Cluster headache: expansion of the clinical spectrum

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Chapter 7

A cross-sectional study on the comorbidity of epilepsy and cluster headache

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Submitted

Introduction

Cluster headache, migraine and epilepsy are considered paroxysmal syndromes of altered brain function with a complex genetic background. Migraine and epilepsy are co-morbid(1) possibly due to shared cortical hyperexcitability.(2)

Studies of the relationship between migraine and cluster headache are conflicting. Some have conjectured that cluster headache and migraine are not associated(3), while others propose that both share underlying pathophysiological mechanisms.(4-6) Cortical spreading depolarisation (CSD) is the likely underlying mechanism of the migraine aura.(7) Events similar to migraine aura have also been described in association with cluster headache attacks.(8-11) It has been suggested that cortical hyperexcitability is also involved in cluster headache(12) potentially increasing the risk of epilepsy.

Here, we assessed the comorbidity of epilepsy and secondarily migraine in a large cohort of people with cluster headache.

Methods

Participants and study design

This was a cross-sectional study as part of the LUCA (Leiden University Cluster headache Analysis) study, a nationwide study on cluster headache in the Netherlands using historical controls and people with migraine and people without headache as control group. The primary outcome was the prevalence of epilepsy in the LUCA population. Validation of the questionnaires and enrolment procedure have been previously described.(13) In summary, participants were Dutch adults aged 18 or older with cluster headache. People with cluster headache and cases identified in previous studies (14) were recruited via a website and asked to complete validated web-based cluster headache questionnaires with a specificity of 88% to diagnose cluster headache, based on the International Classification of Headache Disorders (ICHD-III beta).(15) A clinically confirmed diagnosis of cluster headache by a physician was available for 94% of the LUCA population.(12) For the remaining 6%, no clinically confirmed diagnosis was available; for instance, if they had

never consulted a physician. Information on the type of cluster headache, age at onset, age at diagnosis, attack frequency and other clinical aspects could be retrieved from the LUCA study database.
For the present survey, we sent out an email with additional questions, including the following:
1a) 'Do you think that you have other headaches besides cluster headache (such as migraine, tension type headache or other)?'
If yes -> 1b) 'Do you think you have migraine?'
2) 'Have you ever been diagnosed with epilepsy?'

The diagnosis of migraine was based on the answer to 1b (and thus self-reported), which has been described previously as a valid method.(16) The single question on having epilepsy is reported to have a high specificity of 93-99% and sensitivity of 75-85%. (31,32) Responders who confirmed that they had ever been diagnosed with epilepsy were asked to provide written consent to obtain their epilepsy history by retrieving the reports from their neurologists, including results from MRI scans and electroencephalography (EEG). Participants for whom no written report could be obtained, were contacted by telephone to acquire the necessary details. We classified attacks of epilepsy as generalised, focal, or unknown, according to the International League Against Epilepsy classification using the written reports obtained from the attending neurologist or individuals history obtained over the phone including EEG, MRI scan, description of seizures, comorbidity and/or age of onset.(17) A generalised epilepsy is one where the constituent seizures have an onset involving bi-hemispheric epileptogenic cortical networks, while a focal seizure is one whose onset is localised to a single, uni-hemispheric cortical area. The distinction between the two can be made using information about the beginning of the attacks, EEG and MRI findings and comorbidity. Individuals with aura symptoms were previously identified in our validation study (11) which was only conducted in the first part of our database and/or identified by using a validated questionnaire on migraine aura symptoms which was conducted in all participants.(18)

For the primary outcome, the prevalence of epilepsy, we used historical controls from a recent meta-analysis on the incidence and prevalence of epilepsy from published international studies. (19) This study included sub-analyses by sex,

age, income and type of seizure. As a second and third control group, we used people with migraine and people without headache (healthy controls) from the Leiden University Migraine Neuro Analysis (LUMINA) programme (18). Participants of the LUMINA study were Dutch adults aged 18 to 74 years with migraine with or without aura according to the ICHD-III beta criteria.(15) Controls did not suffer from migraine, cluster headache, chronic tension type headache or medication overuse headache.(20) People with migraine and controls were recruited via public announcements, advertising in the lay press and via the research website. They were considered eligible after a two-step inclusion process using validated questionnaires.(15) For the LUMINA survey, we sent an email with additional questions on a range of possible comorbid disorders. The question on epilepsy was the same as in the LUCA study. Epilepsy history and type of epilepsy in people with migraine and controls, however, were not obtained.

Statistical method

Demographic and clinical characteristics were reported as mean ± standard deviations (SD) or percentages. We tested for differences in means using independent two-tailed samples t-tests and differences in proportions using Chi-Square tests. The Wilson method was used to calculate 95% confidence intervals (CI) for each parameter. Statistical significance was defined as non-overlapping 95% CI or $p < 0.05$.(21)

This study was approved by the Medical Ethics Committee of Leiden University Medical Centre. All participants provided written informed consent.

Results

Figure 1 shows the flowchart and results of the LUCA study. The questionnaires were sent to 798 people with cluster headache and 606 (75.9%) responded. Responders differed from non-responders (n=192) for age (48.5 vs. 43.1 years, $p<0.001$) but not for gender or type of cluster headache (episodic vs. chronic). Demographic and clinical characteristics of the study population are provided in table 1.

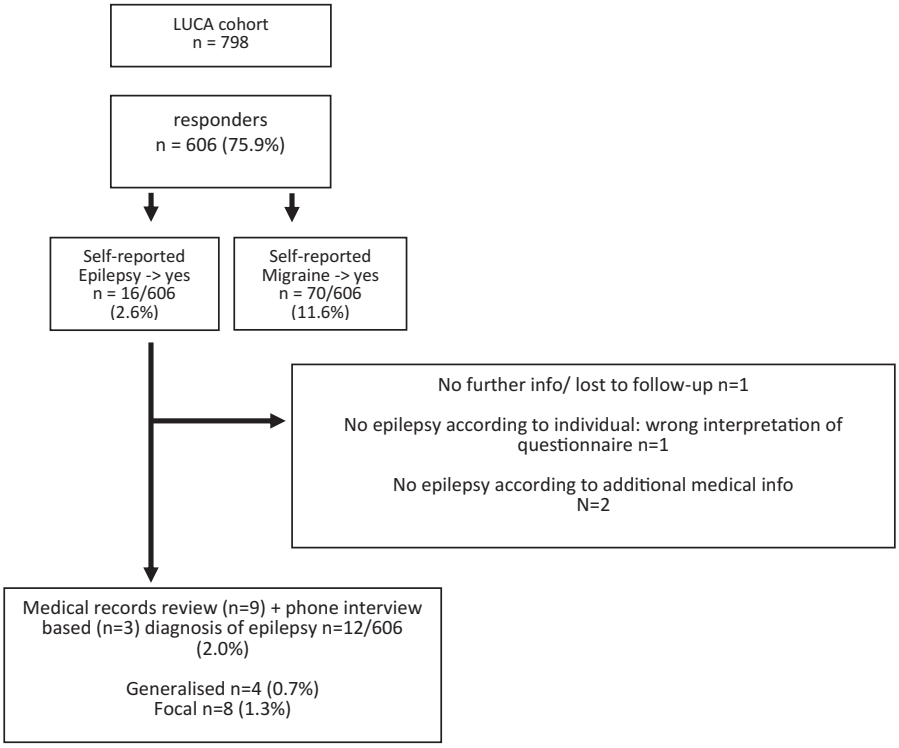

Figure 1. Study flow

Table 1. Demographic and clinical characteristics of people with cluster headache

Variable	**Total population n=606 (%)**
Male Female	435/606=71.8% 171/606=28.2%
Age (years)	50.7 ± 11.6
BMI (kg/m^2)	25.6 ± 3.9
Age at onset cluster headache	31.1 ± 13.0
Age diagnosis cluster headache	37.2 ± 11.7
Chronic cluster headache Episodic cluster headache	128/606=21.7% 478/606=78.9%
Physician diagnosis cluster headache	581 (95.9%)

Values are presented as means ± standard deviation (SD) or as numbers (percentages)
BMI = body mass index

Of the 606 individuals included, 16 (2.6%) answered 'yes' to the question of a previous diagnosis of epilepsy. Two authors (LAW JH) confirmed the diagnosis in 12/606 (2.0% 95% CI: 1.1, 3.4) based on reports from their attending neurologists (n=9) or by telephone interview (n=3). Details of the 12 participants with epilepsy are provided in table 2: 4/606 (0.7%) had generalised seizures and 8/606 (1.3%) focal seizures.

The life-time prevalence of epilepsy in our case with cluster headache was higher than described in a recent meta-analysis of international studies (0.76% 95% CI: 0.62, 0.94).(19) The LUCA population consists of people with relatively high income, adults, and mostly males, therefore we compared our results with the following sub analysis of the meta-analysis and found a remaining significant result after comparing with only males (0.70% 95% CI: 0.53-0.92) and the high income group (0.52% 95% CI: 0.38-0.72), but not when comparing to the adult group (0.86% CI: 0.59-1.25).

In total 70/606 (11.6%) (95% CI: 9.2, 14.3) had migraine, more women (n=38/171 22.2%) than men (n=32/435 7.4%). None of the participants reported migraine and epilepsy.

Of the 12 individuals with cluster headache and epilepsy, 11 answered subsequent questions on aura symptoms. Of these, 5/11 (45%) reported aura, of which 4/11 (36%) reported aura in relation to cluster headache attacks. Three of these reported strictly visual aura and one reported visual and sensory aura symptoms.

We identified 5924 people with migraine in the LUMINA database, of which 2136 (36.1%) had migraine with aura and 955 (16.1%) were male. Mean age was 43.8 (± 12.8 SD). In total 123/5924 (2.1% 95% CI: 1.7, 2.5) reported to have epilepsy, n=75 (2.0%) in migraine without aura vs n=48 (2.3%) in migraine with aura, (p=0.496).

We identified 472 headache-free controls (194/472 41.0%) male, mean age 43.7 ±6.8 of whom in total 4 (0.85%) (95% CI: 0.33, 2.2) reported to have epilepsy, which is not different from the prevalence of epilepsy in individuals with cluster headache in the LUCA population.

Table 2 People with cluster headache from LUCA database with epilepsy

Subjects	Age	Sex	Chronic or episodic cluster headache	Cluster headache aura	Family with cluster headache	Other headache than cluster headache	Type of seizures	Age onset epilepsy	Type of epilepsy
1	61	F	Chronic	Visual aura	No	DK	Focal seizures	13	Focal
2	48	F	Episodic	No	No	DK	Generalised seizures (not further specified)	14	Generalised
3	70	M	Episodic	No	Maybe father	No	Focal seizures on vascular aetiology	57	Focal
4	54	F	Chronic	Visual aura	No	No	Focal seizures (aphasia) on vascular aetiology	38	Focal
5	51	M	Chronic	No	No	TTH	Generalised seizures (not further specified)	23	Generalised
6	44	M	Episodic	No	No	No	Generalised tonic clonic seizures during childhood	6	Generalised
7	60	M	Chronic	Visual aura	No	No	Seizures (not further specified) on vascular aetiology	'older age'	Focal
8	63	M	Episodic	Visual aura unrelated to CH	No	No	Secondary generalised tonic clonic seizure	63	Focal
9	60	M	Episodic	No	Brother (1)	No	Secondary generalised tonic clonic seizure	47	Focal
10	47	F	Episodic	Visual and sensory aura	No	No	Generalised seizures (Absence)	6	Generalised
11	46	M	Chronic	?	No	DK	Focal seizures with secondary generalisation on vascular aetiology	21	Focal
12	65	M	Chronic	No	No	No	Focal seizures (polyopia)	56	Focal

M = male
F = female
DK = don't know
TTH= tension type headache
CH = cluster headache
? = did not complete this question

Discussion

We studied in a very large cohort the comorbidity of epilepsy and secondarily migraine in people with cluster headache. The life-time prevalence of epilepsy in our cases of cluster headache was higher compared to the general population described in a recent meta-analysis of international studies.(19) Supporting our finding, the prevalence of epilepsy in our LUCA study is the same as in our migraine (LUMINA) cohort and similar to the increased prevalence of epilepsy in migraine (compared to the general population) described in the literature of 0.7-2.3%.(1) The life-time prevalence of epilepsy in cases with cluster headache was not significantly different from the prevalence of epilepsy in our controls, most likely due to this small control group and thereby lack of power.

Comorbidity of cluster headache and epilepsy has been investigated before in one study: 1.0% of people with cluster headache also had unspecified epilepsy. (22) Our study used validated questionnaires for cluster headache, a very large cohort and provided details on epilepsy. In other studies 0/255 (23) and 2/388 (0.5%)(24) of people with epilepsy had cluster headache.

Earlier studies suggested that aura might occur in association with attacks in 6-23% of people with cluster headache.(8-11, 22, 25-27) A previous study described a prevalence of 7.0% and 9.0% , respectively, of aura in cases of cluster headache in the LUCA population. (28,11) These figures are lower than in the present study in people with cluster headache and epilepsy (5/11 45%). A possible explanation for this could be that in the present study we defined a group of subjects who have cluster headache and epilepsy, which might make them more sensitive to have aura because of hyperexcitability of the cortex. These findings, however, need replication. Conversely, we identified no subjects having all three conditions: cluster headache, epilepsy and migraine which suggests that cortical hyperexcitability will not necessarily result in all conditions related to this phenomenon. Another explanation might be that comorbidity between epilepsy and cluster headache would be explained by something else, for instance former head trauma, alcohol use or illicit drug use. In this study, we did not control for alcohol because of the small numbers of cluster headache people with epilepsy, and, in one of our earlier studies we did not find a difference in alcohol use between individuals with cluster headache

and controls.(29) The prevalence of illicit drug use, however, was found higher among cases of cluster headache in the LUCA study compared to the general population.(30) In epilepsy frequent illicit (non-cannabis) drug use can cause seizure worsening, but there is no relationship in causing the disease.(31) Head trauma might also be a confounding factor between cluster headache and epilepsy, as head trauma is described to be a possible risk factor for both. (32, 33) We do not have information on previous head trauma, because we deem that (mild) head trauma is difficult to define in retrospective and very common.

Few small experimental studies support the hypothesis of cortical hyperexcitability in cluster headache by using transcranial stimulation(12) and using functional magnetic resonance imaging (fMRI).(34) Current drug treatment, however, does not support the hypothesis of cortical hyperexcitability in cluster headache. Anti-epileptic drugs that act on ion channels to decrease hyperexcitability like topiramate and gabapentin are not first -line treatments, but have been described to treat cluster headache. Studies are not conclusive because of contradictory results and the retrospective nature of most studies. (35)

The prevalence of migraine in our study was similar to that previously published in the general population, of 22.4 % for women and 6.5% for men for comparable age groups,(36) confirming that migraine is not more prevalent in cluster headache than in the general population.

A strength of our study is that we investigated the prevalence of epilepsy in a large cohort of people with a validated diagnosis of cluster headache and migraine and headache-free controls. We used a questionnaire to diagnose active and not life-time prevalence of migraine in the cluster headache population, which likely has resulted in an underreporting of migraine. We probably also underreport the prevalence of epilepsy, as reported sensitivity of a single self-report question in epilepsy is 75-85% (specificity 93-99%).(37, 38) On the other hand, there can also be some amount of overestimation of the diagnosis of epilepsy, because the evaluation of the people with cluster headache, who reported to have also epilepsy, to confirm they indeed had epilepsy, was unblinded. We, however, think that in this study underestimation is more likely because of the reasons listed above.

In conclusion, 2.0% of the subjects with cluster headache also had epilepsy which appears higher compared to the general population, and is similar to what we and others found in people with migraine. This supports the hypothesis that cortical hyperexcitability is involved in cluster headache.

Key point box

- Lifetime prevalence of epilepsy is increased in cluster headache, similar to migraine
- Migraine prevalence is not increased in cluster headache
- Comorbidity of cluster headache and epilepsy supports the hypothesis that cortical hyperexcitability is involved in cluster headache.

Disclosure of conflicts of interest:
MDF reports grants and consultancy or industry support from Medtronic and independent support from the European Community, Netherlands Organization for Scientific Research (NWO) and the Dutch Heart Foundation. MK and JWS are based at UCLH/UCL Comprehensive Biomedical Research Centre, which receives a proportion of funding from the UK Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. MK reports speaker and advisory fees for Novartis, Sage Therapeutics, and UCB as well as an unrestricted educational grant from UCB. The other authors report no conflicts of interest.

Funding acknowledgement:
This work was supported by grants of the European Community (EC) [FP7-EUROHEADPAIN - no. 602633]; They had no role in the design or conduct of the study.

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