JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2021;17(2):229-235 / https://doi.org/10.3988/jcn.2021.17.2.229

Smoking History and Clinical Features of Cluster Headache: Results from the Korean Cluster Headache Registry

Pil-Wook Chung[a], Byung-Su Kim[b] Jeong-Wook Park[c], Jong-Hee Sohn[d] Mi Ji Lee[e], Byung-Kun Kim[f] Min Kyung Chu[g], Jin-Young Ahn[h] Yun-Ju Choi[i], Tae-Jin Song[j] Dae-Woong Bae[k], Daeyoung Kim[l] Jae-Moon Kim[l], Soo-Kyoung Kim[m] Kwang-Yeol Park[n], Jae Myun Chung[o] Heui-Soo Moon[a], Kyungmi Oh[p] Chin-Sang Chung[e], Soo-Jin Cho[q]

[a]Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
[b]Department of Neurology, Bundang Jesaeng General Hospital, Daejin Medical Center, Seongnam, Korea
[c]Department of Neurology, Uijeongbu St. Mary's Hospital, Uijeongbu, Korea
[d]Department of Neurology, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Korea
[e]Department of Neurology, Neuroscience Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[f]Department of Neurology, Nowon Eulji Medical Center, Eulji University, Seoul, Korea
[g]Department of Neurology, Severance Hospital, Seoul, Korea
[h]Department of Neurology, Seoul Medical Center, Seoul, Korea
[i]Department of Neurology, Dr. Choi's Neurology Clinic, Jeonju, Korea
[j]Department of Neurology, Ewha Womans University School of Medicine, Seoul, Korea
[k]Department of Neurology, College of Medicine, The Catholic University of Korea, Suwon, Korea
[l]Department of Neurology, Chungnam National University College of Medicine, Daejeon, Korea
[m]Department of Neurology, Gyeongsang National University College of Medicine, Jinju, Korea
[n]Department of Neurology, Chung-Ang University College of Medicine, Seoul, Korea
[o]Department of Neurology, Inje University College of Medicine, Seoul, Korea
[p]Department of Neurology, Korea University College of Medicine, Seoul, Korea
[q]Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Korea

Received July 21, 2020
Revised November 13, 2020
Accepted November 13, 2020

Correspondence
Soo-Jin Cho, MD, PhD
Department of Neurology,
Dongtan Sacred Heart Hospital,
Hallym University College of Medicine,
7 Keunjaebong-gil,
Hwaseong 18450, Korea
Tel +82-31-8086-2310
Fax +82-31-8086-2317
E-mail dowonc@naver.com

Background and Purpose Epidemiologic data suggest that cluster headache (CH) is significantly associated with cigarette smoking. The aim of this study was to determine differences in features between patients with a smoking history and those who are never-smokers, using data from a prospective multicenter registry.

Methods Data used in this study were obtained from the Korean Cluster Headache Registry that collected data from consecutive patients diagnosed with CH. We compared clinical and demographic features between ever-smokers (current or former smokers) and never-smokers.

Results This study enrolled 250 patients who were diagnosed with CH, of which 152 (60.8%) were ever-smokers and 98 (39.2%) were never-smokers. The age at CH onset was significantly lower in the never-smoker group than in the ever-smoker group [27.1±12.9 years vs. 30.6±10.9 years (mean±standard deviation), p=0.024]. Seasonal rhythmicity (58.1% vs. 44.7%, p=0.038) and triptan responsiveness (100% vs. 85.1%, p=0.001) were higher in never-smokers, while other clinical features such as pain severity, duration, attack frequency, and associated autonomic symptoms did not differ significantly between the groups. The male-to-female ratio was markedly higher in ever-smokers (29.4:1) than in never-smokers (1.7:1).

Conclusions Most of the clinical features did not differ significantly between patients with a smoking history and never-smokers. However, the age at CH onset, sex ratio, and seasonal rhythmicity were significantly associated with smoking history.

Key Words cluster headache, smoking, sex differences.

INTRODUCTION

Cluster headache (CH) is an excruciating form of primary headache that is characterized by recurrent unilateral headache attacks accompanied by ipsilateral autonomic features.[1,2] Salient features of CH are its male predominance, circadian rhythmicity, and trigeminal autonomic features. CH is significantly associated with cigarette smoking, which is unique among all primary headache disorders,[3-6] but a satisfactory explanation for this relationship or pathogenetic association has not been established. Numerous studies have indicated that the prevalence of cigarette smoking is high in the CH population, with up to 90% of males and 70% of females being smokers.[7-11] Secondary smoke exposure during childhood may trigger CH even in nonsmokers.[12] Distinct clinical features between smokers and nonsmokers or between those exposed and not exposed to smoking have rarely been reported. Recent population-based studies noted that patients with CH who are not exposed to smoking develop CH at a lower age than do those who are exposed to smoking.[3,13] There is also increasing evidence that smoking affects the disease severity. Several studies have indicated that smoking is associated with more-severe CH phenotypes, such as a longer bout duration, higher attack frequency, and higher pain severity.[3,5,14,15] However, a study investigating the ef-

fect of smoking cessation on CH found that the condition of patients rarely improves after they stop cigarette smoking.[14]

The above-described situation means that it remains questionable how the close association between CH and smoking should be interpreted. Furthermore, studies investigating differences in clinical and demographic features between smokers and nonsmokers are scarce, especially in Asian populations. Therefore, the aim of this study was to identify differences between ever-smokers (current and former smokers) and never-smokers using data from the Korean Cluster Headache Registry (KCHR), which prospectively enrolled patients with CH.

METHODS

Patients

This study was conducted using data from the KCHR, which is a multicenter, cross-sectional registry that prospectively collected data from consecutive patients with CH who visited the neurology outpatient departments of 16 hospitals in Korea between August 2016 and December 2018. Board-certified neurologists who specialize in headache at each hospital conducted the study.

All participants were evaluated by board-certified neurologists in each center to confirm that the diagnosis fulfilled the criteria of the third edition (beta version) of the International Classification of Headache Disorders (ICHD-3β) for CH.[16] Participants who met the criteria for definite CH or probable CH were identified for inclusion in this study. Their final inclusion was based on the criteria of ICHD-3, since those criteria were published during the course of this project.[2]

The study protocol and informed consent form were approved by the institutional review board at each hospital (Dongtan Sacred Heart Hospital, IRB 2016-09-396). Written informed consent was obtained from all participants before they were enrolled in this study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical information

Data obtained and used in the study included the following: demographic factors, age, age at onset, headache characteristics, seasonal and diurnal rhythmicity, and treatment response. Clinical information regarding current headache episodes included the location, severity, duration, and frequency of headache attacks; autonomic symptoms; and diurnal rhythmicity. The previous history of CH included the time since the first CH attack, total number of cluster bouts, and pattern of seasonal periodicity. Triptan responsiveness was defined as a reduction of ≥50% in pain intensity compared to the usual pain intensity according to the patient's judgement. The personal history of cigarette smoking was obtained and used to classify patients into ever-smokers and never-smokers. Ever-smoker patients were further classified into current and former smokers.

Statistical analysis

Demographics and clinical features were compared between ever-smokers and never-smokers. The two-sample *t*-test and Mann-Whitney U-test were used to compare the mean values between ever-smokers and never-smokers, according to whether or not each variable conformed to a normal distribution based on the Kolmogorov-Smirnov test. The chi-square test or Fisher's exact test was used to compare categorical variables. Probability values of $p<0.05$ were considered indicative of statistical significance. All analyses were performed using the Statistical Package for the Social Sciences (version 24.0, IBM Corp., Armonk, NY, USA).

RESULTS

Characteristics of patients

One of the 251 patients identified as having CH based on ICHD-3β was excluded for not meeting the criteria of ICHD-3. Of the remaining 250 patients ultimately enrolled in this study, 176 were classified as having episodic CH, 12 were classified as having chronic CH, 27 were classified as having probable CH, and the remaining 35 who met the criteria of CH but had the first episode of CH without a determined remission period or recurrence were classified as having first CH (Table 1).[17] The male-to-female ratio was 5.1:1, with 209 male and 41 female patients. The 250 patients comprised 152 (60.8%) ever-smokers and 98 (39.2%) never-smokers. The prevalence of smoking differed significantly with sex, with 70.3% of male patients and 12.2% of female patients being ever-smokers. The 152 ever-smokers comprised 96.7% (n=147) males and 3.3% (n=5) females, yielding a male-to-female ratio of 29.4:1. In the never-smoker group, the male-to-female ratio was 1.7:1 (n=62 vs. 36), while 49.8% of males and 12.2% of females were current smokers.

We compared different features between the ever-smoker and never-smoker groups. The age at the time of investigation was 35.0±11.3 years (mean±standard deviation; range 18−79 years) for the never-smokers and 39.7±9.7 years (range 21−69 years) for the ever-smokers ($p<0.001$) (Table 1). The age at onset was significantly lower in never-smokers than in ever-smokers (27.1±12.9 years vs. 30.6±10.9 years, $p=0.024$). Similarly, the distribution of onset age differed between the never-smokers and ever-smokers, with a tendency toward a lower age at onset in the never-smoker group ($p=0.033$) (Fig. 1). The prevalence of migraine history was higher in never-smokers (21.4%) than in ever-smokers (9.9%), which might reflect a

Table 1. Comparison of demographics between the ever-smoker and never-smoker groups

	All (*n*=250)	Ever-smokers (*n*=152)	Never-smokers (*n*=98)	*p*
Male	209 (83.6)	147 (96.7)	62 (63.3)	<0.001
Age, years	37.9±10.5 (18–79)	39.7±9.7 (21–69)	35.0±11.3 (18–79)	<0.001
Subtypes of CH				0.234
ECH	176	110	66	
CCH	12	9	3	
PCH	27	12	15	
fCH	35	21	14	
Onset age, years	29.3±11.9 (9–78)	30.6±10.9 (10–62)	27.1±12.9 (9–78)	0.024
CH history, years	8.6±7.9 (0–39)	9.1±8.2 (0–39)	7.9±7.4 (0–32)	0.228
Migraine history	36 (14.4)	15 (9.9)	21 (21.4)	0.011
Current alcohol drinking	140/236 (59.3)	101/146 (69.1)	39/90 (43.3)	<0.001

Data are mean±standard deviation (range), *n*, or *n* (%) values. fCH was CH that could not be classified as either ECH or CCH because a participant's CH was their first bout and persisted for less than 1 year or did not recur after the first bout. fCH, ECH, CCH and PCH were defined as codes 3.1, 3.1.1, 3.1.2, and 3.5 in the third edition of the International Classification of Headache Disorders.
CCH: chronic CH, CH: cluster headache, ECH: episodic CH, fCH: first CH, PCH: probable CH.

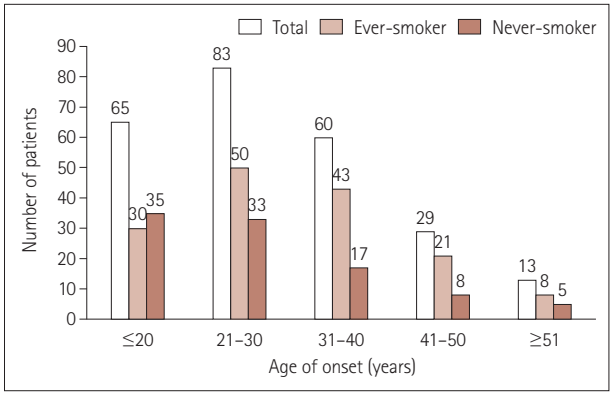

Fig. 1. Distributions of ages at onset of cluster headache in ever-smokers and never-smokers.

higher migraine prevalence in females. Chronic CH was rare in both groups, with no significant intergroup difference (5.9% vs. 3.1%, p=0.234). Multivariable logistic analysis suggested that male sex (OR=32.01, 95% CI=8.02–127.78), higher age at CH onset (OR per year=1.04, 95% CI=1.01–1.08), and alcohol drinking (OR=2.37, 95% CI=1.22–4.61) were independently associated with an ever-smoker history (Supplementary Table 1 in the online-only Data Supplement).

Headache characteristics

The clinical features of CH were comparable between ever-smokers and never-smokers, without significant differences in the characteristics of pain or cluster bouts (Table 2). The severity of current headache attack as assessed using a numeric rating scale from 0 to 10 did not differ between the ever-smokers and never-smokers (9.0±1.2 vs. 9.0±1.2). There was also no significant difference between the ever-smokers and never-smokers in the duration of each attack (107.6±122.6 minutes vs. 97.0±75.6 minutes, p=0.459), daily attack frequency (2.1±1.7 vs. 2.1±1.9, p=0.835), total number of cluster bouts since the first attack, or the reported presence of diurnal rhythmicity. However, seasonal rhythmicity was reported more frequently by never-smokers than by ever-smokers (58.1% vs. 44.7%, p=0.038).

Table 2. Clinical characteristics of cluster headache

	Ever-smokers (*n*=152)	Never-smokers (*n*=98)	*p*
Headache severity, NRS	9.0±1.2	9.0±1.2	0.968
Attacks per day	2.1±1.7	2.1±1.9	0.835
Attack duration, minutes	107.6±122.6	97.0±75.6	0.459
Total number of bouts	11.9±14.3	10.9±16.2	0.637
Triptan effectiveness	74/87 (85.1)	66/66 (100)	0.001
Diurnal rhythmicity	81 (53.3)	57 (58.1)	0.449
Seasonal rhythmicity	68 (44.7)	57 (58.1)	0.038
Bouts duration, weeks	6.3±7.1	5.7±5.8	0.542
HIT-6 score	67.6±8.3	68.9±7.8	0.224
GAD-7 score	7.95±5.51	7.40±6.31	0.483
PHQ-9 score	7.54±5.99	7.68±7.02	0.862

Data are mean±standard deviation or *n* (%) values.
GAD-7: Generalized Anxiety Disorder-7, HIT-6: Headache Impact Test-6, NRS: numeric rating scale from 0 to 10, PHQ-9: Patient Health Questionnaire-9.

Overall, 153 patients reported the efficacy of triptans during headache attacks. Because triptan formulations of nasal spray or subcutaneous injections are currently not available in Korea, all triptan use was via oral formulations. Triptan effectiveness (defined as a reduction of ≥50% in pain intensity) was reported in 89.2% (74/87) of ever-smoker patients and 100% (66/66) of never-smokers (p=0.001), suggesting a more-favorable response to triptans in the never-smoker population.

Lacrimation and conjunctival injection were the most frequently reported autonomic symptoms both in ever-smokers

(86.2%) and never-smokers (78.6%), with no significant differences (p=0.116). Other cranial autonomic symptoms also did not differ significantly between the groups (Table 3).

Current smokers versus never-smokers and former smokers

We further compared the characteristics between current smokers and never-smokers and between current smokers and former smokers (Table 4). The age at CH onset differed between current smokers and never-smokers, and the effect of triptan was again better for never-smokers than for current smokers. However, other clinical characteristics did not differ between current smokers and never-smokers, and so the differences between current smokers and never-smokers were consistent with those between ever-smokers and never-smokers. There were no significant differences between current smokers and former smokers.

Table 3. Comparison of cranial autonomic features between ever-smokers and never-smokers

	Ever-smokers (n=152)	Never-smokers (n=98)	p
Conjunctival injection/tearing	131	77	0.116
Eyelid edema	35	32	0.093
Ptosis	27	25	0.141
Miosis	4	2	>0.999
Rhinorrhea/nasal congestion	81	58	0.360
Forehead/facial sweating	61	30	0.127
Restlessness/agitation	76	43	0.344
No autonomic symptom	3	6	0.086

DISCUSSION

The main findings of this study were as follows: 1) The age at CH onset was lower in never-smokers than in ever-smokers (current or former smokers). 2) Most of the clinical features of CH did not differ significantly between never-smokers and ever-smokers, with the exception that never-smokers experienced more favorable triptan responses and higher seasonal rhythmicity. 3) The male-to-female ratio was much lower in never-smokers than in ever-smokers (1.7:1 vs. 29.4:1).

The hypothalamus is involved in the pathogenesis of CH.[1,18] Primary headache disorders such as migraine,[19] short-lasting neuralgiform headache attacks with conjunctival injection and tearing,[20] and paroxysmal hemicrania[21] are also considered to be disorders that are modulated by the hypothalamus.

Table 4. Comparison of current, former, and never-smokers

	Current smoker (n=109)	Former smoker (n=43)	Never-smoker (n=98)	p*	p†
Male	104 (95.4)	43 (100)	62 (63.3)	<0.001	0.153
Age, years	39.2±9.2	41.2±10.7	35.0±11.3	0.004	0.254
Onset age, years	30.0±10.1	32.1±12.7	27.1±12.9	0.075	0.338
Subtypes of CH				0.468	0.305
ECH	80	30	66		
CCH	4	5	3		
PCH	9	3	15		
fCH	16	5	14		
CH duration, years	9.2±7.8	9.1±9.4	7.9±7.4	0.233	0.946
Migraine history	8 (7.3)	7 (16.3)	21 (21.4)	0.004	0.096
Current alcohol drinking	70/104 (67.3)	31/42 (73.8)	39/90 (43.3)	0.001	0.441
Severity, NRS	9.0±1.2	9.0±1.2	9.0±1.2	0.973	0.847
Attacks per day	1.9±1.6	2.5±1.8	2.1±1.9	0.376	0.051
Attack duration, minutes	104.2±139.9	116.6±83.7	97.0±75.6	0.655	0.592
Total number of bouts	12.1±15.1	11.4±12.1	10.9±16.2	0.620	0.829
Triptan effectiveness	58/65 (89.2)	16/22 (72.7)	66/66 (100)	0.006	0.061
Diurnal rhythmicity	60 (55.1)	21 (48.8)	57 (58.2)	0.651	0.490
Seasonal rhythmicity	49 (45.0)	19 (44.1)	57 (58.2)	0.058	0.932
Bouts duration, weeks	5.8±6.2	7.5±9.1	5.7±5.8	0.894	0.247
HIT-6 score	68.0±8.2	66.6±8.5	68.9±7.8	0.440	0.330

Data are mean±standard-deviation, n, or n (%) values.
*p value between current smokers and never-smokers, †p value between current smokers and former smokers.
CCH: chronic CH, CH: cluster headache, ECH: episodic CH, fCH: first CH, HIT-6: Headache Impact Test-6, NRS: numeric rating scale from 0 to 10, PCH: probable CH.

Toxic chemicals from cigarette smoking may alter hypothalamus-based neurotransmitter function, leading to the development of CH in susceptible patients. Although the relationship between migraine and smoking is controversial,[22] CH is peculiar in its strong association with cigarette smoking, and numerous studies have revealed an epidemiologic association between CH and smoking.[4,5,7,8,23,24] Some studies have even shown that secondary smoke exposure during childhood may be related to the subsequent development of CH.[12] However, the mechanism underlying the pathogenetic role of cigarette smoking in the development of CH has not been clarified.[25]

In the prospectively maintained KCHR, 60.8% of patients were ever-smokers and 39.2% were never-smokers, while 70.3% of males (147/209) and 12.2% (5/41) of females were ever-smokers. The proportion of ever-smokers was lower than in previous reports. The smoking rate was 83.9% among the population included in an Italian study conducted from 1975 to 1980, but sex differences in smoking prevalence were not reported for that study.[7] Bahra et al.[8] reported that 89% of males and 71% of females were former or current smokers, while 84% of males and 65% of females were current or former smoker in a German study.[9] Males were more likely to have a smoking history than were females (75% vs. 69%, p= 0.02) in a US study involving a CH survey.[10] A large observational study involving 590 subjects in Italy found a smoking rate of 90% in males and 59% in females.[11] Overall, 75−90% of male patients and 59−71% of female patients in Western studies have had a smoking history. Smoking habits in Asian populations have been rarely reported, but one Taiwanese study found that 78.9% of male patients and 35.7% of females were ever-smokers, while 63.3% of males and 28.6% of females were current smokers.[26]

We found that the proportions of both male and female patients with CH who were ever-smokers were lower than in previous studies. This finding might reflect a decrease in the smoking population influenced by strict contemporary smoke-free regulations in Korea and worldwide, or there may be some ethnicity differences in the association between smoking and CH in different populations. According to Korean Statistical Information Service, the prevalence of a current smoking habit in Korean male aged >19 years decreased from 66.3% in 1998 to 36.7% in 2018, while it did not change among Korean female (6.5% in 1998 and 7.5% in 2018).[27]

The male-to-female ratio was much lower in never-smokers than in ever-smokers (1.7:1 vs. 29.4:1), which is probably due to the high proportion of male smokers in the general population. However, this discrepancy in sex ratio between smokers and never-smokers was greater in our CH cohort than the estimated sex ratio of smokers in the general population. Although the male-to-female ratio of the ever-smoker population was much higher in the present study than in Western studies, the sex ratio in the never-smoker population was similar to that found in Western and Taiwanese studies (1.5−2:1).[9,11,26] Recent data suggest that the male predominance of the CH prevalence has decreased, especially in Western studies.[28,29] Identifying the associations and causality of the changing sex ratio of CH (increasing prevalence in females) and changing smoker ratios over time requires further large cohort studies.

Recent studies showed that CH patients not exposed to smoking or who were never-smokers are significantly more likely to develop CH at a lower age than exposed patients (including to secondary smoke exposure) and ever-smokers.[3,13] Consistent with previous reports, our study also found that the age at CH onset was lower in never-smokers than in ever-smokers. In addition, seasonal rhythmicity was more frequent among never-smokers in our study. The lower age at onset in the never-smoker group suggests a genetic or biology-based etiology, while the higher age at onset in ever-smokers is suggestive of the consequences of smoke exposure.[3] However, a lower age at CH onset could cause patients to avoid smoking, so the influence of smoking before and after the onset of CH needs to be investigated further.

While other studies have suggested that the symptoms of CH are more severe in smokers,[3,5,14] our study did not find such a relationship, with indeed most of the clinical features not differing significantly between the groups. The treatment response to oral triptan seems more favorable in never-smokers; however, other studies have found no differences in triptan responses between groups,[3] or that triptan has a better treatment effect in patients with a smoking history.[5] Therefore, the reports of treatment responses according to smoking habits have been inconsistent.

One study found that autonomic symptoms and agitation are more common in smoking-exposed patients,[3] but we found no difference in cranial autonomic symptoms between ever-smokers and never-smokers.

The significance of smoking for the pathophysiology of CH remains unknown. Nicotine affects trigeminal nociception in healthy people,[30] increases the release of calcitonin-gene-related peptide in many tissues,[31] and could trigger the activation of the trigeminal autonomic reflex in the brainstem, causing cranial autonomic symptoms of CH.[32] Also, nicotine and other toxic agents act on the hypothalamus or cortex and may consequently cause CH.[25] Smoking may therefore be a risk factor for the development of CH, but the latency between smoking onset and CH onset was too long to suspect a direct causal relationship (mean 15.6 years).[5] Furthermore, smoking cessation was not found to improve CH.[14] Therefore, a causal relationship between smoking and CH remains to be proven.

There are several limitations to this study. First, detailed information regarding smoking habits such as the amount of cigarette smoking, debut age of smoking, and exposure to second-hand smoke were not available in this registry-based study. Second, the participants in this study consisted only of patients referred to a secondary or tertiary hospital, and so the results might not be generalizable to all patients with CH, especially those with milder forms of the disorder. Third, although smoking was suggested to be a risk factor for chronic CH,[3] we were unable to evaluate this association since the proportion of subjects with chronic CH was very low. Fourth, we defined triptan responsiveness according to patients' recall of a subjective reduction in pain intensity of >50%. Since the treatment responsiveness was assessed only using a questionnaire based on patients' recall, individual attacks of CH are very short, and triptan use was only reported in 153 of 250 patients, the association between the smoking pattern and triptan response should be interpreted cautiously.

In conclusion, this study found that the age at CH onset, sex ratio, and seasonal rhythmicity are significantly associated with a history of smoking. The later onset of CH among ever-smokers than never-smokers suggests the smoking acts as a secondary environmental contributor to CH.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.2.229.

Author Contributions

Conceptualization: Pil-Wook Chung, Soo-Jin Cho. Data curation: all authors. Writing—original draft: Pil-Wook Chung, Soo-Jin Cho. Writing—review & editing: all authors.

ORCID iDs

Pil-Wook Chung	https://orcid.org/0000-0002-8726-4812
Byung-Su Kim	https://orcid.org/0000-0003-4014-9400
Jeong-Wook Park	https://orcid.org/0000-0001-5360-2951
Jong-Hee Sohn	https://orcid.org/0000-0003-2656-9222
Mi Ji Lee	https://orcid.org/0000-0003-1364-1969
Byung-Kun Kim	https://orcid.org/0000-0003-1053-4682
Min Kyung Chu	https://orcid.org/0000-0001-6221-1346
Tae-Jin Song	https://orcid.org/0000-0002-9937-762X
Daeyoung Kim	https://orcid.org/0000-0001-9056-0017
Jae-Moon Kim	https://orcid.org/0000-0002-5035-9877
Soo-Kyoung Kim	https://orcid.org/0000-0002-7230-4033
Kwang-Yeol Park	https://orcid.org/0000-0003-4570-3538
Heui-Soo Moon	https://orcid.org/0000-0002-6847-497X
Kyungmi Oh	https://orcid.org/0000-0002-7304-0308
Chin-Sang Chung	https://orcid.org/0000-0002-0049-558X
Soo-Jin Cho	https://orcid.org/0000-0002-4053-3763

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgements

This study was supported by a grant from Korean Neurological Association (KNA-16-MI-09) and research fund from Korean Headache Society.

REFERENCES

1. Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. *Lancet Neurol* 2002;1:251-257.
2. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38:1-211.
3. Rozen TD. Cluster headache clinical phenotypes: tobacco nonexposed (never smoker and no parental secondary smoke exposure as a child) versus tobacco-exposed: results from the United States cluster headache survey. *Headache* 2018;58:688-699.
4. Levi R, Edman GV, Ekbom K, Waldenlind E. Episodic cluster headache. II: High tobacco and alcohol consumption in males. *Headache* 1992;32:184-187.
5. Lund N, Petersen A, Snoer A, Jensen RH, Barloese M. Cluster headache is associated with unhealthy lifestyle and lifestyle-related comorbid diseases: results from the Danish Cluster Headache Survey. *Cephalalgia* 2019;39:254-263.
6. Lund NLT, Snoer AH, Jensen RH. The influence of lifestyle and gender on cluster headache. *Curr Opin Neurol* 2019;32:443-448.
7. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache--clinical findings in 180 patients. *Cephalalgia* 1983;3:21-30.
8. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology* 2002;58:354-361.
9. Schürks M, Kurth T, de Jesus J, Jonjic M, Rosskopf D, Diener HC. Cluster headache: clinical presentation, lifestyle features, and medical treatment. *Headache* 2006;46:1246-1254.
10. Rozen TD, Fishman RS. Female cluster headache in the United States of America: what are the gender differences? Results from the United States Cluster Headache Survey. *J Neurol Sci* 2012;317:17-28.
11. Manzoni GC, Micieli G, Granella F, Martignoni E, Farina S, Nappi G. Cluster headache in women: clinical findings and relationship with reproductive life. *Cephalalgia* 1988;8:37-44.
12. Rozen TD. Cluster headache as the result of secondhand cigarette smoke exposure during childhood. *Headache* 2010;50:130-132.
13. Steinberg A, Fourier C, Ran C, Waldenlind E, Sjöstrand C, Belin AC. Cluster headache - clinical pattern and a new severity scale in a Swedish cohort. *Cephalalgia* 2018;38:1286-1295.
14. Ferrari A, Zappaterra M, Righi F, Ciccarese M, Tiraferri I, Pini LA, et al. Impact of continuing or quitting smoking on episodic cluster headache: a pilot survey. *J Headache Pain* 2013;14:48.
15. Cho SJ, Lee MJ, Kim BK, Moon HS, Chung PW, Sohn JH, et al. Clinical features of chronic cluster headache based on the third edition of the International Classification of Headache Disorders: a prospective multicentre study. *PLoS One* 2019;14:e0221155.
16. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629-808.
17. Chung PW, Lee MJ, Park JW, Sohn JH, Kim BK, Chu MK, et al. Differences of cluster headache on the basis of sex in the Korean Cluster Headache Registry. *Headache* 2019;59:1722-1730.
18. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol* 2018;17:75-83.
19. Schulte LH, Mehnert J, May A. Longitudinal neuroimaging over 30 days: temporal characteristics of migraine. *Ann Neurol* 2020;87:646-651.
20. Sprenger T, Valet M, Platzer S, Pfaffenrath V, Steude U, Tolle TR. SUNCT: bilateral hypothalamic activation during headache attacks and resolving of symptoms after trigeminal decompression. *Pain* 2005;113:422-426.
21. Matharu MS, Cohen AS, Frackowiak RS, Goadsby PJ. Posterior hypothalamic activation in paroxysmal hemicrania. *Ann Neurol* 2006;

59:535-545.
22. Volans GN, Castleden CM. The relationship between smoking and migraine. *Postgrad Med J* 1976;52:80-82.
23. Kudrow L. Physical and personality characteristics in cluster headache. *Headache* 1974;13:197-202.
24. Manzoni GC. Cluster headache and lifestyle: remarks on a population of 374 male patients. *Cephalalgia* 1999;19:88-94.
25. Rozen TD. Linking cigarette smoking/tobacco exposure and cluster headache: a pathogenesis theory. *Headache* 2018;58:1096-1112.
26. Lin KH, Wang PJ, Fuh JL, Lu SR, Chung CT, Tsou HK, et al. Cluster headache in the Taiwanese -- a clinic-based study. *Cephalalgia* 2004; 24:631-638.
27. Korean Statistical Information Service. Current smoking rate [Internet]. Daejeon: Statistics Korea [updated 2021 Jan 7; cited 2021 Mar 18]. Available from: http://www.index.go.kr/unify/idx-info.do?idxCd=4237.
28. Manzoni GC. Male preponderance of cluster headache is progressively decreasing over the years. *Headache* 1997;37:588-589.
29. Lund N, Barloese M, Petersen A, Haddock B, Jensen R. Chronobiology differs between men and women with cluster headache, clinical phenotype does not. *Neurology* 2017;88:1069-1076.
30. Holle D, Heber A, Naegel S, Diener HC, Katsarava Z, Obermann M. Influences of smoking and caffeine consumption on trigeminal pain processing. *J Headache Pain* 2014;15:39.
31. Dussor GO, Leong AS, Gracia NB, Kilo S, Price TJ, Hargreaves KM, et al. Potentiation of evoked calcitonin gene-related peptide release from oral mucosa: a potential basis for the pro-inflammatory effects of nicotine. *Eur J Neurosci* 2003;18:2515-2526.
32. Rozen TD. A history of cigarette smoking is associated with the development of cranial autonomic symptoms with migraine headaches. *Headache* 2011;51:85-91.