Cluster headache is the most severe primary headache disorder known. Ten to 20% of cases are medically intractable. DBS of the posterior hypothalamic area has shown effectiveness for alleviation of cluster headache in many but not all of the 46 reported cases from European centers and the eight cases studied at the University of California, San Francisco. This surgical strategy was based on the finding of increased blood flow in the posterior hypothalamic area on H215O PET scanning during spontaneous and nitroglycerin-induced cluster headache attacks. The target point used, 4–5 mm posterior to the mammillothalamic tract, is in the border zone between posterior hypothalamus, anterior periventricular gray matter, and inferior thalamus. Recently, occipital nerve stimulation has shown efficacy, calling in question the use of DBS as a first line surgical therapy. In this report, we review the indications, techniques, and outcomes of DBS for cluster headache.

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Available online on ScienceDirect (www.sciencedirect.com).

0969-9961/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.nbd.2009.05.020
Introduction

Cluster headache (CH) is the most severe of the primary headache disorders. It affects approximately 1 in 1000 persons, and 20% of patients are significantly disabled in spite of optimal medical therapy (Russell 2004). Peripheral nerve ablation procedures have been performed for CH, with little benefit. Positron emission tomography (PET) using 15-O-H2O as the tracer has shown a focal increase in cerebral blood flow in the ipsilateral posterior hypothalamic region during a CH attack in addition to areas with increased cerebral blood flow with other pain syndromes (May et al., 1998, 2000). Based on this finding, in 2000 a promising new surgical procedure for severe CH was introduced in Milan, Italy: chronic deep brain stimulation (DBS) of the posterior hypothalamic region (Leonе et al., 2001). To date, four open-label case series have been published, three from European centers and four from our own (Schoenen et al., 2005; Leone et al., 2006; Starr et al., 2007; Bartsch et al., 2008). Additional centers have published case reports bringing the number of reported cases above 50 (Wilkinson et al., 2004; Benabid et al., 2006; D’Andrea et al., 2006; Rasch et al., 2006; Mateos et al., 2007; Owen et al., 2007). In the four case series, most patients received major benefit, but approximately 25% of patients were nonresponders.

Many aspects of this novel therapy remain to be elucidated, including the actual proportion of patients who respond favorably, the degree and duration of response, presurgical predictors of outcome, the mechanism of action, the time course of onset and washout of the therapeutic effect, optimal programming parameters, and the safety of the procedure. Currently, no commercial DBS device has US or European regulatory approval for this emerging indication. This report reviews the relevant features of CH, surgical indications for DBS, surgical techniques, clinical outcomes, and possible mechanism of action.

Overview of cluster headache

The international headache society defines cluster headache as a primary headache disorder characterized by recurrent attacks of excruciating unilateral periorbital pain, usually with evidence of ipsilateral cranial autonomic hyperactivity, including lacrimation, conjunctival injection, ptosis, or meiosis (2004). Attacks may occur from once every other day to eight times a day and last 15–180 min. Attacks tend to occur at regular times of the day. The prevalence of CH is approximately 0.2% (Russell 2004). In the episodic form of CH, affecting 80–90% of patients, attacks occur seasonally, with periods of complete remission. In the chronic form, affecting 10–20% of patients, remissions do not occur or last less than 1 month (May and Leone, 2003). During the active period of headache attacks, a CH attack may be triggered by sublingual nitroglycerin, and has been used to experimentally trigger attacks (May 2005). Alcohol consumption is also a common trigger and this history is considered useful diagnostically.

Prophylactic medical therapy of CH includes verapamil, ergot derivatives such as methysergide, lithium carbonate, divalproic acid, melatonin, and corticosteroids (May and Leone, 2003). Abortive medical therapy includes the use of 100% oxygen, injectable sumatriptan, ergotamines, indomethacin, intranasal lidocaine or capsaicin, corticosteroids and opiates medications (May and Leone, 2003). Among those patients who fail medical therapy, the chronic form is disproportionately represented, and those who have had chronic CH for at least one year are unlikely to have a spontaneous remission in the following year (Manzoni et al., 1991).

Prior to 2000, surgical therapy for CH was directed at interruption of the trigeminal nerve by chemical ablation, balloon compression, partial or complete surgical sectioning of the trigeminal root (Jarrar et al., 2003), or radiosurgical ablation of the trigeminal dorsal root entry zone (Donnet et al., 2005). The results of these procedures have been disappointing, with a low rate of persistent headache relief and a high rate of facial anesthesia. In addition, there are case reports of patients with CH who had no relief of pain with complete interruption of the trigeminal nerve, despite having complete facial anesthesia, indicating that peripheral nociception is not necessary to the experience of pain in CH (Matharu and Goadsby, 2002; Leone 2004).

Evidence for hypothalamic area involvement in CH

May and colleagues referenced the striking circadian pattern of cluster attacks and suggested involvement of hypothalamic centers (May et al., 1998). Hypothalamic centers including the supraoptic and paraventricular hypothalamic regions have been associated with circadian rhythms (Saper et al., 2005). Recently, both functional and structural imaging have provided evidence for specific abnormalities within the hypothalamic area in CH. Positron Emission Tomography (PET) using H2O has shown increased regional cerebral blood flow (rCBF) in the ipsilateral posterior “hypothalamic grey matter” in nine CH patients during nitroglycerin-induced CH attacks, in comparison with eight control CH patients who were not having headache (May et al., 1998, 2000). Voxel-based MRI morphometry has shown an increase in the size of the same area showing PET activation in 25 patients with CH, compared with 29 healthy controls (May et al., 1999). Significant increases in rCBF in this region have also been shown in an individual CH patient during a spontaneous headache, in comparison with the same individual without headache (Sprenger et al., 2004). The results of SPECT imaging in CH have been inconsistent (May and Leone, 2003). Functional MRI (fMRI) has been used to study isolated cases of headache disorders closely related to cluster headache, including under the broader heading of trigeminal autonomic cephalgia (May et al., 1999; Sprenger et al., 2004, 2005). fMRI has shown blood oxygen level dependent (BOLD) contrast changes in the ipsilateral hypothalamic area during spontaneous pain attacks in these disorders.

Indications for DBS

The European group who developed this procedure has published guidelines for surgical treatment (Leonе et al., 2004). These criteria emphasize the need for the accurate diagnosis of the disorder, the failure of standard medical therapy at maximally tolerated doses, and the exclusion of those in whom the natural course of spontaneous or episodic remissions would be mistaken for a DBS treatment response. Patients who fail to respond to preventative treatments such as verapamil, lithium, methysergide, melatonin, and prednisolone may still respond to abortive agents such as sumatriptan, zolmitriptan, oxygen, dihydroergotamine, or octreotide (Goadsby 2007). The time course for CH symptom onset as compared to relief from abortive medications may leave the patient in sufficient distress to continue consideration for surgical intervention, however.

Two recent publications on occipital nerve stimulation (ONS) for CH show similar efficacy overall to the world experience with hypothalamic DBS, with approximately 60% of patients as responders based on >50 reduction in headache severity or frequency (Burns et al., 2007; Magis et al., 2007). Since the publication of these two papers, we have changed our algorithm for surgery: patients with medically intractable chronic CH are offered ONS, with the possibility of proceeding to DBS after 1 year if the ONS fails.

Our own criteria (†), modified and expanded from the published guidelines (Leonе et al., 2004), are as follows:

Inclusion criteria

1) Patients must meet the International Headache Society (IHS) diagnostic criteria for CH (2004).

2) At least 6 debilitating headaches per week which should be rated by the patient at least 6 on a visual-analog scale of 1–10.
3) Inadequate relief from prophylactic therapy, to include: verapamil, lithium, divalproex sodium, methysergide, topiramate, gabapentin, nonsteroidal anti-inflammatory agents including indomethacin, and short-term use of corticosteroids.

⁎ Inadequate relief from abortive therapy, to include: oxygen, sumatriptan, opiates.

5) Chronic form of CH for at least two years, with headache always lateralizing to the same side.

⁎ Successful completion of daily headache diaries over a one-month period prior to surgery, to measure pre-operative headache characteristics.

⁎ Failure of occipital nerve stimulation therapy for at least one year.

Exclusion criteria

1.) Serious untreated psychiatric comorbidity.

2.) Any medical condition that increases the risk of stereotactic neurosurgery, including untreated hypertension, coagulopathy, severe diabetes, serious cardiac or pulmonary disease, or medical need for chronic anticoagulation with coumadin.

3.) Any medical condition that greatly limits the life expectancy of the patient.

⁎ Concomitant headache disorder distinct from CH, such as migraine, which affects the patient greater than twice per month.

5.) Any other serious chronic neurologic disorder (such as epilepsy, multiple sclerosis, degenerative brain disease).

6.) Inability to undergo screening brain MRI.

7.) Screening MRI showing a brain mass, prior stroke, brain atrophy as well as the neurosurgeon to check inclusion and exclusion criteria.

8.) Age <18 or >75.

9.) Pregnancy.

Pre- and postoperative evaluation

Patients undergo a screening visit with a headache neurologist as well as the neurosurgeon to check inclusion and exclusion criteria for surgical therapy. Prior to surgery, patients are required to complete headache diaries daily for four consecutive weeks in the month prior to surgery, during the first 3 months after surgery, and during the 6th and 12th months following surgery. Patients were carefully instructed on how to score their daily headache diary: 1) the time of day each headache episode occurred, 2) the duration of the headache, 3) the intensity on a visual-analog scale of 1–10 of the headache (1– slight pain, 10—worst imaginable pain), and 4) the use of abortive and prophylactic medications. Patients were also instructed to make note of headaches that were not characteristic of their usual cluster attacks, in order to screen for the presence of other concurrent primary headache disorders. Headache characteristics are averaged from headache diaries over a one-month period. In our practice, patients are considered “responders” to DBS therapy if at the one year time point, there is a >50% reduction in headache frequency, intensity, or both, compared to the pre-operative baseline.

Surgical technique

The surgical technique is similar to that used for placement of DBS electrodes into the basal ganglia for movement disorders: MRI based stereotaxy, microelectrode recording in the region of the MRI-defined target, and intra-operative test stimulation using an external pulse generator, to define voltage thresholds for stimulation-induced adverse effects (Starr 2002). Intravenous sedation is used during the initial exposure of the surgery. Sedation is not normally used for microelectrode recording or test stimulation.

Defining the brain target by brain atlas and by MRI

Following placement of the stereotactic headframe (Leksell series G, Elekta, Inc.), MRI is performed on a 1.5 T scanner (Phillips Intera, Best, the Netherlands). Two MR image sets are obtained: 1.) A volumetric gadolinium-enhanced gradient echo (3D-GRE) MRI covering the whole brain in 1.5 mm axial slices, which is mainly for trajectory planning and visualization of the anterior and posterior commissures (parameters: TR = 3000, TE = 90, matrix = 268 × 512, NEX = 6, bandwidth = 183 Hz/pixel, interleaved). Both image sets are imported into a stereotactic surgical planning software package (Framelink version 5.1, Medtronic-SNT, Boulder, CO), computationally fused, and reformatted to produce images orthogonal to the anterior commissure–posterior commissure (AC–PC) line and midsagittal planes.

As reported by the Milan group, the anatomic target in commissural coordinates is 2 mm lateral to the midline, 5 mm inferior to the axial plane containing anterior and posterior commissures, and 3 mm posterior to the midcommissural point (Franzini et al., 2003). This target was selected to correspond to the brain region that has increased rCBF on H215O PET during CH attacks in the study of May et al. (2000). The target is plotted in Fig. 1 with respect to the appropriate axial slice from the Schaltenbrand et al. human brain atlas (Schaltenbrand et al., 1977). This brain slice (which is slightly oblique with respect to the commissural plane) shows the continuous rim of grey matter lining the inferior wall of the third ventricle and the upper Sylvian aqueduct. This continuum includes the hypothalamus proper, the periventricular grey (PVG), and the periaqueductal grey, bordering the parafascicular and subparafascicular nuclei of the thalamus. The asterisk in Fig. 1 indicates the Milan DBS target, which has been the surgical target in all published series. Some anatomists consider the mammillothalamic tract as the posterior border of the hypothalamus (Schaltenbrand et al., 1977; Swaab 2003), but some human brain atlases depict the hypothalamus, periventricular grey (PVG) and periaqueductal grey (PAG) from the Schaltenbrand and Warren human brain atlas (Schaltenbrand et al., 1977, Starr et al., 2007), reprinted with permissions. MTT = mammillothalamic tract, RN = red nucleus. The asterisk marks the target point for DBS in cluster headache, based on the work of Franzini et al. (2003).
To account for possible variations in diencephalic anatomy that may affect target coordinates as measured from the commissures, we utilize the T2FSE sequence to confirm that the intended target point is located 3–5 mm posterior to the mammillothalamic tract and is medial to the anterior border of the red nucleus, on the axial plane 5 mm inferior to the intercommissural line. The AC–PC based coordinates are modified, if needed, to ensure that the anatomic target lies in a consistent relationship to the mammillothalamic tract and red nucleus.

A “default” trajectory through the brain is set at 60° from the AC–PC line in the sagittal projection and 10° lateral from the vertical in the coronal projection. This trajectory is visualized on the Gadolinium-enhanced volumetric MRI. Small adjustments in the arc and ring angles are then made to avoid traversing sulci, lateral ventricle, cortical veins, and dural venous lakes.

**Single unit recording**

A single microelectrode penetration is made to the stereotactic target, allowing monitoring of the implant trajectory and potentially guiding DBS electrode implant depth. Only two recent publications explore single unit recordings in the posterior hypothalamic region (Cordella et al., 2007; Sani et al., 2009). Examples of spontaneous single unit discharge in the target region are shown in **Fig. 2**. In twenty-four neurons analyzed from our limited series, the target area is characterized by sparse, low amplitude, wide action potentials in a regular pattern at a low frequency (13.2 ± 12.2 Hz; mean ± SD). The inferior boundary of the target is marked either by the interpeduncular cistern or the red nucleus, depending on the angulation of the lead and the patient’s individual anatomy (Sani et al., 2009). If the most distal segment of the recording shows electrical silence (characteristic of cisternal entry) or dense neuronal units with narrow action potentials and high-frequency discharge 30–50 Hz (characteristic of the red nucleus), the recording is stopped and the lead depth accordingly adjusted slightly more superiorly. Continued advancement of a microelectrode into a region of electrical silence beyond the target is not recommended due to proximity to the basilar artery bifurcation and associated perforating branches.

**Lead placement and intra-operative test stimulation**

Following confirmation of target depth with microelectrode recording, the permanent lead is placed. We have used the Medtronic model 3387 lead (contacts spaced over 10.5 mm) while others have used the model 3389 lead (contacts spaced over 7.5 mm). Test stimulation is performed in bipolar mode using contacts 0–+, 3–+, 185 Hz, and 60 μs pulse width (model 3625 external tester, Medtronic, Inc., Minneapolis MN). After cautioning the patient about potential stimulation-induced sensations (double vision, dizziness, vertigo, mood changes) voltage is increased at 0.5 V/sec up to 6 V, during continuous examination of the patient’s cranial nerve function. Voltage threshold for oculomotor disturbance, or subjective phenomena such as mood change, are noted. The patient’s blood pressure and pulse are carefully monitored during test stimulation, although no changes in vital signs have been noted during our preliminary studies. A threshold for oculomotor disturbance (typically gaze paralysis, skew deviation, nystagmus or subjective double vision) of 2–6 V is consistent with lead placement at the intended target. Some patients experience dysphoria at >3 V.

**Lead anchoring and IPG placement**

Leads are anchored to the skull with a lead anchoring device (Stimlock, Medtronic Inc.). After scalp closure and headframe removal, general anesthesia is induced for placement of the lead extender and pulse generator (Soletra, Medtronic Inc. Minneapolis MN).

**Documentation of electrode locations**

Postoperative MRI to demonstrate the location of the electrode tip is performed in all cases, according to the published safety guidelines for performing brain MRI in patients with implanted DBS systems (Medtronic; Rezai et al., 2004). **Fig. 3** shows the typical location of the electrode tip on axial MRI, 5 mm inferior to the intercommissural line, from our series. In this axial plane, the mean (+/− standard deviation) distance of the lead posterior to the mammillothalamic tract is 4.8+/−0.9 mm (N = 7 cases).

**Device programming**

Programming parameters in our patients were based on the two previously published case series (Franzini et al., 2003; Schoenen et al., 2000).
Table 1
Outcome of hypothalamic DBS for CH in five patients.

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age (yrs) / sex</th>
<th>Disease duration (yrs)</th>
<th>Follow-up (months)</th>
<th>Pre-operative status</th>
<th>Most recent status with [% change]</th>
<th>Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td># HA per week</td>
<td>Mean HA intensity (VAS 1–10)</td>
<td># HA per week</td>
</tr>
<tr>
<td>1</td>
<td>58 / M</td>
<td>30</td>
<td>12</td>
<td>13</td>
<td>6.7</td>
<td>12 (−8%)</td>
</tr>
<tr>
<td>2</td>
<td>42 / M</td>
<td>9</td>
<td>12</td>
<td>22</td>
<td>4.9</td>
<td>4 (−82%)</td>
</tr>
<tr>
<td>3</td>
<td>41 / M</td>
<td>12</td>
<td>12</td>
<td>16</td>
<td>7.5</td>
<td>16 0%</td>
</tr>
<tr>
<td>4</td>
<td>66 / F</td>
<td>16</td>
<td>12</td>
<td>51</td>
<td>6.4</td>
<td>56 (+10%)</td>
</tr>
<tr>
<td>5</td>
<td>38 / M</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>7.8</td>
<td>1 (−83%)</td>
</tr>
<tr>
<td>Averages</td>
<td>40 / M:1F</td>
<td>15</td>
<td>10.8</td>
<td>21.6</td>
<td>6.66</td>
<td>17.8 (−17.8%)</td>
</tr>
</tbody>
</table>

The percentage change in headache parameters compared to the baseline preoperative status is given in parentheses. Headache intensity is rated on a 1–10 visual analog scale with 10 equal to the most severe possible pain, and 1 equal to mildest perceivable pain. The mean values are averaged from all headaches in a one-week period as reported on headache diaries completed daily at home. Cases 1, 2, and 5 are considered "responders" to DBS based on a >50% reduction in headache intensity or frequency. Averages appear below in each column. Adapted from Starr et al. (2008), with kind permission of Springer Science+Business Media.

Abbreviations: M = male, F = female, HA = headache, VAS = visual analog scale.

2005): Monopolar stimulation, pulse width of 60 μs, frequency 185 Hz, and voltage 1–3 V (stopping short of the threshold for acute persistent stimulation-induced adverse effects). Devices were kept activated at all times postoperatively. Our detailed postoperative programming protocol is as follows:

Week 0 (one week post surgery):

1.) Activate the device in monopolar mode using pw = 60 μs, frequency = 185 Hz. Record voltage threshold for stimulation-induced adverse effects (typically dizziness or visual disturbance), at all contacts in monopolar mode.

2.) Review postoperative MRI to determine which contact is closest to the intended target (usually contact 0 or 1), and select this contact. Slowly increase the voltage up to 2.0 V, or to 0.1 V less than the threshold for persistent side effects, whichever is higher.

3.) Verify normal impedances and battery life using the programmer.

Weeks 4,8,12,26:

1.) Review headache diaries. If debilitating headaches have persisted in the prior month, increase voltage by 0.5 V, or to 0.1 V less than the threshold for persistent side effects whichever is greater.

2.) If the patient has reached 3.0 V without headache relief, switch contact choice to the next most superior contact. Slowly increase the voltage up to 3.0 V, or to 0.1 V less than the threshold for persistent side effects, whichever is greater. Verify normal impedances and battery life using the programmer.

Clinical outcomes

The short-term clinical outcomes of DBS for CH appear promising in many but not all patients. The Milan group has published the largest series with sixteen patients and mean follow-up time of 4 years (Leone et al., 2006, 2008). Patients were not followed using headache diaries, quality of life measures, or other standardized tools. They report "major improvements" in pain during the first two years in 13 patients. They report a persistent "pain-free state" in 10 patients (62%) at four-year follow-up. Efficacy has been lost in three patients during the last two years of follow-up. They do report a change in illness from chronic to episodic in these three patients. Formal blinded trials with DBS on and off were not performed. Several patients had inadvertent inactivation of the device (due to electrical malfunction of the device) with recurrence of attacks, indicating that the benefit of stimulation was unlikely to be due to placebo. A detailed four-year follow-up on their initial patient was published, showing that the headache attacks have been consistently eliminated with the stimulator on (Leone 2004).

A German multi-center group recently reported six patients with mean follow-up of 17 months. Four of six patients showed a "profound" decrease of their attack frequency and pain intensity during the first 6 months. One patient returned to baseline after 6 months of response. Two patients had experienced only a marginal, non-significant decrease within the first weeks under neurostimulation before returning to their former attack frequency. At 17 months, three patients were "almost completely attack free," with three treatment failures (Bartsch et al., 2008).

A group in Liege, Belgium reported on four of their six implanted patients with a mean clinical follow-up of 14.5 months (Schoenen et al., 2005). Two of the four are free of headache attacks; a third had the frequency of attacks reduced to less than 3/month, while the fourth has had only transient benefit with each reprogramming.

Our own series includes eight patients, with follow-up on five (Table 1). Patients were followed using headache diaries in which the frequency, intensity, and duration of headaches were recorded daily for one month prior to surgery and for one month at the 6 month and 12 month follow-up times. The length of follow-up is 12 months for the first four patients and 6 months for the final patient. Three of five patients (cases 1, 2, and 5) may be considered "responders" based on a >50% reduction in headache frequency, intensity, or both. One of the three responders (case 2) had been using sumatriptan injections to reduce the intensity and duration of each headache, and has not required any abortive therapy postoperatively due to the much lower intensity. Case 3 had transient complete suppression of headaches for 1–2 weeks following each re-programming session, but no persistent benefit in headaches, or reduction in abortive therapy, in the intervals

Table 2
Outcomes published in the literature with at least one-year follow-up.

<table>
<thead>
<tr>
<th>Publication(s)</th>
<th>Reported patients</th>
<th>Follow-up (years)</th>
<th>Responders (number)</th>
<th>Responders (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leone et al. (2006)</td>
<td>16</td>
<td>4</td>
<td>10</td>
<td>62%</td>
</tr>
<tr>
<td>Rasche et al. (2008); Bartsch et al. (2008); Rasche et al. (2008)</td>
<td>6</td>
<td>1.4</td>
<td>3</td>
<td>50%</td>
</tr>
<tr>
<td>Starr et al. (2007, 2008); Starr and Ahn (2008)</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>Schoenen et al. (2005)</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>50%</td>
</tr>
<tr>
<td>D’Andrea et al. (2006)</td>
<td>3</td>
<td>2.5</td>
<td>2</td>
<td>66%</td>
</tr>
<tr>
<td>Mateos et al. (2007)</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>100%</td>
</tr>
<tr>
<td>Benabid et al. (2006)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
</tbody>
</table>

Adapted from Leone et al. (2008), with permission.
between programming changes. He no longer uses the device. Case 4 has had a 30% reduction in headache intensity, which failed to meet the 50% threshold to be considered a “responder”.

In sum, these open-label series indicate that 50–75% of CH patients have substantial relief of headache symptoms 1–4 years postoperatively (Table 2). In those who benefit, headache episodes remain present but are decreased in intensity and frequency. Prophylactic and abortive medications are reduced in many cases. Improvements with DBS appear durable over time, although Leone, et. al have reported a decrease in efficacy in the last two years of follow-up. These early findings should be confirmed with controlled blinded studies. Since a proportion of patients with CH appear to not benefit in a significant way from DBS, a method of prospectively predicting response to therapy is needed.

Time course for stimulation-induced relief

The time course for wash-in and wash-out of the stimulation-induced relief has been studied in detail in only one published case (Leone 2004). This patient had the unusual occurrence of bilateral attacks and was thus implanted bilaterally. The devices were turned off several times over four years, and only turned on again when headaches recurred. The mean time for onset of headache suppression following DBS activation was 16 days (range 2–46 days) and the mean time for headache recurrence following DBS inactivation was 73 days (range 2–290 days). The longest time for headache recurrence, 290 days, occurred on the side of the head where headaches were episodic, not chronic, and thus may reflect a temporary spontaneous remission on that side rather than a true prolonged washout time. Other patients in the Milan series, as well as those in the University of California, San Francisco and Liege series were also noted to require days to weeks for onset of benefit, but the exact time course was not quantified.

Complications

Perioperative complications

The authors of the Milan series of 16 patients reported one asymptomatic third ventricular hemorrhage. In the Liege series, there were surgical complications in two of the six patients: one died of a large intracerebral and intraventricular hemorrhage several hours after surgery, and one could not complete the implantation due to a panic attack during physiological mapping of the target site. In our series of 8 patients, there was a single surgical complication: an intra-operative transient ischemic attack (TIA) in the first case. This occurred immediately following intra-operative test stimulation using the deepest contact at 60 μs, 185 Hz, up to 10 V. The patient was noted to be drowsy and hemiplegic on the side ipsilateral to the implant, which resolved completely in 5 min. Pulse and blood pressure were unchanged during the episode. Emergent head CT scan showed no hemorrhage. However, the DBS tip was noted to be slightly deep to the target, having exited the floor of the third ventricle, in the interpeduncular cistern at the midline. It is possible that test stimulation in the setting of the interpeduncular tip placement may have induced spasm of a contralateral thalamoperforator, resulting in transient capsular ischemia and ipsilateral motor deficit. Contact 0 was not used in subsequent programming. TIAs did not recur in this patient and did not occur in the subsequent six patients.

Stimulation-induced adverse events

In all three series, voltage-limiting stimulation-induced adverse effects were reported to be oculomotor disturbance or dizziness above 1.5–3 V. One patient developed stimulation-induced bradycardia at therapeutic stimulation parameters requiring temporary cessation of therapy (Leone 2004). Long-term stimulation-induced adverse effects of unilateral implantation have been minor: In the Milan series, detailed blood pressure measurements showed that chronically stimulated patients developed asymptomatic orthostatic hypotension (Frazini et al., 2004). Persistent mood changes have not been observed. In the Milan series, most patients experienced a mild weight loss, attributed to cessation of corticosteroids (Leone et al., 2006).

Potential mechanism of action

CH may be triggered by heat, is associated with ipsilateral autonomic signs, has been associated with systemic autonomic and vascular changes. Cyclic phenomenon in daily pattern and yearly pattern along with symptoms have indirectly implicated involvement of the supra-chiasmatic nucleus, hypothalamic area, thalamus, midbrain, and trigeminovascular systems (Swaab 2003). Although metabolic studies have suggested involvement in the bilateral anterior cingulate cortex, contralateral posterior thalamus, ipsilateral basal ganglia, bilateral insulae, and cerebellar hemispheres, anatomic and metabolic studies have identified unique features of the ipsilateral hypothalamic area.

The anatomy of the target region immediately posterior to the mammillothalamic tract is complex. An initial MRI tractography study has documented cortical and subcortical connectivity (Owen et al., 2007). Axons associated with the medial forebrain bundle, containing fiber tracts involved in all major ascending catecholaminergic systems, as well as hypothalamic efferent projections to brainstem and spinal cord, probably traverse this area (Jones and Moore, 1977; Saper et al., 1979; Swanson and Cowan 1979). The fasciculus retroflexus, a pathway connecting the habenular nucleus with the serotonergic interpeduncular nucleus, also travels within the target region.

The superior border of the target region contains the parafascicular and subparafascicular nuclei. The subpafafascicular nucleus has been implicated in pain medication via calcitonin gene-related peptide (CGRP)-containing neurons (De Lacalle and Saper, 2000) and has been shown to have hypothalamic (Wang et al., 2006) and posterior insular connectivity (Shi and Cassell, 1998). Recently CGRP antagonists, which have a vasodilatory effect, have shown promise in treating vascular headache including migraine (Olesen et al., 2004). Indeed in our series, the most frequently activated contact was 3 mm rostral to the distal electrode contact and closer to thalamic nuclei than the distal contact.

Although this complex anatomy raises many possible mechanisms, several physiologic studies have proven informative. In the four implanted patients in the Liege series, (Schoenen et al., 2005), chronic DBS had no effect on urinary excretion of cortisol or melatonin, and no effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on urinary excretion of cortisol or melatonin, and no effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin. There was no long-term effect on plasma levels on oxytocin and vasopressin.
does not work through these descending systems in spite of their extensive hypothalamic connections. This PET study only examined acute effects of DBS (within minutes of activation). These acute DBS-induced changes may not reflect chronic changes underlying the HA suppression, given that the time course for onset of the anti-headache effect appears to be days to weeks.

Although the treatment of CH with DBS of the posterior hypothalamic region is a new approach, nearby brain targets have been previously explored for the treatment of other chronic pain disorders. A number of investigators, working mainly between 1975 and 1990, reported deep brain stimulation of the PVC for neuropathic pain syndromes. Young et al. (1985) reported the PVC target to be 10 mm posterior to the midcommissural point and 3–4 mm lateral to the midline. This target is 8.5 mm superior and posterior to the Milan CH target. An autopsy study of 7 patients who had undergone DBS for neuropathic pain confirmed that effective electrodes were located near the posterior commissure, well posterior to the CH target (Baskin et al., 1986). Based on anatomic considerations, the Milan procedure is in a brain region that is distinct from prior attempts at neuromodulation for other chronic pain conditions. Likewise, previously explored targets for ablative surgeries for pain were not identical to the CH target. Sano et al. (1975) utilized hypothalatomy for chronic neuropathic pain, but his target was immediately lateral to the mammillothalamic tract and thus 3–5 mm anterior to the CH target.

The thalamic centromedian and parafascicular nuclei have also been lesioned for pain treatment, but this target is 6–8 mm superior and lateral to the CH target (Jeanmonod et al., 1993; Whittle and Jenkinson, 1995; Young et al., 1995). Stimulation of periaqueductal gray, posterior hypothalamus, anterior hypothalamus, subcommisural structures, is now being attempted via implanted intraventricular electrodes (Benabid et al., 2006).

Summary

CH is the most severe primary headache disorder known. Ten to 20% of cases are medically intractable. DBS of the posterior hypothalamic area has shown effectiveness for alleviation of CH in many but not all of the 46 reported cases from European centers and the eight cases studied at the University of California, San Francisco. This surgical strategy was based on the finding of increased blood flow in the posterior hypothalamic area on H215O PET scanning during spontaneous and nitroglycerin-induced CH attacks. The target point used, 4–5 mm posterior to the mammillothalamic tract, is in the border zone between posterior hypothalamus, anterior periventricular gray matter, and subparafascicular nucleus within the intermediate thalamus. Important questions remain to be answered, including evaluation of the role of occipital nerve stimulation prior to DBS, a determination of the proportion of patients who respond to this therapy in blinded studies, measurement of wash-in and wash-out times, pre-operative predictors of clinical success, risks of hemorrhage and stimulation-induced adverse effects, optimal location of the active contact, and mechanism of action. Further characterization of this stimulation procedure in humans and in experimental systems may also yield important physiological insights into the pathogenesis of this primary headache disorder.

Acknowledgments

Many thanks to Dr. Andrew Ahn for his contributions to a previous publication (Starr and Ahn, 2008) from which this chapter was adapted.

References


