Hypothalamic Deep Brain Stimulation for the Treatment of Chronic Cluster Headaches: A Series Report

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Introduction

Chronic cluster headache (CH) is one of the most severe facial pain syndromes. Pain usually starts in or around the eye or the temple and may occasionally affect also the face, the neck, the eye or the entire hemicranium. Attacks are generally unilateral and start with sudden, deep, non-fluctuating and excruciating pain, which shifts to the contra-lateral side in about 15% of patients. Attacks may last from 15 min to 3 h, range in frequency from 8/day to 1/week, and occur 5 to 10 times daily in severe chronic forms. Pain is accompanied by autonomic symptoms such as lacrimation from the eye in the affected side, nasal discharge, eye reddening and sweating. Pain attacks may usually be triggered by the sublingual administration of 1 mg nitroglycerin.

CH has traditionally been considered as a vascular headache but there is clinical evidence suggesting that vascular reactions observed during the attacks are primarily due to CNS discharge. Posterior hypothalamus has been recently identified as the possible central generator of pain: positron emission tomography (PET) has shown activation in the ipsilateral inferior hypothalamic gray matter during CH attacks [1] and morphometric magnetic resonance imaging (MRI) has demonstrated an increase in neuronal hypothalamic size and density in CH patients [2]. In 1970, Sano [3] performed posterior ipsilateral hypothalamotomy to treat cancer facial pain. Since the target area was close to the hypothalamic area evidenced by PET during CH, this prompted the authors to investigate the effects of hypothalamic stimulation in CH patients and stereotactic hypothalamic surgery was successfully performed in the first patient in July 2000 [4].

Methods

Since July 2000, seven additional patients have been undergone to stereotactic hypothalamic surgery. The patient selection was performed by a co-operative team of neurologists experienced in headache and of neurosurgeons. The initial diagnosis of CH was made according to the classification of the International Headache Society [5]. Patients were receiving treatment with a number of drugs, alone or in combination such as corticosteroids, lithium, methysergide, ergotamine, calcium channel blockers, beta-adrenergic blockers, tricyclic antidepressants, valproate, topiramate, gabapentin, melatonin and non steroidal anti-inflammatory agents. Transnasal endoscopic block of sphenopalatin ganglion was performed twice in all patients before taking into consideration more invasive surgical procedures. Patients who after at least 1 year did not have pain remission were considered to be candidates for hypothalamic surgery, were examined to exclude psychiatric complications and informed on the classical surgical procedures available for treatment of intractable CH.
Of the 8 patients who underwent hypothalamic surgery since July 2000, 5 were males and 3 females, their ages ranged from 27 to 63 years (median age: 42 years), the duration of CH ranged from 1 to 7 years and the number of daily bouts ranged from 1–4 to 6–8.

Stereotactic implants were performed under local anesthesia and a pre-operative MRI was used to obtain high definition anatomic images which made possible the precise determination of both anterior commissure and posterior commissure line and of position and limits of basal ganglia and main mesencephalic nuclei. A rigid cannula was inserted through a frontal paramedian burr hole and positioned up to 10 mm from the target. This cannula was used both as a guide for micro-recording (Lead Point, Medtronic) and for placement of the definitive electrode (DBS-3389, Medtronic). After macro-stimulation to evaluate potential side effects, the guiding cannula was removed and the electrode secured to the skull, then an extension cable was connected to the electrode, tunneled subcutaneously and brought out of the skin through a stab wound. After 7–10 days of trial stimulation, the electrodes were connected to a permanent, implanted neuropulse generator (Itrel II, Medtronic) positioned subcutaneously in the subclavicular area and chronic stimulation was started after daily CH attacks reappeared. The stimulation parameters employed were: amplitude: 0.5–3.8 V, frequency: 185 Hz, pulse width: 60 microsec. Voltage was gradually increased until the therapeutic effect appeared.

Results

All patients experienced complete pain relief after 1 to 10 weeks of high-frequency hypothalamic stimulation (on average: 4.4 weeks). Three of 8 patients remained pain-free without the need of any medication, while in 5 cases attacks recurred but responded satisfactorily to low doses of methysergide or verapamil, drugs which had been completely ineffective prior to the surgical intervention. No unwanted effects attributable to chronic stimulation nor acute complications from the implant procedure were observed. There was no clinical evidence of autonomic effects related to hypothalamic stimulation: 24-hour monitoring of arterial BP showed asymptomatic orthostatic hypotension in 4 patients. In 2 cases the stimulation had to be turned off and this resulted in the sudden reappearance of CH attacks which immediately disappeared on resumption of stimulation.

The first patient who was operated in July 2000, required a contralateral second implant because of bilateral CH. Chronic stimulation of left posterior hypothalamus was successful in producing complete ipsilateral pain relief, but 8 months after right radio-frequency trigeminal rhizotomy, which had been effective in obtaining cessation of attacks, right-sided, drug refractory pain attacks recurred at a rate of 3–8 per day. After stereotactic implant in the right posterior hypothalamus and the immediate start of continuous stimulation, right sided attacks disappeared.

In another patient, who showed only a 20% decrease in attacks after the intervention, MRI showed that the electrode was 4 mm posterior to the optimal estimated target and a replacement procedure was therefore performed. A marked reduction in pain attacks occurred only a few days after the intervention.

Conclusions and Implications for Clinical Practice Today

Although a broad range of pharmacological agents is employed for treatment of CH, there are patients who develop chronic, unremitting CH refractory to any medical management. Surgical treatments based on the interruption of autonomic pathways and/or on partial or total trigeminal lesion show that success is inevitably accompanied by complications such as sensory deficit and subsequent dysesthesias, painful anaesthesia, facial numbness, keratitis, etc. Recurrence rate also remains high after complete trigeminal deafferentation.

The recent PET findings during attacks and the hypothalamic abnormalities found in these patients suggest that a central dysfunction involving hypothalamic circuitry is involved in CH. Data supporting this hypothesis are:

- the effect of stimulation is strictly ipsilateral, as shown by one of our cases;
- the correct placement of the electrode in the posterior hypothalamus is mandatory to obtain a satisfactory result;
- in CH patients, opiates are not effective, ruling out a generic analgesic effect due to the release of endogenous opiates;
- the prolonged duration of pain relief in the absence of the development of tolerance, which on the contrary appears in patients undergoing peri-acqueductal gray matter stimulation for different types of pain [6].
Contrary to the findings of Sano [3] no undesirable autonomic responses were observed in these patients.

**Future Directions**

The cases reported in this paper represent the largest series of patients with chronic CH, successfully treated with high-frequency hypothalamic stimulation.

The results described suggest that this technique may represent an effective and safe treatment of CH and that it can also be employed bilaterally in case of attacks affecting both sides of the cranium. Dedicated software is being developed at Istituto Neurologico Besta to facilitate a precise placement of the electrode during the stereotactic intervention for target planning.

**References**