Cluster headache: expansion of the clinical spectrum

Wilbrink, L.A.

Chapter 4

Allodynia in Cluster Headache

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Pain. 2017 Jun;158(6):1113-1117

ABSTRACT

Background

Cutaneous allodynia is an established marker for central sensitization in migraine. There is debate whether cutaneous allodynia may also occur in cluster headache, another episodic headache disorder. Here we examined the presence and severity of allodynia in a large well-defined nation-wide population of people with cluster headache.

Methods

Using validated questionnaires we assessed, cross-sectionally, ictal allodynia and comorbid depression and migraine in the nation-wide "Leiden University Cluster headache Analysis" (LUCA) study. Participants with cluster headache were diagnosed according to the International Classification of Headache Disorders criteria. Multivariate regression models were used, with correction for demographic factors and cluster headache subtype (chronic vs. episodic; recent attacks < 1 month vs. no recent attacks).

Results

In total 606/798 (75.9%) participants with cluster headache responded of whom 218/606 (36%) had allodynia during attacks. Female gender (OR 2.05, 95% CI 1.28-3.29), low age at onset (OR 0.98, 95% CI 0.96- 0.99), lifetime depression (OR 1.63; 95% CI 1.06-2.50), comorbid migraine (OR 1.96; 95% CI 1.02-3.79), and having recent attacks (OR 1.80; 95% CI 1.13-2.86), but not duration of attacks and chronic cluster headache, were independent risk factors for allodynia.

Conclusion

The high prevalence of cutaneous allodynia with similar risk factors for allodynia as found for migraine suggests that central sensitization, like in migraine, also occurs in cluster headache. In clinical practice, awareness that people with cluster headache may suffer from allodynia can in the future be an important feature in treatment options.

Introduction

Cluster headache is a rare brain disorder, typically characterised by attacks of excruciating, unilateral, (peri-)orbital or temporal headache, associated with ipsilateral, facial autonomic features and restlessness. In most patients (85%), headache attacks occur in bouts of several weeks to months (episodic), in the remaining patients long attack-free periods of more than one month are absent (chronic) (2;3;27). Some aspects of the pathophysiology of cluster headache have become clear over the past decades with an important role of the hypothalamus (26) and activation of the trigeminovascular and cranial parasympathetic systems (25).

Cutaneous allodynia, the perception of pain in response to non-noxious thermal, static mechanical or dynamic mechanical stimuli to the normal skin has been described in pain syndromes (17). The pathophysiological mechanism is thought to be central sensitization; an augmentation of responsiveness of central pain-signalling neurons to input from low threshold mechanoreceptors. Allodynia and hyperalgesia are seen in various peripheral neuropathies and central pain disorders, including migraine, and affect 15-50% of people with neuropathic pain (17). In migraine, allodynia is a marker for sensitization of nociceptive neurons in the trigeminal nucleus caudalis, which receive convergent input from the dura mater and the peri-orbital skin (9), with also activation of second and third order neurons in other regions of the brain including the thalamus (10). Cutaneous allodynia occurs in up to 70- 80% of people with migraine (4;11;20), in particular in those with comorbid depression (22), and is an independent risk factor for chronification of migraine (21).

Although cluster headache has certain overlapping clinical features, treatments, and mechanisms with migraine, the presence of allodynia has not been widely investigated. Moreover, the results of the few existing small studies are contradictory. While some researchers believe that allodynia does not play a role in cluster headache (8;19), others suggest that allodynia is a frequent feature of cluster headache (14;15;24). Here we examined the prevalence and severity of cutaneous allodynia in a large well-defined population of people with cluster headache with special focus on potential risk factors such as subtype, recent attacks, and comorbid depression and migraine.

Methods

Study design and population

Our study was conducted as a part of the Leiden University Cluster headache Analysis programme; a nationwide study on the mechanisms of cluster headache. Participants were Dutch adults aged 18 or older with cluster headache. Enrolment in the Leiden University Cluster headache Analysis programme has been described elsewhere in detail (31). In short, we use a dedicated website and two validated web-based screening and diagnostic questionnaires, with a specificity of 88% to diagnose cluster headache according to the International Classification of Headache Disorders (ICHD-III beta) criteria (3). The questionnaire also distinguished between episodic and chronic cluster headache; in short, chronic cluster headache patients have no attack free periods longer than a month. A clinically confirmed diagnosis of cluster headache by a physician was available for 94% of our population (31). For the remaining, we don't know, for instance, because they never consulted a doctor. Recently, new ICHD-III criteria were published (3) with in comparison with the ICHD-II criteria (2) two additional possible diagnostic features: ipsilateral sensation of ear fullness and ipsilateral forehead and facial flushing (3). These new criteria, however, showed no relevant additional diagnostic value in our study population (13).

All 798 subjects with cluster headache in the Leiden University Cluster headache Analysis programme data base received three validated questionnaires; the extended questionnaire on cluster headache (31), the Allodynia Symptom Checklist (ASC-12) (20) on cutaneous allodynia and the Hospital Anxiety and Depression Scale (depression subscale) (HADS-D) and the Centre for Epidemiologic Studies Depression Scale (CESD) questionnaires on depression (7;18). Participants without the needed internet skills were allowed to fill out the questionnaires on paper.

This study was approved by the Medical Ethics Committee of Leiden University Medical Centre, the Netherlands. All participants provided written informed consent.

Measurements

The extended cluster headache questionnaire included questions to distinguish (i) between chronic (no attack-free periods of more than one month in the past year) and episodic (attack-free periods of at least a month in the past year) cluster headache; and (ii) between participants suffering recent attacks (last attack < 1 month) and no recent attacks (last attack > 1 month). We asked for mean attack duration with and without attack medication and for current and past use of medication (oxygen, sumatriptan, verapamil and lithium). To adjust for potential confounding effects of demographic variables, we also assessed gender, age, education, and body mass index (BMI).

The Allodynia Symptom Checklist (ASC-12) has been validated in migraine (16,20) and, after translation used in Dutch migraine patients (22), although without formal revalidation in the Dutch language. The questionnaire starts with the question: "How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage each of the following?". This question is then followed by 12 sub-items (for details, see suppl. table 1). Cutaneous allodynia was measured as a continuous variable, counting up the scores of all 12 allodynia items for each patient. Answers as "never", "rarely", or "does not apply to me" were scored as 0, "less than half of the time" was scored as 1, and "half the time or more" was scored as 2. The resulting scores ranged from 0 to 24. Secondly, based on this continuous scale, we divided cutaneous allodynia, in concordance with the ASC-12, in four categorical classes; no cutaneous allodynia (0-2), mild cutaneous allodynia (3-5), moderate cutaneous allodynia (6-8) and severe cutaneous allodynia (>8) (20). In concordance with the ASC-12, we also made a dichotomous outcome: allodynia (ASC-12 score 3-24) and no allodynia (ASC-12 score 0-2) (20).

Lifetime depression was measured as a dichotomous variable. We used validated cut-off scores for the Hospital Anxiety and Depression Scale (depression subscale) (HADS-D) and the Centre for Epidemiologic Studies Depression Scale (CESD) questionnaires (7;18), both validated in Dutch (12;29) in combination with a previously used and published algorithm for depression (30). Although the HADS-D and CESD questionnaires focused only on the previous two weeks, we aimed to reliably measure lifetime depression by adding questions on

antidepressant use and depression diagnoses. Previously, validation of this life-time depression diagnosis showed a sensitivity of 78% and a specificity of 64%, by carrying out a telephonic Composite International Diagnostic Interview (CIDI)[1) in a subset of 102 randomly selected people with migraine (22).

External validation of questionnaire

We used factor analysis to identify factors in the questionnaire as a method for validation of the Allodynia Symptom Checklist (ASC-12) in our population. This method was used before in people with migraine to investigate independent factors that represent various dimensions of cutaneous allodynia (thermal, static mechanical and dynamic mechanical allodynia) for validation in our group and by Lipton et al. (20;21). Factor analysis was performed using principal components analysis. Eigenvalues with a minimum of 1 were used for retention of factors. Items were retained in the factor on which they had the highest loading.

Data analysis and statistics

Primary analyses consisted of descriptive statistics of gender, BMI, age at onset, type of cluster headache, medication use, attack duration, attack frequency, and comorbid depression and migraine. Baseline characteristics were reported as mean $\pm$ standard deviations (SD) or percentages. Differences in means between groups were tested with independent samples *t*-tests or non-parametric tests if appropriate. Differences in proportions were tested using χ^2 tests.

For the secondary analysis, we used multivariate logistic regression models to test the association between cutaneous allodynia and the following determinants: gender, migraine comorbidity, life-time depression, age at onset of cluster headache (disease onset), cluster headache subtype (chronic vs. episodic) and having recent attacks (< 1 month) versus no recent attacks. Results were reported as odds ratios with 95% confidence intervals and corresponding p-values. For all analyses p-values < 0.05 were considered as statistical significant. All statistical analyses were performed using SPSS Statistics 20.0 (IBM, Armonk, NY, USA)

Results

Main results

The study flow diagram is shown in figure 1. Of the 798 participants with cluster headache who were sent questionnaires on allodynia, 606 (75.9%) responded and were suitable for the primary analysis. Responders (n=606) versus non responders (n=192) differed slightly in age (48.5 vs. 43.1 years, p<0.001) but did not differ in gender, type of cluster headache (episodic vs. chronic) and years of education. Of these 426/606 (70.3%) also filled out the questionnaires on depression.

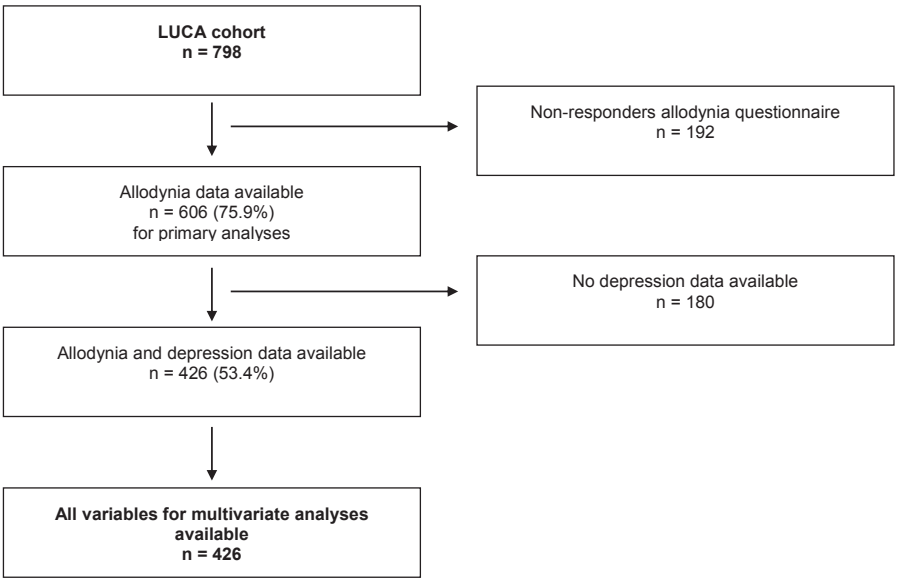

Figure 1. Flow chart

Baseline characteristics of the 218/606 (36%) participants with cluster headache who reported allodynia during attacks (n=107 mild; n=62 moderate; n=49 severe) versus those who did not are shown in Table 1 and the results of the multivariate analysis of risk factors (odds) for allodynia are summarized in Table 2. Participants with allodynia more often were females (43.2% vs. 20.4%, p < 0.001; OR 2.05, 95% CI 1.28-3.29), and more often had lower age at onset (28.8 $\pm$ 12.1 SD vs 32.4 $\pm$ 13.3 SD, p = 0.003; OR 0.98, 95% CI 0.96-0.99) and lower age at diagnosis (35.8 $\pm$ 11.2 SD vs. 38.1 + 12.0 SD, p = 0.047), and comorbid life time

depression (51.3% vs 38.4%, p=0.028; OR 1.63, 95% CI 1.06-2.50) or migraine (17.9% vs 8.0%, p<0.001; OR 1.96, 95% CI 1.02-3.79). Presence of allodynia was higher in participants with recent attacks (51.8%) compared to participants with no recent attacks (24.4%; p<0.001; OR 1.80, 95% CI 1.13-2.86) but was not influenced by type of cluster headache (chronic or episodic), presence of current or past medication use, or mean duration of the attacks (with or without attack medication). Allodynia was most frequently reported during exposure to heat (46.3%), cold (40.4%), while resting the head on a pillow (45.5%) and/or combing hair (52.4%). In the presence of allodynia, over 40 % of participants reported on these symptoms in more than half of their attacks.

Table 1. Baseline characteristics of participants with cluster headache and allodynia (n=218) versus those without allodynia (n=388).

Variable	**Total population n= 606**	**Allodynia n= 218 (36.0%)**	**No allodynia n= 388 (64.0%)**	***p***	***95% CI***
Male	435 (71.8%)	126 (57.8%)	309 (79.6%)	***<0.001***	
Age (years)	50.7 ± 11.6	51.3 ± 11.9	49.6 ±11.0	*0.071*	*-.015-3.68*
BMI (kg/m^2)	25.6 ± 3.9	25.6 ± 3.7	25.5 ± 4.1	*0.78*	*-0.59-0.74*
Age at onset	31.1 ± 13.0	28.8 ± 12.1	32.4 ± 13.3	***0.003***	*1.19-5.98*
Age at diagnosis	37.2 ± 11.7	35.8 ± 11.2	38.1 ± 12.0	***0.047***	*0.034-4.46*
CCH (vs ECH)	128 (21.7%)	51 (23.9%)	77 (20.4%)	*0.311*	
CH duration (years)	20.5 ± 12.1	20.1±12.0	21.3 ± 12.3	*0.307*	*-.344-1.08*
Medication use					
- oxygen	335 (55.4%)	125 (57.6%)	210 (54.1%)	*0.443*	
- sumatriptan	441 (72.9%)	168 (77.4%)	273 (70.4%)	*0.070*	
- verapamil	391 (64.5%)	151 (69.3%)	240 (61.9%)	*0.077*	
- lithium	74 (12.2%)	28 (12.8%)	46 (11.9%)	*0.796*	
Attack duration without attack medication (minutes)	131.1± 298.4	144.8±384.2	123.2± 235.6	*0.413*	*-73.40-30.17*
Attack duration with attack medication (minutes)	51.0 ± 277.1	34.4±42.1	60.6± 346.2	*0.284*	*-21.85-74.28*
Attack frequency last month	10.6 ± 32.9	13.0 ± 44.5	9.2 ± 24.1	***0.006****	
Time since last attack (years)	1.2 ± 2.7	0.9 ± 2.3	1.3 ± 2.8	***0.003****	
Recent attacks (< month) (vs no recent attacks)	261 (43.1%)	113 (51.8%)	148 (24.4%)	***<0.001***	
Lifetime depression# (% yes)	184 (43.2%)	80 (51.3%)	104 (38.4%)	***0.028***	
Comorbid migraine	70 (11.6%)	39 (17.9%)	31 (8.0%)	***<0.001***	

Values are the absolute numbers with corresponding % or mean ± SD and 95% confidence intervals (95% CIs). P-values depicted in bold indicate significant differences (P < 0.05), using independent samples t-tests, nonparametric tests, and $\chi 2$ tests appropriately.

* Nonparametric tests.

† Lifetime depression questionnaires were available in n = 427 people with CH.

BMI, body mass index; CCH, chronic cluster headache; CH, cluster headache; ECH, episodic cluster headache.

Table 2. Logistic associations between allodynia and possible determinants in 426 participants with cluster headache

Variable	Odds Ratio	95% CI	*p*
Gender (female vs. male)	2.05	1.28-3.29	**0.003**
Age at onset (of cluster headache) (years)	0.98	0.96-0.99	**0.003**
Chronic vs episodic cluster headache	0.962	0.53-1.74	0.898
Recent attacks (< 1 month) vs no recent attacks	1.80	1.13-2.86	**0.013**
Depression (yes vs. no)	1.63	1.06-2.50	**0.026**
Migraine comorbidity (yes vs. no)	1.96	1.02-3.79	**0.044**
Constant	-.479		0.288

Data are odds ratios (multivariate, adjusted for all mentioned covariates) with 95% confidence intervals (95% CIs) and P-values. For further description of adjustments, see Methods.
Chronic cluster headache = no attack-free periods >1 month; episodic cluster headache = attack-free periods.

External validation of questionnaire

Exploratory factor analysis showed clustering of i) wearing contact lenses, wearing glasses, wearing a pony tail, wearing tight clothes, wearing earrings, and wearing a necklace (static mechanic allodynia); ii) taking a shower, shaving the face, resting the head on a pillow and combing the hair (dynamic mechanic allodynia); iii) exposure to heat and exposure to cold (thermal allodynia) (suppl table 2). These three factors had a Cronbach's Alpha of 0.44, 0.60 and 0.67 respectively.

Discussion

We assessed the prevalence and risk factors for ictal allodynia in a very large, nation-wide population of well-defined people with cluster headache, using validated questionnaires. More than three quarters of the invited persons participated and more than one third of these reported cutaneous allodynia during attacks. Women and those with recent attacks, low age at onset, and comorbid depression or migraine were at particularly high risk of allodynia.

Previous studies on allodynia in cluster headache have provided conflicting results with prevalence ranging from 0% (0/16) to 100% (4/4)[14;15;19;23;32) likely due to inclusion of small study groups, use of non-validated or even not-described methods to assess allodynia, and variable timing (outside or during attacks) and test areas of the allodynia. In one study, comorbid migraine was like in our study, a risk factor for allodynia, but unfortunately the method of assessing allodynia was not described (15).

The presence of allodynia suggests that central sensitization, like in migraine, might also occur in cluster headache (5). Cephalic allodynia is believed to be driven by sensitization of second-order trigeminovascular neurons in the spinal trigeminal nucleus which receive converging sensory input from the meninges, the scalp and facial skin (5). The development of extracephalic allodynia is mediated by sensitization of third-order trigeminovascular neurons in the posterior thalamic nuclei which receive converging sensory input from the meninges, facial and body skin (5).

It is not clear whether the mechanism of cutaneous allodynia in cluster headache and migraine is similar or different and syndrome-specific. There are reasons to believe it is a similar mechanism. Firstly, it is clear that in both types of headache the trigeminovascular system plays a role. Secondly, cutaneous allodynia in migraine and cluster headache clinically share the three types of allodynia: thermal, static mechanic and dynamic mechanic. Thirdly, independent associations of depression and female gender with cutaneous allodynia are present in both headache types (6;11;21;22).

A difference between cluster headache and migraine is that cutaneous allodynia was described to develop more rapidly in cluster headache compared to migraine (28). The methods of our study did not allow for such an evaluation. Another difference is the lower presence of allodynia in cluster headache compared to migraine. Allodynia has been reported to occur almost twice as often in migraine than in cluster headache (11;21). A possible explanation might be that attacks of episodic and chronic cluster headache last much shorter (up to three hours) than attacks of migraine (up to three days) and that during migraine attacks, patients may have activities which are known to specifically pick up allodynia such as turning on cloths, washing face, and combing hair. As a result, patients with cluster headache might be less likely than patients with migraine to notice allodynia, irrespective of whether or not allodynia is actually present. Lastly, the precise clustering of the three factors of allodynia differed slightly compared to an earlier study in migraine by our group (21). Resting the head on a pillow ended up in the thermal factor in people with migraine, but was included in the mechanic dynamic factor in our analysis. This could be explained by the fact that people with cluster headache, in contrast to people

with migraine, would not lie still in bed during a headache attack.
As only a minority (18%) of the participants with ictal allodynia had comorbid migraine we do not believe that comorbid migraine might have been an important contributing factor. We carefully instructed participants to report on their attacks of cluster headache only and not also on possible migraine attacks. As participants with recent attacks reported allodynia more frequently than those without recent attacks and the majority of participants (57%) suffered not recently from attacks, allodynia might have been underreported in the present study.

Although quantitative sensory testing is considered the current gold standard for assessing allodynia, we decided to use the ASC-12 questionnaire (16) in our study because of the following main reasons: i) ASC-12 has been validated in migraine against the gold standard quantitative sensory testing (16); ii) results obtained with ASC-12 in migraine were consistent with earlier results in migraine obtained with quantitative sensory testing (20;21); iii) quantitative sensory testing during acute attacks of cluster headache might worsen the pain and might be logistically challenging because of the often prominent ictal restlessness; and (iv) quantitative sensory testing in large study populations might be very challenging because it requires specialized equipment, training, and testing. We realize that ASC-12 has not yet been formally validated in cluster headache against quantitative sensory testing. However, a factor analysis of our results revealed a similar distinction between thermal, static and dynamic mechanical cutaneous allodynia for ASC-12 in cluster headache as has previously been shown in migraine, which is an accepted measure for external validation (20). Some of the questions of the ASC-12 questionnaire, including wearing earrings, a necklace, or a ponytail, are predominantly female-oriented and might thus potentially bias the results towards women. We therefore conducted an additional analysis, including only the 'sex-neutral' questions and leaving out the 'sex-dependant' questions. We found that even in this sex-neutral analysis, scores in women with cluster headache were higher than in men (Median = 4 vs. Median = 2, Mann-Whitney Test U=1025.00, z=-2.80, p=0.005) confirming a real difference in risk of allodynia between sexes.

Major strengths of our study include the, certainly for a rare disease such as cluster headache, very large and clinically well-defined study population,

high response rate, no differences with non-responders (thus no bias), the detailed information on allodynia and potential risk factors such as headache characteristics and comorbid depression and migraine. Moreover we used factor analysis for the external validation of the Allodynia Symptom Checklist, which is exactly the same method used in former studies showing similar results (20;21).

This clinical finding of presence of allodynia will not only contribute to the understanding of the pathophysiologic mechanism of cluster headache, but may also be helpful in treatment decisions in the future. If the presence of allodynia in cluster headache has any predictive value in treatment response, for instance in occipital nerve stimulation, needs to be investigated.

Disclosure of conflicts of interest:
M.D. Ferrari reports grants and consultancy or industry support from Medtronic and independent support from the European Community, Netherlands Organization for Scientific Research (NWO) and the Dutch Heart Foundation. G.M. Terwindt reports independent support from NWO, European Community, the Dutch Heart Foundation, and the Dutch Brain Foundation. The other authors report no conflicts of interest.

Funding acknowledgement:
This work was supported by grants of the Netherlands Organization for Scientific Research (NWO) [VIDI 91711319, G.M.T.) and the European Community (EC) [FP7-EUROHEADPAIN - no. 602633); They had no role in the design or conduct of the study.

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Supplementary table 1. 12-item Allodynia Symptom Checklist (ASC-12)[19]

Question: How often do you experience increased pain or an unpleasant sensation on your skin during your most severe type of headache when you engage each of the following?	Does not apply to me	Never	Rarely	Less than half of the time	Half of the time or more
	Score: 0	Score: 0	Score: 0	Score: 1	Score: 2
wearing a necklace					
wearing earrings					
wearing glasses					
wearing tight clothes					
wearing a pony tail					
wearing contact lenses					
shaving the face					
taking a shower					
combing the hair					
resting the head on a pillow					
exposure to cold					
exposure to heat					
Total score:					
Sum of score:					

Suppl table 2. Exploratory factor analysis of Allodynia Symptom checklist (ASC-12)

	Factor 1	Factor 2	Factor 3
wearing a necklace	.75		
wearing earrings	.75		
wearing glasses	.66		
wearing tight clothes	.55		
wearing a pony tail	.53		
wearing contact lenses	.50		
shaving the face		.80	
taking a shower		.72	
combing the hair		.68	
resting the head on a pillow		.47	
exposure to cold			-.78
exposure to heat			-.65
% of variance	27.6	12.5	8.6