Chapter 12
Refractory Chronic Migraine: Therapy with Combined Peripheral Neurostimulation

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About 3 % of patients with episodic migraine each year trend toward a process of chronicity. These patients become refractory to prophylactic pharmacological therapy, leading to a high level of disability that affects their activities of daily living.

In 2003 Popeney published the first case series of 27 patients with refractory migraine who underwent occipital neurostimulation (ONS). After an 18-month follow-up, the results of this initial study were encouraging: 88 % of patients had a reduction in the number of attacks, and the intensity of headache was reduced by ≥50 %.

Anatomically, there is a functional relationship between the upper cervical sensitive afferents and the nucleus of the trigeminal nerve. This relationship has been demonstrated using animal models, from which the concept of the trigeminal cervical complex (TCC) was developed. The activation of the TTC is able to activate the parasympathetic autonomic response, which involves the sphenopalatine ganglion (SPG).

12.1 Case Description

The patient is a 49-year-old female shop assistant who has been under treatment at our center for about 10 years for progressive, difficult-to-treat migraine and tension-type headache localized to the occipital, left frontal, and left periorbital regions,

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with no coexisting painful diseases in anamnesis. During these years she has been treated prophylactically with anticonvulsants, tricyclic antidepressants, calcium channel blockers, and onabotulinumtoxin A.

She also has a history of uncontrolled use of drugs for acute migraine ranging throughout all of the pharmacological classes, such as acetaminophen, nonsteroidal anti-inflammatories, triptans, ergot derivatives, and drugs containing barbiturate combinations. Moreover, via "doctor shopping" she obtained opioids on prescription, which she tried without therapeutic success. She has since stopped using this wrong and harmful therapeutic approach.

For this reason she has fallen into a state of medication-overuse headache (MOH), which has been treated with seven repeated detoxification procedures, unresponsive to corticosteroids.

Visits to the emergency department became more frequent, with an increasing number of absences from work, and with a psychopathological profile clearly more oriented toward suicidal intent.

12.2 Differential Diagnosis

The absence of secondary pathology underlying the clinical diagnosis of chronic migraine followed by refractory chronic migraine was excluded twice, using magnetic resonance imaging, in November 2009 and then in December 2011.

12.3 Surgical Management

Considering the refractoriness to pharmacological therapy, it was decided in February 2012 to refer the patient for peripheral neurostimulation treatment.

Both ONS and supraorbital nerve stimulation (SONS) were the object of discussion regarding the therapeutic decision. As the current evidence base at the time reported the ONS to be the best interventional treatment for refractory chronic migraine with or without MOH, we decided to proceed with ONS, reserving the possibility to use SONS later.

In the 4 weeks before implant, the average self-reporting pain intensity was 5/6 on the Numeric Rating 11–point Scale (NRS), with 56 crises lasting 5–6 h with NRS 9/10. The patient took 32 tablets of ibuprofen 400 mg, 12 tablets of rizatriptan 10 mg, and 10 tablets of acetaminophen 500 mg/codeine 300 mg.

In April 2012, the patient was submitted to a workup in preparation for ONS.

She was first referred for psychological assessment to evaluate the psychosocial risk factors, after which colonization by methicillin-resistant *Staphylococcus aureus* was excluded by nasal swabbing.

The patient was placed in the prone position. After infiltration with local anesthetic, a midline access was chosen to avoid the occipital arteries and greater occipital nerve injury (5–28 mm lateral to midline). A vertical incision was made, extending approximately 4 cm caudal from a point 1 cm below the occipital protuberance. A subcutaneous pocket was fashioned by a lateral blunt dissection, exposing the fascia for anchoring.

A curved Tuohy needle, with a plastic stylet for easy removal, was advanced laterally 6–7 cm off midline, in a subcutaneous plane under ultrasound guidance to place the lead just above the fascia to a depth of approximately 0.8–1.2 cm.

One quadripolar lead (Pisces Quad Model 3487A-45; Medtronic, Inc, Minneapolis, MN, USA) was placed on each side and then anchored to the fascia of the lateral pocket by a plastic anchor and 2-0 nonabsorbable suture. To prevent lead migration, a strain loop was positioned in the occipital pocket.

Extensions were then tunneled and externalized to be connected to an external pulse generator.

The patient reported a significant reduction in the frequency and severity of her headaches during the 2-week trial period, and proceeded to permanent implantation under local anesthesia. Two extensions were tunneled down and connected to an implantable pulse generator (IPG) (Restore Ultra Model 3; Medtronic, Inc).

At 6-month follow-up, the patient's headache symptoms and prestimulator medications were significantly reduced.

In December 2012 the patient required an urgent visit because of worsening symptoms. In the previous month the symptoms had returned to the levels of the preimplantation period.

We tested different stimulation programs to change the polarity of contacts, rate, and pulse width, but with no therapeutic effect, so we decided to implant an additional electrode.

In January 2013 the patient underwent a new surgical procedure to activate the trigeminovascular complex, which is able to activate the parasympathetic autonomic response that involves the SPG. A left supraorbital eight-pole lead (Model 3778; Medtronic, Inc) was placed under local anesthesia and sedation.

The lead was positioned subcutaneously under ultrasound guidance, tangentially to the superciliary arch. It was tunneled under the skin above the ear to the occipital region and then to the IPG.

The occipital four-pole leads were both programmed (0−, 1−, 2−, 3+), with an amplitude of 1.6 V (right lead) and 1.4 V (left lead), pulse width of 110 ms, and frequency of 40 Hz. The eight-pole supraorbital lead was programmed (0+, 1+, 2−, 5+, 7−) with an amplitude of 1,2 V, pulse width of 90 ms, and frequency of 60 Hz.

At 6-month follow-up after supraorbital implant, the patient's headache symptoms and the intake of medication were significantly reduced. The average pain score was NRS 2/4, with 11 crises lasting 5–6 h with NRS 6/7. She took 2 tablets of ibuprofen 400 mg and 2 tablets of rizatriptan 10 mg.

At 12-month follow-up the patient's headache symptoms and medication regimen were stable to an extent comparable with the previous control.

12.4 Review

The positive outcome of this case confirms the results from Slavin, Reed, Linder, and Datta, whereby the ONS combined with SONS produced a synergistic effect.

In 2009 Reed published the first report on the use of combined ONS-SONS for chronic migraine. Promising results were reported in the series of seven patients, with six describing near complete resolution of the pain and associated neurological findings.

Linder first described the use of combined ONS-SONS in a group of adolescents, and reported very good results over the long term.

According to the Melzack and Wall theory of "gate control," the somatosensory neurostimulation of afferent fibers A and B stops the metameric nociceptive transmission. Therefore, the generally accepted clinical approach for the treatment of pain using neurostimulation is to produce a paresthesia in the same region where pain is perceived.

Despite this, previous studies have shown that ONS is able to modulate the pain even in regions metamerically discordant from C2/C3. For example, Schwedt, Magis, Dodick, Burns, Amin, and Asensio-Samper used ONS to treat frontal or supraorbital pain.

This particular analgesic effect of peripheral stimulation in the head is due to the particular and unique anatomy and physiology of the TCC, where all of the cephalic somatosensory afferents converge.

The combined neurostimulation, in particular from the occipital and trigeminal territory, synergistically activate the TCC.

Combined neurostimulation can be used for the management of refractory chronic migraine. In the case reported here, the patient was able to significantly reduce the intake of medications in addition to headache frequency and intensity. The efficacy of treatment was found to prevail at 12-month follow-up.

Key Points

- *Criteria for diagnosis of refractory chronic migraine*
  1. Diagnostic definition of chronic migraine following the International Classification of Headache Disorders 3 beta
  2. Unresponsive over time to preventive drugs including onabotulinumtoxinA
  3. Presence of MOH
  4. Unresponsive over time to the detoxification procedure for MOH
- *Multidisciplinary approach*
- The success of ONS depends on the close cooperation of the migraine physician, the psychologist, and the interventional pain physician.

1. The migraine physician makes the correct diagnosis, and states the indication for neurostimulation having established the ineffectiveness of medical therapy.
2. The psychologist assesses, by interview and the use of standardized measures, the mental health and social risk factors, in addition to the understanding of ONS by the patient and the expectations for the relief of pain.
3. The pain physician expert in neurostimulation performs the implant, minimizing the adverse events.

- *ONS adverse events*

1. Lead migration
2. Infection
3. Lack of efficacy
4. Lead malfunction
5. Battery malfunction
6. Pain at IPG
7. Lead skin erosion

Suggested Reading

1. Amin S, Buvanendran A, Park KS, Kroin JS, Moric M (2008) Peripheral nerve stimulator for the treatment of supraorbital neuralgia: a retrospective case series. Cephalalgia 28(4):355–359
2. Asensio-Samper JM, Villanueva VL, Pérez AV, López MD, Monsalve V, Moliner S, De Andrés J (2008) Peripheral neurostimulation in supraorbital neuralgia refractory to conventional therapy. Pain Pract 8(2):120–124
3. Bartsch T, Goadsby PJ (2003) Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater. Brain 126:1801–1813
4. Becser N, Bovim G, Sjaastad O (1998) Extracranial nerves in the posterior part of the head. Anatomic variations and their possible clinical significance. Spine 23(13):1435–1441
5. Burns B, Watkins L, Goadsby PJ (2009) Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. Neurology 72:341–345
6. D'Amico D, Leone M, Grazzi L, Bussone G (2008) When should "chronic migraine" patients be considered "refractory" to pharmacological prophylaxis? Neurol Sci 29(Suppl 1):S55–S58
7. Datta S, Reed KL, Will KR (2011) Combined supraorbital and occipital nerve stimulation in failed surgical treatment of migraine: case report and review of the literature [abstract]. Presented at American Society of Intervention Pain Physicians 2012 Annual Meeting, Washington DC, Pain Physician, 2011
8. De Filippis S, Erbuto D, Gentili F, Innamorati M, Lester D, Tatarelli R, Martelletti P, Pompili M (2008) Mental turmoil, suicide risk, illness perception, and temperament, and their impact on quality of life in chronic daily headache. J Headache Pain 9(6):349–357
9. Deshpande KK, Wininger KL (2011) Feasibility of combined epicranial temporal and occipital neurostimulation: treatment of a challenging case of headache. Pain Physician 14:37–44, This is the first report on combined cephalic neurostimulation since our original article (45 above)
10. Dodick DWST, Trentman TL, Zimmerman RS, Hentz J (2007) Trigeminal autonomic cephalalgias: current and future treatment. Headache 47:981–986

11. Goadsby PJ, Knight YE, Hoskin KL (1997) Stimulation of the greater occipital nerve increases metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn of the cat. Pain 73:23–28
12. Goadsby PJ, Zagami AS (1991) Stimulation of the superior sagittal sinus increases metabolic activity and blood flow in certain regions of the brainstem and upper cervical spinal cord of the cat. Brain 114:1001–1011
13. Goadsby PJ, Hargreaves R (2008) Refractory migraine and chronic migraine: pathophysiological mechanisms. Headache 48(9):1399–1405
14. Hoskin KL, Zagami AS, Goadsby PJ (1999) Stimulation of the middle meningeal artery leads to Fos expression in the trigeminocervical nucleus: a comparative study of monkey and cat. J Anat 194:579–588
15. Linder S (2011) Combined occipital/supraorbital nerve stimulation for treatment of refractory headaches: initial adolescent experience (ages 12–17) [abstract]. Headache 51:47
16. Lionetto L, Negro A, Palmisani S, Gentile G, Del Fiore MR, Mercieri M, Simmaco M, Smith T, Al-Kaisy A, Arcioni R, Martelletti P (2012) Emerging treatment for chronic migraine and refractory chronic migraine. Expert Opin Emerg Drugs 17(3):393–406
17. Magis D, Allena M, Bolla M (2007) Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol 6:314–321
18. Mammis A, Gudesblatt M, Mogilner AY (2011) Peripheral neurostimulation for the treatment of refractory cluster headache, long-term follow-up: case report. Neuromodulation 14:432–435
19. Martelletti P, Jensen RH, Antal A, Arcioni R, Brighina F, de Tommaso M, Franzini A, Fontaine D, Heiland M, Jürgens TP, Leone M, Magis D, Paemeleire K, Palmisani S, Paulus W, May A (2013) Neuromodulation of chronic headaches: position statement from the European Headache Federation. J Headache Pain 14(1):86
20. Narouze SN, Kapural L (2007) Supraorbital nerve electric stimulation for the treatment of intractable chronic cluster headache: a case report. Headache 47:1100–1102
21. Palmisani S, Al-Kaisy A, Arcioni R, Smith T, Negro A, Lambru G, Bandikatla V, Carson E, Martelletti P (2013) A six year retrospective review of occipital nerve stimulation practice–controversies and challenges of an emerging technique for treating refractory headache syndromes. J Headache Pain 14(1):67
22. Pompili M, Di Cosimo D, Innamorati M, Lester D, Tatarelli R, Martelletti P (2009) Psychiatric comorbidity in patients with chronic daily headache and migraine: a selective overview including personality traits and suicide risk. J Headache Pain 10(4):283–290
23. Popeney C, Alo K (2003) Peripheral neurostimulation for the treatment of chronic, disabling transformed migraine. Headache 43:369–375
24. Reed KL, Black SB, Banta CJ, Will KR (2010) Combined occipital and supraorbital neurostimulation for the treatment of chronic migraine headaches: initial experience. Cephalalgia 30:260–271
25. Reed KL, Will KR, Chapman J, Richter E (2011) Combined occipital and supraorbital neurostimulation for chronic migraine headaches: an extended case series [abstract]. Presented at 15th Congress of the International Headache Society, Berlin. Cephalalgia. pp 98–99
26. Schwedt TJ, Dodick DW, Trentman TL (2006) Occipital nerve stimulation for chronic cluster headache and hemicrania continua: pain relief and persistence of autonomic features. Cephalalgia 26:1025–1027
27. Schulman E, McGeeney BE (2013) Current concepts in refractory migraine. Curr Treat Options Neurol 15(1):40–55
28. Serafini G, Pompili M, Innamorati M, Gentile G, Borro M, Lamis DA, Lala N, Negro A, Simmaco M, Girardi P, Martelletti P (2012) Gene variants with suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation. Eur Rev Med Pharmacol Sci 16(10):1389–1398
29. Slavin KV, Colpan E, Munawar N, Wess C, Nersesyan H (2006) Trigeminal and occipital nerve stimulation for cranio-facial pain: a single-institution experience and review of the literature. Neurosurg Focus 21:1–5
30. Spencer SE, Sawyer WB, Wada H, Platt KB, Loewy AD (1990) CNS projections to the pterygopalatine para-sympathetic preganglionic neurons in the rat: a retrograde transneuronal viral cell body labeling study. Brain Res 534:149–169