

Paper 1

Research Submission

Insomnia and Periodicity of Headache in an Arctic Cluster Headache Population

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Objective.—To assess the prevalence of chronic insomnia and the periodicity of headache attacks in an Arctic cluster headache population.

Background.—Cluster headache is a sleep-related disorder, and attacks have both circadian and circannual rhythmicity.

Methods.—Through a retrospective hospital chart review, we identified all subjects diagnosed with episodic cluster headache (ICD-10 G 44.0) at the Neurological Departments in Northern Norway (located north of 66°33'N) between January 1, 2000 and December 31, 2010. Patients with a confirmed diagnosis (ICHD-2) received a comprehensive questionnaire covering demographic data, clinical characteristics, sleep, and periodicity of attacks.

Results.—A total of 196 subjects were registered, and 178 received the questionnaire. The response rate was 88/178 (49%). Fifty-eight men (aged 49.2 ± 13.6) and 12 women (aged 49.7 ± 15.5) were included. Forty percent of the responders suffered from chronic insomnia (Diagnostic and Statistical Manual of Mental Disorders 4th edition). Forty-nine percent of the responders and 42% of the non-responders were shift workers, which is much higher than compared with the general population (24%). Insomnia was significantly associated with shift work and experiencing longer-lasting cluster bouts. One third attributed their insomnia to the cluster headache. Thirty-seven percent reported a seasonal predilection of the cluster periods, and 58% a diurnal periodicity of attacks. Eighty percent often or always had headache attacks during sleep, the most frequent time interval being at 12:00-4:00 AM. Shift workers were significantly more likely to see lack of sleep as a cluster attack trigger than daytime workers.

Conclusions.—Chronic insomnia and shift work seem to be common among Arctic cluster headache patients. The small number of subjects included in this study implies that conclusions should be drawn with caution, but the findings support the idea of cluster headache as a circadian rhythm disorder.

Key words: cluster headache, insomnia, shift work, epidemiology, periodicity

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INTRODUCTION

The true pathogenesis of cluster headache is not known, but it is a widely held view that it is a chronobiological disorder and that the hypothalamus plays a pivotal role in generating, or regulating,

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attacks.^{1,2} The International Classification of Sleep Disorders classifies cluster headache as a sleep-related headache.³ More than 70% of cluster headache patients report nocturnal attacks, often waking them from sleep,⁴ and the peak incidence is usually between 4:00 and 7:00 AM.⁵ Several studies with small number of subjects have connected cluster attacks to rapid eye movement sleep stages, but the results are conflicting.^{6,7} The prevalence of obstructive sleep

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apnea seems to be higher among cluster headache patients than in the general population,⁸⁻¹⁰ and transient situational insomnia during active bouts has been described in a single patient.¹¹ Insomnia is the most common form of sleep complaint among patients with migraine and tension-type headache,¹² but to our knowledge, there have been no previous studies documenting the prevalence of insomnia in a cluster headache population.

Located north of the Arctic Circle, the Arctic part of Norway has extreme variations in natural illumination, with 24-hour daylight in part of the summer and 24-hour darkness in part of the winter. This makes it an interesting region for studying biological rhythms. We aimed to assess the prevalence of chronic insomnia and the periodicity of headache attacks in the episodic cluster headache population of this region.

METHODS

Arctic Norway has approximately 450,000 inhabitants and is essentially served by only 2 neurological departments: at Nordland Hospital Trust in Bodø and at the University Hospital of North Norway in Tromsø. As cluster headache patients are often referred to secondary care, we assumed that we could identify the majority of them by reviewing hospital records. Through a retrospective chart review at the Nordland Hospital Trust and University Hospital of North Norway, all subjects diagnosed with cluster headache (ICD-10 G 44.0) between January 1, 2000 and December 31, 2010 were identified. Diagnoses were validated by headache specialists (K.B.A. and S.B.), and patients with a confirmed diagnosis according to the ICDH-2 criteria,¹³ and who were permanently living in North Norway, received a comprehensive questionnaire. Information obtained from the questionnaire was validated with past medical records. When diagnostic doubt, the subjects were interviewed by telephone. We also tried to contact all non-responders. Subjects not fulfilling the ICDH-2 criteria for episodic cluster headache or who were having a secondary or chronic cluster headache were excluded. Information about the employment of non-responders was retrieved from patient journals. The

subjects did not receive any form of compensation for participating in the study.

Questionnaire.—The questionnaire consisted of three parts, covering: (1) personal and demographic data and questions regarding sleep (10 items), (2) attack characteristics and treatment (5 items), and (3) headache periodicity and follow up (2 items). Altogether, there were 92 questions, mainly multiple choices, but some with request of focused answers while others opening for writing freely. A few questions were mutually validating.

Chronic insomnia was defined in accordance with the DSM-IV criteria:¹⁴ difficulties initiating sleep and/or maintaining sleep at least 3 nights a week for more than 1 month, *and* the sleep disturbance or associated daytime fatigue causes clinically significant distress in daytime functioning. The participants were asked if they had experienced this during the last year, if they thought their sleep disturbance was caused by the cluster headache, and whether the insomnia was better or worse in the light season. They were also asked whether they regarded themselves as “early risers” or “night owls” (A or B chronotype, respectively). The use of acute and prophylactic medication for cluster headache was recorded, but no specific enquiries of sleep medication were made. The responders were divided in subgroups of “insomnia” and “non-insomnia” for subgroup analysis.

Sleep as a trigger was covered in each part of the questionnaire. In part A, the participants had to answer how frequent cluster headache woke them from their night sleep (all attacks, >50% of attacks, <50% of attacks, rarely, or never). In part B, they had to answer whether sleep or supine position triggers cluster headache when having bouts (no, yes, or don't know). In part C, surveying diurnal periodicity of attacks, participants had to answer whether attacks occurred during sleep (always, often, rarely, or never), and finally, what they considered most correct in their case: (1) sleep triggers attacks, (2) lack of sleep triggers attacks, (3) supine position triggers attacks, or (4) there is no connection among position, sleep, and attacks.

Headache periodicity was further described by the frequency and duration of cluster attacks and bouts, the onset of attacks and bouts in relation to

time of day, year, month, and season, and whether the participants subjectively regarded their headache to come in regular intervals. The term “shift work” was not precisely defined in the survey, so the subjects had to choose between the options “shift work,” “daytime only,” or “shift work for many years.” There were no inquiries as to what sort of shifts the participants were working.

Ethical Approval and Data Analyses.—The regional Ethics Committee of Northern Norway reviewed the research protocol and recommended the study. Data registration was approved by the Norwegian Data Inspectorate. All participants signed an informed consent form. The data were analyzed using the SPSS Software package for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). A chi-square test was performed when comparing frequencies, and an independent *t*-test was used for comparing means. The null hypothesis (H_0) in each case was that there was no difference between means, and the *P* values refer two-tailed significance at 5%.

RESULTS

A total of 196 subjects were registered with ICD-10 G 44.0 cluster headache. Of these, 8 were deceased. In March 2011, we submitted 188 questionnaires by mail, of which 10 were returned by the postal service because of invalid addresses (Fig. 1). Seventy-nine subjects did not respond to our invitation, and 11 actively declined participation. We received 88 completed questionnaires. After validation, 18 were excluded because of improbable diagnosis of episodic cluster headache or other reasons as explained in flow chart. Seventy individuals were included in the study, 58 men and 12 women. This gives a male to female ratio of 4.8:1. See Table 1 for personal and demographic data. Table 2 shows clinical characteristics.

Twenty-eight (40%) of the responders met the DSM-IV criteria for chronic insomnia (Table 3). One participant did not answer the question and was excluded from subgroup analysis. Cluster patients with insomnia were the same age and sex as the non-insomnia responders, but reported shorter time from onset of symptoms until diagnosis (3.9 vs 7.1 years, $P = .050$). There was no association with self-defined

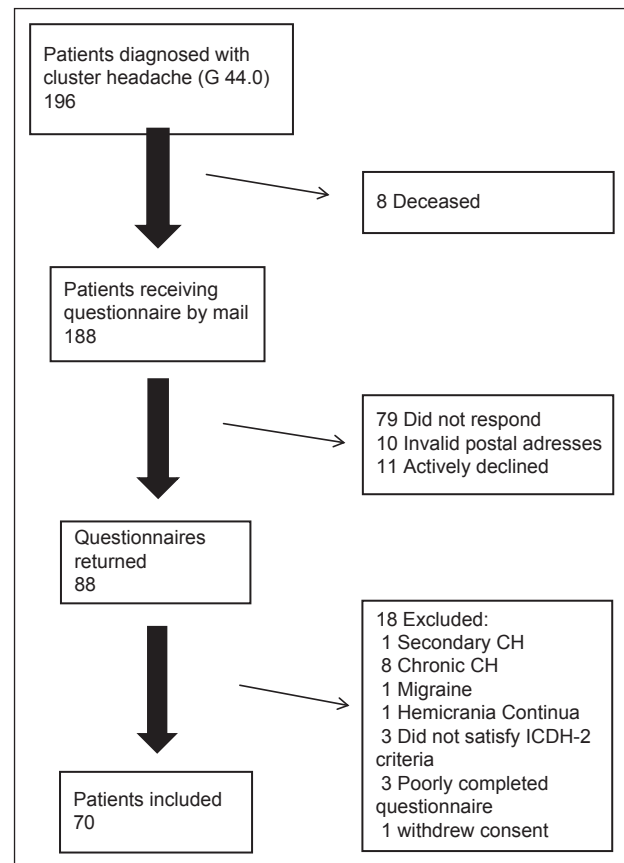


Fig 1.—Flow chart. CH = cluster headache.

chronotype, and they were not more likely to report seasonal or diurnal variation in cluster bouts. Insomnia was associated with significantly longer-lasting cluster bouts, as the cluster periods lasted by average 8.7 weeks in insomnia vs 5.1 weeks in non-insomnia responders ($P = .022$). Each cluster attack lasted in average 84 minutes with insomnia compared with 64.7 minutes without insomnia, but the difference was not statistically significant. There was no difference in the frequency of cluster attacks per day or bouts per year. The insomniacs were significantly more often employed in shift work compared with the non-insomniacs ($P = .034$), but they were not more likely to have comorbidity or receive social benefits. Lack of sleep as a trigger for cluster attack was not significantly different in the insomnia or non-insomnia group. Ten of the 28 insomniacs (35.7%) attributed their insomnia to cluster headache. Five said that their sleeping problems got worse during the light season, 3 said they got better, and 15 reported no difference.

Table 1.—Personal and Demographic Data in Arctic Cluster Headache Patients

	Total (%)	Male (%)	Female (%)
N	70 (100)	58 (83)	12 (17)
Mean age, years	49.3, SD ± 13.8	49.2, SD ± 13.6	49.7, SD ± 15.5
Married/partner	57 (81.5)	48 (83)	9 (75)
Divorced	3 (4)	2 (3.5)	1 (8)
Education			
Primary school	16 (23)	14 (24)	2 (16.5)
High school	35 (50)	29 (50)	6 (50)
College/university	19 (27)	15 (26)	4 (33)
Social security			
Retired	9 (13)	7 (12)	2 (16.5)
Disability pension	10 (14)	8 (14)	2 (16.5)
Current sick leave	4 (5.5)	2 (3.5)	2 (16.5)
Rehabilitation funding	2 (3)	2 (3.5)	0
Lifestyle/personality			
Current smoker	31 (44)	22 (38)	9 (75)
Previous smoker	27 (38.5)	26 (45)	1 (8)
Alcohol consumption			
Less than average	28 (40)	20 (34.5)	8 (67)
Average	32 (45.5)	29 (50)	3 (25)
More than average	4 (5.5)	4 (7)	0
Mean BMI, kg/m ²	26.5, SD ± 4.2	26.9, SD ± 4.3	24.9, SD ± 3.5
Early riser	35 (50)	31 (53.5)	4 (33)
Night owl	22 (31.5)	18 (31)	4 (33)
Eye color			
Brown	8 (11.5)	6 (10)	2 (16.5)
Green	13 (18.5)	11 (19)	2 (16.5)
Headache burden			
Cluster in family	3 (4)	1 (1.5)	2 (16.5)
Migraine in family	32 (45.5)	24 (41.5)	8 (66.5)
Comorbid migraine	12 (17)	7 (12)	5 (41.5)
Other headaches	16 (23)	14 (24)	2 (16.5)
Comorbidity			
Comorbidity general	43 (61.5)	32 (55)	11 (91.5)
Previous stroke	1 (1.5)	1 (1.5)	0
Sinus problems	9 (13)	7 (12)	2 (16.5)
Allergies	13 (18.5)	9 (15.5)	4 (33)
Hypertension	18 (25.5)	16 (27.5)	2 (16.5)

BMI = body mass index; SD = standard deviation.

Thirty-one of the 70 included (44%) reported that their cluster bouts came at regular intervals of the year. The majority of patients reported no specific month of onset, but February was reported most frequently (4 responders), followed by October and November (both 2 responders). Twenty-six (37%) said that the bouts came at specific seasons, mostly spring (14, 20%) and autumn (9, 13%). Forty-one (58.5%) said that their cluster attacks came at regular times during the day, the most frequent interval being at 12:00-4:00 AM (Fig. 2). A total of 56 responders (80%) often or always had cluster attacks during

sleep. Forty-eight (68.5%) reported being woken up by headache in over 50% of the cluster attacks, whereas sleep was reported a trigger during bouts in 34 (49%) of the patients. Thirteen (19%) saw lack of sleep as a trigger. Figures 3 and 4 show the reported frequency of cluster headache attacks and bouts, respectively.

Of the 45 responders currently working, 22 (49%) were shift workers. Of the total study population, 33 (47%) reported current or previous shift work, and 27 reported daytime work only. Ten did not answer the question. The shift workers reported insomnia signifi-

Table 2.—Clinical Characteristics in Arctic Cluster Headache Patients

	Total (%)	Male (%)	Female (%)
Mean age of onset, years	32.5, SD ± 13.4	31, SD ± 12.5	38.5, SD ± 16.4
Mean time to diagnosis, years	5.8, SD ± 6.8	6.3, SD ± 7.4	3.8, SD ± 4.0
Pain location, left/right	35/35	29/29	6/6
Side shift	11 (15.5)	9 (15.5)	2 (16.5)
Triggers, general			
Sleep	32 (45.5)	24 (41.5)	8 (66.5)
Bright light	29 (41.5)	25 (43)	4 (33)
Lack of sleep	13 (18.5)	10 (17)	3 (25)
Lying flat	11 (15.5)	8 (14)	3 (25)
Triggers during bout			
Sleep	34 (48.5)	27 (46.5)	7 (58)
Lying flat	27 (38.5)	21 (36)	6 (50)
Alcohol	22 (31.5)	20 (34.5)	2 (16.6)
Aura			
Sensory aura	25 (35.5)	22 (38)	3 (25)
Visual aura	16 (23)	14 (23)	2 (16.5)
Headache characteristics			
Throbbing	4 (5.5)	3 (5)	1 (8.5)
Pressing	16 (23)	13 (22.5)	3 (25)
Stabbing/shearing	26 (37)	22 (38)	4 (33)
Combinations	23 (33)	19 (33)	4 (33)
Accompanying symptoms			
Ptosis	47 (67)	41 (70.5)	6 (50)
Miosis	29 (41.5)	23 (39.5)	6 (50)
Red eye, lacrimation, or rhinorrhea	64 (91.5)	52 (89.5)	12 (100)
Facial sweating, blushing, paleness	33 (47)	29 (50)	4 (33)
Agitation, restlessness	56 (80)	44 (76)	12 (100)
Migrainous symptoms			
Nausea	17 (24.5)	14 (24)	3 (25)
Phonophobia	29 (41.5)	22 (38)	7 (58.5)
Photophobia	48 (68.5)	42 (72.5)	6 (50)
Systemic symptoms			
Sweating	12 (17)	10 (17)	2 (16.5)
Tachycardia	19 (27)	17 (29.5)	2 (16.5)
Bradycardia	2 (3)	2 (3.5)	0

SD = standard deviation.

cantly more often than daytime workers (17 vs 6, $P = .034$). There was no difference in gender, age, or comorbidity between shift workers and daytime workers, neither did we find differences in the frequency or duration of cluster attacks per day or bouts per year. Previous and current shift workers were significantly more likely to see lack of sleep as a cluster attack trigger than daytime workers (10 vs 1, $P = .008$). We identified the occupation of 72 of the 100 non-responders and found 30 (42%) to be shift workers. Table 4 shows the number of shift workers in our cluster headache patients compared with the general working population of Norway.

DISCUSSION

The present study documents a high frequency of chronic insomnia (40%) among cluster patients in the Norwegian Arctic region, much higher than the 11.7% found in the adult general Norwegian population¹⁵ and the 13.5% found in mid-Norway.¹⁶ The general prevalence of insomnia in Arctic regions may be slightly higher, but studies have reported various and conflicting results on the subject.^{17,18} In a recent study from Tromsø (69°39'N),¹⁹ 17.4% of the adult population suffered from sleeplessness monthly or more often related to a specific season, of which 70% reported polar night sleeplessness, and 16% reported

Table 3.—Results and Subgroup Analysis of Insomnia and Non-Insomnia Responders

	Insomnia n (%)	Non-insomnia n (%)	P value
Mean age, years	49.2, SD ± 12.4	48.8, SD ± 14.6	.915
Sex, male/female	23/5	34/7	1.000
Mean BMI, kg/m ²	26.9, SD ± 4.7	26.3, SD ± 3.9	.554
Mean time to diagnosis, years	3.9, SD ± 4.3	7.1, SD ± 7.9	.050
Early riser	11 (39)	23 (56)	
Night owl	9 (32)	13 (31.5)	
Cluster attack frequency			
1 attack per day	2 (7)	8 (19.5)	
2 attacks per day	8 (28.5)	10 (24.5)	
3-8 attacks per day	16 (57)	19 (46.5)	
>8 attacks per day	1 (3.5)	2 (5)	
Cluster bout frequency			
>2 bouts per year	12 (43)	12 (29)	
1 bout per year	6 (21.5)	8 (28.5)	
<1 bout per year	2 (7)	2 (5)	
<1 bout per 2 years	3 (10.5)	6 (14.5)	
Cluster attacks often or always occur during sleep	22 (78.5)	34 (83)	.745
Duration of attacks, minutes	84.0, SD ± 92.4	64.7, SD ± 45.5	.339
Duration of bouts, weeks	8.7, SD ± 6.6	5.1, SD ± 4.1	.022
Comorbidity	21 (75)	22 (53.5)	.083
Social security	10 (35.5)	15 (36.5)	1.000
Shift work occupation	17 (60.5)	16 (39)	.034
Sleep triggers attacks	15 (53.5)	17 (41.5)	.461
Lack of sleep triggers attacks	7 (25)	6 (14.5)	.357
Circadian regularity	16 (57)	24 (58.5)	1.000
Circannual regularity	12 (43)	19 (46.5)	1.000
Seasonal regularity	9 (32)	16 (39)	.798
Total: 69	28 (40.5)	41 (59.5)	

BMI = body mass index; SD = standard deviation.

sleeplessness in the midnight sun period. The majority of insomniacs in our study reported no difference in sleep disturbances in relation to season. It is well known that comorbidity, especially psychiatric and pain disorders, is strongly associated with insomnia symptoms, and this was not thoroughly investigated in the present study. Neither did we ask our patients to specify when their insomnia occurred in relation to cluster headache bouts or season of the year, which also would have helped the interpretation of the results. A little more than one third stated that the insomnia was caused by cluster headache, which may suggest that these patients experienced insomnia within cluster bouts.

Female gender and migraine seem to be associated with an increased risk of insomnia.¹⁶ In a previous study from our group of 169 Arctic female migraineurs, almost 30% suffered from chronic

insomnia.²⁰ In the present study, we found no difference between genders, and our patients, predominantly males, actually reported a higher frequency of insomnia than the female migraineurs of the same area. Male sex and obesity, especially body mass index (BMI) > 25 kg/m², are strongly associated with obstructive sleep apnea syndrome (OSAS), and it is claimed that cluster headache patients have an 8-fold higher risk of OSAS than normal individuals.⁹ In the present study, the mean BMI was 26.5 kg/m², but there was no difference in BMI between the insomnia and non-insomnia subgroup, neither were the males who suffered from insomnia significantly heavier than the males who did not (27.7 vs 26.3 kg/m², $P = .253$).

Shift work is a well-known cause of insomnia, as up to 32% of night-shift workers and 26% of rotating-shift workers suffer from shift work disorder,²¹ a condition that typically manifest as difficulties falling

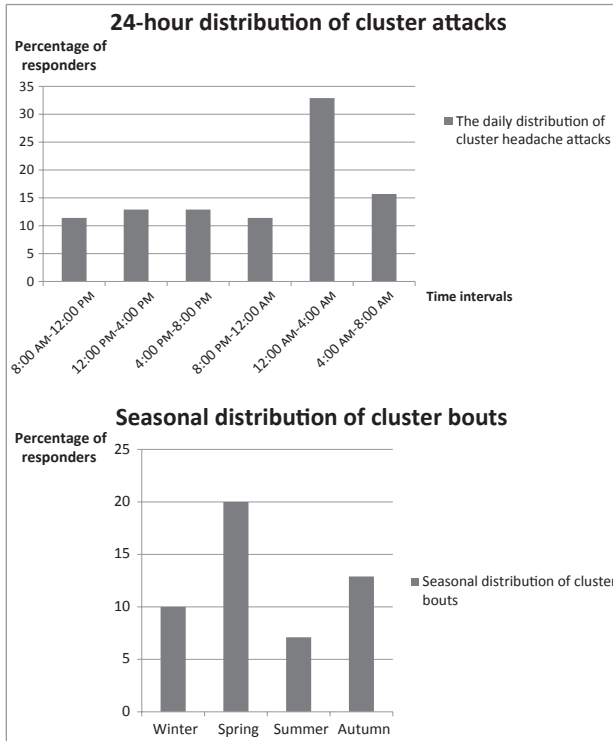


Fig 2.—Daily distribution of cluster headache attacks (top) and seasonal distribution of cluster bouts (bottom) in Arctic cluster headache patients.

asleep and excessive day-time sleepiness. Shift work disorder is believed to be the result of a circadian misalignment that derives from working schedules that require wakefulness and activity during the biological night and sleep during the biological day. In

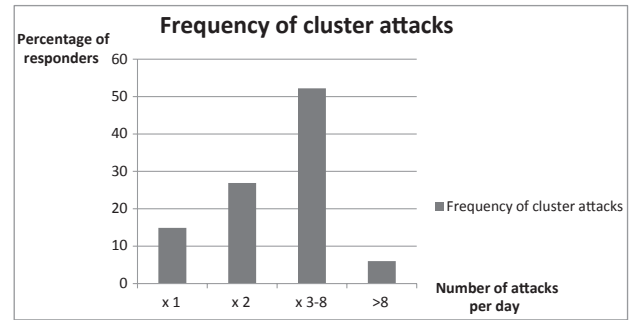


Fig 3.—The frequency of cluster headache attacks in Arctic cluster headache patients.

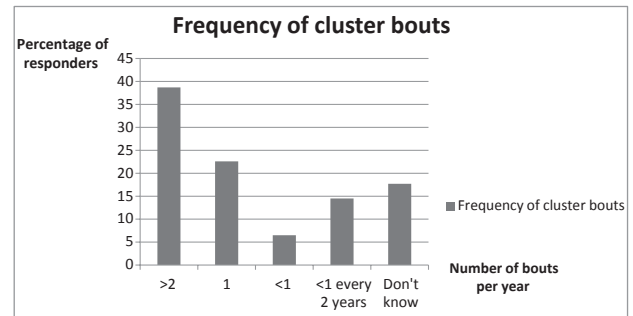


Fig 4.—The frequency of cluster bouts in Arctic cluster headache patients.

2012, 33% of the adult working population of Norway worked outside regular office hours (Monday-Friday 8:00 AM to 6:00 PM). The majority, 23.7%, was defined as shift workers, meaning regularly rotating work hours including nights and weekends.²² Estimates of

Table 4.—Percentage of Shift Workers in the General Working Population of Norway and in the Working Arctic Cluster Headache Population, Related to Age and Gender

Shift workers, sex	15-24 Years		25-54 Years		55-74 Years	
	CH	GP	CH	GP	CH	GP
Males†	1/1 (100%)	28%	13/28 (46%)	20%	4/10 (40%)	13%
Males‡		46%		28%		20%
Females†	0	36%	3/5 (60%)	27%	1/1 (100%)	26%
Females‡		65%		34%		32%
Both sexes†	1/1 (100%)	32%	16/33 (48%)	23%	5/11 (45%)	19%
Both sexes‡		56%		31%		26%

†Working regularly rotating shifts. ‡Working outside regular office hours.
CH = Arctic cluster headache population; GP = general population.

the prevalence of shift work in USA, UK, and Finland are 20%, 22%, and 25%, respectively.²³ The prevalence may be slightly higher in our region where more people are employed in health and transport industries, but Table 4 shows that the prevalence in our cluster population is much higher than expected compared with people of the same age and gender in the general population. By comparing with everyone working “outside regular office hours” in the general population, the vague definition of shift work provided in our study is outweighed. Thus, we believe that the high frequency found is a genuine trait of the Arctic cluster headache population.

As expected, the insomniacs were significantly more often employed in shift work occupation than the daytime workers, but the frequency of insomnia was also high among the daytime workers, as 6 out of 26 (23%, 1 missing) reported insomnia. Interestingly, the shift workers were significantly more likely to see lack of sleep as a trigger for cluster headache attacks than the daytime workers, whereas the insomniacs did not see lack of sleep as a trigger more often than the non-insomniacs. One should think that merely being awake at night would initiate attacks, but this does not seem to be the case. Do the shift workers get headache during or after night shifts? Or does the shift work cause insomnia or sleep disruption, which they associate with cluster attacks? When analyzing the subgroups with and without insomnia, the shift workers propensity to see lack of sleep as a trigger was only significant in the proportion of shift workers who did *not* suffer from insomnia ($P = .011$). This would suggest that it is not the accompanying insomnia that triggers the attacks, but the nocturnal activity or stress factors following shift work per se.

Few population based studies of cluster headache have examined the occupation of their patients, and, to the authors' knowledge, none have studied the actual prevalence of shift work. Manzoni found a higher prevalence of occupations involving greater responsibilities, such as being a manager, businessman, or municipal policeman.²⁴ Furthermore, Manzoni studied the decline in the male to female ratio of cluster headache from 1950 to 1995 and found the rising prevalence of cluster headache in women corresponding both to a growing female prevalence of smokers and

a higher employment rate.²⁵ Sjöstrand et al reported that cluster headache patients worked significantly more full time than their non-affected relatives.²⁶ Thirty-seven of the 45 cluster headache patients currently working in our study worked full time, and this is in accordance with the prevalence in the general population, also when adjusted for age and sex.

The periodicity of attacks seems to be robust to regional differences in external light, as the circannual and circadian periodicity reported in our population is very similar to what has been found in previous studies.^{4,27,28} Thirty-seven percent reported a seasonal regularity of cluster bouts, and cluster attacks most often occur during the night or early morning hours. Among those who reported a seasonal regularity, cluster bouts were most likely to start in spring or autumn.

However, Kudrow found January and July to be the most common months of cluster period onset in cluster headache patients living in California.²⁹ They related these findings to the turning of the sun and changes in natural illumination, as the peak frequency of onset occurred 7-10 days after the solstices (ie, longest and shortest day of the year). These findings should be reinforced in our Arctic population, being exposed to much more extreme variations in natural illumination. But as referred, we found cluster bouts more likely to start in spring and autumn, closer to the equinoxes in March and September. The daily change in natural lighting is much larger and more noticeable around the equinoxes than the solstices, making the synchronization of external light cues with the internal biological clock more challenging. The resulting mismatch may set off the cluster period.

If the major external cue for triggering cluster attacks is changes in daylight, the prevalence of cluster headache in Arctic areas should be high, and there should be a higher tendency of periodicity compared with patients living further south. The present study does not support that idea. One may speculate whether shift work and/or insomnia increases the risk of cluster headache. Battling our internal clock has health consequences, and this may depend on one's innate vulnerability to circadian misalignments. If shift work acts as a trigger for developing the disease, the cluster headache population would consequently

display a high prevalence of shift workers, as found in the present study. Fifty percent of our cluster population defined themselves as early risers, thus not well suited for working night shift. Thorough chronotyping of cluster headache patients has not been done and would be essential for understanding the chronobiology of the disorder. Vulnerability to circadian misalignments could also, together with the special light conditions of the Arctic and/or shift work, cause the high frequency of insomnia.

Further studies on the relationship among cluster headache, sleep, and circadian biology should be done. The findings in the present study should be confirmed in other populations, and larger prospective studies of the temporal patterns of cluster headache in relation to sleep patterns and season is also warranted. Adaptation of the circadian system to shift work and other possible circadian misalignments may depend on clock genes.³⁰ Polymorphism in the *PER3* gene has been associated with circadian preference and insomnia in several studies,³¹ and such genotype–phenotype association should also be studied in cluster headache.

Strength and Weaknesses.—In general, the accuracy of information based on interviews or questionnaires may be poor, and the small number of participants in our study imply that conclusions should be drawn with caution.³² We intended to identify the majority of patients with cluster headache in Arctic Norway, but a prevalence of 0.04% is lower than expected,³¹ and we may have missed a large proportion of patients. The response rate was reasonably high (49%), as surveys based on postal questionnaires tend to have response rates as low as 20%.³³ However, volunteer bias is possible, and we had no second mailing for those who did not respond to the invitation letter. The non-responders did not differ from the subjects included in age, gender, or shift work occupation; otherwise, we do not have any information on this group. Diagnoses were validated by 2 headache specialists, but no interrater reliability was determined. General demographic and clinical findings were in accordance with previous studies. There is a high frequency of aura reported, but aura was vaguely defined in the questionnaire, and 13 of the patients had aura not related to headache. Of the 12 responders with comorbid migraine, 6 reported having aura and 6 did not.

We excluded 17 (19.5%) of the responders, of which 8 (9%) had chronic cluster headache, which usually comprises about 10–15% of the total cluster headache population. Our questionnaire was not validated, which may be particularly problematic in respect to patient chronotyping and the vague definition of shift work occupation. More detailed information on the actual work hours of our patients should have been retrieved, but the comparison with the general population (although not true sex- and age-matched controls), together with the high prevalence even in non-responders, strengthens the findings. We were not able to provide healthy controls for insomnia.

CONCLUSION

Chronic insomnia and shift work employment seem to be common among Arctic cluster headache patients. The high prevalence of insomnia may partly be caused by the high number of shift workers, which seem to be a genuine trait of the population. The response rate of this study was low, and results should be confirmed in other cluster headache populations. Whether shift work and/or insomnia increase the risk of cluster headache is not known. However, the present study adds up to the idea of cluster attacks as a result of circadian misalignment.

STATEMENT OF AUTHORSHIP

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REFERENCES

1. Leone M, Bussone G. A review of hormonal findings in cluster headache. Evidence for hypothalamic involvement. *Cephalalgia*. 1993;13:309-317.
2. Holle D, Obermann M. Cluster headache and the hypothalamus: Causal relationship or epiphenomenon? *Expert Rev Neurother*. 2011;11:1255-1263.
3. American Academy of Sleep Medicine. *The International Classification of Sleep Disorders, Diagnostic and Coding Manual*, 2 edn. Westchester, IL: American Academy of Sleep Medicine, in association with the European Sleep Research Society, Japanese Society of Sleep Research, Latin American Sleep Society; 2005:255.
4. Bahra A, May A, Goadsby PJ. Cluster headache: A prospective clinical study with diagnostic implications. *Neurology*. 2002;58:354-361.
5. Russell D. Cluster headache: Severity and temporal profiles of attacks and patient activity prior to and during attacks. *Cephalalgia*. 1981;1:209-216.
6. Dexter JD, Weitzman ED. The relationship of nocturnal headaches to sleep stage patterns. *Neurology*. 1970;20:513-518.
7. Terzaghi M, Ghiotto N, Sances G, Rustioni V, Nappi G, Manni R. Episodic cluster headache: NREM prevalence of nocturnal attacks. Time to look beyond macrostructural analysis? *Headache*. 2010;50:1050-1054.
8. Kudrow L, McGinty DJ, Phillips ER, Stevenson M. Sleep apnea in cluster headache. *Cephalalgia*. 1984;4:33-38.
9. Nobre ME, Leal AJ, Filho PM. Investigation into sleep disturbance of patients suffering from cluster headache. *Cephalalgia*. 2005;25:488-492.
10. Barloese M, Jennum P, Knudsen S, Jensen R. Cluster headache and sleep, is there a connection? A review. *Cephalalgia*. 2012;32:481-491.
11. Sahota PK, Dexter JD. Transient recurrent situational insomnia associated with cluster headache. *Sleep*. 1993;16:255-257.
12. Rains JC, Poceta JS. Sleep and headache. *Curr Treat Options Neurol*. 2010;12:1-15.
13. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd edn. *Cephalalgia*. 2004;24(Suppl. 1):9-160.
14. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV*, 4th edn. Washington, DC: The American Psychiatric Association; 1994.
15. Pallesen S, Nordhus IH, Nielsen GH, et al. Prevalence of insomnia in the adult Norwegian population. *Sleep*. 2001;24:771-779.
16. Sivertsen B, Krokstad S, Overland S, Mykletun A. The epidemiology of insomnia: Associations with physical and mental health. The HUNT-2 study. *J Psychosom Res*. 2009;67:109-116.
17. Fetveit A, Straand J, Bjorvatn B. Sleep disturbances in an arctic population: The Tromso Study. *BMC Health Serv Res*. 2008;8:117.
18. Sivertsen B, Overland S, Krokstad S, Mykletun A. Seasonal variations in sleep problems at latitude 63 degrees-65 degrees in Norway: The Nord-Trondelag Health Study, 1995-1997. *Am J Epidemiol*. 2011;174:147-153.
19. Johnsen MT, Wynn R, Bratlid T. Is there a negative impact of winter on mental distress and sleeping problems in the subarctic: The Tromso Study. *BMC Psychiatry*. 2012;12:225.
20. Alstadhaug KB, Salvesen R, Bekkelund SI. Seasonal variation in migraine. *Cephalalgia*. 2005;25:811-816.
21. Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: Prevalence and consequences beyond that of symptomatic day workers. *Sleep*. 2004;27:1453-1462.
22. Horgen EH, Håland I. Patterns of working time, Labour force survey, 2012. Statistics Norway. Available at: <http://www.ssb.no/en/arbeid-og-lonn/statistikker/akutidord> (accessed October 17, 2013).
23. Drake CL, Wright KP, Jr. Shift work, shift-work disorder, and jet lag. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*, 5th edn. St. Louis, MO: Elsevier Saunders; 2011:784-798.
24. Manzoni GC. Cluster headache and lifestyle: Remarks on a population of 374 male patients. *Cephalalgia*. 1999;19:88-94.
25. Manzoni GC. Gender ratio of cluster headache over the years: A possible role of changes in lifestyle. *Cephalalgia*. 1998;18:138-142.
26. Sjostrand C, Russell MB, Ekbohm K, Waldenlind E. Familial cluster headache: Demographic patterns in

- affected and nonaffected. *Headache*. 2010;50:374-382.
27. Rozen TD, Fishman RS. Cluster headache in the United States of America: Demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache*. 2012;52:99-113.
 28. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache—Clinical findings in 180 patients. *Cephalalgia*. 1983;3:21-30.
 29. Kudrow L. The cyclic relationship of natural illumination to cluster period frequency. *Cephalalgia*. 1987;7(Suppl. 6):76-78.
 30. Gamble KL, Motesinger-Reif AA, Hida A, et al. Shift work in nurses: Contribution of phenotypes and genotypes to adaptation. *PLoS ONE*. 2011;6:e18395.
 31. Dijk DJ, Archer SN. PERIOD3, circadian phenotypes, and sleep homeostasis. *Sleep Med Rev*. 2010;14:151-160.
 32. Sanders BS. Have morbidity surveys been oversold? *Am J Public Health Nation's Health*. 1962;52:1648-1659.
 33. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. *Int J Qual Health Care*. 2003;15:261-266.