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Neuromodulation in treatment of refractory headaches

Angelo Franzini · Massimo Leone · Giuseppe Messina · Roberto Cordella · Carlo Marras · Gennaro Bussone · Giovanni Broggi

Abstract The field of neuromodulation is emerging as a promising and alternative therapeutical option for many drug-resistant clinical conditions, including painful syndromes such as refractory chronic cluster headache (CCH) and trigeminal neuralgia. We here report a series of patients who have undergone Deep Brain Stimulation (DBS) of Posterior Hypothalamus for chronic cluster headache, trigeminal neuralgia and atypical facial pain, matching their corresponding clinical results and also suggesting a role for Great Occipital Nerve Stimulation (which is a much less invasive procedure) in the treatment of CCH. According to us, the refinement of surgical techniques and of metabolic and functional brain neuroradiological investigations will lead to a refinement of the therapeutical strategies in such patients.

Keywords Trigeminal neuralgia · Cluster headache · Neuromodulation

A. Franzini (✉) · M. Leone · G. Messina · R. Cordella · C. Marras · G. Bussone · G. Broggi
Neurological Institute Foundation "C. Besta"
Milan, Italy

Introduction

After the first successful operation on a patient affected by chronic cluster headache (CCH) [1], neuromodulation became an available procedure for patients affected by painful syndromes of the face refractory to conservative treatments. Chronic high-frequency stimulation of the posterior hypothalamus (pHyp) has been the first therapeutic application of functional neuroimaging data [2] to plan a restorative reversible procedure for the treatment of an otherwise refractory neurological condition. Sano et al. [3] were the first to report the correspondent stereotactic pHyp lesional technique. The surgical techniques of deep brain stimulation (DBS) and great occipital nerve (GON) stimulation are reported and discussed.

Material and methods

The technique of DBS in CCH patients has been extensively reported in many published papers [1, 4–10]. DBS of the pHyp has also been performed in three patients affected by atypical facial pain and in five patients affected by multiple sclerosis (MS) and trigeminal neuralgia involving the first trigeminal division (paroxysmal pain within the second and third divisions had been previously treated by repeated selective percutaneous thermorhizotomies). The risks of corneal reflex impairment and cheratitis led us to consider a neuromodulation procedure as an alternative to lesional procedures in MS patients.

In spite of its long-lasting benefits, DBS of the pHyp must be considered a major surgical procedure and so since 2005 we have also used chronic stimulation of the GON [1, 4–8, 11–17] to treat CCH and other painful syndromes of the face before considering DBS. This procedure, in our experience, may provide relief in about 30% of CCH

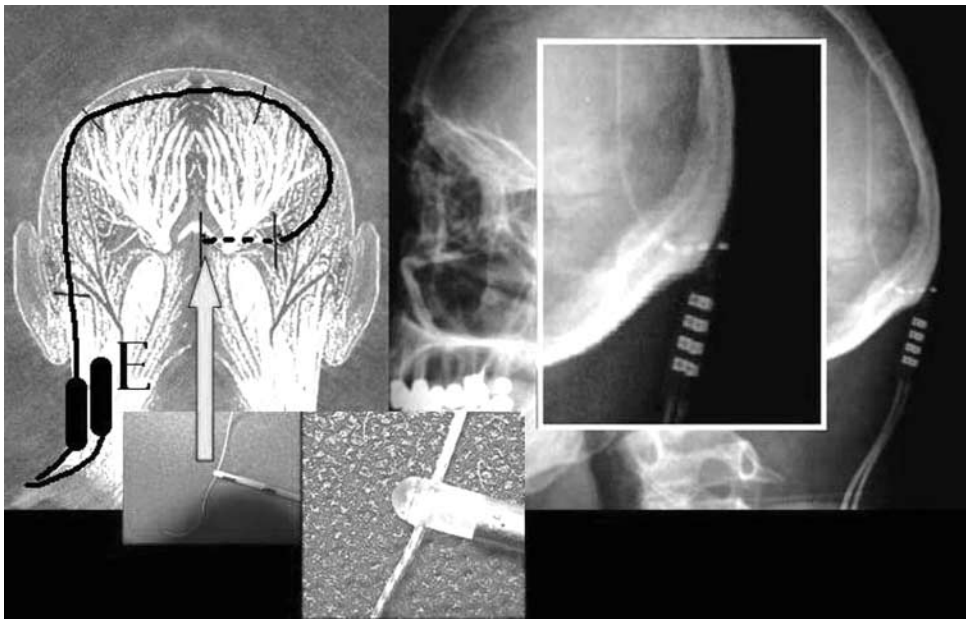

Fig. 1 Stimulation of the GON performed before the pHyp electrode implant. Note the free extension (*E*) of the dual-channel Kinetra (Medtronic inc. Minneapolis) IPG ready for connection to the deep brain electrode

patients, while results in other painful syndromes of the face are promising but still limited to only five patients who are currently under evaluation and whose follow-up is still too short for drawing any conclusion about them.

Surgical technique of GON stimulation

A wired quadripolar electrode lead (PISCES Medtronic, Minneapolis, USA) is placed within the first dividing branches of the GON on the affected side and the tip of the electrode is secured to the fascia of the splenium capitis muscle just laterally to the occipital protuberance. The technique is represented in Figure 1. The lead is then tunnelised subcutaneously to the subclavicular region and connected to the pulse generator (Kinetra, Medtronic, Minneapolis, USA). The stimulation parameters for GON are 50 Hz, 2–4 V and 90 ms PW.

Results of posterior hypothalamus DBS

CCH series

The mean follow-up is 24 months (range 12–62 months). The recently reported detailed results of DBS [6] are summarised in the following remarks:

- In the whole series, 71% of postoperative days were pain free and intensity and duration of pain bouts were significantly reduced.
- Drugs were reduced to less than 20% of the preoperative condition.
- The mean time to stable benefit (pain free or reduction) was 42 days (range 1–86 days).
- The mean stimulation amplitude was 2.4 V (range 0.6–3.3 V).

Twelve of the stimulators (9 patients) were switched off at least once in single-blind fashion. After switching off, pain recurred after an interval of 2 months, which seemed to be unrelated to the duration of previous stimulation; the pain improved or disappeared when the stimulator was turned back on. In patients with bilateral crises, turning the stimulation on and off abolished or improved crises only on the ipsilateral side.

Neuropathic pain and atypical facial pain

After surgery, the 3 operated patients had no reduction in pain. The stimulation parameters were the same as for CCH and SUNCT patients (180 Hz, 60 ms, mean voltage 1.3 V). After four months of continuous stimulation (6, 8 and 10 months, respectively) the continuous pain was the same as preoperatively. Increase of amplitude did not offer any pain relief. Amplitude higher than 3 V induced dizziness and oculomotor activation in all cases. Bipolar stimulation did not offer any improvement. When the internal pulse generator (IPG) was switched off with the patient being unaware of it, the episodes of paroxysmal pain were described by the patient as being slightly more intense than those that occurred during stimulation.

MS trigeminal neuralgia

At 1–3 years of follow-up, two out of five operated patients were pain free and drug free after chronic stimulation, while the remaining three patients had improved

and felt their pain was under control, though they were still taking medication in combination with pHyp stimulation. DBS had beneficial effects on pain limited to the first trigeminal branch for an average of 23 months. After the implant (median 20 months), three patients underwent a further thermorhizotomy lesional procedure to selectively alleviate the pain in the II and III branch, but not in the first, so as to preserve the corneal reflex.

Conclusion and discussion

DBS in CCH patients has achieved a significant reduction of pain bouts. The procedure is also well tolerated. Transient reversible diplopia is the main limitation to increasing amplitude. Before the operation, none of the patients were able to work. As a result of stimulation, most patients' lives have gradually returned to normal; most have resumed work.

Nevertheless, some problems may be seen from our experience. The diagnosis of CCH must be precise and supported by the headache classification criteria [15]. Comorbidity with other painful syndromes of the face and sometimes with personality disorders [18] may result in wrong diagnosis. To avoid this bias in patient selection we suggest strict cooperation with headache specialists, psychiatrists and dedicated headache units. pHyp stimulation benefits only CCH patients and is uneventful in other pain syndromes of the face such as atypical facial pain and neuropathic pain [4].

About 30% of CCH patients may have significant improvement after peripheral neuromodulation procedures (GON), suggesting the existence of different subtypes of patients in the same nosographic class. In other words, in a certain amount of CCH patients the peripheral pathogenetic mechanisms may be more relevant than the central ones. To fix this problem we suggested GON stimulation and sphenopalatine ganglion local anaesthetic blocks prior to DBS surgery. In the future PET studies and brain functional MRI may provide preoperative imaging of hypothalamic involvement in individual patients affected by CCH [13], allowing further refinement of the indication for DBS.

Although an up-to-date worldwide literature analysis limits the percentage of DBS responder patients to about 50%–60% [9, 10], we think that refinement of the targeting procedure and patient selection will further improve the success rate of pHyp stimulation in CCH patients. Nevertheless, DBS has changed the poor therapeutical outcomes in CCH patients we operated on.

Finally, we have to remember that CCH is a dramatic debilitating condition leading to abuse of steroids (two patients of the operated series were unable to walk due to severe leg myopathy induced by chronic steroid abuse). Also, the abuse of triptans may be life-threatening (one patient died before the implant due to myocardial infarct). DBS benefits this condition and the cost of the procedure is largely compensated for within the first year of induced remission, even if the disease cannot be definitively cured by DBS.

Atypical facial pain did not respond at all. Trigeminal paroxysmal pain attacks responded only when limited to the first trigeminal division. These data suggest pathogenetic and anatomic links between the pHyp, the first trigeminal division, the reticular formation and the autonomic system of the face [19]. GON stimulation allows a less invasive way to interact with the descending nucleus of the fifth nerve and brainstem nuclei through an antidromic activation via the C1-C2 roots; the safety of this procedure and the promising preliminary results suggest a future role of GON stimulation in the treatment of refractory headaches.

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