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Cluster Headache- A New Threat to Encounter

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Abstract- Cluster headache (CH) is a form of primary headache so called because of its characteristic temporal pattern. The pain during attacks is so intense that CH is also known as "suicidal headache". Cluster headache is a neurological disorder that presents with unilateral severe headache associated with ipsilateral cranial autonomic symptoms. Cluster headache attacks often occur more than once a day, and typically manifesting in bouts. It has a point prevalence of 1 in 1000 and is the most common trigeminal autonomic cephalalgia. This article aims to guide general neurologists to an accurate diagnosis and practical management options for cluster headache patients.

I. INTRODUCTION

Cluster headache (CH) is a form of primary headache so called because of its characteristic temporal pattern. The pain during attacks is so intense that CH is also known as "suicidal headache". The headache is usually in the orbital, supraorbital and temporal regions and is always accompanied by a series of autonomous phenomena.

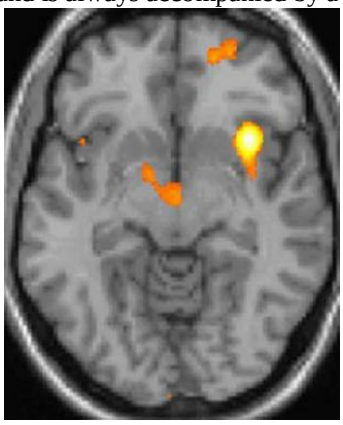


Figure 1 Cluster pain

Cluster headache is rare (lifetime prevalence of 0.07%). Smoking seems to increase the risk, but there is contradictory evidence on the role of coffee and alcohol. The diagnosis is based entirely on the clinical features. No laboratory or radiological studies with sufficient sensitivity and specificity have been identified. The pain is described as very intense and can last up to 3 hours. There is often parasympathetic hyperactivity, such as tearing and rhinorrhea. In some patients, facial redness or pallor, dysesthesia of scalp hair, carotid artery tenderness on this side and bradycardia are observed. Sympathetic activity can cause miosis or ptosis on this side of the face. The main differential diagnosis is migraine. The attacks are usually nocturnal (when sleep apnea may occur) and may be caused by alcohol, notroglycerin and histamine, leading to the hypothesis that oxygen desaturation triggers an attack.[2]

Cluster headache is a typical, severe unilateral headache episode, usually lasting between 15 and 180 minutes, with a frequency of once every two days to eight times daily, associated with autonomic symptoms ipsilateral to pain or [1] According to epidemiological surveys conducted in the United States and Europe, the prevalence of cluster headache in the general population is approximately 0.1%. However, it is unclear whether prevalence varies geographically [2]. Cluster headache is more common in men and the average age of onset is about 30 years (3). The duration of the disease has not been well studied, but it can exceed 15 years for most patients. Because of the high frequency of seizures and the long course of the disease, the syndrome has a significant impact on the quality of life of patients, increasing the burden on individuals and society [4,5].

II. EPIDEMIOLOGY

Given the low prevalence of cluster headaches compared to migraine, it is difficult to accurately assess the prevalence of cluster headaches in the community. However, given the specific characteristics of cluster headache, it is possible to identify possible cases in the community, using questionnaires based on the ICHD criteria. Community studies have been conducted to determine the prevalence of cluster headaches. They are usually modeled according to a two-step process. The first step is to identify possible cluster headache cases, either through mailed

questionnaires or through structured interviews based on ICHD criteria. Then the interviews are conducted by neurologists or investigators trained in the subsequent evaluation of the cases. Fischera et al. reviewed 16 population-based studies published up to August 2007, specifically analyzing the prevalence of cluster headache in a meta-analysis, and found that year-over-year prevalence varied considerably from one study to the next and ranged from 3 to 150/100 000. Its combined lifetime prevalence was 0.12%. [6] The study with the highest prevalence found in this meta-analysis is the Vågå study in Norway, where lead investigator Sjaastad personally interviewed and surveyed 1,828 people in Vågå. The study identified seven subjects with cluster headache, which corresponds to a prevalence of 381 per 100,000 population (95% confidence interval 153-783). [7] Since August 2007, two other population studies have been conducted, one in the Republic of Georgia, with a prevalence of 87 per 100,000 [8] and in rural Ethiopia, with a prevalence of 1.3%. [9]

III. PATOPHYSIOLOGY

The pathophysiology of cluster headache is complex and the underlying mechanisms are not completely clear. Cluster headache is a neurovascular rather than a vascular headache, characterized by changes in the vascular brain caused by the effects of activation of the trigeminal-autonomic reflex. [38,39] The trigeminal-autonomic reflex is a pathway that consists of a brainstem connection between the trigeminal nerve and the parasympathetic flow of the facial cranial nerve [39] and which is activated by stimulation of the trigeminovascular pathways [Figure 2] . The afferences of the pain of the trigeminal system pass through the ophthalmic division of the trigeminal nerve by taking signals from the cranial vessels and the dura mater (represented by purple fibers). These inputs are synchronized in the TDC and project onto higher brain structures, such as the thalamus (T) and the cortex, leading to a perception of pain (represented by the blue fibers). Activation of the trigeminovascular system by stimulation of the dura mater structures also causes neuronal activation in the SSN within the protuberance, which is responsible for the cells for the autonomic parasympathetic vasodilator cranial pathway. This parasympathetic reflex is activated by the exit of the SSN and is transmitted by the SPG (indicated by the pink fibers), but also by the facial nerve (skull VII) (not shown). Activation of the trigeminal and autonomic nerves defines the autonomic reflex arc of the trigeminal nerve, which is an integral part of the pathophysiology of cluster headache and other CT scans. HT is functionally connected to the ipsilateral trigeminal system and other areas of the brain of the painful matrix. The red dotted lines indicate the pathways by which HT controls or triggers pain. A third-order sympathetic nerve injury that could be caused by vascular changes of ICA in the cavernous sinus, followed by irritation of the local plexus of nerve fibers, may result in sympathetic symptoms (incomplete Horner syndrome) (shown by yellow fibers). IML = intermediate lateral medullary tract, SCG = superior cervical ganglion, SN = suprachiasmatic nucleus, CBT = trigeminal complex, SSN = superior salivary nucleus, SPG = sphenopalatine ganglion, HT = hypothalamus, ICA = internal carotid

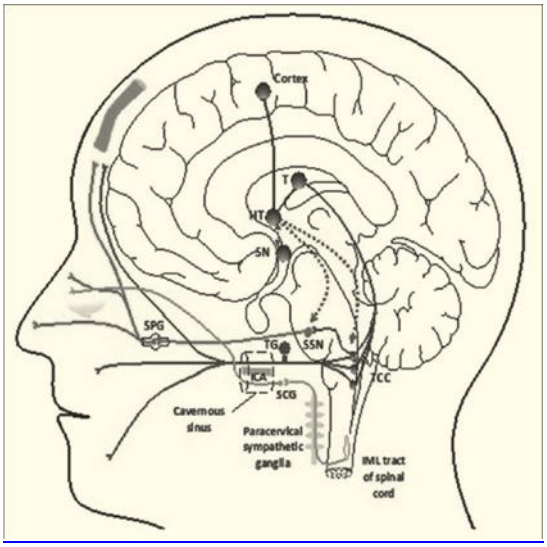


Figure 2 cluster headache pathophysiology

The trigeminovascular pathway consists of neurons that innervate the cerebral vessels and the dura mater through the cell bodies of the trigeminal ganglion. The ganglion contains bipolar cells, with a synaptic connection to the cerebral vessels and the dura at the periphery, and in the

center there are synaptic fibers in the trigeminocervical complex (CBT), which are the trigeminal caudalis nucleus in the trunk. caudal cerebral and cervical cord high in the dorsal. Horns C1 and C2. There are projections of CBT to the thalamus, resulting in the activation of cortical structures involved in the treatment of pain, such as the frontal cortex, isolates and cingulate cortex. The trigeminal ganglion cell bodies contain several vasodilator peptides that innervate the blood vessels. These include calcitonin gene-related peptide (CGRP), substance P and neuroquinin A. CGRP increases in spontaneous clusters of headaches [40] and is triggered by nitroglycerin [41].], which provides evidence. that the trigeminovascular pathway is activated during attacks.

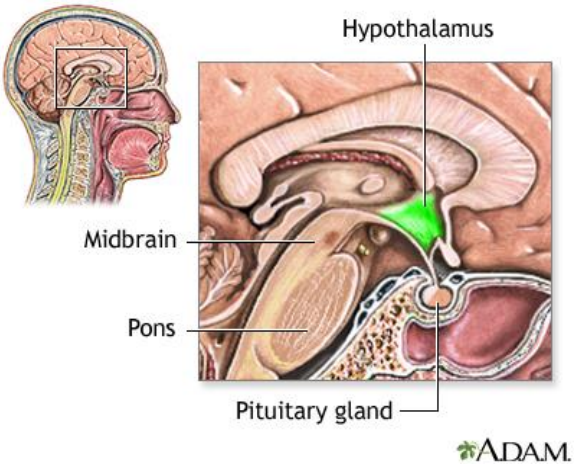


Figure 3 site of cluster pain.

The associated symptoms associated with headache, characteristic of cluster headache, result from the reflex activation of the trigeminal-autonomic reflex pathway through the parasympathetic flow of the upper salivary nucleus, [42] the cranial facial nerve, to [43] causing vasodilation and parasympathetic activation Clinically, this results in tearing, conjunctival injection and nasal congestion. When the pain causes activation of the first division of the trigeminal nerve, such as an injection of capsaicin, carotid vasodilatation and parasympathetic activation are observed. [44]

These clinical features of cluster headache suggest a central mechanism, particularly the hypothalamus. Kudrow noted that cluster headache episodes occur at the same time every year in a circus pattern, especially when switching to daylight saving time. He postulated that this was related to photojournalism, also known as daylight duration, and that this could be centrally attributed to the hypothalamus, suggesting an inability to synchronize the inner circulatory stimulator with the external ambient light. [45] Melatonin is produced in the pineal gland and its secretion rate has a circadian rhythm strongly regulated by the suprachiasmatic nucleus, which receives the sympathetic innervation of the hypothalamus and the autonomous centers of the thoracic spinal cord, the cervical plexus. sympathetic and carotid plexus. The main environmental stimulus for melatonin production during the day is the intensity of light. This information reaches the suprachiasmatic nucleus of the hypothalamus via a direct pathway connecting the retina. [46] During episodes in patients with coronary heart disease, melatonin secretion was lower, the characteristic nocturnal peak decreased [47,48] with abnormal excretion of melatonin metabolites. [48,49] The utility of melatonin replacement in the treatment of cluster headache has been reported in case reports [50,51], a small placebo-controlled study, [52] and a study analyzing melatonin as a complementary therapy in the prevention of cluster headaches. [53] Other studies analyzing the role of other neuroendocrine hormones such as cortisol, [47,54] testosterone, [54,55,56,57,58] and orexin [59] have provided evidence additional involvement of the hypothalamus in cluster headache.

Functional neuroimaging studies have shown that the posterior hypothalamus is activated during attacks of spontaneous headache [60,61] and cluster headache attacks triggered by intravenous nitroglycerin. [62] The role of the hypothalamus in cluster headache was reinforced by the therapeutic effect of focusing on posterior hypothalamic gray by deep brain stimulation in patients with cluster headache. [63.64.65]

3.1 Clinical Features and Diagnosis

Compared to other CAT disorders, cluster headache patients experience multiple severe headache attacks of relatively short duration. Headaches are generally unbearable, unilateral and usually involve first division of the

trigeminal nerve, peri-retrobial areas and in the temple. [12] It can be seen that the pain is from the sinuses or the dentition, and patients often consult an otolaryngologist or dentist for this reason. [66] The quality of the pain is severe, intense, acute and burning, and is usually described as worse than childbirth. It is also called "suicidal headaches". The attack usually accumulates rapidly in intensity, causing intense pain, which dissipates over a similar period, with a sharp start and resolution of the attack. The attacks are strictly one-sided. However, they can sometimes change sides in the same fight (14%) or a lateral move from one fight to another (18%) can occur. [12]

Figure 4 clinical feature and diagnosis

Without treatment, cluster headache attacks can last from 15 minutes to 3 hours, with an average duration of 45 to 90 minutes. [67] During an attack, patients experience symptoms of cranial function, including tearing, redness of the eyes, eye discomfort, such as dust, ptosis, nasal congestion, rhinorrhea, auditory fullness, swelling of the throat and redness. These symptoms of cranial autonomy are present in ipsilateral pain and are due to parasympathetic activation. [68,69] In addition, sympathetic deterioration may occur [70] as miosis and partial Horner syndrome. Wilfred Harris was the first to recognize that Horner syndrome can occur in cluster headaches. [3]

The feeling of restlessness and agitation is a striking feature of the attacks. This is a useful feature that can help distinguish cluster headaches from migraine headaches. During an episode, migraine patients prefer to stay still. In contrast, patients with cluster headaches progress or oscillate during seizures and attempt to decrease the intensity of pain by applying pressure to the affected area. [67,70] In general, once the attack is over, patients experience no pain until the next attack. . Patients can have attacks that vary from once every two days to 8 times a day. [5] Attacks tend to occur at night and patients report a sleep association. A notable observation is that the attacks seem to be happening at the same time each day and in a circadian pattern.

The length of time patients have cluster headache attacks is called an epidemic and can vary on average between 6 and 12 weeks. [5] Patients with cluster headaches may have episodes separated by months or even years of remission. [67,70] Headaches in episodic and chronic clusters are defined by the duration of remission between episodes. Patients with HCC have persistent seizures lasting more than one year without remission or a remission period of less than three months without preventive medication. [5] About 15% to 20% of patients suffer from chronic headache. [71] It is important to distinguish between episodes and CCH, as this can help guide management decisions. Patients with coronary heart disease may notice a tendency in their episodes, which usually occurs in the spring and fall, at the time of the equinoxes. Some CCH patients may notice an increase in attacks during these times of the year. [45] This circanent phenomenon is not clearly understood, but may implicate the hypothalamus in pathogenesis.

Patients have noticed that their attacks can be caused by various substances. These include alcohol, strong odors such as oil and nail polish, as well as foods containing nitrate, such as cold cuts. [72] Triggers can provoke attacks in patients with CHD who are fighting or in patients with CHD. As part of the investigation, administration of intravenous nitroglycerin can induce cluster headache attacks in a reproducible manner. [73.74,75]Cluster headache is still underdiagnosed and suboptimally managed, and patients often have a delay to their diagnosis.

3.2 Management

Management of cluster headache is broadly divided into acute and preventive; furthermore, there are novel neuromodulation devices that can be used for either (figure 5).

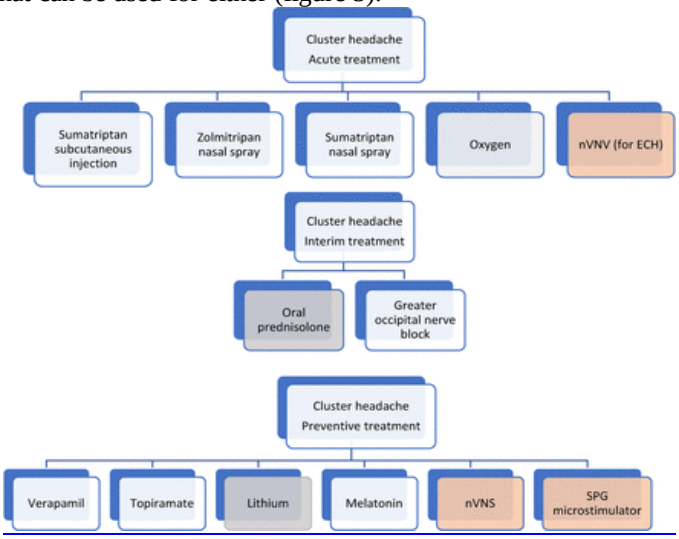


Figure 5 Current landscape for cluster headache treatment: the grey boxes indicate the medications that should be phased out, orange boxes indicate neuromodulation techniques. ECH, episodic cluster headache; nVNS, non-invasive vagus nerve stimulator; SPG, sphenopalatine ganglion.

3.3 Acute treatment of cluster headaches

Acute evidence-based treatments for the treatment of headache include intracutaneous sumatriptan, sumatriptan and zolmitriptan, high-flow oxygen through a mask without rebreather and, in the episodic group only, non-invasive stimulation. Vagus nerve (nvns). Double-blind randomized control studies are effective in stopping attacks in 15 minutes: subcutaneous sumatriptan, high-performance oxygen per mask without rebreather and nvns, and within 30 minutes for sumatriptan intranasally and zolmitriptan (see table 5) comparison). Oxygen is particularly useful in patients who have more than two seizures a day, although sometimes this is less convenient than sumatriptan. In the united kingdom, the prescription of oxygen requires a request for home oxygen form; part a is for static cylinders and part b is a restricted document for home oxygen assessment and review services, as well as for pediatric equipment and other specialists, used to control oxygen. Outpatient before submitting the home oxygen order form, part a, you must obtain the patient's consent using the initial home oxygen risk mitigation tool and the consent for home oxygen [76]

3.4 Is the oxygen system on demand useful?

The oxygen system of the demand valve has a valve that allows oxygen to flow when the patient inhales and closes after inhalation. The device has the advantage of supporting hyperventilation. In a cross-blind, semi-randomized, placebo-controlled study, the primary endpoint of pain relief after 15 minutes was not significant compared to the simple mask and o2ptimask (specialized mask without rebreather). Equipped with a 3 l tank, oxygen dilution is minimized). However, patients preferred the oxygen system on demand and could discuss with it a lower oxygen consumption. Although more research is clearly needed, many patients have very clear benefits and we have no problem with its use. [76]

3.5 Provisional processing options

Patients can use provisional measures while waiting for preventive treatment to have a therapeutic effect; these measures can also help patients with episodic cluster headache with short-term seizures. Although oral prednisolone is often used, caution should be exercised, given its long list of side effects and its cyclical pattern of cluster headache. Patients with headaches in episodic clusters should undergo at least one annual or bi-annual treatment for a long time.

To avoid the cumulative side effects of corticosteroids, we prefer to perform a unilateral block of the superior occipital nerve, using 80 mg of methylprednisolone with 2 ml of 2% lidocaine. This reduces the frequency and severity of headaches, sometimes enough to transport patients throughout their struggle. On average, the effects can last 4 weeks and a larger injection of the occipital nerve can be repeated within 3 months. [76]

IV. PREVENTIVE TREATMENT

4.1 Verapamil

Verapamil was initially effective in an open study31 and then in two randomized clinical trials. It is widely accepted as a first-line preventive therapy for cluster headache, which usually begins with 80 mg three times a day to increase the dose by 80 mg every 2 weeks, depending on the response; the maximum recommended dose is 320 mg three times a day.

Treating clinicians should aware that up to one in five patients taking verapamil develop cardiac arrhythmia, bradycardia or lengthening of the PR interval.34 Hence, it is recommended to perform a baseline 12-lead ECG before starting treatment, then at 10 days after each dose increment. After reaching a stable dose, ECGs should be checked once every 1–2 months and then every 6 months. There are reports of delayed onset of ECG abnormalities up to 2 years after being on a stable verapamil maintenance dose. Other less serious side effects to verapamil therapy include constipation and pedal oedema.

Once a bout of cluster headache is over, the patient should withdraw verapamil cautiously to stop, with view to going straight on the effective dose of verapamil in the next cluster bout, provided the baseline ECG is normal. It is important not to keep patients on verapamil after their bout ends; anecdotally, we have found that this prolongs future bouts and there is a risk of tachyphylaxis.[76]

4.2 Lithium

The evidence is limited for lithium, but is generally accepted as a reasonable second-line option. It is most commonly used in chronic headaches compared to episodic headaches, but its potential impact on thyroid function and the risk of interference with diuresis can complicate and limit its use. Lithotherapy requires regular blood control to maintain a serum concentration of 0.4 to 1.2 mEq / L due to its narrow therapeutic index and the potential risk of toxicity resulting in a wide range of gastrointestinal symptoms. and neurological

The dose of lithium begins at 300 mg once daily, with weekly increases of 300 mg depending on the response, up to a maximum dose of 1200 mg / day; It is better to verify serum concentrations 12 hours after administration; Once the dose is stable and seizures have been controlled, serum lithium should be monitored every 1 or 2 months38.

4.3 Melatonin

There are many plausible theories to explain the possible link between melatonin and cluster headache attacks. Melatonin 10 mg at night may help prevent headaches in episodic clusters, but a melatonin trial for chronic cluster headache could not replicate this positive effect. However, it could be argued that the formulation used or the timing of the medication may have been confusing.

Due to its tolerable profile of side effects, melatonin is still widely used to prevent cluster headache at doses between 10 and 25 mg at night.

4.4 Topiramate

The evidence of the efficacy of topiramate in preventing cluster headache is limited to an open, high-dose study (100 to 200 mg / day), with good efficacy in more than two thirds of patients.

Side effects are an important barrier to the use of topiramate, particularly cognitive decline, teratogenicity, nephrolithiasis and depressed mood, as well as its potential effect on the effectiveness of oral contraception, which may be a contributing factor. important in preventive choice. [76]

4.5 When to stop preventive treatment

There is no clear guide on the duration of continuation of preventive oral therapy. In general, it is accepted that preventive treatment should not last more than 4 weeks after the resolution of the seizures, as evidenced by the lack of shadows or reactions to the triggers, or after the usual duration of the fight.

The experience of patients in their previous episodes can guide the decision to stop preventive treatment of headaches in episodic clusters. It is important to suspend preventive treatment after each access and not allow patients to simply continue, given the wide range of side effects and the possibility of loss of efficacy. When restarting a preventive treatment such as verapamil for later access, it is generally not necessary to make a new discount. provided that the baseline ECG is normal, patients can be resumed at the dose that was effective for the last episode. [76]

4.6 Neuromodulation

Neuromodulation is a useful development to treat cluster headache in patients for whom oral preventive therapy was ineffective or contraindicated.

According to the data, we will focus on two neuromodulatory methods: the nVNS and the sphenopalatine ganglion microstimulator (SPG).

Non-invasive stimulation of the vagus nerve

The gammaCore device (nVNS) demonstrated the effectiveness of the use of three ipsilateral 2-minute stimulations of the cervical branch of the vagus nerve, in the acute treatment of cluster headache attacks in an open study and demonstrated its effectiveness in the treatment of episodic cluster headache two randomized, double-blind, simulation-controlled studies No similar benefit was found in the treatment of stroke in chronic cluster headache, which could be related to the high placebo response rate; A recent study explained this observation through a modulating effect on the trigeminal-autonomous reflex by the simulated device.

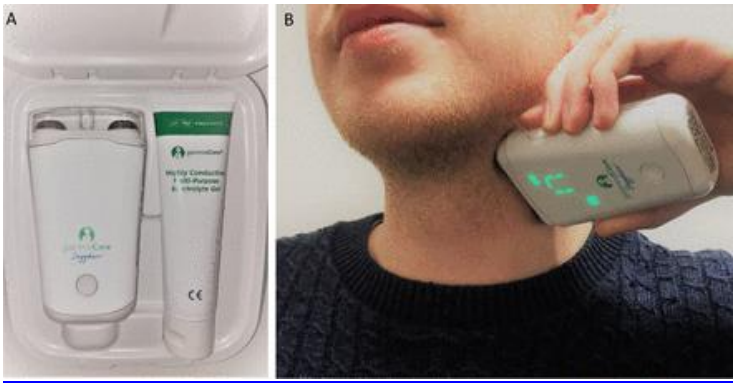


Figure 6 The gamma Core device (A) device shown with electrolyte gel and (B) device demonstration Image published with permission of the individual.

The preventive effect of GammaCore has been demonstrated in a prospective observational study in which almost 75% of patients presented a general improvement. Similar results were obtained for chronic cluster headaches in an open randomized trial using GammaCore as a complementary therapy48 using three-sided stimulation of three 2-minute stimulations, twice a day [76].

4.7 Sphenopalatine ganglion microstimulator

GSP has long been a goal for different treatment options. However, a small pacemaker implanted in the pterygopalatine fossa has been shown to be effective in reversing acute cluster attacks in a randomized, double-blind, controlled and simulated trial, chronic and medically refractory cluster headache. The study found a preventive effect of SPG stimulation in one third of the patients included, with an average reduction of 83% in the frequency of attacks compared to the beginning of long-term open treatment. The second study, CH-2, randomized 93 patients with chronic headache (1: 1) to stimulation with sSPG or an active simulator. The stimulation group had more pain relief and pain relief after 15 minutes than the simulated group, and there was still a preventive effect. A large European registry indicated that the approach was profitable over time. Our experience is consistent with clinical trials, which this treatment offers a way forward for a group of very disabled patients.

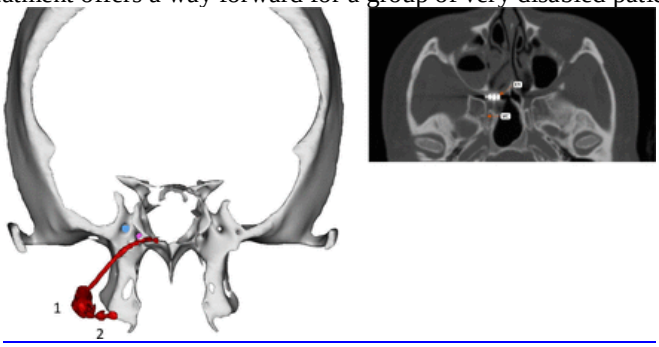
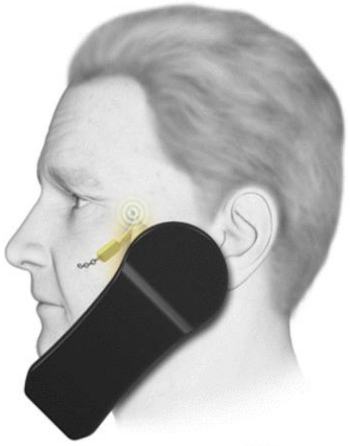


Figure 7 Right-sided SPG microstimulator from a patient in our centre. (A) Postoperative reconstructed CT scan of head, coronal view, showing the microstimulator in red, with electrode lead in the right pterygopalatine fossa, the

body of the neurostimulator with the microprocessor and the RF-antenna (1) and the fixation plate (2), the pink indicates the vidian canal and the blue indicates foramen rotundum. (A) Axial view showing the relation of the VC and the first electrode of the microstimulator (E1). SPG, sphenopalatine ganglion; VC, vidian canal.



Like any other surgical procedure, the stimulator implantation comes with risks, the most common being sensory disturbances and postoperative pain and swelling, which were mild to moderate, and resolved within 2–3 months. The decision to proceed to surgery is best addressed via a multidisciplinary approach in a centre with the appropriate specialist expertise.[76]

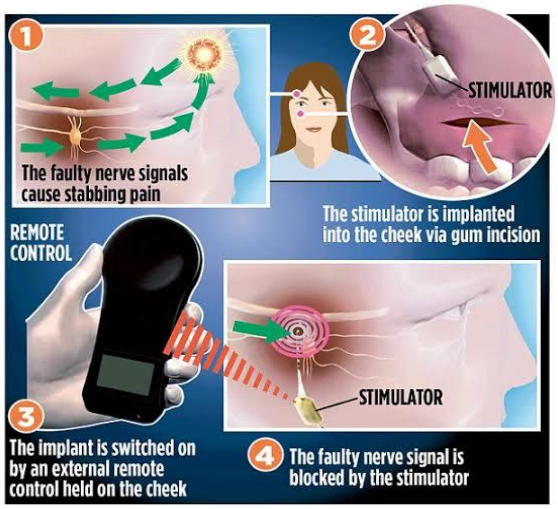


Figure 8 The SPG device and the remote controller. The patient activates the stimulator via a hand-held device which the patient puts on the cheek ipsilateral to the pain, the device should be held for 15 min. Courtesy of Autonomic Technologies. SPG, sphenopalatine ganglion.

4.8 Monoclonal antibody peptides related to the calcitonin gene

The plasma peptide related to the calcitonin gene rises in spontaneous groups and is triggered by nitroglycerin during the outbreak. In addition, its infusion can trigger seizures in patients with episodic cluster headache, but only in the case of a seizure. To date, only galcanezumab has been shown to reduce the number of weekly cluster headache attacks in episodic cluster headache in a placebo-controlled trial. The results were not replicated for headaches in chronic clusters. [76]

V. CONCLUSION

Cluster headache is a typical, severe unilateral headache episode, usually lasting between 15 and 180 minutes, with a frequency of once every two days to eight times daily, associated with autonomic symptoms to pain. On the basis of this review we can treat cluster pain with different drugs on the other hand we can also use different types of devices for maintaining the cluster pain.

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