Clinical Features of Cluster Headache without Cranial Autonomic Symptoms: Results from a Prospective multicentre study

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Abstract

Background: Although cranial autonomic symptoms are typical in cluster headache, some individuals with cluster headache show no cranial autonomic symptoms during their headache attacks. Probable cluster headache is a subtype of cluster headache that fulfils all but one of the five criteria for cluster headache. This study aimed to investigate the frequency and clinical features of cluster headache and probable cluster headache without cranial autonomic symptoms in comparison to those with cranial autonomic symptoms.

Methods: We analysed data from the Korea Cluster Headache Registry, a prospective multicentre registry involving data from 16 hospitals.

Results: Of the 216 participants with cluster headache and 26 with probable cluster headache, 19 (8.8%) and 7 (26.9%), respectively, did not have cranial autonomic symptoms. Participants with cluster headache without cranial autonomic symptoms exhibited less severe anxiety (General Anxiety Disorder-7 score, median [interquartile range], 2.0 [1.0-6.0] vs 8.0 [3.0-12.0], $p = 0.001$) and depression (Patient Health Questionnaire-9 score, 3.0 [1.0-7.0] vs 7.0 [3.0-11.0], $p = 0.042$) than those with cranial autonomic symptoms. Other clinical features, including headache intensity, daily headache frequency, attack duration, bout duration, and location of the pain, did not differ between participants with cluster headache with and without cranial autonomic symptoms. Headache intensity was less severe in participants with probable cluster headache without cranial autonomic symptoms than in those with cranial autonomic symptoms (numeric rating scale, 8.0 [7.0-8.0] vs 9.5 [8.0-10.0], $p = 0.015$).

Conclusions: A significant proportion of participants with cluster headache and probable cluster headache did not have cranial autonomic symptoms. Some clinical features of cluster headache and probable cluster headache differed based on the presence of cranial autonomic symptoms.

Background

Cluster headache (CH) is one of the most painful primary headache disorders. It is characterised by recurrent severe unilateral headache attacks and accompanied by ipsilateral cranial autonomic symptoms (CAS) [1, 2]. The term CH originates from the tendency of these headache attacks to cluster during bout periods that usually last for several weeks to months [3]. The third edition of the International Classification of Headache Disorders (ICHD-3) has divided the CH population into CH (code 3.1) and probable CH (PCH; code 3.5.1) [2]. PCH is a subtype of CH that fulfils all but one of the five criteria for CH and was reported to account for approximately 10–20% of CH cases [2, 4, 5]. Some clinical features of PCH differ from those of CH. Individuals with PCH have a lower incidence of conjunctival injection and forehead sweating than those with CH, but these groups have showed comparable disability [5, 6].

Although CAS have been recognised as typical symptoms of CH, 3–7% of individuals with CH were noted to never experience CAS during their CH attacks [7–9]. The frequency and clinical features of CH without CAS have been reported in only one study. A Portuguese study from a single university hospital reported

in 2005 that headache intensity was less severe in individuals with CH without CAS than in those with CAS [7]. However, since this study did not distinguish between CH and PCH in its analysis, the frequency and clinical features of CH and PCH compared to those with CAS remain unclear. Furthermore, this study used data from a single hospital; thus, an additional analysis using data from various settings is needed to validate these findings.

This study aimed to assess (1) the frequencies of CH and PCH without CAS among participants with CH and PCH and (2) the differences in the clinical features of participants with CH and PCH with and without CAS. For this purpose, we used data from the Korean Cluster Headache Registry (KCHR), a prospective, multicentre registry of CH.

Methods

Study design and participants

This descriptive, cross-sectional study aimed to investigate the frequency and clinical features of CH and PCH without CAS using data from the KCHR. The KCHR enrolled consecutive participants with CH aged ≥ 19 years from 16 hospitals (14 university hospitals and two secondary referral general hospitals) in Korea. Participants were enrolled between September 2016 and December 2018.

Detailed information about the KCHR has been described previously [5, 10]. In the KCHR, participants fulfilling the diagnostic criteria for CH and PCH based on the beta version of the ICHD-3 (ICHD-3 beta), the available diagnostic criteria at the time, were enrolled. For the present study, we included participants fulfilling the diagnostic criteria for CH and PCH based on ICHD-3. A flow diagram of the participant selection process is presented in Fig. 1.

The KCHR collected data on the following parameters for all participants: sex, age at onset, body mass index, time from first headache onset to the diagnosis of CH, headache intensity using a numeric rating scale (from 0 to 10), CH frequency, mean CH duration since the first episode, CH bout duration during the ictal period, total number of CH bouts, smoking history, impact of headache (Headache Impact Test-6 [HIT-6] score), anxiety (General Anxiety Disorder-7 [GAD-7] score), and depression (Patient Health Questionnaire-9 [PHQ-9] score). Participants with a GAD-7 score of ≥ 10 were classified as having anxiety [11], while participants with a PHQ-9 score of ≥ 10 were classified as having depression [12, 13]. The bout duration was defined as the duration between the first and last day of each cluster period. The cluster period was designated as cluster attacks occurring in a series persisting for weeks to months, separated by remission periods, usually lasting for several months or even years. The total number of bouts was defined as the total number of bouts (cluster periods) diagnosed as CH. The history of migraine was evaluated in all participants. Investigators assessed the circadian and circannual rhythms by asking participants whether the attacks in the bout tended to occur at the same time of the day and year, respectively.

Diagnosis of cluster headache and probable cluster headache

The diagnoses of CH and PCH were based on the ICHD-3 criteria. We further classified participants into one of the following groups based on the bout period duration: no definitive period, episodic, or chronic. Participants whose first episode of headache attacks fulfilled the CH or PCH criteria were classified, respectively, as having CH or PCH without a definitive period. Participants whose CH or PCH attacks lasted at least 1 year without a remission period or with remissions lasting < 3 months were classified as having chronic CH (CCH) or PCH, respectively. Participants whose CH or PCH attacks occurred in bouts (cluster periods), in whom two or more cluster periods lasted from 7 days to 1 year when untreated, and in whom cluster periods were separated by pain-free remission periods of ≥ 3 months were classified as having episodic CH (ECH) or episodic PCH.

Case definitions of cluster headache and probable cluster headache without cranial autonomic symptoms

According to the ICHD-3, we evaluated CAS in participants with CH and PCH based on the presence of the following conditions: (1) conjunctival injection and/or lacrimation, (2) nasal congestion and/or rhinorrhoea, (3) eyelid oedema, (4) forehead and facial sweating, and (5) miosis and/or ptosis. Since our study started in September 2016, when only the ICHD-3 beta was available, we also assessed the presence of (1) a sensation of fullness in the ear and (2) forehead and facial flushing, which were included as CAS in the ICHD-3 beta but not in the ICHD3.

Ethical considerations

The institutional review boards of the 16 participating hospitals approved this study. All participants provided written informed consent before study enrolment. All clinical investigations were conducted following the principles expressed in the Declaration of Helsinki.

Statistical analyses

The Kolmogorov–Smirnov test was used to evaluate the normality of data distribution. When a normal distribution was confirmed, Student's *t*-test or one-way analysis of variance was used to compare continuous variables. If a normal distribution was not confirmed, the Mann–Whitney *U* test or Kruskal–Wallis test was used, and values were expressed as medians (interquartile ranges). The chi-squared test was used to evaluate categorical variables. If an expected value was less than five, Fisher's exact test was used instead of the chi-squared test. Results were considered statistically significant when two-tailed *p*-values were less than 0.05. The sample size was based on the available data. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Participants

A total of 251 participants were enrolled. One participant was excluded for not fulfilling the ICHD-3 criteria, and eight were excluded due to incomplete data. Finally, 216 participants with CH and 26 participants with PCH were included in this study (Fig. 1). The reasons for a diagnosis of PCH were as follows: an atypical attack duration ($n = 8$, 30.7%), where the duration was longer ($n = 6$) or shorter ($n = 2$) than typical; missing accompanying symptoms ($n = 6$, 23.1%); <5 total number of attacks ($n = 5$, 19.2%); <1 attack every other day ($n = 3$, 11.5%); not a severe headache intensity ($n = 2$, 7.7%); and a bilateral pain location ($n = 2$, 7.7%). None of the participants with CH or PCH without CAS had a sensation of fullness in the ear or forehead and facial flushing, which were indicated as accompanying CAS in the ICHD-3 beta.

The frequencies of CAS in participants with CH and PCH are summarised in Table 1. Conjunctival injection and/or lacrimation was the most common CAS in participants with CH, followed by nasal congestion and/or rhinorrhoea. Ptosis or miosis was the least common CAS. Similar patterns were seen in participants with PCH, with conjunctival injection and/or lacrimation being the most common CAS and ptosis or miosis being the least common.

Table 1
Distribution of cranial autonomic symptoms in the participants

Accompanying symptoms	All participants with CH or PCH <i>n</i> = 242, <i>n</i> (%)	CH (code 3.1, 3.1.1, and 3.1.2) <i>n</i> = 216, <i>n</i> (%)	ECH (code 3.1.1) <i>n</i> = 172, <i>n</i> (%)	CCH (code 3.1.2) <i>n</i> = 12, <i>n</i> (%)	PCH (code 3.5) <i>n</i> = 26, <i>n</i> (%)
Cranial autonomic symptoms					
Conjunctival injection and/or lacrimation	202 (83.5)	187 (86.6)	151 (87.8)	11 (91.7)	15 (57.7)
Nasal congestion and/or rhinorrhoea	134 (55.4)	123 (56.9)	110 (64.0)	3 (25.0)	11 (42.3)
Eyelid oedema	64 (26.4)	60 (27.8)	50 (29.1)	3 (25.0)	4 (15.4)
Forehead and facial sweating	68 (28.1)	66 (30.6)	54 (31.4)	5 (41.7)	2 (7.7)
Miosis and/or ptosis	50 (20.7)	48 (22.2)	39 (22.7)	2 (13.3)	2 (7.7)
Forehead and facial flushing	38 (15.7)	37 (17.1)	34 (19.8)	1 (8.3)	1 (3.8)
Sensation of fullness in the ear	22 (9.1)	20 (9.3)	19 (11.0)	0 (0.0)	2 (7.7)
No cranial autonomic symptoms	26 (10.7)	19 (8.8)	15 (8.7)	1 (8.3)	7 (26.9)
A sense of restlessness or agitation	116 (47.9)	107 (49.5)	85 (49.4)	8 (66.7)	9 (34.6)
CH: cluster headache, PCH: probable cluster headache, ECH: episodic cluster headache, CCH: chronic cluster headache					

Clinical features of all participants according to the presence of cranial autonomic symptoms

The clinical features of all 242 participants are summarised in Table 2. The headache intensity was less severe in participants without CAS than in those with CAS. Anxiety (GAD-7 score ≥ 10) and depression (PHQ-9 score ≥ 10) were less prevalent in participants without CAS than in those with CAS. All other features were similar in participants with and without CAS.

Table 2
Clinical features of participants with CH and PCH according to the presence of CAS

	Participants with CH and PCH <i>n</i> = 242, <i>n</i> (%)	Participants with CH and PCH with CAS <i>n</i> = 216, <i>n</i> (%)	Participants with CH and PCH without CAS <i>n</i> = 26, <i>n</i> (%)	<i>p</i>- value
Female	37 (15.3)	33 (15.3)	4 (15.4)	1.000
Age (year)	37 (30.0–44.0)*	37.0 (30.3–43.8)*	37.0 (28.8–44.3)*	0.822
Attack frequency per day	37 (15.3)	33 (15.3)	4 (15.4)	0.409
Headache intensity (numeric rating scale)	37 (30.0–44.0)*	37.0 (30.25–43.8)*	37.0 (28.75–44.3)*	0.011
Attack duration (minutes)	37 (15.3)	33 (15.3)	4 (15.4)	0.796
Migraine history	33 (13.6)	30 (14.30)	3 (11.5)	1.000
Circadian rhythm	134 (55.4)	121 (56.0)	13 (50.0)	0.560
Circannual rhythm	219 (90.5)	198 (91.7)	21 (80.8)	0.073
Current smoking	106 (43.8)	99 (45.8)	7 (26.9)	0.066
Location of pain				
Orbital	193 (79.8)	174 (80.6)	19 (73.1)	0.370
Supraorbital	121 (50.0)	112 (51.9)	9 (34.6)	0.097
Temporal	138 (57.0)	121 (56.0)	17 (65.4)	0.362
Headache Impact Test-6 score	69.0 (63.0–75.0)*	69.0 (63.0–75.0)*	67.5 (57.8–72.8)*	0.259
Anxiety (Generalized Anxiety Disorder-7 score)	7.0 (3.0–11.0)*	7.0 (3.0–12.0)*	2.0 (1.0-7.5)*	0.001
Generalized Anxiety Disorder-7 score ≥ 10	87 (36.0)	83 (38.8)	4 (15.4)	0.018
Depression (Patient Health Questionnaire-9 score)	6.0 (3.0–11.0)*	7.0 (3.0–11.0)*	4.0 (2.0-7.3)*	0.029
Patient Health Questionnaire-9 score ≥ 10	80 (33.1)	76 (35.3)	4 (15.4)	0.047
CAS: cranial autonomic symptoms, CH: cluster headache, PCH: probable cluster headache				
Median and interquartile range				

Clinical features of participants with cluster headache based on the presence of cranial autonomic symptoms

Of the 216 participants with CH, 19 (8.8%) did not have CAS. Headache intensity, anxiety, and depression were less severe in participants with CH without CAS than in those with CAS. Other characteristics were not associated with the presence of CAS (Table 3).

Table 3
Clinical features of participants with CH according to the presence of CAS

	Participants with CH <i>n</i> = 216, <i>n</i> (%)	Participants with CH with CAS <i>n</i> = 197, <i>n</i> (%)	Participants with CH without CAS <i>n</i> = 19, <i>n</i> (%)	<i>p</i>-value
Female	30 (13.9)	29 (14.7)	1 (5.3)	0.484
Age (year)	37.0 (30.0–44.0)*	37.0 (30.0–43.5)*	38.0 (25.0–45.0)*	0.933
Attack frequency per day	1.5 (1.0–3.0)*	1.5 (1.0–3.0)*	1.5 (1.0–2.5)*	0.686
Headache intensity (numeric rating scale)	9.0 (8.0–10.0)*	9.0 (8.0–10.0)*	9.0 (8.0–10.0)*	0.303
Attack duration (minutes)	90.0 (60.0–120.0)*	90.0 (60.0–120.0)*	120.0 (60.0–120.0)*	0.581
Migraine history	28 (13.0)	27 (13.7)	1 (5.3)	0.479
Circadian rhythm	125 (57.9)	116 (59.5)	9 (47.4)	0.306
Circannual rhythm	197 (91.2)	181 (92.3)	16 (84.2)	0.221
Current smoking	98 (45.4)	91 (46.2)	7 (36.8)	0.434
Location of pain				
Orbital	172 (79.6)	158 (80.2)	14 (73.7)	0.500
Supraorbital	109 (50.5)	102 (51.8)	7 (36.8)	0.214
Temporal	120 (55.6)	110 (55.8)	10 (52.6)	0.788
Headache Impact Test-6 score	69.0 (63.0–75.0)*	69.0 (63.0–75.0)*	70.0 (64.0–76.0)*	0.938
Anxiety (Generalized Anxiety Disorder-7 score)	7.0 (3.0–11.75)*	8.0 (3.0–12.0)*	2.0 (1.0–6.0)*	0.002
Generalized Anxiety Disorder-7 score ≥ 10	81 (37.5)	78 (39.6)	3 (15.8)	0.048
Depression (Patient Health Questionnaire-9 score)	6.0 (3.0–11.0)*	7.0 (3.0–11.0)*	3.0 (1.0–7.0)*	0.030
Patient Health Questionnaire-9 score ≥ 10	71 (32.9)	68 (34.5)	3 (15.8)	0.126
CAS: cranial autonomic symptoms, CH: cluster headache				
*Median and interquartile range				

Among the 172 participants with ECH, 15 (8.7%) did not have CAS. The mean duration of headache attacks was longer and anxiety and depression were less prevalent in participants with ECH without CAS than in those with CAS. Other clinical features were similar between participants with ECH with and without CAS (Table 4). Of the 12 participants with CCH, two (16.7%) did not have CAS. The frequencies of the absence of CAS in ECH and CCH were similar (8.7% [15/172] vs 16.7% [2/12], $p = 0.612$, Table 4).

Table 4
Clinical features of participants with ECH according to the presence of CAS

	Participants with ECH <i>n</i> = 172, <i>n</i> (%)	Participants with ECH with CAS <i>n</i> = 157, <i>n</i> (%)	Participants with ECH without CAS <i>n</i> = 15, <i>n</i> (%)	<i>p</i>-value
Female	22 (12.8)	21 (13.4)	1 (6.7)	0.696
Age (year)	37 (30.25–44.0)*	37.0 (31.5–44.0)*	38.0 (24.0–44.0)*	0.565
Onset age (year)	10.0 (5.0–16.0)*	10.0 (5.0–16.0)*	60. (2.0–10.0)*	0.067
Cluster duration (year)	7.0 (3.0–12.0)*	7.0 (3.0–12.0)*	7.0 (2.0–10.0)*	0.263
Total bout (number)	7.0 (3.0–12.0)*	7.0 (3.0–12.0)*	7.0 (2.0–10.0)*	0.263
Attack frequency per day	10.0 (5.0–16.0)*	10.0 (5.0–16.0)*	60. (2.0–10.0)*	0.067
Headache intensity (numeric rating scale)	7.0 (3.0–12.0)*	7.0 (3.0–12.0)*	7.0 (2.0–10.0)*	0.263
Attack duration (minutes)	10.0 (5.0–16.0)*	10.0 (5.0–16.0)*	6.0 (2.0–10.0)*	0.067
Average bout duration (month)	4.0 (3.0–8.0)*	4.0 (3.0–7.0)*	6.0 (4.0–10.0)*	0.020
Average remission period (month)	12.0 (10.0–24.0)*	12.0 (10.0–24.0)*	12.0 (6.0–12.0)*	0.502
Regular attack pattern	121 (70.3)	113 (72.0)	8 (53.3)	0.131
Migraine history	17 (9.9)	17 (11.0)	0 (0.0)	0.368
Circadian rhythmicity	103 (59.9)	96 (61.1)	7 (46.7)	0.426
Circannual rhythmicity	170 (98.8)	155 (98.7)	15 (100.0)	1.000
Current smoking	80 (46.5)	75 (47.8)	5 (33.3)	0.417
Location of pain				
Orbital	137 (79.7)	127 (80.9)	10 (66.7)	0.191
Supraorbital	84 (48.8)	78 (49.7)	6 (40.0)	0.474

CAS: cranial autonomic symptoms, ECH: episodic cluster headache

*Median and interquartile range

	Participants with ECH <i>n</i> = 172, <i>n</i> (%)	Participants with ECH with CAS <i>n</i> = 157, <i>n</i> (%)	Participants with ECH without CAS <i>n</i> = 15, <i>n</i> (%)	<i>p</i> -value
Temporal	92 (53.5)	84 (53.5)	8 (53.3)	0.990
Headache Impact Test-6 score	69.0 (63.0–75.0)*	69.0 (63.0–75.0)*	70.0 (64.0–76.0)*	0.938
Anxiety (Generalized Anxiety Disorder-7 score)	7.0 (3.0–11.8)*	8.0 (3.0–12.0)*	2.0 (1.0–6.0)*	0.002
Generalized Anxiety Disorder-7 score ≥ 10	81 (37.5)	78 (39.6)	3 (15.8)	0.048
Depression (Patient Health Questionnaire-9 score)	6.0 (3.0–11.0)*	7.0 (3.0–11.0)*	3.0 (1.0–7.0)*	0.030
Patient Health Questionnaire-9 score ≥ 10	71 (32.9)	68 (34.5)	3 (15.8)	0.126
CAS: cranial autonomic symptoms, ECH: episodic cluster headache				
*Median and interquartile range				

Clinical features of participants with probable cluster headache based on the presence of cranial autonomic symptoms

Of the 26 participants with PCH, 7 (26.9%) did not have CAS. Headache intensity was less severe in participants with PCH without CAS than in those with CAS. The prevalence of anxiety and depression and other clinical features were similar in participants with PCH with and without CAS (Table 5). The frequency of not having CAS was higher in participants with PCH than in those with CH (26.9% [7/26] vs 8.7% [19/216], $p = 0.005$).

Table 5
Clinical features of participants with PCH according to the presence of CAS

	Participants with PCH <i>n</i> = 26, <i>n</i> (%)	Participants with PCH with CAS <i>n</i> = 19, <i>n</i> (%)	Participants with PCH without CAS <i>n</i> = 7, <i>n</i> (%)	<i>p</i>- value
Female	7 (26.9)	4 (21.1)	3 (42.9)	0.340
Age (year)	38.5 (33.75–43.25)*	40.0 (35.0–44.0)*	36.0 (30.-43.0)*	0.534
Onset age (year)	32.0 (28.75–42.25)*	32.0 (28.0–42.0)*	36.0 (29.0–43.0)*	0.572
Cluster duration (year)	1.0 (0.0-6.25)*	2.0 (0.0–9.0)*	1.0 (0.0–3.0)*	0.427
Total bout (number)	1.5 (1.0–4.0)*	2.0 (1.0–4.0)*	1.0 (1.0–2.0)*	0.534
Attack frequency per day	1.0 (1.0–2.0)*	1.0 (1.0–3.0)*	1.0 (1.0–2.0)*	0.778
Headache intensity (numeric rating scale)	8.5 (7.75-10.0)*	9.5 (8.0–10.0)*	8.0 (7.0–8.0)*	0.015
Attack duration (minutes)	60.0 (35.0-180.0)*	60 (30–195.0)*	6.0 (6.0–12.0)*	0.790
Average bout duration (month)	3.5 (2.25-4.0)	4.0 (2.0–4.0)*	3.0 (2.0–3.0)*	0.727
Average remission period (month)	23.0 (5.0–29.0)	23.0 (4.0-28.5)*	12.0 (6.0–12.0)*	> 0.999
Regular attack pattern	6 (23.1)	5 (26.3)	1 (14.3)	> 0.999
Migraine history	5 (19.2)	3 (15.8)	2 (28.6)	0.588
Circadian rhythm	9 (34.6)	5 (27.8)	4 (57.1)	0.205
Circannual rhythm	22 (84.6)	1 (5.6)	2 (28.6)	0.180
Current smoking	8 (30.8)	8 (42.1)	0 (0.0)	0.062
Location of pain				
Orbital	21 (80.8)	16 (84.2)	5 (71.4)	0.588
Supraorbital	12 (46.2)	10 (52.6)	2 (28.6)	0.391
Temporal	18 (69.2)	11 (57.9)	7 (100.0)	0.062

CAS: cranial autonomic symptoms, PCH: probable cluster headache, *Median and interquartile range

	Participants with PCH <i>n</i> = 26, <i>n</i> (%)	Participants with PCH with CAS <i>n</i> = 19, <i>n</i> (%)	Participants with PCH without CAS <i>n</i> = 7, <i>n</i> (%)	<i>p</i> -value
Headache Impact Test-6 score	65.5 (57.0–72.0)*	67.0 (58.0–76.0)*	58.0 (50.0–68.0)*	0.107
Anxiety (Generalized Anxiety Disorder-7 score)	5.0 (2.0–9.75)*	5.0 (3.0–11.0)*	4.0 (3.0–8.0)*	0.455
Generalized Anxiety Disorder-7 score ≥ 10	6 (23.1)	5 (26.3)	1 (14.3)	> 0.999
Depression (Patient Health Questionnaire-9 score)	5.0 (2.0–9.75)*	5.0 (3.0–11.0)*	4.0 (3.0–8.0)*	0.455
Patient Health Questionnaire-9 score ≥ 10	6 (23.1)	5 (26.3)	1 (14.3)	> 0.999
CAS: cranial autonomic symptoms, PCH: probable cluster headache, *Median and interquartile range				

Discussion

The main findings of the present study were as follows: (1) Approximately one-eleventh of participants with CH and a quarter of those with PCH did not have CAS; (2) Anxiety and depression were less severe in participants with CH without CAS than in those with CAS; and (3) Headache intensity was milder in participants with PCH without CAS than in those with CAS. Other clinical features of CH and PCH did not differ between participants with and without CAS.

CH has been characterised by recurrent attacks of severe unilateral headache and ipsilateral CAS [1, 14]. CAS were considered a key characteristic of CH and included as a diagnostic criterion since the publishing of the first edition of the ICHD [8, 15]. Nevertheless, it has been reported that some individuals with CH-like headaches did not experience CAS during headache attacks [9, 16]. The second edition of the ICHD, published in 2004, included a sense of restlessness or agitation as an accompanying symptom of CH, in addition to CAS, and a diagnosis of CH without CAS became possible [4]. The subsequent editions of diagnostic criteria for CH retained restlessness or agitation as an accompanying symptom along with CAS [2, 17]. Therefore, CH and PCH without CAS are currently included in the ICHD-3, and our study enrolled participants based on these definitions.

We found that 8.8% of participants with CH did not have CAS. This frequency was similar or somewhat higher than that found in previous studies. A case series of 163 patients with CH in Sweden found that 3.1% did not have CAS [16], while an Italian clinic-based study of 251 patients with CH found that 2.8% did not have CAS [8]. Another Italian study found that 7.5% of patients with CH did not have CAS [9]. In a clinic-based study in Portugal, not having CAS was reported in 6.1% of patients with CH or PCH [7]. Possible causes for the discrepancy between the findings from our study and those from previous studies include differences in the diagnostic criteria, ethnicity, and study setting. The mentioned Swedish study

used three criteria for CH diagnosis (World Federation of Neurology, Ekbom, and ICHD-1) [16, 18]. The two Italian studies used the ICHD-1, which did not include restlessness and agitation as accompanying symptoms. All four studies were conducted in European countries, while our study was conducted in Korea. Individuals with CH in Asian countries showed lower attack frequencies and shorter attack durations than those in Western countries [19]. All four previous studies used data from a single hospital, while the present study used data from the KCHR, which contained data from 16 hospitals.

It has been consistently reported that individuals with CH have a higher frequency of anxiety and depression than those with migraine or without headache [10, 20–24]. Additionally, it has been demonstrated that individuals with CCH are more likely to be affected by anxiety and depression than those with ECH [10]. High frequencies of anxiety and depression were observed in the CH and PCH groups in the present study. Furthermore, to the best of our knowledge, this study is the first to report that anxiety and depression were less severe in participants with CH without CAS compared to those with CAS. What is the possible mechanism underlying the association of anxiety and depression with CAS? One possible explanation is the role of shared anatomical substrates between the affective symptoms and CH in the pathogenesis of CAS. Neuroimaging findings have revealed an altered metabolism of the pain matrix and hypothalamus in patients with CH and affective disorders [25–27]. Therefore, decreased frequencies of anxiety and depression in participants with CH without CAS may be related to the roles of the pain matrix and hypothalamus in the pathogenesis of CAS. This hypothesis could be evaluated by comparing the neuroimaging findings between individuals with CH with and without CAS.

Conjunctival injection and/or lacrimation has been consistently reported to be the most common CAS in individuals with CH [8, 28–30]. In the present study, conjunctival injection and/or lacrimation, as the most frequent CAS, was observed in 86.6% of participants with CH. Conjunctival injection and/or lacrimation was the most frequent CAS in Asian as well as Western countries [6, 19, 31, 32]. The frequency of CAS in the present study was similar to that found in previous studies from Asian countries. The frequency of ptosis or miosis in the present study (22.2%) was lower than that found in studies from Western countries. A prospective clinical study in the UK found that 76% of individuals with CH had ptosis [30]. A Danish study reported that ptosis was present in 44.8% of patients with CH [29]. In Asian studies, a lower frequency of ptosis or miosis has been observed—a Japanese study showed a ptosis frequency of 8.1% [6], while a study at a Chinese tertiary headache centre revealed that ptosis or miosis was present in 16.7% of patients with CH [32] and a Korean multicentre study reported a rate of 8.5% [31]. The similarity in CAS frequencies mentioned above suggests that this parameter was correctly evaluated in the present study.

Our study had some limitations. First, it was conducted as a multicentre prospective study, but it did not represent the whole CH and PCH population. Therefore, our findings should be validated using another dataset to enhance the generalisability. Second, we included relatively small samples of patients with PCH and CCH. Although we tried to enrol all eligible patients with PCH and CCH over the 3-year study period, the number of relevant cases may have been too small for some subgroup analyses. In other words, the statistical power was weakened by the limited sample size. Further studies that include a

sufficient number of participants with PCH and CCH are needed to verify our findings. Third, we used the GAD-7 and PHQ-9 to assess anxiety and depression, respectively. However, these instruments only indicate a state of anxiety and depression and cannot be used to confirm the diagnosis. Additional analyses diagnosing anxiety and depression according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders will confirm the relationship of anxiety and depression with CAS in CH.

Conclusions

Among the participants with CH, 9% did not have CAS. The prevalence of anxiety and depression was lower in these patients than in those with CAS. Other clinical features were similar between participants with and without CAS. One-quarter of the participants with PCH did not have CAS and headache intensity was less severe in these participants than in those with CAS. The frequency of anxiety and depression did not differ between participants with PCH with and without CAS. Our study proposed that some clinical features of CH and PCH differed based on the presence of CAS. The findings of the present study will help to enhance the understanding of the pathophysiology of CH.

Abbreviations

CAS: cranial autonomic symptoms; CCH: chronic cluster headache; CH: cluster headache; ECH: episodic cluster headache; GAD-7: Generalized Anxiety Disorder-7; HIT-6: Headache Impact Test-6; ICHD-3: The third edition of the International Classification of Headache Disorders; ICHD-3 beta: The third edition beta version of the International Classification of Headache Disorders; KCHR: Korean Cluster Headache Registry; PCH: probable cluster headache; PHQ-9: Patient Health Questionnaire-9.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee in each participating hospital and complied with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients fully understood the study aims and gave written informed consent before participation.

Consent for publication

Not applicable.

Availability of data and materials

The data used in the present study are available from the corresponding author on reasonable request.

Competing interests

Drs. BS Kim, PW Chung, BK Kim, MJ Lee, JW Park, JY Ahn, DW Bae, TJ Song, JH Sohn, K Oh, D Kim, JM Kim, SK Kim, YJ Choi, JM Chung, HS Moon, CS Chung, and KY Park declare that they have no competing interests.

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Authors' contributions

MKC and SJC conceptualised the idea and designed the study. BSK, PWC, BKK, MJL, JWP, MKC, JYA, DWB, TJS, JHS, KO, DK, JMK, SKK, YJC, JMC, HSM, CSC, KYP, and SJC contributed to data acquisition, analysis, and interpretation. MKC and SJC drafted the initial manuscript. PWC, BKK, MJL, JWP, MKC, JYA, DWB, TJS, JHS, KO, DK, JMK, SKK, YJC, JMC, HSM, and CSC made critical revisions to the manuscript with important intellectual content. All authors reviewed and approved the final manuscript. All authors agreed to be responsible for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of this work will be appropriately investigated and resolved.

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References

1. May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ (2018) Cluster headache. Nat Rev Dis Primers 4:18006. doi:10.1038/nrdp.2018.6
2. Headache Classification Committee of the International Headache Society (IHS). (2018) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 38(1):1-211.

doi:10.1177/0333102417738202

3. Nesbitt AD, Goadsby PJ (2012) Cluster headache. *BMJ* 344:e2407. doi:10.1136/bmj.e2407
4. Headache Classification Committee of the International Headache Society. (2004) The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 24 Suppl 1:9-160
5. Sohn JH, Choi YJ, Kim BK, Chung PW, Lee MJ, Chu MK, Ahn JY, Kim BS, Song TJ, Oh K, Lee KS, Kim SK, Park KY, Chung JM, Moon HS, Chung CS, Cho SJ, Park JW (2018) Clinical Features of Probable Cluster Headache: A Prospective, Cross-Sectional Multicenter Study. *Front Neurol* 9:908. doi:10.3389/fneur.2018.00908
6. Imai N, Yagi N, Kuroda R, Konishi T, Serizawa M, Kobari M (2011) Clinical profile of cluster headaches in Japan: low prevalence of chronic cluster headache, and uncoupling of sense and behaviour of restlessness. *Cephalalgia* 31(5):628-633. doi:10.1177/0333102410391486
7. Martins IP, Gouveia RG, Parreira E (2005) Cluster headache without autonomic symptoms: why is it different? *Headache* 45(3):190-195. doi:10.1111/j.1526-4610.2005.05043.x
8. Nappi G, Micieli G, Cavallini A, Zanferrari C, Sandrini G, Manzoni GC (1992) Accompanying symptoms of cluster attacks: their relevance to the diagnostic criteria. *Cephalalgia* 12(3):165-168. doi:10.1046/j.1468-2982.1992.1203165.x
9. Torelli P, Cologno D, Cademartiri C, Manzoni GC (2001) Application of the International Headache Society classification criteria in 652 cluster headache patients. *Cephalalgia* 21(2):145-150. doi:10.1046/j.1468-2982.2001.00185.x
10. Kim BS, Chung PW, Kim BK, Lee MJ, Park JW, Chu MK, Ahn JY, Bae DW, Song TJ, Sohn JH, Oh K, Kim D, Kim JM, Kim SK, Choi YJ, Chung JM, Moon HS, Chung CS, Park KY, Cho SJ (2020) The impact of remission and coexisting migraine on anxiety and depression in cluster headache. *J Headache Pain* 21(1):58. doi:10.1186/s10194-020-01120-7
11. Spitzer RL, Kroenke K, Williams JB, Löwe B (2006) A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 166(10):1092-1097. doi:10.1001/archinte.166.10.1092
12. Choi HS, Choi JH, Park KH, Joo KJ, Ga H, Ko HJ, Kim SR (2007) Standardization of the Korean Version of Patient Health Questionnaire-9 as a Screening Instrument for Major Depressive Disorder. *J Korean Acad Fam Med* 28(2):114-119
13. Kroenke K, Spitzer R (2002) The PHQ-9: A New Depression Diagnostic and Severity Measure. *Psychiatric Annals* 32:509-521. doi:10.3928/0048-5713-20020901-06
14. Wei DY, Yuan Ong JJ, Goadsby PJ (2018) Cluster Headache: Epidemiology, Pathophysiology, Clinical Features, and Diagnosis. *Ann Indian Acad Neurol* 21(Suppl 1):S3-s8. doi:10.4103/aian.AIAN_349_17
15. Headache Classification Committee of the International Headache Society. (1988) Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. . *Cephalalgia* 8 Suppl 7:1-96
16. Ekblom K (1990) Evaluation of clinical criteria for cluster headache with special reference to the classification of the International Headache Society. *Cephalalgia* 10(4):195-197. doi:10.1046/j.1468-2982.1990.1004195.x

17. Headache Classification Committee of the International Headache Society. (2013) The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 33(9):629-808. doi:10.1177/0333102413485658
18. World Federation of Neurology Research Group on Migraine and Headache (1969) Classification of headache. *J Neurol Sci* 9(2):202
19. Peng KP, Takizawa T, Lee MJ (2020) Cluster headache in Asian populations: Similarities, disparities, and a narrative review of the mechanisms of the chronic subtype. *Cephalalgia* 40(10):1104-1112. doi:10.1177/0333102420923646
20. Donnet A, Lanteri-Minet M, Guegan-Massardier E, Mick G, Fabre N, Géraud G, Lucas C, Navez M, Valade D (2007) Chronic cluster headache: a French clinical descriptive study. *J Neurol Neurosurg Psychiatry* 78(12):1354-1358. doi:10.1136/jnnp.2006.112037
21. Louter MA, Wilbrink LA, Haan J, van Zwet EW, van Oosterhout WP, Zitman FG, Ferrari MD, Terwindt GM (2016) Cluster headache and depression. *Neurology* 87(18):1899-1906. doi:10.1212/wnl.00000000000003282
22. Robbins MS, Bronheim R, Lipton RB, Grosberg BM, Vollbracht S, Sheftell FD, Buse DC (2012) Depression and anxiety in episodic and chronic cluster headache: a pilot study. *Headache* 52(4):600-611. doi:10.1111/j.1526-4610.2011.02024.x
23. Jürgens TP, Gaul C, Lindwurm A, Dresler T, Paelecke-Habermann Y, Schmidt-Wilcke T, Lürding R, Henkel K, Leinisch E (2011) Impairment in episodic and chronic cluster headache. *Cephalalgia* 31(6):671-682. doi:10.1177/0333102410391489
24. Robbins MS (2013) The psychiatric comorbidities of cluster headache. *Curr Pain Headache Rep* 17(2):313. doi:10.1007/s11916-012-0313-8
25. Buture A, Boland JW, Dikomitis L, Ahmed F (2019) Update on the pathophysiology of cluster headache: imaging and neuropeptide studies. *J Pain Res* 12:269-281. doi:10.2147/jpr.S175312
26. Yang FC, Chou KH, Kuo CY, Lin YY, Lin CP, Wang SJ (2018) The pathophysiology of episodic cluster headache: Insights from recent neuroimaging research. *Cephalalgia* 38(5):970-983. doi:10.1177/0333102417716932
27. Yoshino A, Okamoto Y, Doi M, Otsuru N, Okada G, Takamura M, Ichikawa N, Yokoyama S, Yamashita H, Yamawaki S (2017) Regional brain functions in the resting state indicative of potential differences between depression and chronic pain. *Sci Rep* 7(1):3003. doi:10.1038/s41598-017-03522-1
28. Gouveia RG, Parreira E, Pavão Martins I (2005) Autonomic features in cluster headache. Exploratory factor analysis. *J Headache Pain* 6(1):20-23. doi:10.1007/s10194-005-0146-5
29. Snoer A, Lund N, Beske R, Hagedorn A, Jensen RH, Barloese M (2018) Cluster headache beyond the pain phase: A prospective study of 500 attacks. *Neurology* 91(9):e822-e831. doi:10.1212/01.wnl.0000542491.92981.03
30. Bahra A, May A, Goadsby PJ (2002) Cluster headache: a prospective clinical study with diagnostic implications. *Neurology* 58(3):354-361. doi:10.1212/wnl.58.3.354

31. Moon HS, Park JW, Lee KS, Chung CS, Kim BK, Kim JM, Sohn JH, Chu MK, Oh K, Cho SJ (2017) Clinical Features of Cluster Headache Patients in Korea. J Korean Med Sci 32(3):502-506. doi:10.3346/jkms.2017.32.3.502
32. Dong Z, Di H, Dai W, Pan M, Li Z, Liang J, Zhang M, Zhou Z, Liu R, Yu S (2013) Clinical profile of cluster headaches in China - a clinic-based study. J Headache Pain 14(1):27. doi:10.1186/1129-2377-14-27

Figures

Figure 1

Flow diagram of participant selection CH: cluster headache, ICHD-3: The third edition of the International Classification of Headache Disorders, ICHD-3 beta: The third edition beta version of the International Classification of Headache Disorders, PCH: probable cluster headache

Figure 1

Flow diagram of participant selection CH: cluster headache, ICHD-3: The third edition of the International Classification of Headache Disorders, ICHD-3 beta: The third edition beta version of the International Classification of Headache Disorders, PCH: probable cluster headache