electrodes and appearance/disappearance of pain

<table>
<thead>
<tr>
<th>Occasions when stimulator was switched off</th>
<th>Days between turning off stimulator and attack recurrence</th>
<th>Days between turning on stimulator and attack cessation</th>
<th>Stimulation amplitude (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left, implanted 14 July, 2000</td>
<td>2 (twice)</td>
<td>2 (twice)</td>
<td>3.0</td>
</tr>
<tr>
<td>August 2000</td>
<td>24</td>
<td>9</td>
<td>1.5</td>
</tr>
<tr>
<td>September 2001</td>
<td>45</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>May 2002</td>
<td>14</td>
<td>3</td>
<td>1.3</td>
</tr>
<tr>
<td>July 2002</td>
<td>24</td>
<td>46</td>
<td>3.2</td>
</tr>
<tr>
<td>October 2002</td>
<td>24</td>
<td>27</td>
<td>2.3</td>
</tr>
<tr>
<td>January 2003</td>
<td>35</td>
<td>34</td>
<td>2.3</td>
</tr>
<tr>
<td>June 2003</td>
<td>120</td>
<td>27</td>
<td>2.3</td>
</tr>
<tr>
<td>Mean (min–max)</td>
<td>33.2 (2–120)</td>
<td>16.1 (2–46)</td>
<td>2.3 (1.3–3.2)</td>
</tr>
<tr>
<td>Right, implanted 31 May, 2001</td>
<td>7</td>
<td>2</td>
<td>3.0</td>
</tr>
<tr>
<td>September 2001</td>
<td>290</td>
<td>2</td>
<td>2.3</td>
</tr>
<tr>
<td>May 2002</td>
<td>47</td>
<td>21</td>
<td>0.8</td>
</tr>
<tr>
<td>September 2002</td>
<td>114.7 (7–290)</td>
<td>8.3 (2–21)</td>
<td>2.0 (0.8–3)</td>
</tr>
<tr>
<td>Mean (min–max)</td>
<td>72.8 (2–290)</td>
<td>16.3 (2–46)</td>
<td>2.2 (0.8–3.2)</td>
</tr>
</tbody>
</table>

*Unknown to the patient; † the electrode became displaced (again unknown to the patient). Stimulator status at latest check-up (December 2003): right side stimulator off since 1 December, 2002; left side stimulator on.
patient’s athletic activities (competition long-distance running). Both stimulators were switched off (26 September 2001). Heart rate gradually increased to 46/min and the vertigo resolved in the course of a week. Twenty-four days after the stimulators had been switched off, the left side CH attacks recurred, but disappeared 9 days after the left stimulator had been turned back on (amplitude gradually increased up to 1.5 V). The right side CH attacks recurred 7 months later (Table 1), almost a year after the right side implantation. The right stimulator was turned back on and the right side attacks disappeared 2 days later.

However, a week later, the right side attacks began again, preceded a few days previously by paraesthesia and electric shock sensations in the right parietal area along the course of the subcutaneous electrode cable. When the stimulation voltage was increased, the sensations of vertigo that generally accompanied amplitude increases did not appear; instead the electric shock sensations in the skin worsened. Cranial X-ray showed that the electrode had come out of position and was lying under the right parietal skin. Surgery to replace the electrode was carried out and stimulation restarted immediately. Forty-eight hours later, the right side CH crises disappeared (Table 1).

Although the patient was not experiencing side effects, he requested on several occasions that the stimulators be switched off. The CH attacks reappeared at variable times afterwards, and also disappeared at variable times on recommencing stimulation (Table 1).

The left stimulator has been on for 800 (64%) of the 1245 days it has been in place (14 July 2000 to 14 December 2003). During this period, the patient experienced 131 days with CH crises on the left (131 out of 1245 = 10.5% of the implanted period; 131 out of 800 = 16.4% of the stimulated period).

The right stimulator has been on for 265 (29%) of the 924 days in place (31 May 2001 to 14 December 2003). During this time, there were 37 days with CH crises on the right (37 out of 924 = 4% of the implanted period; 37 out of 265 = 14% of the stimulated period). From the date of the first hypothalamic implant on the left, the patient has had an overall total of 168 days with crises (168 out 1245 = 13.5%).

The stimulators have been on together for 164 days (164 out of 924 = 18%) in four different periods of 116, 10, 20 and 18 days.

The 168 days on which CH attacks occurred after the implants are the sum of the days between recurrence of attacks after an electrode had been switched off and the days required for the crises to subside after an electrode was switched back on. Crises have never reappeared on any side when the ipsilateral stimulator was on.

The characteristics of the pain and autonomic phenomena during the crises that occurred after electrode implant were identical to those before deep brain stimulation (including hypertension). The longest period of absence of the right attacks is >1 year: the right stimulator was turned off on 1 December 2002 and had not been turned back on since; the crises have not reappeared (Fig. 3).

Blood pressure has remained normal since the hypertensive crises were first brought under control, irrespective of whether one or both stimulators are off. No prophylaxis for CH or hypertension has been given or considered necessary. The facial and ocular autonomic phenomena have not recurred. However, stimulation has had no effect on the right anaesthesia dolorosa which began after the operations on the right trigeminal.

ECG and electrolyte balance remain normal. Before the operations, cortisol and testosterone were low, prolactin was sometimes increased, and growth hormone was normal. After the operations, these hormones were normal. The pre-operation cortisol and testosterone alterations were probably induced by steroid administration; the prolactin alterations were probably a response to pain-induced stress.

Discussion
Ours is the first patient to have electrodes implanted bilaterally in the posterior inferior hypothalamus. Prolonged bilateral stimulation at these sites has produced long-lasting CH relief without the need for pharmaceutical prophylaxis and without major side effects.

Background to decision to implant hypothalamic electrodes bilaterally
The implantation of a second hypothalamic electrode was rendered necessary by the poor general condition of the patient. He was supporting his chronic and unrelieved condition poorly. He had spent a lot of time in hospital and had lost his job. His relations with his wife and children were at a low ebb particularly since during the crises he sometimes became so aggressive as to constitute a danger to them. He
had attempted suicide twice. Most importantly, the several times daily hypertensive crises were putting his life at risk.

**Efficacy**

Most of the drugs administered had no effect whatsoever; transient benefit was obtained only with bolus i.v. steroids (Attanasio et al., 2000; Leone et al., 2001). After four destructive interventions on the trigeminal, temporary relief from the crises was only obtained after the fourth operation. In contrast, hypothalamic stimulation eliminated the CH crises in our patient relatively quickly after the stimulators were turned on, and, during a follow-up of 3.5 years, the crises have never reappeared while stimulation was occurring. On two occasions, the stimulators were turned off without the patient’s knowledge, and in both instances crises reappeared within 48 h. On another occasion, an electrode became displaced and again crises returned. This latter occurrence constitutes an undesired double-blind trial of the efficacy of stimulation. It is therefore possible to exclude beyond reasonable doubt that any placebo effect is occurring and to conclude that hypothalamic stimulation is really effective in our patient. The severity of the patient’s condition while undergoing crises precluded systematic investigations to identify a possible placebo effect.

**Postoperative condition of the patient**

Unexpectedly, hypothalamic stimulation resolved the patient’s hypertensive crises, averting the danger of further deterioration in vision. However, because of poor sight, he remains unemployed. The disappearance of daily CH attacks resulted in a marked improvement of behaviour and family life.

**Lateralized therapeutic effect**

Stimulation on one side has never resolved CH attacks on the opposite side in our patient, suggesting that the mechanisms leading to CH attacks are lateralized and that in bilateral CH both hypothalami are involved, although perhaps not simultaneously (Sjaastad, 1988). PET studies on bilateral cases showing no changes in the brain after long-term deep brain stimulation (Haberler et al., 2000). Body temperature has always remained stable. Appetite was depressed after the operations in relation to steroid withdrawal; subsequently it returned to normal.

**Possible mode of action**

Various mechanisms have been proposed to explain therapeutic effects of deep brain stimulation. High frequency stimulation has been proposed to inhibit, while low frequency stimulation seems to increase neuronal activity (Montgomery and Baker, 2000). If CH attacks are attributable only to hypothalamic involvement, one would expect immediate cessation of attacks when high frequency stimulation is applied and worsening of attacks during low frequency stimulation. In our patient, the median lag between beginning high frequency stimulation and the disappearance of the crises was 4 days (range 1–46 days); when low frequency stimulation was tried, the crises did not increase in rate, severity or duration. These observations lead us to speculate that a more complex mechanism than simple inhibition or excitation of hypothalamic nuclei is involved, and that several brain structures may be implicated. The latter suggestion is consistent with the results of recent PET studies showing that hypothalamic stimulation activates certain brain areas and deactivates others (May et al., 2003), all of which form part of pain-modulating pathways. Thus, areas of the brain concerned with pain modulation, as well those responsible for CH per se, may be involved in the relief of intractable CH by hypothalamic stimulation.

The lag, in our patient, between turning off stimulation and the recurrence of CH attacks also supports the idea that hypothalamic stimulation may gradually restore functional equilibrium between the structures involved. We can go further: when right side stimulation was switched off after prolonged stimulation, our patient remained pain free on the right for more than a year, without the need for drugs. It is possible therefore that prolonged hypothalamic stimulation may transform chronic CH into an episodic form. We also found that the latency to efficacy after switching back the stimulator on tended to increase, and that the stimulation amplitude required for efficacy was variable. These observations suggest that the threshold for efficacy/pain varies, as also indicated by variations in drug efficacy in CH patients. Studies
on more patients could clarify these aspects (Leone et al., 2004).

Cluster pain, pain arising from the trigeminal nerve, and hypothalamic stimulation

Our patient received two balloon compressions followed by two thermal rhizotomies before relief from the right side CH attacks was obtained. However, these attacks recurred 9 months later, even though deep anaesthesia had been induced in all three branches of the right trigeminal. That CH crises may recur after a surgical deafferentation that results in complete trigeminal anaesthesia is well documented (Ekbom and Solomon, 2000; Matharu and Goadsby, 2002; Jarrar et al., 2003) and is evidence for a mainly central cause of CH. In our patient, hypothalamic stimulation effectively controlled the CH but had no effect on the anaesthesia dolorosa induced by trigeminal deafferentation. This observation is further evidence of a central origin for CH and suggests that hypothalamic stimulation exerts its therapeutic effect via a specific mechanism rather than a more general one on the craniofacial pain circuits.

In conclusion, bilateral hypothalamic stimulation was the only procedure able to control the severe, daily, intractable bilateral CH crises in our patient. It did so with only trivial side effects. Clearly, hypothalamic stimulation is a promising treatment for chronic intractable CH.

References