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Cluster headache in Asian populations: Similarities, disparities, and a narrative review of the mechanisms of the chronic subtype

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Abstract

Objective: Headache disorders like migraine show geographic and ethnic differences between Asian and European/North American countries. In cluster headache, these differences are rarely mentioned and discussed. This article aimed to review the characteristics of cluster headache in Asian countries and compare the clinical features to those in European and North American populations.

Methods: We conducted a narrative literature review on the demographics, clinical presentations, and treatments of cluster headache in Asian countries.

Results: Patients with cluster headache in Asian populations showed a stronger male predominance compared to European and North American populations. Chronic cluster headache was rare in Asian countries. The clinical presentation of restlessness was not as common in Asian as it was in European and North American countries, and Asian patients with aura were extremely rare. Patients in Asian countries may have a lower circadian rhythmicity of cluster headache and a lower headache load, as demonstrated by lower attack frequencies per day, bout frequencies, and bout durations.

Conclusions: Regional differences in the presentation of cluster headache exist. Greater awareness for cluster headache should be raised in Asian regions, and further studies are warranted to elucidate the mechanisms behind observed differences.

Keywords

Chronobiology, chronic cluster headache, disease load, Asian

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Introduction

Regional differences in headache disorders exist. The characteristics of patients with a primary headache disorder such as migraine differ in Asian countries from those in Europe and North America. For instance, the one-year migraine prevalence in Asian countries is on average 10% compared to 15% in European studies (1), and the proportions of migraine with aura among all migraineurs are relatively low, approximately 1 in 8 to 10 patients (2–4), in comparison to 1 in 3 in European and North American studies (5).

Regional differences in other types of headache have not been well investigated. Cluster headache (CH) is one of the most severe headache disorders, with

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extremely high disability levels (6). The prevalence of CH is lower than that of migraine. In one meta-analysis involving 16 population-based studies, the lifetime prevalence of cluster headache was 124 per 100,000 persons (7). However, most of those data are from European and North American populations except for two: One in Malaysia, in which the authors did not observe patients with CH among the 595 participants (2); the other study, conducted in Ethiopia, reported a lower one-year prevalence of 32 per 100,000 persons (8). The prevalence of CH outside European and North American countries has yet to be explored.

Despite the scarcity of population-based studies, several hospital-based studies of CH have been conducted in Asian countries (9–15), most being East Asian countries (9–11,13–15). In these studies, patients with CH showed somewhat different characteristics in comparison to European and North American populations; for example, an inclination to higher male-to-female ratios and the rarity of chronic cluster headache (cCH) (9–15); that is, attacks occurring for more than 1 year without remission or with remission lasting less than 3 months according to the diagnostic criteria of the International Classification of Headache Disorders, 3rd edition (ICHD-3) (16). How CH differs in Asian populations and what the specific reasons are for such low cCH prevalence in Asian countries remains unknown. We, hence, intended to review the characteristics of CH in Asian countries and the possible mechanisms behind the low prevalence of cCH in these populations.

Methods

We searched the PubMed database from 1980 up to December 2019 for studies on CH conducted in Asian countries using the following terms: Cluster headache and the names of Asian countries. The research was not restricted to full papers in English if an English abstract was available. In the case of studies exploring the same population at different time windows with partially overlapping subjects, the early study (or earlier studies) was excluded unless it dealt with a specific topic that was not included in the latest publication. The latest study of a series was always enrolled in the final analysis. Publications were also accessed through the authors' personal collection of scientific literature.

Results

Demographics and characteristics of patients with episodic and chronic cluster headache in Asian countries

A final sample of five studies qualified for the analysis with a total number of 614 patients. The mean age at onset of cluster headache in Asian countries ranged from 26.7 to 37.9 years (9,12–15). The overall male-to-female ratio (M:F) was 5.1:1, compared to 2.0–4.8:1 in European/North American studies (17–22). Specifically, two Asian countries showed decreasing M:F ratios over the years: In Taiwan, this ratio was 11.0:1 in 1982, 8.7:1 in 1997, and 3.6:1 in 2001 (9); in Korea, the M:F ratio was 7.0:1 in the years 2002–2013 (10) and 5.0:1 in 2016–2018 (23). This trend of a decreasing M:F ratio is consistent with studies conducted in Europe (24,25).

Lacrimation/conjunctival injection is unanimously the most frequent cranial autonomic symptom among all studies (67.0–83.3%), and weighted restlessness is approximately 51.3% among all patients (9,12–15). The information regarding family history was available in three of the five studies (9,12,13) and a family history of cluster headache was only present in 14 of 254 patients (3.6%). Patients with cCH accounted for only 3.9% (24 of 614) of all CH patients (9,12–15).

Table 1. Demographic and clinical characteristics of cluster headache in Asian countries.

	Taiwan 2004 (9)	Japan 2013 (14)	China 2013 (13)	India 2014 (12)	Korea 2019 (15)
Number	104	110	120	30	250
Male:Female ratio	6.4	3.1	7.0	9.0	5.1
Chronic cluster headache (%)	0	2.8	7.5	0	4.9
Mean age at onset in years	26.9	30.7	26.7	38.0	37.9
Smoking (%) (current and previous)	73.1	51.7	55.0	53.3	44.1
Family history (%) (cluster/migraine)	5.8/–	–/–	6.7/–	0/0	–/–
Predominant laterality	Right	Right	Right	Right	–
Most frequent cranial autonomic feature (%)	Lacrimation (83.0)	Lacrimation (67.0)	Lacrimation (72.5)	Lacrimation (83.3)	Lacrimation (83.2)
Restlessness (%)	51.0	66.0	38.3	80.0	47.6
Aura (%)	1	–	0	0	–

The demographic comparison of CH patients in Asian countries is summarized in Table 1.

Rhythmicity and disease load of cluster headache in Asian populations

Circadian rhythmicity. Patients with CH are known to experience their headache attacks during a specific time of the day defining the circadian rhythm of CH. In a recent large-scale Korean study recruiting 193 patients, only 86 (49.1%) of 175 patients reported circadian rhythmicity in their active period whereas, in past bouts, up to 70.9% experienced circadian rhythmicity, suggesting that the circadian rhythmicity is not stable but changes over time (26). Other Asian studies reported circadian rhythmicity in 65.0–67.5% of the patients (9,13). These ratios are low compared to European and North American studies (82.1% in Denmark, 82.0% in the US) (25,27); however, European and North American studies do not unanimously show a high percentage of circadian rhythms in their study populations. In Norway, the circadian rhythmicity was reported to be relatively low with only 58% (20).

Attack frequency and duration. In Taiwan, the majority of patients (56.0%) reported only one attack per day, followed by every other day (13.5%) (9). In Korea, the median attack frequency was 2 per day, and the majority of patients had an attack frequency of 1–3 in the active period (26). In Japan, the majority of patients had an attack frequency of 1–2 per day (44.0%) (14), followed by >2 attacks per day (18.0%). Most patients in India (63.3%) and in China (73.3%) had an attack frequency of 1–2 per day (12,13). Among European and North American studies, the US data showed more than half (54.0%) of the patient had ≥3 attacks per day (27). In Norway, over 50.0% of the patients reported 3–8 attacks per day (20). In Germany, patients had an average of 3.2 ± 2.4 attacks a day (19), whereas in Denmark the average was 3.8 ± 2.9 attacks per day (25). The mean maximum number of attacks was 4 or 5 in a UK study (21). Regarding the attack duration, the interstudy variation is large. In Asian studies, the majority of patients has an average attack duration in the range of 1–2 h, which is similar to values in European and North American studies (9,13,14,20,21, 26). In summary, no evidence suggests that the attack duration differs between European/North American and Asian populations; however, European and North American patients have a higher daily attack frequency and hence more hours per day with active headaches.

Circannual rhythmicity. CH patients are known to have circannual rhythmicity – onset or worsening of cluster attacks concentrated during a specific period of the year. These concentrated attacks are also referred as the cluster bout, which usually lasts for ≥1 week. More than half (54.7–59%) of the patients in European and American studies reported circannual rhythmicity (25,27). In Korea, 51.7% of the patients reported a seasonal rhythmicity; however, those who reported a seasonal rhythmicity (vs. those without) were nearly twice as likely to report circadian rhythmicity as well (66.2% vs. 37.1%, $p < 0.001$), suggesting a close relationship between circadian and circannual rhythmicity (26).

Despite a circannual rhythmicity, the peak and nadir months differed among studies. Studies from Denmark, US, Norway and Taiwan showed a similar trend, that the nadir of CH occurred in summer (9,20,25,27). One hypothesis is that sunlight exposure reduces the occurrence of CH attacks: the study in Taiwan found an inverse relationship between sunlight exposure and the monthly incidence of cluster bouts (9); another study in Denmark showed an inverse relationship between the daylight hours and the cluster attack in a day (25). However, the peak occurrence is not necessarily in winter and varied greatly among studies. In Denmark, CH symptoms are most commonly experienced in the transition from autumn to winter (25); in US, Norway, and Taiwan, the peak occurs in spring and autumn (9,20,27). The diverse peak months suggest the influence of other factors than merely sunlight exposure. Sunlight and other environmental factors (temperature, climate, humidity, etc) are geographically diverse and contribute synergistically to the seasonal differences. Therefore, the circannual rhythmicity may be driven by the interaction between these factors and the internal biological clock. The roles of environmental factors are beyond the scope of this review.

Bout frequency and bout duration. The CH bout frequencies in Asian regions also differ from those in European countries. One UK study showed that 43% of episodic CH patients (eCH) had an average of one cluster bout per year, (21) whereas in Norway most patients reported ≥2 bouts per year (20) and in Denmark, the average number of bouts per year was 1.9 (28). In a German study, eCH patients had an average bout frequency of 1.2 ± 1.1 per year (19). In Asian studies, a bout frequency of >1 per year is relatively rare. In Taiwan, only 11.5% reported ≥1 bout per year, and in Japan, most commonly (40%) patients have less than 1 bout per year (14). In Korea, patients enrolled during their within-bout period presented approximately 1 bout per year (26), whereas the average inter-bout duration ranged from 16–20 months (23), and the estimated bout frequency was <1 per year when patients of within- and inter-bout periods were taken together (15). In China, most patients with CH had a bout frequency of <1 per year (38.3%), followed by 1–2 per year (35.8%). Patients in Asian countries may have a lower bout frequency compared to their European and North American counterparts, but this awaits further confirmation by studies using the same methodology to allow for a direct comparison. Before drawing a firm conclusion on differences in bout frequencies between Asian and European/North American regions, we should consider the study settings and inclusion criteria of patient enrolment in these studies. If only patients during a bout are enrolled, they are more likely to have an increased disease activity, thus the bout frequency would be higher compared to studies where all patients regardless of their current status are enrolled (15,26). This is also associated with country-specific differences in healthcare systems, which we will discuss in the Limitations section.

The bout duration may be relatively shorter in Asian countries: In China, 42.5% and 75.0% of the patients have a bout duration of ≤1 month and ≤2 months, respectively (13); in Japan, 79.0% of CH patients have a bout duration of ≤2 months (1); in Korea, the median bout duration is 4 weeks in eCH patients (15), whereas another Korean study combining eCH and cCH cases reported a mean of 6.1 weeks (23); and in Taiwan, the average bout duration was 5 weeks (9). Compared to an average of 5–6 weeks in Asian countries, most European and North American studies showed an average bout duration of ≥8 weeks: 8.6 weeks in the UK (21), 8.5 weeks in Germany (19), 8.7 weeks in Norway (20), and 8.3 weeks in Denmark (25).

In summary, the frequency and duration of bouts are different in Asian countries compared to European and North American countries. Even though the attack duration is similar, European and North American populations experience more attacks per day. Furthermore, the average bout durations in European and North American countries are longer than those in Asian countries. In short, the headache load in patients with eCH, as defined by the time one experiences headache, is lower in Asian patients with CH compared to European and North American populations.

Comorbidities and lifestyle factors

Smoking. The majority (70–90%) of patients with cluster headache are either current or previous smokers (18,29). Compared to non-smoking CH patients, CH patients who smoke have more frequent attacks and longer bout durations (29). Furthermore, patients with cCH are more likely to be smokers than those with eCH (21,30). One study even found that eCH in patients with any kind of cigarette exposure (i.e. personal smoking history or parental secondary smoke exposure) was more likely to transform into cCH than in those without (23% vs. 14%, $p = 0.02$) (22). According to the Global Health Observatory Data published by the World Health Organization, the prevalence of smoking in the general population in 2016 was 38% in men and 21% in women in Europe, and 25% in men and 19% in women in the US (31). In Asia, however, the prevalence of smoking is different and highly concentrated in men: China (48% in men, 2% in women), India (21% in men, 2% in women), Japan (34% in men, 11% in women), Korea (41% in men, 6% in women), and Taiwan (29% in men, 4% in women) (31,32). The prevalence of smoking in men differs from country to country in Asia, but the prevalence is consistently lower in women compared to European and North American countries. This low prevalence of smoking among Asian women may be related to the male predominance of CH patients in these countries. However, the strong association between smoking and the occurrence of CH headache does not imply causation. CH patients do not improve after quitting smoking (29). Besides, smoking is associated with alcohol consumption and promotes excessive drinking (33). Therefore, such an association between smoking and CH may be mediated by alcohol consumption. This may underlie a stronger sex predisposition observed in Asia (10).

The impact of smoking on the lower prevalence of cCH in Asian regions has not been fully elucidated yet. One Korean study comparing cCH and eCH did not find a difference in the prevalence of current smoking. However, among prior eCH patients developing cCH, the proportion of smokers was significantly higher compared to those with consistent eCH, suggesting a role of smoking in the transition from eCH to cCH (23). Taken together, smoking seems associated with the transformation from eCH to cCH and may play a role in explaining the lower prevalence of cCH in Asian regions. We need more elaborate studies with larger numbers of patients to examine the association between smoking and cCH in Asian populations, and the potential interaction between smoking, alcohol consumption, and genetics should be explored.

Alcohol. Alcohol can trigger cluster attacks in more than 50% of the patients during their CH bouts (13,34,35). Therefore, contrary to smoking, patients with CH tend to avoid alcohol in order to prevent cluster attacks. Studies conducted in Denmark and Germany showed that alcohol consumption in CH patients is lower compared to that in the general population (18,36). However, in Denmark, damaging alcohol intake, defined as a weekly alcohol intake of $\geq$252 g, was more frequent in CH patients than in controls (5.0% vs. 1.5%) (18), whereas in Germany CH patients tended to avoid hazardous alcohol consumption (36). Alcohol consumption in patients with eCH and cCH showed a consistent trend: Patients with cCH consumed less alcohol compared to those with eCH, whereas whether patients with cCH were more likely to engage in hazardous drinking is inconclusive (18,36). The issue of alcohol consumption in patients with CH is less studied in Asian populations. Approximately 51.3–75.0% of the CH patients in Asia drank alcohol (37,38), and patients who drink had somewhat different cranial autonomic symptoms, such as more conjunctival injection but less nasal congestion injection (38).

Coffee. In Italy, patients with cCH were more likely to be heavy coffee drinkers compared to those with eCH (39); however, the association between coffee consumption and the specific risk of cCH is inconclusive and not observed in other studies (18). The coffee consumption in Asian countries is, in general, lower compared to European and North American countries (40). The influence of coffee consumption on the prevalence and types of CH may be minor at best. Further studies are needed before any conclusion can be drawn.

Treatment response of cluster headache in Asian countries

There are no published placebo-controlled trials on CH treatment in Asian countries. Regarding acute treatment, the response rate to triptan ranges in Asian studies from 80.0–97.3% (9,14,37,41), and high-flow oxygen works for 71.0–85.7% of the patients (9,14,41). One Korean study reported a 100% response rate to high-flow oxygen in CH patients with cutaneous allodynia vs. 50% in those without ($p = 0.07$), but the case number was small (37). Considering chronic prevention, only a limited number of studies on treatment responses in Asian regions exist. In one study, prednisolone was effective as a transition therapy in 84% of patients (9), whereas verapamil was proven effective in 74–93% of the patients in various studies (9,14,41). One study in Taiwan showed a dose-dependent response to verapamil as a cluster headache prophylactic treatment. The response rate was 63% with a daily dosage of 120 mg, 80–90% with a dosage of 240–360 mg, and $\geq$90% with a dosage of 480–720 mg (9). In Japan, 82% of the patients responded to a mean dosage of 241 mg (14). The response rates of acute and chronic medications are similar to those reported in European and North American countries (42); however, a direct comparison would be difficult because drug tolerability and prescription regulations differ in Asian countries. The comparisons between Asian and European/North American studies are summarized in Table 2.

Biological differences between eCH and cCH and possible mechanisms for the low cCH prevalence in Asian countries

Genetic predisposition. A genetic predisposition may contribute to the development or transformation of cCH. A French study showed that a family history of CH was twice as common in cCH compared to eCH patients (20.0% vs. 9.5%) (43). Additionally, a case report was published describing a familial CH in which a young boy in the third generation developed cCH at the age of 8 (44). This hypothesis was supported in a recent large study. Barloese et al. recruited 400 CH patients and 200 controls and showed a family history of CH was more prevalent in cCH vs. eCH

Table 2. Main differences between Asian and European/North American studies.

	Asian countries (9,12–15, 61)	France (17)	Denmark (18)	Germany (19)	Norway (20)	UK (21)	US (22)
Number	614	113	400	209	70	230	1,134
Male:Female ratio	5.1	4.6	2.0	3.4	4.8	2.5	2.6
Chronic cluster headache (%)	3.9	15.2	36.8	31.1	10.2	21.0	20.0
Smoking (%) (current and previous)	52.9	87.0	74.5	87.0	82.5	67.0	88.3
Family history (%) (cluster/migraine)	3.6/–	5.0/49.0	–/–	–/–	4.0/45.5	5.0/33.0	18.0/52.0
Restlessness (%)	51.3	–	–	83.0	80.0	93.0	–
Aura in %	0.4	–	–	–	35.5	14.0	–
Comorbid migraine (%)	15.6	–	–	9.0	17.0	26.0	–

(23% vs. 13%, $p = 0.008$) (45). A family history of CH is rare in Asian countries (3.6%) (9,12,13) compared to European and North American countries (4–18%) (17,20,21,27). There might be certain (unidentified) genetic variants predominantly expressed in European and North American populations that may account for a higher proportion of family history among these populations and provide, by the absence of these variants, a possible explanation for why cCH is so rare in Asian countries.

Sex differences and CH type. Generally, males are predominantly affected by cluster headache. Following the same trend as CH in general (24), the M:F ratio of cCH dropped from nearly 20.0 in the 1980s (46,47) to 3.0 in 2001 (48). One recent large Danish cohort reported a low M:F ratio of 1.8. Another study in patients with childhood-onset cCH even observed a reversed F:M ratio of 6.0 (49). It has been noted that the observed male sex predominance gradually decreased over the past decades in European and North American studies (24). However, cluster headache in Asian studies still showed a predominant male predominance (M:F ratio of 5.1) (9,12–15). One recent Korean study reported nearly identical sex ratios in patients with eCH (M:F ratio of 6.0) and cCH (M:F ratio of 5.0) (23). The influence of sex on different CH types remains inconclusive in Asian regions.

Clinical features as risk factors of a transformation from eCH to cCH. It has been reported that a cluster bout duration lasting ≥8 weeks and a bout frequency of >1 per year are both associated with a higher risk of chronification of cluster headache (39). This observation is similar to those in migraine. Patients with a higher disease load, e.g. higher frequency or longer duration, are more likely to develop a chronic form (50). Generally, eCH patients in Asian countries, compared to those in European and North American countries, have a lower disease load as shown by a lower attack frequency, lower bout frequency, and shorter bout duration (9,13,14,26). Therefore, Asian populations may be less likely to transform from eCH to cCH. Besides, untreated CH attacks lasted longer in cCH compared to eCH in general (28), suggesting that a biological brake; that is, a mechanism terminating untreated CH attacks, may also be involved in the chronification of cluster headaches.

Possible differences in the pathophysiology of eCH and cCH. Patients with eCH are known for their circadian rhythmicity. However, a recent study on the chronobiology of CH patients showed that many of the cCH patients had, in addition to their circadian rhythm, an ultradian rhythm – a period with a length between 1 to 24 h; that is, 4.8 h in this study (28). The generator of this ultradian rhythm and its potential role in cCH are worth further exploration. There were few imaging studies on different CH types. One study compared patients with eCH, those with cCH, and healthy controls and found in patients with cCH decreased grey matter volumes in the pain matrix, limbic system, and inferior temporal lobes. Several of these regions are known to be associated with chronic headache (51), including chronic migraine (52).

The role of calcitonin gene-related peptide (CGRP) may also differ in episodic and chronic CH. It has been shown that CGRP levels are elevated during CH attacks and normalized after successful treatment of CH (53). In patients with eCH, infusion of CGRP successfully provoked CH attacks in 89% of the patients; however, this rate was only 50% in patients with cCH (54). Recent trials with anti-CGRP antibodies demonstrate that galcanezumab is superior to placebo in preventing cluster headache attacks in patients with eCH (55) but not in those with cCH (56). The possible differences in the pathophysiology of CH; for example, the role of CGRP in CH, have not been investigated in Asian populations. Future comparable studies are needed, preferably conducted in parallel, to answer this question, whether populational differences in the pathophysiology of CH exist.

Treatment response. Medications commonly used to treat CH attacks show differential responses in patients with eCH and cCH. Patients with cCH are less likely to respond to triptan (21,57). Some studies show a differential response to lithium as a preventive medication in patients with cCH compared to those with eCH. The efficacy of lithium in patients with cCH is comparable to that of verapamil (58); however, in patients with eCH, it is not superior to placebo (59). One study found that the suboccipital injection of steroids is effective to prevent CH attacks irrespective of the CH type (eCH or cCH) (60). There are no comparable data in Asian countries regarding whether differential responses to treatment exist between patients with eCH and cCH. Whether different treatment responses contribute, at least in part, to differences in cCH prevalence warrants further investigations.

Limitations

The influence of country-specific medical systems cannot be measured or quantified in this review. The universal healthcare system in several Asian countries allows for a self-referral to tertiary medical centres. Therefore, compared to European and

North American studies, the patients' characteristics in certain Asian regions may be more similar to community-based instead of hospital-based CH patients. This may partially account for differences in disease load. Environmental factors including latitude, sunlight exposure, or climate are also different between Asian countries and European/North American countries, or even within the Asian countries in this review. These factors and their influences on CH occurrence have not been systemically investigated. Last, cultural factors and daily routine may also influence the occurrence of CH.

Conclusion

Regional differences regarding the presentation of cluster headache exist in Asian countries. These differences, including the low prevalence of cCH, may reflect disparate genetic predispositions and possibly interactions with other environmental factors that synergistically contribute to the observable differences in disease load. Greater awareness of cluster headache should be raised in Asian countries with their population of more than 3.5 billion people potentially comprising more than 3.5 million patients with CH.

Clinical implications

- Regional differences in the presentation of cluster headache in Asian populations exist.
- Asian patients showed a stronger male predominance.
- Chronic cluster headache or cluster headache with aura was rare in Asian countries.
- Headache load, as demonstrated by attack frequencies per day, bout frequencies, and bout durations, may be lower in Asian populations.

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