Greater occipital nerve modulation and clinical aspects of cluster headache

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CHAPTER 1

General introduction

Cluster headache is a relatively rare but extremely severe headache disorder and is part of the Trigeminal Autonomic Cephalalgias, a group of five distinct headaches types with overlapping clinical and pathophysiological features. It consists of unilateral headache attacks lasting from 15 to 180 minutes that can occur as often as 8 times per day (or even more).[1] It is believed that one of the first descriptions of cluster headache was given by Dr Nicolaas Tulp in his 1641 publication *Observationes Medicae*.[2] Since then, several names have been used to describe this type of headache: Horton's Neuralgia, Horton's Headache, Migraneous Neuralgia, Histaminergic Headache and even Suicide Headache, reflecting the intensity of the pain experienced by patients. The pain that is experienced during cluster headache attacks is one of the most intense forms of pain known. It is most often described as an intense periorbital or temporal stabbing sensation. The impact of cluster headache on quality of life can be so severe that suicidal ideation occur in approximately 55% of people, of whom 2% actually attempt suicide.[3] Typically, there is restlessness during the attacks and/or prominent autonomic features ipsilateral to the pain. Autonomic features include; tearing of the eye, a red eye, miosis, ptosis, eyelid oedema, nasal congestion, rhinorrhoea and forehead and facial sweating.[4]

Epidemiology

The estimated life-time prevalence of cluster headache is 124 in 100.000 persons with a one-year prevalence of 53 per 100.000, corresponding to 0.12% and 0.05%, respectively.[5] Historically, cluster headache has been regarded as a 'male' disease, with a male to female ratio of 6 to 1 in the 1960s.[3, 6, 7] However, due to an improved recognition of cluster headache in woman, recent studies report a 2-3 to 1 ratio.[8, 9]

Despite the relatively high prevalence (comparable with m. Parkinson)[10], cluster headache awareness remains low. Unfortunately, this can lead to a high diagnostic delay in which only 20% of people are diagnosed correctly during their first visit. Thankfully, observations in Denmark showed that this appears to be improving with a diagnostic delay of 0,9 years in 2010. However, diagnostic delay in other countries remains high.[11]

Clinical characteristics

Cluster headache can present in one of two forms: episodic cluster headache (approximately 80%) or chronic cluster headache (20%). People with episodic cluster headache suffer from 'clustered' (hence the name cluster headache) episodes of attacks that last weeks to months, with prolonged attack-free periods between episodes. In chronic cluster headache, these attack-free periods are shorter than 3 consecutive months or can be absent. Despite the fact that there are two distinct names, it is thought that cluster headache can present itself in a continuum in which chronic cluster headache is the most severe form. Although both entities

can respond to the same treatment, there is evidence that chronic cluster headache can be more difficult to treat.[12]

Cluster headache is often associated with psychiatric comorbidity (bipolar disorder) which may complicate treatment and increase disease burden. People with cluster headache show a three times higher odds to develop depression than controls. [13] Other frequent comorbidities are anxiety, aggressive behaviour and sleeping problems.

In clinical experience, people with cluster headache are more likely to smoke and use (illicit) drugs and appear to more frequently have piercings and tattoos.[14-19] The association between cluster headache and smoking appears to be quite evident with 60% to 90% of patients being smokers. Due to this evident association, a possible pathophysiological role is attributed to first and second hand smoking through the release of cadmium. This causes significant toxicity and alteration of the Hypothalamus-Pituitary-Gonadal axis and may exert their influence on cluster headache pathogenesis through this pathway.[15, 18, 20, 21] Recently, Mendelian randomization has supported this theory by implicating smoking as a causal factor as well. [22]

Rhythmicity

A fascinating aspect of cluster headache is its rhythmicity, highlighted by the episodic nature in which cluster periods occur and where they appear to follow an annual rhythm in more than 50% of patients.[23] Most cluster episodes start around the solstices, most likely related to daylight changes.[24] This hypothesis is emphasized by the fact that the seasonal rhythmicity of cluster headache appears to be lower in patients that live closer to the equator, where they experience less seasonal change in daylight.[24]

Rhythmicity also occurs in individual cluster attacks, as they may occur in a predictable 24-hour rhythm with most attacks occurring between 00:00 and 04:00 hours.[8, 25] This can cause patients to have a fear of going to bed, leading to actively postponing sleep or the use of voluntary sleep deprivation to try to avoid attacks. Since attacks often occur around one to two hours after sleep onset, a link with REM-sleep has been suggested.[26] However, recent results from several small actigraphy studies did not show any relationship between sleep stages and attacks but showed the presence of a continuing or slowly recovering disturbance of sleep outside the bout rather than a disturbance secondary to attacks. [26-28]

Pathophysiology

Cluster headache is most often regarded as a neurovascular disease although its exact cause remains unknown.[29] Several structures have been identified which are thought to play key roles in attacks. Firstly, the pain is perceived in the region of the ophthalmic division of the

trigeminal nerve. Secondly, autonomic symptoms occur with a parasympathetic activation and an sympathetic deficit. Thirdly, the hypothalamus has been identified as a possible 'attack generator'.[30]

Trigeminal nerve

The trigeminal nerve consists of peripheral axons that project to the dura mater and cerebral vessels, and central axons that project to the trigeminal caudal nucleus (TCN) in the trigeminocervical complex (TCC). The TCC acts as a relay station that projects peripheral signals to cerebral structures involved in pain processing (e.g. the thalamus and the cerebral cortex), causing the experience of pain upon activation. Due to the unilateral nature of the pain, activation of the trigeminal nerve is thought to be unilateral as well. Trigeminal nerve activation alone, however, is not sufficient as demonstrated by continuation of attacks after trigeminal nerve root section. [31]

Activation of the trigeminal nerve leads to Calcitonin Gene-Related Protein (CGRP) release from the central and perivascular afferents, which causes vasodilation and appears to lower the activation threshold of the TCN. Elevated serum CGRP levels in spontaneous and triggered cluster headache attacks were found.[32, 33] Despite the high concentration of CGRP during attacks, CGRP appears to be just one factor contributing to the appearance of cluster headache attacks. Infusion of CGRP can cause a cluster headache attacks, but only in chronic patients or episodic patients who were in a bout indicating a fluctuating susceptibility to CGRP.[34]

Autonomic system

Unilateral autonomic features are one of the hallmarks of cluster headache attacks and are caused by a sympathetic and parasympathetic imbalance. The trigeminal nerve is connected with the superior salivatory nucleus (SSN) from which parasympathetic nerve fibers project to the periphery via the sphenopalatine ganglion (SPG). Activation of these neurons causes release of neuropeptides (VIP and PACAP), called the trigeminal autonomic reflex. Notably, this reflex can only be induced via stimulation of the ophthalmic division of the trigeminal nerve.[35] Although the autonomic features appear to be a consequence of attacks, successes in SPG stimulation and blockade suggest a larger role in cluster headache.[36, 37]

Hypothalamus

The hypothalamus is regarded as the 'attack generator'. PET-CT and fMRI studies show activation of the hypothalamus during both triggered and spontaneous attacks.[38, 39] Of note, no hypothalamic activation was shown during direct painful nociceptive stimulation in the region of the trigeminal nerve, suggesting that the activation is likely to be causal and not a consequence of the pain itself.

The apparent relation between sleep and attacks, and the characteristically circadian and annual rhythm in which attacks occur suggests involvement of the biological clock. The biological clock resides in the suprachiasmatic nucleus in the anterior part of the hypothalamus[40], which is enlarged in people with cluster headache.[41] Regulation of the biological clock is partly due to melatonin. Production and excretion of this hormone takes places in the pineal gland and is suppressed by light, causing melatonin peak levels in the night. Melatonin peaks were shown to be diminished or absent in people with cluster headache further implying hypothalamic dysfunction.[42]

Genetics

A genetic component in the pathophysiology of cluster headache has long been suggested. This suggestion was strengthened by epidemiological studies indicating a 5-18 times increased risk to develop cluster headache in first degree relatives of people with cluster headache, whereas second degree relatives exhibit a 1-3 fold increased risk.[43] Small genetic association studies focusing on the hypocretin receptor-2 gene [44], PER3 clock gene [45], CACNA1A gene [46] and PACAP receptor gene variant [47] were inconclusive. Recently, two large Genome Wide Association Studies (GWAS) identified and replicated genetic risk loci for cluster headache with effect sizes larger than those typically seen in complex genetic disorders, increasing evidence for a significant genetic component.[48, 49]

HORMONES

The majority of people with cluster headache are male with a current M:F ratio of 2:1.[11] Onset of cluster headache before puberty is extremely rare[50] and people with cluster headache have been, possibly unfairly, characterized as 'over-masculinized'. These observations led to the hypothesis of an (important) role of androgens in cluster headache pathophysiology. Several (small) studies have looked into the role of androgens and testosterone in particular with conflicting results. Contrary to what was expected, testosterone appears to be low or normal in people with cluster headache.[51-55] This led to a small case series describing positive results using testosterone replacement therapy in 9 patients (7 male).[56] Two small trials report normal estrogen levels in people with cluster headache. [55, 57]

It is not clear if the possible alterations in sex hormone levels are contributing in the pathophysiology of cluster headache, are a consequence of cluster headache pathophysiology, or an epiphenomenon.

DIFFERENTIAL DIAGNOSIS

Due to the typical clinical appearance of cluster headache, differential diagnosis is small. However, cluster headache can be difficult to distinguish from other trigeminal autonomic cephalalgias, or TACs. This is a group of five different headaches with overlapping pathophysiological and clinal features that can be distinguished primarily by their attack duration *(table 1)*. Among cluster headache the others include 'Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or autonomic symptoms' (SUNA), paroxysmal hemicrania and hemicrania continua.

SUNCT and SUNA have an estimated prevalence of 0.001-0.1%. Attacks are short-lasting (1-600 seconds) and occur in single or multiple stabs or in a sawtooth pattern with a frequency of >30 per day.[58] Paroxysmal hemicrania has an unknown prevalence and is characterized by short-lasting (2-30 minutes) attacks with an average of c.a. 10 attacks per day.[59] Because of the severe pain, attack duration and cranial autonomic symptoms, paroxysmal hemicrania may be easily confused with cluster headache. However, as opposed to cluster headache, paroxysmal hemicrania exhibits a response to indomethacin treatment with patients showing complete remission or a significant reduction in attack frequency.[60] Hemicrania continua is characterized by a continuous mild to moderate, strictly unilateral, mostly periorbital, headache with exacerbations of varying duration (minutes to days) and intensity. During the exacerbations, ipsilateral cranial autonomic symptoms and, in 60% of cases, migrainous features occur, complicating the differentiation between migraine and hemicrania continua. However, as in paroxysmal hemicrania, hemicrania continua is indomethacin responsive. The headache of hemicrania continua is side-locked and does not show remission periods between attacks.[61, 62]

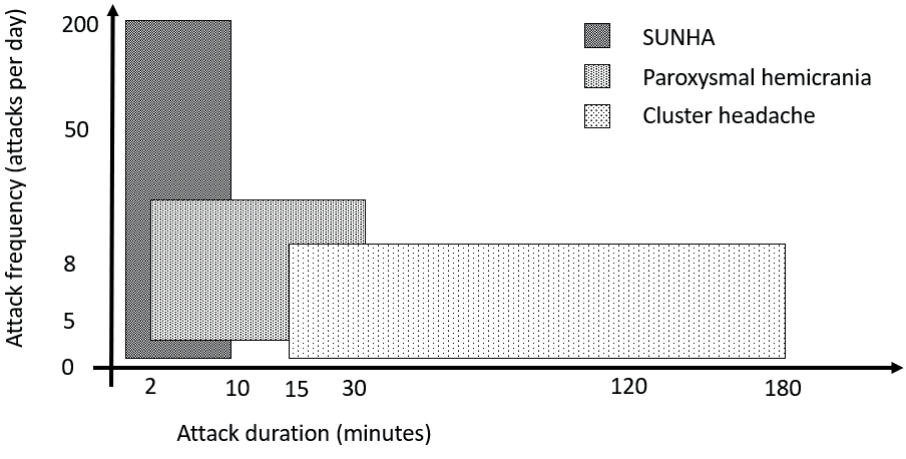
Differentiation between the TACs can be difficult. Especially paroxysmal hemicrania and cluster headache can show remarkable overlap. Since no laboratory test or imaging technique can differentiate between the TACs, the clinical history is important. In general, TACs can be distinguished by differences in attack duration and attack frequency *(figure 1)*. Furthermore, attack pattern (e.g. series of stabs, nightly attacks, etc.) and response to treatment can help distinguish between them *(table 1)*. Finally, especially the near-absolute response to indomethacin can confirm the diagnosis of a hemicrania variant.

Table 1 - *Differentiation between the different TACs*

	Cluster headache	Paroxysmal hemicrania	SUNHA	Hemicrania continua
Attack frequency	1-8 attacks daily	>5 attacks daily	1-200 daily	Continuous pain, fluctuating excacerbations
Attack duration	15-180 minutes	2-30 minutes	1 – 600 seconds	Varying excacerbation durations (minutes-days)
Restlessness	>90%	80%	30%	50%
Circadian pattern	Evident	Very rare	Rare	Very rare
Treatment response				
100% oxygen	>75%	No effect	No effect	No effect
Sumatriptan s.c.	>75%	20%	<10%	No effect
Indometacine	No effect	100%	No effect	100%

Generally, cluster headache and migraine can be relatively easy distinguished. Migraine attacks are longer lasting, the pain has a more throbbing instead of stabbing quality, and patients tend to lie still in bed in a dark room, as opposed to the restlessness that occurs during a cluster headache attack. However, some overlap in symptoms can occur. Increased sensitivity to light and patterns, which is a recognized feature of migraine, has also been reported in cluster headache.[3, 63-65] However the prevalence, severity, possible laterality, and timing (ictal, interictal, inter-bout) of visual hypersensitivity in cluster headache are unknown.[7, 66, 67]

Figure 1 - *Attack frequency and attack duration for the different TACs*



CLUSTER HEADACHE TREATMENT

The treatment of cluster headache can be divided into three types. Above all, a fast-acting abortive treatment is vital due to the severity of the attacks. Usually, treatment to prevent attacks, prophylactic treatment, is necessary as well. Finally, transitional treatment is used to bridge the period in which patients are starting their preventive treatment and when they assert their effect. The main goal in cluster headache treatment should always be to prevent all attacks. Unfortunately, especially in chronic cluster headache patients, attack freedom cannot always be achieved. In those cases, it is vital to have effective attack treatment options and to achieve the best effect/side-effect ratio in close collaboration with the patient.

Acute treatment

The short duration and severity of cluster headache attacks call for a fast-acting abortive treatment. A limited number of drugs are known that can treat cluster attacks in an effective manner. Sumatriptan, a selective 5-hydroxytryptamine (5HT1B/1D) receptor agonist, has been proven to be the most effective abortive treatment for cluster headache attacks when used in subcutaneous dose of 6mg.[68, 69] Pain relief is usually achieved in 75% of patients within 15 minutes with one third of patients reporting pain freedom. Triptans are generally well tolerated. The incidence of triptan related serious cardiovascular events appears to be extremely low in patients without known cardiovascular disease.[70] Official guidelines state that no more than two injections per day can be used. However, due to the high number of daily attacks, patients frequently use multiple sumatriptan injections per day. Little evidence of unsafety exists when using more than two injections per day.[71-73] Triptan nasal spray is a less effective method to abort a cluster headache attack since resorption of the drug through the mucosa is too slow. However, when the use of injections is not tolerated by the patient and the attacks are relatively long (>1 hour), triptan nasal spray can be used as an alternative though slower acting treatment.[74, 75]

In addition to sumatriptan, high flow oxygen is a valid first-choice treatment when used as soon as possible after the onset of the attack. The mechanism of effect needs further clarification, but the most likely mechanism is through inhibition of neuronal activation in the trigeminocervical complex and the inhibition of dural inflammation.[76, 77] The great advantage of oxygen over other acute treatments are the fact that no adverse events have been established. Efficacy was proven many years ago and was confirmed in two randomised, double blind trials.[78-80]

Although numerous other drugs and therapies have been suggested, there is very limited evidence supporting this use. Acute neuromodulatory treatment options are scarce but efficacy of sphenopalatine ganglion stimulation has been proven, but unfortunately, the

device has been discontinued. [81, 82] Efficacy of non-invasive vagus nerve stimulation (nVNS) has been proven in episodic cluster headache, but not in chronic cluster headache. [83]

Prophylactic treatment

Current guidelines include various options for prophylactic therapy, based upon different levels of evidence. Prophylactic treatment drugs of first choice are verapamil, lithium and topiramate. Prophylactic drugs are summarized in table 3.

Verapamil

The drug of first choice in the preventive treatment of cluster headache is verapamil. The mechanism of action of verapamil remains to be elucidated, but current understanding is that verapamil exhibits its effect through CGRP release modification and possible circadian rhythm modification. It has been shown that blockade of presynaptic calcium channels prevents CGRP-release[84], possibly inhibiting the CGRP-induced hyper responsive state[85]. Furthermore, calcium channels appear to play a role in the circadian rhythm, which is hypothesized to play a major role in cluster headache pathophysiology.

Despite being recognised as drug of first choice, prophylactic effect of verapamil in cluster headache has only been studied in 5 trials, of which only 2 RCTs.[86-90] Nowadays, in daily practice patients receive verapamil with a mean dose of 578mg per day (maximum 1200 mg daily). Verapamil dosage must be slowly increased to minimize side effects and to determine the lowest effective dosage. Adverse events include mainly cardiac related side effects. Current guidelines suggest to always perform a pre-treatment ECG and a subsequent ECG before or after dose increase. [91]

Lithium

Lithium is next in line if verapamil fails or if patient is unable to start or continue verapamil treatment. Lithium therapy in cluster headache has only been studied in three trials of which the only placebo controlled RCT did not show any effect. However, the relatively low dose and early endpoint (1 week after start) are likely to be the cause of the negative trial.[89, 92] Two later trials, albeit no RCTs, did show a reduction in headache frequency, although more studies are needed to confirm this effect.[89, 93]

Despite its positive therapeutic effect, side effects can cause discontinuation of the therapy. Nausea, dizziness and tremor are among the many side effects of lithium. Furthermore, long term use of lithium can cause kidney dysfunction and provoke hypothyroidism. To minimize negative side effects, and monitor possible toxic effects, serum concentrations and liver, thyroid and kidney function should be checked regularly during the treatment.

Other drugs

High doses of corticosteroids are highly effective in the treatment of cluster headache, as described in four open-label trials [94-97] and one case series [98]. Recently, a RCT showed efficacy of prednisone as an effective first line treatment in episodic cluster headache.[99] However, since chronic use of corticosteroids is related to potentially serious adverse events, only short-term use is recommended. Other drugs that are used in the prophylactic therapy in cluster headache are topiramate, sodium valproate, gabapentin, melatonin, clomiphene, pizotiphene and methysergide (not available). Evidence on their effect however is scarce.

Neuromodulation

In addition to drug treatment, neuromodulatory therapy has become increasingly available over the past two decades (figure 2).[100] Since the pathophysiological mechanism of cluster headache has not yet been fully elucidated, the modulation targets are variable and mainly limited to- more or less- easily accessible peripheral nerves.

The most direct, and invasive, form of neuromodulation is deep brain stimulation (DBS). The first reported case of DBS as treatment for CCH was reported in 2001.[101] The electrode was placed in the posterior hypothalamus, after identification of this region as a region of interest in cluster headache.[102] However, subsequent studies suggested that the optimal stimulation target would be more posterior to the posterior hypothalamus in the region of the ventral tegmentum. [103] Later case series varied with regards to stimulation protocol and electrode placement, but consistently observed an >50% responder rate in CCH. A recent meta-analysis of 40 cases reported a 77% reduction in attack frequency with an overall response rate of 75%.[104] However, the only RCT comparing DBS with sham stimulation did not show a difference between active and sham stimulation. [105] The inconsistent results and highly invasive nature of DBS, with its potentially fatal side effects, make it a last resort and an unattractive treatment option for many physicians.

Greater occipital nerve modulation

The greater occipital nerve is a pure sensory nerve innervating the posterior aspect of the skin on the head. The afferents of the greater occipital nerve terminate in the C2 and, to a lesser extent, C3 spinal segments where most of the trigeminal nerve afferents terminate as well. This structural convergence between the GON afferents and some afferents of the trigeminal nerve in the C2 spinal segments may explain the interaction between the GON and the trigeminal nociceptive transmission[106]. In animal studies, a functional connection was shown as well. Stimulation of the GON induced an increased excitability of dural afferent input and an increased metabolic activity of the trigeminal nucleus caudatus. This functional connectivity was further studied with the use of the nociceptive blink reflex as a measure of the trigeminal transmission.[107-109] This is a trigeminofacial brainstem reflex and refers to

contraction of the orbicularis oculi muscle (eyelid closure) after provocation by a stimuli. In electrophysiological studies the blink reflex is elicited by electrical stimulation of the supraorbital nerve. After this stimulation an ipsilateral component (R1 component) and two bilateral components (R2- and R3-component) can be distinguished[107, 110, 111]. Greater occipital nerve blockade appears to inhibit the trigeminal nociceptive transmission as shown by an increase of the ipsi- and contralateral R2 latency[112, 113], highlighting the interaction between the GON and the trigeminal nerve and providing a promising neuromodulation target.

A local steroid injection- with or without a local anaesthetic- around the greater occipital nerve (GON) has been shown to reduce the number of attacks or can even result in attacks freedom [114-123]. As highlighted in a recent meta-analysis [124], this was shown in open-label studies and two small trials [114-119, 121, 123], in a mixed study population of episodic and chronic cluster headache [116, 118, 121, 123]. 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 [115, 120, 122]. Despite its probable good tolerability and rapid onset of efficacy, GON injections have not been included in standard treatment protocols for episodic cluster headache worldwide and are only used in specialised headache clinics [124].

Another, more invasive, option is occipital nerve stimulation. After several small uncontrolled studies showed promising results[125-129], a randomised, double-blind, electric dose-controlled occipital nerve stimulation study confirmed that high and low dose ONS substantially reduced attack frequency and was safe and well tolerated in people with medically intractable CCH.[130, 131] Since true sham stimulation would cause deblinding, a dose controlled design was used. The 130 participants in this study had not responded to, were intolerant of or had a contraindication to verapamil *and* lithium, as well as at least one of the following medications: methysergide, topiramate or gabapentin and were therefore deemed medically intractable (MICCH).[1],[132] The overall median relative reduction in attack frequency was 50% and in attack intensity 32%. Half of the participants had a ≥50% reduction in attack frequency. Treatment was well tolerated and more than 90% of participants were satisfied or very satisfied.

Previous retrospective [129, 133, 134] and prospective [125-128, 135-138] open-label observational studies had shown promising results on the long-term as well, although in two smaller studies the effectiveness of ONS actually decreased over time. [136, 138] However, these observational studies all had a number of important methodological concerns, including mostly small numbers of participants, short or ill-defined baseline periods and duration of follow-up, ill-defined outcome measures and inclusion criteria, lack of information on efficacy

and adverse events in participants lost to follow-up and how this was handled statistically, and incomplete analyses of the effectiveness and side effects.

Other neuromodulation targets

Non-invasive vagus nerve stimulation (nVNS) is a technique that stimulates the vagus nerve in the neck. nVNS has been shown to be effective either as an attack treatment for eCH[139-141] or as a prophylactic treatment for CCH. [142] However, nVNS is not available in the Netherlands.

Another neuromodulation target is the SPG. Stimulation of the SPG was shown to be effective in for CCH but, unfortunately, the device is no longer produced. Recently, a small prospective study showed promising results for radiofrequency ablation or pulsed radiofrequency of the SPG.[143] Furthermore, an SPG block has been used in the treatment of cluster headache as well. [144]

OUTLINE OF THIS THESIS

The exact pathophysiology of cluster headache remains to be elucidated. Through reports of several observations and studies, we try to further explore the cluster headache phenotype and its pathophysiological basis. Furthermore, since current prophylactic therapy can be insufficient, we aimed to study new treatment methods. We focused on GON-stimulation for MICCH and GON-block as a new, minimally invasive add-on treatment.

In- **section one**- we explore several new, or lesser known, clinical aspects of cluster headache. First, we further explore the 'cluster headache phenotype', by reporting on risk- and reward seeking behaviour in people with cluster headache in *chapter 2*. In *chapter* 3, intrigued by the possible hormonal influences on the pathophysiology of cluster headache and the differences in phenotype between cluster headache and migraine patients, we compare symptoms of clinical androgen deficiency between these two groups. Consequently, in *chapter 4*, we report on sensitivity to light and patterns in patients with cluster headache with the use of a previously developed questionnaire. As this sensitivity is widely considered to be a migraneous phenomenon, we compared these scores with the scores from migraine patients. During the work on this thesis, the COVID-19 pandemic hit, and we noticed a particularly large number of cluster headache patients that reported the onset of a new cluster episode after COVID-19 vaccination. We hypothesize on the pathophysiological basis of this possible trigger in *chapter 5*.

In recent years, focus has shifted from 'hard' endpoints (e.g. attack frequency) to more patient-driven 'soft' endpoints (e.g. quality of life, treatment satisfaction). In *chapter 6*, we translated and validated the Dutch translation of a cluster headache specific quality of life questionnaire to be used in future studies. *Chapter 7* describes the attack variability in MICCH to provide a scientific basis for sample size and power calculation and to expand our knowledge of the natural fluctuations in attack frequency in cluster headache.

In- **section two**- we explore two different aspects of neuromodulation. First of all, we report retrospective data of CH patients that have been treated with a GON-injection in the outpatient clinic in *chapter 8*. We subsequently performed an investigator-initiated, multicentre, randomised, double-blind, placebo-controlled clinical trial in which we studied the safety and efficacy of a GON-injection with methylprednisolone as an add-on to standard treatment with verapamil versus verapamil alone. We aim to show in *chapter 9* that a GON-injection with 80mg methylprednisolone at the start of a cluster headache episode just before the start of standard therapy with verapamil, provides a faster reduction in attack frequency at a lower required dosage of verapamil with fewer side effects compared to standard therapy with verapamil alone. *Chapter 10* reports a case series of side switch of the headache attacks after GON-injection, in which we propose a possible pathophysiological explanation for this side-switch. In *chapter 11*, the long-term follow-up data from the investigator initiated ICON study is described, in which we explore the long-term safety and efficacy of occipital nerve stimulation in MICCH. Finally, *chapter 12* explores possible predictive factor for efficacy of occipital nerve stimulation in this population.

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