Prevalence and Characteristics of Cutaneous Allodynia in Migraine and Probable Migraine: A Population-Based Study

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Abstract

Background: Cutaneous allodynia (CA) is a common feature of migraine and a clinical marker of central sensitization. Probable migraine (PM) is a subtype of migraine that fulfils all but one criterion of migraine. The present study aimed to evaluate the prevalence and characteristics of CA and those of migraine in PM.

Methods: We used the data of the Korean Sleep-Headache study, which was a nation-wide population-based study on headache and sleep. CA was evaluated using the Allodynia Symptom Checklist-12 (ASC-12) questionnaire with ASC-12 score ≥ 3 classified as CA.

Results: Of 2501 participants, the prevalence of migraine and PM were 5.0% and 11.6%, respectively. The prevalence of CA did not significantly differ between migraine and PM (16.0% vs. 14.5%, respectively, $p = 0.701$). Individuals with PM with CA reported a higher monthly frequency of headache (3.3 ± 4.3 vs. 1.8 ± 3.6, respectively, $p = 0.044$), more severe intensity of headache (Visuals Analogue Scale, median and interquartile range, 6.0 [4.0–7.0] vs. 5.0 [3.0–6.0], respectively, $p = 0.002$), and higher impact of headache (Headache Impact Test-6, 56.3 ± 7.2 vs. 48.3 ± 8.0, respectively, $p < 0.001$) and disability (Migraine Disability Assessment, 1.00 [0.00–10.00] vs. 0.00 [0.00–1.00], respectively, $p < 0.001$) than individuals with PM without CA. Multiple regression analyses revealed that the frequency and intensity of headache, anxiety, and depression were significant factors of CA in individuals with PM.

Conclusions: Approximately one-sixth of individuals with migraine and PM experienced CA in a representative sample of Korea. Anxiety, depression, and high frequency of headaches were significant factors of CA in individuals with PM.

Background

Cutaneous allodynia (CA) refers to a condition in which pain is caused by tactile stimulus that generally does not result in pain [1]. The underlying mechanism of CA includes sensitization of the trigeminal nucleus caudalis, which receives afferent input from the meninges and periorbital skin regions [2, 3]. Central sensitization is a manifestation of increased excitability of neurons in the central nociceptive pathways, and CA is a clinical marker of central sensitization [2, 3]. It has been reported that a significant proportion of individuals with migraine experience CA [4–6] during episodes of headache. Individuals with migraine combined with CA were reported to have poorer response to acute treatment and a higher rate of progression to chronic migraine (CM) compared to individuals with migraine not combined with CA [7]. High attack frequency, depression, and obesity were reported to be significant factors of CA in these individuals; therefore, CA provides clues on the pathophysiology of migraine.

Probable migraine (PM) is a subtype of migraine that fulfils all but one criterion of migraine [8]. It was previously reported that 5–15% of the general population experienced PM during the previous year, and the disability of individuals with PM was similar or lower compared with that in those with migraine [9–12]. The prevalence of CA in PM was previously reported in an American study, which was slightly lower than that in migraine [6]. Nevertheless, the information on the associated factors and characteristics of CA in individuals with PM in a population-based setting is currently limited. The present study aimed to investigate the prevalence, characteristics, and associated factors of CA in individuals with PM along with those in individuals with migraine.

Methods

Survey

We used the data of the Korean Sleep-Headache Study (KSHS), which was a nation-wide population-based cross-sectional survey on headache and sleep. Korea is geographically divided into 15 administrative divisions, which were designated as primary sampling units in the first stage. In the second stage, we selected representative basic administrative units from each primary sampling unit. Overall, 60 representative basic administrative units were selected for this study. For each representative basic administrative unit, we assigned a target sample size based on the age, sex, and occupation. We targeted 2500 individuals aged ≥ 19 years and sampled using two-stage clustered random sampling methods proportional to the population distribution of all Korean territories, except Jeju-do [13]. The estimated sampling error was ± 1.9%. The survey was conducted via door-to-door visits and face-to-face interviews using questionnaires by trained interviewers. All interviewers were employees of Gallup Korea and were not medical personnel. The KSHS survey was conducted between October 2018 and November 2018. KSHS was approved by the Institutional Review Board of Severance Hospital, Yonsei University (Approval No. 2018-1269-001).

Migraine and probable migraine diagnosis

Migraine was diagnosed based on the diagnostic criteria for migraine without aura according to the third edition of the International Classification of Headache Disorders (ICHD-3; code 1.1) [8]. If the characteristics and accompanying symptoms of a participant's headache fulfilled A–D criteria of migraine without aura, the diagnosis of migraine was established. The sensitivity and specificity for the diagnosis of migraine were 75.0% and 88.2%, respectively, compared with the diagnosis in additional telephone interviews by doctors [11].

Probable migraine was diagnosed according to code 1.5 of ICHD-3. If the characteristics and accompanying symptoms of a participant's headache fulfilled all but one of the A–D criteria of migraine without aura, the diagnosis of PM was established. We did not separately analyse the individuals according to the presence of aura; therefore, migraine included both migraine with aura (ICHD-3 code 1.2) and migraine without aura (ICHD-3 code 1.1) in the present study. Accordingly, PM included both PM with aura (ICHD-3 code 1.5.2) and PM without aura (ICHD-3 code 1.5.1).

Assessment of CA

We investigated CA using the 12-item Allodynia Symptom Checklist (ASC-12). ASC-12 measures interictal CA over the previous month using 12 questions on the thermal, mechanical static, and mechanical dynamic symptoms of CA [4]. Participants were asked to rate 12 questions using any of the following responses: 'does not apply to me'; 'never'; 'rarely'; 'less than half the time'; and 'half the time or more'. The first three responses were scored as 0, while 'less than half of the time' was scored as 1, and 'half the time or more' was scored as 2. If the ASC-12 score was ≥ 3, the participant was identified to have CA. ASC-12 scores were further subclassified as mild (score 3–5), moderate (score 6–8), and severe (score ≥ 9) CA, respectively [5]. ASC-12 was previously validated in the Korean language for individuals with migraine [14].

Impact and disability of headache

The impact of headache was assessed using the Headache Impact Test-6 (HIT-6). We classified the impact of headache based on the HIT-6 score as follows: < 50, little or no impact; 50–55, some impact; 56–60, substantial impact; and ≥ 60, severe impact [15]. We used the Korean version of HIT-6, which was previously validated in the Korean language [16].

We used the migraine disability assessment (MIDAS) questionnaire to assess the disability of headache. The MIDAS questionnaire is composed of five questions on the loss of or decrease in productive days because of headache during the previous 3 months. We categorized the disability because of migraine based on MIDAS score as follows: < 49, little or no disability; 50–55: mild disability; 56–59: moderate disability; and ≥ 60: severe disability. The MIDAS questionnaire was previously validated in the Korean language with good sensitivity and specificity.

Statistical analyses

The 1-year prevalence of migraine was calculated as the number of cases per 100 persons. For continuous variables, normality was assessed using the Kolmogorov–Smirnov test. Student's *t*-tests or analyses of variance was used for normally distributed date and Mann–Whitney *U* test or Kruskal–Wallis test was used for non-normally distributed data, as appropriate. For comparing categorical variables, we used chi-squared tests.

We evaluated the odds ratios with 95% confidence interval to determine the factors contributing to CA using univariable and multivariable logistic regression analyses. In individuals with migraine and PM, factors that demonstrated significant differences between those with CA and those without CA were included in the univariable analyses. For multivariable analyses, four models were developed to examine the association of CA with migraine and PM. Model 1 included the sociodemographic variables (age, sex, and educational level) and was used to investigate the association between sociodemographic factors and CA. Model 2, which included features of Model 1 and the intensity and frequency of headache, was used to investigate the association between headache-related parameters and CA. Model 3, which incorporated anxiety (Generalized Anxiety Disorder-7) and depression (Patient Health Questionnaire-9) into Model 1, was used to investigate the association between psychiatric conditions and CA. The last model, Model 4, included the sociodemographic variables, headache-related parameters, and psychiatric conditions; it was used to investigate the association between these features and CA.

SPSS v24.0 (IBM, Armonk, NY, USA) was used to perform the statistical analyses. Statistical significance was set at $p < 0.050$. As with most survey studies, missing data resulting from non-responses were present for several variables; the reported data are based on the available data. Imputation techniques were not applied to minimize effects of non-responses [17].

Results

Survey

Overall, 2501 participants completed the survey. The distribution of the sex, age, and educational level of our participants did not significantly differ from the total population of Korea (see Supplementary Table, Additional File 1). Of the 2501 participants, 1186 responded positively to the question ‘Did you have headache during the previous one year?’. Of the 1186 respondent, 125 (5.0%) and 289 (11.6%) participants had migraine and PM, respectively (Fig. 1). Of the 289 individuals with PM, 193 (66.8%) missed the typical duration (criterion B), 94 (32.5%) missed the typical headache characteristics (criterion C), and two (0.7%) missed the typical accompanying symptoms (criterion D) of migraine without aura.

Allodynia in individuals with migraine and PM

The responses to ASC-12 in individuals with migraine and PM are summarized in Table 1. The responses to ASC-12 were scored as described above. In individuals with migraine, CA was most frequently reported with ‘exposure to cold’, followed by ‘combing hairs’ and ‘resting your face or head on a pillow’. The items ‘wearing a necklace’ and ‘wearing earrings’ demonstrated the least frequently positive responses. Finally, 11 (8.8%), seven (5.6%), and two (1.6%) individuals with migraine were identified with mild, moderate, and severe CA, respectively. The prevalence of CA in individuals with migraine and PM with $\geq$ 15 headaches per month was significantly higher in those with < 1 headache per month (Fig. 2).

Table 1
Responses of Allodynia Symptom Checklist-12 in individuals with migraine and probable migraine

	Migraine, N = 125						Probable migraine, N = 289					
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?	Never, N (%)	Rarely, N (%)	Less than half, N (%)	Half the time or more, N (%)	N/A, N (%)	Mild or more (ASC-12 score ≥ 3) response, N (%)	Never, N (%)	Rarely, N (%)	Less than half, N (%)	Half the time or more, N (%)	N/A, N (%)	Mild or more (ASC-12 score ≥ 3) response, N (%)
Combing hairs	75 (58.4)	35 (28.0)	6 (4.8)	8 (6.4)	3 (2.4)	14 (11.2)	176 (60.9)	75 (26.0)	16 (5.5)	12 (4.2)	10 (3.5)	28 (9.7)
Pulling your hair back	67 (53.6)	33 (26.4)	6 (4.8)	6 (4.8)	13 (10.4)	12 (9.6)	160 (55.4)	81 (28.0)	16 (5.5)	8 (2.8)	24 (8.3)	24 (8.3)
Shaving your face	48 (38.4)	12 (9.6)	4 (3.2)	3 (2.4)	58 (10.4)	7 (5.6)	116 (40.1)	19 (6.6)	12 (4.2)	7 (2.4)	135 (46.7)	19 (6.6)
Wearing eyeglasses	34 (27.2)	16 (12.8)	4 (3.2)	0 (0.0)	71 (56.8)	4 (3.2)	103 (35.6)	28 (9.7)	12 (4.2)	7 (7.4)	139 (48.1)	19 (6.6)
Wearing contact lens	32 (25.6)	6 (4.8)	2 (1.6)	0 (0.0)	85 (68.0)	2 (1.6)	86 (29.8)	14 (4.8)	11 (3.8)	2 (0.7)	176 (60.9)	13 (4.5)
Wearing earrings	59 (47.2)	10 (8.0)	1 (0.8)	0 (0.0)	55 (44.0)	1 (0.8)	144 (49.8)	29 (10.0)	9 (3.1)	0 (0.0)	107 (37.0)	9 (3.1)
Wearing a necklace	65 (52.0)	10 (8.0)	1 (0.8)	0 (0.0)	49 (39.2)	1 (0.8)	152 (52.6)	23 (8.0)	12 (4.2)	2 (0.7)	100 (34.6)	14 (4.8)
Wearing tight clothing	64 (51.2)	17 (13.6)	8 (6.4)	3 (2.4)	33 (26.4)	11 (8.8)	150 (51.9)	60 (20.8)	17 (5.9)	9 (3.1)	53 (18.3)	26 (9.0)
Taking a shower	79 (63.2)	35 (28.0)	7 (5.6)	0 (0.0)	4 (3.2)	7 (5.6)	184 (63.7)	68 (23.5)	21 (7.3)	9 (3.1)	7 (2.4)	30 (10.3)
Resting your face or head on a pillow	59 (47.2)	48 (38.4)	6 (4.8)	8 (6.4)	4 (3.2)	14 (11.2)	169 (58.5)	83 (28.7)	26 (9.0)	7 (2.4)	4 (1.4)	33 (11.4)
Exposure to heat	64 (51.2)	46 (36.8)	6 (4.8)	4 (3.2)	5 (4.0)	10 (8.0)	162 (56.1)	96 (33.2)	25 (8.7)	2 (0.7)	4 (1.4)	27 (9.3)
Exposure to cold	56 (44.8)	46 (36.8)	12 (9.6)	6 (4.8)	5 (4.0)	18 (14.4)	135 (46.7)	113 (39.1)	29 (10.0)	8 (2.8)	4 (1.4)	37 (12.8)
Total						20 (16.0)						42 (14.5)

ASC-12: Allodynia Symptom Checklist-12, N/A: not applicable.

In individuals with PM, ‘exposure to cold’ was the most common response, and ‘resting your face or head on a pillow’ was the next frequent response. The items ‘wearing a necklace’ and ‘wearing earrings’ demonstrated the least frequencies. Of 289 individuals with

PM, 12 (4.1%), 15 (5.2%), and 15 (5.2%) individuals with migraine were identified with mild, moderate, and severe CA, respectively. The prevalence of CA in individuals with PM missing the typical duration was significantly higher than that in those with missing the typical characteristics of headache (19.2% vs. 5.3%, respectively, $p = 0.002$). The overall prevalence of CA was not significantly different between individuals with migraine and those with PM (16.0% vs. 14.5%, respectively, $p = 0.701$).

Clinical characteristics of migraine and PM according to the presence of CA

Headache frequency per month, headache intensity (Visual Analogue Scale), impact of headache (HIT-6), and disability (MIDAS) were significantly higher in individuals with migraine and PM combined with CA than in those without CA. Anxiety and depression were more prevalent in both individuals with migraine and PM with CA than in those without CA. Photophobia and phonophobia were more prevalent in individuals with PM; however, they were not significantly different according to the presence of CA in individuals with migraine (Table 2).

Table 2
Clinical characteristics of migraine and probable migraine according to the presence of cutaneous allodynia

	Migraine			PM		
	Migraine with CA, N = 20	Migraine without CA, N = 105	*p*-value	PM with CA, N = 42	PM without CA, N = 247	*p*-value
Headache frequency per month	5.6 ± 8.4	2.1 ± 3.5	0.009	3.3 ± 4.3	1.8 ± 3.6	0.044
Headache intensity (Visual Analogue Scale)	7.0 (6.0–7.0)*	6.0 (5.0–7.0)*	0.019	6.0 (4.0–7.0)*	5.0 (3.0–6.0)*	0.002
Attack duration (hours)	9.1 ± 7.8	7.6 ± 6.6		2.2 ± 0.9	1.5 ± 1.1	< 0.001
Unilateral pain	14 (70.0)	73 (69.5)	0.382	19 (45.2)	145 (58.6)	0.103
Aggravation by movement	11 (55.0)	48 (45.7)	0.966	27 (64.3)	86 (34.8)	< 0.001
Pulsating quality	15 (75.0)	87 (82.8)	0.446	31 (73.8)	197 (86.4)	
Nausea	19 (95.0)	93 (88.6)	0.406	38 (90.5)	230 (93.1)	0.542
Vomiting	12 (60.0)	44 (41.9)	0.388	19 (45.2)	117 (47.4)	0.798
Photophobia	8 (40.0)	37 (35.2)	0.136	25 (59.5)	67 (27.1)	< 0.001
Phonophobia	11 (55.0)	55 (52.4)	0.684	29 (69.0)	112 (45.3)	0.004
Osmophobia	7 (35.0)	41 (39.0)	0.830	21 (50.0)	95 (38.5)	0.158
Depression (PHQ-9 score) ≥ 10	7 (35.0)	17 (16.2)	0.733	22 (52.4)	40 (16.2)	< 0.001
PHQ-9 score	8.6 ± 4.9	7.9 ± 3.7	0.050	11.1 ± 5.5	7.8 ± 3.5	0.001
Anxiety (GAD-7 score) ≥ 7	9 (45.0)	11 (10.5)	0.476	14 (33.3)	13 (5.3)	< 0.001
GAD-7 score	6.6 ± 5.4	2.2 ± 2.8	< 0.001	4.7 ± 5.0	2.0 ± 2.6	0.001
HIT-6 score	61.5 ± 9.2	51.4 ± 7.9	< 0.001	56.3 ± 7.2	48.3 ± 8.0	< 0.001
MIDAS score	5.0 (2.0–13.8)*	0.0 (0.0–2.0)*	< 0.001	1.0 (0.0–10.0)*	0.0 (0.0–1.0)*	< 0.001
Body mass index	22.73 ± 2.45	22.75 ± 2.46	0.966	23.07 ± 2.41	23.05 ± 2.62	0.964

PM: probable migraine, CA: cutaneous allodynia, MIDAS: migraine disability assessment, HIT-6: Headache Impact Test-6, PHQ-9: Patient Health Questionnaire-9, GAD-7: Generalized Anxiety Disorder-7.

*Median and interquartile range

Factors associated with CA in migraine and PM

Univariable analyses in individuals with migraine indicated that ≥ 15 headaches per month, moderate and severe headache intensity, anxiety, and depression were significantly associated with CA. Multivariable analysis with Model 1 indicated that these factors were not significantly associated with CA. In Model 2, sociodemographic and headache-related variables were not significantly associated

with CA. In Model, anxiety was significantly associated with CA. In Model 4, only anxiety was significantly associated with CA (Table 3).

Table 3
Factors associated with cutaneous allodynia in individuals with migraine in univariable and multivariable analyses

		Univariable	Model 1	Model 2	Model 3	Model 4
		OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
Sex (Female)		1.3 (0.5–3.5)	1.2 (0.4–3.5)	1.5 (0.5–4.9)	0.9 (0.3–3.2)	1.0 (0.3–3.8)
Age (year)	20–29	REF	REF	REF	REF	REF
	30–39	1.4 (0.3–6.4)	1.4 (0.3–6.3)	1.1 (0.2–5.4)	1.3 (0.3–6.4)	1.1 (0.2–5.9)
	40–49	1.4 (0.3–6.8)	1.3 (0.3–7.2)	0.9 (0.2–5.3)	0.7 (0.1–4.2)	0.5 (0.1–3.3)
	50–59	0.5 (0.07–3.4)	0.4 (0.1–3.2)	0.3 (0.4–2.6)	0.2 (0.2–1.9)	0.2 (0.2–1.7)
	60–69	1.3 (0.3–7.8)	3.2 (0.4–25.7)	1.1 (0.1–14.2)	0.5 (0.3–7.9)	0.2 (0.1–4.9)
	> 70	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*
Educational level	High school	REF	REF	REF	REF	REF
	Middle school or less	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*	0.0 (0.0–0.0)*
	College or more	0.9 (0.3–2.4)	0.7 (0.2–2.5)	0.6 (0.2–2.2)	0.4 (0.1–1.5)	0.4 (0.1–1.5)
Headache frequency per month	< 1	REF		REF		REF
	1–14	2.5 (0.9–7.3)		2.0 (0.6–6.3)		1.0 (0.3–3.8)
	≥ 15	9.8 (1.6–59.9)		7.0 (0.7–65.7)		2.6 (0.4–18.6)
Headache intensity	Mild	REF		REF		REF
	Moderate	2.5 (1.6–4.0)		0.8 (0.2–3.6)		0.9 (0.2–4.6)
	Severe	8.5 (4.4–16.1)		2.2 (0.4–12.4)		2.6 (0.4–18.6)
Anxiety (GAD-7 score ≥ 7)		11.3 (2.5–52.4)			11.8 (2.4–58.5)	11.6 (2.0–67.3)
Depression (PHQ-9 score ≥ 10)		2.8 (1.0–8.0)			1.2 (0.3–4.9)	1.1 (0.2–5.3)

OR: odds ratio, CI, confidence interval, GAD-7: Generalized Anxiety Disorder-7, PHQ-9: Patient Health Questionnaire-9. REF: Reference.

*No participants with migraine was middle school or less

In individuals with PM, univariable analyses revealed that moderate and severe headache intensity, anxiety, and depression were significantly associated with CA. In Model 1, no factor was significantly associated with CA. Model 2 revealed that moderate and severe headache intensity were significantly associated with CA. In Model 3, depression was significantly associated with CA. Model 4 demonstrated that moderate and severe headache intensity and anxiety were significantly associated with CA (Table 4).

Table 4
Factors associated with cutaneous allodynia in individuals with probable migraine in univariable and multivariable analyses

		Univariable	Model 1	Model 2	Model 3	Model 4
			OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI
Sex (Female)		1.4 (0.7–2.7)	1.4 (0.7–3.0)	1.3 (0.6–2.6)	1.4 (0.6–3.1)	1.4 (0.6–3.2)
Age (year)	20–29	REF	REF	REF	REF	Reference
	30–39	1.1 (0.4–3.5)	1.2 (0.4–3.5)	1.5 (0.5–4.7)	1.4 (0.4–5.0)	1.5 (0.4–5.6)
	40–49	0.6 (0.2–1.7)	0.6 (0.2–8.9)	0.6 (0.2–2.1)	0.8 (0.2–2.8)	0.8 (0.2–2.9)
	50–59	0.9 (0.3–2.5)	0.9 (0.3–2.9)	1.1 (0.3–3.6)	1.2 (0.3–4.4)	1.2 (0.3–2.9)
	60–69	0.6 (0.2–2.0)	0.5 (0.1–2.3)	0.5 (0.1–2.4)	0.5 (0.1–2.7)	0.4 (0.1–2.3)
	> 70	1.3 (0.4–3.8)	1.1 (0.3–5.4)	1.6 (0.3–8.2)	1.2 (0.2–6.7)	1.4 (0.3–8.2)
Educational level	High school	REF	REF	REF	REF	Reference
	Middle school or less	1.6 (0.6–4.2)	1.3 (0.4–4.7)	1.1 (0.3–4.1)	1.6 (0.4–6.0)	1.6 (0.4–6.3)
	College or more	1.3 (0.6–2.7)	1.2 (0.5–2.9)	1.1 (0.4–2.6)	1.1 (0.4–2.9)	0.9 (0.3–2.4)
Headache frequency per month	< 1	REF		REF		Reference
	1–14	1.3 (0.7–2.5)		1.1 (0.5–2.2)		0.6 (0.2–1.3)
	≥ 15	1.6 (0.2–15.4)		1.5 (0.1–15.3)		1.1 (0.1–11.9)
Headache intensity	Mild	REF		REF		Reference
	Moderate	2.7 (1.3–5.8)		2.9 (1.3–6.3)		2.4 (1.1–5.4)
	Severe	5.7 (1.9–16.8)		6.6 (2.0–21.2)		4.0 (1.1–13.9)
Anxiety (GAD-7 score ≥ 7)		9.0 (3.8–21.1)			2.5 (0.5–11.7)	5.2 (1.7–16.3)
Depression (PHQ-9 score ≥ 10)		5.7 (2.8–11.4)			4.9 (2.3–10.3)	3.3 (1.5–7.6)

OR: odds ratio, CI, confidence interval, GAD-7: Generalized Anxiety Disorder-7, PHQ-9: Patient Health Questionnaire-9. REF: Reference.

Discussion

The primary findings of the present study were the following: (1) approximately one-sixth of individuals with migraine and PM experienced CA, and the prevalence of CA was not significantly different between those with migraine and those with PM; (2) individuals with migraine and PM with CA experienced more severe symptoms and higher impact of headache and disability than those without CA; and (3) headache intensity, anxiety, and depression were significant factors of CA in individuals with PM. In those with migraines, anxiety was a significant factor of CA.

The present study found that 16.0% and 14.5% of individuals with migraine and PM, respectively, had CA. Our results are similar to those of a previous Korean clinic-based study, which reported that CA was observed in 14.5% of patients with migraine [14]. These

values were lower than those reported in previous studies from the Western countries. American Migraine Prevalence and Prevention (AMPP) study, a large population-based in USA, reported that 62% of individuals with migraine had CA [6]. Migraine in America Symptoms and Treatment study, another American large population-based study, reported that the prevalence of CA in those with migraine was 40% [5]. A Dutch cohort study revealed that CA was present in 70% of participants with migraine [7]. One possible explanation for the lower prevalence of CA in the present study is the difference in the migraine symptoms in the Asian countries. The symptoms are milder in the Asian countries than in the Western countries. Moderate headache intensity was reported in 30–65% of individuals with migraines in Asian countries [18, 19]. In the Western countries, 80–85% of individuals with migraine reported severe headache intensity [20, 21]. Photophobia was reported in 40–65% of individuals with migraine in Asian countries and 75–85% of individuals with migraine in Western countries [18, 21–23]. Headache intensity and photophobia were reported as significant predictors of CA in individuals with migraine [5]. Therefore, milder headache intensity and lower photophobia might result in lower prevalence of CA. Another possible explanation is the difference in the body mass index (BMI), which has been reported to be lower in Asian populations than in Western populations [24]. High BMI was reported to be a significant factor for CA in the AMPP study [4]. That study found that obese (BMI, 30–40 kg/m^2) and morbidly obese (BMI, ≥ 40 kg/m^2) individuals had higher risk of CA. In the present study, there was no significant difference in BMI in individuals with migraine and PM according to the presence of CA. This discrepancy might be because of differences in BMI. Only two individuals with migraine and four individuals with PM were obese. Furthermore, none of the individuals with migraine and PM qualified for morbid obesity. Ethnic differences could be another possible explanation. It has been reported that pain sensitivity varies among ethnic groups [25]. Further studies in various migraine populations are required for a better understanding of the prevalence and contributing factors of CA.

In the present study, ‘exposure to cold’ and ‘resting your face or head on pillow’ were most frequently positively responded items in both individuals with migraine and PM. ‘Combing hairs’ and ‘pulling your hair back’ followed the next frequency. Allodynia is classified as mechanical dynamic, mechanical static, and thermal allodynia. They differ in terms of the transmission nerve fibres and nociceptors [26, 27]. Each item of ASC-12 complied three types of CA. ‘Exposure to cold’ and ‘resting your face or head on pillow’ corresponded to thermal allodynia, and ‘combing hairs’ and ‘pulling your hair back’ items corresponded to mechanical dynamic allodynia [4]. High positive response rate to items of thermal and mechanical dynamic allodynia in individuals with migraine was previously reported in a Brazilian study [28]. The present study is the first to identify a high positive response rate to items corresponding to thermal and mechanical dynamic allodynia in individuals with PM, which is similar to that in individuals with migraines.

The headache frequency, headache intensity, disability, and impact of headache were higher in those with migraine and PM combined with CA than in those without CA in the present study. Further, CA was more prevalent in those with the chronic form (≥ 15 episodes per month) of migraine and PM than in those with low headache frequency (< 1 episode per month) (Fig. 2). The close associations of CA with symptom severity and chronicity have been previously reported in migraine [4, 6]. The present study provides evidence that such an association is also present between CA and PM.

In the present study, anxiety and depression were identified as significant factors of CA in individuals with PM. The significant association of anxiety and depression with CA has been reported previously. Kao et al. reported that anxiety was a significant factor of CA using multivariable regression analyses. Furthermore, comorbid anxiety and depression were also associated with the severity of CA [29]. Louter et al. reported that CA was associated with higher prevalence of depression in individuals with migraine [30]. CA, anxiety, and depression a significant risk factor of CM transformation from episodic migraine (EM) [7, 31]. CM has a higher prevalence in the presence of anxiety, depression, and CA than EM [6]. Therefore, our findings added an evidence for the significant association of anxiety and depression with CA and suggested sharing pathophysiological mechanisms of CA with anxiety and depression. Biogenic amines might be involved in a possible shared mechanism. Allodynia is a characteristic of FM, which is a chronic condition of widespread pain [32]. In an animal model of fibromyalgia, decreased tactile threshold was correlated with depressive behaviours [33]. The animal model demonstrated a decreased level of biogenic amines including dopamine, 5-hydroxytryptoptamine, and norepinephrine in the spinal cord, thalamus, and prefrontal cortex.

The prevalence of migraine in the present study was lower than that in previous Western studies. The prevalence of migraine in Asian countries is 3–10%, which is lower than that in Western countries where it is 11–18% [34]. Therefore, migraine prevalence in the present study was similar to those in previous Asian studies. The reported prevalence of PM ranges widely (USA, 4.5%; Singapore, 6.2%; France, 10.0%; Korea. 11.5%; England: 14.6%) [9, 10, 12, 35]; therefore, the prevalence of PM in the present study was broadly

similar to those in previous studies. The similarities in the prevalence of migraine and PM between the present and previous studies suggest that appropriate evaluation of migraine and PM in the current study.

The present study has some limitations. First, we used ASC-12 in the evaluation of CA. The gold standard of assessing CA is quantitative sensory testing (QST); it requires specialized equipment and is difficult to conduct in clinical practice and epidemiological studies. ASC-12 was previously validated in comparison with QST [7]. It was also validated in Korean individuals with migraine [14]. Second, we did not investigate the disease durations of migraine and PM. Disease duration was reported to be a significant factor of CA in patients with migraine. Since medical consultation and awareness of migraine diagnosis is not high in Korea, it would be difficult to know participants' exact disease duration of migraine. We believed that the assessments of disease duration were less feasible and, therefore, did not include them in the analyses. Finally, we did not evaluate the use of medications in the participants. Some medications for migraine prevention, such as serotonin-norepinephrine reuptake inhibitors and anticonvulsants, might relieve CA [36–38]. Further studies on the use of medications are required to provide accurate information of CA in patients with migraine and PM.

The present study includes several strengths. First, we used a two-stage clustered random sampling method proportional to the distribution of the total population of Korea. Furthermore, the estimated sampling error was low. This approach allowed us to successfully assess CA in individuals with migraine and PM in a population-based setting. Second, in the present study, the responses of 12 items in addition to the total score of ASC-12 were analysed. We found that 'exposure to cold', 'resting your far or head on a pillow', and 'combing hair' were the most frequently responses both in individuals with migraine and PM. Third, our study used questionnaires which were specialized validated in Korea language for assessing migraine, anxiety and depression. Such process enabled us to accurately evaluate migraine, PM, anxiety and depression in the present study.

Conclusions

Approximately one-sixth of individuals with migraine and PM experienced CA in a general-population-based sample in Korea. The prevalence of CA was not significantly different between those with migraine and those with PM. Individuals with migraine and those with PM combined with CA had more severe symptoms than those not combined with CA. Anxiety, depression, and high frequency of headaches were significant factors of CA in individuals with PM.

List Of Abbreviations

AMPP, American Migraine Prevalence and Prevention; ASC-12, Allodynia Symptom Checklist-12; BMI, Body mass index; CA, Cutaneous allodynia; CM, Chronic migraine; EM, Episodic migraine; HIT-6, Headache Impact Test-6; KSHS, Korean Sleep-Headache Study; ICHD-3, International Classification of Headache Disorders, 3rd edition; MIDAS, migraine disability assessment; PM, Probable migraine; QST, Quantitative sensory testing

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University (approval No. 2019-1721-001). Written consent was obtained from all participants before the survey interviews.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SJC was involved as a site investigator of a multicentre trial sponsored by Otsuka Korea, Eli Lilly and Co., and Novartis; functioned as an advisory member for Teva; and received research support from the Hallym University Research Fund 2016 and a grant from the Korean Neurological Association (KNA-16-MI-09). MKC was a site investigator for a multi-centre trial sponsored by Otsuka Korea, Novartis, International AG, and Eli Lilly and Co. He functioned as an advisory member for Teva, and received lecture honoraria from Allergan Korea, Handok-Teva, and Yuyu Pharmaceutical Company over the past 24 months. He received grants from the Yonsei University College of Medicine (2018-32-0037) and National Research Foundation of Korea (2019R1F1A1053841). The other authors declare no conflict of interest.

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Author contributions

SMH conceptualized and designed the study, analysed the data, and drafted the manuscript. KMK, SJC, KIY, DYK, and CHY conceptualized the study and collected the data. MKC conceptualized and designed the study, collected and analysed the data, and darfted the manuscript. All authors have read and approved the final manuscript.

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Figures

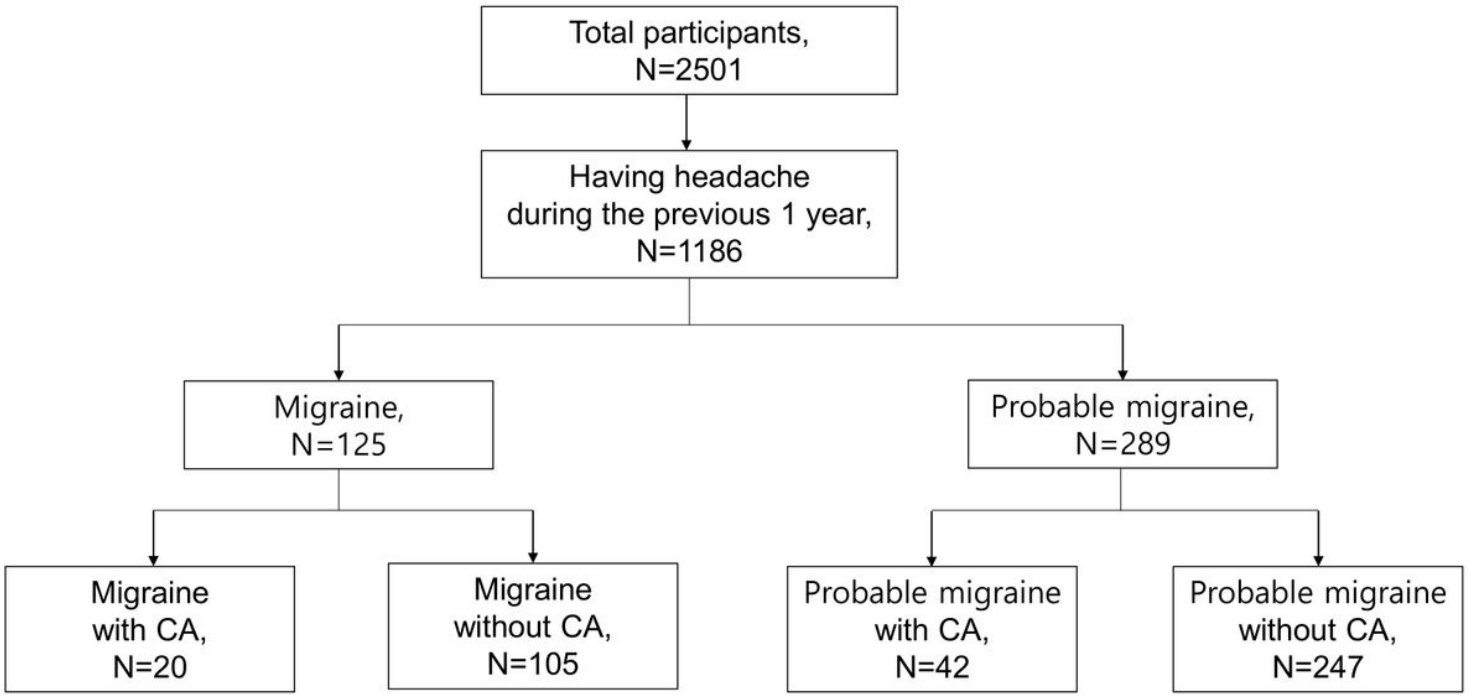

Figure 1

Flow chart depicting the inclusion of participants in the study. CA: cutaneous allodynia, PM: probable migraine

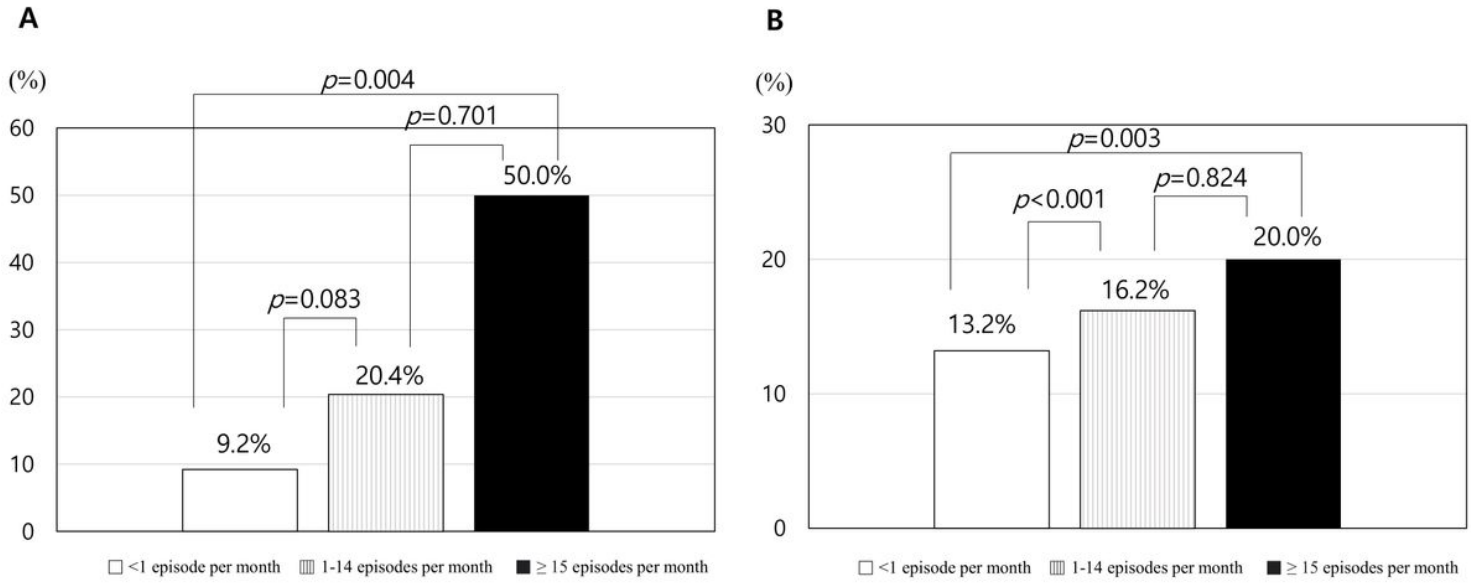

Figure 2

Prevalence of cutaneous allodynia in participants with migraine (A) and probable migraine (B) according to the headache frequency per month.

Supplementary Files

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