Greater occipital nerve modulation and clinical aspects of cluster headache

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CHAPTER 13

General discussion

Cluster headache is an extremely painful and debilitating disease leading to a great disease burden. The impact on quality of life, however, appears to not solely stem from the excruciating headache attacks themselves. Other factors often also come into play, such as treatment side-effects and the fear of anticipation because soon the next attack will strike.

Thankfully, diagnostic accuracy has greatly improved over the past decades. Physicians can thus more quickly focus on treatment. Standard preventive treatment with verapamil can be effective, but in many cases can lead to side effects. In some people all medicinal treatment is ineffective, deeming them medically intractable. In these patients, other treatment options such as neuromodulation should be investigated. In this thesis, we investigated different clinical aspects of cluster headache in **section 1**, while we focused on therapy with greater occipital nerve modulation in **section 2**.

Cluster headache characteristics

People with cluster headache are often anecdotally regarded as a 'typical' patient, i.e. 'over-masculinized', smoking and engaging in risk seeking behavior. Our research has tried to broaden these clinical characteristics and show that there is no 'typical cluster headache patient'. We should think of cluster headache more as a spectrum. There are 'typical' patients, but many people with cluster headache are 'atypical', which would perhaps make the 'typical' patient, by definition, 'atypical'.

Risk-seeking behavior and the role of hormones

Clinical anecdotal evidence suggests that people with cluster headache are more likely to engage in risk-seeking behavior, particularly using illicit drug, smoking and having tattoos. Using questionnaires and a risk task (the Balloon Analogue Risk Task, BART), we show in **chapter 2** that this increased tendency for risk seeking is indeed present in people with episodic cluster headache, particularly in women. We propose some possible hypotheses. First, we propose an underlying biological susceptibility that predisposes to both addictive behavior and cluster headache; [1] second, the increased prevalence of substance abuse can be explained as attempts to self-treat CH [1-3]; finally, tobacco use may increase the susceptibility to develop cluster headache;[1, 4, 5] chronic tobacco use and the subsequent release of cadmium are associated with significant toxicity and alteration of the Hypothalamus-Pituitary-Gonadal axis and may influence the pathogenesis of cluster headache through this pathway. [4] Recently, Mendelian randomization has supported this theory by implicating smoking as a causal factor [6]..

The combination of the, perhaps unfairly, proposed 'over-masculinization' phenotype and the rarity of cluster headache onset before puberty suggests a possible role for androgens in cluster headache. [7] Surprisingly, several older studies have reported low to normal

testosterone levels in men with cluster headache. [8-12] A recent prospective study reported a state of hypogonadism in men with cluster headache. In **chapter 3**, we describe a cross-sectional questionnaire in which we showed that men with cluster headache are more likely to have symptoms consistent with a (relative) androgen deficiency. The symptomology is broad, ranging from mood disturbances to sexual symptoms such as decreased libido and number of morning erections, and may vary between patients. However, as we have not carried out direct hormonal measurements, we cannot exclude the possibility that (part of) these symptoms may be explained by the effects of a chronic disease. Whatever the cause, it is important to recognize these symptoms in patients as they can have a negative impact on quality of life. We therefore advise clinicians to be proactive in assessing mood and sexual symptoms in patients with migraine and cluster headache.

Based on the available evidence, there appears to be an alteration in sex hormone levels in people with cluster headache. However, it is not clear whether the changes in sex hormone levels are a factor contributing to the pathophysiology, a consequence of the pathophysiology of cluster headache or an unrelated epiphenomenon. In recent decades, the complex feedback mechanism involving androgens has been elucidated. To develop a better understanding of the role of androgens in cluster headache, measurements of activin and inhibin, two proteins that exert direct opposite biological effects in the feedback mechanism of the hypothalamic-pituitary-gonadal axis proteins involved in this mechanism, could be valuable. However, in order to assess the role of androgens in general in cluster headache, it is important to investigate other androgens (androstendione, DHEA, DHT and 11oxC19) involved in the hypothalamic-pituitary-gonadal axis. [13]

Summary

- While an increase in risk-reward seeking behavior was observed in ECH, a decrease in risk-reward seeking behavior was observed in CCH.
- We hypothesize that there is an inherent increase in risk-reward seeking behavior in CH, which is dampened in the chronic form of the disease, possibly explaining the increased use of illicit drugs, smoking and frequent tattoos that are anecdotally observed.

- An apparent difference in risk-seeking behavior between men and women is observed in the migraine- and control groups, but this difference is less clear in the cluster headache subgroups. This observation supports the idea that men and women may present with a slightly different phenotype of the disease

- Men with migraine and cluster headache more often suffer from symptoms consistent with clinical androgen deficiency than males without a primary headache disorder.
- Whether this is the result of hormonal imbalances or an epiphenomenon reflecting chronic disease remains to be elucidated.

- It is important to recognize these symptoms in patients as they can have a negative impact on quality of life. We therefore advise clinicians to be proactive in assessing mood and sexual symptoms in patients with migraine and cluster headache.

Sensitivity to light and patterns

Despite the often quite evident presentation of cluster headache, the diagnostic delay is high (median 5 years) and almost 80% of patients receive an incorrect diagnosis at their first visit. [14] Factors contributing to diagnostic delay are the presence of photophobia or phonophobia, nausea, an episodic attack pattern and a young age of onset. [15, 16] Photophobia, or increased sensitivity to light and patterns, is a well-known feature of migraine occurring in up to 90% of patients during attacks. [17-21] However, increased sensitivity to light has only been reported anecdotally in cluster headache. In **chapter 4**, we describe the increased visual sensitivity and unilaterality of photophobia in cluster headache. It is interesting to note that more than 90% of the participants reported subjective visual sensitivity, even though this has not been a commonly reported symptom in other studies. [22-25] Furthermore, the fact that two-thirds of participants reported the visual hypersensitivity to be unilateral to the pain, may help to differentiate between cluster headache and migraine. We therefore suggest that unilateral mild to moderate photophobia ipsilateral to the pain can be considered a common part of the clinical spectrum of cluster headache and could be added to the diagnostic criteria to facilitate clinical differentiation from migraine.

Another remarkable observation is an increased interictal sensitivity to light. This interictal sensitivity has been reported in migraine as well and indicates a 'lingering visual hypersensitivity'.

Increased ventral occipital responsiveness to light has been postulated to explain ictal photophobia in migraine and presence of trigeminal pain increases this responsiveness.[26, 27] By analogy, since many patients with cluster headache have 'shadow pain', a mild pain in the trigeminal region between attacks, increased occipital responsiveness to light could possibly explain visual hypersensitivity in cluster headache.

Similar to the observations in **chapter 2**, where an increase in risk seeking behavior was observed most evidently in women, we report a higher visual sensitivity in women in **chapter 4**. This is consistent with previous studies showing that women present with a different phenotype then men. Furthermore, it has been suggested that female cluster headache patients are more severely affected than male cluster headache patients. Alternatively, a relatively 'mild' cluster headache phenotype in woman could not be adequately recognized by the treating physician, therefore only diagnosing the more severe cases. [28] Given the increasing focus on gender differences in medicine and the observed clinical differences between males and females with cluster headache, it would be wise to stratify future studies by gender. Moreover, although no data have been published on differences in therapeutic response to treatment, this should be further investigated, especially as the therapeutic response to triptans in migraine differs between men and women. [29]

Summary

- We showed an increased visual sensitivity in people with cluster headache, particularly during attacks, but also outside attacks and bouts.
- In two thirds of cases, the visual hypersensitivity was unilateral, and mostly (ipsilateral to the side of the ictal pain.
- Unilateral mild to moderate photophobia, ipsilateral to the ictal pain side, can thus be considered a frequent part of the clinical spectrum of cluster headache and could be added to the diagnostic criteria to facilitate clinical differentiation from migraine.
- In females with cluster headache, the visual sensitivity was slightly higher than in males, which could indicate the presence of a slightly more 'migrainous' phenotype in women with cluster headache

COVID-19 and cluster headache

Part of this thesis was written during the COVID-19 pandemic. Headache is often one of the symptoms of COVID-19 infections and frequently had characteristics of migraine and tension-type headache. [30] Since the start of COVID-19 vaccination in the Netherlands, we have observed several long-term attack-free CH patients who reported the onset of a new unexpected cluster episode shortly after vaccination. We describe these cases in **chapter 5** and speculate on the pathophysiological mechanism. One of the theories is that in people with CH the trigeminovascular system is in a constant fluctuating pro-inflammatory state [31,

32] and that certain unknown events cause trigeminal activation, CGRP release and trigeminovascular inflammation. [33] An autoimmune response following vaccination could be such a trigger. Recently, a new case series reported not only similar cases, but *de novo* onset of cluster headache after COVID-19 vaccination as well. [34] Interestingly, no cases of new cluster episodes after vaccination against other diseases have been reported. This could be due to the stronger immunological effect of the vaccinations or to the specific properties of the COVID-19 virus, as we know that headache is a common complication of COVID-19 vaccination [35-37], especially in people with migraine or tension-type headache. [38, 39]

Summary

- COVID-19 vaccination could be a trigger for cluster headache episodes
- This trigger could imply an important role for neuroinflammation in the pathophysiology of cluster headache

(New) trial design in cluster headache

The impact of cluster headache on quality of life can be very high. [40, 41] Until recently, key outcome measures in (pivotal) trials have been 'hard' endpoints (i.e. % reduction in attack frequency). As physicians, we want to treat the patients as well as we can, but sometimes focusing on reducing attack frequency may not be the best treatment for the patient. In most cases, medications used in the prophylactic treatment of cluster headache have many side effects when used in a therapeutic dose, and we may decide, in corroboration with the patient to reduce the dosage, thereby 'allowing' attacks to occur. However, this can have a positive effect on the quality of life as the attacks are manageable with fewer side effect. We describe another example of an increased quality of life without an apparent reduction in attack frequency in **chapter 11**. We observed that patients reported a subjective improvement compared to baseline, even when their attack frequency is similar. The focus on quality of life has improved considerably in recent years with the increased emphasis on patient-reported outcome measures (PROMs). In line with this development, the newly revised clinical trial guidelines for cluster headache state that these measures should be included as clinical trial endpoints. [42]

No cluster headache specific QoL questionnaires were available until 2016. In that year the English version of the Cluster Headache Quality of Life scale (CHQ) was developed. [43] In **chapter 6**, we translated and validated the CHQ into a Dutch translation, the Cluster Headache Quality of Life scale – Dutch version (CHQ-D), to be used in future studies. Despite the validation of the CHQ-D, it would be interesting to see how this questionnaire relates to the

commonly used, more general QoL questionnaire, 'short form 36' (SF-36), which we have used in the ICON trial and in **chapter 11** as well. [44, 45]

One of the difficulties in cluster headache studies is the episodic and fluctuating nature of the disease. In episodic cluster headache, it is important to start treatment as soon as possible because of the limited duration of episodes, but a baseline period of sufficient length is needed to observe a reliable effect. In chronic cluster headache however, a longer baseline period is advisable because disease activity may fluctuate and potential participants will seek additional help when the cluster headache is more severe, increasing the chance of regression to the mean due to the natural fluctuating course of the disease. However, the longer the length of the baseline period, the greater the risk of dropouts and missing data. This is also emphasized in the new guidelines. [42] The optimal length of the baseline observation period has not been formally established. It has been assumed that the attack frequency in chronic cluster headache patients, although variable, is relatively stable. In **chapter 7**, we report on the 3-months observation period that participants in the ICON trial had prior to implantation.

One of the main conclusions was that weekly retrospective recordings were as good as a prospective daily registration, which is very convenient for trial design. We also showed that the attack frequency in chronic cluster headache patients is not as stable as we thought. In particular, a high variability was observed in participants with ≤3 attacks per day, whereas the variability was lower in participants with >3 attacks per day. Based on our observations, we tabulated the accuracy ranges of different baseline periods for different attack frequencies. These calculations can be used to determine an appropriate evidence-based baseline period length for future trials. Finally, we showed that attack frequency was highest in spring, confirming previous reports of seasonal rhythmicity. [46]

Summary

- Until recently, key outcome measures in trials have been 'hard' endpoints, such as % reduction in attack frequency.
- The focus on quality of life has improved considerably in recent years with an increased emphasis on patient-reported outcome measures (PROMs)
- We translated and validated the Cluster Headache Quality of Life scale (CHQ) into a Dutch translation, the Cluster Headache Quality of Life scale – Dutch version (CHQ-D).
- The CHQ-D is a valid and practical instrument for QoL in individuals with cluster headache.
- The episodic and fluctuating nature of cluster headache creates the need for specific trial design.
- A baseline period that is as short as possible (possibly retrospective) is advised in episodic cluster, where a longer baseline period (6-7 weeks, depending on the attack frequency) is advised in chronic cluster headache.
- Weekly retrospective attack recordings are as good as a prospective daily attack registration.
- We tabulated the accuracy ranges of different baseline periods for different attack frequencies for trials in chronic cluster headache.
- A higher attack frequency was observed in spring, confirming previous reports of seasonal rhythmicity.

GREATER OCCIPITAL NERVE MODULATION

Despite the relatively large number of currently used, off-label, prophylactic drugs (e.g. verapamil, lithium, topiramate, pizotiphene, etc.), preventive therapy is not yet ideal. The most commonly used prophylactic drug is off-label verapamil, primarily designed as antihypertensive drug.[47, 48] Often, a very high dose of verapamil is needed to sufficiently prevent cluster headache attacks, which can cause serious, sometimes life-threatening side effects such as cardiac arrhythmias and cardiac failure..[48] To reduce the risk of side effects, the dosage is titrated slowly, usually over several weeks with frequent ECG monitoring. Due to this slow titration, it may take many weeks before effective doses are achieved [47, 49] during which the patient continues to suffer from attacks. Other preventive treatment options are lithium and topiramate which often have similar if not more debilitating side effects that can hamper adequate treatment and quality of life. [33, 47, 50] In some people with chronic cluster headache, patients continue to have frequent, often daily, attacks despite a variety of standard prophylactic medication: medically intractable chronic cluster headache (MICCH): the most extreme and disabling form of cluster headache. [33, 51-54]

These examples highlight the need for therapy that rapidly reduces attacks and is effective in MICCH. In our studies, we focussed on GON modulation, either as a GON-block that quickly reduces the attack frequency and reduces side effect of other prophylactic drugs (**Chapter 8 – Chapter 10**), or as occipital nerve stimulation for people with MICCH (**Chapter 11**).

Greater occipital nerve injection

In **chapter 9**, we showed that a single GON-injection of 80mg of methylprednisolone together with a standard verapamil regimen was well-tolerated, reduced the required dose of verapamil and reduced attack frequency and intensity faster than verapamil in combination with a placebo injection in participants with episodic cluster headache. The results from this trial underline that a single GON-injection of 80mg of methylprednisolone administered just before the start of standard therapy with verapamil is safe, confirming the earlier results from **chapter 8**. [55]

In previous studies, different injection compounds were used (i.e. long-acting or short-acting corticosteroids or a combination of both, or of the addition of a local anaesthetic [56-59]) However, no superiority of any combination was observed. We therefore decided to use only methylprednisolone, a relatively short-acting corticosteroid, without the addition of a local anaesthetic. Furthermore, due to the double-blind nature of the trial, the addition of a local anaesthetic could have led to paraesthesia's and thus possible unblinding. A similar trial studying oral prednisone in combination with verapamil showed comparable efficacy. This could lead to the question whether or not the observed effect in **chapter 9** could be attributed

to a systemic effect.[60] However, to adequately suppress cluster headache attacks, a very high dose of oral prednisolone is administered (100mg daily for five days with tapering for a total dose of 1100mg over 17 days). The subcutaneous administration of 80mg dexamethasone (equivalent dose of 100mg oral prednisolone) would not be expected to have a systemic effect.[61] Furthermore, from clinical evidence, we know that when treatment with oral prednisone stops or the dosage drops below a certain level the attacks return. In contrast, the effect of a single GON-injection can last for several weeks to months.

The results from **chapter 9** show that attacks can return after a couple of weeks and the verapamil dosage should be increased in some participants. In this subgroup, it may be useful to administer a repeated GON-injection. However, safety and efficacy of repeated injections and the appropriate injection interval should be studied further. Available evidence from previous studies (amongst other evidence from **chapter 8**), although limited, suggest this is safe. [55] Currently, a trial studying repeated greater occipital nerve injections is conducted in chronic cluster headache, but if repeated injections are safe, this regimen could be used in episodic cluster headache as well. The theoretical risks of repeated injections are, amongst others, alopecia, subcutaneous atrophy and a theoretical corticosteroid induced adrenal insufficiency. However, in all likelihood, the risk comes primarily from the accumulation of injections. Because cluster episodes usually last only weeks to months and are separated by several months to years of attack-free periods, the risk of serious corticosteroid-induced side effects should be minimal.

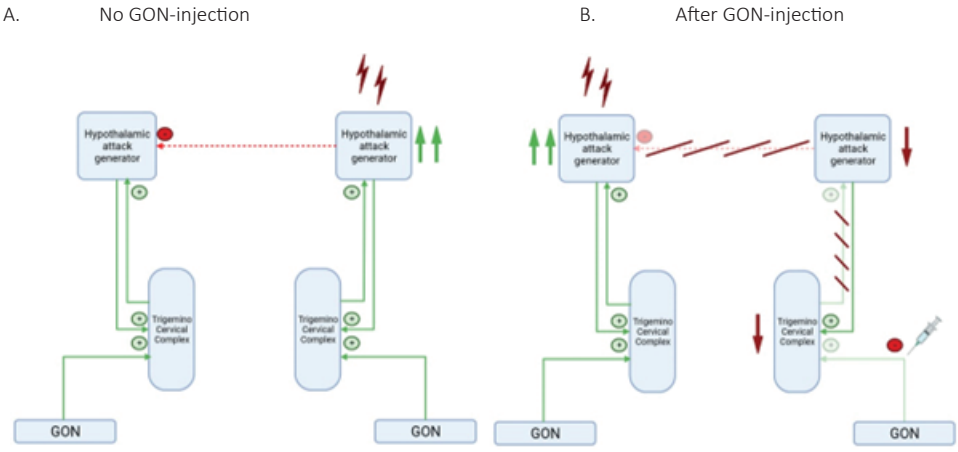
Summary

- A single GON-injection of 80mg of methylprednisolone in combination with verapamil quickly reduces the attack frequency and attack intensity in episodic cluster headache.
- A single GON-injection of 80mg of methylprednisolone administered just before the start of standard therapy with verapamil reduces the need for high-dose verapamil.
- A single GON-injection of 80mg of methylprednisolone is safe and well tolerated.
- GON-injection can be a viable treatment option in medically intractable chronic cluster headache.
- Repeated GON-injections show similar effect to a first GON-injection in (medically intractable) chronic cluster headache.

Cluster headache side switch – a treatment related phenomenon?
In line with previous studies, no serious treatment related adverse events were observed in our studies investigating GON injections (**chapter 8 and chapter 9**). Some minor, transient, treatment related adverse events were reported (e.g. injection site pain) and there were some reports of a *side switch* of the headache attacks. This is a very interesting phenomenon that we further explored in **chapter 10**. All studies performed in cluster headache report that in the large majority of patients (84-91%) the attacks are side-locked. [62] This observation is in line with the notion that there is a hypothalamic activation ipsilateral to the headache. [63] A spontaneous side-shift of the attacks has been reported between, but rarely within cluster episodes. [62, 64] However, a provoked side-switch of the attacks was described after unilateral occipital nerve stimulation in patients with chronic CH, which prompted the use of pre-emptive bilateral stimulation. [65, 66]

Since the mechanism of effect of greater occipital nerve injection and stimulation remains to be unravelled, an explanation for this side switch remains hypothetical. In **chapter 10**, we do propose a mechanism by which this could occur. The hypothalamus is widely regarded as the 'attack generator', and it has been postulated that both sides of the hypothalamus can act as such. During a CH episode, one side appears to be more active than the other and suppresses the contralateral hypothalamus causing clinical features on the ipsilateral side (Figure 1A). [67] When the more active side of the hypothalamus cannot suppress the other side sufficiently, a side-shift may occur. This hypothesis is supported by the observation that even outside a cluster episode the hypothalamic side ipsilateral to the attacks is hyperexcitable to external pain stimuli compared to the contralateral side. [68] Unilateral injection of the GON with methylprednisolone reduces the normally present excitatory effect of the GON on the trigeminal system ipsilaterally, resulting in reduced activity of the ipsilateral hypothalamic attack generator (Figure 1B). In turn, this will result in (relative) overactivation of the "initially weaker" contralateral hypothalamic attack generator, causing a side-shift. Similarly, unilateral electrical neurostimulation of the GON can also cause a disturbance of this balance and consequently a side-shift. [65, 66]

Figure 1 – Proposed mechanism of side-shifts after GON injection



Legend: GON = greater occipital nerve; '+' = excitatory; '-' = inhibitory

Location of the Greater occipital nerve injection

Another topic of debate is the location of the GON-injection. In our studies in **chapter 8**, **chapter 9** and **chapter 10**, we used a location that was based on visual and palpable landmarks (1/3 of the line between the occipital protuberance and the mastoid process, figure 1), as has been described in previous trials. [56] This location is based on the assumption that there is little interpersonal anatomic variability. However, a recent literature review showed that there is not only *interpersonal* variability, but *intrapersonal* variability as well (asymmetry). [69] To make sure the GON-injection is in the right place, the injection can be ultrasound-guided. However, this complicates the procedure and since a minimum of 2 cc is injected, the consensus is that the injected fluid spreads under the skin, reaching the GON. Another option would be to inject more proximally. The GON is an afferent nerve that arises from the C2 and C3 spinal nerve. A proximal injection could have the advantage of blocking the nerve better. However, this is contrary to the idea of nerve field stimulation, which is frequently used in chronic pain management, where small afferents are stimulated as distally as possible to include the entire nerve field. [70] The unstandardised approach and lack of evidence for one technique could explain (part of) the variation in effect that is observed in GON-injection studies.

A trial studying different injection targets, including a subcutaneous injection on one of the limbs to exclude a systemic effect of the corticosteroids in which the injection would act as a 'depot' for methylprednisolone, would be very informative.

Summary

- The large majority of cluster headache attacks are strictly unilateral on the same side.
- We observed a possible greater-than-chance occurrence of side switch of the cluster headache attacks after a GON-injection.
- We propose a mechanism in which one side of the hypothalamus is active during the cluster period but is suppressed by to the GON-injection, allowing for the other side of the hypothalamus to become active, resulting in a side switch of the attacks.
- GON-injections are most frequently administered based on visual and palpable landmarks (1/3 of the line between the occipital protuberance and the mastoid process). No evidence for superiority or inferiority of this location however exists.
- A trial studying different injection targets, including a subcutaneous injection on one of the limbs to exclude a systemic effect of the corticosteroids in which the injection would act as a 'depot' for methylprednisolone, would be very informative.

Occipital nerve stimulation

Finally, we describe a large prospective cohort of people with medically intractable chronic cluster headache who received occipital nerve stimulation as part of the ICON trial in **chapter 11**, and analysed possible predictors for effect in **chapter 12**. At present, occipital nerve stimulation is only available for people with medically intractable chronic cluster headache. Until recently, no proven treatment option was available for this specific population, causing a feeling of hopelessness in both the patients and the treating physicians. Often, the best clinical practice was to try all the available drugs (verapamil, lithium, topiramate, frovatriptan, high dose prednisone) again, sometimes a combination, with the hope of some relief. Fortunately, ONS became available as a new treatment option with the completion of the ICON trial and its subsequent approval for reimbursement.[44]

The ICON trial showed a major, rapid and sustained reduction in attack frequency compared to baseline at high and low stimulation intensity. Since the ICON trial was a randomized, dose-controlled trial and no separation between groups was observed, the trial is sometimes, in our perspective incorrectly, deemed 'negative'. During the extensive 12-week baseline observation period, the mean attack frequency remained relatively stable. Furthermore, with the abrupt and pronounced attack reduction that was observed in both groups, especially in this specific population (participants with a, per definition, long and unremitting history of frequent attacks) a sole placebo effect is highly unlikely.

In **chapter 11**, we showed that the observed effect in the initial trial is sustained (for some participants up to at least 9,5 years after implantation) and that the treatment is safe. [45] Moreover, more than one third of the initial non-responders even became ≥50% responders. One of the most striking results of this study, however, was the fact that most participants

(78%), even those in whom attack frequency has not significantly decreased, reported subjective improvement from baseline and would recommend ONS to other patients with MICCH.

This finding highlights a very important aspect of not only studies in cluster headache, but studies in headache in general as well. Over the past decades, most studies have been focused on 'hard' outcome measures, such as >50% attack reduction. However, as stated previously, we believe that attack frequency alone, although a very important measure of disability and response, does not tell the whole story. As we can infer from the observations in **chapter 11**, quality of life and treatment satisfaction does not solely depend on attack frequency reduction. This is reflected in the newly published trial guidelines for controlled clinical trials in cluster headache, in which there is an increased emphasis on patient reported outcome measures. [42] As mentioned previously, we aim to incorporate these PROMs in our future trials with the use of, amongst others, the cluster headache specific quality of life scale that we translated in **chapter 6**. [71]

Since ONS is an invasive (but safe) therapy in which patients will undergo general anesthesia, reliable predictors could help to better identify suitable patients. Unfortunately, in **chapter 12** we could not identify any a priori predictors and showed that only a rapid onset of effect seemed to predict for long-term effect. Therefore, we reiterate our recommendation to offer ONS to all MICCH patients because a large proportion of patients improve with ONS.

One of the concerns that was raised by the recently published EAN guidelines for the treatment of cluster headache was that of a poor safety profile. [72] However, these concerns were based on studies that were conducted in the early stages of ONS. In the earlier trials as well as the ICON trial, non-rechargeable implantable pulse generators were used. Since these devices were developed for epidural spinal cord stimulation, a relatively high rate of replacement surgery had to be performed due to battery depletion, lead fracture or dislocation of the leads. However, although replacement surgery must be formally reported as a serious adverse event, surgery risk is low and hospital admission time is usually less than a day. Furthermore, a rechargeable pulse generator and new, more flexible and tined leads have been developed, all reducing the need for resurgery. No formal data regarding these new techniques has been published, but we expect the adverse event rate to decline.

Summary

- Occipital nerve stimulation is a safe, well-tolerated and long-term effective treatment for MICCH.
- A sustained reduction in attack frequency for at least five years was observed in participants with MICCH who were treated with occipital nerve stimulation.
- Even participants without an objective reduction in attack frequency reported subjective improvement and satisfaction, and continued ONS therapy. This was probably due to a reduction in attack severity and an improved response to acute and prophylactic medical treatment.
- We found no significant predictors of long-term response to occipital nerve stimulation.
- No participants were administered to the hospital due to lead infection and all ONS-related SAEs required only minor surgery with minimal hospitalization.
- The efficacy, safety and economic value of the even more advanced and less invasive forms of ONS currently under development should be studied and compared with those of existing standard medical treatments in MICCH and sub-optimally drug-responsive common chronic cluster headaches.

FUTURE PERSPECTIVES

Despite the increasing number of studies on cluster headache, the exact pathophysiological basis remains to be elucidated. The hypothalamus has been implicated as the 'attack generator', but why the hypothalamus becomes active and becomes the attack generator is unclear. One of the theories is that the trigeminovascular system is in a constantly fluctuating pro-inflammatory state in people with CH, but to date no evidence has been found to support this theory.. However, with the appearance of possible new triggers such as COVID-19 and vaccination against the virus, this theory has become more plausible. With the rapid improvement in (functional) imaging capabilities there was hope that a more specific cause and subsequent therapy might have been discovered. However, the results from these studies remain conflicting and difficult to interpret. This may be partly due to the fact that cluster headache is relatively rare, making it difficult to conduct adequately powered studies in homogeneous groups. Another explanation may be that we are focusing on the wrong proposed pathophysiological mechanism and using the wrong tools.

Perhaps a 'back to basics' approach would be more appropriate, as many of the 'basic' questions remain unclear. For example, the natural course of cluster headache is poorly documented. Chronic cluster headache and episodic cluster headache are increasingly considered to be two separate entities, but we also know that episodic cluster headache can develop in chronic cluster headache and vice versa. Perhaps we should consider cluster headache (and possible paroxysmal hemicrania and hemicrania continua) as a spectrum with people with low frequency episodic cluster headache on the one end and people with

medically intractable chronic cluster headache on the other. Another aspect is the remarkable overrepresentation in males which strongly suggests a hormonal influence on the pathophysiology. Unfortunately, there are only old, small-scale studies on several specific hormones, which are also contradictory. As mentioned previously, in order to assess the role of androgens in general in cluster headache, it is important to investigate other androgens (androstendione, DHEA, DHT and 11oxC19) involved in the hypothalamic-pituitary-gonadal axis.

As long as we do not know the cause of cluster headache, treatment remains symptomatic and there is little incentive for the pharmaceutical companies to invest in new drug treatments because the target group is relatively small, and the chances of success are relatively low. Therefore, new drug treatments are mostly piggybacked on new migraine treatments, such as the (new) CGRP (receptor) antagonists and their derivatives. Despite the very high CGRP concentration in venous blood during cluster headache attacks, even higher than in migraine, the effect of the CGRP antibodies is not yet convincing. The efficacy of the new CGRP-based drugs (gepants) remains to be proven.

At present, the most promising emerging therapies are neuromodulatory treatments. The efficacy of occipital nerve stimulation, sphenopalatine ganglion stimulation and vagal nerve stimulation have paved the way for other neurostimulation targets. Interestingly, all stimulation targets appear to be more or less effective, leading to studies of stimulation (or blockade) of multiple cranial nerves. Finally, there are increasing reports of deep brain stimulation as a last resort option are being published. Despite the risk of very serious adverse events, the extreme impact that cluster headache can have on quality of life can make the chance of a beneficial treatment effect worth the risk. However, as physicians, we must be aware of: (i) the fact that the natural course of cluster headache can fluctuate, and (ii), the hopelessness that patients may feel and their consequent willingness to try very invasive therapies, and should therefore guard the best interest of the patient. Chronic cluster headache may revert to episodic cluster headache, or the attack frequency may decrease, while serious adverse events may be potentially permanent.

I would like to conclude with the notion that until recently, the most commonly used key trial endpoint to determine the efficacy of a treatment was the percentage of attack reduction. However, attack frequency does not tell the whole story. We all know stories of cluster headache patients with 8 daily attacks who can more or less function and live their lives and patients with one attack per day whose lives are turned upside down. Our main goal should therefore always be to maximize quality of life, even if this means 'accepting' several weekly attacks to avoid serious side effects. In addition, people with chronic cluster headache are people who live with chronic pain, and appropriate psychological counselling on pain

management strategies and sometimes rehabilitation should be provided in addition to regular treatment.

Summary

- The pathophysiology of clusterheadache remains poorly understood, but the hypothalamus seems to play an important role in the attack generation.
- Cluster headache could be considered as a spectrum with people with low frequency episodic cluster headache on the one end and people with medically intractable chronic cluster headache on the other.
- Neuromodulatory treatment seems very promising, although we should be cautious when offering (highly) invasive treatment options that have not been adequately studied.
- The main goal of cluster headache treatment should be to maximize quality of life even if this means 'accepting' several weekly attacks to avoid serious side effects.
- Appropriate psychological counselling on pain management strategies and sometimes rehabilitation should be provided in addition to regular treatment.

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