Headache
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ISSN 0017-8748
doi: 10.1111/j.1526-4610.2011.02028.x
Published by Wiley Periodicals, Inc.

Research Submission

Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden*

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Objective.—To present results from the United States (US) Cluster Headache Survey including data on cluster headache demographics, clinical characteristics, suicidality, diagnostic delay, triggers, and personal burden.

Background.—There are few large-scale studies looking at cluster headache patients and none from the USA. This manuscript will present data from The US Cluster Headache Survey, the largest survey ever completed of cluster headache patients living in the USA.

Methods.—The total survey was composed of 187 multiple-choice questions that dealt with issues related to cluster headache including demographics, clinical characteristics, comorbid medical conditions, family history, triggers, smoking history, and personal burden. The survey was placed on a Web site from October through December 2008.

Results.—A total of 1134 individuals completed the survey (816 male, 318 female). Some key highlights from the survey include the following: (1) diagnostic delay: there remains a significant diagnostic delay for cluster headache patients on average 5+ years with only 21% receiving a correct diagnosis at time of initial presentation. (2) Suicidality: suicidal ideations are substantial, occurring in 55%. (3) Eye color: the predominant eye color in cluster headache patients is brown and blue, not hazel as suggested in previous descriptions. (4) Laterality: cluster headache has a right-sided predominance. (5) Attack profile: in US cluster headache sufferers, most attacks occur between early evening and early morning hours with peak time of headache onset between midnight and 3 am; the circadian periodicity for cluster headache is present but is not as predominant in the population as previously thought. (6) Triggers: beer is the most common type of alcohol trigger in US cluster headache patients; noted migraine triggers such as weather changes and smells are also very common cluster headache triggers. (7) Medical comorbidities: peptic ulcer disease does not have a high prevalence in US cluster headache patients as suggested by previous literature; cluster

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Funding: Study was supported by an unrestricted educational grant from Linde Healthcare, The Linde Group. The authors received no honoraria for this study.

***Results from the US Cluster Headache Survey.**

Accepted for publication August 22, 2011.

Disclosure: This study was supported by an unrestricted educational grant from Linde Healthcare, The Linde Group.

The authors received no honoraria for this study.

Dr. Rozen reports no disclosures.

Royce Fishman was Director of Business Development, Linde Healthcare, The Linde Group, Munich, Germany, during the time the survey was developed, conducted, and completed. He is currently a medical device and pharmaceutical industry consultant and has no commercial relationship with Linde Healthcare.

Conflict of Interest: None

headache is associated with a low prevalence of cardiac disease as well as cerebrovascular disease even though the majority of patients are chronic heavy smokers. In US cluster headache sufferers, there appears to be comorbidity with restless leg syndrome, and this has not been demonstrated in non-US cluster headache populations. (8) Personal burden: cluster headache is disabling to the individual as almost 20% of cluster headache patients have lost a job secondary to cluster headache, while another 8% are out of work or on disability secondary to their headaches.

Conclusion.—Some findings from the US Cluster Headache Survey expound on what is currently known about cluster headache, while some of the results contradict what has been previously written, while other information is completely new about this fascinating headache disorder.

Key words: cluster headache, suicidality, smoking, burden, triggers

(*Headache* 2011;••:••-••)

Cluster headache is a unique syndrome marked by short lasting attacks of excruciating head pain and associated cranial autonomic features. Even though the recognition of cluster headache as a distinct syndrome was noted more than 50 years ago, there are very few large-scale studies looking at cluster headache patients and none from the USA.[1] Cluster headache is a fairly rare primary headache syndrome compared with migraine, but in the USA alone, more than 500,000 individuals probably suffer from cluster headache.[2] The goal of this article is to present data from the United States (US) Cluster Headache Survey, the largest survey ever completed looking at cluster headache patients living in the USA and one of the largest studies of cluster headache patients ever completed worldwide. Data related to cluster headache demographics, clinical characteristics, triggers, and personal burden will be presented.

METHODS

The complete survey methods have been published previously.[3,4] The US Cluster Headache Survey was conceived by author R.F., and author T.D.R. was asked to contribute as a headache specialist. The questions were developed and finalized by both authors with input from directors of the US Organization for the Understanding of Cluster Headache (US OUCH), of which several members are cluster headache sufferers. The survey was tested with randomly selected episodic and chronic cluster headache sufferers who were members of OUCH prior to finalization and implementation. Previous published surveys of cluster headache patients were evaluated for their deficiencies and unaddressed key clinical questions. The survey questions themselves were structured to be mutually validating and amenable for cross-tabulation. The survey was simultaneously promoted on the Internet by US OUCH and cluster-headaches.com on their websites by a dedicated survey Web page promotion linked to searches using the phrases "cluster headache" and "cluster headache therapies" and by search advertising promotions on other key headache therapy Web sites. In addition, the survey was promoted by the American Headache Society in its monthly newsletter to member neurologists, a mailing to headache neurologists and clinics in the USA using the American Headache Society and the American Medical Association neurologist headache specialist lists asking physicians to suggest that their cluster headache patients participate in the survey and issuance of approximately 9000 emails by US OUCH and clusterheadaches.com to their Web site users. Surveys were completed on a first-come, first-served basis and were thus accumulated on a randomized basis from interested participating cluster headache sufferers. The resulting survey results were not dominated by any one geographic area, one specific medical practice, or one type of medical practice. Only patients who were diagnosed with cluster headache by a neurologist were able to complete the survey. Even those individuals who were initially diagnosed by a non-neurologist had to have the diagnosis confirmed by a neurologist. The diagnosis of cluster headache, however, was not validated by the authors. The total survey was composed of 187 multiple-choice questions and addressed various clinical, epidemiologic, and economic issues related to cluster headache. The survey was placed on an Internet Web site from October 2008 through December 2008. Only fully completed surveys were included in the data analysis. Incomplete surveys were automatically rejected by the survey service

computer. The survey responders were a select population as only individuals who were able to complete an internet questionnaire could be involved in the study. The study was approved and given exempt status by the Geisinger institutional review board.

Statistical Analysis.—The service that programmed the survey, tabulated the results, and established statistical validity was InfoSurv in Atlanta, GA. The direct and cross-tabulated results were then analyzed by author T.D.R. The present study was mostly descriptive so statistical analysis was used sparingly, but when utilized, the chi-square test was used for categorical data. Statistical significance was defined as $P < .05$. SPSS software package for Windows version 18 (Chicago, IL, USA) was used for statistical analysis.

RESULTS

A total of 1134 individuals completed the survey. There were 816 male responders (72%) and 318 female responders (28%). The ages of survey responders were as follows: less than 20 years (7 responders/0.6%), 21-30 years (137 responders/12%), 31-40 years (311 responders/27%), 41-50 years (384 responders/34%), 51-60 years (238 responders /21%), and 61+ years (57 responders/5%). Every state was represented in the survey. The highest responder rates (50 or more people) came from California, Florida, Illinois, Michigan, New York, and Texas.

Demographics.—*Age of Onset of Cluster Headache (Table 1).*—Cluster headache began at age 20 years or younger in 35%, ages 21-30 years in 36%, 31-40 years in 16%, and ages 41-50 years in 10%. In only 3% did cluster headache start after the age of 51 years.

Physician Type Who First Diagnosed Cluster Headache Correctly.—In 34% of the patients surveyed, their general practitioner made the initial diagnosis of cluster headache, while in 52%, a non-headache specialist neurologist made the diagnosis, while in 22%, a headache specialty neurologist made the diagnosis. At the time of the survey, 48% of the survey responders were not currently seeing a neurologist for their cluster headache. Of those still seeing a neurologist, it was an almost even percentage of those seeing a headache specialty neurologist 26% vs those seeing a non-headache specialty neurologist 25%.

Table 1.—Cluster Headache: Age of Onset, Time Delay to Diagnosis, and Aura Duration

	Percentage (%)
Age of onset	
20 years or younger	35
21-30 years	36
31-40 years	16
41-50 years	10
51 years and older	3
Time delay to diagnosis	
Less than 1 year	25
1 year	7
2 years	10
3 years	9
4 years	6
5 years	7
6 years	4
7 years	4
8 years	4
9 years	2
10+ years	22
Aura duration	
Less than 5 minutes	25
5-10 minutes	30
11-15 minutes	17
16-20 minutes	10
21-25 minutes	10
Greater than 25 minutes	8

Time Delay for Correct Diagnosis (Table 1).—The majority of patients either had a proper diagnosis of cluster headache in less than 1 year from symptom onset (25%) or 10+ years after their headaches began (22%). In 42% of the survey responders, it took 5 years or longer to receive a correct diagnosis of cluster headache. A correct initial diagnosis of cluster headache occurred in only 21%. Incorrect diagnoses included sinusitis 21%, migraine 34%, allergies 6%, and tooth-related issues 5%.

History of Prior Head Trauma.—A history of any significant head trauma prior to cluster headache onset was noted in 18%. The amount of time that lapsed between the head trauma and onset of cluster headache was not obtained.

Family History of Cluster Headache.—Of the surveyed patients, 82% denied a family history of cluster headache. Of those with a positive family history, a first-degree relative was noted in 17%, with fathers being the most commonly cited relative in 6%, while mothers were noted to have cluster headache in 3%.

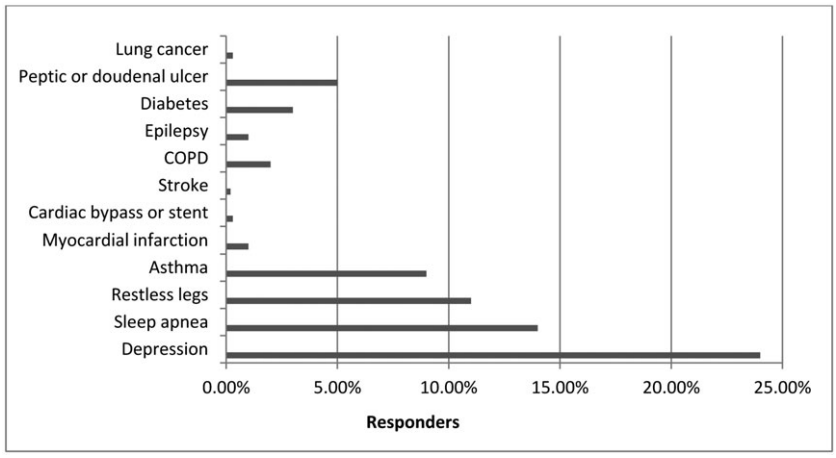

Fig 1.—Medical conditions in cluster headache patients.

A large percentage of survey responders stated that they had a family history of migraine (52%). A family history of Parkinson's disease was also ascertained, and this occurred in 5% of the total cluster headache population.

Concomitant Medical Conditions in Cluster Headache Patients (Fig. 1).—A personal history of depression occurred in 24% of the survey responders, while 14% had a history of sleep apnea, 11% restless leg syndrome, and 9% asthma. Interestingly, a very low percentage had known cardiovascular disease (myocardial infarction 1%, bypass surgery 0.3%, and coronary stent placement 1%). Strokes were rare occurring in only 0.2%. A diagnosis of emphysema or chronic obstructive pulmonary disease (COPD) was noted in only 2%, while lung cancer occurred in only 3 patients or 0.3%. Peptic or duodenal ulcer disease was noted in only 5%, while diabetes occurred in 3%. Epilepsy was noted in only 1%. A personal history of migraine and other headaches was not obtained.

Clinical Characteristics.—*Eye Color (Fig. 2).*—The most common eye color in cluster headache patients was brown (34%) and blue (33%), while 21% had hazel colored eyes, 11% green eyes and black eye color was noted in only 0.6%. The remainder (0.4%) stated they had an eye color other than those stated.

Aura History (Table 1).—A total of 21% of survey responders noted an aura history before a cluster headache attack. Survey responders were asked if they ever experienced any symptoms including aura prior to cluster headache onset. Auras could be visual, sensory, language/speech, and brainstem (dizziness and vertigo). Aura duration was less than 5 minutes in 25%, 5-10 minutes in 30%, 11-15 minutes in 17%, 16-20 minutes in 10%, 21-25 minutes in 10%, and 25 minutes or more in 8% of patients. Almost all auras with cluster headache lasted less than 25 minutes (92%), and 55% of patients with cluster headache had auras that lasted 10 minutes or less.

Associated Symptoms (Fig. 3).—The most common cranial autonomic associated symptom along with cluster headache was eye lacrimation noted in 91% of responders, followed by nasal rhinorrhea 84% and forehead sweating 59%. In regard to

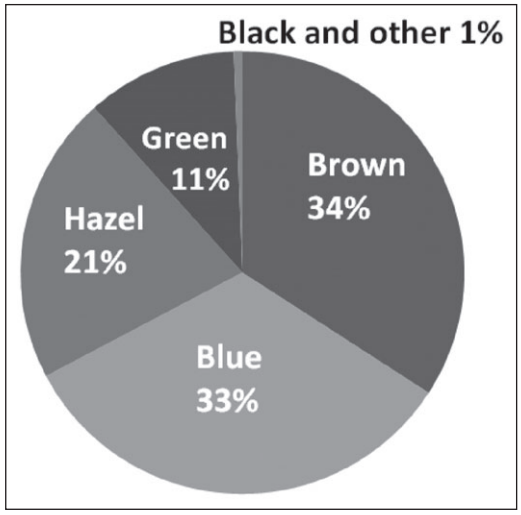

Fig 2.—Eye color of cluster headache patients.

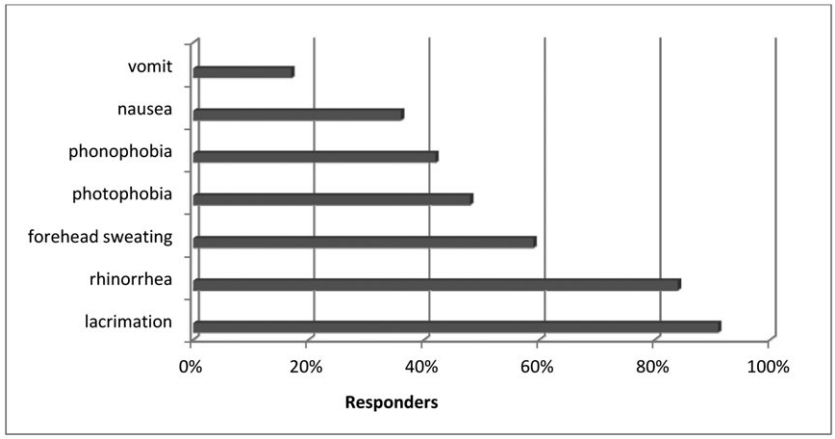

Fig 3.—Cluster headache associated symptoms.

"migrainous associated symptoms," 48% were photophobic (no side specified), 42% phonophobic, while nausea occurred in 36% and vomiting 17%. The presence of an eyelid ptosis and a miotic pupil was not ascertained.

In regard to a sense of agitation during an individual headache, 20% stated they always paced or rocked back and forth, 55% would sometimes pace or rock, while 50% would either hit themselves in the head or punch their fists against the wall. Only 0.8% would have no agitation with their headache.

Pain Location and Quality (Table 2).—Almost 85% of patients stated the cluster headache pain was sharp in quality, while 45% stated it was also pulsating, and 44% stated it could be pressure-like. The predominant pain side was right-sided in 49%, while 44% stated it was predominantly left-sided, and this was a statistically significant difference ($P = .02$). Bilateral cluster headache or experiencing pain on both sides of the head during an attack occurred in 3%. Pain would switch sides in 8% during an individual cluster headache attack, while 31% stated that they had experienced some side shift in between individual headaches or cycles. Pain location was in a retro-orbital distribution in 88%, upper teeth 44%, jaw 37%, ear 28%, and shoulder region 16%.

Suicidal Thoughts.—In the USA, 55% of the survey responders stated they have had thoughts about suicide, and 2% have actually tried to commit suicide.

Smoking History (Table 3).—In regard to current or prior tobacco exposure (cigarette smoking or chewing tobacco), 73% had a positive history. In 72%, 1 or both of the survey responder's parents smoked while that individual was living with that parent. Only 17% stated they had never smoked prior to cluster headache onset, while 51% stated they were smoking at the time they developed cluster headache. Only 18% stopped smoking after their headaches began, while 45% continued to smoke at the same rate, 16% decreased their

Table 2.—Cluster Headache: Laterality, Pain Location, and Side Shifting

Cluster Headache Factors	Rozen/Fishman (N = 1134) (in %)	Bahra et al Study (N = 230) (in %)
Laterality		
Right	49	60
Left	44	38
Bilateral	3	2
Location		
Retro-orbital	88	92
Upper teeth	44	50
Jaw	37	45
Ear	28	17
Shoulder	16	13
Side shifting		
Side shift during individual headache	8	–
Side shift in between cycles or headaches	31	38

Table 3.—Cigarette Smoking and Cluster Headache in the USA

Smoking Issue	Percent of Total Survey Responders (%)
Smoking history	
Positive smoking history	73
Smoking at time their cluster headaches started	51
Never smoked prior to cluster headache onset	17
Parenteral smoking history	72
Smoking pattern after cluster headache onset	
Stopped smoking	18
Smoked at same rate	45
Decreased rate of smoking	16
Increased rate of smoking	8
Smoking and response of cluster headache	
Smoking reduced attack frequency	2
Smoking reduced attack severity	8
Smoking used to relax during or after cluster attack	27
Extent of smoking history	
Smoking history of 10 or more years	61
Smoking history of 25 or more years	29

smoking rate, and 8% increased their rate of smoking. Of the survey responders, 8% stated that smoking cigarettes would reduce the severity of an individual headache attack, 2% stated smoking reduced their attack frequency, while 27% used cigarettes to relax themselves during or after a cluster headache attack. Of the survey responders, 29% had a smoking history past or present of more than 25 years, while 61% used tobacco for 10 or more years.

Alcohol (Usage and as a Trigger) (Fig. 4).—Almost 65% of the surveyed patients stated they drank alcohol, but only 3% reported they had been diagnosed as an alcoholic. Of the survey responders, 52% noted that alcohol triggered a cluster headache. Beer statistically was the most common alcohol trigger in 57%, while red wine and hard liquor were noted as a trigger in 50% and 49%, respectively ($P = .0004$) (Fig. 4). A majority (85%) of cluster headache sufferers would stop drinking alcohol during a cluster headache cycle.

Other Noted Triggers (Fig. 4).—After alcohol, the next most mentioned trigger was weather changes in 36%, followed by smells (not specified by type) 28%, bright lights 23%, flashing lights 17%, watching television 12%, hot wrap or hot shower 8%, and nitroglycerin 3%.

ATTACK CHARACTERISTICS

1. Months of the year that cluster headache cycles would start (Fig. 5): In 41% of the survey responders, their cycles varied during the year, and there was no particular month the cycles would always begin. By percentages, the months of October (26%), September (21%), April (21%), March (20%), and November (20%) were the most likely for cluster headache suffers to start a cycle. The remainder of the months of the year were evenly distributed with 11-13% stating their headaches

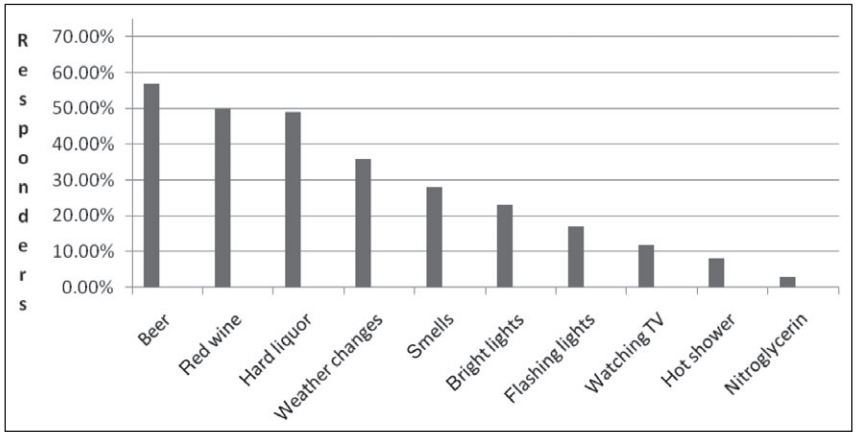

Fig 4.—Cluster headache triggers.

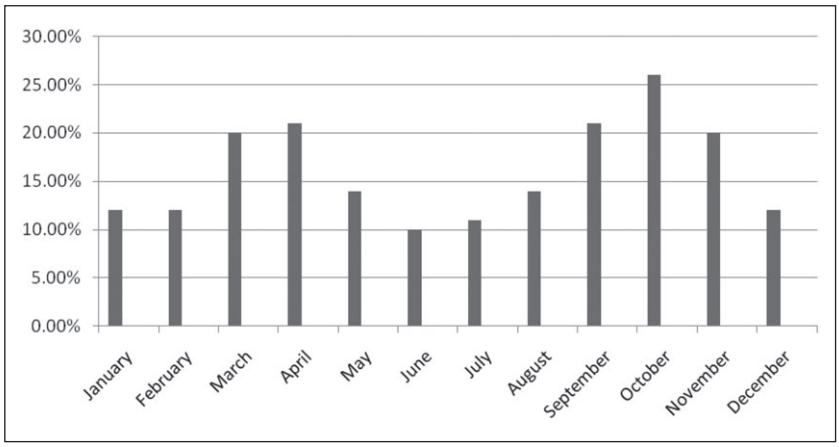

Fig 5.—Cluster headache cycles and months of the year.

cycles would start during these particular months. The lowest percentage was noted for the month of June at 10%.

2. Average number of attacks per day: The most common attack frequency was 2 cluster headaches per day (24%), followed by 1 attack per day in 22%, 3 attacks per day in 18%, and 4 attacks per day in 12%. About 20% of survey responders would have between 5 and 8 attacks per day. Most patients would have headaches on a daily basis (80%).
3. Time of day for cluster headache attacks (Fig. 6): In 82% of the survey responders, the headache attacks occurred more or less the same time each day. The most frequently cited time of the day to have a cluster headache attack was at 2 am, and this was noted by 41% of the survey responders. This was followed by 1 am and 3 am, which occurred in 35% of the responders, and midnight in 32%. The least frequently noted time for cluster headache attacks was at 8 am noted in only 18%. On average, 58% had attacks between 7 pm and 7 am vs 42% between 7 am and 7 pm. This was a statistically significant difference ($P < .00001$).

In regard to pain intensity and time of day of attacks, 48% stated that their headaches were more severe during the nighttime hours, 7% during daytime hours, while 45% said there was no difference in attack intensity between morning and evening hours.

Cluster Headache Personal Burden.—In the USA, 17% of the surveyed population had lost a full-time job due to their cluster headaches. A total of 8% were

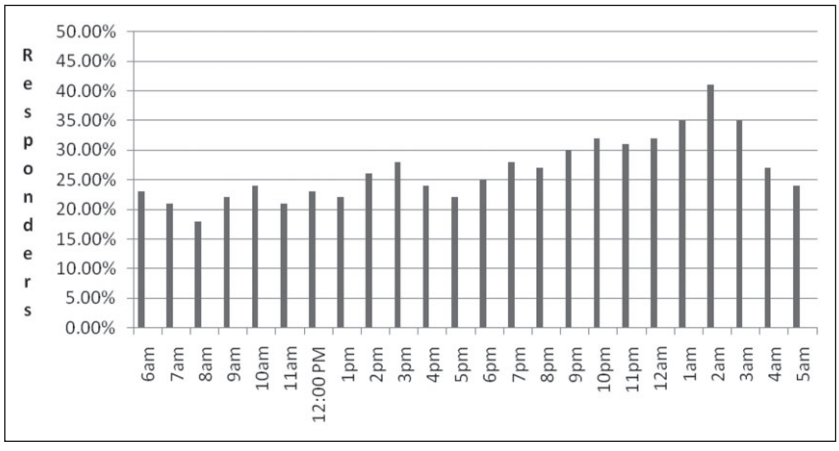

Fig 6.—Time of day and cluster headache attacks.

currently out of work or were on work-related disability secondary too their headaches. Full lost days of work per year secondary to cluster headache were 1 to 10 days in 47%, 11 or more days in 21%, while 32% had never lost a single day of work. A total of 38% were unable to leave their homes between 1 and 12 days per year because of their cluster headaches, while 11% stated they were literally bed-bound for 31 days or more per year because of headaches, while 28% had never lost a single day because of head pain. In regard to emergency department visits, the majority or 63% had not gone a single time to the emergency room within the past 2 years, while 95% of the population had gone 2 times or less.

Regarding procedures having been done to treat cluster headache, 70% of the surveyed population had no procedures, 15% had teeth removed, 8% had occipital nerve blocks, 7% had sinus surgery, 2% had occipital nerve stimulator placement, and less than 1% had gamma knife and/or trigeminal nerve-based surgery.

COMMENTS

The US Cluster Headache Survey is the largest study of cluster headache patients ever completed in the USA and one of the largest studies looking at cluster headache ever done in the world. Some of the results from this study have never been published before about cluster headache. The survey responders were from a selected population drawn from treating physicians and cluster headache support groups; however, the exact composition of the survey responders (for example, the number from support groups) cannot be obtained from our data. This type of epidemiologic investigation has been done previously, although not exactly by several groups. Bahra et al[5] in a UK study looked at individuals from cluster headache support groups as well as those from a specialty headache clinic. In contrast to our study, this was not an Internet-based investigation, and the diagnosis of cluster headache was validated. Schürks et al[6] from Germany looked at 246 cluster headache patients in total of which 60 patients were clinic-based, while 186 patients were recruited from cluster headache self-help groups and also via the Internet. This study also validated cluster headache diagnosis. Finally, a large investigation from France actually collected data from 2074 cluster headache patients but only reported on 113 patients with chronic cluster headache.[7] Our present study is novel based on the size of the studied population and the amount of data obtained. A significant amount of information was generated from our survey study, and all of it cannot be addressed in this article. Much of our data support what has been previously written about cluster headache including young age of onset in the majority of patients, rare family history of cluster headache but large percentage of family members with migraine, and a large percentage of "migrainous associated symptoms with cluster headache attacks"[5,6] and thus will not be discussed.

Delay for Cluster Headache Diagnosis.—In 2000, Klapper et al[8] using an Internet survey noted an average time delay of 6.6 years before a proper diagnosis of cluster headache was made in a US population of 789 respondents. Our study completed 8 years later showed the same disturbing trend as in 42%, it took 5 years or longer to get a proper diagnosis, and in 22%, it took 10 years or longer. This trend has also been observed in a Dutch investigation of 1163 individuals in which the median time to diagnosis was 3 years.[9] Even though cluster headache with its unique presentation should be fairly easy to diagnose, only 21% in our study received the proper diagnosis at their initial presentation to a physician; this same percentage was noted in the Dutch investigation.[9] Possible reasons for misdiagnosis include the prevalence of migraine associated symptoms with cluster headache, a larger number of females with the disorder than previously thought, the presence of migrainous aura with cluster headache (see later section), and possibly the large percentage of migrainous triggers for cluster headache (see later section). This diagnostic delay may lead to some of the personal burden associated with cluster headache as this syndrome is very treatable but only if proper therapy is provided.

Medical Conditions in Cluster Headache Patients.—In our investigation, depression was the most commonly noted associated medical condition in one-quarter of the survey responders. In a large chronic cluster population from France, Donnet et al noted depression in 43%.[7] There are very few studies

that have looked at psychiatric comorbidities with cluster headache. Surprisingly, in our population with a significant smoking history, there was very little cardiac and cerebrovascular disease noted. This does not appear to be a US population effect as Manzoni et al[10] in a study of 180 cluster headache patients from Italy also noted a similar finding where only 3% had coronary artery disease compared with only 1% in our population. Kudrow noted the same trend in 140 patients showing no difference in incidence of coronary artery disease between cluster sufferers and controls.[11] One could hypothesize that cluster headache may, in some manner, have a protective effect against atherosclerotic disease in both the heart and brain as our study also showed that stroke occurred in almost a nonexistent amount of the survey population (0.2%). However, this may also be due to a survivor effect. Another interesting trend and again suggesting a protective role of cluster headache on the individual was the very low incidence of lung cancer in our population, and this has recently been addressed in another article.[12] Older literature has suggested a high prevalence of peptic ulcer disease in cluster headache patients (frequencies of 13% to 22%), but this did not bear out in our investigation as only 5% stated they had this medical issue.[11,13,14] In the USA, the overall prevalence for gastrointestinal ulcer disease is 8% so actually, the US cluster headache population has less ulcer disease than the general population.[15] The difference in frequency of peptic ulcer disease in our study and older investigations may reflect the pre-triptan and post-triptan eras as in the past, patients were more likely relegated to take nonsteroidal anti-inflammatory drugs (NSAIDs) or oxygen for their headaches; now, they use triptans and oxygen, which are both nonulcer-causing medications. Head trauma occurred in almost 20% of our population, and that is consistent with prior studies (ranges of incidence 5-37%) suggesting a possible connection with cluster headache.[16] The percentage of our survey population with restless leg syndrome was 11%, which is the same percentage noted in migraineurs in a large clinic-based study from Taiwan.[17] However, in this same population, only 2% of cluster headache suffers had restless leg syndrome, while in another study from Italy, 0% of cluster headache patients had restless leg syndrome.[17,18] Either restless leg syndrome was overestimated in our patient population or US cluster headache sufferers are more likely to develop restless leg syndrome, and as noted with migraine, there appears to be a comorbidity for restless legs and cluster headache. This may relate to a possible dopaminergic influence on cluster headache pathogenesis, which has been suggested by one of the authors previously.[19] In regard to familial medical conditions, Parkinson's disease occurred in 5% of survey responder families. This appears, however, to reflect normal population expected lifetime risk of Parkinson's and does not suggest a familial risk factor.[20] Finally, asthma occurred in 9% of the survey population, which is about the prevalence of asthma in the general US population (8.2%).[21]

Clinical Characteristics of Cluster Headache.— *Cluster Headache and Aura.*—Aura was not recognized as a clinical symptom of cluster headache until fairly recently, but studies now have indicated that upwards of 20% of patients with cluster headache may have aura, about the same percentage of migraine sufferers who have aura.[5,6,22] Auras occurred in 21% of the survey responders, thus matching aura frequency in other smaller clinic-based and nonclinic-based studies. Our study is the first, however, to look at aura duration in cluster headache sufferers. Greater than 90% of auras with cluster headache lasted less than 25 minutes, and 55% had auras that lasted 10 minutes or less. The aura duration in cluster headache appears to be shorter than the aura duration in migraine. Very few studies have actually looked at migraine aura duration. In Russell and Olesen's analysis of aura in a general Danish population, visual aura mean duration was 33 minutes, sensory aura duration 74 minutes, and motor aura duration 13 hours.[23] As survey responders were asked if they had experienced an aura prior to a cluster headache, but no definition of aura was provided in the survey questionnaire, what patients reported as aura symptoms may not have been true aura by headache classification standards.

Eye Color.—In 1972, Graham first indicated a specific facial characteristic in cluster headache patients.[14] This was followed by Kudrow's landmark observations in 1974 where he added the propensity of cluster headache patients to have hazel eye color.[24]

Hazel eye color was the predominant eye color in his cluster population, but only 40 patients were studied. Hazel eyes were noted in 38%, followed by blue eyes in 34% and brown eyes in 28%. The results from the US Cluster Headache survey contradict the Kudrow findings in that brown and blue eye color and not hazel eye color are the predominant eye color of cluster headache patients in a much larger studied population. Both brown and blue eyes were significantly more common in the cluster headache survey responders than hazel eyes ($P < .00001$ for both associations), although there was no statistical significant difference in the prevalence of brown vs blue eyes. Hazel eyes were, however, significantly more prevalent than green eyes ($P < .00001$). As 21% of our survey patients had hazel eye color, is this a higher prevalence of hazel eyes than what is seen in the general population and thus overrepresented in the cluster headache population as suggested by Kudrow? In Kudrow's original work, he found hazel eyes in only 10% of non-headache controls but that involved only 230 subjects. Data on the prevalence of hazel eye color or any other primary iris color in the US population are lacking. As prevalence of iris color is geographically dependent, one needs to compare the eye color prevalence of US cluster headache sufferers to eye color prevalence from a general US population to determine if there is overrepresentation in a specific subgroup. The study that best estimates prevalence of iris color in a general US population comes from the Beaver Dam Eye Study published in 2003, which investigated 3624 individuals from Beaver Dam, WI.[25] The population makeup was individuals 43-86 years of age, and all individuals living in this particular region were eligible to be studied. Overall hazel or green eye color was noted in 21% (not separated out). The most frequent eye color was gray or blue in 52% and tan or brown eye color in 27%. Based on this study, hazel eye color is not rare in the US population. Our survey results appear to debunk the idea that hazel eye color is predominant in the cluster headache population and suggest but cannot definitively prove that hazel eye color prevalence in cluster headache patients reflects normal eye color prevalence rather than an overrepresentation in the cluster headache subgroup. Finally, in a study of 23 Swedish cluster headache families (42 affected and 41 non-affected individuals), there was no statistical difference between affected and non-affected individuals for eye color. Green and brown and mixed eye color occurred more often in family members with cluster headache, although their prevalence ranged from only 4-6%, while blue eye color was the predominant eye color in both groups, occurring in about 22% of cluster headache sufferers.[26]

Suicidality.—Cluster headache has been nicknamed the suicide headache but no studies have ever looked at the rate of suicidal ideations or true suicide attempts in a large cluster headache population. Very alarming is that 55% of the US cluster headache population has had suicidal thoughts while 2% have tried to commit suicide. In addition, 50% of survey responders also demonstrated self-injurious behavior during attacks, making the situation more deleterious to the cluster headache sufferer. These numbers, combined with the extensive delay in getting a correct diagnosis for cluster headache, put such emphasis on the need for proper diagnosis and treatment in this syndrome because with delay or mistreatment, the patient may actually harm themselves. Cluster headache in a way should be considered a neurologic emergency condition based on this issue.

Triggers.—Alcohol has always been recognized as a main trigger for cluster headache, and indeed, it is the most frequently named trigger in the survey. Of our cluster headache survey responders, 52% stated that alcohol could trigger an attack of headache. These numbers are somewhat lower than noted in studies from Europe (Sweden 79%,[27] UK 63%[5]) and are about the same as from a German study in which 54% stated alcohol elicited attacks.[6,28] Our study, however, is one of the few to look at specific types of alcoholic beverages as triggers of cluster headache. Beer statistically was the most common trigger in 57%, followed by red wine and hard liquor at 50% and 49%, respectively, and this was a statistically significant difference ($P = .0004$) between alcohol subtypes. One previous study by Schürks et al[6] from Germany did look at red wine as a cluster headache trigger and found this in 70%, beer in 23%, and other kinds of alcohol in 6.5%. Why beer would be

more likely to trigger cluster headaches than red wine or hard liquor in US cluster headache patients is unknown. These data would need to be reproduced from other countries, and if beer is a predominant trigger in most populations then looking into the individual components of beer may help us to better understand cluster headache pathogenesis. These data may be somewhat misleading, however, as beer is the most commonly consumed alcoholic beverage in the US, and thus, the numbers could look different in other countries where wine, for example, is more commonly drunk than beer. It may end up that the country of origin and the type of alcoholic beverage most often consumed in that country will be the type of alcohol most commonly noted to trigger a cluster headache, and really, it is alcohol, in general, that is a trigger more than specific types of alcoholic beverages. Our survey did not denote the amount of alcohol consumed by individuals so we cannot ascertain if the 65% of cluster headache responders who stated they used alcohol were mild, moderate, or excessive drinkers. Self-reporting of alcoholism, however, was low at 3%, somewhat contradicting past reports of extreme alcohol use in cluster headache patients. The majority of patients (85%) stopped using alcohol when in a cluster headache cycle, and this compares with data from Sweden where 79% decreased alcohol usage during active headache cycles.[27]

A very interesting finding from our survey data and one that has not been readily written about in the cluster headache literature is the triggers most frequently cited after alcohol including the following: weather changes (36%), smells (28%), and bright or flashing lights (20%), which are typically considered migraine triggers rather than cluster headache triggers. Donnet et al[7] in a study of chronic cluster headache patients (N = 113) noted weather changes to trigger cluster attacks in 29% and smells in 14% but did not look at light as a trigger. Only one other previous study mentioned weather changes as a cluster headache trigger.[29] We did not ascertain if cluster headache patients had food or stress triggers that are also very common migraine triggers. One major issue is that we did not determine the number of cluster headache patients with a concomitant history of migraine. It would be interesting to note if those with a migraine history are more likely to have "migraine triggers" for their cluster headaches. On the other hand, should we now think of these as triggers for trigeminal activation rather than being migraine-specific triggers and the phenotypic presentation after exposure to a certain trigger more depends on the individuals underlying genetic and nongenetic issues rather than trigger type itself. Our survey study also verifies one of the author's prior findings of television watching as a trigger of cluster headache, now in a much larger population.[30] Finally, nitroglycerin was rarely cited as a trigger of cluster headaches, but this may reflect lack of exposure to nitroglycerin in US cluster headache patients as only a very small percentage had cardiac disease.

Laterality.—In regard to laterality, the predominant pain side was right in our patients (right 49%, left 44%, $P = .02$), and this was a statistically significant difference. The clinical significance of this finding is, however, unknown. Other studies have also suggested a right-sided predominance for cluster headache, although the pathogenesis behind this finding is uncertain. The largest previous investigation came from Sweden in which 383 patients were studied, and there was a right-sided predominance noted (right 54%, left 46%), but this did not reach statistical significance.[31] In the Bahra et al[5] study, 60% had right-sided attacks vs 38% left-sided. In regard to side shifting between cycles, this occurred in 31% of our patients, in 15% in the Swedish study,[31] 18% in the Bahra et al study,[5] and in 19% from the Schürks et al study from Germany.[6] In regard to bilateral cluster headache, which is felt to be rare and has basically only been reported as single-case reports, this occurred in 3% of our patients, 2% in the Bahra et al study,[5] and 3% in the Schürks et al study from Germany.[6]

Timing of Attacks.—One of the hallmarks of cluster headache is its supposed clock-like regularity with attacks occurring the same time each day and being of the same duration. This is supposed to be secondary to a hypothalamic/circadian influence over the syndrome.[16] From the initial descriptions of cluster headache, it was also noted there is a nocturnal predominance for cluster headaches and particularly attack times between 1 am and 2 am or early

morning hours.[32] Only a few studies, however, have really looked at timing of attacks during the day and night in large cluster headache populations. In our investigation, there was not a single time of the day that attacks occurred in the majority of patients, with the highest prevalence being 41% of survey responders for one time period. However, there was a statistically significant likelihood of attacks to occur during late evening and early morning hours vs daytime to early evening hours. In addition, the most frequently cited time of attacks was between 12 am and 3 am, with 2 am being the most likely to have a cluster headache. Our study results also help prove why most cluster sufferers who work regular daytime shifts can get through the work day without headaches and not miss work, but when they get home, that is when their attacks occur. Our findings contradict what was noted in Manzoni et al's[10] study of 180 patients from Italy where 1 pm to 3 pm was the time of highest frequency of attacks, and more are in line with the study by Russell from Norway who noted a peak frequency between 4 am and 10 am, with the highest peak at 6 am.[32] As in our investigation, Russell noted that attacks most commonly occurred during sleep hours. Manzoni et al[10] commented that in Italy, most people are not working between 1 pm and 3 pm, thus it is also a time of relaxation, although maybe not sleep. In regard to time of day and attack intensity, it has been thought that sleep-induced attacks are more severe than daytime attacks. This scenario was noted in 48% of our patients; however, almost the same percentage stated there was no difference in pain intensity between daytime and nocturnal attacks.

Seasonal Predilection.—As cluster headache is considered a circadian-based syndrome, it has been noted that episodic cluster attack cycles typically begin either around the time of the clock changes (spring and fall) or around the solstices (winter, summer). The seasonal occurrence of cluster headache was first noted by Ekbom[33] (spring and fall) and Kudrow.[34] Kudrow,[34] in a US population, noted higher cluster periods in February and June and the least amount in August. In our survey study, more than 40% of cluster headache sufferers stated their cycles varied throughout the year and did not have a particular month that a cycle would start. Looking at specific months, October (most common), September, April, March, and November were the most commonly cited months for cycles to begin, but only in 20-26% of responders. The least likely month was June, which is opposite of what was found in Kudrow's study.[34] In reality, it appears that the circadian periodicity is not as strong as previously thought in cluster headache patients at least in the US; however, the times around-the-clock changes of fall and spring are more likely to be times of cluster headache onset.

Smoking and Cluster Headache.—The present survey presents significant data on smoking history and cluster headache. The majority of US cluster headache patients have a history of smoking (73% total, with 51% actively smoking at time of cluster headache onset). Schürks and Diener looked at the weighted average from 5 European cluster headache studies (N = 1012) and noted a current smoking history in 72%, 14% past smokers, and 14% had never smoked.[28] In Klapper's population-based Internet survey from the USA, 77% of responders had a smoking history.[8] Overall, a smoking history is high in both US and European cluster headache populations. The percentage of cluster headache sufferers who never smoked is almost equal in the USA (17%) and in Europe (14%),[28] suggesting that smoking is a risk factor for developing cluster headache. Only a small percentage of US cluster headache patients stopped smoking after cluster headache onset (18%). A unique finding from our survey was that a small number of patients stated that smoking reduced the severity of an individual cluster attack (8%), while others (2%) stated it reduced cluster attack frequency. Improvement of cluster headache pain with smoking was previously shown in a Swedish study by Levi et al[27] in 26% of 49 studied male cluster patients, while ours is the first to document reduction in attack frequency in some individuals with acute nicotine exposure. There are data to suggest that cessation of smoking may improve the natural history of cluster headaches so how could acute tobacco exposure improve an individual cluster headache? This could be explained by the recent discovery that acute nicotine administration in rats activates orexin A neurons as well as upregulates the expression of orexin A and its receptors in the rat brain.[35] Orexin A is a hypotha-

lamic neuropeptide with antinociceptive properties and is able to modulate nociceptive input to the trigeminal nucleus caudalis. Recently, orexin has been suggested as a possible participant in cluster headache pathogenesis.[36]

Personal Burden.—Very few studies have actually looked at the economic burden of cluster headache on the individual. In our investigation, almost 20% of cluster headache patients had lost a job secondary to cluster headache, while another 8% were out of work or on disability secondary to their headaches. Even though these headaches are extremely severe, 32% had never lost a single workday attributed to their headache, but this may more reflect the fact that cluster headaches typically occur in the evening or after typical work hours rather than during workday hours (see earlier section). About 50% of survey responders stated that they were unable to leave their home at least 1 time per year secondary to cluster headache, but 11% stated they were homebound more than 30 days per year. The majority of cluster headache patients do not visit the emergency department (63% had never gone and 95% went 2 times or less) because of their headaches. Of note, of those who visited the emergency department, 70% stated the physicians there were unfamiliar with cluster headache as a distinct headache condition. The number of emergency department visits may be low because cluster headache patients recognize that their attacks are of short duration so by the time they travel to the emergency department and then wait to be seen by a provider, their attacks, in most instances, have already ended. Jensen et al[37] looked at the burden of cluster headache in 85 individuals in Denmark, so a much smaller series than our study, but noted very similar results in that 16% of their patients had lost a job secondary to cluster headache, while 8% needed early retirement. In their study, 30% had missed at least 1 day of work during 1 year's time (range 0-150 days) from headaches, and this compared with 47% of our patients who had missed between 1 and 10 days of work and 11% who missed 30 days or more in a year. The use of emergency services was also very low (11%) in the Jensen et al[37] study. Overall cluster headache is disabling to the individual and can lead to loss of livelihood. If our numbers are extrapolated to the projected number of cluster headache sufferers in the US at the time of the survey (0.2-0.4% of the US population in 2008), between 170,000 to 340,000 individuals have lost their jobs or are out of work from cluster headache.[38]

Study Limitations.—There are several major limitations of this survey study. First, we cannot verify any of the patient's answers to the survey questions. We had to assume the responses were accurate. Along with this issue, there is inherent recall bias in the survey responses. Second, the study is lacking diagnostic validation. Even though all study participants had their headache diagnosis made by a neurologist, these specialists can still make an incorrect diagnosis of cluster headache. It is possible that a certain percentage of survey responders had another type of trigeminal autonomic cephalalgia such as paroxysmal hemicrania (of note, a significant percentage of survey responders [80%] had never tried indomethacin; however, of those who did try it, only 15% stated that it had some effect on their headache, and less than 2% were currently using it) or the survey responders may have had migraine with associated cranial autonomic features.[39] At present, there are no available data looking at cluster headache misdiagnosis rates in US medical clinics. However, as a large number of survey responders frequented cluster headache Web sites, this actually may reflect a more sophisticated headache population about their disease state and thus more knowledgeable about cluster headache than a general headache population and thus less likely to be misdiagnosed. Third, in regard to comorbid medical issues, we did not ascertain how many of these diagnoses were made by the medical community vs illnesses the patients thought they had but were never properly diagnosed. Fourth, another deficiency of the survey study in regard to cluster headache associated symptoms is that we did not ask about the presence of an eyelid ptosis or a miotic pupil, which are part of the International Classification of Headache Disorders-2 criteria for cluster headache.[40] Anecdotally, however, many cluster headache sufferers may not even notice these symptoms during their attacks as they rarely look in the mirror when they are having a headache. Also, as they do not

want anyone in the room with them, this would not be noticed by a family member, thus results from other studies are probably falsely low in regard to these physical signs and cluster headache. This same issue was found in a study of migraineurs with cranial autonomic symptoms and the inability for them to know if they had a ptosis or miosis during their headache attacks.[41] Finally, it would have been very helpful to document the number of cluster headache patients with a concomitant history of migraine especially in regard to the prevalence of "migraine triggers" in cluster headache patients. We also do not have the ability to match family history of migraine and migraine triggers as these data were not cross-tabulated. Overall, we can only present data from individuals who completed the Internet survey. Our study population may have differed from individuals who either did not want to complete the survey or were nonresponders for some other unknown reasons and thus possibly limiting the generalization of our study results to the entire US cluster headache population.

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REFERENCES

1. Horton BT. Histaminic cephalgia. *J Lancet*. 1952;72: 92-98.
2. Russell MB. Epidemiology and genetics of cluster headache. *Lancet Neurol*. 2004;3:279-283.
3. Rozen TD, Fishman RS. Results from the United States cluster headache survey. *Cephalalgia*. 2009;29 (Suppl. 1):43.
4. Rozen TD, Fishman RS. Inhaled oxygen and cluster headache sufferers in the United States: Use, efficacy and economics. *Headache*. 2011;51:191-200.
5. Bahra A, May A, Goadsby PJ. Cluster headache: A prospective clinical study with diagnostic implications. *Neurology*. 2002;58:354-361.
6. Schurks M, Kurth T, de Jesus J, Jonjic M, Rosskopf D, Diener H-C. Cluster headache: Clinical presentation, lifestyle features, and medical treatment. *Headache*. 2006;46:1246-1254.
7. Donnet A, Lanteri-Minet M, Guegan-Massardier E, et al. Chronic cluster headache: A French clinical descriptive study. *J Neurol Neurosurg Psychiatry*. 2007;78:1354-1358.
8. Klapper JA, Klapper A, Voss T. The misdiagnosis of cluster headache: A nonclinic, population-based Internet survey. *Headache*. 2000;40:730-735.
9. van Vliet JA, Eekers PJ, Haan J, Ferrari MD, Dutch RUSSH Study Group. Features involved in the diagnostic delay of cluster headache. *J Neurol Neurosurg Psychiatry*. 2003;74:1123-1125.
10. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache-clinical findings in 180 patients. *Cephalalgia*. 1983;3:21-30.
11. Kudrow L. Prevalence of migraine, peptic ulcer, coronary heart disease and hypertension in cluster headache. *Headache*. 1976;16:66-99.
12. Rozen TD. Individuals with cluster headache appear to have a reduced risk of developing lung cancer from chronic cigarette smoking. *Headache*. 2011;51:1174-1176.
13. Ekbom K. Patterns of cluster headache with a note on the relation to angina pectoris and peptic ulcer. *Acta Neurol Scand.* 1970;46:225-237.
14. Graham JR. Cluster headaches. *Headache*. 1972;11: 175-185.
15. Garrow D, Delegge MH. Risk factors for gastrointestinal ulcer disease in the US population. *Dig Dis Sci*. 2010;55:66-72.
16. Matharu M, Goadsby PJ. Trigeminal autonomic cephalalgias: Diagnosis and management. In: Silberstein SD, Lipton RB, Dodick DW, eds. *Wolff's Headache and Other Head Pain*, 8th edn. Oxford: Oxford University Press; 2008:379-430.

17. Chen PK, Fuh JL, Chen SP, Wang SJ. Association between restless legs syndrome and migraine. *J Neurol Neurosurg Psychiatry*. 2010;81:524-528.
18. d'Onofrio F, Bussone G, Cologno D, et al. Restless legs syndrome and primary headaches: A clinical study. *Neurol Sci*. 2008;29(Suppl. 1):S169-S172.
19. Rozen TD. Olanzapine as an abortive agent for cluster headache. *Headache*. 2001;41:813-816.
20. Rocca WA, McDonnell SK, Strain KJ, et al. Familial aggregation of Parkinson's disease: The Mayo Clinic family study. *Ann Neurol*. 2004;56:495-502.
21. Centers for Disease Control and Prevention (CDC). Vital signs: Asthma prevalence, disease characteristics, and self-management education – United States, 2001-2009. *MMWR Morb Mortal Wkly Rep* 2011;60:547-552.
22. Silberstein SD, Niknam R, Rozen TD, Young WB. Cluster headache with aura. *Neurology*. 2000;54:219-221.
23. Russell MB, Olesen J. A nosographic analysis of the migraine aura in a general population. *Brain*. 1996;119:355-361.
24. Kudrow L. Physical and personality characteristics in cluster headache. *Headache*. 1974;13:197-202.
25. Tomany SC, Klein R, Klein BE. The relationship between iris color, hair color, and skin sun sensitivity and the 10-year incidence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology*. 2003;110:1526-1533.
26. Sjöstrand C, Russell MB, Ekbom K, Waldenlind E. Familial cluster headache: Demographic patterns in affected and non-affected. *Headache*. 2010;50:374-382.
27. Levi R, Edman GV, Ekbom K, Waldenlind E. Episodic cluster headache II: High tobacco and alcohol consumption in males. *Headache*. 1992;32:184-187.
28. Schürks M, Diener H-C. Cluster headache and lifestyle habits. *Curr Pain Headache Rep*. 2008;12:115-121.
29. Niczyporuk-Turek A. Factors contributing to so-called idiopathic headaches. *Neurol Neurochir Pol*. 1997;31:895-904.
30. Rozen TD. Atypical presentations of cluster headache. *Cephalalgia*. 2002;22:725-729.
31. Meyer EL, Laurell K, Artto V, et al. Lateralization in cluster headache: A Nordic multicenter study. *J Headache Pain*. 2009;10:259-263.
32. Russell D. Cluster headache: Severity and temporal profiles of attacks and patient activity prior to and during attacks. *Cephalalgia*. 1981;1:209-216.
33. Ekbom K. A clinical comparison of cluster headache and migraine. *Acta Neurol Scand*. 1970;46 (Suppl. 41):1-48.
34. Kudrow L. *Cluster Headache: Mechanisms and Management*. New York: Oxford University Press; 1980.
35. Pasumarthi RK, Fadel J. Activation of orexin/hypocretin projections to basal forebrain and paraventricular thalamus by acute nicotine. *Brain Res Bull*. 2008;77:367-373.
36. Holland PR, Goadsby PJ. Cluster headache, hypothalamus, and orexin. *Curr Pain Headache Rep*. 2009;13:147-154.
37. Jensen RM, Lyngberg A, Jensen RH. Burden of cluster headache. *Cephalalgia*. 2007;27:535-541.
38. US Census Bureau. US population estimate. Available at: http://www.census.gov (accessed July 1, 2008).
39. Lai T-H, Fuh J-L, Wang S-J. Cranial autonomic symptoms in migraine: Characteristics and comparison with cluster headache. *J Neurol Neurosurg Psychiatry*. 2009;80:1116-1119.
40. Headache Classification Committee of the International Headache Society. The international classification of headache disorders (second edition). *Cephalalgia*. 2004;24(Suppl. 1):1-160.
41. Rozen TD. A history of cigarette smoking is associated with the development of cranial autonomic symptoms with migraine headaches. *Headache*. 2011;51:85-91.