Stimulation of the Posterior Hypothalamus for Treatment of Chronic Intractable Cluster Headaches: First Reported Series

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OBJECTIVE: To describe the results of deep brain stimulation of the ipsilateral posterior hypothalamus for the treatment of drug-resistant chronic cluster headaches (CHs). A technique for electrode placement is reported.

METHODS: Because recent functional studies suggested hypothalamic dysfunction as the cause of CH bouts, we explored the therapeutic effectiveness of posterior hypothalamic stimulation for the treatment of CHs. Five patients with intractable chronic CHs were treated with long-term, high-frequency, electrical stimulation of the posterior hypothalamus. Electrodes were stereotactically implanted in the following position: 3 mm behind the midcommissural point, 5 mm below the midcommissural point, and 2 mm lateral to the midline.

RESULTS: Since this treatment, all five patients continue to be pain-free after 2 to 22 months of follow-up monitoring. Two of the five patients have remained pain-free without any medication, whereas three of the five required low doses of methysergide (two patients) or verapamil (one patient). No adverse side effects of chronic, high-frequency, hypothalamic stimulation have been observed, and we have not encountered any acute complications resulting from the implant procedure. There have been no tolerance phenomena.

CONCLUSION: These preliminary results indicate a role for posterior hypothalamic stimulation, which was demonstrated to be safe and effective, in the treatment of drug-resistant chronic CHs. These data point to a central pathogenesis for chronic CHs.

KEY WORDS: Cluster headache, Hypothalamus, Neurostimulation, Stereotactic surgery


Cluster headaches (CHs) (migrainous neuralgia, Horton’s syndrome, or histaminic cephalgia) are characterized by the sudden onset of excruciating unilateral pain that begins around the eye, temple, or cheek and is often accompanied by local signs of autonomic dysfunction. This pain may very well be the most severe form of pain known in human experience. CH attacks last for minutes to hours and may occur daily for periods of 6 to 12 weeks, often followed by periods of remission. The prevalence of CHs varies from 0.006% in China to 0.07% in the San Marino Republic and 0.24% in the United States (5). Approximately 10% of CH sufferers develop chronic CHs, which may occur for more than 1 year without remission (12).

Although CHs have been well recognized in the literature for more than two centuries (27), the pathophysiological mechanism remains poorly understood. The well-known circadian rhythm of CHs, with hormonal findings (13), suggests a central origin. Neuroimaging studies recently confirmed this central hypothesis and suggested that hypothalamic hyperactivity might be related to CH bouts (8, 21). Positron emission tomography revealed activation in the ipsilateral postero inferior hypothalamic gray matter during CH attacks (9), and morphometric magnetic resonance imaging data demonstrated increases in neuronal hypothalamic density and hypothalamic size among patients with CHs (20). Because the possibility of a neuromodulatory role for deep brain stimulation was recently recognized in the field of movement disorders (1), we sought to apply the same therapeutic logic to rebalance the allegedly hyperfunctioning hy-
implant was required. We performed this treatment for five patients with medically refractory chronic CHs. To our knowledge, this is the first reported series of its kind.

**PATIENTS AND METHODS**

**Patients**

A multidisciplinary team of neurologists with experience in headache treatment and neurosurgeons with a special interest in functional and stereotactic neurosurgery cooperated in both the evaluation and the selection of patients. Initial diagnoses were made by the neurologists, according to the criteria for the diagnosis of chronic CHs defined by the International Headache Society (11). Patients who were referred for neurosurgery had been suffering from CHs for at least 1 year without remission, despite medical treatment. The medical treatment for these patients before referral for neurosurgery consisted of a regimen of the following drugs, alone or in combination: corticosteroids, lithium, methysergide, ergotamine, calcium channel blockers, beta-blocking agents, tricyclic antidepressants, melatonin, and nonsteroidal anti-inflammatory drugs. All surgical candidates were screened for psychiatric complications with neuropsychological testing and were informed of the classic surgical procedures that were available at our institution for the treatment of intractable CHs (open microvascular decompression/lesioning of cranial nerves in the cerebellopontine angle and percutaneous radiofrequency trigeminal rhizotomy). Five patients selected stereotactic ipsilateral hypothalamic surgery. The first of those patients was successfully treated in July 2000 (Fig. 1), and the results of that surgical procedure were previously reported (14). Since that earlier report, four additional patients with CHs have been treated with deep brain ipsilateral posterior hypothalamic stimulation; the baseline data for all five patients are presented in Table 1. Because one of the five patients was experiencing bilateral pain (Patient 1), an additional contralateral implant was required.

**Surgical Technique for Electrode Implantation in the Ipsilateral Posterior Hypothalamus**

Stereotactic implants (Leksell G stereotactic frame; Elekta, Stockholm, Sweden) were placed with local anesthesia. When sedation was required, low doses of midazolam (0.05–0.1 mg/kg) or propofol (0.5–1 mg/kg) were used. Antibiotic treatment was administered to all patients during the perioperative period. Preoperative magnetic resonance imaging (brain axial volumetric fast spin echo inversion recovery) was used to obtain high-definition anatomic images, which allowed precise determination of the anterior commissure-posterior commissure line. Magnetic resonance imaging scans were fused with 2-mm-thick computed tomographic slices obtained under stereotactic conditions, by using an automated technique based on a mutual-information algorithm (Frame-link 4.0, StealthStation; Medtronic Sofamor Danek, Inc., Memphis, TN). The workstation also provided stereotactic coordinates for the target, 3 mm behind the midcomissural point, 5 mm below the midcomissural point, and 2 mm lateral to the midline (Figs. 2 and 3).

A rigid cannula was inserted through a precoronal parame- dish burr hole and positioned up to 10 mm from the target. This cannula was used as a guide for both microweereording (Lead Point; Medtronic, Inc., Minneapolis, MN) and placement of the definitive electrode (DBS-3389; Medtronic). Macrostimulation (1–7 V, 60 μs, 180 Hz) was used to evaluate potential side effects. All patients subjected to stimulation intensities of more than 4 V demonstrated conjugated ocular deviation, which was followed by verbal reports of extreme proportions (e.g., “I feel near to death” or “I am at the edge of the end”). No pupillary reactions were evoked. When other side effects could be eliminated with standard stimulation parameters, the guiding cannula was removed and the electrode was secured to the cranium with microplates. The extension was then connected to the electrode, tunneled, and brought out percutaneously, for subsequent trial stimulations.

On the day after surgery, an additional magnetic resonance imaging study was performed, to confirm the electrode position. After 7 to 10 days of trial stimulation, the electrodes were

**TABLE 1. Baseline clinical data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>Side</th>
<th>Bouts per day</th>
<th>Chronic CH duration (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>39/M</td>
<td>Left</td>
<td>1–4</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>50/M</td>
<td>Left</td>
<td>3–8</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>63/F</td>
<td>Left</td>
<td>3–8</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>52/M</td>
<td>Right</td>
<td>2–8</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>30/M</td>
<td>Right</td>
<td>4–7</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> CH, cluster headache.

<sup>b</sup> Bilateral CHs. This patient was first treated with trigeminal radiofrequency rhizotomy on the right side and obtained 10 months of complete pain relief. During that period, he experienced tremendous exacerbation of left CHs, with striking oculofacial vegetative phenomena (14), and received the first implant.

**FIGURE 1.** Preoperative (A) and postoperative (B) photographs of Patient 1. The dramatic improvement in neurovegetative vasoconstrictor changes is evident.
connected to a pulse generator (Itrel II; Medtronic), which was positionned subcutaneously in the subclavicular area. The following parameters were used for chronic continuous stimulation: 0.7 to 3 V; frequency, 180 Hz; pulse width, 60 microseconds.

RESULTS

The results of this study are presented in Table 2. All patients achieved complete pain relief as a result of the long-term, high-frequency, hypothalamic stimulation, which continued in follow-up evaluations (2–22 mo). Pain disappearance was never immediate but occurred after a few hours in two cases and later (1–4 wk) in the other three cases. Two of the five patients remained pain-free without medication (Patients 1 and 5), whereas three remained pain-free with low doses of methysergide (Patients 2 and 4) or verapamil (Patient 3). It should be noted that these drugs were completely ineffective before the surgical procedure. In one case in which stimulation was turned off to allow cardiovascular investigations, pain attacks recurred after 3 days and disappeared a few hours after reactivation of the stimulator. We observed no adverse side effects of the chronic, high-frequency, hypothalamic stimulation and no acute complications resulting from the implant procedure. There were no tolerance phenomena. Patient 1 exhibited signs of mild hypersexual and hyperphagic behavior before the operation, which seemed to be resolved with stimulation. In fact, that patient exhibited a 25-kg weight reduction at the 18-month follow-up examination. Figure 2 presents examples of the type of neuronal activity observed at the target site with microelectrode recording.

DISCUSSION

The management of CHs is primarily a medical and not a surgical problem. Unfortunately, some patients develop a form of chronic unremitting CHs that is refractory to all medical management, including long-term corticosteroid treatment. A remarkably broad range of pharmacological agents are currently being used for the treatment of CHs, including serotonin inhibitors, corticosteroids, ergotamine, lithium, melatonin, tryptans, calcium channel blockers, beta-blocking agents, indomethacin, and oxygen inhalation agents (4, 17). These cases pose a very real challenge to the scientific community (2). In fact, it is not an overstatement to say that the surgical treatment of CHs remains a most frustrating endeavor. Surgical treatment is based on interruption of the autonomic pathways (greater superficial petrosal nerve or intermedius nerve sectioning or sphenopalatine ganglion lesioning) (7, 28, 29, 34–37, 39–41) and/or partial or total trigeminal lesioning (thermal rhizotomy, glycerolysis, direct nerve sectioning, or peripheral avulsion) (18, 19, 23–26, 39). These seem, however, to be a direct relationship between sensory deficits (and subsequent discomfort involving facial numbness, keratitis, dysesthesia, and sometimes anesthesia dolorosa) and success rates. In addition to these troubling side effects, the recurrence rate for CHs remains high (17), and even complete trigeminal deafferentation can be followed by the persistence of CH attacks (16). Microvascular decompression of the trigeminal and facial nerves represents the only attempt to date to obtain pain relief without producing nervous system lesions. Unfortunately, the long-term results of these procedures continue to be quite disappointing (15, 32). Although the pathophysiological mechanism of CHs remains poorly understood, CHs have traditionally been considered and treated as having a peripheral vasogenic origin (10). However, the fact that a circadian rhythm is associated with the
symptoms of CHs casts doubt on the concept of a purely vasogenic origin. Recent functional and morphological studies shed light on a new pathophysiological process to explain CHs, with a central mechanism involving the hypothalamus playing a primary role. May et al. (22), using positron emission tomography to assess the changes in regional cerebral blood flow during nitroglycerin-induced CH attacks, observed hypothalamic activation among patients with CHs during CH bouts, which was not observed among patients with CHs when bouts were not occurring. The same group also observed morphometric and structural abnormalities in the hypothalamic region of patients with CHs (20), which further supports the hypothesis of a central origin of the disease. If a central dysfunction involving hypothalamic circuitry is linked to CHs, then it seems reasonable to question whether surgical strategies can be used to rebalance unbalanced or disturbed circuits. According to current models of basal ganglion circuitry, the akinetic and rigid symptoms of Parkinson’s disease result from hyperactivity of the globus pallidus internus and the substantia nigra pars reticulata, as a consequence of increased glutamatergic drive from a disinhibited subthalamic nucleus. Although the mechanism of high-frequency, deep brain stimulation remains unknown, the therapeutic effect observed after long-term, high-frequency, deep brain stimulation in Parkinson’s disease seems to be the result of an inhibitory effect of current delivery on hyperactive neurons in the subthalamic nucleus (1). Using the same kind of logic, we now suggest that a similar mechanism may account for our preliminary success with the use of deep brain, hypothalamic stimulation among patients with CHs. Such a mechanism may be involved in the proposed role that a hyperactive posterior hypothalamus may play in chronic CHs. Although our results are consistent with the hypothesis that rebalancing of a hyperactive hypothalamus is responsible for the observed therapeutic effect, we cannot exclude the possibility of a more generic analgesic effect resulting from activation of some pain-modulating pathway, such as that involving the release of endogenous opiates (3). However, at least two findings argue against that concept. First, we observed no preoperative responses to opiates for any of our patients. Second, we observed prolonged pain relief, without the development of the kind of tolerance that has been observed among patients undergoing periaqueductal gray matter stimulation for treatment of chronic pain of different origins.

For determination of the target coordinates, we integrated new data from functional neuroradiological studies with old data from the literature on hypothalamic stereotactic surgery. The first evidence of surgical manipulation of the hypothalamus for pain relief was reported by Fairman (6) in 1972. Before Fairman, Spiegel et al. (33) performed stereotactic procedures on the lateral hypothalamus for the treatment of psychosis. Surgical procedures on the posteromedial hypothalamus to treat behavioral disorders, such as violence and aggression, and to relieve malignant facial pain were reported by Sano (30). Sano et al. (31) also reported studies in which intraoperative high-frequency stimulation of the hypothalamus was used to target a lesion area. In that report, they noted analgesic effects, autonomic responses (such as hypertension, tachycardia, respiratory suppression, hyperpnea, tachypnea, and mydriasis), and somatomotor responses. No such effects were observed for our series of patients with CHs, probably because of differences in both the targeting and the stimulation parameters.

**CONCLUSIONS**

To our knowledge, this is the first report of the successful treatment of a series of patients with chronic CHs with the use of long-term, high-frequency stimulation of the ipsilateral posterior hypothalamus. These preliminary results provide evidence suggesting that hypothalamic stimulation might offer a safe and effective treatment for CHs, without the troublesome side effects associated with lesioning procedures. The therapeutic rationale for our work is based on advanced functional studies that identified the hypothalamus as the origin of CH attacks. We suggest that the disappearance of CH attacks we observed might be attributable to stimulation-induced rebalancing of the allegedly hyperfunctioning hypothalamic neu-

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Date of surgery</th>
<th>Follow-up period (mo)</th>
<th>Complete pain control</th>
<th>Medication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (right side)</td>
<td>July 14, 2000</td>
<td>22</td>
<td>After 1 mo</td>
<td>None</td>
<td>None, Sex and food intake normalization</td>
</tr>
<tr>
<td>1 (left side)</td>
<td>May 31, 2001</td>
<td>12</td>
<td>Immediate</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>November 17, 2000</td>
<td>18</td>
<td>After 2 mo</td>
<td>Methysergide, 3–4.5 mg/d</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>May 22, 2001</td>
<td>12</td>
<td>After 2 mo</td>
<td>Verapamil, 80–360 mg/d</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>October 11, 2001</td>
<td>7</td>
<td>After 4 mo</td>
<td>Methysergide, 4.5 mg/d</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>March 22, 2002</td>
<td>2</td>
<td>After 48 h</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Hypothalamic Stimulation for Chronic Cluster Headaches

rons, an hypothesis that supports the central origin of CHs. Finally, it should be noted that this is the first direct therapeutic application of neuroimaging functional data leading to a restorative reversible approach to the treatment of this type of disabling condition.

REFERENCES


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Comments

Franzini et al. report an interesting series of five patients with intractable cluster headaches (CHs) who were treated with chronic electrical stimulation of the hypothalamus. CH is one of the most severe types of headache and affects approximately 0.1% of the population. Approximately 4% of CH cases may be completely refractory to medical treatment, and only these cases are considered for surgical treatment. The cause of CH has not been defined with certainty, and the disease is presumed to be of central etiology, including vasoreactivity, hypothalamic dysfunction, or oxyhemoglobin desaturation. According to current theories, some nerve fibers deep within the hypothalamus that regulate bodily rhythms may be responsible for regular triggering of CH. The action of lithium carbonate, which is a drug that has been used to prevent CH, may be related to its regulative effect on hypo-
thalamus. Only a few sporadic experiences have been described, however, in which an analgesic effect was reported after hypothalamic stimulation. The authors, theoretically and appropriately, propose that hypothalamic inhibition with high-frequency electrical stimulation may be effective in the treatment of patients with CH. Furthermore, they have performed the procedure in a series of cases. We think that this attempt to treat patients with CH is rather brave and creative. Hypothalamic stimulation seems to be effective in all cases. The number of cases studied is not adequate, however, to conclude that this treatment may be effective in all intractable cases. The length of follow-up is short in some cases (e.g., 1 month), and long-term follow-up is needed to reach a definitive conclusion about the treatment’s effectiveness. A large series with long-term follow-up reported by the same investigators would be valuable in terms of its clinical and neurophysiological aspects.

Invasive procedures, such as trigeminal radiofrequency rhizotomy, glycerol rhizolysis, sphenopalatine ganglion lesions, have been performed in patients with medically intractable CH with varying success rates. In our opinion, deep brain stimulation (DBS) should not be considered as a minimally invasive procedure with a low risk rate. The destructive procedures are less sophisticated and less expensive than neurostimulation. We have performed trigeminal radiofrequency rhizotomy in 10 patients with intractable CH, and complete or satisfactory pain relief was obtained in 8 of 10 cases. A series of patients who were treated with glycerol rhizolysis also was reported, with promising results demonstrated. We think that hypothalamic stimulation should be considered for patients whose CH is refractory to medical and percutaneous destructive procedures.

As a result of this experimental and clinical neurosurgical series, hypothalamic stimulation seems to be an effective treatment for patients with intractable CH. We think, however, that this treatment modality should be considered only if all other surgical techniques have failed.

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This report undoubtedly marks a breakthrough in the management of perhaps the most incapacitating and difficult-to-treat pain condition. Any clinician who has faced a patient who presented with a therapy-resistant CH attack knows that this experience is a most frustrating one, because there is virtually nothing to offer the patient; in desperation, one tends to administer increasing doses of intravenous opioids to no avail. Some have also tried administering gasserian ganglion stimulation through an electrode implanted in the foramen ovale, but with limited beneficial effect. Needless to say, one of the attractive features of the novel therapy that the authors describe is its nondestructive, reversible nature. The authors explain that the stimulation target is identical to that explored for lesioning interventions described by Sano (1, 2) as a treatment for patients with aggressive and violent behavioral dis-
(1) depicts this area posterior to the hypothalamus and medial to the red nucleus in the region of the PVG. The authors provide little information concerning their microelectrode recordings. Given their coordinates, however, the microelectrode recording data may actually be from the red nucleus. Arguments for a target distinct from PVG on the basis of both the lack of opioid responsiveness and tolerance are not necessarily valid. It is well known that PVG stimulation has both opioid and nonopioid analgesic effects.

The authors’ technique certainly represents a promising treatment for patients with refractory CH, although the results need to be confirmed in a larger series. It is unclear, however, whether this treatment represents a new target for DBS or merely a new application of an old DBS target. Perhaps more detailed microelectrode recordings from this region or a study comparing classic PVG stimulation with posterior hypothalamic stimulation would answer the question whether this target for DBS is truly new and distinct.

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