Neuromodulation in Cluster Headache

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Abstract Medically refractory chronic cluster headache (CH) is a severely disabling headache condition for which several surgical procedures have been proposed as a prophylactic treatment. None of them have been evaluated in controlled conditions, only open studies and case series being available. Destructive procedures (radiofrequency lesioning, radiosurgery, section) and microvascular decompression of the trigeminal nerve or the sphenopalatine ganglion (SPG) have induced short-term improvement which did not maintain on long term in most of the patients. They carried a high risk of complications, including severe sensory loss and neuropathic pain, and consequently should not be proposed in first intention.

Deep brain stimulation (DBS), targeting the presumed CH generator in the retrohypothalamic region or fibers connecting it, decreased the attack frequency >50 in 60 % of the 52 patients reported. Complications were infrequent: gaze disturbances, autonomic disturbances, and intracranial hemorrhage (2).

Occipital nerve stimulation (ONS) was efficient (decrease of attack frequency >50 %) in about 70 % of the 60 patients reported, with a low risk of complications (essentially hardware related). Considering their respective risks, ONS should be proposed first and DBS only in case of ONS failure.

New on-demand chronically implanted SPG stimulation seemed to be efficient to abort CH attacks in a pilot controlled trial, but its long-term safety needs to be further studied.

Keywords Cluster headache • Neuromodulation • Deep brain stimulation • Occipital nerve stimulation • Sphenopalatine ganglion • Trigeminal nerve

Cluster Headache

Cluster headache (CH) is a primary headache and belongs to the group of the trigeminal autonomic cephalalgias in the International Classification of the Headache Disorders (ICHD-II) [17]. CH mainly affects men and smokers and is characterized by strictly unilateral severe pain attacks associated with ipsilateral prominent parasympathetic features (conjunctival injection, lacrimation, rhinorrhea or nasal congestion, and agitation). The attacks last 15–180 min and usually occur once or several times per day. Episodic cluster headache affects 80–90 % of patients who describe periods of attacks (cluster) and periods of remission. Chronic CH (CCH) (unremitting from onset or evolved from episodic form) lacks the remissions and is diagnosed after 1 year without remission or with remission periods lasting less than

1 month [17]. Once the chronic cluster syndrome is established, the prophylactic medical treatment (verapamil, lithium) often fails to prevent the attack occurrence. The pain attack can be usually stopped by the abortive treatments (subcutaneous injection of sumatriptan, oxygen inhalation), but their use is limited. Refractory CCH is one of the most debilitating headache syndromes and is often referred to as "suicidal headache," justifying a surgical treatment.

The clinical criteria for invasive surgery (initially DBS) in CCH have been proposed by a group of experts [27]: CCH according to ICHD-II [17] for at least 2 years, at least one attack per day, resistance to pharmacotherapy (including at least verapamil and lithium), headache "locked" to the same side (this criterion does not concern occipital nerve stimulation), normal neurological examination, and absence of psychiatric comorbidity.

The pathophysiology of CH is not completely identified yet. Current hypothesis involves a trigeminal and autonomic (via the sphenopalatine ganglion) activation, explaining the trigeminal topography of pain and the ipsilateral autonomic features [15]. This activation is probably induced by a generator of attacks, potentially located in the posterior hypothalamic gray matter. Indeed, several arguments have pointed out the potential role of the hypothalamus as the central generator of the disease: (1) CH attacks occur usually with a circadian and annual rhythm [15]; (2) neuroendocrine changes are frequent in CH patients, including melatonin secretion changes; and (3) positron-emission tomography (PET) imaging during CH attacks showed a specific activation of an area located at the diencephalo-mesencephalic region, under the floor of the third ventricle [32]. Based on its projection on the Talairach grid, this region has been called posteroinferior hypothalamus. Moreover, a study in voxel-based morphometry showed an increase in gray matter density in this area [31].

Based either on empiricism or neuroscientific knowledge, surgical procedures aiming to alleviate CH symptoms, via lesion or electrical modulation, have targeted regions involved in the CH pathophysiology: trigeminal nerve or ganglion, sphenopalatine ganglion, brain stem trigemino-cervical complex, and hypothalamic nuclei or pathways.

Lesion Procedures

For patients with severe CCH refractory to medical prophylactic treatment, due to pain severity, absence of remission, and treatment resistance, surgery has been considered as a feasible option for pain control. Several lesion procedures have been tried in the past, without satisfactory long-term relief of pain.

Surgical rhizotomy [49] or section [20] of the trigeminal nerve provided immediate but not sustained improvement of pain with major sensory (severe hypoesthesia, anesthesia dolorosa, keratitis) and motor (mastication difficulties) complications. Microvascular decompression (MVD) of the trigeminal nerve eventually associated with MVD or section of the intermedius nerve (carrying parasympathetic fibers to

the sphenopalatine ganglion) has been performed in a series of 28 CCH patients [28]. Initially 73 % of them reported an improvement >50 %, but this favorable outcome did not maintain over time, despite repeated procedures. The favorable outcome might be related to nervus intermedius MVD or section, as MVD limited to the trigeminal nerve was a failure in 2/3 of the cases. Stereotactic radiosurgery (SRS) of the intracisternal portion of the trigeminal nerve has been investigated in 3 series accounting for 24 patients (mean follow-up 3 years) [9, 21, 34]. Only 5 (20 %) patients reported an improvement >50 %, but 50 % of them had facial hypoesthesia and up to 20 % developed neuropathic pain across series [9, 21]. Considering their poor results, high risk of complications and the availability of neuromodulation techniques, the lesional procedures on the trigeminal nerve should be avoided in first intention.

Associating SRS of the sphenopalatine ganglion (SPG) to trigeminal nerve SRS seems slightly more efficient than trigeminal nerve SRS alone [21]. SRS targeting only the SPG has been reported to be efficient in single cases [7, 23] and might be a promising SRS target inducing less sensory disturbances.

In two series cumulating 25 patients [37, 42], thermolesion of the SPG, using a percutaneous infra-zygomatic approach, decreased the mean frequency of CCH attacks by half (mean follow-up 12 and 24 months, respectively). However the rate of complications was high: epistaxis (80 %), lesion of the maxillary division of the trigeminal nerve (40 %), and transient hypoesthesia of the palatine area (90 %). Globally, destructive procedures on the SPG appeared more efficient on CCH attacks than lesion concerning the trigeminal nerve. These overall results encouraged the development of new nonlesional procedures targeting the sphenopalatine ganglion (see further).

Deep Brain Stimulation

Deep brain stimulation (DBS) of the posteroinferior hypothalamus has been proposed by the team of Milan [14, 25] soon after the identification of the "posteroinferior hypothalamic" activation concomitant to CH attack, with the aim to inhibit the presumed generator of pain attacks.

Results

Up to now, about 50 patients treated with DBS of this region have been reported in the literature (Table 1) [2, 11, 12, 14, 24–26, 40, 46, 47]. The overall responder rate (attack frequency decrease ≥50 %) was 60 %, including 30 % of patients being almost pain-free at longest follow-up. Only one study tried to evaluate this approach in controlled conditions [12] but failed to demonstrate a significant decrease of CH attacks between the stimulation "on" and "off" 1-month periods,

Table 1 Main studies of deep brain stimulation for refractory chronic cluster headache

Author	Patients (*n*)	Follow-up (years)	Almost pain-free patients (*n*)	At least ↓ attack frequency >50 % (*n*)	Complications
Leone [14, 24–26]	17	8.7	6	6	Electrode misplacement (2) or malpositioning (1), infection (4), ICH (1), seizure (1), permanent weakness (1)
Schoenen [43]	6	4	2	1	Fatal ICH (1); panic attack (1); oculomotor disturbances
Starr [47]	4	1	0	2	Oculomotor disturbances, transient loss of consciousness
Owen [40]	1	0.7	1	0	–
Bartsch [2]	6	1.4	2	1	–
Fontaine [11, 12]	11	1	3	3	Oculomotor disturbances (3), transient loss of consciousness (1), micturition syncopes (1)
Seijo [46]	5	2.8	2	3	Euphoria, oculomotor disturbances, headache, increased appetite, cervical dystonia
Total	52		16 (30 %)	16 (30 %)	

due to the too short duration of these periods. Indeed, the therapeutic effect of retro-hypothalamic DBS may be delayed, the mean time to obtain a clinically significant headache reduction ranging from 1 to 86 days. Several authors have reported that few patients with long follow-up displayed few bouts of attacks per year, similar to an episodic CH.

Technical Aspects, Anatomical Concerns, and Mechanisms of Actions

Surgery may be conducted under general or under local anesthesia which allows a preoperative stimulation to assess eventual side effects, especially gaze disturbances. The use of microelectrode recordings (MER) is not recommended because it does not bring additional information useful to optimize electrode placement and increases the risk of intracerebral hemorrhage (ICH). Common stimulation parameters used for chronic stimulation are frequency 130 Hz, pulse width 60–210, and amplitude 1.5–3.5 V.

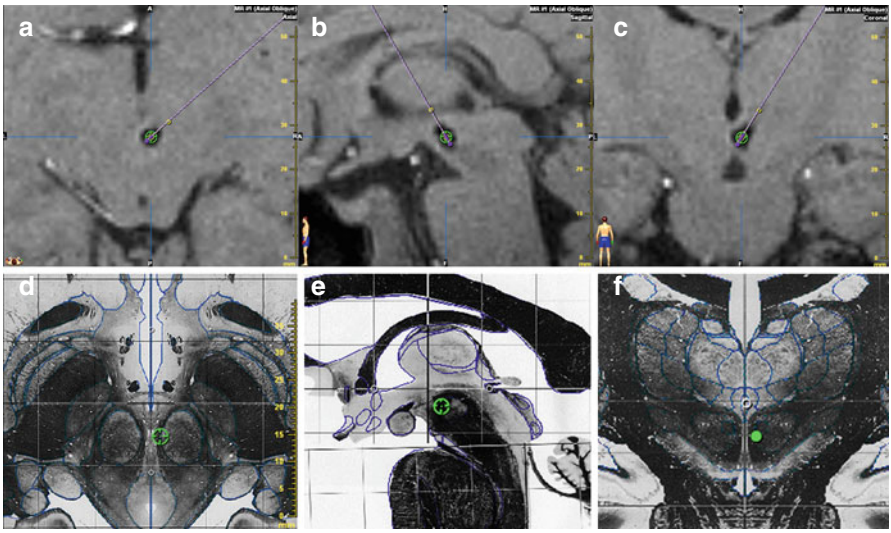

Fig. 1 Postoperative T1-weighted MRI in chronic refractory cluster headache patient treated by deep brain stimulation of the retro-hypothalamic region. Intended stereotactic target (*green circle*) ($x=2$ mm; $y=-3$ mm; $z=-5$ mm, relative to the mid-commissural point) is projected within the artifact generated by the electrode on axial (**a**), sagittal (**b**), and coronal (**c**) slices and on the corresponding sections of the Schaltenbrand atlas (**d**–**f**)

The functional target of DBS in CCH is virtual and is consequently defined indirectly using its stereotactic coordinates according to the bi-commissural plan. The most often used target has been initially proposed by Franzini et al. [14] and is located 2 mm lateral to the midline, 3 mm posterior to the mid-commissural point (MCP), and 5 mm below MCP (Fig. 1). A useful anatomic landmark visible on MRI is the anteromedial border of the red nucleus. The neural structure corresponding to these coordinates and whose stimulation induces the therapeutic effect is still debated. An anatomical study of electrode locations has identified several candidate structures [11], including the mesencephalic gray substance and several fascicles connecting the hypothalamus with the autonomic nuclei of the brain stem (Fig. 2). Moreover, the electrode location did not differ between responders and nonresponders, suggesting that other factors not related to electrode misplacement may be responsible for failure of DBS treatment in nonresponders.

However, two additional neighboring targets seem to be efficient. The first one is actually located in the posterior hypothalamus (4 mm from the third ventricle wall, 2 mm posterior to and 5 mm below the MCP) [46]. Ventriculography-guided implantation of electrode on the floor of the third ventricle via the foramen of Monro was also efficient [3].

Tractography studies confirmed that DBS targets for CCH were located close to fibers connecting the hypothalamus with the brain stem [39, 40]. A positron emission

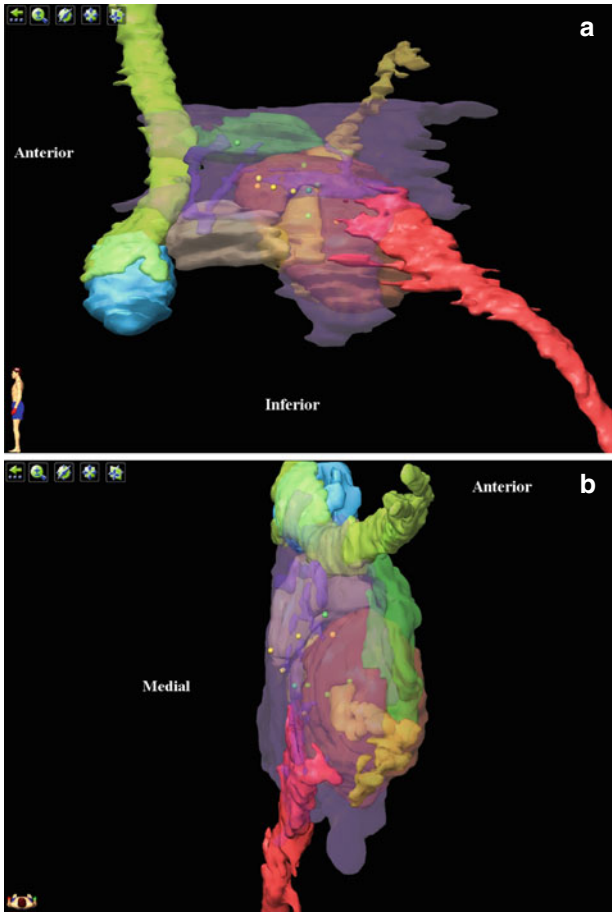

Fig. 2 Location of DBS electrodes on 3D rendering of relevant anatomic structures of the retrohypothalamic region, from medial (**a**) and superior (**b**) views, in a series of 11 refractory cluster headache patients [11]. Contacts of responders are in green and nonresponders in yellow. The region of interest is centered by the red nucleus (transparent, *orange*). Medially, the mesencephalic gray substance (transparent, *purple*) belongs to the wall of the third ventricle and is in continuity with the posterior hypothalamus anteriorly and with the periaqueductal gray substance posteriorly. The mammillary body (*light blue*), with the mammillothalamic fascicle (*light green*) and the mammillotegmental fascicle (transparent, *dark green*), constitutes the macroscopic posterior border of the hypothalamus. The ventral tegmental area (*beige*) is located immediately posterior to the mammillary bodies. Several bundles cross this area. The fascicle retroflexus of Meynert (*yellow*, transparent) makes a notch in the medial region of the red nucleus and links the habenula with the interpeduncular nucleus. The medial longitudinal fascicle (*red*) connects the hypothalamus with autonomic centers in both the brain stem and spinal cord. The dorsal longitudinal fascicle (transparent, *purple*; only thin portions are individualized at this level) connects the paraventricular nucleus of the hypothalamus with the periaqueductal gray matter, the locus coeruleus, and autonomic centers of the brain stem. Several structures have been erased for simplification

study comparing retro-hypothalamic DBS "on" and "off" conditions showed that the stimulation induced activation in the ipsilateral posterior hypothalamic gray (site of electrode implantation), ipsilateral thalamus, somatosensory cortex and precuneus, anterior cingulate cortex, and ipsilateral trigeminal nucleus and ganglion [33].

Plotted together, these data suggest several putative mechanisms of action for DBS in CCH: (1) inhibition of a CH generator actually located in the hypothalamus and modulated through stimulation of afferent fibers in the retro-hypothalamic area; (2) inhibition of a CH generator located in the retro-hypothalamic region or in the mesencephalic gray substance; and (3) modulation of nonspecific antinociceptive systems, including mesencephalic gray substance or orexinergic system [18].

Complications

Few stimulation-related side effects have been reported: sensation of imminent death, transient loss of consciousness with palsy (stimulation of reticular formation?), micturition syncope, and gaze disturbances (probably related to the stimulation of supranuclear gaze control pathways including rostral interstitial nucleus of medial longitudinal fascicle and interstitial nucleus of Cajal). Two ICH (one death and one permanent neurological deficit) have been reported in early series using MER, probably related to the injury of the paramedian thalamo-peduncular deep penetrating midbrain vessels.

However, considering the high risk of ICH in pioneer DBS studies, some centers rapidly abandoned DBS and opted to a less invasive procedure as occipital nerve stimulation (ONS).

Occipital Nerve Stimulation

The principle of ONS is to deliver a continuous electrical stimulation to the greater occipital nerve (GON) (Fig. 3) and/or to the lesser occipital nerve (LON), via a subcutaneous chronically implanted electrode adjacent to the nerve and connected to a generator. ONS induces paresthesias in the occipital region. Originally described by Weiner [53] to control occipital nerve neuralgia, this technique has been proposed to treat primary headaches, including CCH.

Results

ONS for CCH has been studied only in open trials (Table 2) [4–6, 13, 29, 30, 36, 48]. The overall success rate (attack frequency decrease >50 %) was about 75 %, and most of the patients would recommend the operation to a fellow CCH patient. ONS

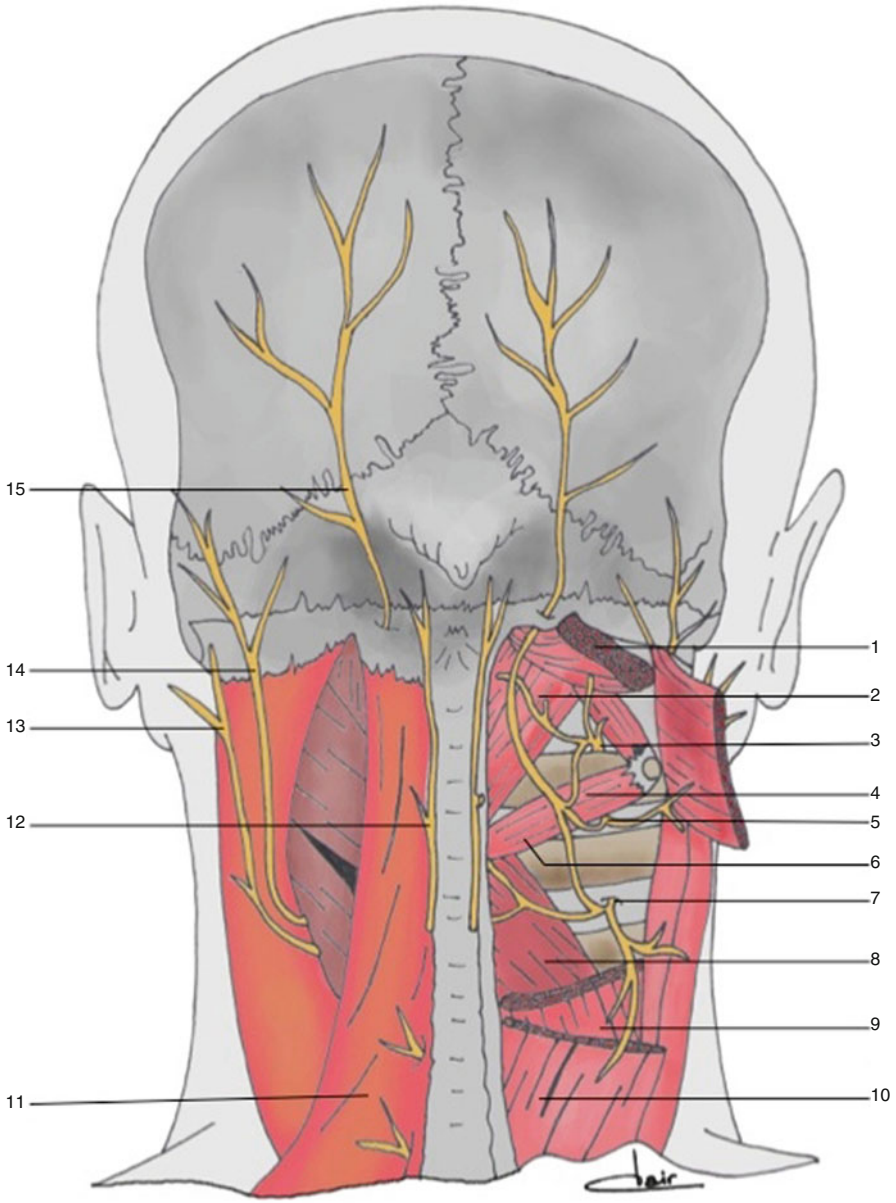

Fig. 3 Anatomy of the occipital and suboccipital regions. *1* Head semispinalis muscle (cut and retracted), *2* rectus posterior muscle of the head, *3* dorsal ramus of C1, *4* head inferior oblique muscle, *5* dorsal ramus of C2, *6* inferior oblique muscle, *7* dorsal ramus of C3, *8* partial section of the head muscle, *9* partial section of the neck muscle, *10* splenius muscle of the head, *11* trapezius muscle, *12* third occipital nerve, *13* great auricular nerve, *14* lesser occipital nerve, *15* greater occipital nerve

Table 2 Main studies of occipital nerve stimulation for chronic cluster headache

Study	Patients (*n*)	Mean follow-up [range] (months)	Recommend the operation	Improved >50 % (*n*)	CH attack frequency	CH attack intensity	Treatment decreased
Burns et al., 2007 [4] and 2009 [5]	14	17.5 [4–35]	11/14	10/14	−33 %	+8 %	6/14
Magis et al., 2007 [29] and 2011 [30]	15	36.8 [11–64]	10/15	12/15	−94.6 %	–	4/14
De Quintana et al., 2010 [6]	4	6 [ ]	4/4	4/4	−56 %	−48.8 %	3/4
Müller, 2011	10	12 [3–18]	–	6/10	−40.3 %	−28.6 %	3/10
Fontaine et al., 2011 [13]	13	14.6 [3–34]	12/13	10/13	−68.2 %	−48.9 %	8/13
Strand et al., 2011 [48]	3	10 [6–12]	–	2/3	−61 %	–	
Total	59		37/59 (63 %)	44/59 (75 %)			24/45 (53 %)

acts like a prophylactic treatment, decreasing the frequency of the CH attacks and their intensity and allowing to decrease the prophylactic drugs in most of the patients, but does not stop the attack once it has begun. Considering their respective risks of complications, ONS should be proposed before DBS in refractory CCH patients.

The feeling of paresthesias appears mandatory to obtain a clinical improvement. Consequently a placebo effect cannot be ruled out, even if its probability is low. However, it will be difficult to show the ONS efficacy in controlled and blinded conditions because the patients perceive ONS-induced paresthesias. Patients who do not feel the paresthesias anymore (lead migration, dysfunction, etc.) often describe a recurrence of their headache attacks within the following days.

ONS has been proposed to treat other medically refractory primary headache, including chronic migraine.

Technical Aspects

The original technique described the implantation of a transverse cylindrical thin electrode crossing the midline from a retro-mastoid incision, allowing to stimulate both sides with one electrode. Multiple variations of this technique have been reported in the literature (Fig. 4), using one or two electrodes, percutaneous cylindrical electrodes or surgical paddle ones, approach from the midline or from one or two retro-mastoid incision(s) [10, 22, 39, 41, 50–53]. Results and complications seemed to be similar whatever the technique was, and no comparative study is available claiming the superiority of one technique over others.

However, in our opinion, several major technical considerations have to be respected. First the subcutaneous electrodes have to cross the nerve in its superficial course. Although there is a great interindividual anatomical variability, the GON becomes superficial after piercing the fascia of the semispinalis capitis muscle (27 mm below the occiput, 12 mm from the midline in average) or the trapezius muscle (9 mm below the occiput, 35.5 mm from the midline in average) and follows then a laterally and superiorly oriented course [38] (Fig. 3). Consequently the “right spot” to place the stimulating electrode contacts would be located approximately 0–1 cm below the occiput and 2–4 cm from the midline. There is no data demonstrating that ONS efficacy in CCH is correlated specifically to the stimulation of GON, LON, or both or correlated to the surface of ONS-induced paresthesias. Consequently, ONS electrodes may be implanted as well under local or general anesthesia, per or intra-operative stimulation not being mandatory in our experience to optimize the electrode placement.

The electrodes have to be implanted subcutaneously above the fascia. Implanting the electrode too superficially or too deep would increase the risk of skin erosion/electrode exteriorization or muscle spasms/unpleasant contractions, respectively. As electrode migration is the most frequent complication, the leads have to be anchored firmly to the epifascial plane, using non-resorbable sutures. Performing one or two loops with the leads is recommended to allow extension of the leads

during cervical movements. Although the internal pulse generator may be implanted in the buttock and the lower abdomen of the infraclavicular pectoral regions, the risk of migration might be higher with the buttock site due to excessive lead elongation during movements [50].

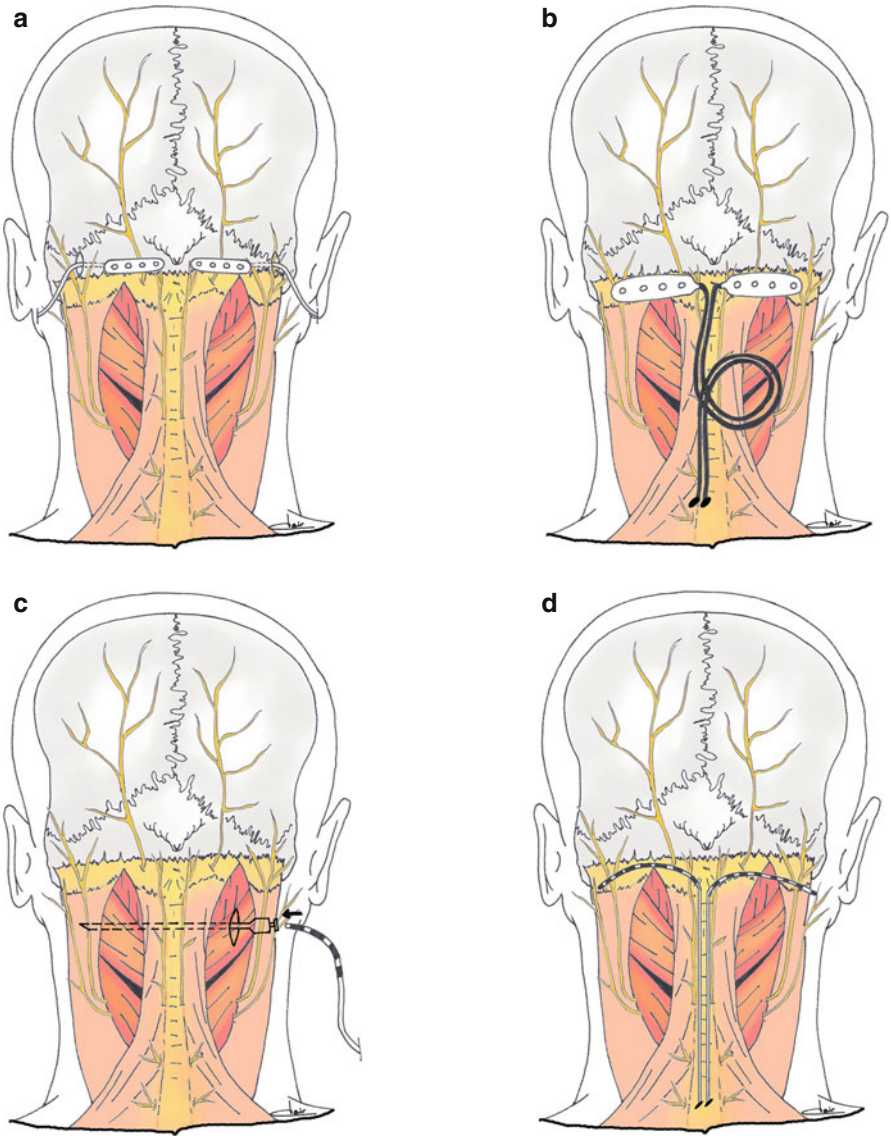

Fig. 4 Examples of different techniques proposed in the literature for bilateral implantation of great occipital nerve stimulation electrodes. Paddle electrodes (**a**, **b**) may be implanted using lateral [39] or midline [22] approaches. Cylindrical (**c**–**e**) electrodes may be implanted percutaneously from lateral [52, 53] or midline [10] entry points

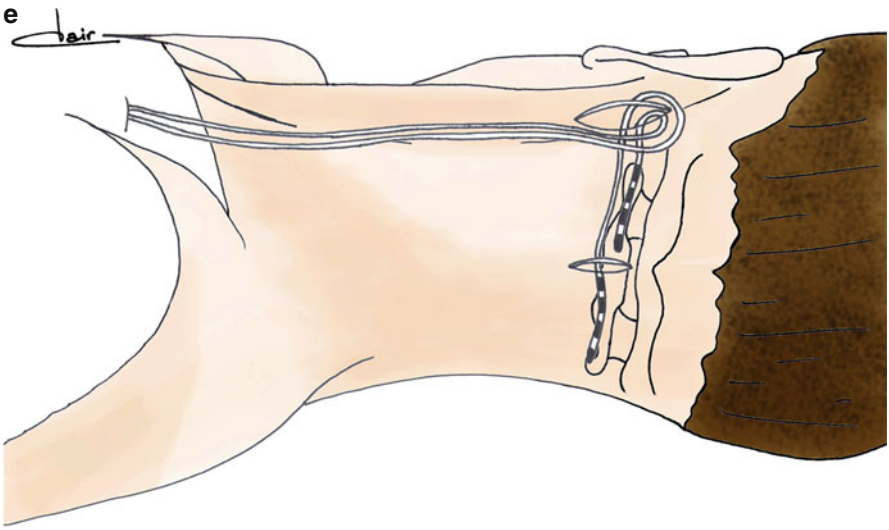

Fig. 4 (continued)

Bilateral stimulation is recommended to treat primary headache to avoid headache side-shift, which has been reported in up to one-third of the patients stimulated unilaterally [29, 30]. Trial stimulation is not useful because some patients can improve after several months of continuous stimulation [13]. Response to occipital nerve block is not useful in predicting the ONS efficacy [45].

Complications

ONS carries a low risk of minor surgical complications. Early studies reported a high rate (25–100 %) of electrode migration due to neck movements, justifying a strict technique to anchor the leads. The risk of superficial infection is about 3 %. Most of the patients develop tolerance, meaning that they have to progressively increase the stimulation intensity to continue to feel the paresthesias. This phenomenon leads to high current consumption and consequently to a rapid battery depletion, leading to frequent battery changes or implantation of rechargeable generator, increasing the cost of the technique.

Mechanisms of Action

The exact mechanisms of action of ONS in CH are still unknown. Several arguments suggest that ONS could act through modulation of convergent nociceptive inputs in the trigemino-cervical complex, involving a “gate control theory-like” mechanism [16].

About one-third of the CCH patients successfully treated by ONS have still autonomic attacks without pain [30]. This suggests that ONS might act through a nonspecific modulation of central pain control systems rather than through modulation of a central CH generator. A functional imaging study performed in ONS responders has shown metabolic changes in the "pain matrix" regions but the persistence of an ipsilateral hypothalamic activation, confirming that ONS does not act on the CH hypothalamic generator [30].

Stimulation of the Sphenopalatine Ganglion (SPG)

Sphenopalatine Ganglion Anatomy

The cranial autonomic symptoms associated with CH attacks probably result from the activation of a trigeminal autonomic reflex [15]. The parasympathetic efferent component of this reflex is mediated, at least in part, through the SPG. The SPG is located in the pterygopalatine fossa (PPF), behind the posterior wall of the maxillary sinus, and is bordered posteriorly by the pterygoid process, superiorly by the sphenoid sinus, and medially by the palatine bone (Fig. 5). Laterally it communicates with the infratemporal fossa. The foramen rotundum, from which the maxillary division of the trigeminal nerve exits, is located superolaterally within the PPF. The SPG contains sensory, parasympathetic, and sympathetic fibers.

SPG Procedures in CH

Several lesioning procedures involving the SPG have been proposed for the treatment of CCH. The success rates of ganglionectomy and radiofrequency lesioning or blocks varied from 46 to 85 % [8, 35, 37, 42]. However, repeated access to the SPG has been required because, in most of the cases, the benefits are transient. Indeed, in destructive procedures, pain often recurs, perhaps because alternative nerve connections are reconstituted over time. Additionally, long-term sequelae such as sensory loss and dysesthesias have been reported.

Stimulation of the SPG in CCH

A first case of chronic SPG stimulation for the treatment of CH with an implantable device was published in 2007 [19]. The report noted marked reduction in pain with acceptable safety. The only complication reported was hardware failure, during which the patient's headaches worsened. After hardware replacement, the

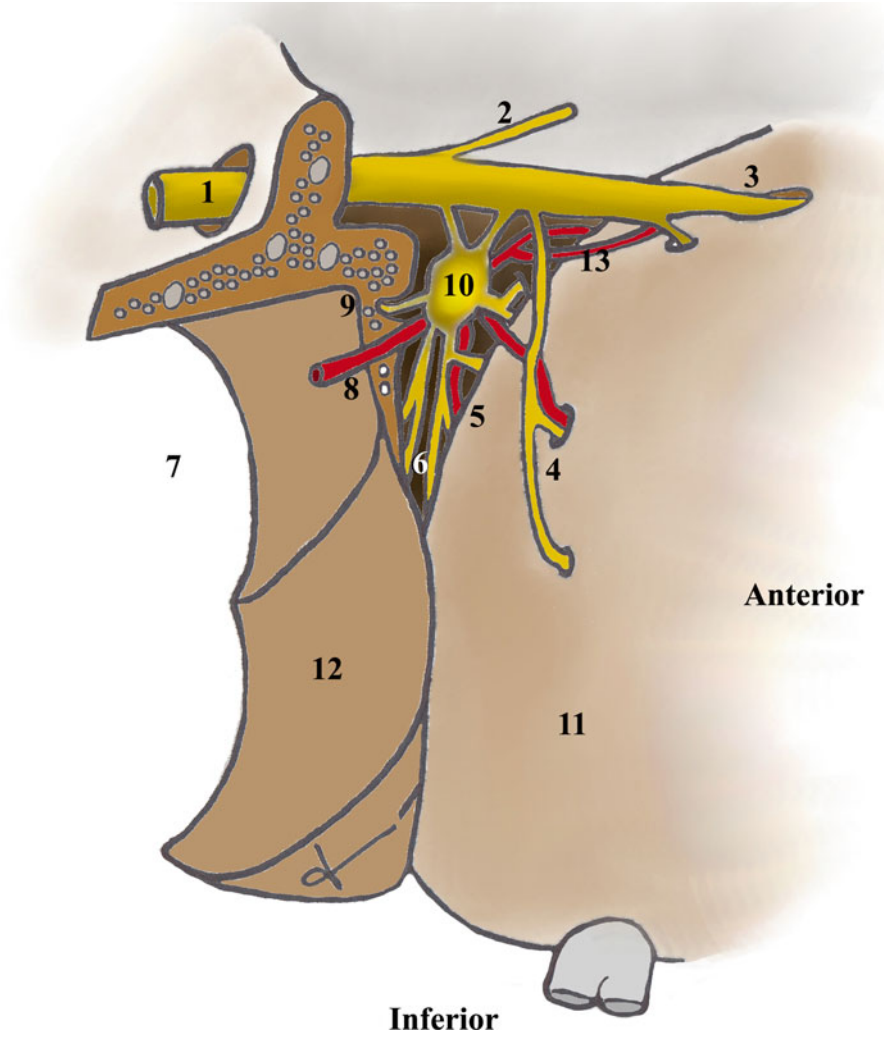

Fig. 5 Anatomical schematic drawing of the right sphenopalatine ganglion within the pterygomaxillary fossa. *1* Maxillary nerve, *2* zygomatic nerve, *3* infraorbital nerve entering its canal, *4* alveolar nerves and artery, *5* descending palatine artery in the pterygomaxillary fossa, *6* palatine nerves, *7* infratemporal fossa, *8* internal maxillary artery, *9* vidian nerve in its canal, *10* sphenopalatine (or pterygopalatine) ganglion in its fossa, *11* maxillary tuberosity, *12* lateral pterygoid plate, *13* sphenopalatine and infraorbital arteries

patient experienced again an improvement in the headaches, strongly suggesting the efficacy of the SPG stimulation. More recently, Ansarinia published a proof of concept study on the response of CH patients to acute SPG stimulation [1]. Effective abolition of induced CH attack was reported within 3 min of SPG stimulation.

With these SPG stimulation experiences in mind, a chronically implantable neuromodulation device, specifically designed for acute SPG stimulation, has been developed, in order to abort the CH attacks on demand. The neurostimulator device is implanted in the PPF, along the posterior wall of the maxillary bone, fixed to the zygomatic process with a screwed plate, the lead being placed in contact with the SPG. The neurostimulator does not contain battery but is activated and powered by a remote controller using radiofrequency energy.

The efficacy and safety of this on-demand abortive SPG stimulation device have been very recently assessed in a multicenter randomized, sham-controlled study, in 28 patients suffering from refractory CCH [44]. Each CH attack was randomly treated with full, sub-perception, or sham stimulation. Pain relief was achieved in 67.1 % of full stimulation-treated attacks compared to 7.4 % of sham-treated and 7.3 % of sub-perception-treated attacks ($p < 0.0001$). Nineteen of 28 (68 %) patients experienced a clinically significant improvement, but only 32 % achieved a pain relief in more than 50 % of the treated attacks, and 43 % experienced a reduction >50 % of attack frequency. Most patients (81 %) experienced transient, mild/moderate loss of sensation within the maxillary (V-2) nerve territory, resolving in most of the patients within 3 months. Further developments of this technique and studies comparing efficacy and safety of SPG stimulation with ONS are needed.

Conclusion

Medically refractory CCH is a severely disabling headache condition for which several surgical procedures may be proposed as prophylactic treatment. None of them have been evaluated in controlled conditions, only open studies and case series being available. Destructive procedures on the trigeminal nerve or the SPG may induce short-term improvement which does not maintain over time in most of the patients. Due to the high risk of complications, including severe sensory loss and neuropathic pain, they should not be proposed in first intention. Retro-hypothalamic DBS and ONS are efficient (decrease of attack frequency >50 %) in about 60–70 % of the patients. Considering the respective risks of ONS and DBS, ONS should be proposed first and DBS should be considered only in case of ONS failure. New on-demand implanted SPG stimulation seems to be efficient to abort CH attack, but its long-term safety needs to be further studied.

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