Navigating the waves of cluster headache: clinical aspects and GON modulation

Naber, W.C.

1

GENERAL INTRODUCTION AND OUTLINE

Adapted from:

The biological clock in cluster headache: A review and hypothesis

Willemijn Naber, Rolf Fronczek, Joost Haan, Patty Doesborg, Chris Colwell, Michel Ferrari, Johanna Meijer

Cephalalgia. 2019 Dec;39(14):1855-1866.

EXPLORING THE WAVES
CLINICAL ASPECTS OF CLUSTER HEADACHE

Classification and clinical characteristics

The syndrome we now know as cluster headache was first medically described in 1641 by Nicolaes Tulp (1593–1674).[1] Over time, the condition was referred to by various names, including Horton's disease and migrainous neuralgia. In 1926 a distinction was made from migraine and in 1952 the term "cluster headache" was adopted, which reflects the characteristic temporal clustering of headache attacks during the disease course.[2]

Cluster headache is a primary headache characterized by unilateral, extremely painful attacks.[3] The attacks are considered to cause one of the most severe types of pain in existence.[4] Cluster headache is a trigeminal autonomic cephalalgia (TAC), a class of headache disorders characterized by brief, side-locked headache attacks accompanied by cranial autonomic symptoms.[3] Diagnosis is made through patient interview by applying the International Classification of Headache Disorders criteria (ICHD-3).[3] The agonizing attacks are usually located in the temporal or periorbital area, have a duration of 15 minutes to 3 hours and can occur up to 8 times per day. Attacks are accompanied by ipsilateral cranial autonomic features such as lacrimation, ptosis, miosis, nasal congestion, or/and rhinorrhoea and a sense of restlessness and/or agitation (Figure 1). Because of the intense and frequent attacks, cluster headache has a major impact on patients' lives, for example by poor sleep quality due to nocturnal attacks. It is therefore associated with decreased quality of life (QoL) affecting all aspects of everyday life.[5, 6] Although physical symptoms resolve during remission, the cyclical nature of cluster headache can lead to lasting decreased QoL.[7, 8] As a result of the disease burden, a high proportion of patients is unemployed.[9,10]

Demographics and risk factors

The prevalence of cluster headache in the general population is around 1 in 1000. The typical age of onset is in young adulthood, most often between 20 and 40 years.[11-13] Aside from the clinical observation that disease activity appears to resolve spontaneously with age, limited epidemiological data exists on its natural progression and prolonged remission.

Historically, cluster headache was considered a "male" disease with patients anecdotally described as exhibiting a "hypermasculine" physical appearance.[14] Currently, the disorder is increasingly recognized in females, but remains more common in men than in women with a ratio of 2-4:1 in Western countries.[15-17]

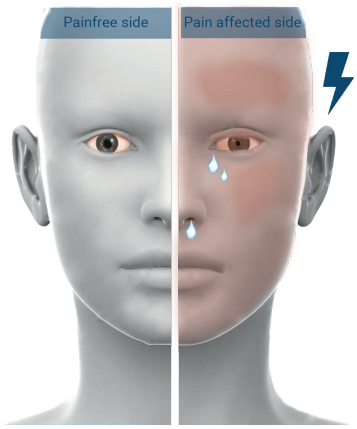

Figure 1. Clinical Features of a cluster headache attack.

The cluster headache phenotype is characterized by cranial autonomic symptoms ipsilateral to the headache. Illustrated symptoms: lacrimation, ptosis, miosis, nasal congestion, or/and rhinorrhoea, eyelid oedema and facial sweating.

Smoking prevalence is high in cluster headache, with reported rates ranging from 70 to 90%.[18] Although smoking is associated with a more severe disease manifestation, quitting does not immediately result in remission of cluster headache.[18] Cluster headache is associated with unfavorable lifestyle factors, not only due to increased smoking, but also higher average alcohol intake, elevated BMI, and a greater prevalence of lifestyle-related diseases (e.g., hypertension, stroke).[19, 20] Additionally, the disorder is associated with increased psychiatric comorbidity, such as bipolar disorder, anxiety, aggressive behaviour and sleeping problems.[7] This might be a consequence of the disease, but an intrinsic susceptibility independent of disease severity has been suggested.

Finally, several triggers for cluster headache attacks have been described. Substances may provoke an attack, such as alcohol, nitro-glycerine or histamine.[18] In addition, patient commonly report triggers. Most frequently reported is nocturnal sleep, with one-third of patients also describing daytime-napping as trigger.[21, 22]

Ebb and flow: the oscillating disease activity in cluster headache

As the name implies, cluster headache is defined by the occurrence of “clusters”. Its symptoms follow a cyclical pattern of oscillating disease activity during the disease course. Disease activity oscillates from periods with high disease activity (symptomatic periods with frequent attacks) to those with minimal disease activity (remission periods without attacks). Based on these patterns, cluster headache is classified into two subtypes: episodic and chronic cluster headache. In episodic cluster headache (ECH, 85% of patients), attacks occur in episodes lasting weeks or months, with remission intervals of three months to several years, Figure 2A).[3] In

chronic cluster headache (CCH, 15% of patients), the most severe subtype, patients have attacks with less than three consecutive months of remission per year (Figure 2B).[3,23] These subtypes are dynamic: the chronic form can be either unremitting from onset (primary CCH, *pCCH)* or can evolve from the episodic form (secondary CCH, *sCCH*) and the chronic form can also become episodic (secondary ECH, *sECH*).[24,25]

Interestingly, the disease activity does not oscillate randomly; most patients report a distinct rhythm and predictability in their disease activity. Attacks occur in clusters of weeks to months with a seasonal rhythm (*in ECH*), or intensity and frequency of attacks may increase in certain months of the year (*in CCH*).[22,26,27] Typically, cluster headache is reported to follow an annual pattern with a peak in the spring (March-

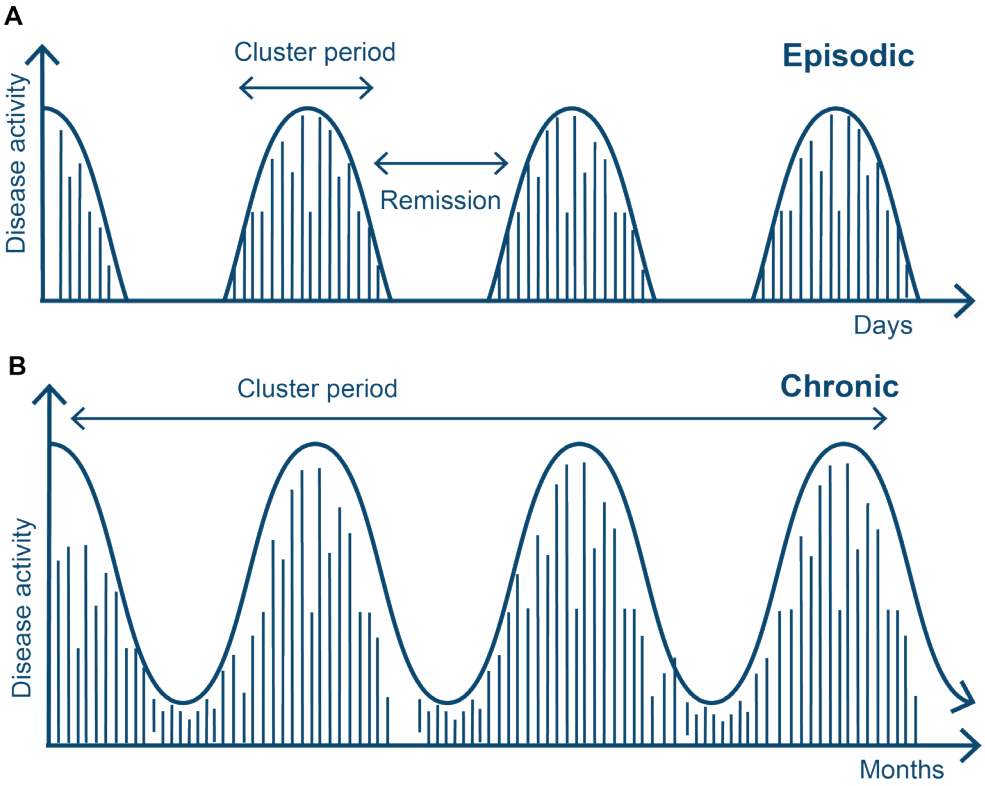

Figure 2. Cluster headache occurs in two subtypes: episodic and chronic.

(A) in episodic cluster headache (ECH), cluster headache attacks occur in episodes lasting 7 days to 12 months, with remission intervals of months to years (≥ 3 months). (B) in chronic cluster headache (CCH), cluster headache attacks occur with ≤ 3 consecutive months of remission per year. Disease activity oscillates from periods with high disease activity (symptomatic periods with frequent attacks) to those with minimal disease activity (remission periods (ECH) or periods with less attacks (CCH)). These subtypes are dynamic: the chronic form can be unremitting from onset (primary CCH, pCCH) or can evolve from the episodic form (secondary CCH, sCCH) and the chronic form can become episodic (secondary ECH, sECH).

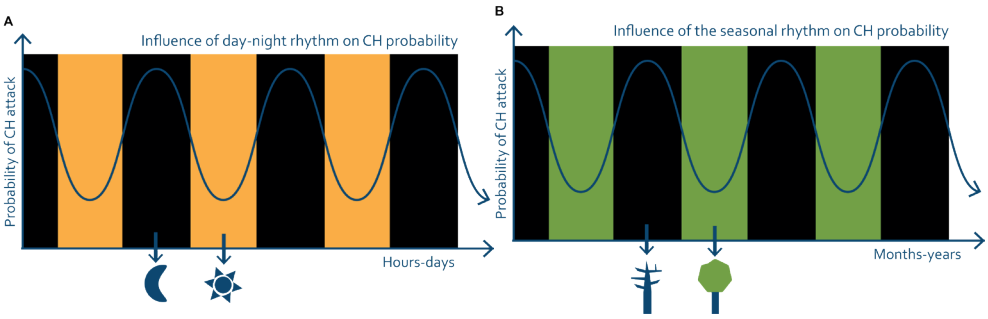

Figure 3. Circadian and seasonal rhythms affect the probability of cluster headache (CH) attacks.

(A) The day-night rhythm (with daytime shown in yellow and nighttime shown in black) leads to a synchronized 24-hour rhythm in the frequency of cluster headache attacks.
(B) Although the seasonal rhythm (with summer shown in green and winter shown in black) is less pronounced, many studies indicate that the pattern of cluster headache attacks is also synchronized to this rhythm.

April) and a peak in autumn (September-October, Figure 3B).[26-31] Within a cluster episode, attacks typically occur at certain times of the day and/or night. Approximately 75% of cluster headache patients report that their attacks generally follow a 24-hour cyclical pattern (Figure 3A).[32] Most cluster headache attacks occur within 90 minutes of falling asleep.[33] Overall, 75% of attacks occur at night between 21:00 and 10:00, with peak incidence around 02:00.[34 32] This rhythmicity of attacks may be due to the effects of the biological clock and/or sleep. Since attacks often occur during the night waking patients from their sleep, there appears to be a connection between cluster headache and sleep.[35-38]

Threshold hypothesis

Based on the phenotype of cluster headache, a threshold-based hypothesis is proposed as a model to explain the oscillating disease activity and fluctuating attack frequency of cluster headache. In both chronic and episodic cluster headache, disease activity follows a wave pattern, with periods of increased and decreased activity over time. Attack probability is high during peaks and low during dips of these waves.

In patients with chronic cluster headache, disease activity follows a rhythmic sinusoidal oscillation consisting of more active and less active periods (Figure 4B). While patients with episodic cluster headache have a similar sinusoidal pattern, it results in cluster headache attacks interspersed with periods of remission. A threshold demarks the transition between these periods for both episodic and chronic cluster headache; when this threshold is exceeded, the brain enters a state in which the attacks can occur (Figure 4A).

Except for temporal differences in occurrence, clinical and demographic characteristics of episodic and chronic cluster headache are similar. Episodic and chronic cluster headache are likely caused by the same pathophysiological processes, but a more "permissive" brain state leads to chronic cluster headache. Based on this theoretical model, such a threshold could be regulated by factors such as the biological clock and sleep.[35-38] An important implication for the threshold hypothesis is that chronic cluster headache can turn into episodic cluster headache (and vice versa) in a given patient, a notion that is supported by clinical anecdotes.

It is hypothesized that a variety of factors, including external light, sleep, and the biological clock, function as "shapers of the waves" and can change the brain's permissiveness, thereby altering the threshold for activation of attacks. These key components are further discussed below.

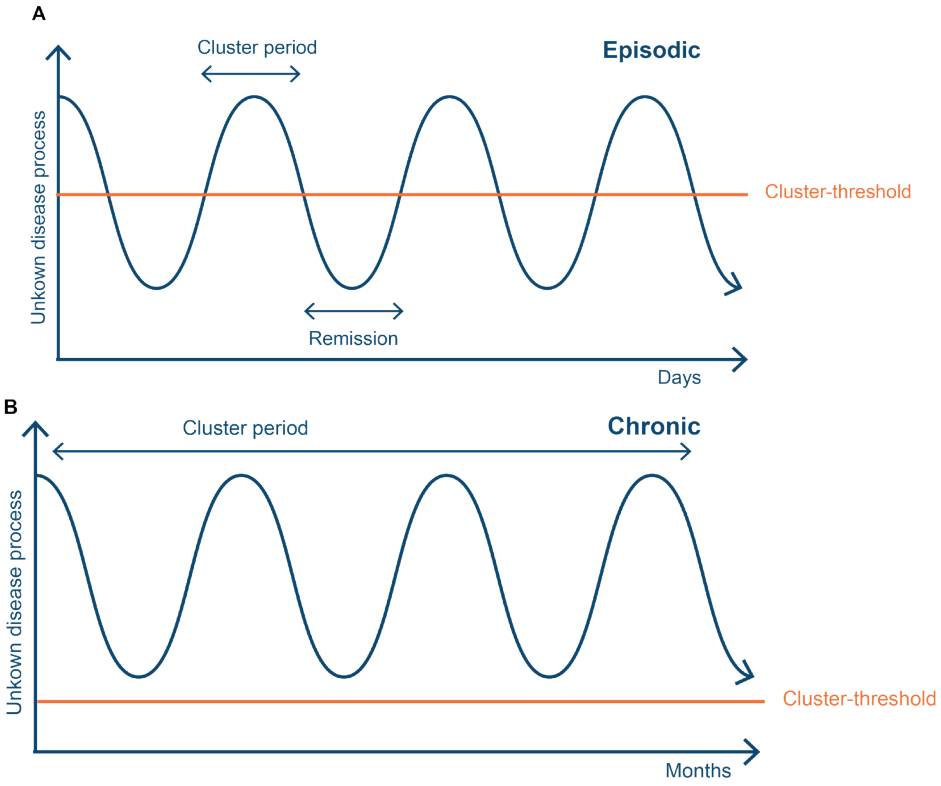

Figure 4. Threshold hypothesis. In both subtypes the disease activity follows a sinusoidal pattern.

(A): in episodic cluster headache, a fluctuating disease process causes cluster headache attacks only when the probability exceeds a predetermined threshold (depicted by the horizontal orange line).
(B): In chronic cluster headache, the disease process always exceeds this threshold but still fluctuates between higher to lower attack probablility. Right: Central to this hypothesis is the notion that this threshold can be adjusted by various factors, including the circadian clock, sleep state and hormonal changes.

Shapers of the waves: core elements of cluster headache pathophysiology

The distinctive features of cluster headache described above have prompted further research to uncover its underlying pathophysiology. Understanding of the phenotype of cluster headache has improved over the years, but the cycling of both attacks and episodes remains poorly understood. Pathophysiological understanding is hindered by the short duration of the attacks and the lack of an suitable animal model representing cluster headache. Therefore puzzle pieces have to be gathered from neuroanatomical pathway studies in animals, human neuro-imaging and clinical studies. Below, evidence is summarized for the key components that are thought to influence the oscillating disease activity in cluster headache.

Hypothalamus

The hypothalamus is a key structure in the central nervous system and regulates homeostasis for the neuroendocrine system, sleep, circadian and circannual rhythms and the autonomic nervous system.[39] Since its core function aligns with the systems affected in cluster headache based on the phenotype, it currently presumed that that cluster headache originates at the level of the hypothalamus. There is no consensus on the area within the hypothalamus, but most studies point to the posterior hypothalamus.

Imaging studies have revealed that the ipsilateral inferior posterior hypothalamic gray area is activated during cluster headache attacks.[40-42] Other brain areas that are associated with the processing of pain (including the thalamus, cingulate cortex, and insular cortex) were activated both during cluster headache attacks as well as during other types of headache.[40, 43] Structural studies have reported enlargements of the posterior and anterior hypothalamus and a correlation with a higher volume of the ipsilateral anterior hypothalamus and the number of attacks.[44-46] The structural abnormalities in the anterior hypothalamus of patients are particularly interesting, given that this is the location of the suprachiasmatic nucleus (SCN), which generates circadian rhythms.[46, 47] Even if the exact location within the hypothalamus (i.e, anterior v.s. posterior) remains unclear, the consensus is that the hypothalamus is an area of great interest in cluster headache. Further evidence supporting a role of the hypothalamus in cluster headache comes from reports where deep brain stimulation of the posterior hypothalamus improved symptoms in patients with therapy-resistant chronic cluster headache.[40-43, 48]

Biological clock

The biological clock is thought to play an important role in cluster headache, as suggested by changes in the hypothalamus, the cyclical pattern of cluster headache attacks and the efficacy of lithium – a medication known to influence circadian

rhytms.[49] The circadian system is controlled by central clock of the SCN, a bilateral structure located at the base of the anterior hypothalamus.[50] Neurons in the SCN have the autonomous ability to produce circadian rhythms.[47] This rhythmicity at the single-cell level arises via a negative-feedback loop between circadian clock genes and their protein products.[51] These protein products activate currently unidentified pathways in order to change the cell's membrane potential and electrical frequency (*for review, see* [52]). In both nocturnal species (e.g., rodents) and diurnal species (e.g., humans), electrical activity in the SCN is relatively high during the day and low during the night,[52] creating a waveform of electrical activity that is directly correlated with the species' temporal pattern of behavioral activity.[53] The rhythm of the SCN is synchronized to the external light-dark cycle (Figure 5).[54] Increased activity of the SCN was observed during cluster headache attacks, which possibly leads to severe disruptions in circadian rhythms and heightened attack susceptibility.[55]

Sleep

The timing of cluster headache attacks, suggests a connection with sleep. Attacks often occur approximately 90 minutes after sleep onset, when REM sleep typically begins. This led to the (HPA) hypothesis that REM sleep might be correlated with cluster headache which was supported by data from an early study.[56] However, this hypothesis could not be confirmed as further studies did not reveal a correlation between cluster headache with any specific sleep stage.[35-38, 57] One interesting theory

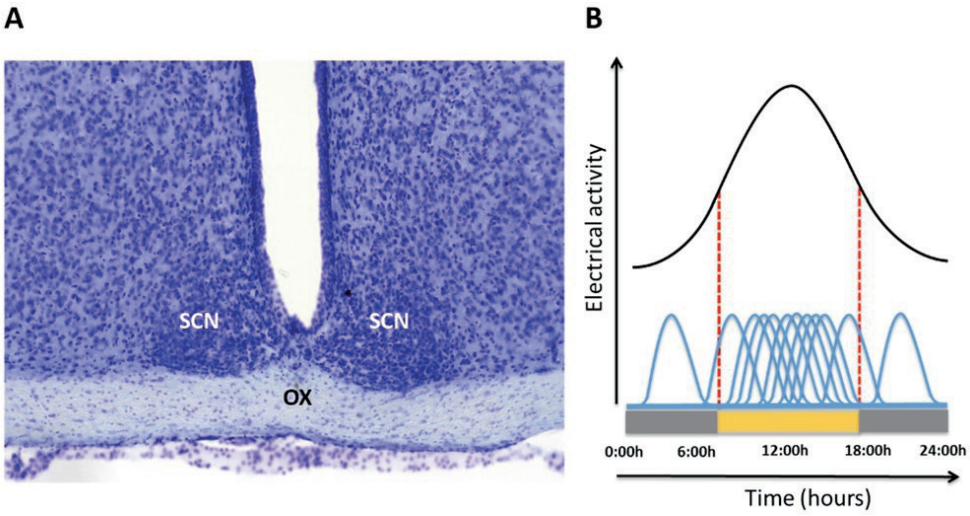

Figure 5. The central pacemaker in mammals.

(A) A coronal mouse brain section stained with Nissl, showing the location of the suprachiasmatic nuclei (SCN) and optic chiasm (OX).
(B) Schematic diagram depicting the electrical activity of individual SCN cells (shown as blue traces) over a 24-hour period. The SCN cells oscillate slightly out of phase and give rise to the ensemble population pattern shown in black. This ensemble signal is transmitted to other areas of the brain, thereby providing rhythmicity to the central nervous system.

is that attacks might be correlated with the transition between sleep stages, as the "switch" mechanism that underlies this transition is also located in the hypothalamus.[58]

Hormones

The gender-biased nature and age dependency suggest that sex hormones may play a role in the pathophysiology of cluster headache. Hormones are closely related to the biological clock, as the SCN imparts its rhythmic activity to the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis.[59] Moreover, case reports have described pituitary tumors that were believed to cause cluster headache attacks.[60, 61] Hormonal changes have been observed in cluster headache patients and include changes in growth hormone, prolactin, cortisol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and melatonin levels.[62] Testosterone levels are often lower in patients during a cluster headache period [63-69]; the resulting compensated hypogonadism may be secondary to disrupted REM sleep and/or increased cortisol levels during a cluster headache period.[70, 71] With the exceptions of FSH and LH, no other changes in sex hormones have been reported in cluster headache patients.[65, 67] Other factors that affect hormonal status such as oral contraceptives, menstruation, pregnancy, and menopause have only a small influence on cluster headache attack probability.[72]

Genetics

Genetic studies in cluster headache have either focused on heritability at the population level or aimed to identify specific genes. Although first-degree relatives have a 5-18 times increased risk at developing cluster headache, no clear hereditary pattern has been identified.[73] This suggests that the cause of cluster headache is likely an interplay between multiple genes and environmental factors. Genome-wide-association studies (GWAS) in European and Han Chinese cohorts identified eight loci that were associated with cluster headache.[9] Of those, three are shared with migraine, affirming the assumption that migraine and cluster headache are distinct disorders that partly overlap in their pathophysiology. Genetic correlations were also found for pain disorders, neuropsychiatric diagnoses and cigarette smoking.[74] Mendelian randomization recently demonstrated a causal effect of smoking intensity on cluster headache.[74] Genetic markers of circadian rhythm genes have been linked to cluster headache, though findings have been inconsistent.[75] However, two of the identified loci include genes associated with circadian rhythm—MER proto-oncogene, tyrosine kinase, and four and a half LIM domains 5 (FHL5). These findings further support the role of the SCN in cluster headache.

Trigeminovascular system

Historically cluster headache was thought to be a vascular disease, where the dila-

tation of vessels caused the intense pain accompanied by autonomic features. This was substantiated by the notion that vasodilators (*nitroglycerin, histamine*) can trigger attacks and vasoconstrictors (*ergotamine, triptans*) abort attacks. Currently, it is thought that the ipsilateral cranial autonomic features during attacks are caused by activation of the autonomic nervous system through hyperactivation of the trigeminal-autonomic reflex.[76] Activation of this reflex results in vasodilation of the internal carotid arteries through the release of vasodilator peptides such as calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP) 38, substance P and neurokinin A.[9, 77] During a cluster headache attack, the levels of plasma CGRP and vasoactive intestinal peptide (VIP) increase. Dilation of the ipsilateral internal carotid artery and the resulting increased blood flow have been observed using magnetic resonance angiography (MRA) and positron emission tomography (PET), supporting activation of the trigeminal-autonomic reflex.[40, 43, 78-80] Interestingly, attacks can also be triggered by injecting capsaicin into the forehead, which is known to activate the trigeminal-autonomic reflex.[34] Additionally, infusions of CGRP, PACAP-38, and VIP have been shown to provoke attacks with a phenotype similar to that of a "natural" cluster headache attack.[40, 81-84]

Neuroanatomy of Cluster headache Attacks

Meanwhile, although the pathophysiology of cluster headache is not fully understood, three neuroanatomical structures are proposed to combine the elements mentioned above and explain the clinical phenotype of cluster headache: the trigeminal vascular pathway, the trigeminal-autonomic system and the hypothalamus (Figure 6).[69, 76] The following section outlines the role of each system to provide a neuroanatomical framework for understanding the proposed origin of cluster headache attacks.

Hypothalamus – the attack generator

Cluster headache attacks are assumed to be generated from deep within the brain and not peripheral. While the trigeminal system can be triggered to cause an individual headache attack, this occurs only during "permissive states" (i.e., cluster episodes). Additionally, the trigeminal system cannot explain the other characteristic features (male predisposition, circadian and circannual rhythmicity, nocturnal occurrence). Therefore, the hypothalamus is suggested to be the "attack generator", where hypothalamic activity coincides with cluster headache attacks and episodes. The hypothalamus is part of the diencephalon and located beneath the thalamus.[55] The hypothalamus regulates pain and autonomic symptoms through a two-way anatomical pathway to the trigeminovascular system and the trigeminal–autonomic reflex, via the trigeminocervical complex (TCC).[18, 85] The TCC consists of the dorsal horn of the cervical spinal C1, C2 and the trigeminal nucleus caudalis (TNC).[18]

The trigeminal system – driving pain and autonomic features

It is proposed that interplay between the trigeminal vascular pathway (resulting in pain) and the trigeminal-autonomic reflex (resulting in autonomic symptoms) are connected and together cause and escalate the stereotypical phenotype of cluster headache attacks.

The trigeminal-autonomic reflex is composed of neurons in the TCC that trigger the parasympathetic pathways via the supra salivatory nucleus (SSN) and the sphenopalatine ganglion (SPG), leading to vasodilation and the manifestation of cranial autonomic symptoms.[18] Activation of the trigeminal-autonomic reflex elicits the secretion of neuropeptides (e.g. CGRP, PACAP-38 etc.)

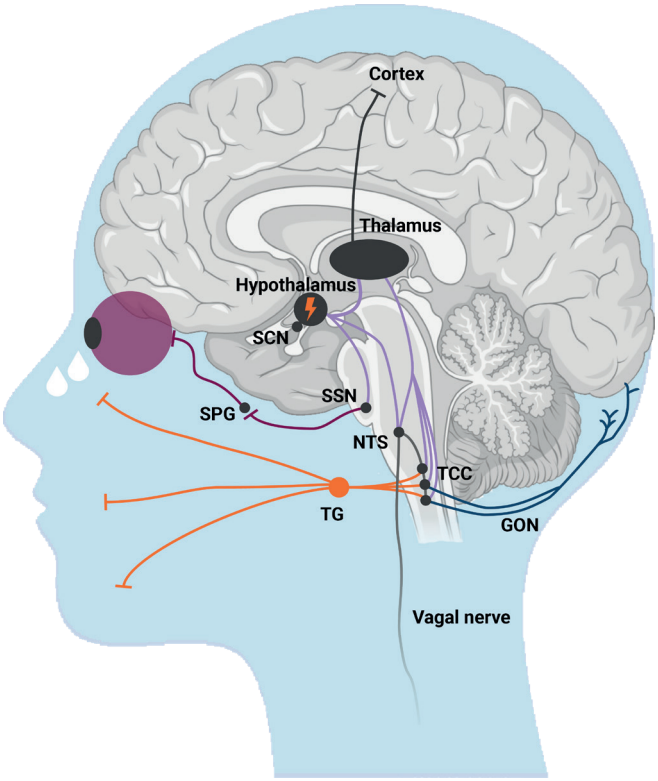

Figure 6. Neuroanatomical pathways of cluster headache pathophysiology.

The trigeminovascular pathway (shown in orange) consists of the neurons from the trigeminal ganglion that have synapses centrally in the trigeminocervical complex and peripherally in the dura mater, cerebral vessels and upper facial (periorbital) structures. Activation of this pathway is perceived as peripheral pain. The trigeminal-autonomic reflex (shown in dark purple) is composed of neurons origination from the trigeminal cervical complex that extend to the superior salivatory nucleus and the sphenopalatine ganglion. These subsequently activate the parasympathetic fibers responsible for cranial autonomic symptoms, such as tearing. The hypothalamus (assumed attack generator, depicted as lightning bolt) is connected to the trigeminocervical complex (shown in light purple) and the thalamus. GON: greater occipital nerve, NTS: nucleus tractus solitarius, SCN: suprachiasmatic nucleus, SSN: superior salivatory nucleus, TCC: trigeminocervical complex, TG: trigeminal ganglion

Activation of the trigemino-vascular pathway results in the release of neuropeptides (e.g. CGRP, PACAP 38) from trigeminal nerve endings, which is perceived as pain in humans.[78, 82] This is likely to be the final step for the pain as experienced in cluster headache; resulting in stereotypical unilateral peri-orbital pain in the first branch of the trigeminal nerve.[86] The involvement of this pathway is proposed to be a final common pain pathway for pain transmission in headache as it is also activated in migraine.

BREAKING THE WAVES — GON MODULATION IN CLUSTER HEADACHE

Current treatment is based on empirical data. Although episodic and chronic cluster headache respond to the same therapies, chronic cluster headache is more difficult to treat.[28] Medication trials are difficult in cluster headache due to the natural fluctuating disease activity and high placebo efficacy (14-43%).[87] The following section provides an overview of current treatment options, with a focus on greater occipital nerve (GON) modulation. These therapies have shown the ability to "*break the waves*" of disease activity, providing (temporarily) relief for patients and enabling clinicians to help patients navigate their "*waves*".

Overview of current treatment options

Treatment of cluster headache entails acute, prophylactic and transitional (temporary) treatment. Acute medication focuses on rapid suppression of individual attacks, - usually with sumatriptan (3/6 mg subcutaneous or 20 mg nasal) or pure oxygen inhalation (100% 12L/min).[88, 89] Sumatriptan is a selective 5-hydroxytryptamine (5HT1B/1D) receptor agonist. Subcutaneous use is generally preferred due the its rapid abortive efficacy in comparison to the nasal formulation. A subcutaneous dose results in pain relief within 15 minutes in 75% of patients.[17] However, the nasal formulation may be considered for patients experiencing longer-lasting attacks. High-flow oxygen is usually administered via a nonrebreather mask for 15 minutes as soon as possible after attack onset resulting in complete pain relief in 54-78% of patients.[88, 90] Nevertheless, even when quickly managed, the high frequency, unpredictability, and pain-intensity of attacks cause profound disruptions in patients' lives. Therefore, the corner stone of cluster headache management is formed by preventative and transitional medication that aim to reduce the number of attacks.[17, 94]

Current guidelines included various options for preventative and transitional therapies, based upon different evidence-levels.[17] First-line preventative treatment is formed by verapamil, lithium and topiramate. Other oral medication that can be

considered are: sodium valproate, gabapentin, melatonin, pizotifen and frovatriptan. Verapamil is the first choice preventative medication for both episodic and chronic cluster headache.[17] While it can be used long-term, verapamil is often ceased due to side effects or reduced efficacy over time.[17] Topiramate has not been tested in placebo-controlled trials, but was effective in open label and case studies when tolerated.[17] When tolerated, lithium can be an effective preventative, but its side-effects often outweigh the benefits and it cannot be combined with verapamil or topiramate, due to increased toxicity risk.

The physician and patient collaborate to find the optimal balance between treatment efficacy, side effects, and quality of life. While the main goal is attack freedom, this is often impossible, especially in chronic cluster headache. In 10-20% prophylactics are not effective. Those patients have refractory chronic cluster headache.[95] These patients are more likely to experiment with alternative treatments, including illicit drugs.[96] In the Netherlands patients with MICCH also qualify for reimbursed invasive therapies, such as occipital nerve stimulation (ONS).

Corticosteroids can be applied as transitional treatment, using it as additive or bridging therapy, e.g. during "peak" disease activity or while titrating other preventative medication to an effective dosage.[17] Corticosteroids can be administered orally, or as a nerve block through infiltration around the greater occipital nerve (GON). High dose oral corticosteroids (starting at 60-100 mg and gradually tapered) are used as a "last resort" temporary option, often resulting in short-lasting remission during the weeks with a higher dosage before attacks usually recur below a daily dosage of 30 mg.

Modulation of the greater occipital nerve (GON)

Modulation of the greater occipital nerve (GON) can effectively alleviate cluster headache. Two main approaches are used to target the GON: subcutaneous infiltration (GON infiltration) and occipital nerve stimulation (ONS). The following section provides a more detailed exploration of their mechanisms, clinical application, and supporting evidence.

GON infiltration

Local injection of steroids around the GON exists as interventional treatment for chronic local neuropathic pain since the 1960's. Since the 1980's its first promising results were reported as treatment for cluster headache.[97, 98] The Greater Occipital Nerve (GON) is a sensory nerve that originates from the C2 dorsal ramus and provides sensation to the posterior scalp, extending from the occipital region to the vertex of the head (Figure 7). It passes between the semispinalis capitis and trapezius muscles before emerging just inferior to the superior nuchal line, where it becomes

more superficial. Infiltration of the GON is done by injecting corticosteroids on 1/3 of the line between the occipital protuberance and the mastoid process (Figure 8). Which corticosteroid is used depends on the hospital, but most commonly 80 mg of methylprednisolone is injected optionally with lidocaine.

The mechanism of action of GON infiltration in cluster headache remains enigmatic. People with cluster headache often experience tenderness in the neck in the region of the occipital nerve before the pain transgresses toward the peri-orbital region (V1 branch of the trigeminal nerve).[99, 100] This phenomenon could be explained by "referred pain" originating from the conjunction of afferent nerve endings of the trigeminal nerve and greater occipital nerve in the trigeminal cervical complex.[101-103] Therefore, it is hypothesized that GON infiltration affects trigeminal transmission within the trigeminal cervical complex, resulting in changes in cluster headache symptoms.

An injection of steroids — with or without a local anaesthetic — around the greater occipital nerve (GON) can reduce the number of attacks or even lead to attack freedom.[104-112] However, as highlighted in recent meta-analyses,[113, 114] this was demonstrated only in open-label studies and two small trials,[104-111] in a mixed study population of episodic and chronic cluster headache.[106, 108, 109, 111] Moreover, many patients were using different forms and doses of prophylactic co-medications and/or received the GON-injection at a non-standardised time-point, sometimes weeks after the onset of a cluster episode.[105, 110, 112] Despite its good tolerability and rapid efficacy, GON infiltration was, until recently, not included in standard treatment protocols and was primarily used in specialized headache clinics. In recent years, however, its use has increased, supported by growing evidence of safety and efficacy. This has led to the inclusion of GON infiltration (with a corticosteroid and sometimes a local anesthetic) in the European Academy of Neurology treatment guidelines.[17, 110, 112, 115, 116]

Occipital nerve stimulation

A more invasive approach to modulate the GON is occipital nerve stimulation (ONS), in which the GON is modulated via electrical impulses through implanted electrodes (Figure 7). A randomized-, double-blind study demonstrated a significant reduction in attack frequency and severity, and a long-term follow-up of these participants showed sustained efficacy up till years.[117, 31] Based on these findings, since 2020, Dutch patients with refractory chronic cluster headache have been eligible for reimbursement of ONS.

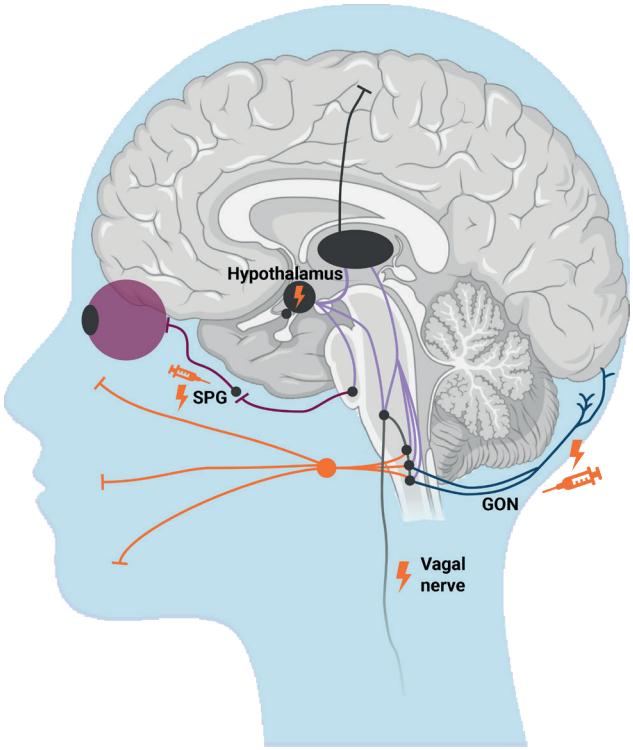

Figure 7. Neuroanatomical pathways that are used for neuromodulation.

A syringe depicts neuromodulation via injection and a lightning bolt depicts nerves that can be stimulated with electronic stimulation. GON: greater occipital nerve, NTS: nucleus tractus solitarius, SCN: suprachiasmatic nucleus, SSN: superior salivatory nucleus, TCC: trigeminocervical complex, TG: trigeminal ganglion

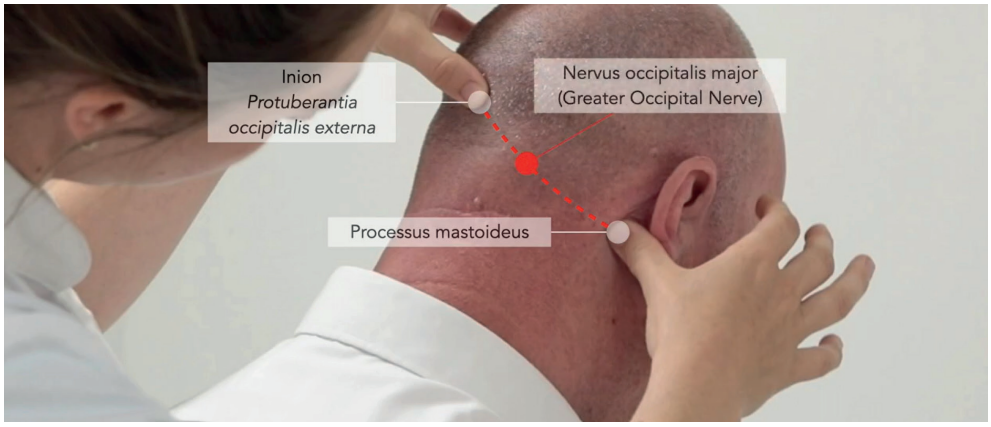

Figure 8. Injection location of GON infiltration.

Infiltration of the GON is done by injecting corticosteroids on 1/3 of the line between the occipital protuberance and the mastoid process.

AIMS AND OUTLINE OF THIS THESIS

In this thesis various studies on clinical aspects and treatment of cluster headache are discussed. The overarching aim of these studies was to improve the ability of patients, physicians and researchers to *navigate the waves of cluster headache*. Managing cluster headache is challenging due it's fluctuating "*waves*" of disease activity. This results in turbulent storms of cluster headache interspersed with calmer intervals of remission. These *waves* create constant challenges for patients, physicians and researchers. First of all, patients struggle to maintain daily functioning while facing unpredictable and highly disruptive and painful attacks. Physicians strive to support them, by tailoring treatment strategies to a fluctuating and difficult-to-treat disease process. Finally, researchers seek to uncover insights that may advance the understanding of cluster headache, but face the difficulty of capturing and interpreting findings against the backdrop of an elusive dynamic natural disease course.

To guide the reader, the different aspects of *navigating the waves of cluster headache*, are divided into two themes: *exploring the waves* and *breaking the waves*.

Part I of this thesis aims to *explore the waves* to gain better understanding of cluster headache. Exploration is done by examining the patterns of the waves and their "*shapers*": phenotypical features, thought to act as key components of the cluster headache pathophysiology. In this part various clinical aspects of cluster headache are discussed, such as the natural course, patient characteristics and the quality of life (**Chapter 2-6**) .

Part II of this thesis aims to evaluate breaking the waves. Here, '*breaking the waves*' serves as a metaphor for therapeutic interventions aimed at reducing the intensity and frequency of cluster headache attacks. It discusses different aspects of GON modulation, with a focus on GON infiltration as treatment in cluster headache (**Chapters 7–8**).

Part I – Exploring the waves – Clinical aspects of cluster headache

To capture the natural patterns of the waves, **Chapter 2** explores the natural course of cluster headache, with a focus on prolonged remission. **Chapter 3** then zooms in on one of the shapers: illicit drugs, reporting the prevalence and effect in cluster headache. Building on this, **Chapter 4** examines a potential explanation for increased substance use by examining whether individuals with cluster headache display more risk seeking behaviour than those without. **Chapter 5** focusses on another shaper, hormones, by comparing (sex) hormone levels between males with and without cluster headache. Finally, the exploration of the waves concludes by investigating

their impact on patients: **Chapter 6 and 7** discuss the validation and implementation of the Cluster Headache Quality of Life (CHQ) to gain a better understanding of QoL in Cluster headache.

Part II – Breaking the waves – GON modulation in Cluster headache

Chapter 8 reports the intriguing observation that GON infiltration can trigger a side-shift of attacks in some patients, offering a hypothesis for the potential underlying mechanism of GON infiltration and side-shifts. Building on this, **Chapter 9** investigates the mechanism of action of GON infiltration by examining changes in the blink reflex, providing insight into how this treatment may modulate the neural circuits that drive the waves of cluster headache.

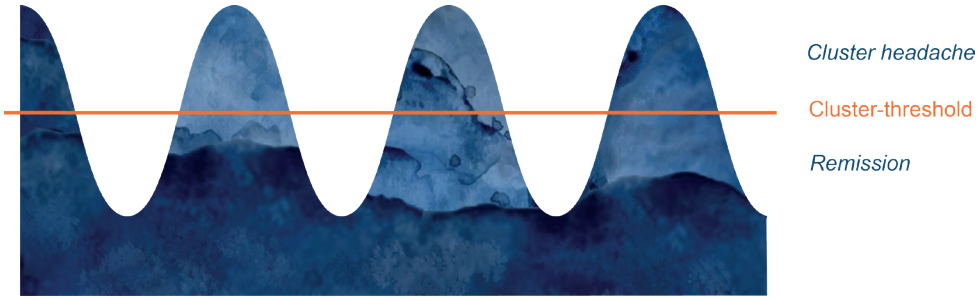

Figure 9. Thematic visualisation of the waves of cluster headache.

Visualusation of the fluctuating disease ativity of cluster headache, as suggested by the threshold hypothesis: Disease activity above threshold manifests as cluster headache and below as remission.

REFERENCES

1. Søborg MK, Petersen AS, Lund N, Wandall-Holm MF, Jensen RH, Barloese M. Transition of cluster headache phenotype: An interview-based study. Cephalalgia. 2023;43(1):3331024221128287.
2. Peng KP, Takizawa T, Lee MJ. Cluster headache in Asian populations: Similarities, disparities, and a narrative review of the mechanisms of the chronic subtype. Cephalalgia. 2020;40(10):1104-12.
3. Sjöstrand C, Waldenlind E, Ekbom K. A follow-up study of 60 patients after an assumed first period of cluster headache. Cephalalgia. 2000;20(7):653-7.
4. Pearce JM. Natural history of cluster headache. Headache. 1993;33(5):253-6.
5. Manzoni GC, Micieli G, Granella F, Tassorelli C, Zanferrari C, Cavallini A. Cluster headache--course over ten years in 189 patients. Cephalalgia. 1991;11(4):169-74.
6. Torelli P, Cologno D, Cademartiri C, Manzoni GC. Possible predictive factors in the evolution of episodic to chronic cluster headache. Headache. 2000;40(10):798-808.
7. Søborg MK, Petersen AS, Lund N, Barloese MCJ, Jensen RH. Transition of cluster headache: Depicting side-changing attacks as a chronic trait in an interview-based follow-up study. Cephalalgia. 2024;44(6):3331024241258485.
8. Torelli P, Manzoni GC. What predicts evolution from episodic to chronic cluster headache? Curr Pain Headache Rep. 2002;6(1):65-70.
9. Fourier C, Ran C, Steinberg A, Sjöstrand C, Waldenlind E, Belin AC. Sex Differences in Clinical Features, Treatment, and Lifestyle Factors in Patients With Cluster Headache. Neurology. 2022.
10. Kim SA, Choi SY, Youn MS, Pozo-Rosich P, Lee MJ. Epidemiology, burden and clinical spectrum of cluster headache: a global update. Cephalalgia. 2023;43(9):3331024231201577.
11. Lund N, Barloese M, Petersen A, Haddock B, Jensen R. Chronobiology differs between men and women with cluster headache, clinical phenotype does not. Neurology. 2017;88(11):1069-76.
12. Lademann V, Jansen JP, Evers S, Frese A. Evaluation of guideline-adherent treatment in cluster headache. Cephalalgia. 2016;36(8):760-4.
13. Ofte HK, Berg DH, Bekkelund SI, Alstadhaug KB. Insomnia and periodicity of headache in an arctic cluster headache population. Headache. 2013;53(10):1602-12.
14. Allena M, De Icco R, Sances G, Ahmad L, Putortì A, Pucci E, et al. Gender Differences in the Clinical Presentation of Cluster Headache: A Role for Sexual Hormones? Front Neurol. 2019;10:1220.
15. Liaw YC, Wang YF, Chen WT, Chen SP, Wu JW, Chen ST, et al. Sex-related differences in cluster headache: A hospital-based study in Taiwan. Cephalalgia. 2022;42(14):1532-42.
16. Lee MJ, Cho SJ, Park JW, Chu MK, Moon HS, Chung PW, et al. Temporal changes of circadian rhythmicity in cluster headache. Cephalalgia. 2020;40(3):278-87.
17. Li K, Sun S, Xue Z, Chen S, Ju C, Hu D, et al. Pre-attack and pre-episode symptoms in cluster headache: a multicenter cross-sectional study of 327 Chinese patients. J Headache Pain. 2022;23(1):92.
18. Rozen TD. Linking Cigarette Smoking/Tobacco Exposure and Cluster Headache: A Pathogenesis Theory. Headache. 2018;58(7):1096-112.
19. Lee MJ, Choi HA, Shin JH, Park HR, Chung CS. Natural course of untreated cluster headache: A retrospective cohort study. Cephalalgia. 2018;38(4):655-61.
20. Kudrow L. Natural history of cluster headache. Part I. Outcome of drop-out patients. Headache. 1982;22(5):203-6.
21. Krabbe A. The Prognosis of Cluster Headache. A Long-Term Observation of 226 Cluster Headache Patients. Cephalalgia. 1991;11(11_suppl):250-1.
22. Manzoni GC, Micieli G, Granella F, Tassorelli C, Zanferrari C, Cavallini A. Cluster Headache Course Over Ten Years in 189 Patients. Cephalalgia. 1991;11(4):169-74.
23. Graham JR. Cluster headache. Headache. 1972;11(4):175-85.
24. Di Lorenzo C, Coppola G, Di Lorenzo G,

Bracaglia M, Rossi P, Pierelli F. The use of illicit drugs as self-medication in the treatment of cluster headache: Results from an Italian online survey. Cephalalgia. 2016;36(2):194-8.
25. Rossi P, Allena M, Tassorelli C, Sances G, Di Lorenzo C, Faroni JV, et al. Illicit drug use in cluster headache patients and in the general population: a comparative cross-sectional survey. Cephalalgia. 2012;32(14):1031-40.
26. Donnet A, Lanteri-Minet M, Guegan-Massardier E, Mick G, Fabre N, Geraud G, et al. Chronic cluster headache: a French clinical descriptive study. J Neurol Neurosurg Psychiatry. 2007;78(12):1354-8.
27. Leroux E, Taifas I, Valade D, Donnet A, Chagnon M, Ducros A. Use of cannabis among 139 cluster headache sufferers. Cephalalgia. 2013;33(3):208-13.
28. Hidalgo H, Uhl V, Gantenbein AR, Sandor PS, Kallweit U. Efficiency of sodium oxybate in episodic cluster headache. Headache. 2013;53(9):1490-1.
29. Khatami R, Tartarotti S, Siccoli MM, Bassetti CL, Sandor PS. Long-term efficacy of sodium oxybate in 4 patients with chronic cluster headache. Neurology. 2011;77(1):67-70.
30. Sewell RA, Halpern JH, Pope HG, Jr. Response of cluster headache to psilocybin and LSD. Neurology. 2006;66(12):1920-2.
31. Koehler PJ, Tfelt-Hansen PC. History of methysergide in migraine. Cephalalgia. 2008;28(11):1126-35.
32. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci Ther. 2008;14(4):295-314.
33. Kooijman NI, al. E. Could psychedelics be the answer to chronic pain? A review of current literature including cancer and palliative related pain, phantom limb pain, cluster headache and migraine: Radboud University, Nijmegen; 2021.
34. Levi R, Edman GV, Ekbom K, Waldenlind E. Episodic cluster headache. I: Personality and some neuropsychological characteristics in male patients. Headache. 1992;32(3):119-25.
35. Littlewood JT, Glover V, Sandler M, Petty R, Peatfield R, Clifford Rose F. Migraine and cluster headache: links between platelet monoamine oxidase activity, smoking and personality. Headache. 1984;24(1):30-4.
36. Case-control study on the epidemiology of cluster headache. II: Anthropometric data and personality profile. Funct Neurol. 2000;15(4):215-23.
37. Buonfiglio M, Di Sabato F. Analytic cognitive style in cluster headache. Neurol Sci. 2011;32(5):875-81.
38. Sakurai T. Roles of orexin/hypocretin in regulation of sleep/wakefulness and energy homeostasis. Sleep Med Rev. 2005;9(4):231-41.
39. Boutrel B, Steiner N, Halfon O. The hypocretins and the reward function: what have we learned so far? Frontiers in Behavioral Neuroscience. 2013;7(59).
40. Holland PR, Goadsby PJ. Cluster headache, hypothalamus, and orexin. Current Pain and Headache Reports. 2009;13(2):147-54.
41. Barloese M, Jennum P, Lund N, Knudsen S, Gammeltoft S, Jensen R. Reduced CSF hypocretin-1 levels are associated with cluster headache. Cephalalgia. 2015;35(10):869-76.
42. Rainero I, Gallone S, Rubino E, Ponzo P, Valfre W, Binello E, et al. Haplotype analysis confirms the association between the HCRTR2 gene and cluster headache. Headache. 2008;48(7):1108-14.
43. Harder AVE, Winsvold BS, Noordam R, Vijfhuizen LS, Børte S, Kogelman LJA, et al. Genetic Susceptibility Loci in Genomewide Association Study of Cluster Headache. Annals of Neurology. 2021;90(2):203-16.
44. Winsvold BS, Harder AVE, Ran C, Chalmer MA, Dalmasso MC, Ferkingstad E, et al. Cluster Headache Genomewide Association Study and Meta-Analysis Identifies Eight Loci and Implicates Smoking as Causal Risk Factor. Ann Neurol. 2023;94(4):713-26.
45. Rozen TD, Fishman RS. Cluster headache in the United States of America: demo-

REFERENCES

graphics, clinical characteristics, triggers, suicidality, and personal burden. Headache. 2012;52(1):99-113.
46. Lund N, Petersen A, Snoer A, Jensen RH, Barloese M. Cluster headache is associated with unhealthy lifestyle and lifestyle-related comorbid diseases: Results from the Danish Cluster Headache Survey. Cephalalgia. 2019;39(2):254-63.
47. Rozen TD. Cluster headache as the result of secondhand cigarette smoke exposure during childhood. Headache. 2010;50(1):130-2.
48. Ferrari A, Zappaterra M, Righi F, Ciccarese M, Tiraferri I, Pini LA, et al. Impact of continuing or quitting smoking on episodic cluster headache: a pilot survey. J Headache Pain. 2013;14(1):48.
49. May A. Cluster headache: pathogenesis, diagnosis, and management. Lancet. 2005;366(9488):843-55.
50. Levi R, Edman GV, Ekbom K, Waldenlind E. Episodic cluster headache. II: High tobacco and alcohol consumption in males. Headache. 1992;32(4):184-7.
51. Borkum JM. Cluster Headache and Hypoxia: Breathing New Life into an Old Theory, with Novel Implications. Neurol Int. 2024;16(6):1691-716.
52. Ekbom K, Svensson DA, Träff H, Waldenlind E. Age at onset and sex ratio in cluster headache: observations over three decades. Cephalalgia. 2002;22(2):94-100.
53. van Vliet JA, Favier I, Helmerhorst FM, Haan J, Ferrari MD. Cluster headache in women: relation with menstruation, use of oral contraceptives, pregnancy, and menopause. J Neurol Neurosurg Psychiatry. 2006;77(5):690-2.
54. Chung PW, Kim BS, Park JW, Sohn JH, Lee MJ, Kim BK, et al. Smoking History and Clinical Features of Cluster Headache: Results from the Korean Cluster Headache Registry. J Clin Neurol. 2021;17(2):229-35.
55. Naber W, van Tilborg P, Zuidgeest A, Wilbrink L, Mulleners W, Brandt R, et al. Exploration of Prolonged Remission and the Natural Course of Cluster Headache: An Interview-Based Cohort Study. Neurology. 2025;105(1):e213795.
56. Kelsey TW, Li LQ, Mitchell RT, Whelan A, Anderson RA, Wallace WHB. A Validated Age-Related Normative Model for Male Total Testosterone Shows Increasing Variance but No Decline after Age 40 Years. PLOS ONE. 2014;9(10):e109346.
57. Petersen AS, Lund N, Goadsby PJ, Belin AC, Wang SJ, Fronczek R, et al. Recent advances in diagnosing, managing, and understanding the pathophysiology of cluster headache. Lancet Neurol. 2024;23(7):712-24.
58. Edvinsson L, Tajti J, Szalárdy L, Vécsei L. PACAP and its role in primary headaches. J Headache Pain. 2018;19(1):21.
59. Barabás K, Kovács G, Vértes V, Kövesdi E, Faludi P, Udvarácz I, et al. Stereology of gonadotropin-releasing hormone and kisspeptin neurons in PACAP gene-deficient female mice. Front Endocrinol (Lausanne). 2022;13:993228.
60. Lepper A, Frese A, Summ O, Nofer JR, Evers S. Hypothalamic dopaminergic stimulation in cluster headache. Cephalalgia. 2013;33(14):1155-9.
61. Waldenlind E, Gustafsson SA. Prolactin in cluster headache: diurnal secretion, response to thyrotropin-releasing hormone, and relation to sex steroids and gonadotropins. Cephalalgia. 1987;7(1):43-54.
62. De Pue A, Lutin B, Paemeleire K. Chronic cluster headache and the pituitary gland. The Journal of Headache and Pain. 2016;17(1):23.
63. Long RJ, Zhu YS, Wang AP. Cluster headache due to structural lesions: A systematic review of published cases. World J Clin Cases. 2021;9(14):3294-307.
64. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol. 2017;16(1):76-87.
65. Burish MJ, Pearson SM, Shapiro RE, Zhang W, Schor LI. Cluster headache is one of the most intensely painful human conditions: Results from the International Cluster Headache Questionnaire. Headache. 2021;61(1):117-24.

66. D'Amico D, Raggi A, Grazzi L, Lambru G. Disability, Quality of Life, and Socioeconomic Burden of Cluster Headache: A Critical Review of Current Evidence and Future Perspectives. Headache: The Journal of Head and Face Pain. 2020;60(4):809-18.
67. Schoenen J, Snoer AH, Brandt RB, Fronczek R, Wei DY, Chung CS, et al. Guidelines of the International Headache Society for Controlled Clinical Trials in Cluster Headache. Cephalalgia. 2022;42(14):1450-66.
68. Abu Bakar N, Torkamani M, Tanprawate S, Lambru G, Matharu M, Jahanshahi M. The development and validation of the Cluster Headache Quality of life scale (CHQ). J Headache Pain. 2016;17(1):79.
69. de Vet HCW TC, Mokkink LB, Knol DL Measurement in Medicine - A practical guide. New York: Cambridge University Press; 2011.
70. Mokkink L, Terwee C, de Vet H. Key concepts in clinical epidemiology: Responsiveness, the longitudinal aspect of validity. J Clin Epidemiol. 2021;140:159-62.
71. Wilbrink LA, de Coo IF, Doesborg PGG, Mulleners WM, Teernstra OPM, Bartels EC, et al. Safety and efficacy of occipital nerve stimulation for attack prevention in medically intractable chronic cluster headache (ICON): a randomised, double-blind, multicentre, phase 3, electrical dose-controlled trial. Lancet Neurol. 2021;20(7):515-25.
72. Kurt E, Volkers RW, Engels Y, Mulleners WM, Witkam RL, van Dongen RTM. A qualitative study on the long-term effectiveness of occipital nerve stimulation in patients with chronic cluster headache. Headache. 2023;63(10):1458-61.
73. Fox J, Gaul C, Slijepcevic M, Ohse J, Peperkorn N, Shiban Y. The impact of fear of attacks on pain-related disability in cluster headache: Insights from the fear avoidance model. Headache. 2025;65(1):45-53.
74. Anthony M. Arrest of Attacks of Cluster Headache by Local Steroid Injection of the Occipital Nerve. In: Clifford Rose F, editor. Clinical and Research Advances 5th International Symposium, London, September 1984; Basel, Karger1985. p. 169-73.
75. Lambru G, Abu Bakar N, Stahlhut L, McCulloch S, Miller S, Shanahan P, et al. Greater occipital nerve blocks in chronic cluster headache: a prospective open-label study. Eur J Neurol. 2014;21(2):338-43.
76. Gantenbein AR, Lutz NJ, Riederer F, Sandor PS. Efficacy and safety of 121 injections of the greater occipital nerve in episodic and chronic cluster headache. Cephalalgia. 2012;32(8):630-4.
77. Afridi SK, Shields KG, Bhola R, Goadsby PJ. Greater occipital nerve injection in primary headache syndromes--prolonged effects from a single injection. Pain. 2006;122(1-2):126-9.
78. Peres MF, Stiles MA, Siow HC, Rozen TD, Young WB, Silberstein SD. Greater occipital nerve blockade for cluster headache. Cephalalgia. 2002;22(7):520-2.
79. Merli E, Asioli GM, Favoni V, Zenesini C, Mascarella D, Sartori A, et al. Great occipital nerve long-acting steroid injections in cluster headache therapy: an observational prospective study. Journal of Neurology. 2022;269(4):2193-9.
80. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain. 2005;118(1-2):92-6.
81. Gaul C, Roguski J, Dresler T, Abbas H, Totzeck A, Görlinger K, et al. Efficacy and safety of a single occipital nerve blockade in episodic and chronic cluster headache: A prospective observational study. Cephalalgia. 2017;37(9):873-80.
82. Leroux E, Valade D, Taifas I, Vicaut E, Chagnon M, Roos C, et al. Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2011;10(10):891-7.
83. Chowdhury D, Kordcal SR, Nagane R, Duggal A. ANODYNE study: A dou-

REFERENCES

ble-blind randomized trial of greater occipital nerve block of methylprednisolone and lignocaine versus placebo as a transitional preventive treatment for episodic cluster headache. Cephalalgia. 2024;44(10):3331024241291597.
84. May A, Evers S, Goadsby PJ, Leone M, Manzoni GC, Pascual J, et al. European Academy of Neurology guidelines on the treatment of cluster headache. Eur J Neurol. 2023;30(10):2955-79.
85. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Functional connectivity between trigeminal and occipital nerves revealed by occipital nerve blockade and nociceptive blink reflexes. Cephalalgia. 2006;26(1):50-5.
86. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Occipital nerve blockade in chronic cluster headache patients and functional connectivity between trigeminal and occipital nerves. Cephalalgia. 2007;27(11):1206-14.
87. Torelli P, Cologno D, Cademartiri C, Manzoni GC. Application of the International Headache Society classification criteria in 652 cluster headache patients. Cephalalgia. 2001;21(2):145-50.
88. Schor LI, Pearson SM, de Castro Sousa B, Ettore U, Rohrer U, Gu Y, et al. The location of pain in cluster headache: Data from the International Cluster Headache Questionnaire. Headache. 2024;64(7):783-95.
89. Pfaller K, Arvidsson J. Central distribution of trigeminal and upper cervical primary afferents in the rat studied by anterograde transport of horseradish peroxidase conjugated to wheat germ agglutinin. J Comp Neurol. 1988;268(1):91-108.
90. Goadsby PJ, Knight YE, Hoskin KL. Stimulation of the greater occipital nerve increases metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn of the cat. Pain. 1997;73(1):23-8.
91. Bartsch T, Goadsby PJ. Stimulation of the greater occipital nerve induces increased central excitability of dural afferent input. Brain. 2002;125(Pt 7):1496-509.
92. Young WB, Rozen TD. Bilateral cluster headache: case report and a theory of (failed) contralateral suppression. Cephalalgia. 1999;19(3):188-90.
93. Schulte LH, Haji AA, May A. Phase dependent hypothalamic activation following trigeminal input in cluster headache. The Journal of Headache and Pain. 2020;21(1).
94. Magis D, Gerardy PY, Remacle JM, Schoenen J. Sustained effectiveness of occipital nerve stimulation in drug-resistant chronic cluster headache. Headache. 2011;51(8):1191-201.
95. Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. Lancet Neurol. 2007;6(4):314-21.
96. Belin AC, Barloese MC. The genetics and chronobiology of cluster headache. Cephalalgia. 2023;43(10):3331024231208126.
97. de Boer I, Hansen JM, Terwindt GM. Hemiplegic migraine. Handb Clin Neurol. 2024;199:353-65.
98. Akerman S, Holland PR, Summ O, Lasalandra MP, Goadsby PJ. A translational in vivo model of trigeminal autonomic cephalalgias: therapeutic characterization. Brain. 2012;135(12):3664-75.
99. Søborg MK, Jensen RH, Barloese M, Petersen AS. Biomarkers in cluster headache: A systematic review. Headache. 2024;64(1):98-116.
100. Petersen AS, Kristensen DM, Westgate CSJ, Folkmann-Hansen T, Lund N, Barloese M, et al. Compensated Hypogonadism Identified in Males with Cluster Headache: A Prospective Case-Controlled Study. Ann Neurol. 2024.
101. Ran C, Olofsgård FJ, Wellfelt K, Steinberg A, Belin AC. Elevated cytokine levels in the central nervous system of cluster headache patients in bout and in remission. J Headache Pain. 2024;25(1):121.
102. Lund NLT, Westgate CSJ, Søborg MK, Snoer AH, Jensen RH, Hansen TF, et al. Distinct Alterations of Inflammatory Biomarkers in Cluster Headache: A Case Control Study. Ann Neurol. 2025;98(1):4-

18.
103. Eichmüller OL, Knoblich JA. Human cerebral organoids - a new tool for clinical neurology research. Nat Rev Neurol. 2022;18(11):661-80.
104. Nilsson Remahl AI, Laudon Meyer E, Cordonnier C, Goadsby PJ. Placebo response in cluster headache trials: a review. Cephalalgia. 2003;23(7):504-10.
105. Goadsby PJ, Dodick DW, Leone M, Bardos JN, Oakes TM, Millen BA, et al. Trial of Galcanezumab in Prevention of Episodic Cluster Headache. N Engl J Med. 2019;381(2):132-41.
106. Jensen RH, Tassorelli C, Tepper SJ, Charles A, Goadsby PJ, Snoer AH, et al. Efficacy and Safety of Eptinezumab in Episodic Cluster Headache: A Randomized Clinical Trial. JAMA Neurology. 2025;82(7):706-14.
107. Dumitriu A, Popescu BO. Placebo effects in neurological diseases. J Med Life. 2010;3(2):114-21.
108. Diener HC, Schorn CF, Bingel U, Dodick DW. The importance of placebo in headache research. Cephalalgia. 2008;28(10):1003-11.
109. Schindler EAD, Sewell RA, Gottschalk CH, Luddy C, Flynn LT, Zhu Y, et al. Exploratory investigation of a patient-informed low-dose psilocybin pulse regimen in the suppression of cluster headache: Results from a randomized, double-blind, placebo-controlled trial. Headache. 2022;62(10):1383-94.
110. Stillman MJ. Testosterone replacement therapy for treatment refractory cluster headache. Headache. 2006;46(6):925-33.
111. Brandt RB, Doesborg PGG, Meilof R, de Coo IF, Bartels E, Ferrari MD, et al. Repeated greater occipital nerve injections with corticosteroids in medically intractable chronic cluster headache: a retrospective study. Neurol Sci. 2022;43(2):1267-72.
112. Holland PR, Barloese M, Fahrenkrug J. PACAP in hypothalamic regulation of sleep and circadian rhythm: importance for headache. J Headache Pain. 2018;19(1):20.
113. Vollesen ALH, Snoer A, Beske RP, Guo S, Hoffmann J, Jensen RH, et al. Effect of Infusion of Calcitonin Gene-Related Peptide on Cluster Headache Attacks: A Randomized Clinical Trial. JAMA Neurol. 2018;75(10):1187-97.
114. Pellesi L, Chaudhry BA, Vollesen ALH, Snoer AH, Baumann K, Skov PS, et al. PACAP38- and VIP-induced cluster headache attacks are not associated with changes of plasma CGRP or markers of mast cell activation. Cephalalgia. 2022;42(8):687-95.
115. Ashina M, Phul R, Khodaie M, Löf E, Florea I. A Monoclonal Antibody to PACAP for Migraine Prevention. N Engl J Med. 2024;391(9):800-9.
116. Grinberg AS, Best RD, Min KM, Schindler EAD, Koo BB, Sico JJ, et al. Cluster Headache: Clinical Characteristics and Opportunities to Enhance Quality of Life. Curr Pain Headache Rep. 2021;25(10):65.