UiT
THE ARCTIC UNIVERSITY OF NORWAY

Faculty of Health Sciences

Department of Clinical Medicine

Hypothalamic clock involvement in cluster headache

A study of chronobiology, sleep, and cranial autonomic function in cluster headache

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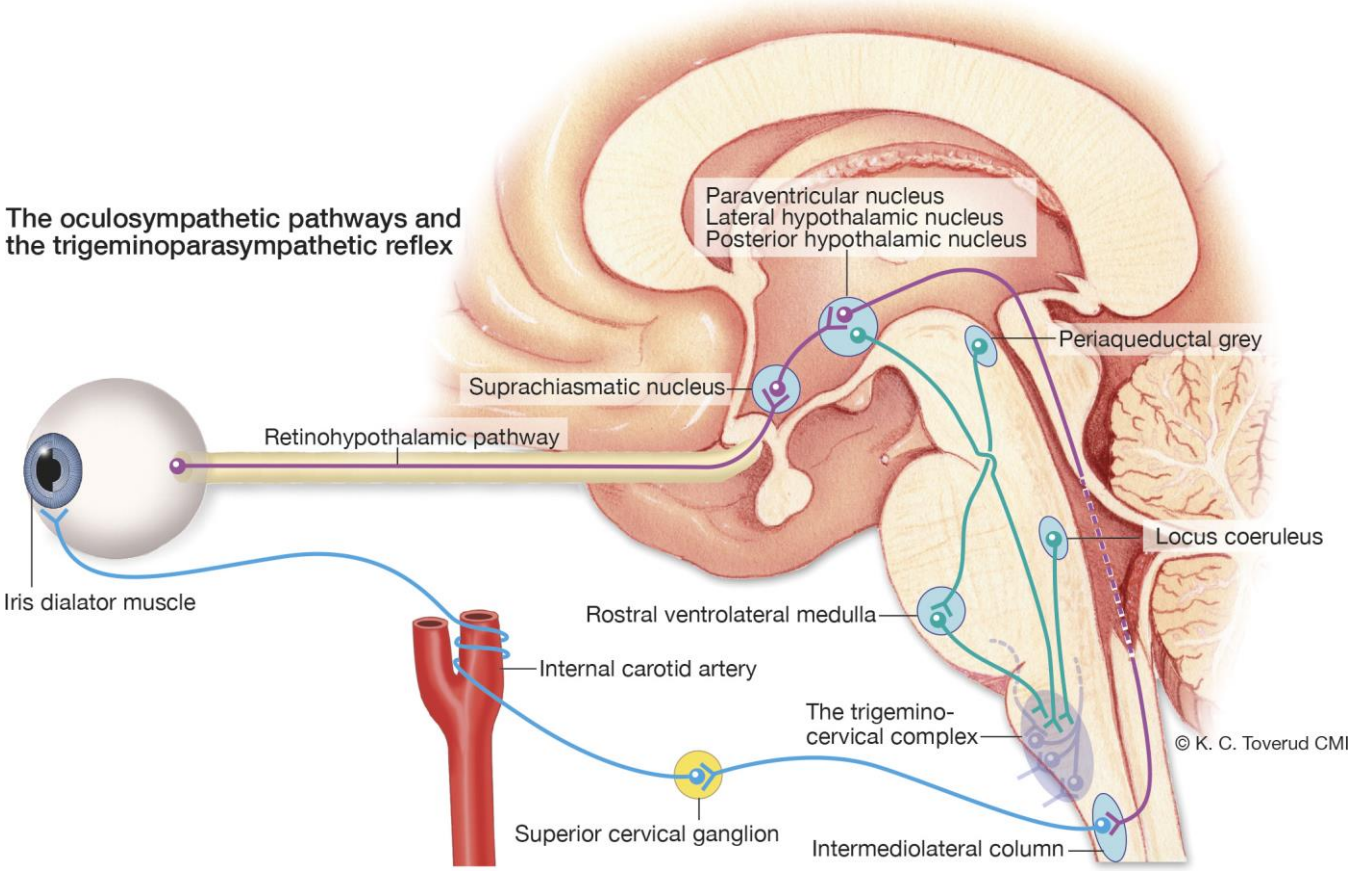
Hilde Karen Ofte

A dissertation for the degree of Philosophiae Doctor – October 2016



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The anatomy lesson of Dr Nicolaes Tulp. Rembrandt van Rejn, 1632

[On the case of Isak van Halmaal, who:]

"… in the beginning of the summer season, was afflicted with a severe headache, occurring and disappearing daily on fixed hours, with such an intensity that he often assured me that he could not bear the pain anymore or he would succumb shortly. For rarely, it lasted more than two hours. And the rest of the day there was no fever, nor indisposition of the urine, nor any infirmity of the pulse. But this recurring pain lasted until the fourteenth day.."

Nicolaes Tulp, Observationes Medicae,1641

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Aknowledgements

There are many people who have helped and inspired me through the course of my doctoral study, and to whom I owe my heartfelt gratitude. First of all, I thank my supervisor Karl Bjørnar Alstadhaug for his excellent guidance and continuous support throughout the process. His profound scientific knowledge, enthusiasm and creativity has been an invaluable source of inspiration to my work. I am also deeply grateful to my co-supervisor Svein Ivar Bekkelund, for his scientific insight, constructive criticism and support.

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Abbreviations

ACV	Average constriction velocity
ADV	Average dilation velocity
ASPS	Advanced Sleep Phase Syndrome
CGRP	Calcitonine gene-related peptide
CH	Cluster headache
CNS	Central nervous system
Con	Constriction in percent (Max-Min/Min)
CRAE	Central retinal artery equivalent
CRVE	Central retinal vein equivalent
DMH	Dorsomedial Hypothalamus
PER3	*PERIOD3* clock gene
DSPS	Delayed Sleep Phase Syndrome
EWN	Edinger Westphal nucleus
ICA	Internal carotid artery
ICHD	International Classification of Headache Disorders
IML	Intermediolateral column
IOP	Intraocular pressure
Lat	Latency of constriction in seconds
LC	Locus Coeruleus
Max	Maximum pupil diameter in darkness
MCV	Maximum constriction velocity
MEQ	The Horne Ostberg Morningness Eveningness Quesionnaire
Min	Minimum diameter of the pupil
NKA	Neurokinine A
OCT	Optical coherence tomography
PSQI	Pittsburgh Sleep Quality Index
PVN	Paraventricular nucleus

RNFL	Retinal nerve fiber layer
SCG	Superior Carotid ganglion
SCN	Suprachiasmatic nucleus
SNP	Single Nucleotide Polymorphism
SSN	Superior Salivary Nucleus
SP	Substance P
SWI	Standard Shift Work Index
TACs	Trigeminal Autonomic Cephalalgias
T_{75}	Time elapsed before pupil diameter redilates to 75% of initial size following constriction
VIP	Vasoactive Intestinal Peptide

Sammendrag

Klasehodepine er en primær hodepine med en slående periodisk opptreden. Mange har derfor påpekt at klasehodepine må være en *kronobiologisk* lidelse, og at den biologiske klokka er involvert i patofysiologien. Få studier har undersøkt dette i detalj.

I denne avhandlingen har vi studert flere aspekter ved kronobiologi hos klasehodepinepasienter. I den første studien kartla vi periodisk opptreden av hodepine, forekomst av søvnforstyrrelser og skiftarbeid i en klasehodepinepopulasjon nord for polarsirkelen. Dette er en geografisk region med ekstreme forskjeller i lysforhold gjennom året. Vi fant at periodisk opptreden av hodepine var den samme her som i andre klasehodepinepopulasjoner. I tillegg fant vi en høy forekomst av kronisk insomni og skiftarbeid blant pasientene.

Dernest undersøkte vi en *variable number tandem repeat* (VNTR) sekvens i klokkegenet *PERIOD3* hos klasehodepinepasienter. Dette er en polymorfisme som har vist seg å korrelere med foretrukket døgnrytme (kronotype) i flere friske populasjoner. Vi kartla også kronotype hos en undergruppe av pasientene ved hjelp av validerte spørreskjema. Sammenlignet med en tidligere publisert frisk, norsk kontrollgruppe, fant vi ingen forskjell i *PERIOD3* VNTR polymorfisme. Vi fant heller ingen sikre avvik i kronotyper.

I den tredje studien undersøkte vi kranial autonom funksjon i remisjonsfasen av klasehodepine. Vi gjorde pupillometri av lysrefleksen, målte tykkelsen av a. temporalis superficialis og tykkelsen av retinale kar ved hjelp av standardiserte metoder hos 30 klasehodepinepasienter. Sammenlignet med kontroller fant vi signifikant redusert parasympatisk respons i pupillens lysrefleks på begge øyne, mer uttalt på den symptomatiske siden. De retinale venene var også signifikant tynnere på symptomatisk side sammenlignet med asymptomatisk side, muligens på grunn av redusert parasympatisk tonus. Funnene antyder en sentral årsak til klasehodepine, og vi lanserer en mer spesifikk sentral hypotese for klasehodepine patofysiologi.

Summary

Cluster headache has been claimed to be a *chronobiological* disorder because of its striking periodic occurrence. This suggests that the biological clock is involved in the pathophysiology of the disease, but few researchers have studied this in depth.

In this thesis, we have studied several aspects of chronobiology in cluster headache patients. First, we assessed the periodicity of headache attacks, the frequency of sleep disturbances and shift work employment in a cluster headache population living north of the Arctic Circle, a region with extreme variations in external light. We found that the periodicity of headache was the same here as in other cluster headache populations, but we also found a high frequency of chronic insomnia and shift work occupation among the patients.

Second, we sequenced a variable number tandem repeat DNA-sequence of the clock gene *PERIOD3* in cluster headache patients. This is a core clock gene mutation known to be associated with preferred daily rhythm in healthy populations. A subpopulation of patients were also chronotyped, meaning that we assessed their preferred daily rhythms through validated questionnaires. Compared to a healthy population of Norwegian students, there was no difference in *PERIOD3* genotype distribution. We also did not find certain deviations in chronotypes.

Finally, we studied cranial autonomic function in the remission phase of cluster headache. Thirty patients were examined in their headache-free period, undergoing light-reflex pupillometry, ultrasound measurement of the superficial temporal artery diameter and computer-assisted retinal vessel caliber measurements of both eyes. We found a significantly reduced parasympathetic response in the pupillary light reflex on both eyes, more pronounced on the symptomatic side, compared to controls. The retinal veins were also smaller on the symptomatic side compared to the asymptomatic side, possibly caused by reduced cranial parasympathetic tone. The findings suggest a central origin of the disease, and we propose a theory of hypothalamic involvement in cluster headache pathophysiology.

List of publications

Paper 1

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.

Paper 2

Ofte HK, Tronvik E., Alstadhaug KB. *Lack of association between cluster headache and PER3 clock gene polymorphism.* The Journal of Headache and Pain 2016; 17(1): 18

Paper 3

Ofte HK, von Hanno T, Alstadhaug KB. *Reduced cranial parasympathetic tone during the remission phase of cluster headache.* Cephalalgia 2015; 35(6): 466-77.

1 Introduction

Cluster headache (CH) is a relatively rare, but severe form of primary headache, affecting between 0,05- 0,5% of the population (1). It is characterized by recurring episodes of intense, unilateral pain, accompanied by ipsilateral cranial autonomic symptoms such as conjunctival injection, lacrimation, miosis and ptosis (2). Headache attacks and bouts often occur in a striking periodic pattern, waking the patient from sleep at the same time every night (3). This cyclic behavior has prompted the theory that cluster headache is a *chronobiological* disorder, and that the pathophysiology may be associated to the hypothalamic biological clock (4). Several studies have examined the periodic patterns of cluster headache in different populations, but few have studied the biological clock itself.

The pathophysiology of CH is largely unknown, but like migraine it was long regarded as a peripheral, vascular headache, linked to changes in cranial vascular tone, and possibly reduced venous drainage from the cavernous sinus (5). However, as in migraine, increased knowledge of the hypothalamus and central structures involved in pain processing have turned the focus of interest from the peripheral to the central nervous system (CNS). Based on the findings in several interesting studies on neuroendocrinology, neuroimaging and the autonomic nervous system, the majority of the scientific community now believe that the origin of disease must lie within the CNS.

The work in this thesis was motivated by the need for further knowledge on the connection between chronobiology, the autonomic nervous system and headache attacks in cluster headache pathophysiology.

2 Background

2.1 Clinical Characteristics of cluster headache

CH is an episodic headache, with repeated attacks that last between 15 to 180 minutes, up to eight times per day (2). The pain is located in the innervation area of the 1st branch of the trigeminal nerve and is strictly unilateral, although it may switch sides between headache bouts in 14-18% of patients (3, 6). The condition is said to be extremely painful, allegedly comparable to renal stones or childbirth. The intense pain is often described as “sharp”, “piercing” or “burning”, and has earned CH the nickname of “suicide headache”. In an internet-based survey from the U.S. of 1134 CH patients, 55% had contemplated suicide, and two percent had actually tried to end their own lives (7). Frequently reported triggers for attacks include small quantities of alcohol, nitrates such as nitroglycerine, and (nocturnal) sleep (6, 7).

The name *cluster headache* refers to the fact that attacks occur in bouts or clusters that usually last from one week up to three months, after which the headache disappears for at least one month. About 70% of patients have one or two bouts per year (8). In a British series, one bout lasted on average 8,6 weeks (3). About 10% of patients have chronic cluster headache, meaning that there are no pauses between bouts (9). The condition was originally named Hortons headache after Bayard Taylor Horton, who in 1939 published a complete description and a theory of pathogenesis for the condition (10), but clinical descriptions of the syndrome are known dating as far back as the 17th century (11).

During attacks, patients may have autonomic symptoms in the form of miosis and ptosis on the symptomatic side, as well as ipsilateral conjunctival injection, lacrimation, nasal congestion or rhinorrhea, edema of the eyelid and sweating of the forehead or face. The International Classification of Headache Disorders (ICHD) classifies CH as one of the Trigeminal Autonomic Cephalagias (TACs), a group of primary headaches that resemble each other because of the combination of headache and cranial autonomic symptoms. The patients are often restless or agitated, unable to lie down or

rest. Migrainous features such as photo- and phonophobia, nausea, vomiting and visual or sensory auras may occur in up to 20% of patients (7).

2.2 Prevalence, diagnosis and predisposing factors

The incidence of CH is unknown, but the prevalence varies from 0.05% to 0.5% in different studies (1). In a Norwegian study from 2003, authors Sjaastad and Bakketeig interviewed 1838 inhabitants between the age of 18 and 65 years in the municipality of Vågå, Norway, and found seven (0.38%) that met the diagnostic criteria of CH (12). Unlike migraine, which has a female predominance, CH affects men 3 to 4 times as often as women (13). Onset is usually between the ages of 20 to 40 years, but CH has been diagnosed in patients as young as 4 and as old as 96 years of age (9). The diagnosis is made by a thorough medical history, evaluating the symptoms and signs in accordance to the criteria set by the ICHD (Box 1).

Despite the characteristic presentation of the disease and the intensity of the symptoms, time to correct diagnosis is persistently long, up to six years in some studies (14). Secondary forms are mainly caused by carotid dissection or tumors in the sellar/parasellar region, and should be ruled out (15).

CH seldom runs in families, but about five percent of patients report that they have relatives who are also diagnosed with the condition (3). When compared to the general population, first-degree relatives of CH patients have a 5-18 times higher risk of being affected, and second-degree relatives a 1-3 times higher risk (16). A genetic predisposition in CH is likely, but there are probably multiple genes and environmental factors involved and the mode of inheritance is uncertain. Studies of CH in families and twins have shown a probable autosomal dominant inheritance with low penetrance in some families, and autosomal recessive or multifactorial inheritance in others (16). An association has been made with the *alcohol dehydrogenase* gene and a novel rearrangement involving the intron-region of the *neurexin 3* gene (17), but the findings should be confirmed in larger populations. A missense single nucleotide polymorphism of the *hypocretine receptor 2* gene has also been associated to CH in several studies, but a recent meta-analysis casts doubt on these findings (18).

Diagnostic criteria for cluster headache:

A. At least 5 attacks fulfilling criteria B-D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)
C. Either or both of the following:
    a. At least one of the following symptoms or signs, ipsilateral to the headache:
        i. Conjunctival injection and/or lacrimation
        ii. Nasal congestion and/or rhinorrhoea
        iii. Eyelid oedema
        iv. Forehead and facial sweating
        v. Forehead and facial flushing
        vi. Sensation of fullness in the ear
        vii. Miosis and/or ptosis
    b. A sense of restlessness or agitation
D. Attacks have a frequency between one every other day and eight per day for more than half of the time when the disorder is active
E. Not better accounted for by another ICDH-3 diagnosis

Episodic cluster headache: Attacks occur in periods lasting from seven days to one year, separated by pain-free periods lasting at least one month.

Chronic cluster headache: Attacks occur for more than 1 year without remission, or with remission periods lasting less than 1 month.

Box 1: Diagnostic criteria for cluster headache, ICDH beta3 version

About 30% of CH patients report of a family history of migraine (3), but they do not have more co-morbid migraine than the general population (19). A high prevalence of smokers seem to be a consistent finding in population studies of CH (9), reporting up to 80% of patients as current or previous smokers (6). However, quitting tobacco does not alter the clinical course of the disease, which indicates that there is no causal link between the two (20). Historically, CH patients were characterized, and to some degree

stigmatized, as the prototypical “testosterone male” in both appearance and behavior: ambitious, hard-working, and a heavy user of tobacco and alcohol (21). Admittedly, alcohol is one of the most frequently cited triggers for CH attacks (7), but so far there is no documentation of a higher alcohol consumption in CH populations.

2.3 Treatment

Medical treatment in CH can be divided in to three categories: acute treatment, preventive treatment and “bridging”. According to the European Federation of Neurological Societies, first-line treatment of CH attacks is inhalation of 100% Oxygen 12-15 L/min via mask, or a subcutaneous injection of 6 mg Sumatriptan (22). For preventive treatment, the drug of choice is Verapamil, but Lithium and Topiramate may also be used. Methysergide is also listed as a second drug of choice, but has potentially serious side effects and is not available in many countries, including Norway. A transitional treatment (“bridging”) of steroids, administered orally or intravenously, may be given to shorten the CH bouts and ease the burden of headache attacks before the effect of the initiated preventive treatment has kicked in (23). In chronic, refractory CH, several surgical interventions have been used through the years with varying success. For the last decade, neuromodulation strategies such as electrical stimulation of the occipital nerves, sphenopalatine ganglion, or even deep brain stimulation have grown into more promising alternatives (24). A detailed presentation of CH treatment is beyond the scope of this thesis. For further information, please see the references given in this section.

2.4 Periodicity of cluster headache

CH has a striking periodic occurrence. In up to 80% of patients, headache attacks occur at the same time each day (7, 25). About half of the patients have two or fewer attacks a day. More than 70% report predictability of attack onset at night, waking them from sleep (3). The most frequent time of the day to have a CH attack seems to be around 2 a.m., although a previous Norwegian study found a peak incidence between 4 and 7 a.m. (26), and an Italian study found a peak incidence between 1 and 3 p.m., coinciding with the southern European time of siesta (8). The observed tendency of CH

attacks to occur during sleep or resting states have made researchers propose that CH attacks are initiated in a state of hypoarousability (27).

Similar to diurnal predictability of CH attacks, up to 43% of patients also report that CH bouts occur at predictable times of year (3). Most patients have one or two bouts per year, but when it comes to the timing of bouts, the results of different studies are diverging. In an American study from 1987, CH bouts started most often in January and July (28), a finding that the author connected to summer and winter solstices, suggesting that the initiation of bouts was related to the length of the photoperiod. However, in two other studies bouts were most likely to begin in spring and autumn, closer to the equinoxes (3, 7). A Danish study did not find a biphasic pattern in the annual rhythmicity of CH attacks, but a clear reduction of attack frequency in the summer, which gave a statistically significant inverse relation between attack frequency and the number of daylight hours (29).

2.5 Sleep in cluster headache

Sleep disturbances are frequent in all headache populations, but there seems to be a special relationship between sleep and CH (30, 31). The International Classification of Sleep Disorders classifies CH as a sleep-related headache, together with hypnic headache, chronic paroxysmal hemicranias and migraine (32). As noted, most CH attacks occur at night, and sleep seem to be one of the most frequent triggers for attacks (29). CH patients score significantly lower on sleep quality measures compared to healthy controls, and continue to do so as long as one year after the last attack, which indicates that it is not merely the nocturnal headache attacks that cause the sleep disturbances. In early studies of sleep and CH, attacks seemed to be related to REM-sleep stages (33, 34), but the number of patients included in these studies was small, and the results somewhat conflicting. Two previous open-label studies and one controlled study have also suggested that the prevalence of sleep-disordered breathing is high in CH populations (35-37). There is no doubt that a complex anatomical and physiological overlap exists between headache and sleep disorders, suggesting a common pathophysiology. Increasing evidence point at the importance of diagnosing and treating the two combined (38).

3 Pathophysiology

The combination of unilateral headache and cranial autonomic symptoms makes CH an interesting disorder to study in view of headache pathophysiology. The central theory of CH pathophysiology grew out of a combination of clinical observations and pathophysiological studies, in which a strict peripheral theory of activation proved inadequate. Reported cases of patients continuing to have CH attacks after rhizotomy of peripheral nerves or ganglions (e.g. the trigeminal nerve), headache side shifts between bouts, and continued attacks of autonomic symptoms after the pain had been successfully treated, suggested a primary involvement of the CNS in CH pathophysiology (39). The hypothalamus early became the center of attention, as this small area of the brain is involved in both pain processing, autonomic function, and neuroendocrine secretion (40). It is also the location of the master circadian clock (the suprachiasmatic nucleus, SCN), which controls the biological rhythms of the body including the sleep-wake cycle. Due to the clock-like regularity of CH, the SCN has been proposed as the generator of attacks, but so far there is no pathophysiological model explaining how this generation might occur.

During attacks, the autonomic symptoms observed seem to be caused both by a hyperactivity of parasympathetic neurons (conjunctival injection, tearing and nasal congestion/rhinorrhea), and a hypoactivity of oculosympathetic neurons (miosis and ptosis). The mechanisms underlying these symptoms are only partly known. In the following, I will summarize the current knowledge and theories of CH pathophysiology.

3.1 Predisposition and initiation of attacks: The hypothalamus

Several neuroendocrine studies have implicated involvement of the hypothalamus in CH pathophysiology. The SCN regulates secretion of melatonin, a sleep hormone secreted by the pineal gland, and studies have shown that the nocturnal peak of melatonin is blunted in CH patients in active bout (41). In addition, the excretion of the melatonin metabolite in urine is abnormal, both in cluster bout and in remission phase (42). Studies have also documented abnormal levels of several hormones connected to the

hypothalamic-pituitary axis in CH, including cortisol, testosterone, prolactin and growth hormone (43). All of these hormones are normally secreted with a circadian rhythmicity, run by the SCN. However, neuroendocrine changes may not be specific to CH, as disturbances are also documented in other disorders such as migraine, fibromyalgia, chronic fatigue syndrome and irritable bowel syndrome (44).

One early structural imaging study found increased grey matter in the posterior inferior hypothalamus in CH patients, using the method of voxel-based morphometry of the brain (45). However, later studies have not been able to reproduce the finding (46, 47). Functional imaging studies using PET and fMRI have repeatedly shown activation of the posterior hypothalamic grey matter during both spontaneous and experimentally induced CH attacks (48-51), an activation pattern initially believed to be specific to the condition. However, a more recent study of spontaneous migraine attacks also showed activation of hypothalamic regions (52). The spatial resolution is a limitation to such studies, and several authors have pointed out that the activation pattern of the studies may not be in the hypothalamus itself, but in the midbrain tegmentum, slightly posterior and inferior to the hypothalamus (53). Deep brain stimulation directed at the posterior hypothalamus seems to be a promising treatment for intractable chronic CH patients, although not without risks (24). The effect of the treatment is often delayed up to six months, which may point at a pain modulating, rather than a direct causative effect. The hypothalamus is undoubtedly involved in CH, but whether it is pivotal in causing the attacks, or merely a part of a larger pain matrix, is still unclear (44).

3.2 The pain in CH attacks

The pain in CH is conducted by the 1st branch of the trigeminal nerve (fifth cranial nerve). This nerve carries afferent nociceptive fibers from the dura mater and cranial blood vessels. A well-described neurovascular reflex arc is activated, called the trigeminoparasympathetic or trigeminovcascular reflex (Figure 1) (54). This reflex causes trigeminal pain combined with parasympathetic efflux, and may be triggered by painful stimulation of the eyes, mouth, nose or facial skin (40). The trigeminal neurons ascend to the

trigeminocervical complex in the caudal trigeminal nucleus, where they meet with the afferent cervical nerves of C1 and C2. The neurons synapse and project to the thalamus where they synapse again and proceed to various cortical areas, leading to pain.

The trigeminal neurons contain several powerful vasodilators: Calcitonine Gene-Related Peptide (CGRP), Substance P (SP) and Neurokinin A (NKA) (54). CGRP is the most powerful vasodilator in the cerebral circulation. In addition, increased levels of Vasoactive Intestinal Peptide (VIP) has been found both during spontaneous CH attacks (55) and nitroglycerine-induced attacks (56). VIP is a marker for parasympathetic activity. Reports of CH patients that describes typical CH pain attacks with no accompanying autonomic symptoms, or attacks with autonomic symptoms but no pain (57, 58), suggest that the reflex is not always activated, and it is unclear how the pain is initiated. The attacks often end as abruptly as they begin, and what terminates the attack is also unknown.

3.3 Symptoms of parasympathetic hyperactivity: Lacrimation, rhinorrhea, conjunctival injection, and flushing

About 90% of CH patients report of ipsilateral lacrimation during attacks, and about 75% report conjunctival injection, nasal congestion or rhinorrhea (3, 7-9). The nociceptive input from the trigeminal nerve leads to a reflex activation of the rostral superior salivary nucleus (SSN) via the posterior hypothalamic grey matter (40). The parasympathetic fibers from this nucleus exit the scull in the intermediate nerve, along with the facial nerve (seventh cranial nerve), and project to the geniculate ganglion where they leave the facial nerve and form the greater superficial petrosal nerve. The fibers synapse in the sphenopalatine (pterygopalatine) ganglion, creating postganglionic neurons that project to the target organs (Figure 1). Activation causes lacrimation from the lacrimation glands, secretion from the nasopalatine mucosa, and cranial vasodilation, including the choroidal vessels of the sclera.

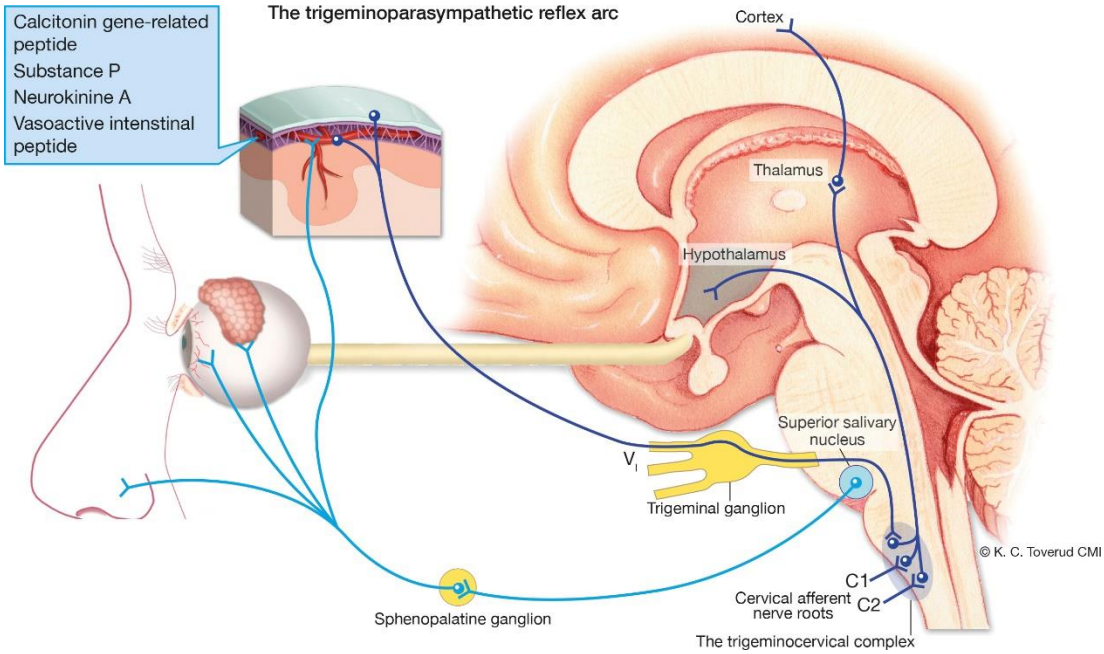

Figure 1: The trigeminoparasympathetic reflex arc. Incoming noxious stimuli from the 1st trigeminal branch and upper cervical afferents ascend to the trigeminocervical complex, where they synapse and project to the thalamus. Here they synapse again and proceed to the cortex, leading to perceived pain. A reflex activation of the superior salivary nucleus produces parasympathetic efflux, leading to secretion from the lacrimation glands and nasopalatine mucosa, and vasodilation of choroidal and cranial vessels. Several powerful vasodilators are secreted by the trigeminal neurons.

Dilation of the ipsilateral ophthalmic artery during cluster attacks has been documented in angiographic studies (59, 60), and transcranial Doppler investigations have shown a reduction of blood flow velocity in the ipsilateral middle cerebral artery, also indicating vasodilation (61). In a study of nine CH patients where the luminal diameters of the superficial temporal arteries was measured both during and in between attacks, the investigators found no asymmetry between the headache side and the asymptomatic side in the pain free state, but a significant reduction of the luminal diameter on the asymptomatic side during attacks (62). The authors interpreted this finding as a result of a general, pain-induced arterial vasoconstriction during attacks, which was opposed by the trigeminoparasympathetic activation on the headache side, causing a relative ipsilateral vasodilation. As mentioned, several powerful vasodilators have been detected in the blood stream during CH attacks, but some of the vasodilatory response may also be caused by a

reduction of ipsilateral sympathetic vascular tone (63). The attack-related parasympathetic discharge may also contribute to the rapid escalation of pain.

However, whereas parasympathetic activation normally includes salivation, increased salivation is not a feature in CH. This fact has previously been a topic of debate among researchers. In my opinion, the organization of the SSN may explain this, as the SSN consists of two separate groups of neurons (64). One group is located in the rostral ventrolateral region of the SSN and sends projections to the lacrimal glands, the nasopalatine mucosa and the cerebral and choroidal vasculature. The other group of neurons lies in the caudal and dorsolateral region and projects to the submandibular and sublingual salivatory glands. Activation of the trigeminoparasympathetic reflex in CH may involve only the former of these.

3.4 Symptoms of sympathetic hypoactivity: Miosis and ptosis

Ipsilateral ptosis during attacks is reported in about 75% of patients, whereas miosis is reported in about 40% (3, 7-9). The combination of the two is often referred to as a partial Horner syndrome. A subgroup of patients has persistent signs of such oculosympathetic dysfunction between attacks, or even in remission phase. The course of the oculosympathetic fibers are complex and not fully understood, but the efferent neurons seem to originate in three nuclei of the posteriolateral hypothalamus: the parvicellular part of the paraventricular nucleus (PVN), the dorsal part of the lateral hypothalamic nucleus, and the posterior hypothalamic nucleus (Figure 2) (65). The neurons project to the intermediolateral column in the upper spinal cord, from which preganglionic sympathetic neurons run to the superior cervical ganglion (SCG). Most of the sympathetic fibers to the pupil leave the spinal cord at the level of TH1, whereas vasomotor and sudomotor fibers to the face leave at level TH2-3 (63). From the SCG, postganglionic neurons to the eyes and the forehead form a plexus around the internal carotid artery (ICA), following the artery into the petrous segment of the carotid canal. From here, they project uninterrupted to the pupil dilator muscle in the eye and to the sweat glands in a small area of the medial forehead, causing pupillary dilation and forehead

sweating. The sympathetic neurons innervating the sweat glands in the lower part of the face follow the external carotid artery.

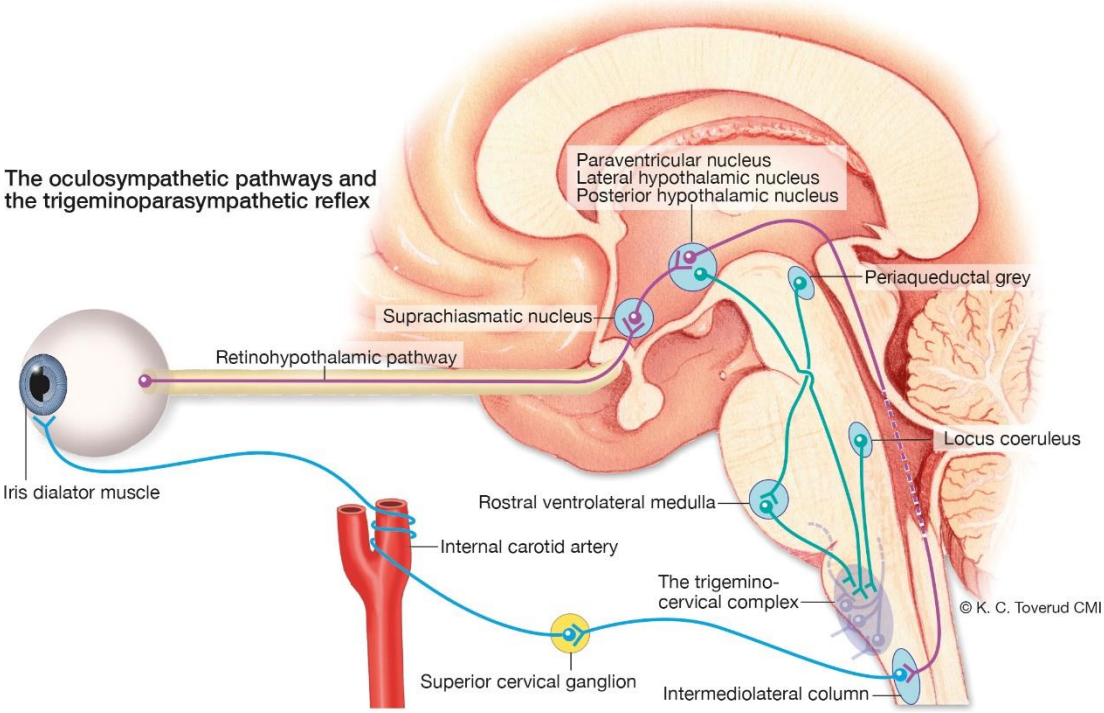

Figure 2: The oculosympathetic pathway. Light evoked impulses are carried from the retina to hypothalamus via the retinohypothalamic pathway. Dilation of the pupil is caused by oculosympathetic fibers originating from the paraventricular nucleus (PVN), the lateral hypothalamic nucleus and the posterior hypothalamic nucleus. These fibers project to the intermediolateral column, where they synapse and go to the superior cervical ganglion. From here, the third order sympathetic fibers form a plexus around the internal carotid artery, before reaching the iris dilator muscle. The figure also shows how the connections between the trigeminocervical complex and the PVN, the periaqueductal grey and the locus coeruleus, which may all be involved in pain modulation in the trigeminocervical complex.

Several studies have assessed the pupillary responses to topically induced pharmaceuticals acting on the autonomic pathways in the eyes of CH patients. Most of these studies, but not all, have found an ipsilateral oculosympathetic dysfunction similar to a third order Horner syndrome (63). Fanciullacci et al. tested 45 CH patients, using the contralateral eye as control, and found a significantly reduced pupillary dilation response to Tyramine, Cocaine and Homatotropine on the headache-affected side, consistent with a third order oculosympathetic defect (66). However, they did not find a supersensitivity reaction to Phenylepinephrine as one would expect in a proper Horner syndrome. Salvesen et al. found a significantly reduced dilation response to the sympathomimetic Hydroxyamphetamine, but not Tyramine, in 32 CH patients compared to healthy controls, but they did find a weak supersensitivity reaction to Phenylepinephrine on the headache-affected side (67). The authors found the results most compatible with a third order Horner syndrome, but pointed out that the lesion could not be complete, and that such moderate reactions also could be seen in central lesions.

The current pathophysiological hypothesis explaining the apparent third order sympathetic lesion in CH came from a case report from 1970, where a CH patient had an unexpected attack during carotid angiography (59). The angiogram showed a localized narrowing of the ipsilateral extracranial part of the ICA, which 15 minutes later had progressed further up beyond the osseous carotid canal. Ekbom et al. interpreted this narrowing as a spasm, or more likely an edema of the carotid vessel wall, possibly caused by parasympathetically derived vasodilation. Theoretically, this edema could cause a distension or compression of the sympathetic plexus following the ICA through the petrous bone, resulting in an ipsilateral third order oculosympathetic dysfunction. A similar finding was observed in another patient who underwent interictal carotid MRI-angiography in cluster period (60). A third patient did not have a narrowing of the ICA on MRI-angiography during a spontaneous attack, but this patient did not have miosis or ptosis during attacks, as the former patients had. This hypothesis is now widely

accepted as the pathophysiological model for oculosympathetic dysfunction in CH, but it must be pointed out that the body of evidence is rather small.

The theory of ICA swelling could also help to explain the forehead sweating during CH attacks. As mentioned, sympathetic fibers to the sweat glands of the medial part of the forehead follow the oculosympathetic fibers along the ICA. CH patients with persistent signs of oculosympathetic deficit also show loss of ipsilateral forehead thermoregulatory flushing and sweating between attacks (68). However, during attacks they often have increased flushing and sweating (63). This may be caused by a hypersensitivity response in denervated muscarinic sweat glands, responding to the parasympathetic efflux of the trigeminoparasympathetic reflex.

3.5 The pupillary light reflex

The efferent oculosympathetic fibers also constitute the efferent sympathetic branch of the pupillary dark response. The pupillary light reflex causing constriction of the pupil in response to light is parasympathetically driven (Figure 3). When light falls on the retina, non-image forming ganglion cells (intrinsically photosensitive ganglion cells) convey signals to the olivary pretectal nucleus in the midbrain, which projects bilaterally to parasympathetic neurons in the Edinger-Westphal nucleus (EWN). From here, preganglionic neurons are carried along the oculomotor nerves (3rd cranial nerve) to the ciliary ganglia in the posterior orbits. Several short postganglionic ciliary nerves innervate the iris sphincter muscle, causing constriction of the pupil.

Redilation of the pupil seems to be a purely sympathetic response, conveyed by the fibers travelling through the efferent pathways described in section 3.4. The size of the pupil reflects the net output of these opposing sympathetic and parasympathetic systems. The non-imaging forming ganglion cells of the retina also convey signals to the SCN via the retinohypothalamic tract (69). This connection not only allows the SCN to influence the pupillary dilation process, but it is also forms the basis for how the SCN is able to align the chronobiological rhythms of the body with the external solar cycle (see section 4.1).

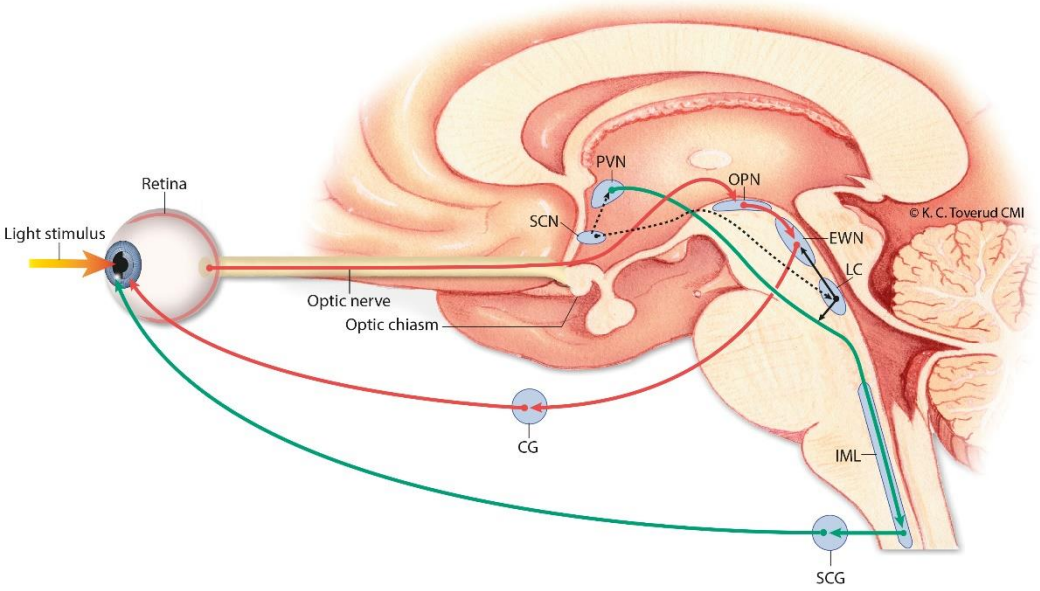

Figure 3: The pupillary light reflex. Light evokes the pupillary light reflex, which is parasympathetically driven (red lines): Non-image forming ganglion cells in the retina convey signals to the olivary pretectal nucleus (OPN), which projects bilaterally to the preganglionic parasympathetic fibers in the Edinger-Westphal nucleus (EWN). From here, the preganglionic fibers project to the ciliary ganglions where they synapse again. Postganglionic fibers reach the iris sphincter muscle and cause pupillary constriction. Redilation of the pupil seem to be a purely sympathetic response (green lines). The paraventricular nucleus (PVN) is a major sympathetic premotor nucleus that projects fibers to the intermediolateral column (IML) in the upper thoracic spinal cord. From here, second order sympathetic fibers travel to the superior cervical ganglion (SCG). Third-order sympathetic fibers project to the iris dilator muscle, causing dilation of the pupil. The locus coeruleus (LC) plays an important role in pupillary control (Black lines), either by contributing to the sympathetic outflow, or attenuating the parasympathetic outflow by inhibiting the EWN. Light also regulates the activity through the complex circadian system (black stippled lines) governed by the suprachiasmatic nucleus (SCN).

4 Chronobiology

Chronobiology is the study of biological rhythms in living organisms, and how they adapt to the solar and lunar cycles. These rhythms may be *circadian*, if they appear to oscillate diurnally (between 19 and 28 hours), or *circannual*, if they appear to oscillate annually or between the seasons (70). A biological rhythm is said to be circadian if it is endogenously generated, has a free-running period close to 24 hours, and can be modified by environmental cycles with 24-hour periods. All cells and tissues of the human body manifest inherent rhythms that drive fundamental processes, such as metabolism and cell division (71). These rhythms are synchronized by the body's master circadian clock, which is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus.

4.1 The suprachasmatic nucleus

The SCN is functionally and anatomically subdivided in two cell clusters: the dorsomedial (shell) region, and the ventrolateral (core) region (72). The cells of the shell region are intrinsically rhythmical and will oscillate in close to 24-hour loops when put in cell culture (73). These loops are caused by transcriptional-translational cycles of so-called clock genes. The cells of the core region receive external input from the retina, where the non-image forming ganglion cells convey light signals from the sun through the retino-hypothalamic pathway to the SCN. Such an external time cue is called a *zeitgeber*, and the solar light-dark cycle is the most important zeitgeber known to man (74). The sunlight activates the core cells of the SCN, which in turn pass the signal on to the pineal gland via the PVN and the superior sympathetic ganglion. The pineal gland secretes melatonin during the night, and the combination of external light and melatonin synchronizes, or entrains, the cells in the SCN shell region to the solar light/dark cycle.

The length of the entrained rhythm decides the period of the biological circadian clock, to which all biological rhythms of the body must adapt. This adaptation takes place through complex interactions in the dorsomedial hypothalamus (DMH), where the rhythmic output of the SCN and the subparaventricular zone is integrated with various endogenous and

exogenous input from the body, resulting in a periodic sleep-wake cycle, thermoregulation, hormone release, feeding, and more (73). Some, but not all blind people exhibit free-running cycles of melatonin secretion, and there is evidence suggesting individual differences in human sensitivity to the external photoperiods (74). A complete destruction of the SCN in animals will eliminate circadian rhythmicity of sleep, locomotion, body core temperature, feeding, heart rate, blood pressure, and secretion of hormones (72).

4.2 Clock genes

Thanks to the introduction of *systems biology approaches*, our knowledge of the clock genes has increased rapidly in the past decade (75). In early models, the clock mechanism was described as a simple transcription-translation oscillator loop, where the *CLOCK* and *BMAL1* gene proteins join to form a complex that initiate transcription of the *PER* (*PER1, 2* and *3*) and *CRY* (*CRY1* and *2*) gene families (76). The protein products of these genes translocate to the nucleus and inhibit further transcription from the CLOCK:BMAL1 complex, thereby inhibiting their own transcription. Degradation of the PER/CRY proteins caused by *CK1δ/ε* gene coded kinases allows the cycle to start over again, setting the intrinsic period of the circadian clock (the circadian period). This cycle is still regarded as the key transcriptional loop in clock function, but at least two additional core loops have been found that work alongside the *CLOCK* and *BMAL1* genes (the so-called *D-box* and *RRE-loop*), and it has gradually become evident that a wide array of gene regulators, post-transcriptional factors and multi-loop oscillators are involved in clock regulation. A genome-wide study screening small interfering RNA (siRNA) showed that more than 200 genes were involved in clock biology, regulating amplitude and period (77).

4.3 Chronotype

True endogenous rhythms should be *free-running* (≠ 24 h) when isolated from external time cues such as the light-dark cycle. Animals kept in constant darkness will reveal their intrinsic circadian period, and studies on humans have shown an average intrinsic free-running period of core temperature, melatonin and cortisol release of 24.18 hours (78). Together with sleep homeostasis and sensitivity to external light, the circadian period constitutes

the basis for observed diurnal preference, or *chronotypes* (79). Individuals with long circadian periods will become tired and go to sleep later in the evening (night owls) than individuals with relatively shorter circadian periods (morning larks) (80). The chronotypes represent a continuum of diurnal preferences, with Advanced Sleep Phase Syndrome (ASPS) and Delayed Sleep Phase Syndrome (DSPS) as extremes in opposite ends of the specter. ASPS patients get tired and go to sleep very early in the evening, while DSPS patients fall asleep very late at night. However, the length and quality of sleep is normal.

Two mutations in clock genes have been found in familial ASPS; one in the *PER2* gene coding for a target in the PER2 protein that is phosphorylated by CK1δ, and one in the *CK1δ* gene itself (81, 82). Interestingly, a recent study of two families with co-occurring ASPS and migraine showed that each family had its own distinct missense mutation of the *CK1δ*, and this mutation was only present in the family members who had both ASPS and migraine (83). Genetically engineered mice that carried one of these mutations were more sensitive to pain after being exposed to the migraine trigger nitroglycerine, and showed a lower threshold for cortical spreading depression. To my knowledge, this is the only study that has linked a specific headache to the clock itself.

4.4 Genetic and environmental influences on chronotype

Diurnal preference is a complex phenotype, produced by the interaction between the sleep and circadian systems, and modulated by the environment (84). Chronotype can be measured by validated questionnaires such as the Horne-Ostberg morningness-eveningness questionnaire (MEQ) (85), or the Munich Chronotype Questionnaire (86). Women seem to be more inclined to morning preference than men, and after adolescence there is a shift towards earlier chronotypes with increasing age (87). The MEQ is also influenced by social factors such as work schedules (88), and the tendency toward evening preference seems to increase with the distance from the Equator (89).

Twin studies have shown that diurnal preference has a heritability of 44-50% (90-92), but systematic screens for circadian clock gene polymorphisms that are associated to diurnal preference in healthy populations have only been

moderately successful. A single nucleotide polymorphism (SNP) of the *CLOCK* gene, the T3111C (or 3092 T→C) *CLOCK* gene mutation has been associated to evening preference in two separate studies (93, 94). However, other studies have failed to replicate this association (95).

The most widely replicated association between chronotype and a clock gene is a variable number tandem repeat (VNTR) polymorphism of the *PERIOD3* (*PER3*) gene, that has been associated to diurnal preference and DSPS in multiple studies (96-101). A VNTR occurs in DNA when a pattern of one or more nucleotides is repeated, and the repetitions are directly adjacent to each other. In the human *PER3* gene, the short allele contains four tandem 54-bp repeats, and the long allele has five such repeats. As each individual has two sets of alleles, this produces three possible genotypes: *PER3* 4/4, 4/5 and 5/5. Most studies on *PER3* VNTR polymorphism and preferred daily rhythm have shown an association between the long (5-) allele and morning preference (97). However, as with the *CLOCK* gene, not all studies have managed to reproduce the association (102).

4.4 Circadian misalignment

The complex interactions in the hypothalamus allow the intrinsic rhythm of the circadian system to be synchronized with the external environment, but the pacemaker cells of the SCN shell region may need several days to adjust to a new rhythm. A situation where the internal clock is unsynchronized with the external environment is called circadian mismatch or *circadian misalignment*. Jet lag and shift work disorder are common examples of circadian misalignment, and there is increasing evidence that such misalignment over time may lead to several health problems (103). Shift work disorder is a well-known problem affecting up to 30% of shift workers (104), and night shift workers have a higher risk of developing cardiovascular disorders, metabolic syndrome and some types of cancer compared to daytime workers (105).

Circadian misalignment is a possible mechanism for the pathophysiological association between the biological clock and CH. That would mean that the internal rhythms and external zeitgebers are periodically unsynchronized, either because of abnormal rhythms in the biological clock itself,

abnormalities in the interactions between the clock and the external zeitgebers, or in the interactions between the clock and the hypothalamic input from the rest of the body. The cyclic activity of the SCN would then repeatedly create conditions that facilitate attacks, explaining the periodic occurrence of CH.

4.5 Clock genes in cluster headache

Only one clock gene mutation has previously been studied in CH, namely the T3111C *CLOCK* gene SNP. Three separate Italian studies, each including 107, 101 and 54 CH patients, have assessed this polymorphism, all of which found no difference between CH patients and healthy controls (17, 106, 107). When we started our project, there had been no previous attempts to chronotype a population of CH patients. During the course of our work, a Danish study from 2014 chronotyped 275 patients using the Horne-Ostberg MEQ, and compared them to 145 healthy controls (29). They found no difference in chronotype distribution.

5 Aims of the study

5.1 Overall aim

To study five different aspects of chronobiology in cluster headache patients: the periodicity of attacks, frequency of sleep disturbances, frequency of shift work employment, preferred daily rhythm and clock gene polymorphism. In addition, we aimed to study cranial autonomic function in the remission phase of cluster headache.

5.2 Specific aims

Paper 1

To assess the periodicity of headache attacks, prevalence of chronic insomnia and shift work employment in an Arctic cluster headache population.

Paper 2

To study the distribution of *PER3* clock gene polymorphism in cluster headache patients, and assess preferred daily rhythm (chronotypes) and frequency of sleep disturbances in the same individuals.

Paper 3

To study the cranial autonomic nervous system in CH remission phase, using non-invasive methods that do not interfere with normal autonomic function.

6 Materials and methods

6.1 Study participants and design

6.1.1 Paper 1

The patients were identified through a retrospective chart review at the Nordland Hospital Trust in Bodø and The University Hospital of North Norway in Tromsø. These are the two regional hospitals in the Arctic region of Norway, and together they serve about 450 000 inhabitants. Assuming that most CH patients at some point would be referred to secondary health care, we identified all patients diagnosed with cluster headache (ICD-10 G44.0) between January 1, 2000 and December 31, 2010, and validated their diagnosis according to the ICHD criteria through hospital charts (108). Only episodic CH patients were included. No reward was offered for participation.

The study was designed as a cross-sectional, questionnaire-based survey. We invited all patients with a confirmed diagnosis to participate by mail, and asked them to fill out a comprehensive questionnaire. The questionnaire (appendix) was primarily developed by dr. Alstadhaug, and consisted of 92 questions covering clinical characteristics of headache, treatment, periodicity, shift work occupation and sleep. Chronic insomnia was defined in accordance with the DSM-IV criteria (109).

6.1.2 Paper 2

The second paper was the result of a collaboration between our research group and the Norwegian Advisory Unit on Headaches in Trondheim. In February 2014, we included all patients registered with CH (episodic and chronic) in the Norwegian Advisory Unit's biobank for genetic analysis of the *PER3* VNTR polymorphism. The biobank contains blood samples from headache patients living in the middle and northern part of Norway. A headache specialist, who validates the diagnosis according to the ICHD criteria, consults all patients included in the biobank. Prior to analysis, we invited the patients from our first study to donate a blood sample to the biobank, and 48 patients did so. They were offered NOK 1000,- for the donation. This part of the study was designed as a case-control candidate gene association study, in which we compared the *PER3* genotype

distribution in the CH population with a previously genotyped healthy population of 432 Norwegian students (110).

All tested patients were subsequently invited by mail to fill out three questionnaires: the Horne-Ostberg MEQ, the Pittsburgh Sleep Quality index (PSQI) and the Shift Work Index. All three questionnaires are available in Norwegian translations, and the MEQ and PSQI (appendix) are also validated in Norwegian. We had no control group of our own, but the MEQ chronotypes were compared to a recently chronotyped Danish population of 275 CH patients and 145 controls. The Danish authors kindly provided us with age-adjusted chronotypes. The results from the questionnaires were also tested for association to *PER3* genotype in our CH patients.

6.1.3 Paper 3

In the third study, the patients who had participated in study 1, who lived in Nordland County, and who had agreed to participate in further studies, were invited to the out-patient clinic of the Nordland Hospital Trust for examination in remission phase. Patients with CH attacks during the last four weeks, or who had undergone previous ocular surgery, were excluded. We performed dynamic pupillometry and computer-assisted retinal vessel caliber measurement on both eyes on all the patients, as well as bilateral ultrasound measurement of the luminal diameter of the superficial temporal artery. The researchers that performed ultrasound and retinal vessel caliber measurements were blinded to which side of the head the patients had their headache.

The study was designed as a case-control study. The results of pupillometry were compared to a group of healthy controls, which were recruited among hospital staff and visiting relatives of in-patients, ensuring a match in age and gender to the CH patients. There was no control group for the superficial temporal artery or the retinal vessel measurements, but the CH patients served as their own controls, as headache-affected side was compared to asymptomatic side both when examined by pupillometry, ultrasound and retinal vessel measurements. If the patients had side shift of their headache, we defined the predominant side as symptomatic.

6.2 The DSM IV criteria for chronic insomnia

The diagnosis of chronic insomnia requires the presence of both criteria A and B (109):

A. The predominant complaint is difficulties initiating or maintaining sleep, or nonrestorative sleep, at least three nights a week, for at least one month.

B. The sleep disturbance (or associated daytime fatigue) causes significant distress or impairment in social, occupational, or other important areas of functioning.

6.3 DNA isolation and PER3 genotyping

DNA was extracted and purified from blood specimens from the Headache biobank, and polymerase chain reaction (PCR) amplification of the *PER3* polymorphism was performed according to previously validated methods (110, 111). Table 1 shows forward and reverse primer, as reported by Ebisawa et al. (2001).

Direction	Sequences
Forward:	5' CAAAATTTTATGACACTACCAGAATGGCTGAC 3'
Reverse:	5' AACCTTGTACTTCCACATCAGTGCCTGG 3'

Table 1. Primer sequences.

6.4 The Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ)

The MEQ is one of the most widely used and best validated tools for measuring diurnal preference (85). It consists of 19 multiple-choice items, producing a score ranging from 16 to 86, with high scores indicating morning preference and low scores indicating evening preference. The initial chronotype cut-off points were validated for a population of young students, and as chronotype is strongly influenced by age and social factors, validated cut-off points for a middle-aged, non-shift working population have later been made by Taillard et al. (112). We used these cut-offs for our study, defining evening types: MEQ scores 16-52, neither types: MEQ scores 53-64, and morning types: MEQ scores 65-86.

6.5 The Pittsburgh Sleep Quality Index (PSQI):

The PSQI is a validated, retrospective measure of subjective sleep quality and sleep disturbances during the past month (113). It consists of 19 items grouped into seven equally weighted component scores, with higher scores indicating poorer sleep quality. The maximum score is 21, and a score above five indicates a poor sleeper.

6.6 The Standard Shiftwork Index (SWI):

The SWI is a standardized battery of questions developed to study the psychological and physiological impact of shift work (114). We used it mainly to identify shift workers, as the small number of participants made detailed studies on adaptation to different shifts less reliable.

6.7 Dynamic pupillometry of the light reflex

We used a handheld NeurOptics PLR-200^{TM} pupillometer for recordings. This device samples data at 32 frames per second, and has a documented high accuracy with no more than maximum 0.3 mm difference from infrared photography measurement (115). We equipped a specialized room for the procedure, and made a standardized procedure for measurement by which all participants were examined. The subjects were adapted to darkness (at 1 lux ambient illumination) for 2 minutes before every measurement, recording one pupil at a time, starting with the left side. Sitting in a chair, they were asked to focus on a black spot on the wall 5 meters away. The device first recorded the maximum diameter of the pupil (Max), before a light flashed with180 micro Watts and 802 milliseconds duration. The following values were obtained: Minimum diameter of the pupil (Min), constriction in percent (Con=Max-Min/Max), onset of constriction in seconds (Lat), average and maximum constriction velocity in millimeter per second (ACV and MCV), average dilation velocity (ADV), and the total time in seconds to recover 75% of pupil resting size after peak constriction (T_{75}).

The pupillometric measures reflecting **sympathetic function** include: Max, ADV and T_{75}. As the T_{75} increases linearly with the amplitude of the light reflex (116), calculations were made using the T_{75}/A ratio, where A is the amplitude of the reflex in millimeters (Max-Min).

Measures reflecting **parasympathetic function** include: Con, MCV and ACV.

6.8 Measurement of the luminal diameter of the superficial temporal artery

For ultrasound measurement of the superficial temporal artery, we used a high resolution Vivid Cardiovascular Ultrasound Systems (Vivid 7, GE Medical Systems, Little Chalfont, UK). The participants were placed in a supine position, and the main trunk of the superficial temporal artery was located by palpation just in front of the ear in the meato-orbittal line. A wide band (4.7 13 MHz) linear 1.25D matrix array transducer was oriented parallel to the artery and a longitudinal section of the main trunk visualized. From a 0.5 cm segment, three diameter measures were obtained (from intima to intima), and the average diameter was used as the reference diameter of the artery. The measurement was then repeated on the contralateral side.

6.9 Measurement of retinal arteriolar and venular diameter

Both pupils were dilated with one drop of Tropicamide 0.5% (Chauvin Pharmaceuticals Ltd. Kingston upon Thames, Surrey, England), and an FF450 plus IR Fundus Camera (Carl Zeiss Meditec, Jena, Germany) captured optic nerve centered retinal photos of both eyes. Retinal vascular diameters were measured computer-assisted with IVAN, the updated version of Retinal Analysis software (University of Wisconsin, Madison, USA) (117). All vessels with a diameter of more than 35-40 µm, coursing through the retina within one-half to one disc diameter from the optic disc margin, were measured. The six largest of each vessel type were summarized as the central retinal artery equivalent (CRAE) and the central retinal vein equivalent (CRVE) (118). The protocol for grader-interaction on the automated measures was in accordance with previously validated protocols (117) with minor modifications according to the Retinal Vascular Imaging Centre (RetVIC) (Centre for Eye Research Australia, University of Melbourne, Australia).

6.10 Statistical analysis

Data were analyzed using the SPSS software package for Windows version 18.0, 20 and 21 (SPPS Inc., Chicago, IL, USA). All p values were two-tailed, and a significance level of 0.05 was used for all analysis. In paper 1, chi-

square tests were used for comparing frequencies, and independent t-tests for comparing means. In paper 2, a chi-square test was used to compare frequencies of genotypes and chronotypes, whereas the association between genotype and MEQ or PSQI scores was tested in a multiple linear regression model, adjusting for age, gender and shift work.

In paper 3, the superficial temporal artery and retinal vessel caliber measurements were analyzed with a paired samples t-test, comparing the headache affected side with the asymptomatic side in each patient. Measurements of the pupillary light reflex by pupillometry were analyzed both in a repeated measures analysis of variance (ANOVA) and in an independent samples t-test. In the repeated measures ANOVA, side was set as the within-subjects factor (affected vs. not affected side in patients, right vs. left side in controls), and patients vs. controls was set as the between-subjects factor. In the independent t-tests, both affected and not affected side in CH patients were tested against the means of left and right side in controls.

7 Summary of results

7.1 Paper 1

196 patients were identified. Seventy patients were included in the analysis, 58 men and 12 women (Figure 4). Mean age was 49.3 years (SD ± 13.8). Mean age of CH onset was 32.5 years (SD ± 13.4), and mean time to diagnosis was 5.8 years (SD ± 6.8). The majority of patients (54%) had ≥ three CH attacks per day, and one third of patients (36%) had ≥ two cluster bouts per year. For demographics and clinical characteristics, please see paper 1.

Of the final 70 participants, 31 (44%) reported that their CH bouts came at regular intervals of the year. February was the most frequent month of onset, followed by October and November. Twenty-six responders (37%) said that their bouts came at specific seasons, mostly spring (20%) and autumn (13%) (Figure 5). CH attacks came at fixed times during the day in 41 responders (58.5%), with the most frequently cited interval between 12 and 4 a.m. (Figure 6). Fifty-six responders (80%) often or always had CH attacks during sleep. Sleep was reported as the most frequent trigger of attacks (48.5%), followed by bright light (41.5%), lying flat (38.5%), alcohol (31.5%) and lack of sleep (18.5%).

Twenty-eight of the seventy participants (40%) met the DSM IV criteria for chronic insomnia. The insomniacs reported shorter time from onset of symptoms until diagnosis (3.9 vs. 7.1 years, p=0.050) and significantly longer lasting CH bouts (8.7 vs. 5.1 weeks, p=0.022) than the non-insomniacs. About one third of the insomnia-patients (35.7%) attributed their insomnia to CH. There was no difference in gender, age, self-reported chronotype (night owls vs. morning larks), periodicity of headache, comorbidity or the frequency of receiving social benefits between patients with and without insomnia, but there were significantly more shift workers among the insomniacs (60.5% vs. 39%, p=0.034). Sleep, or the lack of it, was not a more frequent trigger of attacks in the insomnia group.

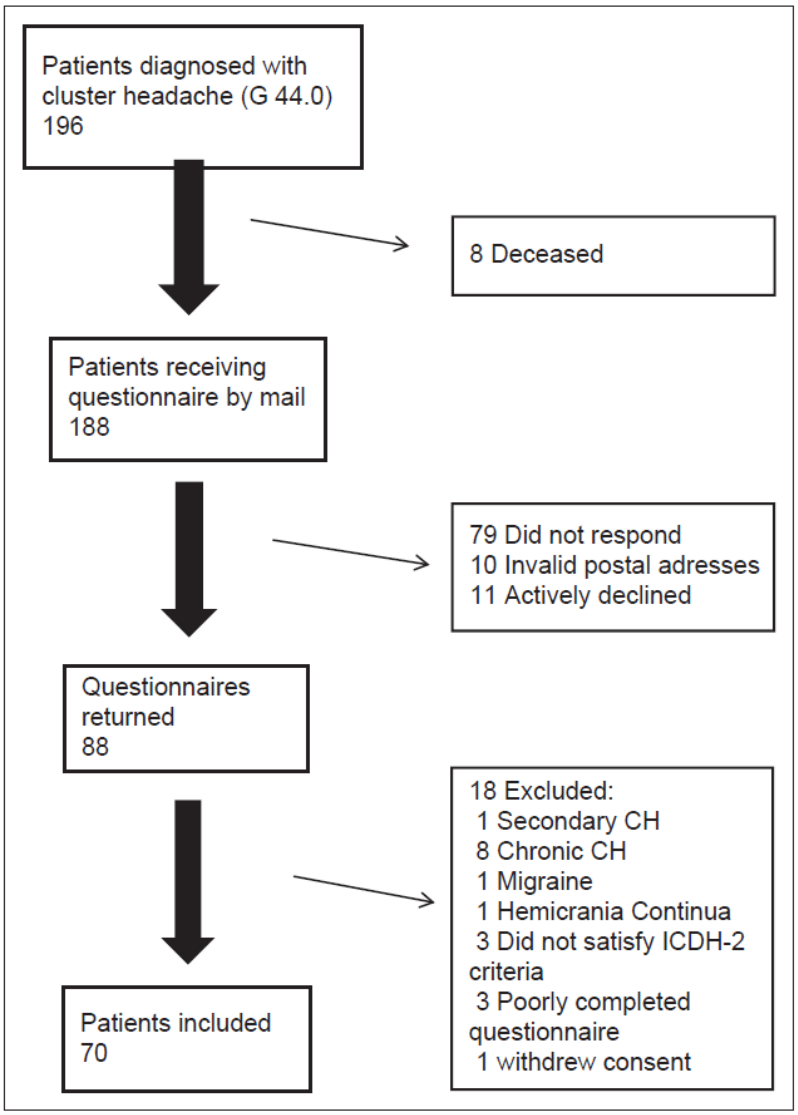

Figure 4: Flow chart.

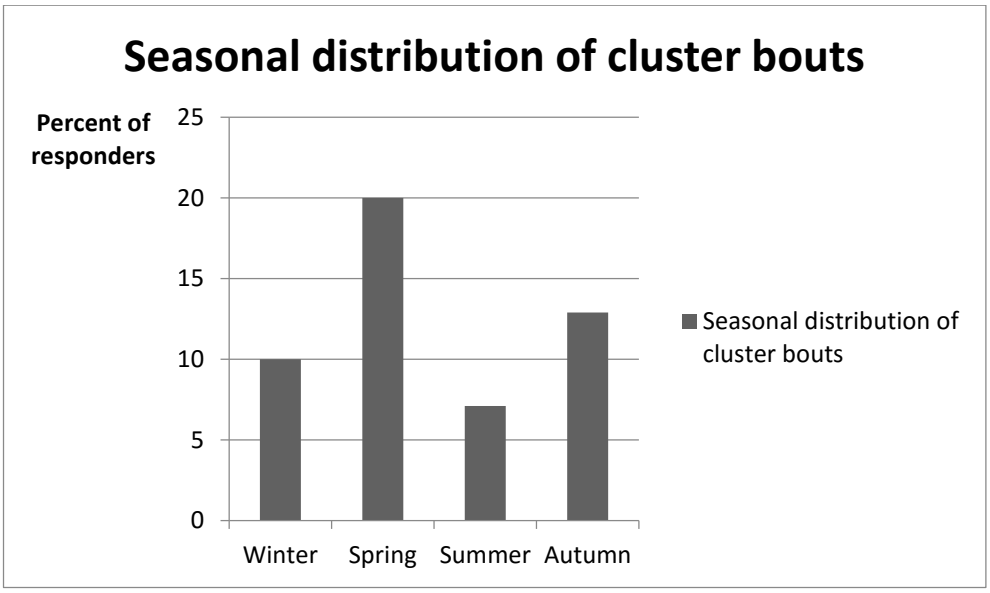

Figure 5: Seasonal distribution of CH bouts in 70 Arctic CH patients.

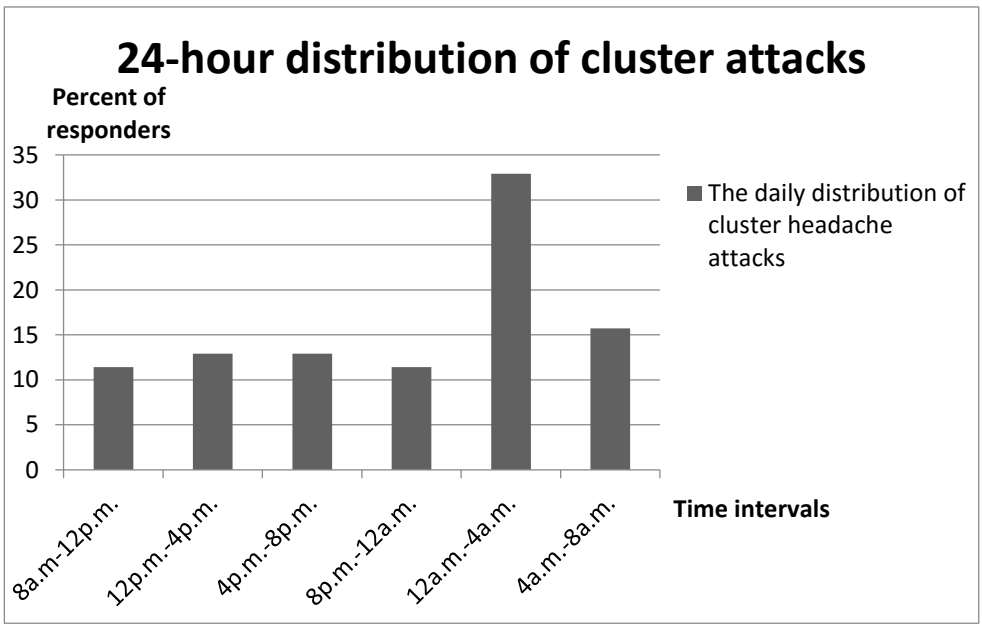

Figure 6: Daily distribution of CH attacks in 70 Arctic CH patients.

Of the 45 responders currently working, 22 (49%) were shift workers, and of the total study population, 33 (47%) reported current or previous shift work. As noted, there was an association between shift work and insomnia. Previous and current shift workers were significantly more likely to see lack of sleep as a CH attack trigger than daytime workers (10 vs. 1, p=0.008).

7.2 Paper 2

Genetic analysis of the *PER3* VNTR polymorphism was performed in 149 CH patients (109 men and 40 women, mean age 54.1 years, SD±14.0). The genotype distribution was as follows: *PER3* 4/4: 45%, *PER3* 4/5: 43.5%, and *PER3* 5/5: 11.5%. Compared to 432 healthy controls, there was no difference in *PER3* VNTR polymorphism (p=0.992).

Seventy-four CH patients completed all three questionnaires (the MEQ, PSQI and SWI) and were included in subgroup analysis. There were 54 men and 20 women, with a mean age of 52.3 years (SD ± 13.4). The mean MEQ-score was 51.4 (SD ± 10.5), and based on individual values we found the following chronotype distribution: 38 (51%) evening type, 27 (37%) intermediate type, and nine (12%) morning type. There was no difference in chronotype distribution when compared to a previously published Danish CH population or their healthy controls (p=0.595) (29).

The mean PSQI was 8.4 (SD ± 4.6), and 44 CH patients (60%) were defined as bad sleepers (PSQI > 5). Of the 49 patients currently employed, 25 (51%) were currently shift workers, and another nine (18%) had previously worked shift. Of the total group of 76 responders, 40 (52%) were current or previous shift workers.

There was no association between shift work employment and PSQI score (p=0.343). We found no association between *PER3* VNTR polymorphism and chronotype (p=0.352). Multiple linear regression adjusting for age, gender and shift work showed no association between *PER3* genotype and MEQ or PSQI scores.

7.3 Paper 3

Thirty patients were included in the analysis: 27 men and three women with a mean age of 50.2 years (SD ± 13.6). Thirty healthy controls were included for dynamic pupillometry (27 men and three women, mean age 50.3 years, SD ± 13.6).

When comparing the headache-affected side to the asymptomatic side in CH patients, pupillometry showed a significantly reduced average constriction velocity of the pupil on the headache-affected side (p=0.007). When

comparing CH patients to healthy controls, we found a statistically significant reduction in all measures of parasympathetic function on both eyes (average constriction velocity, mean constriction velocity, constriction in percent and constriction latency). The differences were more pronounced on the headache-affected side.

We found no differences in the superficial temporal artery diameters between the headache-affected and the asymptomatic side (p=0.525).

The mean central retinal vein equivalent (CRVE) on the headache-affected side was significantly smaller than on the asymptomatic side (221.10 µm vs. 226,60 µm, p=0.043). The mean central retinal artery equivalent (CRAE) was also slightly smaller on the headache-affected side, but this was not statistically significant (147.54 µm vs. 150.22 µm, p=0.111).

8 Methodological considerations

8.1 External validity- sampling bias

CH is a relatively rare disease, and research on rare diseases is often hampered by small sample sizes. This poses a threat to the external validity of the studies, as the results from the study population may not be representative to all CH patients. External validity refers to what extent the results of a study can be generalized and valid to people beyond the study population, which in our case would mean beyond CH patients living in the North of Norway.

In the first study, we presumed that most CH patients would be referred to secondary care at some point, and that our chosen method of recruitment would identify the vast majority of patients in our region. We identified 196 patients, which would give a prevalence of 0.04% in North Norway. This is lower than expected. We have no reason to believe that the prevalence of CH is lower in this region than in other geographical areas, although it is possible. Five of the 88 responders even appeared to have been wrongly diagnosed, indicating a potential misclassification bias. Nevertheless, we probably missed a proportion of patients, and there may be a sampling bias in our material. A sampling bias is by most researchers classified as a subtype of selection bias, in which a sample is collected in such a way that some members of the intended population are less likely to be included than others. A distinction between sampling and selection bias is that while selection bias is usually regarded as a problem for the internal validity, the sampling bias may affect the external validity and undermine the generalizability of the study results.

The patients identified in paper 1 had all been in contact with secondary health care during the 11 years defined in the study. This could either mean that they are more affected by their headache than the ones we potentially missed, and forced to seek help for it, or that they are less affected by their headache, and therefore more able to take action in their suffering. Alternatively, patients diagnosed before 2000 did not make contact because of previous experiences with the healthcare system, either good or bad.

8.2 Internal validity – selection bias

The internal validity of a study refers to how valid the results are for the actual study population. The internal validity is usually not affected by random errors, but will be threatened by systematic errors such as selection bias, information bias and confounding. In addition, the internal validity may be reduced by the use of incorrect statistical methods and effect sizes. The risk of a selection bias in our first study was reinforced by the low response rate of only 49% (88/178). The response rate in study 2 was also low at 53% (80/149). Studies show that response rates in surveys based on postal questionnaires are generally low, sometimes as low as 20% (119). Nevertheless, we may have a volunteer bias in our population. Usually, the sickest patients are less likely to participate in studies. This is called the *healthy user bias*.

When comparing the responders to the non-responders in paper 1, we found no difference in age, gender or shift work occupation between the groups. In addition, the general demographic and clinical findings in our studies are very much in accordance with previous published studies on other CH populations (3, 6-8, 29). We therefore believe that, in spite of low response rates, the participants included in the studies are representable to the CH population in the region.

8.2 Internal validity - recall bias

In addition to a selection bias, our data may also be affected by a recall bias. This is a classic form of information bias, where the participants in retrospective studies may recall events differently in different groups. Their recollection may be influenced by the purpose of the study, or by the nature of the questions asked. Our questionnaire asked about periodicity of headache and sleep disturbances in retrospect, and simply by asking these questions we risk to overestimate the frequency of both. A prospective design would have been the best way to assess both periodicity and sleep disturbances. Unfortunately, prospective designs are quite difficult to achieve in CH, as most of the patients only have headache bouts a few months every year.

8.3 Statistical power in genetic studies

Low statistical power is an important threat to the statistical validity of a study, and this is the greatest limitation to the genetic association analysis in paper 2. Power calculations in genetic association studies rely heavily on the effect size that the candidate gene exerts on the disease or trait studied. In this case, the effect size is unknown, and calculating power must therefore be based on presumptions. It is generally accepted that common complex diseases are unlikely to be caused by a single locus of large effect, and that genotypic relative risks are likely to be in the range of 1-1.5 (120). CH is not a common disease, but it is most probably of complex genetic origin, and we should not presume the effect of a single allele to be too large. If we use the Purcell Genetic Power Calculator (121) and assume an additive model, a CH prevalence of 0.2%, a frequency of the *PER3* 5-allele of 0.33, and a relative risk of 1.5 for the 5/5 genotype to have CH compared to the 4/4 genotype, we would find a statistical power of 46% in our study. Raising the presumed relative risk of the 5/5 genotype to 2.0 increases the power to 89%. As the former seems a more realistic presumption, our study is most probably underpowered. This means that we are at risk of not finding an effect in our study, when in reality there is an effect (type II error).

Studies with low statistical power are regarded as an increasing problem in neuroscience (122). The low power not only reduces the chance of detecting a true effect, but also reduces the likelihood that a statistically significant result reflects a true effect. In other words, low power produces low positive predictive values. In addition, when a true association is detected, the magnitude of the effect is often exaggerated, making the risk of not confirming the association in replication studies large. This is called the “winners curse”, and is likely to occur in situations where a threshold, such as statistical significance, is used to define a positive finding. A meta-analysis of neuroscience articles published in 2011 indicated a median statistical power of 21% (122). To compensate for the general lack of power in studies of genetics, it is recommended to set the level of significance to 0.01, instead of the usual 0.05. This will reduce the risk of making a type I error, but it also

increases the risk of a type II error (123). We used a significance level of 0.05 in our paper, but the results were still negative.

The limited access to patients makes large genetic studies on CH difficult to conduct. However, genetic studies are important to develop a better understanding of the pathophysiology even in rare headache disorders, and if strict rules of statistical power were to be followed, very little research would be done on these conditions. We therefore believe that despite its small sample size, or study does add to the knowledge of CH pathophysiology.

9 Ethical aspects

The research protocols for each of the three projects were reviewed and approved by the Regional Ethics Committee of North Norway before inclusion of patients. The patient's privacy, physical and mental integrity, personality as well as confidentiality was respected and protected through all three studies, in accordance with the World Medical Association Declaration of Helsinki (124). Participation in all projects required a written, informed consent. The subjects could at any point withdraw the consent.

The use of biobanks in medical research requires special attention to ethical considerations. In Norway, biobanks used for research are regulated by the Health Research Act of 2008 (www.lovdata.no/dokumen/NL/lov/2008-06-20-44). The Health Research Act defines who may initiate and terminate a biobank, how the specimens should be stored and treated, who should have access to the biobank, and how to transfer specimens from one country to another. The ethical debate concerning the use of biobanks have increased proportionally with the number of biobanks the last years (125). Three topics in particular have been frequently discussed (126): 1) What is an adequate informed consent in a biobank setting? Should the participant give a general consent that includes all possible projects that might occur in an unpredictable future, or should he be asked for consent every time a new project is initiated? 2) How do you secure confidentiality for all participants, data security and facilitate research at the same time? 3) How do you handle research results or incidental findings that might be of interest to the participants or their genetic relatives?

In our second study, we used blood samples from an existing biobank, in which the majority of the donators had given their consent and samples ignorant of the fact that it would be used for a study on clock gene polymorphism in the future. They were only made aware of our study when they received a follow-up invitation to complete the three questionnaires after the blood samples were tested. They could decline participation in the questionnaire-based part of the project, but they could not refuse the use of their blood to genetic testing. When being asked to contribute to a biobank the participant should be informed that this might happen, but the rapid

increase of biotechnological research has made it virtually impossible to inform the patients of every thinkable use of their donations, putting the concept of *informed consent* to the test. The informed consent has been the foundation of research ethics since the Nürenberg process following World War II. In the biotechnological area, this ideal is often put up against the duty of the researcher to ensure that the participants' donations come to the best possible use, giving as much new and valid knowledge as possible.

Genetic information is special in the sense that it may be of importance not only to the donator himself, but also to his biological relatives. We did not offer our patients to be informed of the results from the genetic analysis. The *PER3* VNTR polymorphism is not linked to any disease or pathological processes that we know of today and the information would be of little clinical importance to the patient. There is consensus that individual feedback on results only should be done in cases where incidental findings could have serious consequences for the donator's life, health or reproductive abilities, and where the condition is potentially curable or treatable (127). Otherwise, return of results could contribute to "the therapeutic misconception"; a phenomenon in which the research participator believes that he will benefit personally from participation, even though it is explicitly explained in the information given that the results only will be of benefit to future patients, or to science as such.

10 Discussion

10.1 Chronobiology in cluster headache

10.1.1 External light cues

The periodicity of headache attacks and bouts in our Norwegian Arctic population is very similar to the periodicity reported in previously published CH populations from other parts of the world (3, 7, 8, 29). The patients in our study live north of the Arctic Circle, a region with extreme differences in daylight throughout the year, ranging from 24 hours daylight in the middle of the summer, to 24 hours darkness in the middle of the winter. As external light is the most prominent zeitgeber to the human biological clock, this makes it a particularly interesting location for studies on chronobiology.

If the theory of circadian misalignment in CH is true, and changes in external daylight is the key external zeitgeber that causes this misalignment, one might expect more CH patients reporting on periodicity in the Arctic, or even a higher incidence of the disease. This is not the case. It is of course possible that the people living in the region through generations have been selected, or adapted, to the special light conditions. However, in our modern world the effect of external light cues is probably reduced by indoor illumination and the activities of social life. Studies of seasonal variation in human birthrates show that the seasonal trends seen in many populations weakened markedly after the industrialization in the 1930s, when people started working indoors (128). Likewise, chronotypes correlate with how much time a person spend outdoors, progressively advancing by more than an hour when people spend up to two hours per day in natural daylight (129). Beyond two hours, the chronotype changes very little. In consequence, the net effect of the sun may end up the same in our Arctic region as in the rest of the industrialized world, because we all lead similar lives.

Nevertheless, humans living indoors in urban cities still show weak signs of seasonal variation in melatonin secretion and reproduction rates (130, 131), implying that the external light affects them. Other external factors such as air temperature and humidity also varies across the seasons, and air temperature is probably the second most important external zeitgeber

affecting the biological clock (128). A recent study from Taiwan showed that changes in temperature following a warm or cold period were associated to the occurrence of CH bouts (132). Most of our patients reported cluster bouts in the spring or autumn, which could support both a theory of rapid day-to-day changes in daylight hours, or changes in temperature, as the predisposing event. Of note, bright light was the second most frequent trigger of CH attacks in our cohort. Researchers on chronobiology have suggested that the sensitivity to light may differ between individuals (74), which may explain why some CH patients show a clear periodic occurrence and others not. It may be that predisposed individuals are unable to adapt completely to the external time cues if they continue to change drastically over a longer period, as they do in the spring and autumn. Hence, we cannot rule out circadian or seasonal misalignment with external light or other zeitgebers as a predisposing factor for facilitating CH.

10.1.2.Shift work

Shift work occupation is another common cause of circadian misalignment. We are the first to assess the frequency of shift work occupation in CH patients. Manzoni et al. found that CH patients often had occupations with a high degree of responsibility, such as manager, municipal policeman or businessman, but he did not register shift work as such (133). He also found an increasing incidence of CH among women from 1955 to 1995, and associated this to an increase of female smokers and a higher employment rate (134). Sjöstrand et al. found that significantly more CH patients worked full time compared to their non-affected relatives (135).

Of the responders currently working, we found 49% shift workers in the first study, and 51% in the second study. Of all the patients included, about 50% reported shift work in both studies. It should be pointed out that some of the patients participated in both studies. In 2012, 33% of the adult Norwegian work force worked outside regular office hours (Monday – Friday 08.00-18.00), and 24% worked regularly rotating shifts including nights and weekends (136). Unfortunately, none of our studies were able to pinpoint which category the CH patients belonged to, but one could argue that the phrase “shift work” in Norwegian usually means rotating shifts. When

comparing different gender and age groups to the general population, the number of shift workers among the CH patients still seems high (Paper 1). It is well known that shift work over time may lead to health problems and sleep disturbances (104). In accordance with this, the shift workers in paper 1 reported significantly more sleep disturbances than the daytime workers did. However, in paper 2 there was no association between shift work employment and PSQI score.

The shift workers reported in paper 1 were more inclined to see lack of sleep as a trigger for attacks than the daytime workers. However, the patients who suffered from insomnia did not see lack of sleep as a trigger for attacks more often than those not suffering from insomnia. This could imply that it is not merely being awake at night that triggers attacks, but also being physically and mentally active, working at hours when the body is programmed to rest and sleep. It would be interesting to know when the shift workers experience their attacks – do they occur immediately after or during shifts, or does shift work cause sleep disturbances that further initiate attacks? If shift work is a trigger or risk factor for developing the disease, this could explain the high prevalence of shift workers in the CH population. However, it could also be the other way around; the CH patients choose to work shift because it suits their inherent rhythm better. The high frequency of shift workers may be specific to our population and should be confirmed in other CH populations.

10.1.3 Sleep disturbances

We found a high frequency of sleep disturbances among the CH patients both in study 1 and 2. In the first study, 40% of responders met the DSM IV criteria of chronic insomnia. There was a significant association to shift work employment, which made shift work a possible confounding factor. However, there was no association between shift work and PSQI score in the second study. The mean PSQI score was high (mean 8.4 ± 4.6), and 60% of patients was defined as bad sleepers with a PSQI score above five. This seems like a high score even when compared with other headache populations. For example, in a study from 2009, the mean PSQI was 5.9 ± 3.0 in migraine patients suffering from ≥ eight migraine days per month (137).

The prevalence of sleep disturbances is probably a bit higher in the Arctic regions because of the special light conditions. The prevalence of insomnia in the adult general population of Norway is estimated to 11.7% (138), and in mid-Norway 13.5% (139). In the high North, 17.4% of the adult population report sleep disturbances linked to a specific season, most often during the polar night (70%) (140). In a study of female migraine patients in North Norway, just under 30% suffered from chronic insomnia according to the DSM IV criteria (141). In conclusion, the prevalence of sleep disturbances is CH is high, even when compared to other headache populations in the same region. One third of the patients suffering from insomnia in paper 1 attributed their sleep disturbances to cluster headache, confirming previous studies suggesting that the majority of CH patients do not have sleep problems simply because they are woken up by nocturnal headache attacks (29).

Recently, a large controlled study has assessed sleep quality in CH for the first time using polysomnography (142). In this study, the authors found no temporal relationship between CH attacks and specific sleep stages, but CH patients in bout had a reduced percentage of REM sleep, longer REM latency and fewer arousals compared to the healthy controls. They could not confirm a higher frequency of sleep disordered breathing in the CH group as previous studies have implied, but pointed out that certain risk factors such as smoking and male gender are frequent in the CH population, which may aggravate an existing disorder.

Nocturnal sleep was the single most important trigger of attacks in our study, regardless of the presence of sleep disturbances. This seems to add to the proposed theory that cluster attacks are elicited in a state of hypoarousability (27). The balance between sympathetic and parasympathetic dominance in healthy individuals differ between REM and NREM sleep stages (73). In addition, there is a transient decrease in sympathetic tone during the night, which is reflected in a period of reduced blood pressure and heart rate (143). This “dipping” is found even in individuals kept awake and in supine position, and seem to be a result of circadian oscillations in cardiovascular tone. As we have seen, most CH attacks occur late at night or during the early morning hours, seemingly coinciding with the dip in sympathetic tone.

The circadian period and sleep homeostasis are more interconnected at the molecular level than previously thought (144). The traditional model of sleep regulation depicts sleep timing as the result of two independent processes; the circadian oscillation of the SCN, and the sleep homeostasis that tracks sleep need. Sleep need and the ability to initiate sleep build up during wakefulness and decrease during sleep. Slow oscillations of the EEG in NREM sleep, quantified as *delta power*, vary as a function of time awake and asleep, and are used as a reliable measure of sleep need. EEG studies of *PER3* 5/5 and 4/4 homozygote individuals show that the *PER3* 5/5 genotypes have higher delta power during sleep, and higher theta and alpha activity during wakefulness, compared to *PER3* 4/4 genotypes (79). This reflects a greater buildup of sleep need in the 5/5 homozygotes. However, the circadian rhythms of melatonin, cortisol and peripheral *PER3* mRNA expression are not affected. This shows that clock genes may affect sleep homeostasis directly, without disturbing the circadian period. In the same manner, *PER3* genotype has been shown to affect the sympathovagal balance in cardiac control during sleep (145). This direct relationship between the clock genes, sleep and autonomic tone is particularly interesting in view of CH, where sleep disturbances and autonomic dysfunction are common features.

10.1.4 The clock

The *PER3* gene tested in paper 2 is the second core clock gene to be sequenced in a CH population, after the T3111C *CLOCK* gene polymorphism. Neither of the genes showed any association between gene polymorphism and CH. However, when taking into account the complexity of the biological clock and its interactions, the lack of association between two single gene loci and a trait does not disprove an actual link. In fact, a single candidate gene association study seems to be a too simplistic approach for assessing genetic association in this setting, although the gene is selected for plausible reasons. In addition, lack of association could be due to small sample sizes. Larger studies, including both more patients and multiple genes, should be sought.

Chronotype may be regarded as an observable expression of clock period and function (phenotype). Although 51% evening types in our CH population seems high, we found no certain difference in chronotype distribution between our patients and the Danish CH patients, nor their healthy controls. As mentioned, the tendency toward evening type seems to increase with the distance from the Equator, which may explain why there are more evening types in our population (99). An age-adjusted control group at the same latitude could would have increased the validity of our findings. However, the results are in accordance with the Danish study who found no difference in chronotype between CH patients and healthy controls (29), and as discussed in section 10.1.1, social and demographic factors may mask a true difference in circadian period.

In conclusion, we have not found definite evidence of clock dysfunction in our CH population, but this does not mean that the clock is not involved in CH pathophysiology. The periodicity of attacks and high frequency of shift work and sleep disturbances still point at a connection. The question is where to look further: 1) The problem may lie within the SCN itself, where a disturbance in clock function causes irregular or contradictory signals, or failure to synchronize with external zeitgebers. 2) The problem may be located in the DMH, which has the difficult task of orchestrating the rhythmic expression of the SCN to the various influx from the rest of the body. 3) The problem may be abnormal processing in other hypothalamic nuclei involved in pain and/or autonomic function.

10.2 The cranial autonomic nervous system in cluster headache

In paper 3, we report a statistically significant attenuation of the pupillary light reflex in CH patients on both eyes compared with healthy controls. All the pupillometric measures of parasympathetic activity were reduced, and the reduction was significantly more pronounced on the headache-affected side when compared to the asymptomatic side. In addition, we found significantly smaller mean CRVE on the headache side compared to the asymptomatic side.

10.2.1 Retinal vessels in cluster headache

The vessels of the retina are autoregulated, and not under direct control by the autonomous nervous system, as are the choroidal vessels and the ophthalmic arteries (146). The central retinal artery is richly innervated by both sympathetic and parasympathetic fibers up to the lamina cribrosa (147), but no autonomous nerve fibers have been documented inside the retina. The overall goal for the autoregulation is to secure optimal blood flow in to the retinal vascular bed under different conditions of perfusion pressure and metabolic needs. This is achieved by arteriolar caliber changes and capillary recruitment, involving myogenic responses, metabolic signals and endothelial function. In addition, both α- and β-adrenergic, muscarinic and angiotensine-II receptors have been located in retinal vessels (148-150).

In a study of ophthalmic artery blood flow velocity in CH patients during Valsalva maneuver, the researchers found an ipsilateral tonic vasodilatory state during cluster bout and a state of increased peripheral vascular reactivity in remission phase (151). According to the authors, the findings reflected a low resistance vascular bed on the headache side in remission phase, with enhanced vasodilatory responses to stimuli. Another study found reduced intraocular pressure (IOP) and ocular pulsatile flow in CH remission phase compared to controls (152), consistent with reduced ocular blood flow, possibly caused by increased pre-ocular vascular resistance, either in the ophthalmic or internal carotid arteries. In general, the mean ocular perfusion pressure equals the mean blood pressure of the ophthalmic artery minus the pressure of the veins leaving the eye, and the pressure of the veins is very close to the IOP. Hence, small retinal veins may reflect a reduced IOP.

Studies on retinal vessels in CH are scarce, but a recent study of retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) found a significant thinning of the RNFL in the temporal areas on both eyes of CH patients compared to healthy controls (152, 153). In the nasal area, they found the RNFL to be thicker. Reduced RNFL have also been reported in migraine patients (154). As the thickness of the RNFL measured by OCT seems to correlate with the main branches of the retinal arterioles and venules (155), the authors explain their findings as a result of

inter-attack retinal vessel vasodilation on the nasal side, and possibly oxygen-induced vasoconstriction on the temporal side. They do not theorize on what could cause the alleged vasodilation in the nasal areas, but point out that the vessels have more branches in this area.

None of our patients used oxygen, and we do not have information on the vessel caliber in the different regions of the retina in our study. Both retinal arterioles and venules were smaller on the symptomatic side, although not statistically significant for the arterioles. As the retinal vessels are autoregulated, the findings of our study are most compatible with a reduced total blood flow to the eye on the headache side, relative to the asymptomatic side. What could cause such a flow reduction is unclear. Repeated parasympathetic storms and vasodilation during attacks may produce local vasoactive substances or environmental changes that continue to affect retinal vessels even in the remission phase. Alternatively, the reduced blood flow may represent an altered pre-ocular autonomic tone, either a relative increase in upstream sympathetically derived vasoconstriction, or a relative decrease in upstream parasympathetically derived vasodilation. As the pupillometry showed no signs of oculosympathetic dysfunction, the former seems less likely. We therefore suggest that our findings imply a reduced parasympathetic pre-ocular vascular tone on the headache-affected side relative to the asymptomatic side in CH patients.

10.2.2 The pupillary light reflex in cluster headache

Attenuated pupillary light reflexes compared to healthy controls have also been documented in migraine patients, measured with pupillometry within 48 hours of spontaneous migraine attacks (156). However, when examined again one week later, there were no differences in pupillary light reflexes. Hence, it is possible that attenuated pupillary light reflexes are a general and transient phenomenon following episodic headache. We know that the time lapse from last attack was at least four weeks in our patients, so it would seem like a more permanent finding in our case. Our results seem contradictory to previous studies, as most of them found evidence of oculosympathetic dysfunction. However, most of these studies were carried out in the pain-free interval of the cluster bout, which most probably is a

different autonomic state than the remission phase. In addition, most studies used pharmacological tests to measure pupillary responses, which may be a more potent trigger of sympathetic responses than light. Drummond et al. recorded pupillary responses to light in 30 CH patients immediately before, during, and within one hour after attack, and found increased pupillary constriction velocity and decreased dilation velocity consistent with increased parasympathetic and decreased sympathetic activity (157). The increased parasympathetic activity was less pronounced one hour after the attack. Our findings may represent a chronic downregulation of parasympathetic output in remission phase, possibly to avoid further attacks.

10.2.3 The locus coeruleus

We know that the locus coeruleus (LC) plays an important role in the pupillary control, both by inhibiting parasympathetic and stimulating sympathetic output to the eye (69). The LC attenuates the pupillary light response by inhibiting the EWN, and it enhances oculosympathetic outflow by excitatory projections to preganglionic sympathetic neurons (Figure 3). Noxious stimuli dilate the pupils without affecting the light reflex (reflex dilation), most probably by activation of the LC. However, anxiety and conditioned fear, in which a neutral stimulus produces anticipation of a noxious stimulus, cause both reflex dilation and attenuation of the light reflex. This suggests activation of both sympathetic and parasympathetic premotor neurons by the LC.

The LC is the main noradrenergic nucleus of the brain. It is connected to a number of regions in the hypothalamus and forebrain, and is involved in a number of vital functions such as wakefulness, responses to stress, regulation of emotions and modulation of pain. The LC densely innervates the neurons of the trigeminal sensory nucleus (Figure 2), and activation of the LC inhibits the neurons of the trigeminal nucleus involved in pain perception (158). It is possible that the LC may be involved in terminating the pain in headache attacks. In a recent neuroimaging study, migraine patients were shown to have increased hypothalamic functional connectivity with a number of brain regions involved in autonomic functions, including the LC (159). What is more, the LC also inhibits the parasympathetic outflow of the

SSN, which is responsible for the CH attack-related cranial vasodilation (158). In other words, activation of LC may explain both our main findings reported in paper 3: a reduced pupillary light reflex caused by inhibition of the EWN, and reduced vasodilation of ipsilateral pre-ocular arteries, caused by inhibition of the rostral, ventrolateral region of the SSN.

10.2.4 The paraventricular nucleus

The PVN is another important hypothalamic nucleus involved in pupillary control. When light hits the retina, the SCN is activated and inhibits the sympathetic premotor neurons of the PVN, which is the main descending autonomous nucleus of the hypothalamus (Figure 2) (158). The activation results in a reduced oculosympathetic outflow from the PVN, and the pupils constrict. At the same time, connections to the LC activate the premotor sympathetic neurons of the LC, working to redilate the pupils. The PVN is, like the LC, also involved in pain modulation, and a recent animal study showed that the PVN sends descending projections to the caudal spinal trigeminal nucleus, which receives trigeminal sensory input (160). These projections were bilateral, but with a clear ipsilateral predominance, and most of them projected to the ophthalmic area (V1) of the trigeminal nucleus. Stimulation of PVN reduces pain, and lesions of the PVN facilitates pain at the spinal level (161), and there is reason to believe that it modulates trigeminal pain the same way.

10.3 A central theory emerges

We propose a central hypothesis for CH pathophysiology involving both the SCN, LC and the PVN. We know that activation of the SCN will inhibit the premotor sympathetic activity of the PVN, causing reduced oculosympathetic outflow to the pupils. In addition, the downregulation of the PVN may result in reduced inhibition of incoming trigeminal somatosensory inflow from the spinal trigeminal nucleus, causing a bilateral, but predominantly ipsilateral, disposition to trigeminal pain. In other words, we propose that the PVN may be involved in the initiation of attacks, introducing pain and central oculosympathetic dysfunction.

Further, the trigeminoparasympathetic reflex is activated, causing parasympathetic efflux and cerebral vasodilation. The following unilateral

vasodilation of the ICA through the osseous carotid canal may reinforce the subtle central oculosympathetic dysfunction, creating an ipsilateral third-order oculosympathetic dysfunction on top of an already reduced central sympathetic outflow from the PVN. This may explain why minor changes in the vessel wall could cause a Horner-like syndrome, and why results from pupillometric studies have been conflicting.

Finally, the attacks may be terminated by the LC, which reduces trigeminal firing, inhibits cranial parasympathetic output and increases oculosympathetic output. In conclusion, we hypothesize that CH represents a condition where a permanent or transient downregulation of the PVN activity is compensated for by an upregulation of the LC activity.

This hypothesis is of course highly speculative, and based on observations made in very different settings. To test the hypothesis one would have to observe the different nuclei simultaneously in the same context, preferably in an animal model. However, it is compatible with previous pathophysiological hypotheses, including the theory of hypoarousability.

11 Conclusions

This thesis shows that CH patients living in the Arctic region of Norway exhibit the same periodicity of headache as CH populations in other geographical areas. It also shows that a high share of CH patients suffer from sleep disturbances, confirming insomnia as an integral part of the CH clinical spectrum. Sleep disturbances may be even more frequent in CH than in other primary headaches. Sleep is the single most important trigger of headache attacks.

In addition, the frequency of shift work occupation is high in our CH population, suggesting that shift work occupation may facilitate CH in predisposed individuals. This may be caused by a circadian misalignment to the internal biological clock.

We found no difference in *PER3* clock gene VNTR polymorphisms or chronotypes in CH patients compared to controls. The SCN may still be involved in the initiation or predisposition of attacks, either by normal fluctuations in SCN that cause abnormal responses in the hypothalamic nuclei influenced by SCN activity, or by abnormal activity in the SCN itself. So far, no evidence of diverting circadian period in CH patients has been produced, measured by chronotype or clock gene polymorphism.

The autonomic nervous system may be more involved the initiation of CH attacks than previously assumed, as reduced sympathetically derived descending inhibition of nociceptive influx from the 1st branch of the trigeminal nerve may facilitate attacks. Our studies document reduced parasympathetic activity in remission phase, proving that the pathology of the disease is present even though the patient does not experience any symptoms. The results also suggest a central origin of the disease, and we propose a central theory of CH pathophysiology.

12 The need for further research

The role of the SCN in CH pathophysiology is still uncertain, and should be studied further. Future studies should focus on the intercept between the clock, sleep and the autonomous nervous system, as these all seem to be involved in CH pathology. Studies of circadian rhythmicity in CH patients should be carried out in laboratory settings, where external zeitgebers can be controlled.

Prospective studies on periodicity of headache and sleep disturbances should be sought, and fluctuations of the autonomic nervous system through the CH cycle (active bout and remission phase) should be studied. Larger, more complex studies on clock genes are warranted, studying multiple genes or even Genome Wide Association Studies.

So far, no suitable animal model has been produced in CH. A preclinical animal model of TACs has recently been proposed (162), but it remains to be proven that this model works and that it truly represents a human CH equivalent. Further endeavors to develop an animal model are welcome, as this would enable us to explore the pathophysiology of CH properly.

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Appendix

A Norwegain Cluster headache survey

SPØRRESKJEMA

Løpenummer:
(Skal ikke fylles ut)

DATO FOR UTFYLLINGEN: _____

PERSONOPPLYSNINGER

Fornavn:
Etternavn:
Fødselsdato:
Adresse:
Fylke:

JEG KAN TENKE MEG EN POLIKLINISK TIME FOR GJENNOMGANG AV MIN SYKDOM, OG EVENT. BLODPRØVE, ULTRALYDUNDERSØKELSE AV ØYNE OG PUPILLOMETRI (timen er selvsagt gratis)

□ Ja □ Nei

JEG HAR BODD I NORD-NORGE I MER ENN ETT ÅR

□ Ja □ Nei

KAN DU SENERE TENKE DEG Å REGISTRERE CLUSTER-ANFALLENE I EN HODEPINEDAGBOK SAMMENHENGENDE I 12 MÅNEDER (dersom det blir aktuelt)

□ Ja □ Nei

A. PERSONOPPLYSNINGER

---

1. SIVIL STATUS

□ Enslig □ Gift/samboer □ Enke/enkemann □ Skilt/separert

2. UTDANNELSE

Hvilken utdannelse er den høyeste du har gjennomført?

□ Grunnskole (inkludert framhaldskole, folkehøyskole)
□ Videregående skole (inkludert realskole, middelskole, yrkesskole, artium, gymnas)
□ Høyskole
□ Universitet

3. JOBB

a)
Yrke:_____ Stillingsandel i %:_____

b)
□ Tungt fysisk arbeid □ Stressende □ Verken stressende eller tungt fysisk

c)
□ Skiftarbeid □ Kun jobbing på dagtid □ Jobbet skift i mange år

4. TRYGDEYTELSER

a) Mottar du trygdeytelser nå?

□ Ja □ Nei

Hvis Ja, hvilke trygdeytelser mottar du?

□Sykepenger □Rehabiliteringspenger □Attføring □Uføretrygd □Annet

Hvis annet, hva da?.....

b) Er clusterhodepinen årsak til at du mottar trygd?

□ Ja □ Nei *Hvis Nei, hva er årsaken?*.....

5. PERSONOPPLYSNINGER

Nåværende vekt (kg).:_____ og

høyde (cm) _____

Øyefarge: □ Brun □ Grønn □ Annen farge

6. CLUSTERHODEPINE I FAMILIEN

□ Ja □ Nei *Hvis ja, hvem?* (mor, far etc..): ……

7. MIGRENE I FAMILIEN

□ Ja □ Nei *Hvis ja, hvem?* (mor, far etc..): ……

8. EGNE PLAGER

a) Alder da din clusterhodepine debuterte?: _____

b) Alder da din clusterhodepine ble diagnostisert? _____

c) Har du annen type hodepine:

□ Nei □ Migrene □ Annen type

Hvis annen type, vet du hvilken?
……..

d) Dersom du drikker noe kaldt eller spiser iskrem raskt, får du da intens kortvarig hodepine (”hjernefrys”)?

□ Nei □ Har opplevd det □ Får det ofte

Minner ”hjernefrysen” om din clusterhodepine når det gjelder smertekarakter?

□ Ja □ Nei □ Uaktuelt

e) Har du annen sykdom?

□ Hatt hjerneslag □ Bihuleplager □ Høyt blodtrykk □ Allergi □ Annen sykdom

Hvis annen sykdom, hva?:

……

9. SØVNPROBLEMER

a) Opplever du deg selv som ”en stresset type”?

□ Ja □ Nei

b) Opplever du deg selv som ”A” eller ”B” menneske?

□ A □ B □ Vet ikke

c) Har du det siste året hatt søvnproblemer?

□ Ja □ Nei

Hvis ja, skyldes søvnproblemene dine clusterhodepinen?

□ Ja □ Nei □ Vet ikke

d) Har du minst 3 ganger per uke, og i mer enn 1 måned, hatt problemer med å sovne inn og/eller vansker med å holde søvnen ved like?

□ Ja □ Nei

e) Medfører søvnproblemene tretthet eller prestasjonsproblemer på dagen?

□ Ja □ Nei

f) Er søvnproblemene dine mindre eller større i årets lyse måneder?

□ Ingen forskjell □ Mindre □ Større □ Ikke relevant

g) Hender det at du våkner om natten av clusterhodepinen?

□ Alle anfall □ Over 50% av anfallene □ Under 50% av anfallene □ Sjelden □ Aldri

10. STIMULANTIA

a) Røyker du?: □ Nei □ Ja □ Gjorde det tidligere

b) Hvor mye alkohol tror du at du drikker i forhold til dine jevnaldrende:

□ Mindre enn gjennomsnittet
□ Gjennomsnittlig
□ Mer enn gjennomsnittet
□ Drikker ikke alkohol

c) Har du noen gang forsøkt narkotiske stoffer?: □ Nei □ Ja

B. ANFALLSBESKRIVELSE OG BEHANDLING

---

1. UTLØSENDE FAKTORER

a) I perioder med clusterhodepine, utløses da anfall av alkohol?

□ Nei □ Ja □ Vet ikke

b) I perioder med clusterhodepine, utløses da anfall av søvn?

□ Nei □ Ja □ Vet ikke

c) I perioder med clusterhodepine, utløses da anfall av liggende stilling?

□ Nei □ Ja □ Vet ikke

d) Andre utløsende faktorer?.....

2. AURA

a) Opplever du forut for clusterhodepine, dvs. mindre enn 1 time før hodepinen, ett eller flere av de symptomene som er nevnt nedenfor?

Synsforstyrrelse, prikking/nummenhet i ansikt/armer/bein, problemer med å finne ord/snakke, lammelser.

□ Nei □ Ja Hvis ja, sett ring rundt de aktuelle symptomer.

b) Hvis ja, hvor ofte opplever du dette i forbindelse med hodepine?

□ Alle anfall □ Over 50% av anfallene □ Under 50% av anfallene □ Sjeldent

c) Hvor ofte har du opplevd dette uten at det har kommet noen påfølgende hodepine?

□ Aldri □ Over 50% av anfallene □ Under 50% av anfallene □ Sjeldent

3. HODEPINEN

a) På hvilen side har du clusterhodepine?

□ Venstre □ Høyre

b) Kan hodepinen skifte side?

□ Nei □ Ja

c) Har du smalere øyespalte på den siden du pleier å ha vondt?

□ Nei □ Ja, under anfall □ Ja, hele tiden

d) Har du mindre pupille på den siden du pleier å ha vondt?

□ Nei □ Ja, under anfall □ Ja, hele tiden

e) Hvor lenge pleier hodepinen å vare (ca hvor mange minutter i snitt):_____

f) Hvor intens er hodepinen?

□ Mild □ Moderat □ Intens

g) Hvordan vil du beskrive din hodepine?

□ Bankende □ Trykkende □ Stikkende □ Borende □ Skjærende

4. LEDSAGENDE SYMPTOMER

a) Under anfall, blir du (*det kan settes 2 kryss)*:

□ Rastløs (må bevege deg)
□ Bevegelseshemmet (må sitte/ligge helt i ro)
□ Det er spesielt ille å ligge horisontalt

b) Ledsages hodepinen av:

□ rødt øye □ renning fra øyet □ renning fra nesen □ ingen av delene

Hvor ofte ledsages hodepinen av dette?

□ Alle anfall □ Over 50 % av anfallene □ Under 50 % av anfallene □ Sjeldent

c) Ledsages hodepinen av:

□ ensidig rødme i ansiktet
□ tørrhet i én ansiktshalvdel
□ ensidig bleket i ansiktet
□ ensidig svette i pannen
□ ingen av delene

Hvor ofte ledsages hodepinen av dette?

□ Alle anfall □ Over 50 % av anfallene □ Under 50 % av anfallene □ Sjeldent

d) Ledsages hodepinen av:

□ kvalme/oppkast □ overfølsomhet for lyd □ overfølsomhet for lys

Hvor ofte ledsages hodepinen av dette?

□ Alle anfall □ Over 50 % av anfallene □ Under 50 % av anfallene □ Sjeldent

e) Ledsages hodepinen av:

□ generell svette/frostri □ rask puls □ langsom puls □ annet □ ingen av delene

Hvis annet, hva?:

……

5. BEHANDLING

a) Benytter du ved anfall noen medisin?*(Sett ring rundt medikamentet)*:

□Ingen
□Imigran (tbl)/ Sumatriptan (tbl)/ Zomig/ Imigran (sprøyter)/ Sumatriptan (sprøyter))/ Naramig/ Maxalt/ Relpax/ Almogran/
□Oksygen
□Annet

Hvis annet, hva (navn på medikament(er) og dosering)*?*

……..

b) På en skala fra 0-10 (0=ingen effekt og 10=fullstendig symptomlindring) hvor bra virker anfallsbehandlingen?_____

c) Benytter du forebyggende behandling mot clusterhodepine?:

□ Ingen □ Verapamil/Isoptin □ Prednisolon □ Lithium □ Annet

Hvis annet, hva (navn på medikament(er) og dosering)*?*

……..

d) Hvor lenge benytter du forebyggende behandling?

□ Hele tiden □ Kun i perioder med clusterhodepine

e) På en skala fra 0-10 (0=ingen effekt og 10=fullstendig symptomlindring); hvor bra virker den forebyggende behandlingen?_____

C. PERIODISITET OG OPPFØLGING

1. CLUSTERPERIODENE

a) Hvor hyppig har du clusterperioder?

□ > 2 per år
□ 1 per år
□ < 1 per år ’
□ < 1 per 2 år
□ Vet ikke da jeg kun har opplevd ≤ 2 perioder

b) Opplever du at clusterperiodene dine kommer med regelmessige intervaller?

□ Nei □ Ja

c) Kommer clusterperiodene i spesielle årstider?

□ Nei □ Sommer □ Vinter □ Vår □ Høst

d) Opplever du at clusteranfall kan utløses av sterkt lys?

□ Alle anfall □ Over 50 % av anfallene □ Under 50 % av anfallene □ Sjelden □ Nei, aldri

e) Hvor lenge varer vanligvis en clusterperiode (i uker)?_____

f) I hvilken måned starter clusteranfallene?_____ □ Ingen fast måned

g) Er clusteranfallene mer intense i noen av årstidene?

□ Nei □ Sommer □ Vinter □ Vår □ Høst

h) Er du overfølsom for lys når du ikke har clusterhodepine?

□ Nei □ Ja, mellom anfallene i en clusterperiode
□ Ja, både mellom anfallene i en clusterperiode, men også i rolige perioder

i) Bruker du solbriller for å unngå ubehag av sollys?

□ Nei □ Ja, store deler av året □ Ja, men bare i den lyse årstiden
□ Ja, bare i perioder med clusterhodepine

j) Bruker du solbriller for å unngå at clusterhodepine inntreffer?
□ Nei □ Ja, store deler av året □ Ja, men bare i den lyse årstiden
□ Ja, bare i perioder med clusterhodepine

2. CLUSTERANFALLENE

a) Hvor ofte har du anfall i løpet av ett døgn (gjennomsnitt) i periodene med clusterhodepine?

□ x1 □ x2 □ x3-8 □> x8

b) Har/hadde clusteranfallene dine en tendens til å komme på samme tidspunkt på dagen?

□ Nei □ Ja □ Ja, men bare før jeg startet med behandling

c) Hvis ja, når?

□ kl.08-12 □ kl.12-16 □ kl.16-20 □ kl.20-24 □ kl.00-04 □ kl.04-08

d) Kommer anfall mens du sover?

□ Alltid □ Ofte □ Sjeldent □ Aldri

e) Hva synes du er mest korrekt i ditt tilfelle?:

□ Søvn utløser anfall
□ Mangel på søvn utløser anfall
□ Det å ligge flatt utløser anfall
□ Det er ingen sammenheng mellom leie, søvn og anfall

f) Er du fornøyd med den behandlingen du har fått av fastlegen?

□ Ja □ Nei

Hvis nei, hva var du misfornøyd med hos fastlegen?

□ Det tok for lang tid før diagnosen ble stillet
□ Jeg behandlet med medisin for annen sykdom
□ Medisinen var riktig, men den virket ikke på meg
□ Det tok for lang tid før jeg kom inn til time hos fastlegen
□ Fastlegen kunne for lite om sykdommen

g) Er du fornøyd med den behandlingen du har fått av spesialister ved nevrologisk avdeling?

□ Ja □ Nei

Hvis nei, hva var du misfornøyd med hos nevrolog?

□ Det tok for lang tid før diagnosen ble stillet
□ Jeg behandlet med medisin for annen sykdom
□ Medisinen var riktig, men den virket ikke på meg
□ Det tok for lang tid før jeg kom inn til time hos nevrologen
□ Nevrologen kunne for lite om sykdommen

□ Jeg har ikke vært hos nevrolog

h) Er du fornøyd med den behandlingen du har fått av andre spesialister? Angi hvilke _____

□ Ja □ Nei

Hvis nei, hva var du misfornøyd med?

□ Det tok for lang tid før diagnosen ble stillet
□ Jeg behandlet med medisin for annen sykdom
□ Medisinen var riktig, men den virket ikke på meg
□ Det tok for lang tid før jeg kom inn til time hos spesialisten
□ Spesialisten kunne for lite om sykdommen

g) Hvor lang tid tok det fra du fikk diagnosen til du fikk en behandling som virket effektivt?

□ Antall måneder _____ □ Jeg er enda ikke fornøyd med behandlingen

i) Har du forsøkt alternativ behandling mot clusterhodepine?

□ Nei □ Akupunktur □ Homeopati □ Kiropraktorbehandling

□ Manuell terapi □ Annen alternativ behandling, angi: _____

j) Hvordan virket den alternative behandlingen? (presiser hvilken behandling det gjelder dersom du har forsøkt flere behandlinger)

Behandling 1 (angi hvilken)_____

□ Ingen endring
□ Clusterperioden ble lenger
□ Clusterhodepinen ble mindre intens
□ Clusterhodepinen ble mer intens
□ Clusterperioden ble kortere
□ Annet, angi _____

Behandling 2 (angi hvilken)_____

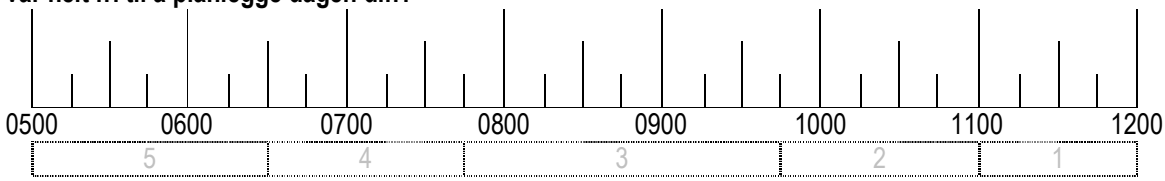
□ Ingen endring
□ Clusterperioden ble lenger
□ Clusterhodepinen ble mindre intens
□ Clusterhodepinen ble mer intens
□ Clusterperioden ble kortere
□ Annet, angi _____

The Horne-Östberg Morningness-Eveningness Questionnaire

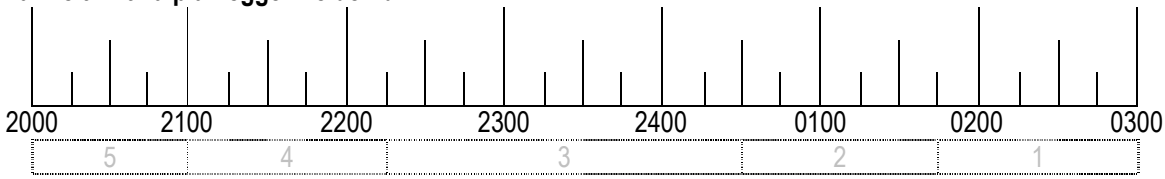
Instruksjon: Les hvert spørsmål nøye før du svarer. Svar på alle spørsmålene i den rekkefølgen de står i skjemaet. Hvert spørsmål skal besvares uavhengig av de andre. IKKE gå tilbake for å sjekke hva du har svart. Alle spørsmålene har bestemte svaralternativer. Sett bare ETT svar for hvert spørsmål ved å sette et kryss ved et av alternativene. Noen spørsmål har en skala istedenfor et sett av svaralternativer. På disse svarer du ved å sette et kryss på det passende stedet på skalaen. Svar så ærlig som mulig på hvert spørsmål. Både dine svar og resultater blir behandlet konfidensielt.

---

1. Hvis du bare tenker på den rytmen som er best for deg, på hvilket tidspunkt ville du stått opp dersom du var helt fri til å planlegge dagen din?



2. Hvis du bare tenker på den rytmen som er best for deg, på hvilket tidspunkt ville du lagt deg dersom du var helt fri til å planlegge kvelden din?



3.	**I hvilken grad er du avhengig av en vekkerklokke om morgenen hvis du må stå opp til et bestemt tidspunkt?**	Ikke avhengig i det hele tatt	☐ 4
		Noe avhengig	☐ 3
		Ganske avhengig	☐ 2
		Veldig avhengig	☐ 1
4.	**Forutsatt at omstendighetene er gode, hvor lett synes du det er å stå opp om morgenene?**	Ikke lett i det hele tatt	☐ 1
		Ikke så veldig lett	☐ 2
		Ganske lett	☐ 3
		Veldig lett	☐ 4
5.	**Hvor våken føler du deg i løpet av den første halvtimen etter at du har våknet om morgenene?**	Ikke våken i det hele tatt	☐ 1
		Litt våken	☐ 2
		Ganske våken	☐ 3
		Veldig våken	☐ 4
6.	**Hvordan er appetitten din i løpet av den første halvtimen etter at du har våknet om morgenene?**	Veldig dårlig	☐ 1
		Ganske dårlig	☐ 2
		Ganske god	☐ 3
		Veldig god	☐ 4
7.	**Hvor trøtt føler du deg i løpet av den første halvtimen etter at du har våknet om morgenen?**	Veldig trøtt	☐ 1
		Ganske trøtt	☐ 2
		Ganske uthvilt	☐ 3
		Veldig uthvilt	☐ 4

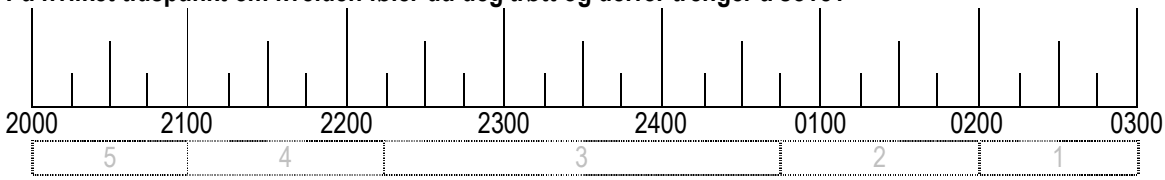
8. **I forhold til din vanlige leggetid, når legger du deg hvis du ikke har noen forpliktelser neste dag?**

- Sjelden eller aldri senere ☐ 4
- Mindre enn en time senere ☐ 3
- 1-2 timer senere ☐ 2
- Mer enn to timer senere ☐ 1

9. **Du har bestemt deg for å trene. En venn forslår at dere skal trene en time to ganger i uken og det beste tidspunktet for ham er mellom 0700 og 0800. Hvis du bare tenker på den rytmen som er best for deg, hvordan tror du dine prestasjoner vil bli?**

- Ville vært i god form ☐ 4
- Ville vært i brukbar form ☐ 3
- Ville synes det var vanskelig ☐ 2
- Ville synes det var veldig vanskelig ☐ 1

10. **På hvilket tidspunkt om kvelden føler du deg trøtt og derfor trenger å sove?**



11. **Du ønsker å være i toppform for en test som du vet kommer til å være mentalt krevende og som vil vare i to timer. Du er helt fri til å planlegge dagen din. Dersom du bare tar hensyn til den rytmen som er best for deg HVILKET av de følgende tidspunktene ville du valgt?**

- 0800-1000 ☐ 6
- 1100-1300 ☐ 4
- 1500-1700 ☐ 2
- 1900-2100 ☐ 0

12. **Hvis du la deg klokken 2300 hvor trøtt ville du da vært?**

- Ikke trøtt i det hele tatt ☐ 0
- Litt trøtt ☐ 2
- Ganske trøtt ☐ 3
- Veldig trøtt ☐ 5

13. **Av en eller annen grunn har du lagt deg flere timer senere enn vanlig. Du trenger ikke stå opp til en bestemt tid neste morgen. HVILKEN av de følgende hendelsene vil du med størst sannsynlighet oppleve?**

- Ville våknet til vanlig tid UTEN å sovne igjen ☐ 4
- Ville våknet til vanlig tid og så halvsove ☐ 3
- Ville våknet til vanlig tid, men så sovnet igjen ☐ 2
- Ville våknet senere enn vanlig ☐ 1

14. **En natt må du være våken mellom 0400 og 0600 for å være nattevakt. Du har ingen avtaler neste dag. HVILKET av de følgende alternativer passer deg best?**

- Ville IKKE sovet før nattevakten var over ☐ 1
- Ville tatt en blund før og sovet etterpå ☐ 2
- Ville sovnet mye før og en blund etterpå ☐ 3
- Ville tatt ALL søvn før nattevakten ☐ 4

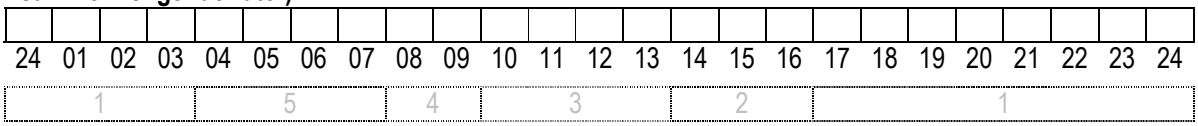
15. **Du må gjøre to timers hardt fysisk arbeid. Du kan planlegge dagen din helt fritt. Med tanke på rytmen som er best for deg HVILKET tidspunkt hadde du valgt?**

- 0800-1000 ☐ 4
- 1100-1300 ☐ 3
- 1500-1700 ☐ 2
- 1900-2100 ☐ 1

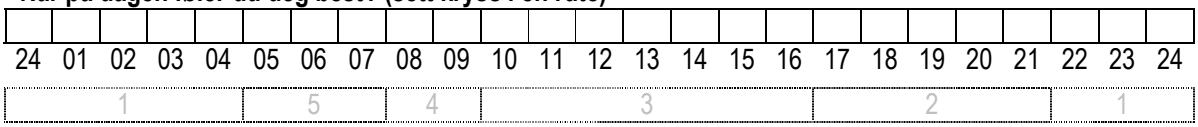
16. Du har bestemt deg for å hardtrene. En venn forslår at dere skal trene en time to ganger i uken og det beste tidspunktet for ham er mellom 2200 og 2300. Hvis du bare tenker på den rytmen som er best for deg, hvordan tror du dine prestasjoner vil bli?

- Ville vært i god form ☐ 1
- Ville vært i brukbar form ☐ 2
- Ville synes det var vanskelig ☐ 3
- Ville synes det var veldig vanskelig ☐ 4

17. Anta at du kan velge din egen arbeidstid, at du jobber 5 timer dagen (inkludert pauser), at jobben var interessant og gav resultater. Hvilke FEM SAMMENHENGENDE TIMER ville du valgt (sett kryss i 5 sammenhengende ruter)



18. Når på dagen føler du deg best? (sett kryss i en rute)



19. Man hører om A-mennesker (morgenfugler) og B-mennesker (kveldsmennesker). HVILKEN av disse typene vil du si at du er?

- Helt klart A-menneske ☐ 6
- Heller et A- enn et B-menneske ☐ 4
- Heller et B- enn et A-menneske ☐ 2
- Helt klart et B-menneske ☐ 0

Referanse: Horne, J. A., & Östber, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. International Journal of Chronobiology, 4, 97-110. Til norsk ved Idalill Udnes, Toril Johansen, Tom Lilleholt og Ståle Pallesen.

PSQI

Instruksjoner: Følgende spørsmål har med ditt vanlige søvnmønster *den siste måneden* å gjøre. Du skal svare på hva som er mest riktig for *de fleste* dager og netter den siste måneden. Vennligst svar på alle spørsmål.

1. I løpet av den siste måneden, når har du vanligvis lagt deg om kvelden?
   VANLIG LEGGETID_____

2. I løpet av den siste måneden, hvor lang tid (i minutter) har det vanligvis tatt deg å sovne om kvelden?
   ANTALL MINUTTER_____

3. I løpet av den siste måneden, når har du vanligvis stått opp om morgenen?
   VANLIGVIS STÅTT OPP KL_____

4. I løpet av den siste måneden, hvor mange timer søvn har du *faktisk* fått om natten? (Dette kan være forskjellig fra hvor mange timer du oppholdt deg i sengen.)
   ANTALL TIMER SØVN HVER NATT _____

For hvert av de følgende spørsmål, kryss av for det beste svar. Vennligst svar på *alle* spørsmålene.

5. I løpet av den siste måneden, hvor ofte har du hatt problemer med søvnen fordi du…

(a) Ikke klarer å sovne i løpet av 30 minutter

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(b) Våkner opp midt på natten eller tidlig om morgenen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(c) Må opp for å gå på toalettet

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(d) Ikke klarer å puste ordentlig

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(e) Hoster eller snorker høyt

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(f) Føler deg for kald

Ikke i løpet av den s iste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(g) Føler deg for varm

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(h) Har vonde drømmer

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(i) Har smerter

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(j) Andre grunner, vennligst beskriv_____
_____

Hvor ofte, i løpet av den siste måneden, har du hatt problemer med søvnen på grunn av dette

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

6. I løpet av den siste måneden, hvordan vil du bedømme søvnkvaliteten din totalt sett?
   - Veldig bra _____
   - Ganske bra _____
   - Ganske dårlig _____
   - Veldig dårlig _____

7. I løpet av den siste måneden, hvor ofte har du tatt medisin (med eller uten resept) som hjelp til å sove?

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

8. I løpet av den siste måneden, hvor ofte har du hatt problemer med å holde deg våken under bilkjøring, måltider eller når du holder på med sosiale aktiviteter?

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

9. I løpet av den siste måneden, hvor stort problem har det vært for deg å ha overskudd nok til å få ting gjort?
   - Ikke noe problem i det hele tatt _____
   - Bare et lite problem _____
   - Et visst problem _____
   - Et stort problem _____

10. Deler du seng eller rom med noen?
    - Deler ikke seng eller rom med noen _____
    - Partner/romkamerat i annet rom _____
    - Partner i samme rom, men ikke i samme seng _____
    - Partner i samme seng _____

Hvis du har en partner eller romkamerat, spør han/henne hvor ofte i løpet av den siste måneden du har hatt…

(a) høy snorking

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(b) lange pustestopp under søvnen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(c) rykninger eller sammentrekninger i beina under søvnen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(d) episoder med desorientering eller forvirring under søvnen

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___

(e) annen type uro under søvnen; vennligst beskriv_____
_____

Ikke i løpet av den siste måneden___	Mindre enn en gang i uken___	En eller to ganger i uken___	Tre eller flere ganger i uken___