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Abstract

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Methods: Participants filled out a questionnaire online. Inclusion criteria were a reported diagnosis of CH and a residency in a European country; exclusion criteria were refusal to give informed consent and to complete the questionnaire.

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Conclusions: In this article, we discuss the applied methodology as well as the properties of the sample. The overall accuracy of the self-reported diagnoses was very good as judged by our questionnaire; women and chronic CH were slightly over-represented. We will present the results of more thorough analyses in future articles and believe that these data will provide deeper insights into the burden of CH and will help to give a voice to those who endure this painful disease.

Introduction

Cluster headache (CH) is a primary headache disorder characterized by excruciatingly painful headaches and associated autonomic symptoms.[1] The attacks last between 15 and 180 min and usually occur in bouts separated by remission periods. By definition, chronic CHs are diagnosed if remission lasts less than 1 month for more than 1 year according to the International Classification of Headache Disorders (ICHD)-3 beta classification and less than 3 months according to the ICHD-3 classification.[1,2] The disease affects around 1/500 in the general population[3,4] and prevalence is higher among men (between 3.5:1

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and 4.3:1).[5–7] Mean onset is about 30 years [8,9] – the time when the basis is laid for a successful career and families are found. Accordingly, previous research found that CH is associated with a substantial burden that extends beyond the impact of the symptoms: Two studies showed that patients suffering from CH were less frequently employed and required sick leave more often than controls with migraine or tension-type headache or no headache complaints at all.[10,11] Also, these patients suffered more frequently from depression than matched controls and often had suicidal ideation.[12,13] Other studies found that health-related quality of life during the active phase is significantly lower than in the general population.[14,15] In addition, for the individual patient, the disease is associated with substantial healthcare costs.[16]

These study results suggest that CH attacks impose more than pain – while the pain eventually subsides, the inter-ictal burden persists.

Growing interest in the burden of a disease led to the Global Burden of Disease Study 1990, in which the impact of diseases was measured in disability-adjusted life years.[17] In order to quantify the burden of headache disorders, appropriate methods were needed. A structured questionnaire was developed and validated as part of the EURO-LIGHT project which allowed to distinguish migraine, tension-type headache chronic headaches, and to assess different aspects of the burden of these major headache disorders.[18] This questionnaire was, however, not designed to diagnose CH or to address the particularities of that disease. In the EUROLIGHT cluster headache project, which we present in this article, adjustments to the questionnaire were made to allow verification of the diagnostic criteria in order to validate the diagnosis and to assess the burden of CH via an Internet-based survey.

It is the aim of this article to present the applied methodology as well as the properties of the sample. We will discuss the results of more thorough analyses in future articles, believing that these data will provide deeper insights into the burden of CH and will help to give a voice to those enduring this painful disease.

Methods

Study design and sampling method

A cross-sectional design was chosen and – due to the prevalence of CH and in order to limit the resources needed – the study was designed as Internet-based. Inclusion criteria were a self-reported diagnosis of CH and a residency in a European country. Exclusion criteria were refusal to give their informed consent or to complete the online questionnaire. The diagnosis was not verified prior to participation but the questionnaire algorithm based upon the International Headache Society (IHS) classification[2] allowed to verify the diagnostic criteria and thereby check the validity of the diagnosis and to control the quality of the data.

In order to include as many participants as possible, patient associations as well as national headache societies in Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom were made aware by Migraine Action Switzerland about the study and were asked to forward study information and the website link to eligible patients.

Potential participants not seeing a doctor or not aware of their diagnosis, on the other hand, could not be contacted.

The website offered the questionnaire in various languages (Czech, Danish, Dutch, English, Finnish, French, German, Italian, Norwegian, Polish, Spanish and Swedish).[19]

Having given their consent, participants were asked to fill out the questionnaire anonymously; they were not followed up or contacted a second time. The survey was published on the Internet from May through August 2012. Participants had to agree to fill out the questionnaire only once. No incentives were offered for participation.

Questionnaire: Structure, development and translation

Since symptoms, time course and treatment options of migraine attacks and CH attacks differ, the original EUROLIGHT questionnaire needed to be adapted for the purpose of this study.

The questionnaire used was subdivided into two different parts (see Online Appendix). The first part was created with the support of headache experts from the IHS as well as representatives of cluster patient organizations specifically for this study in order to assess the particularities of CHs: symptom burden (items 1–12), family history (item 13), diagnosis and treatment (items 14–18) and self-injury during headache attacks (item 19).

Questions on symptom burden were based upon the IHS classification and assessed autonomic features accompanying headache attacks, attack frequency, duration of remission periods, pain intensity, age at symptom onset, disease duration as well as occurrence of headache attacks during sleep. In the category 'family history', we inquired about relatives suffering from CH. The 'diagnosis and treatment' section had the purpose to assess how and when the diagnosis was made and what treatment was used. In the final section, we asked about self-injury during attacks.

In order to ensure correctness and consistency in all the used languages, translations were carried out according to the Lifting The Burden 'Translation protocol for hybrid documents'.[20]

The second part consisted of the EUROLIGHT questionnaire,[21] from which only certain screening and diagnostic questions (items 10 and 11, 17–25 as well as 31) had been removed.

The EUROLIGHT questionnaire is a 103-item self-reporting questionnaire to assess the burden of primary headache disorders and has undergone a solid validation process.[21] It consists of the following sections: social situation questions (items 4–9), screen questions (items 10–12), daily headache questions (items 13–16), 'most bothersome headache' questions (item 17), diagnostic questions (items 18–31), questions about headache the day before (items 32–43), healthcare questions (items 44–49), questions on impact (items 50–56), lost time because of headaches (items 57–61), inter-ictal burden (items 62–64), impact on social life (items 65–73), questions on the household partner (items 74–78), body mass index (items 79–81), the quality of life questionnaire EUROHIS-QOL (items 82–89) and the Hospital Anxiety and Depression Scale (items 90–103).

Questions had been adapted to the home country of the participant whenever needed. For example, only drugs available in the relative country were listed and household income options were adapted to the median income of that country.

Data analysis

As no proof of the diagnosis of CH was requested for participation, the answers to questions about headache duration, localization, frequency and accompanying symptoms were used to verify the diagnostic criteria published in the ICHD-3 beta.[2] If all criteria were met, the diagnosis 'definite CH' and if all but one criterion were met, the diagnosis 'probable CH' were assumed. The only diagnostic criterion not assessed in this study was the number of CH attacks that the participants had already gone through.

Likewise, the diagnosis of chronic CHs was considered valid if (i) remission time was less than 1 month and (ii) the disease duration was more than 1 year, according to the ICHD-3 beta criteria.

When filling out the questionnaire, participants could decide freely whether or not they wanted to answer a question. Therefore, missing data had to be expected. In this article, we will refer to missing data as 'not specified'.

Analyses were performed at the University of Basel and University Hospital Zurich using SPSS version 25 (IBM, Armonk, New York, USA) and Microsoft Excel 2016 (Microsoft, Redmond, Washington, USA). Categorical variables are described as proportions (%) and continuous variables in terms of means and standard deviations (SDs). We calculated 95% confidence intervals to show associations in bivariate analyses. Means were compared using analysis of variance. Chi-squared and Fisher's exact tests of significance were used. Significance level was set at 0.05.

Results

In this article, we report on the descriptive characteristics of the sample as well as the accuracy of the diagnosis of CH.

A total of 1827 accessed the survey online, 1795 agreed to fill out and 1514 completed the questionnaire. By reason of the methodology (Internet-based), the participation rate is unknown. However, based upon epidemiological data of the Census 2011[22] and the assumption of the prevalence being about 1/500, we estimated the number of patients suffering from CH in each country and calculated the participation rate using these values. Participation ranged between 0.01% and 0.62% of the theoretical maximum (see Table 1).

More males than females participated (1000 males (66.2%), 510 females; 4 not specified); mean age was 42.1 years $\pm$ 10.9 (8 not specified). Over three-quarters (78.0%; 31 not specified) were employed or studied and the vast majority (74.1%; 45 not specified) were married or living with a household partner. Participants came from 17 different countries, among which Germany, France and the United Kingdom were named most frequently and accounted for 59.1%. See Table 1 for further details. Three-quarters of the participants (73.6%; 195 not specified) reported having had at least one headache attack in the last 30 days.

Sufficient data to check the validity of the diagnosis of CH (i.e. information on headache duration, frequency and localization) were provided by 1439 participants (95.0%). Fifty patients who had claimed having both uni- and bilateral headaches were considered having bilateral headaches in this analysis in order not to impair the calculations using doubtful or incorrect data.

Among these, diagnosis seemed valid – that is, all the criteria were met – in 1165 participants (81.0%). Of those 274, who did not meet all the criteria, a majority (225; 82.1%) deviated in exactly one criterion and will be referred to 'probable CH'. See Table 2 for further details.

Five participants had very frequent and short-lasting attacks with autonomic symptoms or restlessness (0.3%) and one (0.1%) had long-lasting (>180 min) unilateral headaches without autonomic symptoms or restlessness. Four participants (0.3%) had bilateral headaches without accompanying symptoms lasting more than 30 min. For these patients, other diagnoses than CH seemed more plausible according to the ICHD.[2] The numbers of patients fulfilling the criteria for definite CH, probable CH, paroxysmal hemicrania, migraine and tension-type headache can be found in Table 2.

In this sample, 458 participants (31.2%; 48 not specified) stated suffering from chronic CH. Among these, the diagnosis of CH was validated in 306 participants (66.8%); only data sets with a validated diagnosis were included into further analyses. Twenty-three patients with a validated diagnosis of CH had not disclosed whether they suffered from episodic or chronic CH. Their mean age was 41.9 years $\pm$ 11.3; a majority (67.6%) was male. Patients with chronic CH were significantly less frequently living with a household partner ($p = 0.022$) and significantly more frequently being unemployed than patients with episodic CH

Table 1. Numbers of participants and demographic characteristics per country.

Country	Participants (n (%))	Sex (% male)	Age (mean (SD))	Employed or student (%)	Married or living with partner (%)	Estimated participation rate (%)
Austria	53 (3.5)	58.5	39.4 (10.4)	80.8	72.5	0.32
Belgium	43 (2.8)	66.7	41.2 (10.5)	75.6	77.5	0.20
Czech Republic	2 (0.1)	100.0	44.0 (9.9)	100.0	100.0	0.01
Denmark	13 (0.9)	69.2	42.1 (15.7)	69.2	69.2	0.12
Finland	67 (4.4)	53.0	43.6 (11.9)	77.3	83.3	0.62
France	304 (20.1)	66.4	39.9 (10.5)	78.6	70.9	a
Germany	345 (22.8)	69.4	42.8 (10.0)	81.0	71.3	0.22
Ireland	5 (0.3)	60.0	47.0 (11.6)	80.0	100.0	0.05
Italy	123 (8.1)	67.5	40.9 (10.6)	86.9	86.1	0.10
Luxembourg	3 (0.2)	66.7	41.0 (11.4)	100.0	100.0	0.29
The Netherlands	21 (1.4)	61.9	42.0 (12.5)	66.7	71.4	0.06
Norway	36 (2.4)	58.3	40.3 (10.3)	81.8	74.3	0.36
Poland	17 (1.1)	64.7	45.9 (12.8)	87.5	56.3	0.02
Spain	127 (8.4)	75.6	39.1 (9.0)	75.2	81.1	0.14
Sweden	55 (3.6)	60.0	44.1 (13.8)	72.7	75.0	0.29
Switzerland	54 (3.6)	74.1	40.9 (10.7)	86.8	71.2	0.34
United Kingdom	246 (16.2)	62.2	45.7 (11.5)	69.3	71.0	a
Total	1514	66.2	42.1 (10.9)	78.0	74.1	–

SD: standard deviation.
[a]Census data unavailable.

Table 2. Symptom frequency.

Duration (min)	Localization	Frequency	Accompanying symptoms[a]	Most likely diagnosis	Number of participants
15–180	Unilateral	Up to 8/day	Present	Definite CH	1165
More than 180	Unilateral	Up to 8/day	Present	Probable CH	110
Less than 15	Unilateral	Up to 8/day	Present	Probable CH	14
15–180	Bilateral	Up to 8/day	Present	Probable CH	42
15–180	Unilateral	More than 8/day	Present	Probable CH	46[b]
15–180	Unilateral	Up to 8/day	Not present	Probable CH	13
5–30	Unilateral	More than 8/day	Present	Paroxysmal hemicrania	5[b]
More than 180	Unilateral		Not present	Migraine[c]	1
More than 30	Bilateral		Not present	Tension-type headache	4

CH: cluster headache; ICHD-3: International Classification of Headache Disorders-3.
[a]Autonomic symptoms or restlessness.
[b]Three participants were listed in both categories.
[c]According to the ICHD-3 beta criteria,[1] the minimal duration for migraine attacks is 4 h. In this questionnaire, the longest duration of one attack that could be chosen was 'more than 180 min'. Therefore, it is not possible to conclude with certainty that these patients actually fulfilled the criteria for migraine attacks.

($p < 0.001$). See Table 3 for further details on differences in demography between chronic and episodic CH.

Among those, who reported suffering from chronic CH, remission duration was 2 weeks or less in a majority (86.5%, 24 not specified). Of those 279 participants, who had provided enough details to check the validity of their diagnosis, some (19, 6.8%) reported usual remission time to be 30 days or more and 1 participant (0.4%) indicated a remission time of 90 days or more. Seven participants (2.5%) communicated disease duration of less than 1 year. In total, short remission periods of less than 30 days and disease duration of at least 1 year were present in 253 cases (90.7%). Thus, the criteria for chronicity were fulfilled by

an ample majority of those who considered themselves suffering from chronic CH.

The portion of definite CH diagnoses was 82.9% in participants with self-reported episodic and 66.8% in participants with self-reported chronic CH ($p < 0.001$).

Discussion

The EUROLIGHT Cluster Headache Study represents a data collection of CH patients coming from 17 European countries. So far, there have been few large-scale studies looking at CH patients and this manuscript presents data from the largest EU Cluster Headache Survey ever

Table 3. Differences in demography between patients suffering from chronic and episodic CHs; 23 participants with a validated diagnosis of CH had not disclosed whether they suffered from episodic or chronic CH.

	Episodic CH	Chronic CH	Significance level
Number (*n* (%))	836 (73.2)	306 (26.8)	–
Sex (% male)	71.0	67.6	0.28
Age (mean (SD))	42.2 (10.4)	41.9 (11.3)	0.61
Employed or student (%)	83.7	66.3	<0.001
Married or living with partner (%)	76.0	69.2	0.02

SD: standard deviation; CH: cluster headache.

completed in Europe. Overall, the vast majority of the participants met the diagnostic criteria for definite CH. Despite great efforts to inform many potential participants about the study and a large sample, the estimated participation rate is low and ranges between 0.01% and 0.62% per country. However, most of the participants reported having had at least one headache day within the 30 days prior to the survey, implying that most of them were in-bout. Thus, participation rate in the in-bout population is likely to be higher. Unfortunately, it is not possible to reliably estimate the number of in-bout patients per country given the fluctuating durations of bouts and remission periods.[23]

In this sample, there were about twice as many men than women. In population-based surveys, male/female ratios between 3.5:1 and 4.3:1 were reported,[5–7] implying that women might be somewhat over-represented in this sample. This finding possibly reflects a sampling bias due to the fact that more women than men participate in online surveys if they are invited to do so by email.[24]

The questions on symptom burden enabled us to check the validity of the CH diagnosis. Or, conversely, supposing that the diagnosis had been made correctly, the collected data allowed checking the accuracy of the participants' responses. Assuming that every patient had already had more than five attacks of his headache disorder, we can conclude that of those who provided sufficient information, virtually everybody fulfilled the criteria for either CH or probable CH. Some diagnostic uncertainty became evident, though: In six patients, the diagnosis of paroxysmal hemicrania seemed more likely. To our knowledge, it has not been systematically studied, how frequently patients initially diagnosed with CHs actually were suffering from paroxysmal hemicrania. In three other patients, migraine should be considered and two participants described symptoms, which suggest a diagnosis of tension-type headache. In total, in 10 patients (0.7%), other diagnoses than CH seemed more likely. We do not know what the diagnostic procedure had consisted of in these patients to suggest the diagnosis of CHs. Those who reported their CHs to last less than 15 min might have mainly considered treated attacks. Overall, the accuracy of the diagnoses seems to be very good.

The proportion of participants in this sample suffering from self-reported chronic CH (31.2%) was rather high. In

a Greek sample, 22.5% were reported to suffer from chronic CH[6] and a meta-analysis of different studies found even lower proportions of about 15%.[7] This suggests a participation bias, in the sense that those affected the most participate more readily. Indeed, a majority of patients who claimed suffering from chronic CHs reported remission periods that do accord with the diagnostic criteria. Some patients in this group, however, reported disease duration of less than 1 year and remission periods of 30 days or even 90 days and more, which clearly points toward the diagnosis of episodic CHs. This suggests an additional measuring bias that might be due to remissions induced by preventive treatments or to a misconception about the term. For instance, some patients might believe the word 'chronic' refers to disease duration rather than remission time. If confirmed, this finding would add to the critique voiced against the use of the adjective 'chronic' when actually describing short remission periods.[25] In the recently published final version of ICHD-3,[1] remission durations of up to 3 months are accepted for the diagnosis of chronic CH, instead of 1 month in ICHD-3 beta used here. This could have led to underestimate chronic CH in our sample. In any case, the large number of patients suffering from chronic CH who shared their data will allow to draw a clearer picture of those affected the most. The fact that in this sample, patients with chronic CH were significantly more frequently living without a partner and being unemployed more often points toward a considerable burden worth further attention.

Conclusion

In this article, we presented the methodology as well as the sample of the EUROLIGHT cluster headache project which was designed to assess the burden of CH in Europe. To that end, the collected data will be analysed thoroughly and be presented in detail in future articles. Many individuals in 17 countries agreed to participate and share their data. In consequence, the numbers of the participants will allow to analyse and differentiate the burden of chronic, episodic and sex differences.

We believe that this data will provide deeper insights into the management, specific burden and comorbidities of CHs and will help to give a voice to those who endure this painful disease.

Declaration of conflicting interests

Funding

Supplemental material

Supplemental material for this article is available online.

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