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RESEARCH SUBMISSIONS

Cluster headache epidemiology including pediatric onset, sex, and ICHD criteria: Results from the International Cluster Headache Questionnaire

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Abstract

Objective: To validate the diagnoses and to investigate epidemiological data from an international, non-clinic-based, and large (n = 1604) survey of participants with cluster headache.

Background: There are several limitations in current epidemiological data in cluster headache including a lack of large non-clinic-based studies. There is also limited information on several aspects of cluster headache, such as pediatric incidence.

Methods: The International Cluster Headache Questionnaire was an internet-based survey that included questions on cluster headache demographics, criteria from the International Classification of Headache Disorders (ICHD), and medications.

Results: A total of 3251 subjects participated in the survey, and 1604 respondents met ICHD criteria for cluster headache. For validation, we interviewed a random sample of 5% (81/1604) of participants and confirmed the diagnosis of cluster headache in 97.5% (79/81). Pediatric onset was found in 27.5% (341/1583) of participants, and only 15.2% (52/341) of participants with pediatric onset were diagnosed before the age of 18. Men were more likely to have episodic cluster headache between ages 10 and 50, but the sex ratio was approximately equal for other ages. An overwhelming majority of respondents had at least one autonomic feature (99.0%, 1588/1604) and had restlessness (96.6%, 1550/1604), but many also had prototypical migrainous features including photophobia or phonophobia (50.1%, 804/1604), pain aggravated by physical activity (31.4%, 503/1604), or nausea and vomiting (27.5%, 441/1604). Interestingly, the first-line medications for acute treatment (oxygen) and preventive treatment (calcium channel blockers) were perceived as significantly less effective in chronic cluster headache (3.2 ± 1.1 and 2.1 ± 1.0 respectively on a 5-point ordinal scale) compared with episodic cluster headache (3.5 ± 1.0 and 2.4 ± 1.1, respectively, $p < 0.001$ for both comparisons).

Conclusions: Cluster headache often occurs in the pediatric population, although they are typically not diagnosed until adulthood. The onset of cluster headache is the inverse of that in migraine; in migraine women are more likely to have migraine between

Abbreviations: CHQ, Cluster Headache Questionnaire; ICHD, International Classification of Headache Disorders.

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ages 10 and 50 but the sex ratio is approximately equal otherwise. Prototypical migrainous features are not useful in differentiating cluster headache from migraine. Participant data from a large international study also suggest that chronic cluster headache is not only less responsive to newer treatments (like noninvasive vagus nerve stimulation and galcanezumab), but to traditional first-line treatments as well.

KEYWORDS
diagnostic delay, incidence, pediatric headache, survey, trigeminal autonomic cephalalgia, verapamil

INTRODUCTION

Cluster headache is an uncommon headache disorder (prevalence 1:1000[1]) and several aspects are poorly understood because current epidemiological data are incomplete. First, there is only a limited number of very large cluster headache surveys (>1000 participants).[2–5] Second, many studies collect data from a single clinic-based population or single country. Third, many studies focus on a few demographic or treatment aspects and thus multiple aspects cannot be statistically compared. Fourth, there is limited information on several characteristics of cluster headache, namely pediatric-onset cluster headache and comparative effectiveness of cluster headache treatments. For pediatric-onset, diagnostic delay in cluster headache is typically 3–9 years, and younger age may be a contributing factor.[6] Prototypical migrainous features (photosensitivity, photosensitivity, and nausea) may be more prominent in pediatrics and partly explain the diagnostic delay,[7] yet two recent systematic reviews suggest that the current literature on pediatric-onset cluster headache is less than 150 detailed cases.[7,8]

We previously presented data on acute treatments[9] and pain intensity[10] from the Cluster Headache Questionnaire (CHQ), an international survey and the largest survey to date with respect to number of cluster headache respondents. Here, we present data on demographics, International Classification of Headache Disorders (ICHD) criteria, and treatment responses. We hypothesized that diagnostic delay would be longer for patients with pediatric onset but not for patients with onset at 50 years or older, that similar headache features would be found between men and women as well as between positive and negative family history of cluster headache, and that chronic cluster headache was more refractory to medications than episodic cluster headache.

METHODS

Methods are described in previous publications[9,10] and are summarized below. Pediatric onset is defined as onset of cluster headache attacks before the age of 18, and adult onset is defined as onset of cluster headache attacks at age 18 or later.

The CHQ is a self-administered internet-based survey of 152 items organized into eight separate sections: (1) Sign up and Verification, (2) Symptom Screening, (3) Demographics, (4) Experience, (5) Medications/Treatment, (6) Beck Depression Inventory, (7) Hopelessness Depression Symptom Questionnaire, and (8) End of Survey—Contact Options. This manuscript focuses on Sections 2–5. The first five sections were newly created by the authors, reviewed by one neurologist, and tested on 10 people with cluster headache from a community support group prior to final release. Authors M.J.B. and R.E.S. provided input as neurologists and assisted in analysis and interpretation. Author W.Z. provided statistical analysis. IRB approval was obtained from the University of West Georgia. Informed consent was obtained at the beginning of the online survey: Respondents were given a summary of the intent and purpose of the research and were given a brief summary of each section, then were required to verify their age as well as agree to participate in the survey by clicking on the appropriate link.

Survey questions are shown in Table S1. Notable details of specific questions are as follows. For the number of attacks per year, respondents were asked to estimate the number of lifetime attacks (up to a maximum of 5000); this number was divided by the number of years with the disease. For family history, respondents were given options for first-degree relatives and "other"; under "other," second-degree and other relatives could be entered as free text. Family history was obtained only through the respondent, with no effort made to verify the diagnosis in family members. Family members were not identified as such in the survey (e.g., if two family members with cluster headache took the survey, it was not disclosed that they were related, and the information on family history was counted for both).

The survey was open online from March 2016 to April 2018. For inclusion, participants must have (1) stated that they were at least 18 years of age, (2) stated that they had been diagnosed with cluster headache by a medical professional, (3) completed at least 90% of the survey including all inclusion/exclusion questions, and (4) filled out the English version (other versions were generated in Google translate but have not been fully verified by native speakers). For exclusion, participants answered several questions that addressed the full ICHD-3-beta diagnostic criteria for cluster headache,[11] including all autonomic features except for rhinorrhea, and all other criteria except criterion E ("not better accounted for by another ICHD-3-beta diagnosis"). The definitions of episodic and chronic cluster headache reflect the new ICHD-3 criteria that were released during this study (i.e., 3 months of headache freedom for episodic cluster headache).[12] Authors M.J.B. and R.E.S. reviewed all inclusion/exclusion criteria; however, a formal clinical diagnosis of cluster headache

was not corroborated by the authors. Recruitment consisted of three efforts: direct email through the Clusterbusters member listserv, website hosting through Clusterbusters and the International Headache Society, and advertising on Google via Google AdWords as well as Reddit forum. No incentives were offered for taking the survey.

The validation step was performed between May 14, 2020 and August 21, 2020. Participants were randomly emailed by author S.M.P. using a random number generator (the RANDBETWEEN function in Microsoft Excel): We excluded patients who declined to be contacted after the survey. We did not stratify our randomization. Participants were emailed in batches of 48–175 people until we successfully interviewed a predefined target of 81 participants, or 5% (81/1604) of the full data set. Participants replied to the study team either by emailing us directly or by filling out an online form in Qualtrics: With each batch, we responded in chronological order to all emails, then to all online forms. Participants were interviewed by phone or internet call by a single headache specialist (author M.J.B.) after providing verbal informed consent (IRB approval for this validation step was obtained from the University of Texas Health Science Center at Houston). Author M.J.B. diagnosed participants using criteria from the ICHD-3.[12] As an additional validation step, all ICHD-3 criteria were asked so that the interview responses could be directly compared with the survey responses. Author M.J.B. was not blind to the data set; however, the data set of 1604 participants was not reviewed before interviewing each participant, so author M.J.B. was not aware of their specific responses.

For age of onset calculations, respondents were excluded if their stated age of onset was older than either their current age or their age of diagnosis. For calculations of frequency and duration, respondents occasionally provided two responses: one for episodic cluster headache and one for chronic cluster headache. The diagnosis of episodic or chronic was made as above, and for frequency and duration, the average of these two responses was used.

No statistical calculation of power was performed prior to the study, and sample size was based on a previous study.[2] All analyses were planned either before the survey began (by authors S.M.P. and L.I.S.) or after the survey started but before analysis began (by authors M.J.B., R.E.S., and W.Z.).

Statistical analyses

All statistical analyses were performed using Statistical Analysis Software (SAS, Cary, NC) version 9.4. Selected demographic and survey variables were summarized using descriptive statistics, such as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate for continuous variables and frequency and percentage for categorical variables. The distributions of all variables were examined to check the validity of normality assumption, using measures of central tendency and a visual inspection of histograms and quantile–quantile plots. When the assumption of normality was not met, equivalent nonparametric approaches like the Wilcoxon rank-sum test were used. Continuous variables were compared via Kruskal–Wallis or Wilcoxon rank tests, and categorical variables were compared via Fisher's exact test. Two-tailed tests were used throughout the study. A Bonferroni correction was used to adjust p values; a separate Bonferroni correction was used for each analysis and was $p < 0.001$ or $p < 0.002$ for all analyses (specific p values listed in each supporting table). An ordinal variable was created (one completely ineffective, two minimally effective, three somewhat effective, four very effective, five completely effective). Details of each statistical test and final adjusted p value are provided in the supplemental tables.

Missing data were as follows. For cluster headache respondents, eight respondents did not provide an answer for chronic versus episodic ($n = 1596$), three respondents did not answer for duration of headache ($n = 1601$), and one respondent did not answer the Beck Depression Inventory-II ($n = 1603$). There were several respondents who answered questions on complications and access to medications that did not answer the question about effectiveness, suggesting missing data on effectiveness for 25 triptans, 11 oxygen, 6 dihydroergotamine, 24 cafergot/ergotamine, 3 ketamine, 8 opioid, 8 capsaicin, 3 caffeine and energy drinks, 16 lidocaine, 50 corticosteroids, 126 calcium channel blockers, 13 methysergide/methylergonovine, 64 anticonvulsants, 43 lithium, 16 testosterone, and 63 beta-blockers. The full range of missing data for medications, however, is unknown: In our survey design, a blank response could mean the respondent did not try a medication but could also mean that they forgot that they tried a medication. Twenty-one respondents either reported an age of diagnosis younger than their age of onset of cluster headaches (implying that they were diagnosed with cluster headaches before the attacks started) or reported a current age lower than their age of diagnosis. These respondents were removed from all calculations of age of diagnosis ($n = 1583$).

RESULTS

A total of 3251 subjects participated in the survey, and 1604 respondents met ICHD criteria for cluster headache: See flow diagram in our previous study.[9] Below, we discuss three aspects of this survey, namely diagnostic validation, demographics, and ICHD-3 criteria.

Diagnostic validation

In our initial study,[9] we outlined our criteria for identifying 1604 cluster headache participants from the original 3251 subjects who agreed to participate in the questionnaire. However, as mentioned in our prior study, we did not confirm the diagnosis of cluster headache in the subjects who completed this online survey. Thus, to validate our survey, a random sample of 5% (81/1604) of respondents with cluster headache underwent a neurology interview by telephone from a single board-certified headache

specialist (author M.J.B.). A total of 79/81 (97.5%) met full ICHD-3 criteria for cluster headache (Table S2). Of the two non-cluster headache respondents, one was diagnosed with probable trigeminal autonomic cephalalgia and the other met full cluster headache criteria but had a potential secondary cause. Statistically, there was no significant difference between our 81 interviewed participants and the remainder of the subjects (n = 1512) in terms of sex, age, episodic versus chronic subtype, pain level, headache duration, headache frequency, cranial autonomic features, or restlessness (Table S2). These findings suggest that the subjects we interviewed, 97.5% of whom were diagnosed with cluster headache, were representative of the entire data set.

Demographics

Table 1 provides basic demographic information from our data set as well as pertinent positive statistical findings, with full statistical analyses provided in the supplemental tables as indicated. We evaluated four basic demographic characteristics: age of onset, diagnostic delay, sex, and family history of cluster headache. We analyzed each characteristic in the context of the rest of the data set to find trends for pediatric- and late-onset cluster headache, females, and family history as discussed below.

For age of onset, our data set had an average of 27.3 ± 12.5 years of age, and 27.5% (341/1583) had pediatric onset (Figure 1A). For episodic cluster headache, there was a clear peak age of onset of 16–20 years of age for both sexes, whereas for chronic cluster headache, the peak age of onset was quite broad (from teens to 50s for both sexes; Figure 1B,C). Pediatric-onset cluster headache respondents reported nausea/vomiting and facial sweating statistically more frequently than their adult-onset counterparts (Table S3). We also evaluated participants with late-onset cluster headache, which was defined as onset of age 50 or older based on previous studies.[13–15] There were 104 participants with late-onset cluster headache, and these participants reported statistically significantly less nausea and vomiting, a shorter attack duration, and more attacks per year (Table S4). There was no difference in medication effectiveness either for the pediatric patients (Table S3) or for the late-onset cluster headache patients (Table S4).

The average diagnostic delay for participants was 6.2 ± 7.0 years (Figure 2A). Diagnostic delay was higher for pediatric-onset (who waited an average of 11.1 ± 9.4 years for a diagnosis) than participants with adult-onset (who waited 4.9 ± 5.5 years). The diagnostic delay was longer when the onset was early in childhood (Figure 2B). Only 15.2% (52/341) of participants with pediatric onset were diagnosed before age 18 and this was not driven entirely by participants close to age 18: For participants with pediatric onset between 1 and 14 years of age, only 23.4% (34/145) were diagnosed before age 18.

The majority of participants were male (68.8%, 1104/1604) and female respondents were statistically significantly more likely to have chronic cluster headache, higher pain intensity, higher depression scores, more nausea/vomiting, and more aggravation with movement (Table S5). Importantly, there were no statistically significant differences in treatment effectiveness between males and females. For family history of cluster headache, 10.5% (168/1603) stated a definite and another 12.4% (198/1603) stated a possible family history of cluster headache. There was a statistically significant difference for age of onset between participants with definite, possible, and no family history of cluster headache, with definite participants having the youngest age of onset (Table S6). There was no difference in medication effectiveness by family history.

Cluster headache criteria

Cluster headache is characterized by five criteria: (A) at least five attacks, (B) severe unilateral pain near the eye lasting 15–180 min, (C) restlessness and/or ipsilateral cranial autonomic features, (D) a frequency between once every other day and eight times a day, and (E) the lack of a better diagnosis to account for the signs and symptoms.[12] In Table 2, we show our analysis of individual components of cluster headache criteria A–D as well as migraine criteria. Pertinent positive statistical findings in the context of the rest of the data set are shown, with full statistical analyses provided in the supplemental tables as indicated.

Criterion A: Participants with episodic cluster headache have, on average, 95 attacks per year (95.4 ± 124.8), whereas participants with chronic cluster headache have about three times as many at 301 (301.3 ± 375.9).

Criterion B: The average attack duration was 85.2 ± 44.4 min. Pain intensity was rated at 9.7 ± 0.6 on a scale of 0–10. For an in-depth examination of this feature we refer you to our previous publication.[10] In short, pain intensity for cluster headache was significantly higher than all other painful conditions examined (including labor pain and nephrolithiasis), and higher pain was associated with more autonomic features.

Criterion C: 99.0% (1588/1604) of participants had at least one autonomic feature, and 96.6% (1550/1604) had restlessness. The statistically significantly most often reported autonomic features were conjunctival injection and/or lacrimation, nasal congestion, and miosis and/or ptosis. The least often reported autonomic feature was a sensation of fullness of the ear, and this feature was removed when the ICHD-3-beta criteria were updated to the ICHD-3 criteria. No participant had fullness of the ear as their only autonomic feature.

Criterion D: Average headache frequency was 3.9 ± 2.0 attacks per day.

Episodic and chronic subtypes: Episodic cluster headache was found in 78.0% (1245/1596) of the participants. Episodic participants had a statistically significantly younger age of onset, whereas participants with chronic cluster headache were more often female with more attacks per day and higher depression scores (Table S7). Interestingly, there was a difference in treatment effectiveness, with both oxygen and calcium channel

TABLE 1 Basic demographics of survey respondents with cluster headache

	Cluster headache	Pertinent positives from statistical analysis
Age		
Current age (in years)	46.1 (13.0) (n = 1583)	Respondents with headache onset <18 years of age with more nausea and vomiting
Age at onset of cluster headache (in years)	27.3 (12.5) (n = 1583)	Respondents with headache onset ≥50 years of age with less nausea and vomiting, shorter attack duration, more attacks per year
Age at time of diagnosis (in years)	33.6 (11.6) (n = 1583)	
Diagnostic delay (diagnosis—onset) (in years)	6.2 (7.0) (n = 1583)	
Sex		
Male	68.8% (1104/1604)	Female respondents more often had chronic cluster headache
Female	31.0% (497/1604)	Female respondents with higher pain intensity
Other	0.2% (3/1604)	Female respondents with higher depression scores
		Female respondents with more nausea/vomiting and more aggravation with movement
Family history of cluster headache		
Yes	10.5% (168/1603)	Respondents with a positive family history of cluster headache have a younger age of onset
Maybe	12.4% (198/1603)	
No	77.2% (1237/1603)	
Positive ("yes") family history		
1 positive family member	75.0% (126/168)	
2 positive family members	23.2% (39/168)	
3 or more positive family members	1.8% (3/168)	
Parent	47.0% (79/168)	
Sibling	28.6% (48/168)	
Child	9.5% (16/168)	
Other	41.1% (69/168)	
Possible ("maybe") family history		
1 positive family member	90.7% (166/183)	
2 positive family members	8.2% (15/183)	
3 or more positive family members	1.1% (2/183)	
Parent	37.7% (69/183)	
Sibling	10.4% (19/183)	
Child	2.2% (4/183)	
Other	59.6% (109/183)	

Note: Data are shown as either average (standard deviation) or as percentage. On the right are pertinent statistically significant findings when analyzing each category: full analyses are available in the supplemental tables for age (pediatric onset in Table S3, onset ≥50 years old in Table S4), sex (Table S5), and family history (Table S6). For missing data for family history, 15 respondents stated "maybe" but did not further elucidate; thus, totals are 198 for a "maybe" family history, but 183 when investigating details of these respondents.

blockers reported to be less effective by participants with chronic cluster headache (Table S7).

Migraine criteria: By definition, 100% of participants in the CHQ met criterion A for migraine without aura (at least five attacks) and 0% met criterion B (headache duration of 4–72 h). For the four parts of criterion C, by definition 100% met parts C1 and C3 (unilateral location and moderate-or-severe pain intensity), and we did not inquire about part C2 (pulsating quality). Criterion C4 (pain aggravated

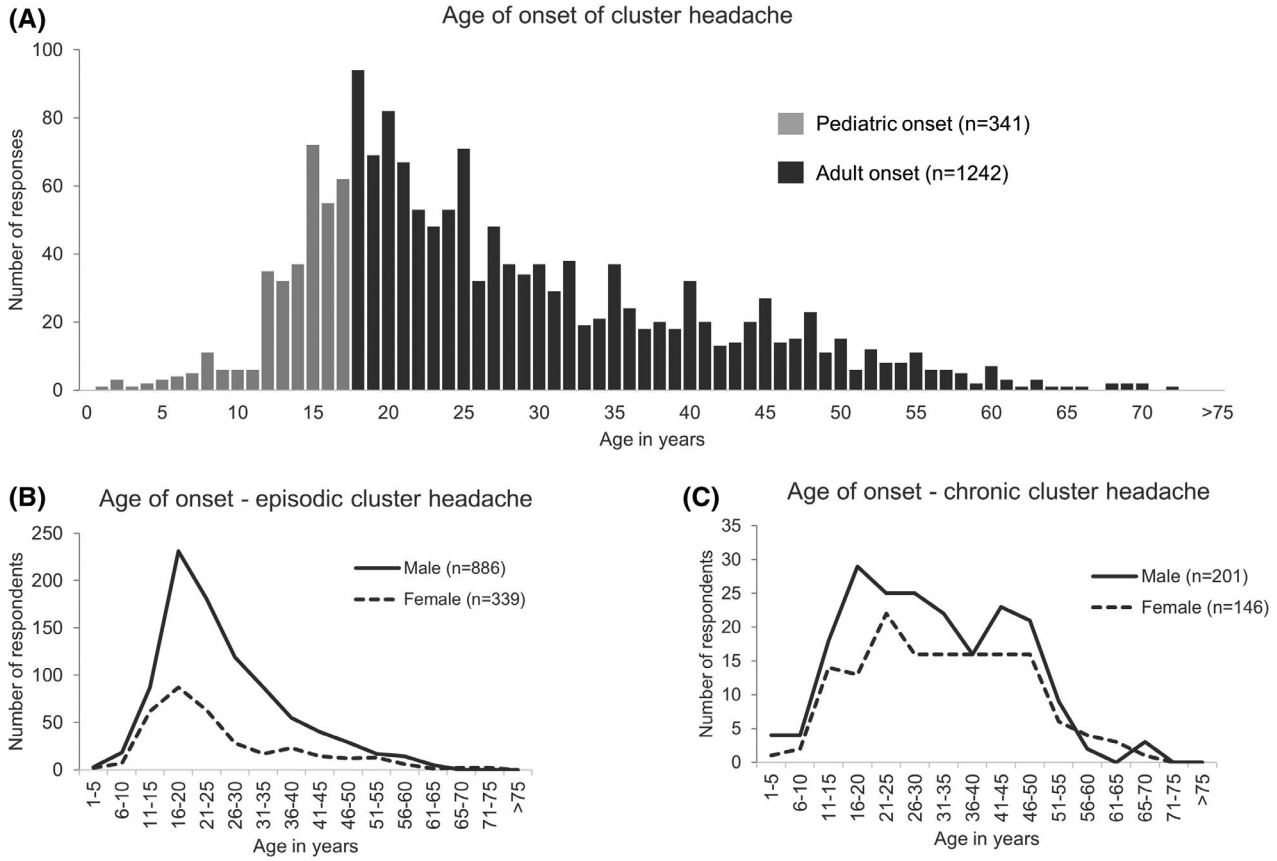

FIGURE 1 Age of onset. (A) Histogram of age of onset in years. Pediatric onset (age <18 years) is shown in light gray. (B,C) Age of onset for episodic (B) and chronic (C) cluster headache, separated by male and female. Ages are binned in 5-year intervals

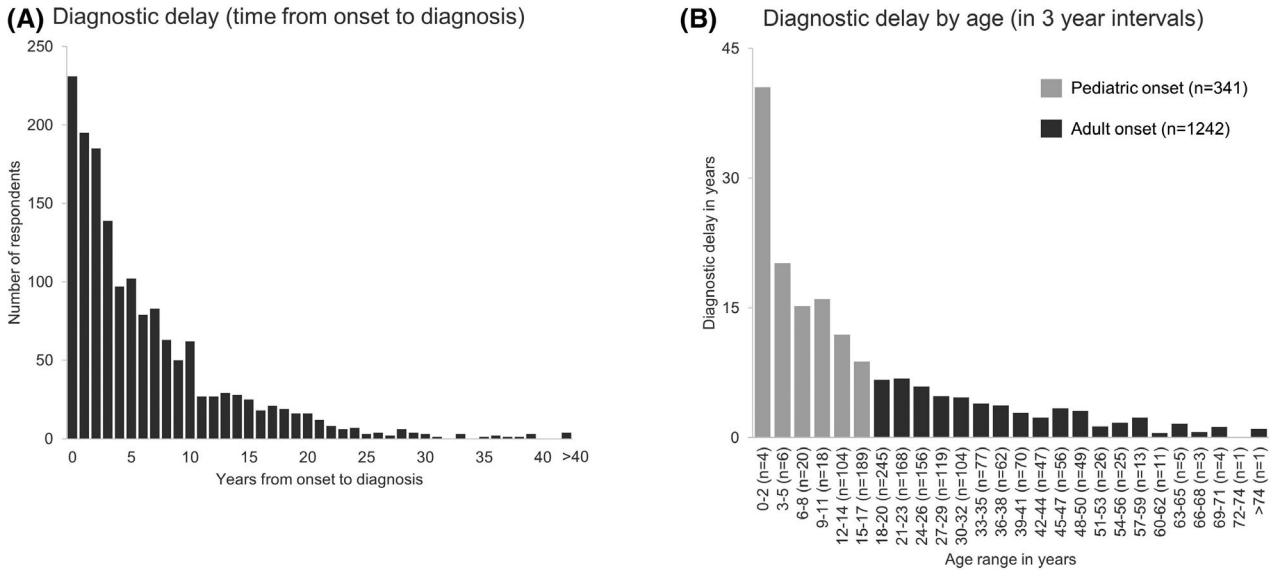

FIGURE 2 Diagnostic delay in cluster headache. (A) Overall diagnostic delay. Average diagnostic delay was 6.2 ± 7.0 years, although many participants had a diagnostic delay of 0 years as indicated. (B) Diagnostic delay by age. Data are binned in 3-year intervals; diagnostic delay is longer at all pediatric ages than at all adult ages

by physical activity) was present in 31.4% of the CHQ participants (503/1604). For criterion D, about a quarter of participants reported nausea and vomiting (27.5%; 441/1604), and about half of the participants had photophobia or phonophobia (50.1%; 804/1604).

DISCUSSION

This study describes the majority of the epidemiological data from the CHQ. This questionnaire adds to the existing epidemiological

TABLE 2 ICHD-3 features of survey respondents with cluster headache

	Cluster headache	Pertinent positives from statistical analysis
Cluster headache criteria		
Criterion A (at least five attacks)	100% (1604/1604)	
Number of attacks per year		
All cluster headaches	141.3 (224.9) (n = 1590)	
Episodic cluster headache	95.4 (124.8) (n = 1235)	
Chronic cluster headache	301.3 (375.9) (n = 347)	
Criterion B (severe or very severe unilateral facial pain lasting 15–180 min)	100% (1604/1604)	
Pain intensity (0–10 scale)	9.7 (0.6) (n = 1604)	
Attack duration (in minutes)	85.2 (44.4) (n = 1583)	
Criterion C (autonomic features and/or restlessness)	100% (1604/1604)	Number of respondents without cranial autonomic features (i.e., only restlessness) = 1.0% (16/1604)
Conjunctival injection and/or lacrimation	89.7% (1438/1604)	
Nasal congestion	90.4% (1450/1604)	
Eyelid edema	73.6% (1180/1604)	
Forehead and facial sweating	56.7% (910/1604)	
Miosis and/or ptosis	82.1% (1317/1604)	
Sensation of fullness in the ear	43.4% (696/1604)	No respondent had ear fullness as their only autonomic symptom
A sense of restlessness or agitation	96.6% (1550/1604)	
Criterion D (frequency between every other day and 8 per day)	100% (1604/1604)	
Headache frequency (attacks per day)	3.9 (2.0) (n = 1583)	
Chronic versus episodic	78.0% episodic (1245/1596), 22.0% chronic (351/1596)	Chronic versus episodic—see Table S7 Episodic cluster headache respondents have a younger age of onset Chronic cluster headache respondents are more often female Chronic cluster headache respondents have more attacks per day Chronic cluster headache respondents have higher depression scores Chronic cluster headache respondents found oxygen and calcium channel blockers less effective
Migraine without aura criteria in cluster headache respondents		
Criterion A: At least five attacks	100% (1604/1604)	
Criterion B (duration 4–72 h)	0% (0/1604)	
Criterion C (at least two of the following)		
Unilateral location	100% (1604/1604)	
Pulsating quality	Not asked	
Moderate or severe pain intensity	100% (1604/1604)	
Aggravated by physical activity[a]	31.4% (503/1604)	
Criterion D (at least one of the following)		
Nausea and vomiting[b]	27.5% (441/1604)	
Photophobia or phonophobia[c]	50.1% (804/1604)	

Note: Data are presented as percentage or as average (standard deviation). At the top are questions that investigate specific ICHD-3 criteria for cluster headache; at the bottom are ICHD-3 criteria for migraine. Criterion E (not better accounted for by another ICHD-3 diagnosis) was not addressed in this study for either migraine or cluster headache. The location of pain (part of cluster headache criterion B) is not included in this publication but was addressed in our previous publication.[10] Cranial autonomic features (part of cluster headache criterion C) do not include rhinorrhea (which was not asked in our survey) and does include sensation of fullness in the ear, which was present in ICHD-3 beta but not in ICHD-3.

[a]Official migraine criterion is aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs); our survey asked about aggravation but not avoidance.

[b]Official migraine criterion is nausea and/or vomiting, but our survey asked about nausea and vomiting, thus may have been interpreted differently.

[c]Official migraine criterion is photophobia AND phonophobia, but our survey asked about photophobia OR phonophobia.

data on cluster headache because it is unusual in several respects: The population is international, non-clinic based, and large. There are several important findings in this study, which we highlight below including age of onset, sex, family history, ICHD criteria, and treatment effectiveness.

There are few studies on pediatric or pediatric-onset cluster headache.[16,17] In the CHQ, 27.5% of participants had pediatric-onset cluster headache, and the peak of onset was 16–20 years of age. Compared with participants with adult onset, participants with pediatric onset had more than twice the delay in diagnosis. Previous studies have suggested that lower age of onset contributes to diagnostic delay.[6,18] The reasons for this are unclear but may include lack of recognition (by patients, parents, or physicians) and lack of access to physicians or specialists. Our data suggest that lack of recognition might be a factor because pediatric cluster headache might be more difficult to diagnose, perhaps related to the fact that pediatric migraine attacks are also often less than 4 h and thus overlap with the duration of cluster headache. Nausea/vomiting was more often seen in participants with pediatric onset than those with adult onset. Nausea/vomiting is typically considered a migrainous feature, and many participants with cluster headache are misdiagnosed with migraine.[6] It should be noted, however, that our study only surveyed adults and did not specifically ask participants if this nausea/vomiting was present when they were younger. For older-onset cluster headache (age 50 or later), our findings from 104 participants (less nausea and vomiting, a shorter attack duration, and more attacks per year) differed from major findings from a study of 73 late-onset patients (which found longer periods of attacks in episodic patients, more women, and more chronic cluster headache but did not find other statistically significant differences).[13] Additional studies on late-onset cluster headache are needed.

For sex and age of onset, our data from Figure 1 very closely mirror an extensive case series of 808 cluster headache patients from an Italian headache center.[19] The proportion of men and women with cluster headache onset is similar before 10 years of age and after 50 years of age. Between 10 and 50, men are more likely to have cluster headache. This is the reverse finding of incidence data for migraine: Incidence is similar between men and women early and late in life, but women are more likely to have migraine between the second and sixth decades.[20] Estrogen and the menstrual cycle have been suggested as explanations for the sex differences in migraine.[21,22] Whether estrogen might therefore be protective in cluster headache is not clear, nor is it clear whether testosterone plays a role. The hypothalamus-pituitary-adrenal axis is known to be important in cluster headache, as pituitary adenomas appear to be one of the more common secondary causes of cluster-like headaches[23–25] and testosterone levels are altered in some cluster headache patients.[26] However, in our study testosterone was not particularly effective for most respondents, and there was no significant difference in testosterone effectiveness between men and women. On a separate note, no acute or preventive medications differed in their effectiveness between men and women despite previous studies reporting sex differences in oxygen,[27] nasal lidocaine,[28] and triptans (specifically injectable sumatriptan[28]). Additionally verapamil, which is likely the most commonly prescribed calcium channel blocker, has been suggested to be less effective in women,[29] demonstrates sex differences in cluster headache circadian studies,[30] and demonstrates sex differences in rodent sleep studies.[31]

For family history, this study had a slightly higher proportion of positive family history of cluster headache (10.5% definite and an additional 12.4% possible family history) than two recent systematic reviews of 6.3% (average)[32] and 8.2% (median).[33] Previous reports suggest multiple patterns of inheritance[33] and multiple potential genetic associations.[34] The most common family member with a positive family history was a parent, and participants with a positive family history had a significantly younger age of onset. This raises the possibility of genetic anticipation in one or more of the potential genes.

For ICHD features, previous studies that evaluated ICHD criteria from Italy[35] and Korea[36] had similar attack durations; those studies found conjunctival injection/lacrimation to be the most common autonomic feature, whereas our study found nasal congestion to be slightly (<1%) more common than conjunctival injection/lacrimation. In our data set, almost all participants had at least one autonomic feature (99%) and had restlessness/agitation (97%). Compared with other studies, this is similar to a very large American study (99% agitation and at least 91% autonomic symptoms[2]) and the restlessness/agitation is somewhat higher than a very large Dutch study (76% agitation[4]). It should be noted that our study was performed only in English and thus does not fully characterize the global demographics of cluster headache; for example, a recent review of five Asian countries (where English is not the primary language) suggests a lower amount of restlessness (38%–80% by country).[37] We had an insufficient number of Asian respondents to comment on this difference, as our population was primarily North American and European.[9] In addition, our study agrees with the removal of "fullness of the ear" between the ICHD-3-beta and the ICHD-3 criteria: Our study used the ICHD-3-beta criteria, and no participant would have been excluded if fullness of the ear were removed from the official criteria. Finally, more than half of the participants in our study had prototypical migraine features of phonophobia, photophobia, nausea, and/or vomiting, suggesting these should not be used to distinguish cluster headache from migraine.

There are several limitations to this study. We attempted to address one limitation by validating the diagnosis of cluster headache in a subset of the population. We randomly selected 5% of our 1604 participants and confirmed the diagnosis of cluster headache in 97.5% by direct interview with a single headache specialist. The other limitations for this study, however, are unchanged from our prior publications on this data set[9,10]; they include recall bias, the grouping of medications (such as all calcium channel blockers) without the assessment of doses, a change in headache features (such as frequency, duration, or autonomic features) when taking preventive medications, and the fact that physical, medical, psychological, and emotional complications may be interpreted differently by different

respondents. This study remains a convenience sampling study, and due to the lack of offline random samples we are not able to compare the characteristics of our survey respondents with the target population.

In summary, data from a large group of international respondents show that cluster headache often begins during childhood and adolescence but is not diagnosed until adulthood. Age and sex data suggest that the incidence of cluster headache is higher in men only between ages 10 and 50 (where previous data suggest in migraine that migraine incidence is higher in women only between ages 10 and 50). The data from ICHD-3 criteria are generally similar to those of previous studies. Finally, chronic cluster headache, however, appears to be more refractory to some first-line treatments.

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CONFLICT OF INTEREST

SM Pearson: No conflicts. MJ Burish: Dr. Burish was an unpaid medical advisor for Praxis Precision Medicines (in lieu of compensation a fee was paid to the University of Texas Health Science Center at Houston) and was an unpaid consultant for Beckley Psytech Limited (in lieu of compensation a donation was made to the Will Erwin Headache Research Foundation). It should be noted, however, that Dr. Burish is employed by the University of Texas Health Science Center at Houston and receives research funding from the Will Erwin Headache Research Foundation. RE Shapiro: Dr. Shapiro has served as a paid consultant to Eli Lilly as a member of the Data Monitoring Committees for galcanezumab multicenter clinical trials for both cluster headache and migraine, as well as on the advisory committee for the OVERCOME study. He is also a consultant for research studies with Lundbeck. Hongyu Miao: Received research funding from Lilly. W Zhang: No conflicts. H Miao: No conflicts. LI Schor: No conflicts.

INSTITUTIONAL REVIEW BOARD APPROVAL

Institutional Review Board approval was granted by the University of West Georgia and UT Health Science Center at Houston.

AUTHOR CONTRIBUTIONS

Study concept and design: Stuart M. Pearson, Larry I. Schor. *Acquisition of data*: Stuart M. Pearson, Larry I. Schor. *Analysis and interpretation of data*: Stuart M. Pearson, Mark J. Burish, Robert E. Shapiro, Wei Zhang, Hongyu Miao, Larry I. Schor. *Drafting of the manuscript*: Stuart M. Pearson, Mark J. Burish, Wei Zhang, Hongyu Miao. *Revising it for intellectual content*: Stuart M. Pearson, Mark J. Burish, Wei Zhang, Robert E. Shapiro, Hongyu Miao, Larry I. Schor. *Final approval of the completed manuscript*: Larry I. Schor, Stuart M. Pearson, Robert E. Shapiro, Wei Zhang, Hongyu Miao, Mark J. Burish.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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