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Hypothalamic deep brain stimulation for intractable chronic cluster headache: a 3-year follow-up

Abstract Cluster headache is the most severe among primary headaches. Positron emission tomography and functional MRI studies have demonstrated that the ipsilateral posterior hypothalamus is activated during cluster headache attacks and is structurally asymmetric in these patients thus indicating that cluster headache may originate at that level. These hypothalamic abnormalities in cluster headache led to the suggestion that deep brain stimulation of ipsilateral posterior inferior hypothalamus might produce clinical improvement in otherwise treatment refractory chronic cluster headache patients. In a patient with severe intractable chronic cluster headache, hypothalamic electrical stimulation produced complete and long-term pain relief with no relevant side effects. So far other operations have been performed and the results are encouraging in terms of both pain relief and safety. The efficacy of hypothalamic electrical stimulation provides some hints into cluster headache pathophysiology.

Key words Cluster headache • Hypothalamus • Deep brain stimulation • Therapy • Pathophysiology

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Introduction

Cluster headache (CH) is the most severe among the primary headaches [1]. The intractable chronic form of CH is rare, nonetheless it constitutes a major clinical problem. Lack of understanding of the mechanisms underlying CH has hampered the development of new treatments [2]. The increase of calcitonin gene-related peptide (CGRP) and vasoactive intestinal polypeptide (VIP) in the blood of the ipsilateral jugular vein during CH attacks indicated activation of the trigeminal nerve and the parasympathetic branch of the facial nerve by way of the trigemino-facial reflex [3]. Trigeminal activation in CH justifies surgical procedures on this nerve to relieve intractable CH cases [4]. The high recurrence rate of attacks and potentially severe side effects (facial sensory loss, facial dysesthesias, anesthesia dolorosa, corneal anesthesia, corneal ulceration, and loss of vision) indicate the need of other therapeutic options [5]. Activation of the trigemino-facial reflex explains the pain and the autonomic phenomena of CH attacks [6], but the question remains: how is this reflex triggered?

Involvement of the hypothalamic pacemaker was suggested by the typical seasonal recurrence of cluster periods and the occurrence of the attacks at fixed times of the day [7, 8]. Neuroendocrinological studies on circadian hormonal rhythms and secretion, particularly melatonin [9, 10], disclosed anomalies suggesting hypothalamic dysfunction in CH [11].

In recent years, positron emission tomography (PET) and functional MRI studies have demonstrated that the ipsilateral posterior inferior hypothalamus is activated during CH attacks and is structurally asymmetric in CH patients, respectively [12, 13]. These anomalies are specific to CH and not reported in other conditions such as migraine and experimental first-division trigeminal pain, or in CH patients given nitroglycerin during a remission phase [14, 15]. Taken together, these data led to the proposal that the hypothalamus is the site of the cluster headache generator [12]. For the first

time the lesion site of a primary headache seems to have been identified.

In movement disorders, the brain structures responsible for clinical phenomena have been established; this knowledge was the rationale for the use of deep brain stimulation (DBS) with stereotactically placed electrodes to treat these patients when drugs were no longer effective [16, 17]. Identification of the hypothalamic anomalies in CH led to the suggestion that DBS into that site might improve intractable forms of CH. We performed hypothalamic DBS in a patient suffering from severe intractable chronic CH (CCH) who previously received four surgical procedures on the trigeminal nerve, and in whom further trigeminal operations were contraindicated [18]. Electrode implantation was performed on July 2000 and the CH attacks disappeared. When the stimulator is turned off, the crises reappear; when it is switched on again, the headaches disappear [18]. So far other operations have been performed and the results are encouraging in terms of both pain relief and safety [19–21].

After this first observation we have now performed 8 more stereotactic implantations in that brain area bringing the total to 9 implants in 7 patients (5 men; age range, 27–63 years). All suffered from chronic intractable cluster headache diagnosed according to IHS criteria. Two patients had bilateral cluster headache and received bilateral deep brain stimulation. A secondary cause was ruled out in all cases by MRI and angio-MRI. The average number of attacks per day was 7.

Results

Up to now the follow-up ranges from 3 to 33 months. No add-on pharmacological therapy is necessary in 6 patients and they are pain free. One patient began to experience attacks again in the last three months after a 18-month pain-free period; he is now taking methysergide (3 mg/day) and verapamil (360 mg/day). In 4 patients, switching off and turning on the stimulator induces reappearance and disappearance of pain attacks respectively.

Blood pressure, heart rate, electrolyte balance, hormone levels and behavior are normal in all patients.

Conclusions

Deep brain stimulation is so far well tolerated by our patients. These results confirm that deep brain stimulation of the ipsilateral posterior inferior hypothalamus is an efficacious and safe treatment for intractable chronic cluster headache. In addition, these results confirm the relevance of this brain area in cluster headache pathogenesis. The effect of hypothalamic DBS is restricted only on the stimulated side since in the two bilateral CH patients DBS did not improve attacks on the opposite side. An interesting finding is that CH attacks improved following hypothalamic DBS notwithstanding sensation in the trigeminal branches was intact. This contrasts with the findings usually observed after surgical procedures on the trigeminal nerve to relieve CH where, in order to relieve CH attacks, it is necessary to obtain marked loss of sensation in trigeminal territories. Taken together these two findings strongly suggests the *central origin* of pain in cluster headache.

When the stimulator is switched off, attacks reappear; this indicates that, as expected, hypothalamic DBS does not induce permanent pain improvement in CH. The latency between switching off the stimulator and pain recurrence may vary deeply, from a few days to months. This suggests a complex mechanisms of hypothalamic DBS in relieving CH pain, involving a complex brain circuit.

During an operation we had the opportunity to record neuronal activity in the posterior inferior hypothalamus [20, 21]. This neuronal activity was recorded during a spontaneous CH attack. The attack ceased few minutes after sumatriptan injecton and the neuronal activity in the hypothalamus also stopped. This observation needs to be observed in other cases. If confirmed, it will lend further support to the hypothesis that the hypothalamic PET activation observed during the attacks is due to an increased neuronal activity at that level. This finding could be the very first proof directly indicating that a neuronal discharge is responsible for a primary headache, validating the use of the term *neurovascular headaches* instead of the old term of *vascular headaches* [12].

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