Chapter 14
Neuromodulation in Other TACS and Other Primary Headaches

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14.1 Introduction

Trigeminal autonomic cephalalgias (TACs) are characterized by usually strictly unilateral headache with ipsilateral cranio-autonomic symptoms. From a clinical perspective, different clinical entities can be distinguished depending on frequency of attacks, duration of the individual attack, and treatment response to medication, in particular to indomethacin in some and to oxygen or triptans in others [1]. In most of the cases, pain intensity and quality are typically excruciating, duration is sometimes continuous (HC) or short lasting and often, medical treatment might be only in part successful or limited by side effects. From a pathophysiological point of view, hypothalamic activation is a common finding in all TACs.

Against the background of severe headache and difficult pharmacological treatment, neuromodulation might be considered a therapeutical opportunity. In this chapter, we will review current evidence for invasive and peripheral neurostimulation for pharmacologically refractory TACs other than cluster headache.

The remaining primary headaches [1] are typically not subject to neuromodulation. One exception in the literature is hypnic headache, which will be briefly reviewed at the end of this chapter.

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14.2 Paroxysmal Hemicrania

Paroxysmal hemicrania can be distinguished from cluster headache by its shorter duration (less than 30 min but longer than SUNCT), higher daily frequency and the absolute response to indomethacin [1–3]. In its chronic form, attacks occur without substantial remissions over longer than 1 year. Similar to cluster headache, the hypothalamus (contralateral, posterior part) might play an important role in its pathophysiology [4]. With regard to medical treatment, headache is characterized by an absolute indomethacin responsiveness. However, since indomethacin is a lifetime treatment, side effects, such as gastric ulcers, renal insufficiency, and cardiovascular events, can occur.

Several reports concern non-pharmacological treatment. Walcott et al. [5] treated with deep brain stimulation (DBS) of the posterior hypothalamus a 43-year-old female patient with chronic paroxysmal hemicrania who had to discontinue indomethacin due to gastritis and Barrett's oesophagus. Headache was well controlled over a follow-up period of more than 2 years. Interestingly, when the stimulator had to be switched off, headaches relapsed and after restarting stimulation, the patient again observed substantial improvement of her symptoms.

In contrast to such invasive central nervous system stimulation, Miller et al. [6] were able to control the pain using occipital nerve stimulation (ONS), an invasive peripheral stimulation, in a 26-year-old female suffering from chronic paroxysmal hemicrania. The patient was unable to tolerate indomethacin due to severe gastric side effects. She was implanted a bilateral greater occipital nerve stimulator and responded well over many years including three successful pregnancies [6]. Interestingly, improvement did not start earlier than several months after initiation. After 2 years, the device had to be replaced, and, again, symptoms improved after a delay of several months.

The GammaCore® device, a novel non-invasive handheld device stimulating the vagus nerve (VNS), was used by Tso et al. [7] for the treatment of six patients with paroxysmal hemicrania. One patient became attack-free while two did not respond. The remaining three had reduced severity, reduced frequency (two), and/or shorter duration (one). Response rate using VNS was thus two-third. Given the excellent side-effect profile of this device, VNS might be a promising add-on therapy or alternative to indomethacin in paroxysmal hemicrania.

14.3 Hemicrania Continua

Clinically, the key feature of hemicrania continua (HC) is a continuous, strictly unilateral and often retroorbital headache with some ipsilateral cranial autonomic symptoms. In addition to the continuous pain, patients often experience severe exacerbations lasting from hours to days with subsequent return to baseline. Together with paroxysmal hemicrania, HC belongs to the indomethacin-responsive

TACs. There is a prodigious clinical improvement to therapeutic doses of indomethacin [1, 2, 8] with similar limitations as described above for paroxysmal hemicrania. Similarly, there was contralateral posterior hypothalamic hyperperfusion in [^{15}O]-water PET, suggesting involvement of the hypothalamus in the generation of the condition and offering a putative target for invasive neuromodulation [9], which, to the knowledge of the authors, has not yet been addressed for therapy.

In 2006, Schwedt et al. [10] reported a case of a 44-year-old female who developed left post-traumatic HC-like headache that initially responded well but later incompletely to indomethacin. The medication was discontinued due to abdominal side effects and dizziness. Electrodes for ONS were implanted ipsilaterally to the headache with significant improvement: the continuous headache subsided and superimposed headache exacerbations were reduced in frequency. Interestingly, the patient continued to experience cranial autonomic symptoms without headache, suggesting that ONS might affect different mechanisms of the HC syndrome. Similarly, Burns et al. [11] reported prospective data from six patients with HC, who could not tolerate or had contraindications to indomethacin. All had ONS-electrode placement ipsilateral to the headache, and four patients improved significantly and one somewhat. All would recommend treatment to other patients. One patient had worsening of pain. Although long-term data have not been provided (median time of follow-up was 13.5 months), this study indicates that ONS could be a useful alternative for treatment of HC in some patients [11]. In respect of long-term data, Brewer et al. [12] reported two patients with HC and treatment with ONS, who were followed up for 85 and 38 months, respectively. Only the former patient had any benefit, which then would continue over the entire period. This suggests that when there is response of HC to ONS, it can be long-lasting. The largest study carried out [13] included 16 patients, who underwent ONS implantation in HC with intolerability of or contraindications for indomethacin and ineffectiveness of at least five alternative medications. Headache information was collected at baseline and then every 3 months. After ONS, patients experienced significant reduction in the number of total headache days per month (from 30 to about 22), average pain intensity, and various other parameters [13]. Interestingly, the typical problems with ONS, such as lead migration, infection or local mechanical irritation of the skin often requiring further surgical interventions [14], did not constitute a major issue in this work [13].

Despite the cautious optimism the above-mentioned studies may show, ONS is still an invasive treatment with inherent medical risks. The non-invasive alternative of vagus nerve stimulation (VNS) with the GammaCore® device was presented in abstract form by Nesbitt and colleagues [15]. Two HC patients with initial response to ONS but who had it explanted were treated with VNS. One patient used the device for prophylaxis and acute therapy and reported a reduction of background pain by 30% and of painful autonomic exacerbations by 20%. Stimulation was effective for acute treatment within 15 min. In the second patient, reduction of background and exacerbation pain was about 75% [15]. Similarly, Eren et al. [16] treated an HC patient with VNS who suffered from three myocardial infarctions under the use of indomethacin and who developed medication overuse of opiates while treating exacerbations. Vagus

nerve stimulation was able to reduce severity of headache exacerbations with subsequent reduction of opiate intake [16]. Similarly, Tso et al. treated nine patients with HC using VNS with GammaCore® as adjunctive therapy, who did not tolerate indomethacin at a therapeutic dose. Seven patients reported a reduction of the continuous pain and some had improvement of exacerbations [7]. These results are consistent with an open-label prospective clinical audit, collecting headache diaries in four patients with HC who were given a treatment trial with VNS because they did not tolerate indomethacin and failed greater occipital nerve blockade, topiramate, verapamil, melatonin, and gabapentin or pregabalin. Two patients responded with a reduction of the number of headache days by at least 30%, with headache day being defined as headache exacerbation lasting at least 4 h on a severity of at least 4/10 [17].

14.4 SUNCT/SUNA

Short-lasting unilateral neuralgiform headache attacks (SUNHA) are some of the most excruciating pain syndromes. Depending on the distribution of cranial autonomic symptoms, SUNCT (with conjunctival injection and tearing) has to be distinguished from SUNA (with cranial autonomic symptoms other than conjunctival injection and tearing). Head pain is frontal/retro orbital, very severe and typically brief. When occurring repetitively, episodes can sum up to many minutes [1, 18, 19]. Similar to the other TACs, functional neuroimaging demonstrated increased activation in the posterior hypothalamus [20]. Patients can have hundreds of attacks per day, and pharmacological treatment is often difficult [21] necessitating alternative treatment approaches.

Based on neuroimaging data [20], DBS of the ipsilateral posterior inferior hypothalamus was performed in a 66-year-old patient who had suffered from SUNCT for 14 years and who did not get any relief from several prophylactic medication including carbamazepine, gabapentin, valproic acid, steroids, and opiates. Stimulation resulted in substantial decrease of headache attacks. Importantly, attacks reappeared after switching off, and disappeared again with turning on the stimulator [22]. Following this, two other groups reported single cases with a similar positive response of SUNCT to DBS of the hypothalamus with a substantial reduction of attacks lasting for several months [23, 24]. The most prominent side effect was erectile dysfunction in one patient [24]. An uncontrolled, open-label prospective observational study of 11 patients with SUNHA (eight with SUNCT, three with SUNA) who underwent DBS of the ipsilateral ventral tegmental area of the hypothalamus demonstrated a reduction in daily attack frequency of 78% with a response rate, i.e., at least 50% improvement in daily attack frequency of 82%. Adverse events were wound infection, oscillopsia, and neck stiffness [25]. Another group reported one patient with SUNCT who responded well to DBS of the ventral tegmental area but was unable to reduce medication due to headache recurrence. In addition, the authors identified an ipsilateral neurovascular conflict between the superior cerebellar artery and the left trigeminal nerve and performed microvascular decompression.

Immediately after surgery, the patient remained pain free, and the stimulator could be even turned off [26]. In contrast, Bartsch et al. reported one SUNCT patient, who first had microvascular decompression for suspected neurovascular conflict, but did not respond. Only escalative DBS finally resulted in substantial pain relief [23]. Both studies suggest some overlap of (1) clinical presentation of SUNHA and trigeminal neuralgia, (2) invasive therapy of DBS of the hypothalamus and the standard operative therapy of trigeminal neuralgia, microvascular decompression, and (3) of pharmacological treatment with response of both conditions to anti-epileptic medication, such as carbamazepine and lamotrigine [21]. This overlap has to be considered for clinical diagnosis and therapy in this severe headache syndrome.

Instead of DBS, Lambru et al. were the first to introduce paraesthesia-free cervical 10 kHz spinal cord stimulation for a group of patients with chronic headache, including two patients with SUNA, who were refractory for various medical treatments. Both patients showed a marked reduction of headache frequency, but further studies are necessary to assess the relevance of spinal cord stimulation for headaches [27].

Similar to the other TACs described above, ONS has also been used for treatment of medically intractable SUNCT and SUNA. In one study, six patients with SUNCT and three with SUNA received implantation of bilateral ONS electrodes. Stimulation resulted in improvement in eight patients (four pain-free, three almost pain-free, one about 80% reduction, and one none-responder) after treatment over a few months. The procedure was well tolerated. Side effects were mainly lead-migration, muscle pain over the leads, and exposure of the electrodes. Only three patients had no such complication, but all responders would still recommend this treatment for other patients when in a similar situation [28]. In the largest series so far involving 31 patients with intractable SUNHA and bilateral ONS, these findings could be confirmed with a reduction of mean daily headache frequency of 69%, a response rate (i.e., percentage of patients with reduction of headache frequency by 50%) of 77% and substantial reduction of headache severity. In contrast to the previous smaller study, there were no side effects, especially no lead migration or electrode erosion over a mean follow-up period of 44.9 months, suggesting that electrode placement is safe when performed at an experienced centre [29].

Given the invasiveness of DBS and ONS, non-invasive neuromodulation approaches would be safe alternatives. Currently, only little experience is available. One smaller study looking into the effect of VNS on chronic headaches included two patients with SUNA. Both did not experience any benefit from 3 months of daily stimulation [17].

14.5 Hypnic Headache

Hypnic headache typically occurs at night in an elderly subject waking the patient from sleep (alarm clock headache). In general, it responds well to medical treatment with lithium, indomethacin or caffeine. Neuroimaging demonstrated a decrease of

grey matter volume in the hypothalamus consistent with some pathological function of circadian rhythm generation [30]. One case report describes a 64-year-old female with hypnic headache who did not use caffeine, refused lithium due to the possible side effects, and did not respond to indomethacin, propranolol, and other medication. She was treated with ONS. Attack frequency was reduced from almost daily to one to two attacks/month, and severity improved to 1–2/10 VAS [31]. When patients are refractory to medical treatment, ONS might thus be an alternative for selected patients with hypnic headaches.

14.6 Conclusion

Trigeminal autonomic cephalalgias other than cluster headache are difficult to treat when indomethacin cannot be tolerated in case of hemicrania continua or paroxysmal hemicrania, or when it does not help as in SUNCT/SUNA. Then, neuromodulation might be an alternative. Invasive therapies involve deep brain stimulation, which can have devastating side effects, and occipital nerve stimulation, which can have some long-term complications requiring further surgery. Due to the rarity of these conditions, randomized controlled studies are difficult to perform, and no general recommendation can be given. However, when standard treatment fails, invasive neuromodulation should have a role in the work-up of such patients.

Occipital nerve stimulation has been used frequently and with some success in all trigeminal autonomic cephalalgias as well as in hypnic headache. It might be useful for indomethacin-sensitive headaches when non-invasive vagal nerve stimulation has been tested without success or for drug-resistant SUNCT or SUNA. There are no data on deep brain stimulation in hemicrania continua and only limited experience in paroxysmal hemicrania, but for patients suffering from the excruciating short-lasting neuralgiform headaches, deep brain stimulation might be an option.

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