The migraine triad: chronification, depression, and medication overuse

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PhD thesis, Leiden University, The Netherlands, 2017

ISBN: 978-94-6332-233-1

Cover design and lay-out: Pjotr Design Studio, Utrecht
Printed by: GVO drukkers & vormgevers B.V.,Ede

The research described in this thesis was supported by grants of the Netherlands Organisation for Scientific Research (NWO): [VICI 918.56.602 to M.D.F., VIDI 917.11.319 to G.M.T.]; the European Community (EC) [FP7-EUROHEADPAIN - no. 602633]; and the Centre for Medical Systems Biology (CMSB) in the framework of the Netherlands Genomics Initiative (NGI). They had no role in the design or conduct of any of the studies.

Financial support for publication of this thesis has been provided by the Nederlandse Hoofdpijn Vereniging, and was gratefully accepted.

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Proefschrift

ter verkrijging van de graad van Doctor aan de Universiteit Leiden
op gezag van de Rector Magnificus Prof. Mr. C.J.J.M. Stolker,
volgens het besluit van het College voor Promoties
te verdedigen op dinsdag 30 januari 2018
klokke 16.15 uur

door

Mark Arend Louter
Geboren te Moerkapelle
Op 24 augustus 1982

Promotores:	Prof. Dr. M.D. Ferrari
	Em. Prof. Dr. F.G. Zitman
Copromotor:	Dr. G.M. Terwindt
Leden promotiecommissie:	Prof. Dr. A.M.W. Evers (Faculteit der Sociale Wetenschappen, Universiteit Leiden)
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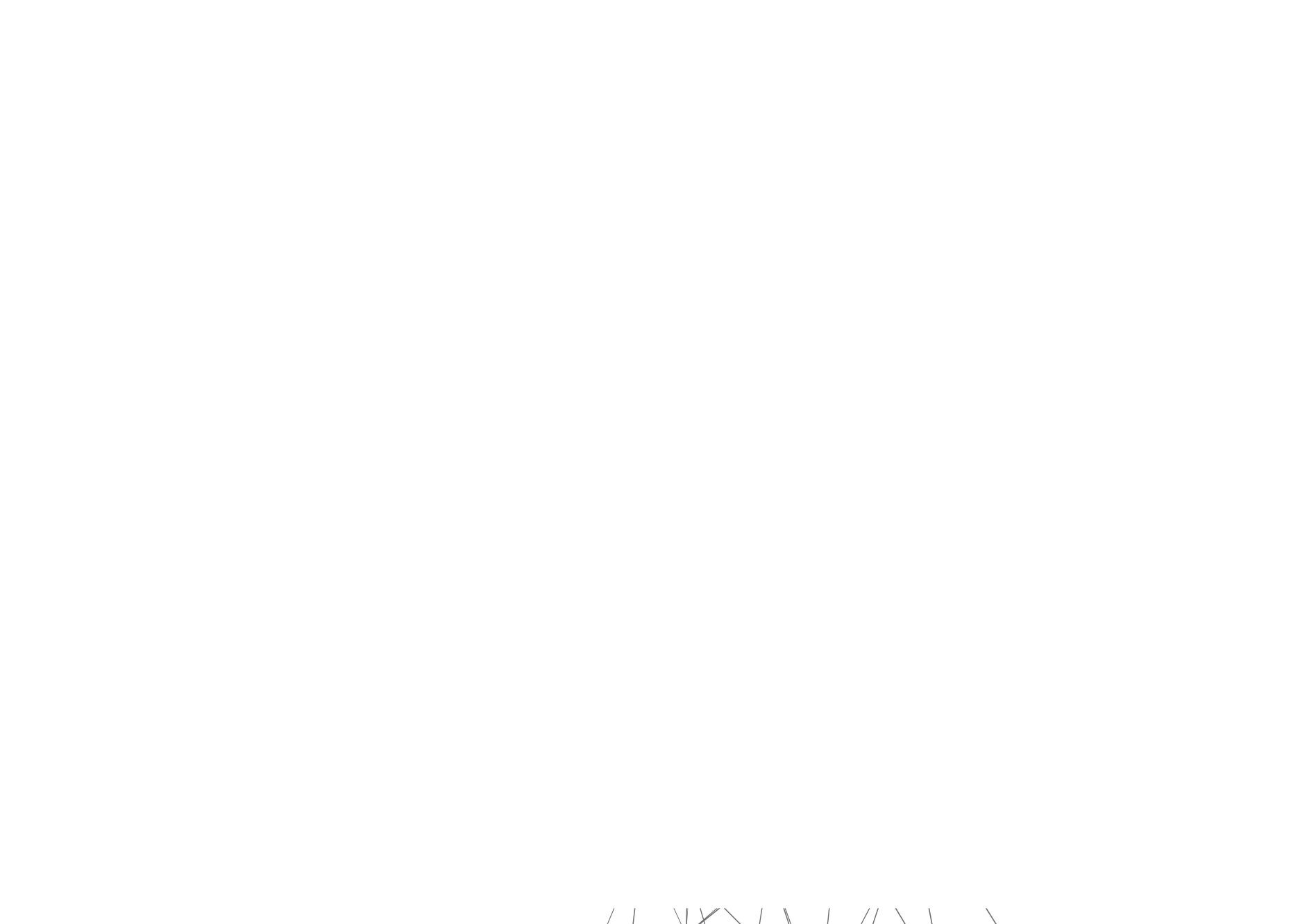

1 CHAPTER | General introduction and scope of the thesis

Adapted from:

Migraine en depressie verdienen gezamenlijke zorg
Nederlands Tijdschrift voor Geneeskunde 2010;154(29):1369-1375

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G.Veen
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and:

Non-vascular comorbidities and complications
Book chapter Oxford Textbook of Headache, to be published

M.A. Louter
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1.1 Migraine

1.1.1 Migraine epidemiology and socioeconomic impact

Migraine is a common neurovascular disease, with a lifetime prevalence of 33% for women and 13% for men. At least 12% of the Dutch population suffers from at least 1-2 attacks per month. (1) The personal and socioeconomic burden of migraine is enormous. A recent report of the Global Burden of Disease Study 2015 listed migraine 8th out of 289 diseases for 'global years lived with disability'. (2, 3) Migraine was the leading cause of disability among neurological disorders, accounting for over half of all years lived with disability. (4) In high-income countries, the total disability due to migraine is more than 1.5 times that due to multiple sclerosis and Parkinson's disease combined, and almost 3 times that due to epilepsy. (2) The economic burden caused by migraine is the second highest of all brain diseases, with an estimated annual cost of €111 billion in the European Union alone. (5)

1.1.2 Migraine criteria and characteristics of the migraine attack

Diagnoses are based on criteria that have been provided by the International Headache Society in 1988 (ICHD-I), being revised in 2004 (ICHD-II) and 2013 (ICHD-III beta). (6-8) Following these criteria, migraine is characterized by recurrent, disabling attacks of severe, unilateral, throbbing headache that aggravates by physical activity. (8) If untreated, attacks last 4-72 hours. The headache is typically accompanied by nausea or vomiting, photophobia and phonophobia, or a combination of these additional symptoms. In up to 30% of migraineurs, attacks may be associated with reversible focal neurological aura symptoms, mostly visual, such as scotomas and scintillations, and sometimes sensory symptoms or dysphasia (migraine with aura). The typical duration of migraine auras is 5-60 minutes. The aura gradually expands, and the aura phase typically precedes the headache phase, although some patients describe an overlap, or a short gap between the end of the aura phase and the onset of headache. (9, 10) A few hours up to 2 days prior to the aura and headache phase, migraine patients may experience a wide variety of non-headache premonitory symptoms. Reported symptoms are fatigue, weariness, yawning, stiff neck, gastrointestinal problems, mood and cognitive changes, temperature change, smell and taste distortion, increased perceived stress and food craving. (11-14). The recovery phase, which can last up to a few days, is characterized by symptoms that are quite similar to premonitory symptoms: tiredness, weakness, cognitive difficulties, mood changes, residual headache, light-headedness and gastrointestinal problems. (15, 16) Table 1 describes the full ICHD-III beta criteria for migraine with and without aura.

Table 1: Classification of migraine without aura and migraine with aura according to the ICHD-III beta criteria.

Migraine without aura

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
    1. Unilateral location
    2. Pulsating quality
    3. Moderate or severe pain intensity
    4. Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following:
    1. Nausea and/or vomiting
    2. Photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis.

Migraine with typical aura

A. At least two attacks fulfilling criteria B and C
B. Aura consisting of visual, sensory, and/or speech/language symptoms, each fully reversible, but no motor, brainstem of retinal symptoms
C. At least two of the following four characteristics:
    1. At least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
    2. Each individual aura symptom lasts 5-60 minutes
    3. At least one aura symptom is unilateral
    4. The aura is accompanied, or followed within 60 minutes, by headache
D. Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

Typical aura with headache

A. Fulfils criteria for *Migraine with typical aura*
B. Headache, with or without migraine characteristics, accompanies or follows the aura within 60 minutes.

Typical aura without headache

A. Fulfils criteria for *Migraine with typical aura*
B. No headache accompanies or follows the aura within 60 minutes

1.1.3 Migraine pathophysiology

Migraine is associated with activation of the trigeminovascular system. (17) Through this system, which connects brainstem nuclei with dural blood vessels via the ophthalmic division of the trigeminal nerve, abnormal pain signals are transferred from the dura to higher order central nervous systems during a migraine attack. Activation of trigeminovascular efferents leads to release of vasoactive neuropeptides (e.g. Calcitonin Gene Related Peptide (CGRP), Substance P), which are believed to be involved in neurogenic inflammation, central pain transmission, and headache. Sustained activation of the trigeminovascular system leads to peripheral sensitization of first-order trigeminal neurons, which thus exhibit increased responsiveness to external stimuli. Central sensitization is elicited by increased excitability of second and third order neurons (in the dorsal horn of the spinal cord and in the thalamus), a result of persistent pain transmission. As a result of central sensitization, non-noxious stimuli of the peri-orbital skin (which is also innervated by the ophthalmic division of the trigeminal nerve) are perceived as painful, a phenomenon known as cutaneous allodynia. This phenomenon occurs during attacks in 50-80% of all migraine patients. (18) It is well accepted that migraine aura is most likely caused by the human equivalent of the cortical spreading depression of Leao, a wave of depolarization that propagates slowly across the cortex. (19)

1.1.4 Migraine genetics

Migraine has a strong genetic component, as shown in population-based family studies and twin studies. (20) A number of loci were discovered over the past decade using the genome wide association (GWA) approach, pointing at genes that cluster in pathways for glutamatergic neurotransmission, synaptic function, pain sensing, metalloproteinases, and the vasculature. (21-25) The individual pathogenic contribution of each gene variant, however, is difficult to assess.

Familial hemiplegic migraine (FHM) is a rare monogenic subtype of migraine with aura, with transient hemiparesis during the aura phase. Ever since the discovery of the three genes that have been associated with hemiplegic migraine (*CACNA1A* (FHM1), *ATP1A2* (FHM2) and *SCN1A* (FHM3)) it has been considered a suitable model to gain more insight into the pathophysiology of common migraine.

(26-28) All three FHM gene products are involved in the modulation of ion transport across neuronal and glial cell membranes, suggesting that FHM, and possibly also common types of migraine, at least in part, are cerebral 'ionopathies'.

1.1.5 Migraine treatment

Acute treatment of migraine attacks follows a stepped-care principle. Medication of first choice is a simple analgesic, like paracetamol or an NSAID. When these appear insufficient, triptans should be prescribed. Triptans are agonists of the 5HT-$_{1B/1D}$-receptor, and were introduced in 1991 as a new treatment for migraine and cluster headache attacks, replacing the ergotamins. When migraine frequency exceeds 2 attacks per month or in case of insufficient response to attack medication, prophylactic medication may be started. Examples of migraine prophylaxis are valproate, propranolol, topiramate and candesartan.

1.1.6 Migraine chronification

Up to 25% of migraine patients will at one point during their lifetime meet the definition for chronic migraine. (29) According to the ICHD-III beta classification criteria, a clinical diagnosis of chronic migraine (the prevalence of which is estimated to be around 0.5 to 2.0% among the general population) is made when a migraine patient has 15 or more days with headache per month, of which at least eight days have features of migraine headache (or being relieved by migraine-specific medication). (8, 30, 31) Table 2 describes the full criteria for chronic migraine.

Table 2: Classification of chronic migraine according to the ICHD-III beta criteria.

Chronic migraine
A. Headache (tension-type-like and/or migraine-like) on ≥15 days per month for >3 months and fulfilling criteria B and C
B. Occurring in a patient who has had at least five attacks fulfilling criteria B-D for *Migraine without aura* and/or criteria B and C for *Migraine with aura*
C. On ≥8 days per month for > 3 months, fulfilling any of the following:
1. Criteria C and D for *Migraine without aura*
2. Criteria B and C for *Migraine with aura*
3. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative
D. Not better accounted for by another ICHD-3 diagnosis.

Chronification of migraine occurs about equally in male and female migraineurs. It is thought that in these patients the threshold for migraine attacks is lowered compared to episodic migraineurs, but the exact mechanism behind this chronically lowered threshold remains unknown. One of the main factors associated with chronic migraine is the overuse of acute migraine medication. (32) In European clinical practice, almost all chronic migraineurs also fulfil the criteria

for medication overuse headache, which is the consequence of regular overuse of acute anti-migraine medication. Table 3 describes the full criteria for medication overuse headache.

Table 3: Classification of medication overuse headache according to the ICHD-III beta criteria.

Medication overuse headache
A. Headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache C. Not better accounted for by another ICHD-3 diagnosis.

Overuse is defined differently for triptans (on ≥10 days per month for >3 months) than for simple analgesics like paracetamol or NSAIDs (on ≥ 15 days per month for >3 months). 'Combination-analgesic-overuse headache' is defined as headache fulfilling the criteria for medication overuse headache, with a regular intake of one or more combination-analgesic medications on ≥10 days/month for > 3 months. 'Medication-overuse headache attributed to multiple drug classes not individually overused' is defined as headache fulfilling the criteria for medication overuse headache, with regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDs and/or opioids on a total of ≥10 days per month for >3 months, without overuse of any single drug or drug class alone.

Although consensus about the optimal treatment for both medication overuse headache and chronic migraine has not yet been reached, withdrawal of the overused medication is strongly suggested as an essential component in the management of these diseases. (33-35) In The Netherlands, treatment of chronic migraine and medication overuse headache consists of cold-turkey withdrawal of all analgesics, triptans, and caffeine, during 3 months (in case of involvement of simple analgesics) or 2 months (in case of isolated triptan overuse). After withdrawal, most patients show a clear decrease in the number of headache days per month, with a more recognizable pattern of migraine attacks and migraine-free periods. Symptomatic and/or prophylactic treatment may be started again after withdrawal, with a clear explanation to the patient about the risks of medication overuse.

Two randomised, double-blind, controlled trials (PREEMPT1 and PREEMPT2) showed an effect of Onabotulinum toxin A injections (without withdrawal of the overused acute headache medications) in the treatment of chronic migraine. (36-38) The pooled results of both trials show a small but significant advantage

of Onabotulinum toxin A injections above placebo (Onabotulim toxin A group: -8.4 headache days; placebo group: -6.6 headache days). This small difference, however, probably does not reach the standard for clinical relevance. Importantly, although there was a decrease in frequency of headache days (both in the verum and placebo groups), there was no decrease in the intake of acute headache pain medication. The risk of unblinding in the PREEMPT trials also remains a topic of discussion.

1.2 Depression

1.2.1 Depression epidemiology and socioeconomic impact

Depression, like migraine, is a chronic episodic brain disorder, with a lifetime prevalence of 19% and a 1-year prevalence of 6% in the Dutch population. (39) Major depressive disorder is among the most disabling psychiatric disorders in adult age and has the second largest global disease burden, after low back pain. (2)

1.2.2 Depression criteria and characteristics of a depressive episode

Clinical diagnoses are based on diagnostic criteria that have been provided by the Diagnostic and Statistical Manual of Mental Disorders, DSM. The first version of this diagnostic classification was published in 1952, and the last version hitherto, DSM-5, has been published in 2013. (40) Depression is characterized by a persistent low or sad mood, anhedonia, difficulties in eating and sleeping, concentration problems, psychomotor agitation or retardation, tiredness, feelings of worthlessness or guilt, and thought about death or suicide. The symptoms must persist for most of the day, nearly every day, for at least 2 consecutive weeks. The course of a depressive episode is highly variable. Some individuals reach rapid remission (a period of 2 months without symptoms, or only one or two symptoms with a mild degree) after treatment has started, while others rarely, if ever, experience remission. Chronicity of depressive symptoms is associated with various comorbidities, such as personality, anxiety and substance use disorders. (41) Table 4 summarizes the full DSM-5 criteria for depression.

Table 4: Classification of major depressive disorder according to the DSM-5 criteria.

Major depressive disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
    1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).
    2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
    3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
    4. Insomnia or hypersomnia nearly every day.
    5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
    6. Fatigue or loss of energy nearly every day.
    7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
    8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
    9. Recurrent thought of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the psychological effects of a substance or to another medical condition.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or hypomanic episode.

Although DSM categories are of great use in clinical practice, they have arbitrary boundaries, and show much overlap and comorbidity. Moreover, high heterogeneity of symptoms and severity within one diagnostic category (i.e. major depressive disorder) is possible. (42) Consequently, studying depression using the DSM-5 criteria provides a rather heterogeneous sample of patients. Current research, followed by the DSM-5 criteria, suggests that it may be more appropriate to study dimensions of psychopathology taking the multidimensionality of symptomatology into account, rather than using dichotomous DSM-5 categories. (40, 43)

1.2.3 Depression pathophysiology

Several hypotheses have been postulated for the pathophysiology of depression, which are not mutually exclusive. (44) Major depressive disorder is likely to have several causes. The monoamine-deficiency hypothesis describes depression as a disbalance in the function of the noradrenergic and serotonergic systems. The second hypothesis describes the role of stress and the hypothalamic-pituitary-adrenal axis (HPA-axis). The role of cortisol and its central releasing factor, CRH, in depression has convincingly been described. (45, 46) Still, a single test for the cortisol level in the blood does not provide a diagnosis of depression, since sensitivity and specificity of the cortisol awakening curve are insufficient. Alternative biological theories of the pathophysiology of depression focus on altered glutamatergic neurotransmission, reduced GABAergic neurotransmission and abnormal circadian rhythms. (44)

1.2.4 Depression genetics

The estimated heritability for major depression is 37%, comparing monozygotic and dizygotic twins. (47) After years of genetic research, it has become clear that depression is not caused by any single gene but, like migraine, is caused by a complex interaction between multiple genes and the environment. Neither linkage nor genome-wide association studies showed clear associations for depression which could be replicated in independent studies. (48) The impressive amount of negative findings, however, imparts important lessons. First, due to the heterogeneity of undifferentiated depression, success of the GWAs approach will depend on very large sample sizes. Second, concentrating on subtypes or dimensions of depression will probably be more successful. Considering depression as a quantitative trait, or focusing on subgroups with certain comorbid disorders, could also increase the probability of significant findings. Altogether, the difficulties of sample size and clinical differentiation are unavoidable if we want to find genetic clues to explain the pathophysiology of depression. (48)

1.2.5 Depression treatment

The first-line pharmacological treatment of depression is following a stepped-care principle, starting with a selective serotonin reuptake inhibitor (SSRI), which in case of non-response after 4 weeks should be changed to another SSRI or a serotonin-norepinephrine reuptake inhibitor (SNRI). In case of non-response after 4 weeks, treatment should be changed to a tricyclic antidepressant (TCA). The next step is addition of lithium, after which it could be changed for a monoamine-oxidase inhibitor (MAO-inhibitor). As a last step in case of treatment resistant depression, electroconvulsive therapy (ECT) should be considered. (49) Psychotherapeutic interventions can be offered to patients with a mild or moderate depression.

Examples of effective psychotherapeutic interventions are cognitive behavioural therapy, interpersonal psychotherapy or psychodynamic psychotherapy.

1.3 Migraine and depression

1.3.1 Comorbidity

Comorbidity was defined in 1970 by Feinstein as 'any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study'. (50) In this definition, the term comorbidity could be used for any entity that occurs before the diagnosis, during the disease, or after treatment of the disease. Even 'non-disease' clinical entities such as pregnancy or dieting were included by Feinstein's definition. Nowadays, the term comorbidity is used mostly for associations between disorders that are greater than could be expected based on the usual individual prevalence of both diseases in the given population.

1.3.2 Migraine-specific comorbidities

The number of suggested comorbidities of migraine as reported in scientific literature has increased immensely over the past decades. Research into comorbidity and its underlying mechanisms has become increasingly interesting, as it might offer new insights in migraine pathophysiology. Furthermore, migraine patients presenting at headache clinics or general neurology practices, will often show multiple problems. (51) Knowledge about and recognition of this phenomenon has grown amongst clinicians. Still, the clinical comorbidities create new challenges for patient management, education, and treatment. From a scientific point of view population-based studies may be preferable when studying the prevalence of comorbid disorders in migraine. However, clinical studies may shed light on detailed cause-consequences of comorbidities, or influence on comorbidities when starting treatment for one of them.

Amongst the most reported migraine comorbidities, clear associations in population studies have been reported for ischemic stroke, epilepsy, vertigo, psychiatric diseases, sleep disorders, and pain disorders. However, most studies are cross-sectional, making causal interpretation of the results impossible. Only when prospective cohort studies have been done, in which the first onset of disease in a given population with another disease has been studied, firm statements on causality can be made. The best example in the field of migraine comorbidity is the relationship between migraine and depression, as described below: not only first onset of depression is increased in migraineurs, but also first onset migraine is increased in depressive patients. (52-54) This has led to the recognition of bidirectional comorbidity, possibly due to shared genetic factors. (55, 56)

1.3.3 Interpretation of comorbidity

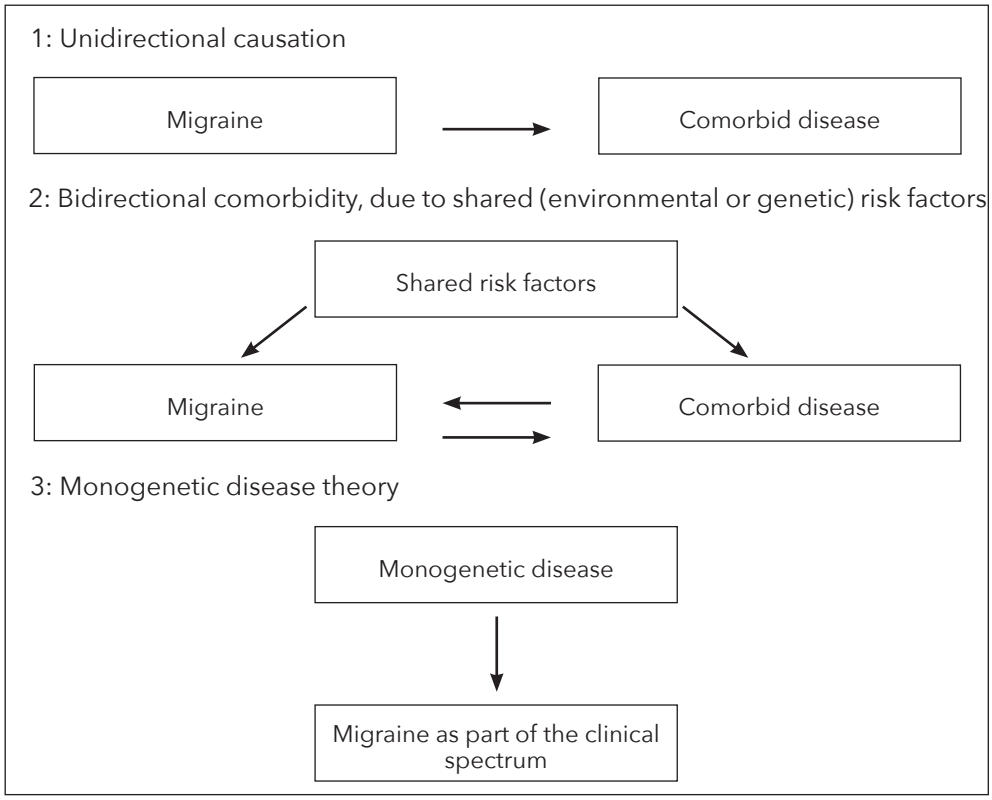
The interpretation of comorbidity is not always simple. In fact, true comorbidity can be caused by different mechanisms (figure 1). The first mechanism is that there is a unidirectional causation, which states simply that migraine may be a risk factor for another disease. In this case, it would be predicted that migraine would occur first. Secondly, when not only migraine increases the risk for a certain disease but also vice versa (the disease increases the risk for migraine either), this is called 'bidirectional comorbidity'. Such a bidirectional relationship is strongly suggestive for shared (environmental and/or genetic) risk factors. In diseases where genetic factors unmistakably play a role, the shared genetic factors hypothesis is particularly attractive. (57) Classical twin studies can be used to test whether shared genetic and/or environmental factors underlie the two disorders (58) but also direct identification of genetic factors can be successful when studying cases with both disorders. As a third mechanism of comorbidity, migraine is part of the clinical spectrum of a clear monogenetic disease.

This discussion of comorbidity started with migraine. Of course, a discussion starting with depression would go along the same lines.

1.3.4 Why study the comorbidity of migraine with depression?

Understanding the associations between migraine and psychiatric disorders is important for various reasons. Migraine and depression are both ranked in the top-10 of disorders with high disability and burden. (2) The presence of psychiatric conditions, especially depression, is a risk factor for migraine chronification. (32) In addition, comorbid migraine is associated with poorer functioning and increased somatic complaints in depressed patients. (59) Migraine patients with comorbid psychiatric disorders are greater consumers of health resources than migraineurs without psychiatric conditions. (60) Lastly, treatment choices for both migraine and psychiatric disorders can be influenced by the presence of comorbidity. Prescription of beta-blockers is (although debated) relatively contraindicated as migraine prophylactic in patients with comorbid depression. Migraine prophylaxis with SSRIs is still controversial because of the suggested risk of developing a serotonin syndrome when prescribed together with triptans, especially when used frequently. In our experience this is, however, not a problem in practice, as long as triptans are not overused, i.e. more frequently than on 2 days per week on a regular basis. Valproate as prophylactic treatment for migraine may be favoured due to its stabilising effect on the mood.

Figure 1: Mechanisms of comorbidity



1.3.5 What is known about migraine and depression comorbidity?

Although it seems logical that persons with chronic, unpredictable headaches get depressed, which often is stated by patients and their family and friends, the association is bidirectional. Also persons with a depression show an increased risk of getting migraine. Population based studies have shown that persons with a lifetime history of depression have an increased risk to develop migraine later during life when compared with persons without a lifetime depression (OR 3.0, 95% CI 1.2-7.6). Vice versa, persons with migraine have an increased risk of first onset major depression, compared with persons without migraine (OR 5.2, 95% CI 2.4-11.3). (53, 54) Such bidirectional association suggests a shared aetiology, which, according to several studies, is at least partly explained by genetic factors. (61-63) Indeed, evidence suggests that migraine and depression share genetic factors. In a large twin study, 20% of the variability of comorbid migraine and depression was estimated to be due to shared genetic factors and 4% to unique

shared environmental factors. (56) A study performed in a genetically isolated Dutch population investigated the extent to which the comorbidity of migraine and depression could be explained by shared genetic factors. Clear indications were found for shared genetic factors in depression and migraine, especially in migraine with aura. (55) It is still unclear to what extent the comorbidity of migraine with depression also counts for a monogenic form of migraine with hemiplegia during the aura phase, Familial Hemiplegic Migraine (FHM). Also, the question which specific genetic factors are involved in the increased liability to both disorders, remains open.

1.3.6 The migraine triad: chronification, depression, and medication overuse

Comorbid depression is particularly common in chronic migraine patients. (64) Depression is also an important predictor of medication overuse, which is seen in up to half of persons with chronic migraine. (65) Depression is considered a major risk factor for migraine chronification. (32) Furthermore, overuse of analgesics is associated with an increased risk of depression. (66) Comorbid depression is thus likely to increase the risk of chronification in migraine and complicate treatment. (67-69) In addition, comorbid migraine is associated with poorer functioning and increased somatic complaints in depressed patients. (59) Altogether, a triad has been suggested of migraine chronification, medication overuse and depression. It is unclear to which extent genetic factors, general determinants and migraine specific factors are involved in this migraine triad.

1.3.7 Depression and cluster headache

Another important question is whether the triad of chronification of attacks, medication overuse and depression is specific for migraine. Hitherto, most studies about headache and depression are about migraine. One of the questions remaining is whether depression also is comorbid with cluster headache, another type of primary, severe, paroxysmal headache. This question is in particular important, as the severity of the pain has earned cluster headache the title 'suicide headache'. Suicidal tendencies have been reported in 25-55% of cluster headache patients. (70-72)

Cluster headache has, especially when compared with migraine, a low prevalence of one in 1000 with a male to female ratio of 4:1. (73, 74) The impact of cluster headache on quality of life, social functioning, and socioeconomic status can be enormous. (75)

Typical attacks of cluster headache consist of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15-180 minutes and occurring from once every other day to eight times a day. The pain

is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid oedema, and/or with restlessness or agitation. (8) In about 85% of patients, attacks are clustered in periods of several weeks to months, alternating with attack-free periods of several months to years (episodic cluster headache); in the remaining patients, long attack-free periods are absent (chronic cluster headache). (73, 76)

As cluster headache shows several clinical, therapeutical, and pathophysiological similarities to migraine, and studies on the comorbidity of cluster headache with depression are lacking, the question remains whether depression is also a comorbid condition in cluster headache.

1.4 Scope of the thesis

In this thesis different components of the migraine triad of chronification, depression, and medication overuse are investigated. The thesis pays attention to epidemiological aspects of the triad (**chapters 2-5**), to clinical implications and applications of the triad (**chapter 6**), to genetic aspects of migraine chronification (**chapter 7**) and to a comparison with a different type of primary headache, cluster headache (**chapter 8**).

In **chapter 2**, we aim to further elucidate the association between migraine and depression and to identify migraine specific factors associated with depression. In **chapter 3**, we assess cutaneous allodynia as a possible predictor of migraine chronification, as it is known as a factor which is involved both in migraine frequency and comorbidity with depression. In **chapter 4**, we analyse the prevalence of lifetime depression in a large cohort of patients with FHM. **Chapter 5** describes whether migraine patients display different symptoms patterns of affective disorders than healthy controls, and persons with a current or past affective disorder. In **chapter 6**, we focus on the chronification part of the triad by investigating the role of the headache nurse in detoxification of acute headache medication. **Chapter 7** describes a genetic association study for migraine chronification. In **chapter 8**, we want to assess whether depression is also comorbid in cluster headache, and to identify cluster headache specific characteristics that might be associated with depression. **Chapter 9** provides a general discussion of the thesis, reviewing the results and discussing future possibilities for research.

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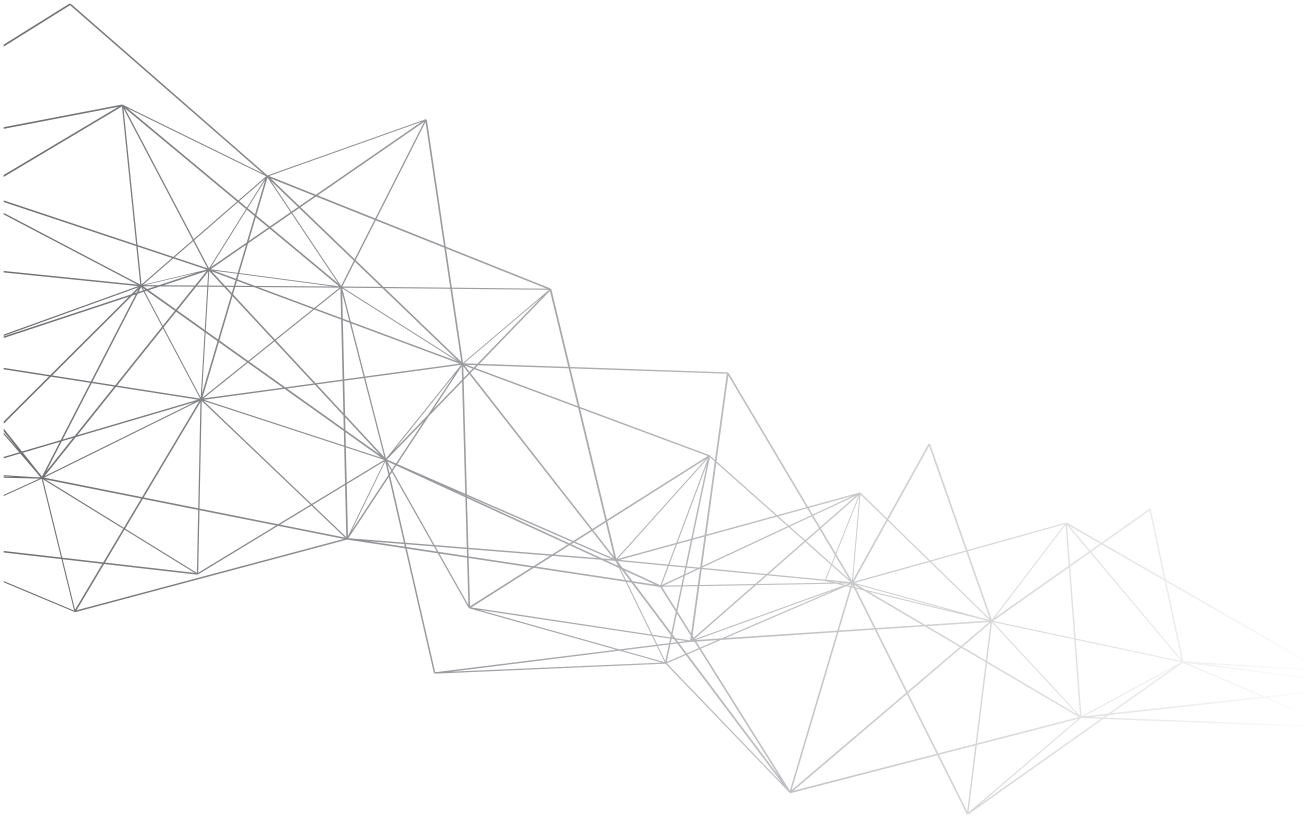
2 CHAPTER

Allodynia is associated with a higher prevalence of depression



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Cephalalgia 2014 Dec;34(14):1187-92

Abstract

Introduction
There is a strong association between migraine and depression. The aim of this study was to identify migraine specific factors involved in this association.

Methods
We conducted a cross-sectional study in a large well-defined cohort of migraine patients (n=2533). We assessed lifetime depression using validated questionnaires, and diagnosed migraine based on the International Classification of Headache Disorders III-beta criteria. Multivariate regression analyses were conducted.

Results
Of the 2533 migraineurs that were eligible, 1137 (45%) suffered from lifetime depression. The following independent factors were associated with an increased depression prevalence: i) migraine specific risk factors: high migraine attack frequency, the presence of allodynia, ii) general factors: being a bad sleeper, female gender, high BMI, being single, smoking, and a low alcohol consumption.

Conclusion
This study identified allodynia, in addition to high migraine attack frequency, as a new migraine specific factor associated with depression.

Introduction

Migraine and depression both rank among the most prevalent and disabling disorders and show a bidirectional increased comorbidity. (1-4) Such bidirectional association suggests a shared aetiology, which is at least partly explained by genetic factors. (5, 6)

Comorbid depression seems to be particularly common in chronic migraine patients. (7) Depression is also an important predictor of medication overuse, which is seen in up to half of persons with chronic migraine. (8) Comorbid depression is thus likely to increase the risk of chronification in migraine and to complicate treatment. (9-11) In addition, comorbid migraine is associated with poorer functioning and increased somatic complaints in depressed patients. (12) Altogether, a triad is suggested of migraine chronification, depression and medication overuse. Identifying migraine specific factors associated with depression will help to detect patients that are at an increased risk of depression and chronification.

The aim of this study was to further elucidate the association between migraine and depression in a large, well-defined, web-based migraine cohort and to identify migraine specific factors associated with depression.

Methods

Participants and procedures

Our study was conducted as a part of the LUMINA project. (13) Participants of the LUMINA project were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders criteria (previously ICHD-II, now ICHD-III beta version). The LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. All subjects provided written informed consent prior to the study. For a further description of the participants and procedures, see Supplementals.

Measures

Lifetime depression was measured, using validated cut-off scores on depression questionnaires and additional questions on lifetime depression. (14, 15) Cutaneous allodynia was measured using the 12-item Allodynia Symptom Checklist. The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep disturbances during the month before assessment. (16) For a further description of the measures, see Supplementals.

Data analysis

Logistic regression analyses were used to test which variables were associated with lifetime depression among migraine patients. For all analyses *p*-values of <0.05 were considered to indicate statistical significance. For an extended description of the data analyses, see Supplementals.

Results

Study population and descriptive statistics

The total study flow is shown in supplemental fig. 1. In total, 3624 migraineurs within the LUMINA project were sent a depression questionnaire (mean age: 41.7 ± 11.9), based on migraine diagnosis and the presence of written informed consent. In total 3177 (87.7%) returned this depression questionnaire. Because of missing data, 2533 were eventually included in the analysis.

Comparison of included vs. excluded participants showed for all analyses that included participants were slightly older and had more often migraine with aura, but did not differ in gender (data not shown). Of the 2533 migraineurs that were eligible 1137 (45%) suffered from life time depression. A total of 1767 migraine patients (70%) suffered from allodynia during migraine attacks.

Correlates of depression in migraine patients

The comparison for migraine patients with depression versus those without depression is shown in Table 1. The results of the initial univariate analyses are shown in Table 2 (left part). Significant univariate associations with depression were found for the following migraine specific variables: attack frequency, number of migraine days, use of prophylactic medication and allodynia. Other statistically significant variables were being a bad sleeper, gender, BMI, level of education, marital status, smoking, and alcohol consumption. These variables (except number of migraine days, because of the high correlation with migraine attack frequency) were entered together in a multivariate logistic regression analysis. The results of this analysis (Table 2, right part) showed the following independent factors associated with depression in migraine patients; i) the migraine specific factors: high migraine attack frequency, allodynia, ii) the general factors: being a bad sleeper, female gender, high BMI, being single, smoking, and alcohol consumption.

Discussion

This large-scale study in a well-defined migraine cohort showed that depression is associated with allodynia and high attack frequency in migraine patients. Our study is the first large, web-based study to show that allodynia is associated with an increased prevalence of depression in migraine patients. Previous studies investigated the reversed association, namely that the risk of allodynia is higher among migraine patients with depressive symptoms. (17, 18) One recent, small clinic-based study showed that the severity of cutaneous allodynia was associated with current mood status, but did not focus on lifetime depression. (19) Thus, according to our study and others, migraine, depression and allodynia are intertwined. In a previous study we showed that allodynia (and depression) make a migraine patient vulnerable for migraine chronification. (20) Since 70% of migraineurs suffer from allodynia, the clinical impact of this finding might be limited. However, the pathophysiological role of allodynia in migraine chronification and the migraine-depression association is of great importance. Allodynia is considered as a clear marker for a central sensitization process of the brain. (21) Central sensitization is an activity-dependent functional plasticity that results from post-translational regulation and transcriptional regulation of key gene products. (22) Once established, sensitization of second order trigeminovascular neurons becomes activity independent, and maintains itself in the absence of sensory input later on. Clinically, central sensitization causes refractoriness to acute treatment. (21) Thus, allodynia has consequences for disease progression and treatment, and it should lead to an increased awareness of comorbidity of migraine and depression, and of risk of chronification of migraine. Pathophysiologically, the triad migraine, depression and allodynia may suggest a self-reinforcing dysfunction of CNS structures involved in the modulation of neuronal excitability and pain.

Poor sleep quality in migraine patients was associated with higher odds of depression. Whereas the hypothalamus is supposedly involved in migraine, depression, and sleep disorders, the association between these three disorders is suggestive of hypothalamic modulation of the trigeminovascular pathway. (23) Pain signals that originate in the trigeminovascular pathway can alter the activity of hypothalamic and limbic structures that integrate sensory, physiological and cognitive signals that drive behavioural, affective and autonomic responses. (24)

The strengths of this study are the large sample size, the well-defined migraine status and detailed information on depression characteristics. Most importantly, this is one of the first studies demonstrating that cutaneous allodynia and sleep disturbances are strongly associated with depression in migraineurs. Possible limitations include the fact that our population might be younger and higher educated than the migraine population in general due to the recruitment of patients via the internet. However, we tried to limit this effect by enabling participants to fill

out the questionnaires on paper. The cross-sectional nature of this study prevented us from drawing conclusions about causality in the relationship between high attack frequency, allodynia, sleep disturbances and depression.

In summary, frequent attacks and allodynia are associated with a higher prevalence of depression in migraine patients. Future research should focus on identifying pathophysiological mechanisms linking migraine and depression.

Tables and figures

Table 1: Baseline characteristics LUMINA population of 2533 migraine patients, separated by the presence of lifetime depression.

	No lifetime depression n = 1396	Lifetime depression n = 1137
Migraine specific variables		
Age at onset migraine	19.4 ± 10.2	19.5 ± 10.9
Migraine type		
MO	856 (61.3%)	702 (61.7%)
MA	540 (38.7%)	435 (38.3%)
Migraine attack frequency		
1-2 attacks per year	71 (5.1%)	31 (2.7%)
3-6 attacks per year	206 (14.8%)	152 (31.4%)
7-12 attacks per year	448 (32.1%)	306 (26.9%)
13-54 attacks per year	577 (41.3%)	517 (45.5%)
more than 54 attacks per year	94 (6.7%)	131 (11.5%)
Number of migraine days		
1-2 days per year	86 (6.2%)	44 (3.9%)
3-6 days per year	150 (10.7%)	93 (8.2%)
7-12 days per year	261 (18.7%)	178 (15.7%)
13-54 days per year	666 (47.7%)	516 (45.4%)
more than 54 days per year	233 (16.7%)	306 (26.9%)
Use of acute medication		
no	119 (8.5%)	112 (9.9%)
yes, if attack	1114 (79.8%)	844 (74.2%)
yes, (almost) daily	163 (11.7%)	181 (15.9%)
Use of a triptan (yes)	998 (71.5%)	835 (73.4%)
Use of prophylactic medication (yes)	483 (34.6%)	482 (42.4%)
Allodynia (yes)	913 (65.4%)	854 (75.1%)
General variables		
Gender (female)	1168 (83.7%)	1001 (88.0%)
Age (years)	44.1 ± 11.6	44.8 ± 11.5
BMI (kg/m^2)	24.4 ± 3.9	24.8 ± 4.4
Years of fulltime education	13.8 ± 3.3	13.4 ± 3.5
Marital status		
Single	194 (13.9%)	215 (18.9%)
Cohabiting / married	1143 (81.9%)	821 (72.2%)
Divorced / widowed	59 (4.2%)	101 (8.9%)
Smoking packyears	4.1 ± 8.2	5.7 ± 9.8
Caffeine consumption (ie per day)	6.0 ± 3.0	5.7 ± 2.8
Alcohol consumption (ie per week)	3.0 ± 3.9	3.4 ± 3.7
Bad sleeper (yes)	799 (57.2%)	890 (78.3%)

BMI, body mass index; MO, Migraine without aura; MA, Migraine with aura.
Values are the absolute numbers with corresponding percentages or means ± SD.
Few (n=35) patients reported more than one attack on one day, probably because migraine recurrences were counted as new attacks

Table 2: Logistic associations between patient characteristics and the odds of lifetime depression: a model for depression in 2533 persons with migraine.

	Univariate OR	95% CI	p-value	Multivariate OR	95% CI	p-value
Migraine specific variables						
Age at onset migraine	1.00	0.99 – 1.01	0.78	.	.	.
Migraine type (MA vs. MO)	1.02	0.87 – 1.20	0.83	.	.	.
Migraine attack frequency						
3-6 vs. 1-2 attacks per year	**1.69**	**1.06 – 2.71**	**0.03**	1.51	0.92 – 2.47	0.10
7-12 vs. 1-2attacks per year	**1.56**	**1.00 – 2.44**	**0.05**	1.35	0.85 – 2.16	0.21
13-54 vs. 1-2 attacks per year	**2.05**	**1.32 – 3.18**	**0.001**	**1.72**	**1.08 – 2.75**	**0.02**
more than 54 vs. 1-2 attacks per year	**3.19**	**1.94 – 5.25**	**<0.001**	**2.30**	**1.36 – 3.92**	**0.002**
Number of migraine days						
3-6 vs. 1-2 days per year	1.21	0.78 – 1.89	0.40	.	.	.
7-12 vs. 1-2 days per year	1.33	0.88 – 2.01	0.17	.	.	.
13-54 vs. 1-2 days per year	**1.51**	**1.04 – 2.22**	**0.03**	.	.	.
> 54 vs. 1-2 days per year	**2.57**	**1.72 – 3.83**	**<0.001**	.	.	.
Use of acute medication						
yes, if attack vs. no	0.81	0.61 – 1.06	0.12	.	.	.
yes, (almost) daily vs. no	1.18	0.85 – 1.65	0.33	.	.	.
Use of a triptan (yes vs. no)	1.10	0.93 – 1.31	0.28	.	.	.
Use of prophylactic medication (yes vs. no)	**1.39**	**1.18 – 1.63**	**<0.001**		0.94 – 1.33	0.23
Allodynia (yes vs. no)	**1.60**	**1.34 – 1.90**	**<0.001**		**1.05 – 1.52**	**0.02**

	Univariate OR	95% CI	p-value	Multivariate OR	95% CI	p-value
General variables						
Gender (female vs. male)	**1.44**	**1.14 – 1.81**	**0.002**	**1.29**	**1.00 – 1.65**	**0.05**
Age (years)	1.01	1.00 – 1.01	0.16	.	.	.
BMI (kg/m^2)	**1.03**	**1.01 – 1.05**	**0.007**	**1.02**	**1.00 – 1.04**	**0.04**
Years of fulltime education	**0.97**	**0.94 – 0.99**	**0.004**	0.98	0.96 – 1.01	0.20
Marital status						
Cohabiting / married vs. single	**0.65**	**0.52 – 0.80**	**<0.001**	**0.66**	**0.53 – 0.82**	**<0.001**
Divorced / widowed vs. single	**1.55**	**1.06 – 2.25**	**0.02**	1.29	0.87 – 1.91	0.20
Smoking packyears	**1.02**	**1.01 – 1.03**	**<0.001**	**1.02**	**1.01 – 1.03**	**<0.001**
Caffeine consumption (ie per day)	0.98	0.95 – 1.00	0.07	.	.	.
Alcohol consumption (ie per week)	**0.96**	**0.94 – 0.98**	**<0.001**	**0.97**	**0.95 – 0.99**	**0.01**
Bad sleeper (yes vs. no)	**2.69**	**2.26 – 3.21**	**<0.001**	**2.34**	**1.95 – 2.81**	**<0.001**
Constant				**0.19**	.	**<0.001**

BMI, body mass index; MO, Migraine without aura; MA, Migraine with aura.
Data are Odds Ratios with 95% confidence intervals and *p*-values. In the univariate analysis all predictors were tested separately. Only the variables with a $p < 0.05$ in the univariate analysis were used as covariates in the multivariate analysis. Values depicted in bold indicate a statistical significant results at the .05 level.

Supplementals

Methods

Participants and procedures

Our study was conducted as a part of the LUMINA project. (13) Participants of the LUMINA project were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders criteria (previously ICHD-II, now ICHD-III beta version).

Our LUMINA study population was invited via the lay press nationwide to enroll via the especially designed, nation-wide LUMINA website. Additionally, patients from our outpatient headache clinic were invited by a letter. This group however, comprises only 3.5% of the total LUMINA population. On the website, patients were asked to fill out a screening questionnaire that has been validated previously. (25) Firstly, if patients fulfilled the screening criteria, they were sent a web-based extended migraine questionnaire, based on the ICHD-II criteria (now ICHD-III beta). (14, 15, 26) This questionnaire was validated by performing a semi-structured telephone interview in 1038 patients who had filled out the extended migraine questionnaire. (13) The specificity of the questionnaire was 0.95. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, acute and prophylactic headache medication use, migraine attack frequency and migraine days, and allodynia (the experience of pain due to stimuli that do normally not provoke pain). Participants without the needed internet skills were able to fill out the questionnaires on paper.

Secondly, a web-based questionnaire on symptoms of (lifetime) depression was submitted to all migraine patients (n=3624). This depression questionnaire consisted of the Hospital Anxiety and Depression Scale (HADS-D), the Centre for Epidemiologic Studies Depression Scale (CES-D) and additional questions on lifetime depression: 'Have you ever used anti-depressants, prescribed for a depression?' and 'Have you ever been diagnosed with a depression'? (14, 15) Lastly, a questionnaire was sent to all participants for details on sleeping disturbances, to be able to adjust for the potential confounding effect of sleep in the relationship between migraine and depression.

The LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. All subjects provided written informed consent prior to the study.

Measures

Lifetime depression diagnoses were based on extended and validated questionnaires, according to the International Classification of Headache Disorders (previously ICHD-II, now ICHD-III beta version). (13, 25, 26) Migraine frequency was measured both as attacks per year and as migraine days per year, using 5 categories: 1-2 attacks/days per year, 3-6 attacks/days per year, 7-12 attacks/days per year, 13-54 attacks/days per year, more than 54 attacks/days per year.

Lifetime depression was measured as a dichotomous variable. We used validated cut-off scores, in combination with a previously used and published algorithm for depression and an additional question on lifetime depression: (lifetime depression = HADS-D ≥ 8 *or* CESD ≥ 16 *or* use of antidepressants (prescribed for a depression) *or* diagnosis depression). (6, 14, 15) Although the HADS-D (depression subscale of the HADS) and CESD questionnaires focused only on the previous two weeks, we aimed to reliably measure lifetime depression by adding questions on antidepressant use and depression diagnoses. Validation of the resulting compound depression diagnoses by performing a telephonic Composite International Diagnostic Interview (CIDI) in a subset of 102 randomly selected patients showed a sensitivity of 78% and a specificity of 64% for DSM-IV classified depression. (27)

To assess cutaneous allodynia, the 12-item Allodynia Symptom Checklist (ASC) was used. (17) The ASC was modified to include dichotomous answer options ('yes' and 'no'), which could be counted up to an allodynia score (range: 0-12). If participants scored two points or more they were classified as having allodynia.

To be able to correct for the potential confounding effect of sleep disorders and possible poor sleep quality, the Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep disturbances during the month before assessment. (16) The PSQI is designed to measure the quality and patterns of sleep in the past month and contains 19 self-rated questions, with a global scoring range of 0 to 21. Higher scores denote a poorer sleep quality. A validated cut-off score of ≥5 was used to separate 'good sleepers' from 'bad sleepers'.

Data analysis

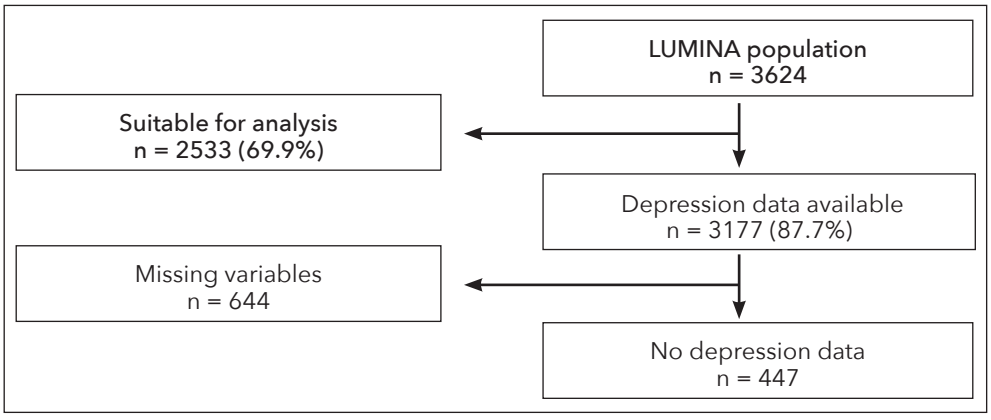
Baseline characteristics were reported as mean (SD) or percentages. Differences in means between groups were tested with independent samples *t*-tests. Differences in proportions were tested by x^2 tests. To determine migraine specific and general determinants of depression, a logistic regression model with lifetime depression as the outcome was developed, using a two-step procedure. First, univariate logistic regression analyses were used to test which potential predictors were associated

with lifetime depression among migraine patients. The following variables were included in the univariate model as migraine specific determinants: age at onset (migraine), migraine subtype, migraine attack frequency, number of migraine days, use of acute medication, use of a triptan, use of prophylactics and allodynia. The following variables were included as general determinants:, gender, age, BMI, educational level, marital status, smoking, caffeine consumption, alcohol consumption, and sleeping disturbances. Second, all predictors with a statistically significant univariate effect were entered in a multivariate logistic regression model. Results were reported as odds ratios with 95% confidence intervals (CI) and corresponding *p*-values.

For all analyses *p*-values of <0.05 were considered to indicate statistical significance. All analyses were performed with SPSS 20.0 (SPSS inc., IBM, USA).

Supplemental Figure 1

Study flow



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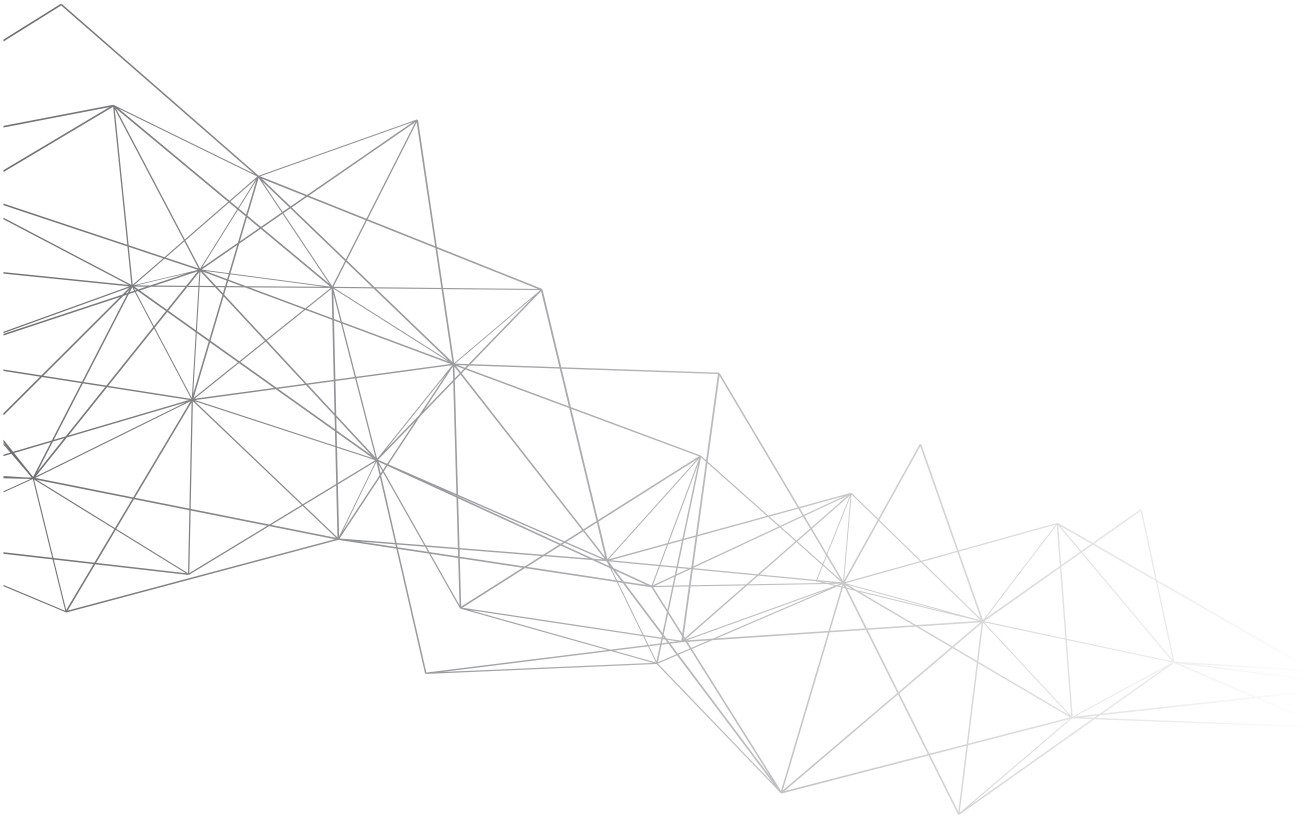
3 CHAPTER

Cutaneous allodynia as a predictor of migraine chronification



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Brain 2013 Nov;136(11):3489-96

Summary

Objectives
Cutaneous allodynia is a common feature accompanying migraine attacks and considered a clinical marker for central sensitization. In a longitudinal study, we wanted to investigate if allodynia in migraine patients is a predictor of increasing frequency of migraine days.

Methods
We included 3,029 well-defined, web-based migraine patients (86% female, mean age 42.8 ± 11.4 years, 61% migraine without aura). Questionnaires on migraine characteristics (including allodynia), depression and demographic factors were applied. The number of migraine days was measured twice. Multivariate regression models were used, with correction for other factors that are involved in the relation between allodynia and the number of migraine attacks or migraine days, with specific focus on depression.

Results
Of all 2,331 eligible migraine patients 1,624 (70%) had allodynia. Lifetime depression was an independent risk factor for allodynia (OR 1.52, 95% CI 1.26-1.84), as well as female gender, low age at onset, and high migraine attack frequency. Analysis of the longitudinal data (in migraineurs with a follow-up period of >6 months) showed that, apart from the known risk factors (low age at onset, high baseline number of migraine days, and depression), allodynia was an independent predictor for increase in number of migraine days over a mean follow-up period of 93 ± 30 weeks (median: 103 weeks, range: 26 – 160 weeks).

Conclusions
Cutaneous allodynia is a risk factor for migraine chronification and may warrant preventive treatment strategies.

Introduction

Cutaneous allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. Migraine patients experience an increased sensitivity of the skin for common daily activities during attacks, such as combing of hair, taking a shower, touching the periorbital skin, shaving, or wearing earrings during migraine attacks. (1, 2) Prevalence estimates of allodynia in migraine patients range from 50 to 80%. (3)

Three distinct forms of allodynia have been described: thermal, static mechanical and dynamic mechanical allodynia. (4) Furthermore, a distinction between cranial and extra-cranial allodynia can be made. Allodynia is a marker for sensitization of nociceptive neurons in the trigeminal nucleus caudalis, which receive convergent input from the dura mater and the peri-orbital skin. (5) During a migraine attack, central sensitization of trigeminal neurons is elicited by persistent pain through activation of meningeal perivascular pain fibers. As a result of this sensitization, non-noxious stimuli of the peri-orbital skin are perceived as painful. Allodynia is a hallmark for success rate of acute headache medication treatment, because the success rate of rendering migraine patients pain-free increases dramatically if medication is taken before the establishment of allodynia and central sensitization. (6) Factors that have been reported to increase the likelihood of having allodynia during migraine attacks are: female gender, high Body Mass Index, headache specific features such as a low age at onset, high frequency of attacks, and comorbidity with depression and anxiety. (1, 2, 7-10) Extensive evidence is available on the comorbidity of migraine with depression, suggesting associations between migraine chronification, depression and medication overuse. (11-13) Because allodynia may be involved in these associations we evaluated the specific relationship between allodynia, depression and total migraine days in a large well-defined, web-based population of migraine patients. (14) This is the first study to assess if allodynia is an independent predictor of (i) migraine chronification (increase of the average number of migraine days per month) and (ii) overuse of acute headache medication.

Methods

Study design and population

Our study was conducted as a part of the LUMINA project, the details of which are reported elsewhere. (15) Participants were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders (ICHD-II) criteria. Our LUMINA study population was recruited via a dedicated, nation-wide website inviting migraineurs to participate

in migraine research. In addition, patients attending our dedicated headache clinic were also invited to participate in this survey. This group, however, comprises only 3.5% of the total LUMINA population. On the website, patients were asked to fill out a screening questionnaire that has been validated previously. (16) Firstly, if patients fulfilled the screening criteria, they were sent a web-based extended migraine questionnaire, based on the ICHD-II criteria. (15, 17) This questionnaire was validated before by performing a semi-structured telephone interview in 1038 patients who had filled out the extended migraine questionnaire. (15) The specificity of the questionnaire was 0.95. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, acute and prophylactic headache medication use, migraine attack frequency and migraine days, and allodynia. Participants without the needed internet skills were able to fill out the questionnaires on paper.

Secondly, all applicable migraine patients (n=3029) were selected for a web-based questionnaire on symptoms of (lifetime) depression. This depression questionnaire consisted of the Hospital Anxiety and Depression Scale (HADS-D), the Centre for Epidemiologic Studies Depression Scale (CES-D) and additional questions on lifetime depression: 'Have you ever used anti-depressants with as indication depression?' and 'Have you ever been diagnosed with a depression'? (18, 19) Only after having filled out the complete depression questionnaire, patients were enrolled in this study.

Thirdly, a questionnaire was sent to a large subset of participants for follow-up details on migraine days (defined as number of migraine headache days per month) and medication use. This allowed us to perform a longitudinal analysis on migraine days. Questions on demographic factors were part of this questionnaire. For the longitudinal analysis on migraine days only participants with a follow-up time of more than 6 months were selected (mean 93 ± 30 weeks, median 103 weeks, range: 26 – 160 weeks).

This LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. All subjects provided written informed consent prior to the study.

Measurements

The extended migraine questionnaire included a 12-item questionnaire on symptoms of cutaneous allodynia (CA). These 12 items were similar to the items of the validated Allodynia Symptom Checklist (ASC). (2) CA was measured as a continuous variable, counting up the scores of all 12 allodynia items for each patient. Herewith "yes" was scored as 1, and "no", "not applicable" and "unknown" were scored as 0. Secondly, based on this continuous scale, we divided CA into

2 categorical classes, in concordance with the ASC. (2) Migraine patients were scored as allodynic when answering "yes" on ≥ 2 CA items. Exploratory cluster analysis was performed to determine whether the 12 items would fit in the known CA subgroups: thermal, static mechanic and dynamic mechanic. The analysis showed the expected clustering of i) resting the head on a pillow, exposure to heat and exposure to cold (thermal allodynia); ii) taking a shower, shaving the face and combing the hair (dynamic mechanic allodynia); iii) wearing contact lenses, wearing glasses, wearing a pony tail, wearing tight clothes, wearing earrings and wearing a necklace (static mechanic allodynia). This confirmed that our questionnaire, which was adapted from the ASC, covered well the construct of CA. Lifetime depression was measured as a dichotomous variable. We used validated cut-off scores, in combination with a previously used and published algorithm for depression and an additional question on lifetime depression: (Lifetime Depression = HADS-D ≥ 8 *OR* CES-D ≥ 16 *OR* use of antidepressants (with indication depression) *OR* diagnosis depression). (18-20) Although the HADS-D (depression subscale of the HADS) and CESD questionnaires focused only on the previous two weeks, we aimed to reliably measure lifetime depression by adding questions on antidepressant use and depression diagnoses. Validation of the depression diagnoses by performing a telephonic Composite International Diagnostic Interview (CIDI) in a subset of 102 randomly selected patients showed a sensitivity of 78% and a specificity of 64%. (21)

At baseline, we measured migraine frequency in two ways: number of migraine attacks and number of migraine days. For both we used five frequency classes, ranging from '1-2 per year' to 'more than 54 per year'. On follow-up we only assessed number of migraine days as continuous variable. We did this for two reasons: 1) definition of CM is arbitrary with cut off values of ≥ 15 headache days and ≥ 8 days migraine, 2) for purposes of statistical power (increased power when using continuous outcome measurement). (22) To assess change in migraine days over the follow-up period, we transformed the frequency classes at baseline into a continuous variable by using for each bracket the mean number of migraine days (i.e. 1-2 days per year -> 1,5 day per year). This was subtracted from the number of migraine days at follow up to obtain a continuous variable for change in number of migraine days per month.

In the follow-up measurement, patients were asked to fill in the number of days on which they had taken acute migraine medications like triptans and painkillers such as simple analgesics or NSAIDs for headache during the past 3 months.

Data analysis and statistics

Baseline characteristics were reported as mean ± standard deviations (SD) or percentages. Differences in means between groups were tested with

independent samples *t*-tests. Differences in proportions were tested using x^2 tests. Multivariate logistic regression models were used to test the association between CA and the following determinants: gender, age, BMI, age at onset of migraine, migraine subtype, the use of prophylactics, migraine attack frequency (categorical) and depression. Supplementary analysis was performed with migraine duration as substitute for age at onset. Results were reported as odds ratios with 95% confidence intervals (CI) and corresponding *p*-values. To test whether the association with migraine attack frequency differed between patients using prophylactics and patients not using prophylactics, the interaction between migraine attack frequency and prophylactics was added. To test whether the associations between CA and depression differed between males and females, the interaction between depression and gender was added.

Determinants of migraine days and number of medication days at follow-up were investigated using univariate and multivariate linear regression models. Because of the expected left-skewed distribution of migraine days, we used a log-transformation of this measure to prevent a skewed distribution of the residuals in the model. Determinants of change in migraine days were investigated using a multivariate linear regression model. For all models the following covariates were included: gender, age, BMI, age at onset of migraine, allodynia, migraine subtype, use of prophylactics, number of migraine days at baseline (categorical), depression and time of follow-up. Supplementary analyses were performed with migraine duration as substitute for age at onset. Results were reported as log-transformed regression coefficients (exp(B)) with 95% CI's, standardized regression coefficients (Beta) and corresponding *p*-values.

For all analyses *p*-values < 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS inc., IBM, USA).

Results

The total study flow is shown in figures 1 and 2. Of 3029 migraine patients who were sent depression questionnaires, 2331 (77.0%) were suitable for primary analysis. Participating (n=2331) versus non-participating (n=698) migraine patients were slightly older (42.8 vs. 39.6 years, $p<0.001$) but did not significantly differ in gender or migraine subtype. A total of 1992 (65.8%) migraine patients were suitable for secondary analysis. Participating (n=1992) versus non-participating (n=1037) patients were again slightly older (43.0 vs. 40.4 years, $p<0.001$) but did not significantly differ in gender or migraine subtype. Table 1 displays all baseline characteristics of the sample suitable for primary analysis, divided by the presence of CA. 1,624 migraine patients (69.7%) suffered from CA during migraine attacks. Of 2331 migraine patients 1423 (61.0%) had migraine without aura, being equally

divided over the groups with and without allodynia. Migraine patients with CA were more often females, had lower age at onset, longer disease duration, higher migraine attack frequency, used more often prophylactic agents, and had more lifetime depression (table 1).

In the first part of the analyses, determinants of allodynia were examined in a multivariate logistic regression analysis (table 2). The following determinants were significantly associated with CA: i) female gender, OR = 2.98 (95% CI 2.33-3.82); ii) lower age at onset, OR = 0.98 per year (95% CI 0.97-0.99); iii) longer migraine duration, OR = 1.02 per year (95% CI 1.01-1.03) iv) higher migraine attack frequency (for individual OR's of all contrasts see table 2); and v) lifetime depression, OR = 1.52 (95% CI 1.26-1.84). Interaction terms migraine attack frequency*prophylactics and lifetime depression*gender were not significant; final analyses were run without interaction terms.

In the follow-up study, associations between CA at baseline and the (log-transformed) number of migraine days at follow-up, with adjustment for several covariates were studied (table 3). The model showed that the following parameters were independent, statistically significant predictors for the number of migraine days at follow-up: i) having CA ($p<0.001$); ii) low age at onset ($p=0.03$); iii) higher migraine duration ($p=0.03$); iv) having migraine without aura ($p=0.008$); v) higher baseline number of migraine days (for individual p-values of all contrasts see table 3); and vi) having lifetime depression ($p<0.001$).

We studied the association between CA at baseline and the change in number of migraine days at follow up (mean duration of follow-up time was 93 ± 30 weeks, median: 103 weeks, range: 26 – 160 weeks). Table 4 presents multivariate linear associations between CA at baseline and the change in migraine days at follow-up, with adjustment for several covariates. The model showed that the following parameters were independent, statistically significant predictors of an increase in migraine days: i) having CA ($p<0.001$); ii) lower age at onset ($p=0.01$); iii) higher migraine duration ($p=0.01$); iv) using prophylactics ($p=0.05$); v) having a depression ($p=0.001$).

The association between CA at baseline and the (log-transformed) number of medication days at follow-up with adjustment for covariates are shown in table 5. The model showed that the following parameters were independent, statistically significant predictors for the number of medication days at follow-up: i) having CA ($p=0.002$); ii) low age at onset, ($p=0.002$); iii) higher migraine duration, ($p=0.002$); iv) using prophylactics, ($p<0.001$); v) higher baseline number of migraine days (for individual p-values for all contrasts see table 5); and vi) having a lifetime depression ($p<0.001$).

Discussion

This is the first longitudinal study demonstrating that cutaneous allodynia is an independent predictor of migraine chronification. Furthermore, we found independent associations of allodynia with several migraine specific determinants. Migraine patients are at increased risk of depression, and shared genetic factors may underlie this association. (20, 23) Comorbid depression is an important predictor of substance dependence and is very common in chronic migraine patients, in particular in those with overuse of acute headache medication. (24, 25) Thus a triad between migraine chronification, depression and medication overuse is suggested. (11-13) In this triad, cutaneous allodynia (CA) plays a role. Our data show that depression and high migraine attack frequency (as a marker of chronification) are independently associated with CA. We hypothesized that recurrent migraine with CA lead to a decreased threshold for subsequent migraine attacks. This statement is supported by the following findings: i) the association between CA and high migraine frequency (measured as migraine attack frequency in the cross-sectional part of the study and measured as migraine days in the longitudinal part of the study); ii) the association between low age at onset and CA; and iii) longer migraine duration is associated with CA in the same magnitude as low age at onset.

The clinical findings from this study correspond with the pathophysiological mechanism of CA. The underlying mechanism of migraine and allodynia is activation of the trigeminovascular neurons. (26) The activation of the trigeminovascular pathway contributes: i) to the headache phase of the migraine attack by sensitization of peripheral trigeminovascular neurons innervating the meninges; ii) to the cephalic allodynia by sensitization of second-order neurons in the spinal trigeminal nucleus (in the medullary dorsal horn) that receive input form the meninges, scalp and facial skin; and iii) to the development of extracephalic allodynia by third-order neurons in the posterior thalamic nuclei which receive input form meninges, facial and body skin. (26) Importantly, once established, sensitization of second order trigeminovascular neurons becomes activity independent, and maintains itself in the absence of sensory input later on. (26) The activity-independent form is the consequence of neurotransmitter and neuromodulator induced activation of multiple intracellular signaling pathways. Activity-independent sensitization develops slowly over several hours and lasts for a prolonged period of time. (27) This has important clinical implications, as late treatment with triptans during an attack is unsuccessful when this independent activity has occurred. (6) Finding out which critical thresholds are exceeded before central sensitization occurs will potentially lead to new medications preventing sensitization. Analyses of differences in brain structure and function, biochemical markers, and genetic profiles between migraine patients with and without CA will further enlighten the basic mechanisms behind CA, migraine chronification and depression.

A possible explanation for the association between CA and migraine frequency may be that repetitive activation of trigeminovascular neurons and consequently repetitive activation of modulatory pain pathways involving the periaqueductal gray may lead to impairment of function or neuronal cell damage in the periaqueductal gray (involved with migraine modulation) or eventually in other areas involved in migraine generation, thus leading to chronification of migraine. (1, 3) Another concept is that of nociception-induced plasticity, which has been demonstrated in animal experiments in the somatosenory cortex, thalamus, trigeminal brainstem neurons, and the cortico-limbic pathway. (28) This model suggests that kindling and related models of neuroplasticity can be used to describe ways in which exposure to a noxious stimulus may, under certain conditions, lead to a sensitized state, and to chronification of pain.

Triptan induced allodynia has been studied in rats, proposing a biological mechanism between increased frequency of headache following triptan use. (29) However, there is no evidence for this phenomenon in humans. In our study, there was no association between triptan use and allodynia (OR 1.07, 95% CI 0.87 – 1.35). The potential role of hormonal use has not been investigated in this study.

Our study did not aim to define subjects as chronic migraineurs or episodic migraineurs. We measured the increase in the number of migraine days, as a marker of chronification. We did this for two reasons: 1) definition of CM is arbitrary with cut off values of ≥ 15 headache days and ≥ 8 days migraine, 2) for purposes of statistical power (increased power when using continuous outcome measurement). (22) We measured the average number of migraine attacks in the baseline measurement, whereas each migraine attack represents one occurrence of allodynia, independent from the duration of the attack.

The strengths of this study are the large sample size, the well-defined migraine status and detailed information on allodynia and depression characteristics. Most importantly, this is the first longitudinal study demonstrating that allodynia is a risk factor for migraine chronification. Possible limitations include the fact that our population might be younger and higher educated than the migraine population in general due to the recruitment of patients via the internet. However, we tried to limit this effect by enabling participants to fill out the questionnaires on paper. A minimum follow up of 6 months was chosen for pragmatic reasons to allow for sufficient statistical power. The median follow-up duration was 103 weeks, indicating that 50% of the study population had a follow up of two years or longer. In addition, one third had a follow up between one and two years, and 11% of subjects had a follow up of 6-12 months.

Although we previously described the LUMINA population as a clinical based cohort, we now feel that it is better to describe it as a 'well-defined, web-based

migraine population'. In our population 70% used triptans. Compared to other countries this may seem high but in the Netherlands and some Scandinavian countries the use of triptans in population based studies is amongst the highest. Furthermore, 87% was previously diagnosed with migraine by a physician, 26% is currently seen by a neurologist, 43% by a GP. The remaining 31% is not seen by a neurologist or a GP.

In conclusion, we found a longitudinal association between cutaneous allodynia and the number of migraine days. Secondly, we confirmed the association between allodynia and depression in the largest well-defined sample of migraine patients so far. In clinical practice, awareness that patients with migraine are at increased risk of chronification, especially when they suffer from a high migraine frequency, allodynia, medication overuse and depression is warranted. Future research should further elucidate these relationships and focus on prevention of allodynia, thereby protecting migraine patients from chronification.

Tables

Table 1. Baseline characteristics of migraine patients who suffer from allodynia (n=1624) versus migraine patients without allodynia (n=707).

	Total population n=2331	Allodynia n=1624	No allodynia n=707	p
Female	1994 (85.5%)	1461 (90.0%)	533 (75.4%)	**<0.001**
Age (years)	42.8 ± 11.4	42.7 ± 11.3	43.3 ± 11.7	0.23
BMI (kg/m^2)	24.5 ± 4.0	24.5 ± 4.1	24.6 ± 4.0	0.54
Age at onset migraine	19.4 ± 10.6	18.7 ± 10.2	20.8 ± 11.2	**<0.001**
Migraine without aura	1423 (61.0%)	991 (61.0%)	432 (61.1%)	0.97
Uses a triptan	1663 (71.3%)	1191 (73.4%)	472 (66.8%)	**0.001**
Uses migraine prophylaxis	875 (37.5%)	650 (40.0%)	225 (31.8%)	**0.001**
Migraine duration (years)	23.5 ± 13.0	23.9 ± 12.6	22.4 ± 13.7	**0.01**
Migraine attack frequency				**<0.001**
(attacks per year)*	98 (4.2%)	50 (3.1%)	48 (6.8%)	
1-2	322 (13.8%)	204 (12.6%)	118 (16.7%)	
3-6	709 (30.4%)	493 (30.4%)	216 (30.6%)	
7-12	991 (42.5%)	713 (43.9%)	276 (39.0%)	
13-54	213 (9.1%)	164 (10.1%)	49 (6.9%)	
more than 54				**<0.001**
Migraine days (per year)*	119 (5.1%)	76 (4.1%)	43 (6.1%)	
1-2	226 (9.7%)	134 (8.3%)	92 (13.0%)	
3-6	401 (17.2%)	269 (16.6%)	132 (18.7%)	
7-12	1060 (45.5%)	745 (45.9%)	315 (44.6%)	
13-54	525 (22.5%)	400 (24.6%)	125 (17.7%)	
more than 54				
Lifetime depression (% yes)	1036 (44.4%)	780 (48.0%)	256 (36.2%)	**<0.001**

Values are the absolute numbers with corresponding % or means ± SD. *P*-values depicted in bold indicate significant differences ($p<0.05$), using independent-samples t-tests and x^2 tests appropriately.
BMI: Body Mass Index

*Migraine attack frequency and number of migraine days per year were self-reported estimates. Few (n=21) patients reported more than one attack on one day, probably because migraine recurrences were counted as new attacks.

Table 2: Logistic associations between allodynia and possible determinants in 2331 participants with migraine.

	Odds Ratio	95% CI	*p*
Gender (F vs. M)	**2.98**	**2.33 - 3.82**	**<0.001**
Age (years)	1.01	1.00 - 1.02	0.17
BMI (kg/m^2)	1.00	0.98 - 1.02	0.84
Age at onset migraine (years)	**0.98**	**0.97 - 0.99**	**<0.001**
Migraine subtype (MA vs. MO)	1.06	0.87 - 1.27	0.61
Prophylactics (yes vs. no)	1.18	0.96 - 1.44	0.11
Migraine duration *	***1.02***	**1.01 - 1.03**	**<0.001**
Migraine frequency (attacks per year)			
3-6 vs. 1-2	**1.64**	**1.03 - 2.63**	**0.04**
7-12 vs. 1-2	**2.12**	**1.37 - 3.29**	**0.001**
13-54 vs. 1-2	**2.24**	**1.45 - 3.47**	**<0.001**
more than 54 vs. 1-2	**2.88**	**1.69 - 4.92**	**<0.001**
Depression (yes vs. no)	**1.52**	**1.26 - 1.84**	**<0.001**

Data are odds ratios (multivariate, adjusted for all mentioned covariates) with 95% confidence intervals and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see methods. Interaction terms migraine frequency*prophylactics and lifetime depression*gender were not significant; the final analyses were run without interaction terms. In the baseline measurement the number of migraine attacks was measured.
F: Female; M: Male; BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

* *Migraine duration* was added in a different model, substituting 'age at onset'

Table 3: Linear associations between baseline migraine characteristics and the natural logarithm of migraine days at follow-up in 1992 persons with migraine (follow-up time > ½ year)

	1. Univariate exp(B)	95% CI	Beta	*p*	2. Multivariate exp(B)	95% CI	Beta	*p*
Allodynia (yes vs. no)	**1.32**	**1.23 - 1.43**	***0.157***	**<0.001**	**1.20**	**1.12 - 1.29**	**0.103**	**<0.001**
Gender (F vs. M)	**1.13**	**1.02 - 1.26**	**0.053**	**0.02**	1.00	0.90 - 1.10	-0.002	0.91
Age (years)	1.00	1.00 - 1.01	0.032	0.15	1.00	1.00 - 1.00	0.020	0.36
BMI (kg/m^2)	1.00	1.00 - 1.01	0.021	0.35	1.00	1.00 - 1.01	0.020	0.31
Age at onset (years)	1.00	0.99 - 1.00	-0.041	0.07	**1.00**	**0.99 - 1.00**	**-0.045**	**0.03**
*Migraine duration**	**1.00**	***1.00 - 1.01***	***0.061***	***0.01***	***1.00***	***1.00 - 1.01***	***0.055***	***0.03***
Migraine subtype (MO vs. MA)	**1.20**	**1.12 - 1.29**	**0.108**	**<0.001**	***1.09***	**1.02 - 1.17**	**0.054**	**0.008**
Prophylactics (yes vs. no)	***1.32***	**1.23 - 1.42**	**0.162**	**<0.001**	1.06	0.99 - 1.14	0.034	0.10
Baseline number of migraine days								
3-6 vs. 1-2 per year	1.14	0.96 - 1.35	0.048	0.14	1.14	0.97 - 1.36	0.050	0.12
7-12 vs. 1-2 per year	**1.57**	**1.34 - 1.84**	**0.208**	**<0.001**	**1.53**	**1.31 - 1.79**	**0.197**	**<0.001**
13-54 vs. 1-2 per year	**2.14**	**1.85 - 2.47**	**0.459**	**<0.001**	**2.03**	**1.75 - 2.34**	**0.426**	**<0.001**
> 54 vs. 1-2 per year	**3.50**	**3.00 - 4.08**	**0.623**	**<0.001**	**3.16**	**2.70 - 3.69**	**0.572**	**<0.001**
Depression (yes vs. no)	**3.94**	**2.55 - 6.07**	**0.138**	**<0.001**	**1.13**	**1.06 - 1.21**	**0.073**	**<0.001**
Follow-up time (years)	**0.86**	**0.80 - 0.92**	**-0.101**	**<0.001**	0.97	0.91 - 1.03	-0.021	0.31
Constant	.	.	.	.	**1.54**	**1.12 - 2.12**	.	**0.008**

Data are log transformed regression coefficients (exp(B)) with 95% confidence intervals, standardized regression coefficients (Beta) and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see Methods. For the follow-up measurement the number of migraine days was measured.
BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

**Migraine duration* was added in a different model, substituting 'age at onset'

Table 4: Linear associations between baseline characteristics and the difference in migraine days between baseline and follow-up in 1992 persons with migraine.

Variable	1. Multivariate B	95% CI	Beta	*p*
Allodynia (yes vs. no)	**11.12**	5.87 - 16.37	**0.07**	**<0.001**
Gender (F vs. M)	-3.06	-10.07 - 3.95	-0.01	0.39
Age (years)	**0.22**	**0.002 - 0.45**	**0.03**	**0.05**
BMI (kg/m^2)	0.46	-0.13 - 1.04	0.02	0.13
Age at onset (years)	**-0.30**	-0.54 - -0.06	**-0.04**	**0.01**
*Migraine duration **	***0.30***	0.06 - 0.54	***0.05***	***0.01***
Migraine diagnosis (MO vs. MA)	3.73	-1.15 - 8.62	0.02	0.13
Prophylactics (yes vs. no)	**5.07**	0.01 - 10.13	**0.03**	**0.05**
Baseline number of migraine days				
3-6 vs. 1-2 per year	-0.24	-12.55 - 12.07	-0.001	0.97
7-12 vs. 1-2 per year	5.36	-6.05 - 16.77	0.03	0.36
13-54 vs. 1-2 per year	-2.17	-12.83 - 8.49	-0.01	0.69
> 54 vs. 1-2 per year	**-137.31**	-148.80 - -125.83	**-0.74**	**<0.001**
Depression (yes vs. no)	**7.99**	3.19 - 12.78	**0.05**	**0.001**
Follow-up time (years)	-2.16	-6.65 - 2.33	-0.02	0.35
Constant	-1.12	-24.51 - 22.28	.	0.93

Data are regression coefficients (B) with 95% confidence intervals, standardized regression coefficients (Beta) and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see Methods. Interaction terms allodynia*prophylactics and allodynia*depression were not significant. Final analyses were run without interaction terms. For the follow-up measurement the number of migraine days was measured.
BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

*Migraine duration was added in a different model, substituting 'age at onset'

Table 5: Linear associations between baseline migraine characteristics and the natural logarithm of number of headache medication use days at follow-up in 1992 persons with migraine (follow-up time > ½ year)

Variable	1. Univariate exp(B)	95% CI	Beta	*p*	2. Multivariate exp(B)	95% CI	Beta	*p*
Allodynia (yes vs. no)	**1.29**	**1.18 - 1.40**	**0.124**	**<0.001**	**1.15**	**1.05 - 1.25**	**0.067**	**0.002**
Gender (F vs. M)	**1.23**	**1.09 - 1.38**	**0.077**	**0.001**	1.11	0.99 - 1.25	0.040	0.07
Age (years)	1.00	1.00 - 1.01	0.020	0.37	1.00	1.00 - 1.01	0.025	0.29
BMI (kg/m^2)	1.01	1.00 - 1.02	0.043	0.06	1.01	1.00 - 1.02	0.041	0.06
Age at onset (years)	**0.99**	**0.99 - 1.00**	**-0.067**	**0.003**	**0.99**	**0.99 - 1.00**	**-0.070**	**0.002**
*Migraine duration **	***1.01***	**1.00 - *1.01***	***0.071***	**0.001**	**1.01**	***1.00 - 1.01***	***0.087***	***0.002***
Migraine diagnosis (MO vs. MA)	**1.10**	**1.02 - 1.20**	**0.052**	**0.02**	1.04	0.96 - 1.13	0.022	0.31
Prophylactics (yes vs. no)	**1.41**	**1.30 - 1.53**	**0.177**	**<0.001**	**1.19**	**1.10 - 1.30**	**0.092**	**<0.001**
Baseline number of migraine days								
3-6 vs. 1-2 per year	1.08	0.76 - 1.14	-0.024	0.48	0.94	0.77 - 1.15	-0.019	0.57
7-12 vs. 1-2 per year	**1.29**	**1.06 - 1.56**	**0.103**	**0.01**	**1.27**	**1.05 - 1.53**	**0.097**	**0.01**
13-54 vs. 1-2 per year	**1.65**	**1.38 - 1.97**	**0.267**	**<0.001**	**1.58**	**1.31 - 1.86**	**0.237**	**<0.001**
> 54 vs. 1-2 per year	**2.33**	**1.93 - 2.80**	**0.371**	**<0.001**	**2.06**	**1.70 - 2.49**	**0.317**	**<0.001**
Depression (yes vs. no)	**1.28**	**1.18 - 1.39**	**0.130**	**<0.001**	**1.16**	**1.07 - 1.25**	**0.078**	**<0.001**
Follow-up time (years)	0.94	0.87 - 1.02	-0.035	0.121	1.03	0.96 - 1.11	0.018	0.42
Constant	.	.	.	.	**1.80**	**1.22 - 2.64**	.	**0.003**

Data are log transformed regression coefficients (exp(B)) with 95% confidence intervals, standardized regression coefficients (Beta) and *p*-values. Values depicted in bold indicate significant findings. For further description of adjustments, see Methods. BMI: Body Mass Index; MO: Migraine without aura; MA: Migraine with aura

*Migraine duration was added in a different model, substituting 'age at onset'

Figures

Figure 1: Study flow primary analysis

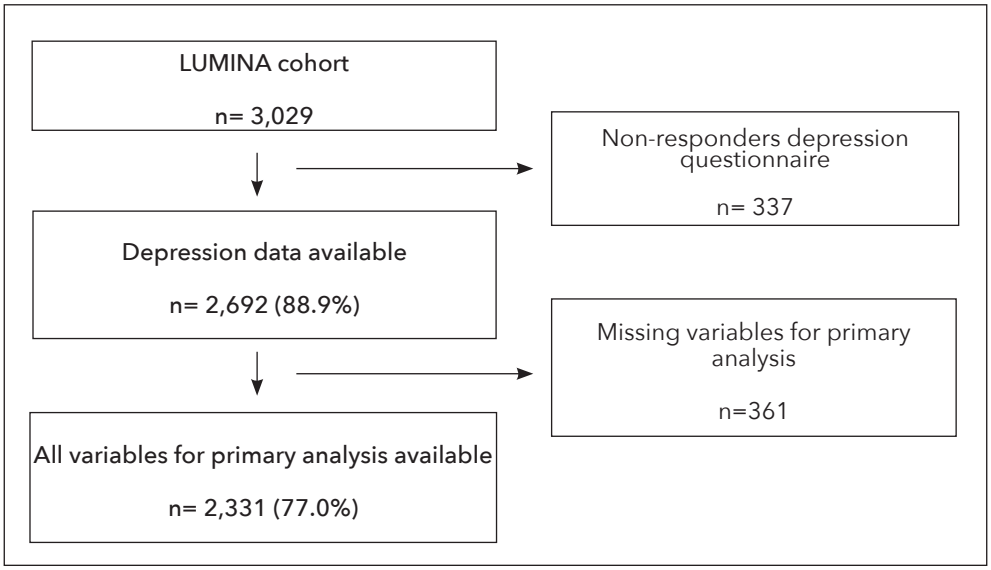
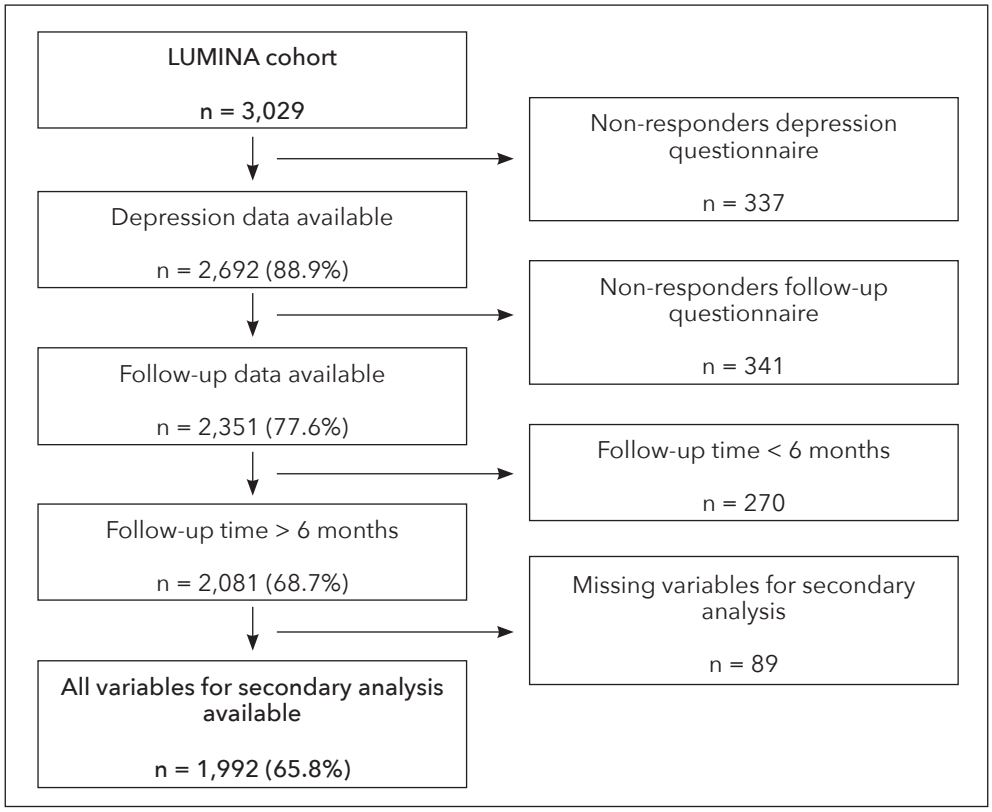


Figure 2: Study flow secondary analyses



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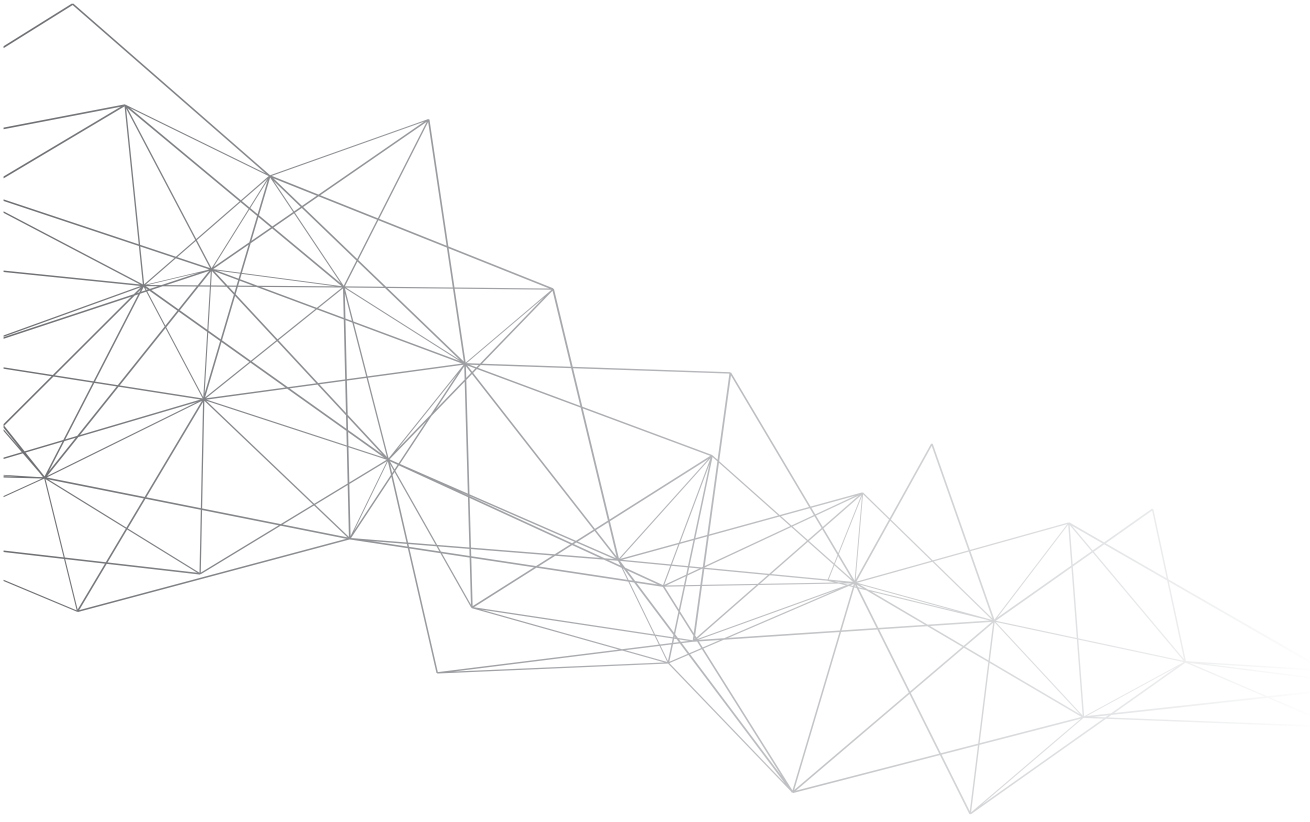
4 CHAPTER

Prevalence of lifetime depression in a large hemiplegic migraine cohort



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Neurology 2016 Nov 29;87(22):2370-74
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Abstract

Objectives
The aim of this study was to determine the prevalence of depression and determinants associated with depression in a large population of Hemiplegic Migraine (HM) patients.

Methods
We conducted a cross-sectional, validated questionnaire study among 89 well-defined HM patients and 235 headache-free controls. The prevalence of lifetime depression, and its relation to migraine characteristics was assessed.

Results
HM patients had increased odds for lifetime depression (OR 3.73, 95% CI 2.18-6.38) compared with controls. Use of acute anti-migraine medication was associated with lifetime depression.

Conclusion
Depression is part of the monogenic hemiplegic migraine phenotype. Further studies are needed to elucidate the pathophysiological role of HM genes in comorbid depression. For now, clinicians should take comorbid depression into consideration when starting prophylactic treatment of HM.

Introduction

Hemiplegic Migraine (HM) is a rare autosomal dominantly inherited migraine subtype, characterized by motor weakness during the aura phase. (1) Three genes (*CACNA1A, ATP1A2* and *SCN1A*) have so far been associated with HM. Involvement of a fourth gene (*PRRT2*) in HM has been proposed, but further evidence is needed to support this claim. (2) HM is divided into two subtypes: Familial Hemiplegic Migraine (FHM), in which at least one first or second degree relative has HM, and Sporadic Hemiplegic Migraine (SHM), in which no first or second degree relative is affected.

The relationship between the common types of migraine and depression has been thoroughly investigated to identify shared aetiological factors. Bidirectional associations have been proven, suggesting shared genetic risk factors. (3, 4) As a monogenic migraine subtype, HM constitutes a more homogeneous model to study migraine pathophysiology than migraine subtypes with a complex genetic background (such as migraine with and without aura). In HM, prevalence of depression has only been studied on a very small scale. (5) It has been hypothesized that the core pathophysiological mechanisms are similar for HM and other types of migraine, with HM representing the severe end of the phenotypic migraine spectrum. If there is a direct relationship between migraine and depression, one could hypothesize that HM, as a more severe migraine phenotype, may be associated with at least an equal prevalence of depression compared to patients with common migraine subtypes. Even more, an increased prevalence of depression in HM may suggest an involvement of ion channels that are mutated in HM in the pathophysiology of (certain subtypes of) depression.

In this study, we studied the prevalence of lifetime depression in HM and the clinical determinants associated with depression in a unique large population of HM patients.

Methods

Participants

HM patients of Dutch origin were recruited from the HM research database of the Leiden University Medical Center including patients who visited our outpatient headache clinic or were interviewed by an experienced research-physician (NP) or neurologist (GMT). Patients were ineligible to participate, when aged <18 years, or when unable to fill in the questionnaires (e.g. due to mental retardation or cognitive decline). Healthy individuals willing to participate had to pass a screening and additional questionnaire online via the research website of the Leiden University

Migraine Neuro-Analysis program (LUMINA). (6) If participants did not report any symptoms of migraine, cluster headache, chronic tension type headache or medication overuse headache, they were considered as 'non-headache' healthy controls. These healthy controls were also sent web-based questionnaires on symptoms of (lifetime) depression and demographic characteristics identical to the questionnaires that were sent to the HM patients.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the medical ethics committee of Leiden University Medical Center and all participants provided informed consent.

Measurements

Symptoms of depression were determined using validated cut-off scores for the Hospital Anxiety and Depression Scale (HADS) and the Center for Epidemiological Studies Depression Scale (CES-D). (7, 8) The HADS questionnaire is been used in clinical studies as it intrinsically corrects for the overlap between symptoms of somatic diseases and depression (e.g. lack of sleep, changes in appetite). Lifetime depression was defined as HADS-D ≥8, or CES-D ≥16, or a (past) depression diagnosed by a physician or (past) use of antidepressants for depression. The combination of current depression questionnaires and lifetime depression questions allowed for analyses on both lifetime and current depression. Current depression was defined as HADS-D ≥8, and current anxiety was defined as HADS-A ≥8. Information about headache frequency and anti-migraine medication use was collected via an additional questionnaire. Healthy controls were sent the same depression questionnaires as the HM patients.

Data analysis

General characteristics were reported as medians (and interquartile range) or percentages. To take into account that some of the HM patients were family-related (originating from 18 separate families) we used a Generalized Estimating Equations (GEE) regression which can correct for this confounding. GEE was applied to study the prevalence of depression corrected for sex, age and the presence of related individuals. GEE regression was also used in the analysis of determinants associated with depression in HM patients. A p-value of <0.05 was considered statistically significant. All analyses were performed with SPSS 20.0 (SPSS inc., IBM, USA).

Results

Study population

We included 89 participants with HM and 235 healthy controls in the study (figure 1). From 132 HM participants in the database, 20 were ineligible because of previously stated unwillingness to participate in further research (n=1) or outdated contact information (n=19), and 23 decided not to participate (19 familial HM, 4 sporadic HM). No differences were observed between participants (n=89) and non-participants (n=43) in age or sex. Differences in headache frequency and medication use between participants and non-participants could not be tested because of missing data in the non-participants. Information on genetic status was missing for three patients, and in ten patients genetic screening was incomplete.

Comparing HM patients with controls

The prevalence of lifetime depression was 51.7% in HM patients compared to 21.3% in controls (table 1). In multivariate analysis, with correction for sex and for the fact that multiple participants belonged to shared families, a strong association with lifetime depression was established (table 2).

Comparing HM patients with and without lifetime depression

HM patients affected by lifetime depression did not differ from patients without lifetime depression in sex, age, HM type, or mutation status (table 3). Migraine attack frequency tended to be higher in the depression group. Use of acute anti-migraine medication (also when analysed separately for analgesics and triptans) was increased in patients with depression. Lastly, current anxiety appeared highly comorbid with depression.

Discussion

Here we studied the prevalence of life time depression in hemiplegic migraine (HM), a rare monogenic subtype of migraine. We found, like in the common types of migraine, a four time increased odds compared with controls.

In a previous study, using the same methodology and questionnaires to diagnose depression, we found a comparable prevalence of 45% for lifetime depression in the common types of migraine. (9) Migraine attacks with typical aura (without weakness) frequently occur in HM patients. (10) Therefore, the comorbidity of HM with depression could, at least partly, be due to presence of common types of migraine in our HM patients. Unfortunately, elaborate migraine characteristics

were not included in the questionnaires used in this study. It would, however, have been difficult to exclude common types of migraine, as the included HM patients may still develop such attacks. We therefore cannot provide exact figures on the prevalence of the common types of migraine in our population.

Depression in common migraine is strongly associated with migraine attack frequency and is a risk factor for chronification. (9) Due to the small number of HM patients we could not show an association with attack frequency. However, use of acute anti-migraine medication (simple analgesics and triptans) was associated with depression. Considering increased use of acute anti-migraine medication as a proxy for migraine severity, the association may not be dependent on attack frequency, but on the severity of accompanying migraine symptoms.

The lifetime prevalence of depression of 21% in the control population corresponds to published prevalence rates for depression (11), indicating that our measurement of lifetime depression appears accurate. HM patients showed increased anxiety which might have contributed to the increased comorbid prevalence of depression. Unravelling the exact role of anxiety should be a topic for future research. A possible limitation of the study is the fact that some of the patients are related to other individuals in the study, because HM families were included. However, it turned out that many different families participated, but each only contributed a few individuals (supplementary table 1). Furthermore, we performed a Generalized Estimating Equations analysis to correct for this possible bias. It should be noted that we did multiple statistical tests but kept the level of significance at 0.05, as is consistent with an exploratory study.

Although recent molecular genetic advances have provided insights into pathophysiological mechanisms of inherited channelopathies such as HM so far no relationship with depression have been shown or investigated. Extensive biophysical characterisation in representative model systems will be required to determine the contribution of different ion channel variants to the common types of migraine in general and the comorbidity with depression. (12)

Because of the cross-sectional design of our study, we can only speculate on the mechanism of action of the comorbidity between HM and depression. Our results may indicate that the genes involved in HM may, directly or indirectly, make patients more susceptible to depression. It would be interesting to study the role of ion channels encoded by *CACNA1A*, *ATP1A2* and *SCN1A* in large cohorts with comorbid depression and common forms of migraine. The high prevalence of depression in our HM cohort also may have clinical implications. HM patients should be screened for depression, and migraine prophylactics such as flunarizine or topiramate which may provoke depressive symptoms should perhaps be prescribed with caution in HM patients with active depression. (13)

Depression is part of the monogenic hemiplegic migraine phenotype. This increased risk of depression in HM patients should receive more attention in clinical practice, especially with regard to the choice of prophylactic anti-migraine medication. In addition, further studies are needed to elucidate the pathophysiological role of HM genes in comorbid migraine and depression.

Figures and tables

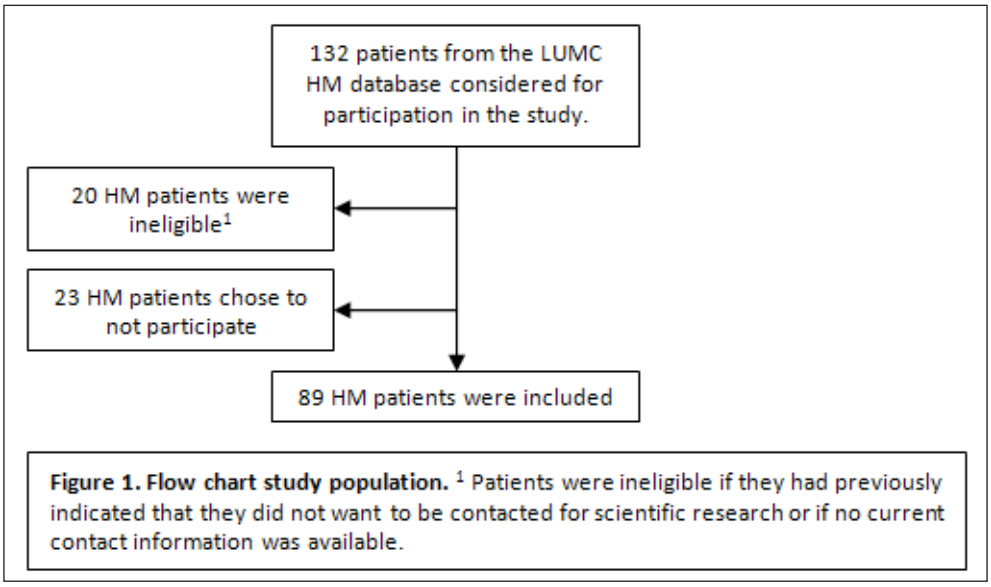

Figure 1. Flow chart study population. [1] Patients were ineligible if they had previously indicated that they did not want to be contacted for scientific research or if no current contact information was available.

Table 1. Sociodemographic and clinical characteristics. Comparison of of HM participants and controls.

	HM participants n=89	Controls n=235
Female sex (n (%))	66 (74.2)	138 (58.7)
Median age in years (IQR) (range)	46 (24) (20-70)	48 (24) (19-77)
HM type FHM (n (%))	65 (73.0)	-
HADS-A median (IQR) (range)	5 (6) (0-17)	3 (3) (0-17)
HADS-D median (IQR) (range)	4 (5) (0-12)	2 (3) (0-16)
CES-D median (IQR) (range)	11 (15) (0-55)	4 (7) (0-41)
Lifetime depression present (n (%))	46 (51.7)	50 (21.3)
Current depression present (n (%))	36 (40.4)	29 (12.3)
Current anxiety present (n (%))	32 (36.0)	24 (10.2)

Current depression: HADS-D ≥8. Current anxiety: HADS-A ≥8.

Table 2: GEE regression with odds of lifetime depression[1]

	Univariate OR	95% CI	P value	Multivariate OR	95% CI	P value
Presence of HM	4.04	2.38-6.88	**<0.001**	3.73	2.18-6.38	**<0.001**
Sex (female v. male)	2.18	1.28-3.70	**0.004**	1.90	1.09-3.30	**0.023**
Age	0.99	0.97-1.01	0.19	-	-	-

[1] Corrected for multiple individuals from the same family.

Table 3: Comparison of HM participants with and without lifetime depression

	HM without lifetime depression n=43	HM with lifetime depression n=46	Univariate OR	95% CI	P value[1]
Sex female (n (%)) (female v. male)	32 (74.4)	34 (73.9)	0.97	0.40-2.37	0.95
Median Age (IQR) (range)	48.0 (25) (22-70)	44.5 (24) (23-69)	1.0	0.95-1.03	0.61
Migraine attack frequency[2,6]			-	-	0.23[5]
Over one year ago (n (%))	15 (38.5)	6 (14.3)	-	-	R
1-2 attacks per year (n (%))	14 (35.9)	17 (40.5)	-	-	-
3-6 attacks per year (n (%))	4 (10.3)	8 (19.0)	-	-	-
7-12 attacks per year (n (%))	3 (7.7)	6 (14.3)	-	-	-
13-54 attacks per year (n (%))	1 (2.6)	4 (9.5)	-	-	-
> 54 per year (n (%))	2 (5.1)	1 (2.4)	-	-	-
Use of acute medication[2,3]			-	-	**0.008**
No (n (%))	23 (59.0)	11 (26.2)	-	-	R
Yes, only when attack starts (n (%))	13 (33.3)	25 (59.5)	4.10	1.69-9.98	**0.002**
Yes, (almost) daily (n (%))	3 (7.7)	6 (14.3)	2.39	0.54-10.7	0.25
Use of standard analgesics[3]					
Yes (n (%)) (R = No)	19 (48.7)	32 (76.2)	3.42	1.55-7.54	**0.002**
Median days per month (IQR)	1.00 (8)	6.50 (10)	1.05	0.98-1.12	0.19
Use of triptans[2,3]					
Yes (n (%)) (R = No)	7 (17.9)	17 (40.5)	3.15	1.32-7.52	**0.01**
Median days per month (IQR)	0.00 (0)	0.00 (2)	1.36	0.89-2.08	0.16
Use of prophylactic medication[2,3]					
Yes (n (%)) (R = No)	14 (35.9)	14 (33.3)	0.88	0.32-2.45	0.81
HM type FHM (n (%)) (R = SHM)	32 (74.4)	33 (71.7)	0.90	0.29-2.81	0.78
Mutation status[4]			-	-	0.53
No mutation found (n (%))	19 (48.7)	22 (59.5)	-	-	R
CACNA1A mutation (n (%))	9 (23.1)	7 (18.9)	-	-	-
ATP1A2 mutation (n (%))	11(28.2)	8 (21.6)	-	-	-
SCN1A mutation (n(%))	0 (0)	0 (0)	-	-	-
Current anxiety present (n (%)) (R = No)	4 (9.3)	28 (60.9)	17.5	5.34-57.4	**< 0.001**

HM type FHM: number of patients that were familial HM cases (and not sporadic).
R, reference category in GEE. [1] Corrected for multiple individuals from the same family. [2] without lifetime depression n=39 and lifetime depression n= 42 (due to missing data). [3] questions specifically stated analgesics for severe headache. [4] no life time depression group n=39 and lifetime depression group n= 37 (due to missing data). [5] GEE regression performed with category 13-54 attacks per year and > 54 per year merged because of small numbers. The Fisher's exact test using all categories gave a p value of 0.13.

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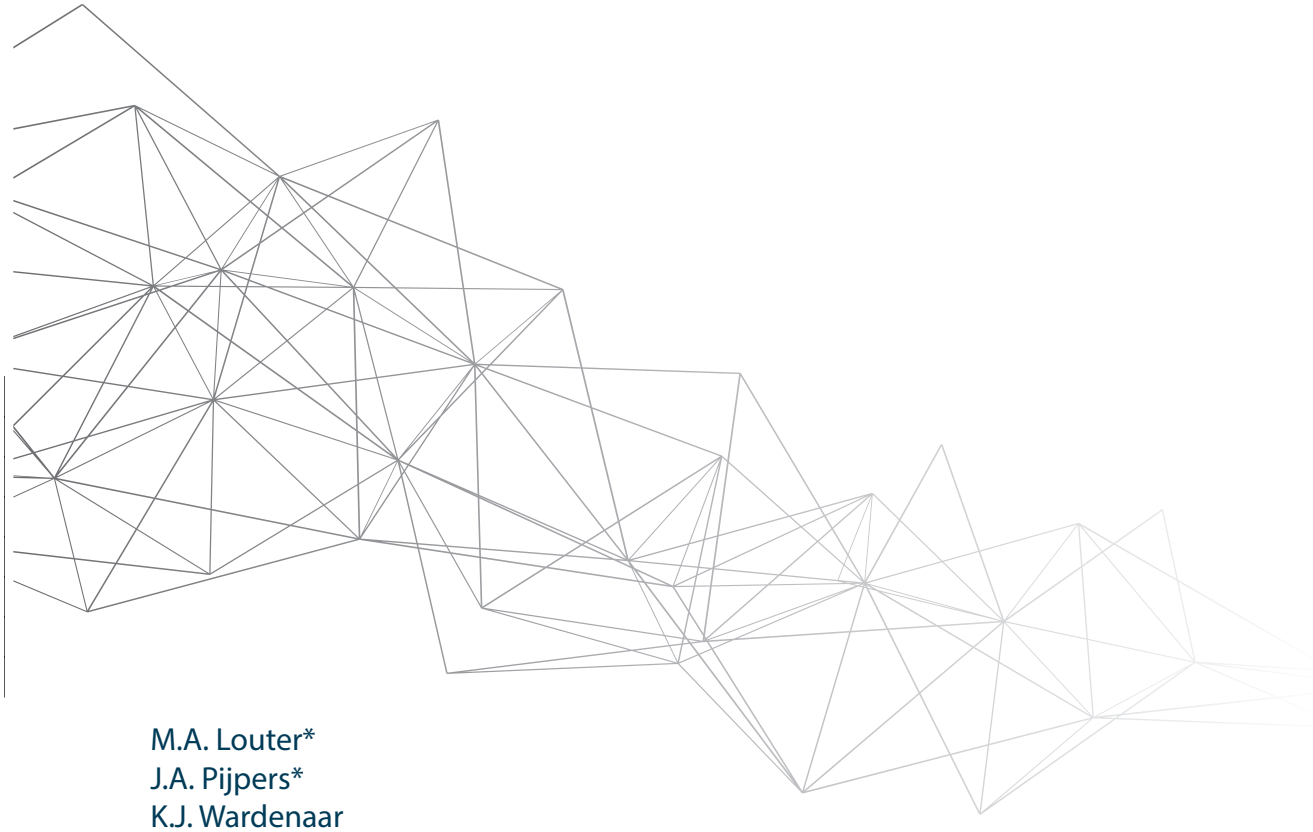
5 CHAPTER

Symptom dimensions of affective disorders in migraine patients



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Journal of Psychosomatic Research 2015 Nov;79(5):458-63
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Abstract

Objective
A strong association has been established between migraine and depression. However, this is the first study to differentiate in a large sample of migraine patients for symptom dimensions of the affective disorder spectrum.

Methods
Migraine patients (n = 3174) from the LUMINA (Leiden University Medical Centre Migraine Neuro-analysis Program) study and patients with current psychopathology (n = 1129), past psychopathology (n = 477), and healthy controls (n = 561) from the NESDA (Netherlands Study of Depression and Anxiety) study, were compared for three symptom dimensions of depression and anxiety. The dimensions –lack of positive affect (depression specific); negative affect (nonspecific); and somatic arousal (anxiety specific)– were assessed by a shortened adaptation of the Mood and Anxiety Symptom Questionnaire (MASQ-D30). Within the migraine group, the association with migraine specific determinants was established. Multivariate regression analyses were conducted.

Results
Migraine patients differed significantly ($p<0.001$) from healthy controls for all three dimensions: Cohen's *d* effect sizes were 0.37 for lack of positive affect, 0.68 for negative affect, and 0.75 for somatic arousal. For the lack of positive affect and negative affect dimensions, migraine patients were predominantly similar to the past psychopathology group. For the somatic arousal dimension, migraine patients scores were more comparable with the current psychopathology group. Migraine specific determinants for high scores on all dimensions were high frequency of attacks and cutaneous allodynia during attacks.

Conclusion
This study shows that affective symptoms in migraine patients are especially associated with the somatic arousal component.

Introduction

Migraine and depression are both rated among the top 20 of most disabling disorders by the World Health Organisation. (1) Previous studies showed that persons with migraine have a fivefold higher risk of first-onset major depression than persons without migraine. In addition, persons with a lifetime depressive disorder have a threefold higher risk of first-onset migraine than persons without a depression diagnosis. (2, 3) This bidirectional association suggests a shared aetiology, which is supported by several studies indicating shared genetic factors in migraine and depression. (4, 5) Besides depression, there is an association between anxiety disorders and migraine as well. (6) The economic impact of migraine is significantly compounded in patients with comorbid psychiatric conditions. (7) Understanding the mechanisms underlying the comorbidity is important in order to gain more insight into the mechanism of both migraine and depression/anxiety and to develop specific preventive treatments.

Previous studies in migraine defined depression using either categorical DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) diagnoses or self-reported questionnaires. However, although DSM-IV categories are of great use in clinical practice, they have arbitrary boundaries, and show much overlap and comorbidity. Moreover, high heterogeneity of symptoms and severity within one diagnostic category is possible. (8) Depression and anxiety severity scales based on self-reported questionnaires also have limitations: two similar scores may indicate different clinical subtypes due to the heterogeneity of the covered range of symptoms as multidimensionality of symptomatology is not taken into account. Consequently, measuring affective disorders with these tools may provide suboptimal phenotyping for clinical and biological (e.g. genetic) research. Thus, in a research setting, it may be more appropriate to study dimensions of depressive and anxiety symptoms in migraine patients as these seem to reflect more homogeneous disease entities.

Several attempts have been made to develop a dimensional model for depression. Within a dimensional approach, a patient is described in terms of scores on a range of coexisting different symptom domains, and not in terms of presence or absence of psychopathology. (9) A well-known model is the tripartite model that accounts for the overlap between depression and anxiety. (10) In this model the broad symptom dimension of negative affect covers symptoms of general psychological distress (e.g. lack of concentration or pessimism). High negative affect has often been indicated as a central clinical feature of both anxiety and depression, accounting for the high rates of comorbidity. (11-14) The lack of positive affect covers anhedonic symptoms, which are mainly specific for depression. The somatic arousal dimension comprises symptoms of hyperarousal which are anxiety specific.

The aim of the present study is to investigate whether migraine patients are characterized by different symptom patterns of depressive and anxiety symptomatology compared with healthy controls, and persons with a current or past depression and/or anxiety disorder. Furthermore, we investigate which migraine specific characteristics are associated with the affective symptom dimensions of the tripartite model.

Methods

Study design and population

Four groups were differentiated for comparison: i) migraine patients, ii) healthy controls without psychopathology and without migraine, iii) persons with 'current psychopathology', a 6-month diagnosis of major depressive disorder, dysthymia or anxiety disorder and without migraine, and iv) persons with 'past psychopathology', a lifetime (but no current) diagnosis of major depressive disorder, dysthymia or anxiety disorder and without migraine.

Migraine patients were collected as a part of the Leiden University Medical Centre Migraine Neuro-analysis Programme (LUMINA) project, a well-defined web-based migraine population, the details of which are reported elsewhere. (15) The LUMINA project is an ongoing cohort study, designed to investigate migraine, its comorbidities, and its long-term course. Participants were Dutch adults aged 18 to 74 years with migraine with or without aura according to the International Classification of Headache Disorders (ICHD-III beta) criteria. (16) The LUMINA study population recruitment is still ongoing, but we included participants recruited between 2008 and 2011. Participants were recruited via nationwide public announcement, advertising in lay press and via the research website, inviting migraine patients to participate in migraine research (see supplementary). In addition, patients attending our dedicated headache clinic were also invited to participate in this survey. This latter group, however, comprises only 3.5% of the total LUMINA population. On the website, patients were asked to fill out a screening questionnaire that has been validated priorly. (17) Firstly, if patients fulfilled the screening criteria, they received a web-based extended migraine questionnaire, based on the ICHD-III beta criteria. (15, 16) This questionnaire was previously validated by a semi-structured telephone interview in 1038 patients who had filled out the extended migraine questionnaire. (15) The specificity of the questionnaire was 0.95. Participants without the needed internet skills could fill out the questionnaires on paper. Secondly, all applicable migraine patients were selected for a web-based questionnaire on symptoms of affective disorders. Patients were enrolled in this study after completion of the affective disorders questionnaire. The response rate to the depression questionnaire was 80%.

Healthy controls and patients with psychopathology were derived from the Netherlands Study of Depression and Anxiety (NESDA), which is an ongoing cohort study designed to investigate the long-term course and consequences of depressive and anxiety disorders. Participants were adults aged 18-65 recruited from community (19%), general practice (54%), and secondary mental health (27%) facilities. A total of 2981 participants, including persons with current or past depressive and/or anxiety disorders and healthy controls, were assessed at baseline between 2004 and 2007. Exclusion criteria for the NESDA study were inability to speak Dutch and a known clinical diagnosis of other psychiatric conditions, such as bipolar disorder, obsessive-compulsive disorder, severe addiction disorder, psychotic disorder or organic psychiatric disorder. A detailed description of the NESDA study design can be found elsewhere. (18) In summary, the baseline assessment was comprised of a face-to-face interview, including a standardized diagnostic psychiatric interview, a medical assessment, computer tasks, written questionnaires, and biological measurement. For the current study, migraine patients, identified through a screening migraine questionnaire largely in accordance to the ICHD-III beta criteria for migraine (described in detail elsewhere), were excluded from the NESDA population. (19)

The LUMINA project was approved by the medical ethics committee of the Leiden University Medical Centre. The NESDA research protocol was approved by the Ethical Committee of participating universities. All respondents provided written informed consent.

Measurements

In the NESDA study, the presence of psychiatric disorders was determined by using the Composite International Diagnostic Interview (CIDI, version 2.1). The CIDI is a standardized psychiatric diagnostic interview that follows the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria to establish diagnoses. The CIDI is a highly reliable and valid instrument for assessing depressive and anxiety disorders and was administered by specially trained research staff. (20) Psychopathology (major depressive disorder, dysthymia, anxiety disorder) status was categorized as follows: current diagnosis (i.e., past 6 months), past diagnosis (i.e., lifetime diagnosis but not in the past 6 months), controls (no lifetime diagnosis). In both the LUMINA and NESDA studies, a 30-item adaptation of the Mood and Anxiety Symptoms Questionnaire (MASQ-D30) was used to measure the tripartite dimensions of depression. On the MASQ-D30, participants were asked to rate to what extent in the past week they had experienced 'feelings, sensations, problems and experiences that people sometimes have' on a 5-point scale, with 1 being 'not at all' and 5 being 'extremely'.

The three 10-item subscales are 'general distress' (lack of positive affect), 'anhedonic depression' (negative affect) and 'anxious arousal' (somatic arousal). The MASQ-D30 scales showed adequate psychometric characteristics and showed good reliability and validity within the NESDA study. (21)

In the LUMINA population, we predefined migraine specific characteristics to be examined: migraine subtype (migraine with or without aura), frequency (migraine days per year), and cutaneous allodynia. Cutaneous allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. A significant part of migraine patients experience an increased sensitivity of the skin for common daily activities during attacks, such as combing of hair, taking a shower, touching the periorbital skin, shaving, or wearing earrings during migraine attacks. Cutaneous allodynia was measured using a validated questionnaire. (22) These migraine specific characteristics are shown to be associated with depression. (23, 24)

Data analysis and statistics

Baseline characteristics were reported as mean ± standard deviations (SD) or percentages. Analysis of covariance (ANCOVA) models were used to test the association between the four different groups and MASQ-D30 symptom profiles, adjusting for gender and age. Post-hoc analyses were run in case of significant findings, performing ANCOVA analysis to test for differences between the migraine group and the three remaining groups. Results were presented as *p*-values with Cohen's *d* (the difference between the means, divided by the pooled standard deviation) as a measure of effect size. Secondary analyses were performed in the migraine population, using multivariate linear regression, testing for the association between general and migraine specific determinants and the three dimensions of affective disorders. Results were presented as *p*-values and *B*-values with 95% confidence intervals. For the primary analyses, we measured three outcomes (the three subscales of the MASQ-D30 questionnaire). Therefore, using Bonferoni correction for multiple testing, *p*-values <0.017 (0.05/3) were considered as statistically significant. Secondary, hypothesis generating analyses, were performed without correction for multiple testing. All analyses were performed using SPSS 20.0 (SPSS Inc., IBM, USA).

Results

Of 2981 NESDA participants, 454 fulfilled the criteria for migraine, and 360 lacked MASQ-D30 data and were excluded for analysis. As a result, the total amounts of participants were 1129 with current psychopathology, 477 with past psychopathology, and 561 healthy controls. A total of 3174 migraine patients with

sufficient data on migraine characteristics and MASQ-D30 data were extracted from the LUMINA database. The total study flow is depicted in figure 1.

Baseline characteristics for the four groups are shown in table 1. Because of differences in gender distribution and age distribution between the four groups ($p < 0.001$), all analyses were corrected for gender and age. As the LUMINA and NESDA cohorts had different assessments of educational level the analyses were not corrected for that socio-demographic characteristic.

In the first analysis (table 2) the four groups (migraine patients, healthy controls, persons with past psychopathology, and persons with current psychopathology) were compared using a multivariate linear regression analysis with adjustment for age and gender. There was a significant difference ($p<0.001$) between the four subgroups for the three symptoms dimensions (lack of positive affect (depression specific); negative affect (nonspecific); and somatic arousal (anxiety specific)). Further pairwise comparison with migraine as reference group is depicted in figure 2. Migraine patients were significantly different ($p<0.001$) for all comparisons to the two psychopathology groups and healthy controls, except for the lack of positive affect compared with the past psychopathology group. In figure 2, differences between the groups are displayed as Cohen's *d*, a measure of effect size, showing that scores on the lack of positive affect (Cohen's $d=0.07$) and negative affect (Cohen's $d=0.30$) dimensions for migraine patients are most closely related to the past psychopathology group. For the somatic arousal subscale scores migraine patients are closer related to current psychopathology (Cohen's $d=0.25$).

Within the group of migraine patients (n=3174), general and migraine specific determinants for the three subscales of affective disorders were analysed using multivariate linear regression (table 3). Age was significantly associated with lack of positive affect and negative affect. Gender was significantly associated with somatic arousal. Migraine frequency and cutaneous allodynia, but not migraine subtype, were associated with all three symptom dimensions of the affective disorder questionnaire.

Discussion

This is the first study differentiating in a large sample of migraine patients for symptom dimensions of depression and anxiety. In comparison with healthy controls and persons with past or current psychopathology, affective disorder symptoms in migraine are specifically associated with higher scores on the dimension somatic arousal which covers symptoms of hyperarousal. Furthermore, the association between MASQ-D30 scores and migraine frequency, which can be considered as an indication of migraine severity, is the strongest on the somatic

arousal subscale. Besides migraine frequency, we show that cutaneous allodynia is associated with higher scores on all three symptom dimensions as well.

Our finding that migraine is particularly associated with the somatic arousal dimension is in accordance with that of several other somatic disorders. Association studies investigating the relationship of depression with chronic diseases like diabetes, obesity, and cardio-vascular disease often show that somatic-affective symptoms of depression rather than cognitive-affective symptoms are related to somatic disease (25-28). Therefore, it is often hypothesized that the association between a somatic disease and depression is primarily through the somatic-affective dimension of depression, the so-called somatic depression (29, 30).

One might also argue that part of the comorbidity between migraine and affective disorders could be due to overlapping symptomatology. Some of the characteristic features of migraine attacks, such as nausea, loss of energy, anhedonia, and sleep disturbances, could lead to misclassification of depressive disorder in migraine patients. However, the association of migraine and depression is still present when questionnaires focusing on the non-somatic aspects of depression are applied, such as the Hospital Anxiety and Depression Scale) (24). Furthermore, the current study clearly shows that the symptom profile of affective disorders in migraine patients differs from healthy controls for all three dimensions of the MASQ-D30 questionnaire, not only for the somatic arousal dimension. Therefore, our study shows that affective disorders in migraine patients cannot be fully explained by somatic depression or overlapping symptomatology. However, our study does suggest an even stronger comorbidity between migraine and symptoms of anxiety, than between migraine and symptoms of depression per se. This is particularly interesting, since most studies hitherto focused on the comorbidity between migraine and depression, whilst the comorbidity of migraine and anxiety is a largely unexplored area. Larger and prospective studies on the comorbidity of migraine and anxiety disorders are necessary to establish the exact magnitude of this comorbidity.

Our study shows that anxiety arousal might be the corresponding component, but the underlying mechanism should be further investigated.

Because the co-occurrence between migraine and affective disorders is not fully explained by mechanisms such as somatic depression or overlapping symptomatology we argue that there is a true comorbidity between migraine and depression. Additionally, previous studies showed a bidirectional relationship, in which the risk for depression is five times increased in migraine patients, and vice versa, the risk for migraine is three times increased in patients with depression (2, 3). This bidirectional association suggests shared underlying mechanisms, presumably shared genetic factors (4, 5). However, further genetic research did

not yet result in clues which exact genes are involved in this association. The current study stresses the importance of a dimensional approach for depression in migraine in a research setting, as the current concept of depression probably is too heterogeneous for detecting genetic variants involved in this association. Using subgroups of migraine patients, based on the tripartite model of depression and anxiety, may be warranted in further genetic research on the comorbidity of migraine and affective disorders.

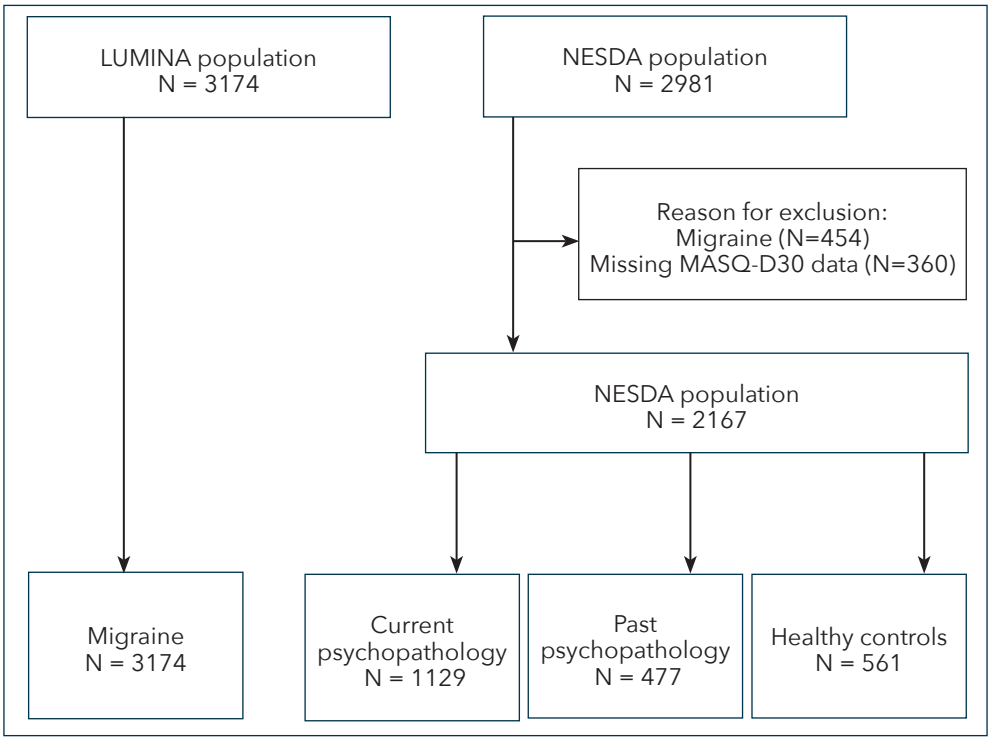
Comorbid depression in migraine is an important predictor of substance dependence and is common in chronic migraine patients, in particular in those with overuse of acute headache medication (31). Thus a triad between migraine chronification, depression and medication overuse has been suggested (32-34). In this triad, cutaneous allodynia plays a role. Allodynia, the perception of pain in response to non-noxious stimuli to the normal skin, is a common feature accompanying migraine attacks. Previously, we showed that depression and high migraine attack frequency (as a marker of chronification) are independently associated with cutaneous allodynia (23). The present study supports this finding and shows that both cutaneous allodynia and high migraine frequency, are associated with all three symptom dimensions of affective disorders, covering general distress as well as anxiety and depression specific symptoms.

The strengths of this study are the large sample size, the well-defined migraine status in the LUMINA population, the well-defined psychopathology status in the NESDA population, and the well-defined healthy control population from NESDA. Most importantly, this is the first study focusing on the different symptom dimensions of affective disorders in migraine patients. Possible limitations include the fact that we compare two different cohorts, in which data was collected in different ways and time periods.

In conclusion, we found that migraine patients, without taking their history of psychopathology into account, differ significantly from healthy controls on all three dimensions of affective disorders. The strongest difference is seen on the somatic-affective component which is suggestive of increased anxiety. Using subgroups of migraine patients, based on the tripartite model of affective disorders, may be warranted in further biological research on the comorbidity of migraine, anxiety and depression.

Figures and tables

Figure 1: Study flow



LUMINA = Leiden University Medical Centre Migraine Neuro-analysis Program
NESDA = Netherlands Study of Depression and Anxiety
MASQ-D30 = Mood and Anxiety Symptoms Questionnaire

Table 1: Descriptive characteristics of the LUMINA and NESDA sample

	LUMINA	NESDA		
	Migraine patients N = 3174	Current psycho-pathology patients N = 1129	Past psycho-pathology patients N = 477	Healthy controls N = 561
Gender (% female)	85.6%	64.0%	68.1%	59.7%
Age (years± SD)	43.2 ± 11.7	42.7 ± 12.6	44.6 ± 13.2	41.5 ± 14.9
NESDA population characteristics				
Current MDD (without anxiety disorder)	.	25.4%	.0%	.0%.
Current anxiety disorder (without MDD)	.	33.1%	.0%	.0%
Current MDD & anxiety disorder	.	41.5%	.0%	.0%
Lifetime MDD (without anxiety disorder)	.	17.4%	45.7%	.0%
Lifetime anxiety disorder (without MDD)	.	16.7%	18.9%	.0%
Lifetime MDD & anxiety disorder	.	65.9%	35.4%	.0%
LUMINA population characteristics				
Migraine with aura	38.2%	.		
Migraine without aura	61.8%	.	.	.
Mean age at onset (years ± SD)	19.3 ± 10.7	.	.	.
			.	.
Migraine attack frequency (migraine days/year)		.		
1-2	5.1%	.	.	.
3-6	10.1%	.	.	.
7-12	16.7%	.	.	.
13-54	46.1%	.	.	.
54+	22.0%	.	.	.
Cutaneous allodynia	70.0%		.	.

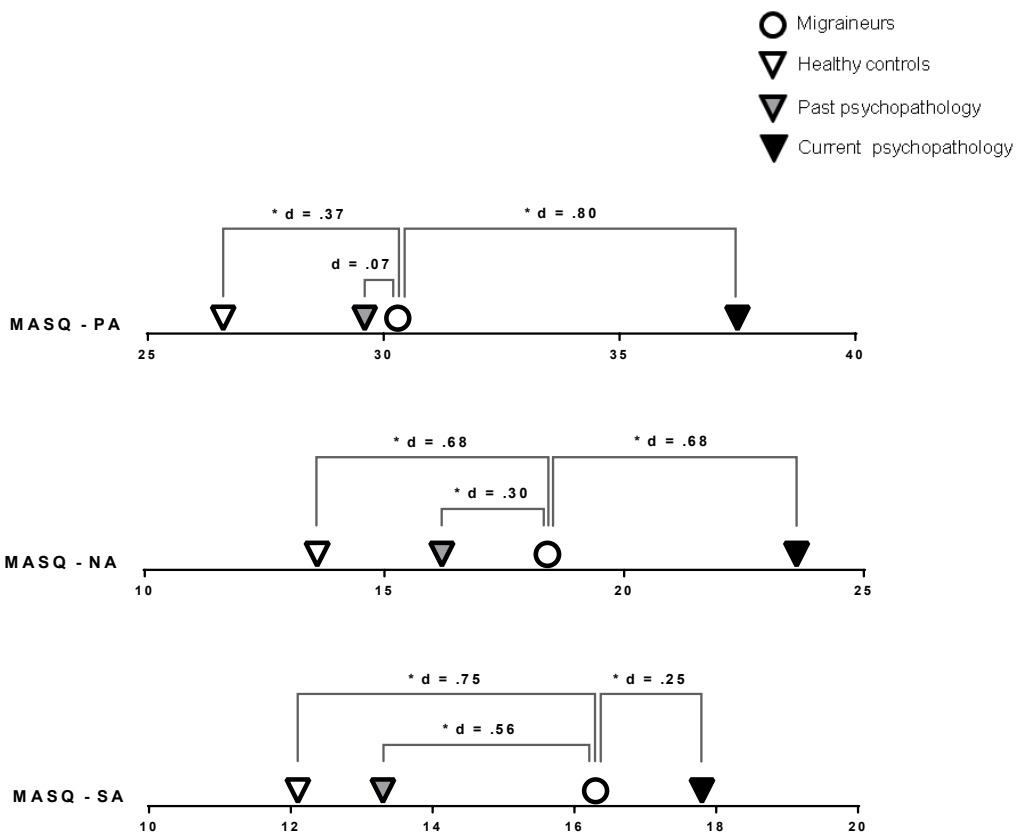
MDD = Major depressive disorder

Table 2: Mean MASQ-D30 scores in the 4 study cohorts, adjusted for age and gender.

	LUMINA	NESDA			
	Migraine patients N = 3174	Current psychopathology patients N = 1129	Past psychopathology patients N = 477	Healthy controls N = 561	P-value (ANCOVA)
MASQ-PA	30.3 ± 9.0	37.5 ± 9.0	29.6 ± 8.9	26.6 ± 9.0	**<0.001**
MASQ-NA	18.4 ± 7.2	23.6 ± 7.1	16.2 ± 7.1	13.6 ± 7.1	**<0.001**
MASQ-SA	16.3 ± 5.4	17.8 ± 5.4	13.3 ± 5.3	12.1 ± 5.4	**<0.001**

MASQ-PA= positive affect subscale
MASQ-NA = negative affect subscale
MASQ-SA = somatic arousal subscale

Figure 2: effect sizes of the difference between migraine patients compared with healthy controls, past psychopathology and current psychopathology.



Cohen's d indicates a small effect if it is around 0.2, a moderate effect if it is around 0.5 and a large effect if it is greater than 0.8. * indicates $p<0.001$

MASQ-PA= positive affect subscale
MASQ-NA = negative affect subscale
MASQ-SA = somatic arousal subscale

Table 3: Determinants of MASQ-D30 subscales in a migraine population (n=3174)

	MASQ-PA		MASQ-NA		MASQ-SA	
	B (95% CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
General determinants						
Age	**0.05 (0.02 – 0.08)**	**<0.001**	**-0.06 (-0.08 - -0.04)**	**<0.001**	0.01 (-0.002 – 0.03)	0.08
Gender (Female vs Male)	0.24 (-0.70 – 1.18)	0.62	0.35 (-0.37 – 1.07)	0.34	**0.83 (0.29 – 1.38)**	**0.003**
Migraine specific determinants						
Migraine subtype (without aura vs with aura)	0.19 (-0.48 – 0.86)	0.58	0.27 (-0.24 – 0.78)	0.30	-0.33 (-0.72 – 0.05)	0.09
Migraine frequency (migraine days/year)						
3-6 vs 1-2	0.04 (-1.69 – 1.78)	0.96	0.41 (-0.92 – 1.73)	0.55	**1.03 (0.03 – 2.03)**	**0.04**
7-12 vs 1-2	1.40 (-0.21 – 3.02)	0.09	0.55 (-0.68 – 1.78)	0.38	**1.49 (0.56 – 2.42)**	**0.002**
13-54 vs 1-2	**1.65 (0.15 – 3.15)**	**0.03**	0.92 (-0.22 – 2.06)	0.11	**1.74 (0.88 – 2.60)**	**<0.001**
54+ vs 1-2	**4.18 (2.60 – 5.75)**	**<0.001**	**2.64 (1.44 – 3.85)**	**<0.001**	**3.30 (2.39 – 4.21)**	**<0.001**
Cutaneous allodynia (yes vs no)	**2.00 (1.29 – 2.72)**	**<0.001**	**1.80 (1.26 – 2.35)**	**<0.001**	**2.04 (1.63 – 2.45)**	**<0.001**

MASQ-PA= positive affect subscale
MASQ-NA = negative affect subscale
MASQ-SA = somatic arousal subscale

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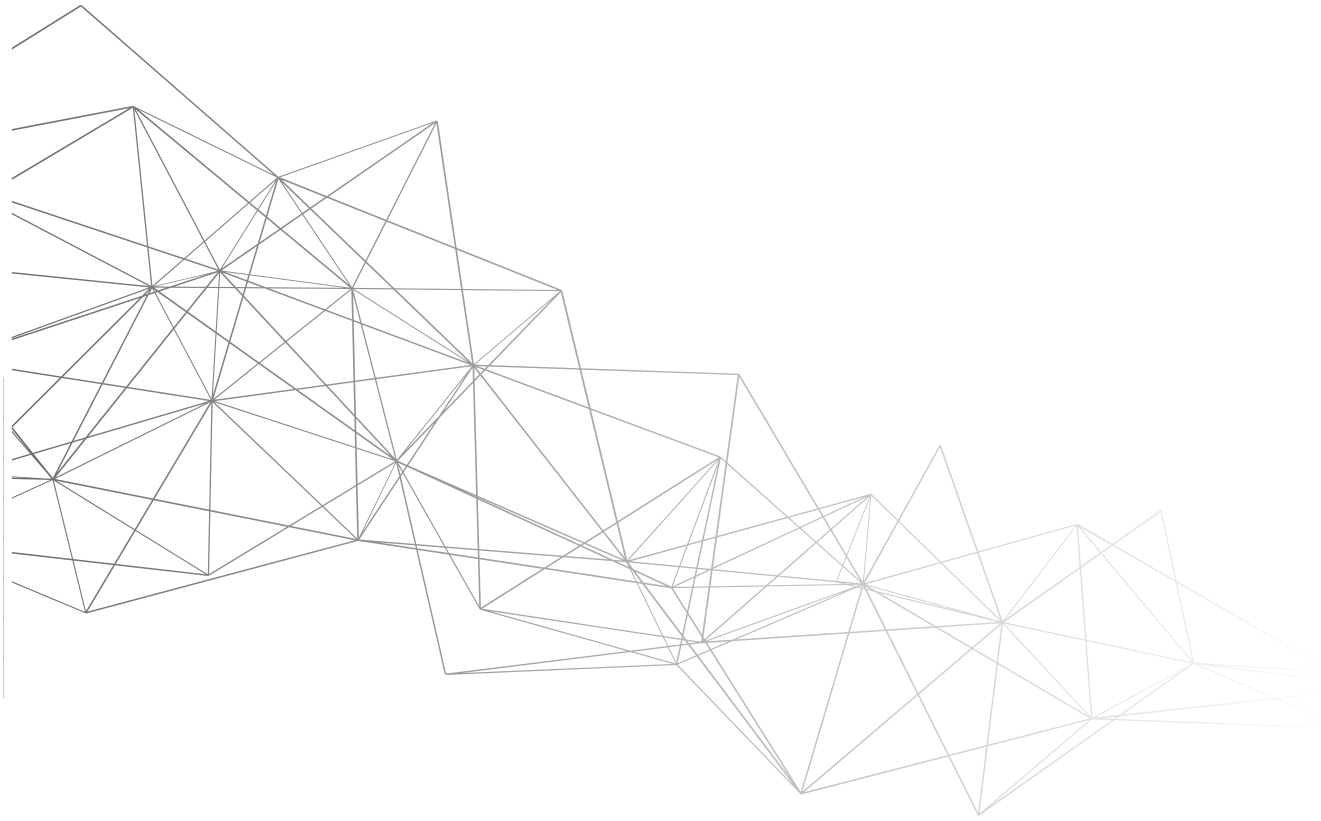
6 CHAPTER

Detoxification in medication-overuse headache, a retrospective controlled follow-up study: Does care by a headache nurse lead to cure?



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Cephalalgia 2016 Feb;36(2):122-30
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Abstract

Aim
To determine whether support of a headache nurse in the treatment of Medication Overuse Headache (MOH) increases successful withdrawal, and to study determinants of response to withdrawal therapy.

Methods
A retrospective controlled follow-up study was performed with 416 MOH patients. All patients were treated with outpatient withdrawal therapy, with two treatment arms: with or without the support of a specialized headache nurse. The outcome measures were: i) successful withdrawal, defined as discontinuation of all headache medication according to the study protocol; and ii) the responder rate, defined as the percentage of patients with ≥ 50% reduction in headache days after successful withdrawal and iii) relative reduction in headache days after successful withdrawal.

Results
Successful withdrawal percentages were significantly higher in the group supported by the headache nurse than in the group without support (73.1% vs. 60.7%; p=0.008), which was confirmed in multivariate analysis (OR 1.73, 95% CI 1.11-2.71, p=0.016). Support by a headache nurse was not associated with response. The underlying headache primary headache diagnosis, determined after withdrawal, was significantly correlated with response.

Conclusion
The support by a headache nurse results in an increased adherence to detoxification.

Introduction

Medication Overuse Headache (MOH) is a highly disabling headache disorder, with a population based prevalence of 0.7 - 1.7% and a preponderance in women. (1-3) The prevalence in headache clinics ranges from 30% in Europe to more than 50% in the USA. (1, 2) MOH is defined in the ICHD-III-beta criteria as headache occurring on half or more days per month as a consequence of regular overuse of acute headache medication (on ≥10 or ≥15 days per month, depending on the type of medication) for more than 3 months. (4) Although consensus about the optimal treatment for MOH is not yet reached, withdrawal of the overused medication is strongly suggested as an essential component in the management of MOH, to reduce headache frequency and improve responsiveness to both acute and prophylactic therapy. (1, 2, 5, 6) Several studies have compared different treatment strategies and some suggested that a simple withdrawal advice is effective. (2, 7-9) In compliance with those studies, acute withdrawal without any concomitant therapy is advised in the national headache guidelines of the Netherlands, and common practice. However, a well-defined selection of patients prone to benefit from simple withdrawal advice has not been established. Withdrawal programmes are increasingly multidisciplinary coordinated, with implementation of patient education and motivational or cognitive behavioural therapy, often realized by a headache nurse. (10-14) Despite of this, the effectiveness of a headache nurse in withdrawal therapy has never been studied in a controlled follow up study. Therefore, the objectives of this study are (i) to determine whether support of a headache nurse in the treatment of MOH increases successful withdrawal, and (ii) to investigate intrinsic patient factors associated with response to withdrawal therapy.

Methods

Study design and population

The current study used a retrospective controlled follow-up approach. Participants were recruited during a period of four years (1 April 2006 - 31 March 2010) among all new patients at the specialized outpatient headache clinic of the Leiden University Medical Centre (LUMC), functioning both as a primary and secondary referral centre with referrals from general practitioners and from colleague neurologists. Inclusion criteria for participants were: (i) age ≥ 18 years; (ii) diagnosis of MOH, defined by the ICHD-II criteria, which are similar to the ICHD-III-b criteria on MOH (supervised by an experienced headache neurologist (MDF, GMT)); and (iii) receiving an advice to withdraw all acute headache medication (triptans, analgesics, combination of both, other medication comprising opioids, ergots or combinations of those medications with analgesics or triptans), prophylactic

medication and caffeine (-containing liquids) during two or three months. (4, 15) Follow up occurred after withdrawal, to determine the final underlying primary headache diagnosis and start further treatment. At the first visit patients were instructed that because of lack of therapeutic options whilst overusing medication, no follow-up visit was offered if they did not succeed to withdraw. Therefore, patients who were lost to follow-up were considered as 'not successfully withdrawn'. Patients were excluded when the final diagnosis was not migraine, tension-type headache or a combination of both. The treatment protocol for patients included between 1 April 2006 and 31 March 2008 (group A) comprised a withdrawal advice by a resident-in-neurology/neurologist. All physicians involved during the total inclusion period, gave the same instructions and maintained the same conditions of withdrawal, according to the standardised protocol at the LUMC. This encompassed an outpatient detoxification with the advice to instantly stop acute headache medication. The duration of the withdrawal period was two months in case of triptan overuse, three months for other types of medication or combinations of medication, and/or caffeine use of ≥ 5 units/day. If patients were on preventive treatment this was tapered off, since the present medication was not effective, and preventive medication regains effectiveness after withdrawal. (6) New preventive treatment was postponed until successful withdrawal was accomplished. Use of escape medication or caffeine (-containing liquids) was not permitted. During the withdrawal period no facility was provided for additional contacts or support. Due to the employment of specialized headache nurse ever since 1 April 2008, patients included between 1 April 2008 and 31 March 2010 (group B), were advised exactly the same withdrawal protocol, but additionally received support during the withdrawal period by a specialized headache nurse. The headache nurse was trained and experienced in headache care, and received additional training on cognitive behavioural therapy. The support by the headache nurse started immediately during the first visit with a 15-30 minutes consultation consisting of a reprise of the withdrawal advice and elaboration on questions of the patient. The consequences for daily professional and social life were discussed and a plan of approach was assembled. Furthermore, strategies for pain management (other than medication treatment) were discussed. Subsequently, the headache nurse contacted all patients two weeks after initiation of the withdrawal period. Depending on the need for support of patients, the headache nurse had additional interaction during the withdrawal period, varying from one to six contacts (median three contacts) by telephone.

Measurement

Two trained examiners obtained medical information from the outpatient clinic administration, patient letters and medical files, using the same methods and criteria to select patients and classify data. The outcome measures were: i) successful withdrawal, defined as a completed medication- and caffeine- free

period; ii) response, defined as ≥ 50% reduction in headache days after successful withdrawal; and iii) relative reduction in headache days after successful withdrawal, since a reduction <50% may be considered clinically relevant as well. (16) The number of headache days at baseline and at follow up were collected to calculate outcomes measures. In case of missing data on response (n=24 patients), patients reporting 'strong improvement', 'nearly no headache' or 'no headache' at follow-up were considered as a ≥ 50% reduction in headache days(responder), and patients reporting 'aggravation', 'no improvement' or 'some to moderate improvement' at follow-up were considered as a < 50% reduction in headache days (non-responder). This subjective classification and the classification based on absolute change in headache days were highly correlated (n=75, r = 0.80, p<0.001). To be able to find associations between potential intrinsic determinants and our outcome measures, we collected data on gender, age, pre-existing headache type, final primary headache after successful withdrawal, number of headache days at baseline, number of medication days at baseline, type of overused medication, and caffeine units per day. Pre-existing headache and final primary headache at follow-up were classified according to ICHD-II/ICHD-III-b criteria as: i) migraine; ii) tension-type headache; and iii) combination of both migraine and tension-type headache. (4, 15) Because of the typical blurred presentation of primary headache at baseline, which is often the case during a period of medication overuse, the pre-existing headache was in some cases impossible to determine (n=85). Therefore, final primary headache diagnosis was used in the analysis. In any case, pre-existing and final headache diagnoses were fairly correlated (n=182, r=0.62, p<0.001). Type of acute medication was classified as: i) triptans, ii) analgesics (paracetamol/acetaminophen and/or NSAIDs), iii) combination of triptans and analgesics, and iv) other medication, comprising opioids, ergots or combinations of those medications with analgesics or triptans. No approval of the local ethics committee was necessary as the study was a retrospective follow-up study and all data were analysed anonymously.

Data analysis and statistics

Baseline characteristics were reported as mean ± SD or absolute numbers with percentages. The number of headache days and medication days at baseline were grouped into daily (30.4 days/month) and non-daily (<30.4 days/month), because of the non-parametric distribution of the data. Differences in means between groups were tested with independent samples *t*-tests and one-way ANOVAs. Differences in proportions were tested using x^2 tests. Patients were stratified into 'successfully withdrawn' and 'not successfully withdrawn', the latter including patient who were lost to follow-up. All patients were included in the analysis of the first outcome (successful withdrawal). Successfully withdrawn patients were included in the analysis of the second and third outcomes (response respectively relative reduction). Univariate logistic regression models were used to test crude

associations. Analyses were rerun as a multivariate model, adjusting for the potential confounding effects of all variables that were tested in the univariate model. For all analyses, two-tailed *p*-values < 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS inc., IBM, USA).

Results

Participants and descriptives

The total study flow is shown in Figure 1. Of 2086 new outpatients, 416 patients were diagnosed with MOH and advised to withdraw medication, 163 without (group A) and 253 with support of a headache nurse (group B). Both groups differed significantly in gender, age, type of medication and daily use of medication (Table 1). Although the absolute number of new headache patients visiting the outpatient headache clinic raised in the last two years of the inclusion period, the proportion of patients who met inclusion criteria remained the same (19.0% in group A and 20.6% in group B). To detect shifts in population composition due to exclusion of patients, lost to follow-up or missing data, differences between the total included population (n=416) and the population that had successfully withdrawn (n=267) were explored. No major differences in composition occurred.

Effectiveness of support by a headache nurse in successful withdrawal in MOH

As shown in Table 2, the percentage of patients with successful withdrawal was significantly higher in the group with support of the headache nurse than the group without support (73.1% vs. 60.7%, p = 0.008, Absolute risk reduction = 12.4%, Number Needed to Treat = 8). As a consequence of the instructions at the first visit (not to come for a second visit if withdrawal was not successful) a larger proportion of patients of group A did not visit for a second time, and were lost to follow up (27.0% vs. 12.3%). However, the results were similar when lost to follow-up patients were analysed as a separate group. The support by a headache nurse was significantly associated with the odds for successful withdrawal in multivariate regression (Odds Ratio [OR] 1.73; 95% CI, 1.11 – 2.71; p=0.016)(Table 3), indicating that the support by a headache nurse enhances successful withdrawal, independent of age, the number of headache days, medication days and type of medication overuse at baseline. Daily use of headache medication and a higher ager were associated with lower odds for successful withdrawal (OR 0.50; 95% CI 0.30 – 0.83; p=0.008 resp. OR 0.98; 95% CI 0.96 – 0.99; p=0.017).

Variables associated with response and relative reduction to withdrawal therapy

The support by a headache nurse was not associated with response (OR: 1.42; 95% CI, 0.78–2.60; p=0.25) (Table 4). The responder rate, defined as the percentage of patients with ≥50% reduction in headache days, was not significantly different in both groups (no support 35.5%, with support 46.0%, p=0.098, Figure 2). The relative reduction in headache frequency, also showed no significant association with support by a headache nurse (B: 1.92; 95% CI, -7.75–11.60; p=0.70) This indicates that there is no effect of the support by the headache nurse on reduction of headache days when successfully withdrawn. The underlying primary headache disorder, that remained after the withdrawal, was significantly associated with relative reduction and response, with a three times increased odds for response in case of migraine when compared to tension type headache (OR 0.31, 95% CI 0.16-0.63; p<0.001), and a nine times increased odds in case of migraine when compared to migraine with tension type headache (OR 0.11; 95% CI 0.05-0.24; p<0.01)(Table 4). This gives a clear indication that the reduction in headache frequency was highest in the migraine group and lowest in the migraine with tension type headache group (Table 4, also depicted in Figure 2). The relative reduction in headache days, was 34.2% ± 38.9 for the total group and was significantly different between persons with migraine, tension type headache, and combined migraine and tension type headache (resp. 56.1% ± 32.1, 26.0% ± 39.6 and 16.0% ± 31.9) (Figure 3). As shown in Table 4, gender and age were not associated with response, nor was the number of headache days or number of medication days at baseline. Furthermore, neither the type of medication that was overused (simple analgesics, triptans, combination of both, or other medication) nor caffeine use was associated with response. These covariates were not associated with relative reduction as well.

Discussion

Being the first controlled follow-up study, this study shows that support of a headache nurse during simple withdrawal therapy increases the chance that a patient with Medication Overuse Headache (MOH) successfully withdraws from overused medication. In this manner, the high drop-out percentage seen in outpatient withdrawal therapy can be reduced. (7) As expected, the reduction in headache days during withdrawal therapy is independent of the support of a headache nurse, as this is more likely to be influenced by intrinsic, patient related factors. The current study shows that patients with migraine as the solely underlying headache disorder have a higher chance at response to withdrawal therapy.

The strengths of this study include the controlled design in a large, representative study population of MOH patients. Although randomisation was not achievable,

the retrospective design is particularly suited to determine the effect of the headache nurse, since we studied the insulated effect of the nurse and there were no ethical issues or risk of blinding failure. We changed our treatment protocol of patients with MOH during our inclusion period by the employment of a headache nurse in April 2008, but no other changes regarding to treatment protocol or referral strategies were introduced. In a prospective controlled study, the recruitment procedure would lead to a highly motivated population, and it would be extremely difficult to blind patients for receiving or not receiving support by a nurse, since patients must be informed about the nature of a study. One group of patients would thus be instructed not to contact the outpatient clinic at any moment, whilst they know about the availability of support to the other group. This will definitely introduce disappointment and other expectations and will bias the results in favour of the intervention. The results of our retrospective study are not influenced by this kind of bias.

There are also some limitations of our study design. Firstly and most importantly, there was no ability to collect data of patients who did not return for a second visit and were, therefore, stated as lost to follow-up. Since patients were explicitly instructed that they were not allowed to revisit in case of unsuccessful withdrawal, and they were informed that no additional treatment would be supplied, we consider the majority of the lost to follow up patients as unsuccessfully withdrawn. We reckon the possibility that lost to follow-up is caused by economic reasons negligible due to the health care system in our country, and the visit could be changed to a 15-30 minute telephonic appointment in case patients definitely could not miss work. Analysis considering lost to follow-up as unsuccessfully withdrawn shows similar result as analysis with lost to follow-up patients as a separate group. Secondly, for the reason of uncertainty about diagnoses before withdrawal, we diagnosed the primary headache disorder only after successful withdrawal, and used this diagnosis. Still, the pre-existing primary headache diagnosis was fairly correlated with final diagnosis. Thirdly, long-term effects of withdrawal were not investigated in this study. Considering the high recidivism rate, it would be interesting in future research to study the long term effect of a headache nurse in patients with MOH after withdrawal. However, the long term effect of a headache nurse on medication overuse was beyond the scope of this study as we specifically wanted to investigate the response to the initial withdrawal period. In many countries patients with MOH are usually unwilling to endure acute withdrawal therapy. Patients in these countries refuse to discontinue their medication on the grounds that the withdrawal symptoms will be too serious or they are afraid to lose their jobs if they will be ill for a longer period because of the withdrawal symptoms. There is usually a drug treatment started with prophylactics although it is recognized that it often fails if the patient continues to overuse acute headache medication. Therefore, it was of our main interest to show the high success rate of acute withdrawal with the support of a headache nurse.

In literature, several withdrawal therapies, sometimes with the support by a headache nurse for MOH patients have been described, but no other study investigated the insulated effect of a headache nurse and uniform endpoints are lacking, hampering direct comparison between studies. (11-14, 16)

Possible explanations and implications

The headache nurse has an unmistakable effect on succeeding withdrawal therapy. Previous studies suggest that patients with (chronic) headache or high headache related disability, are more prone to use unsuitable coping mechanisms (17), score low on pain acceptance (18) and high on catastrophizing scales, and experience a low internal pain control. (19) In patients with migraine, pain control and self-management can be improved by behavioural therapy. (20) We hypothesize that contact with a headache nurse influences the above mentioned factors and thus will help patients to endure the withdrawal period. Patients with tension-type headache and the combination of migraine and tension-type headache seem to benefit less from withdrawal therapy than patients with migraine alone, which may suggest that the pathophysiological mechanism of medication overuse differs between different underlying primary headache syndromes.

Nowadays the view on treatment of MOH shifts from the traditional 'withdrawal therapy first' towards an approach in which prophylactic therapies are started before patients are withdrawn from the overused medication. Randomised trials in chronic migraineurs with topiramate and onabotulinum toxin A, contributed significantly to the debate whether, and when, detoxification is necessary in the treatment of MOH. (21-24) From these trials the question remains, however, whether the effect is clinically relevant. Moreover, the studies lack adequate reporting of plausible blinding failure, and most importantly, in these trials withdrawal was not advocated. To illustrate, the responder rate of migraineurs in our study is comparable to the responder rate in the pooled results of the onabotulinum toxin A trials. We realize that in our population not many patients overuse barbiturates or opiates, which enables acute medication withdrawal, in accordance with our national guidelines. Nevertheless, our study shows that with the support of a headache nurse, comprising only one face-to-face contact and a median of three contacts by telephone, 75% of MOH patients succeed to undergo a highly cost-effective outpatient withdrawal therapy, which is easily implemented in general neurology practice.

Figures and tables

Table 1: Baseline characteristics of patients with medication overuse headache, included for primary analysis, without (group A) and with (group B) support by a headache nurse (n = 416).

	A. No headache nurse (n=163)	B. Headache nurse (n=253)	*p*
Gender, % female	102 (63%)	196 (78%)	**0.001***
Age at time of diagnosis	47.5 ± 10.7	44.4 ± 14.6	**0.014****
Headache days			
% daily	93 (57%)	151 (60%)	0.60*
median (interquartile)	30.4 (17.4-30.4)	30.4 (19.1-30.4)	0.41***
Medication			**0.040***
Analgesics only	83 (51%)	126 (50%)	
Triptans only	20 (12%)	13 (5%)	
Analgesics + triptans	51 (31%)	93 (37%)	
Other medication	9 (6%)	21 (8%)	
Caffeine units/day	5.7 ± 4.2	5.3 ± 3.6	0.55**
Medication days			
% daily	73 (45%)	95 (38%)	0.14*
median (interquartile)	21.7 (15.0-30.4)	20 (14.3-30.4)	0.37***

Values are the absolute numbers with corresponding % or means ± SD. Significant p values are depicted in bold.

* x^2 test
** two-tailed independent samples *t*-test
*** Independent Samples Mann-Whitney U test

Table 2: Successful medication withdrawal, defined as a 2-3 months medication- and caffeine-free period, in patients with MOH following withdrawal therapy without (group A) and with (group B) support by a headache nurse (n = 416).

	A. No headache nurse (n=163)		B. Headache nurse (n=253)		*p*
Medication withdrawal					
Successful	99	(60.7%)	185	(73.1%)	**0.008****
Not successful *	64	(39.3%)	68	(26.9%)	

MOH = Medication Overuse Headache. Values are the absolute numbers with corresponding %.

* Including patients who are lost to follow-up and therefore considered not successfully withdrawn 44 (27.0%) resp. 31 (12.3%).
** x^2 test

Table 3: Odds Ratios (1. univariate; 2. multivariate, adjusted for all mentioned covariates) for successful withdrawal, defined as a 2-3 months medication- and caffeine-free period (n = 416).

Variable	1. Univariate OR [95% CI]	*p*	2. Multivariate OR [95% CI]*	*p*
Gender				
Male	1.00	.	1.00	.
Female	1.09 [0.69 – 1.72]	0.72	0.88 [0.53 – 1.44]	0.60
Age	**0.98 [0.96 – 0.99]**	**0.002**	**0.98 [0.96 – 0.99]**	**0.017**
Headache nurse				
No support	**1.00**	**.**	**1.00**	**.**
Support	**1.76 [1.16 – 2.68]**	**0.008**	**1.73 [1.11 – 2.71]**	**0.016**
Headache days (baseline)				
Non-daily	1.00	.	1.00	.
Daily	0.97 [0.64 – 1.48]	0.90	1.36 [0.82 – 2.25]	0.24
Medication				
Analgesics	1.00	.	1.00	.
Triptans	0.97 [0.44 – 2.16]	0.94	1.22 [0.52 – 2.25]	0.65
Analgesics/triptans	0.87 [0.55 – 1.38]	0.55	0.80 [0.50 – 1.30]	0.37
Other	0.55 [0.25 – 1.20]	0.14	0.68 [0.29 – 1.61]	0.38
Caffeine use *	0.99 [0.94 – 1.05]	0.84	1.00 [0.94 – 1.06]	0.93
Medication days (baseline)				
Non-daily	**1.00**	**.**	**1.00**	**.**
Daily	**0.54 [0.35 – 0.81]**	***0.003***	**0.50 [0.30 – 0.83]**	**0.008**

* n=409, due to missing data

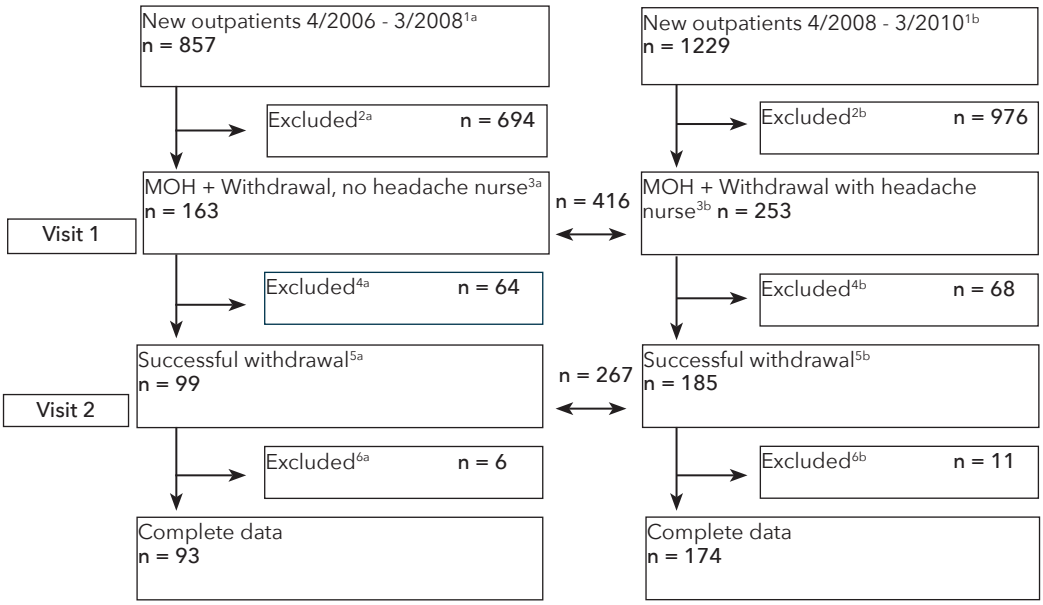
Table 4: Odds Ratios (1. univariate; 2. multivariate, adjusted for all mentioned covariates) for response, defined as a ≥ 50% reduction in headache days, following medication withdrawal (n = 267).

Variable	1. Univariate OR [95% CI]	*p*	2. Multivariate OR [95% CI]	*p*
Gender				
Male	1.00	.	1.00	.
Female	1.43 [0.82 – 2.49]	0.21	1.14 [0.59 – 2.18]	0.70
Age	1.00 [0.98 – 1.02]	0.87	1.00 [0.98 – 1.02]	0.78
Headache nurse				
No support	1.00	.	1.00	.
Support	1.55 [0.92 – 2.60]	0.10	1.42 [0.78 – 2.60]	0.25
Diagnosis				
Migraine	**1.00**	**.**	**1.00**	**.**
TTH	**0.26 [0.14 – 0.46]**	**< 0.001**	**0.31 [0.16 – 0.63]**	**< 0.001**
TTH and migraine	**0.10 [0.05 – 0.22]**	**< 0.001**	**0.11 [0.05 – 0.24]**	**< 0.001**
Headache days (baseline)				
Non-daily	**1.00**	**.**	1.00	.
Daily	**0.47 [0.28 – 0.77]**	**0.003**	0.84 [0.45 – 1.57]	0.58
Medication				
Analgesics	1.00	.	1.00	.
Triptans	1.00 [0.41 – 2.47]	1.00	0.54 [0.18 – 1.61]	0.27
Analgesics / triptans	1.63 [0.95 – 2.78]	0.08	1.24 [0.64 – 2.41]	0.52
Other	0.52 [0.16 – 1.69]	0.28	0.38 [0.11 – 1.33]	0.13
Caffeine use	1.01 [0.94 – 1.08]	0.79	1.02 [0.94 – 1.11]	0.61
Medication days (baseline)				
Non-daily	**1.00**	**.**	1.00	.
Daily	**0.45 [0.27 – 0.77]**	**0.003**	0.63 [0.33 – 1.22]	0.17

TTH: Tension-type headache

Figure 1: Study population flow chart

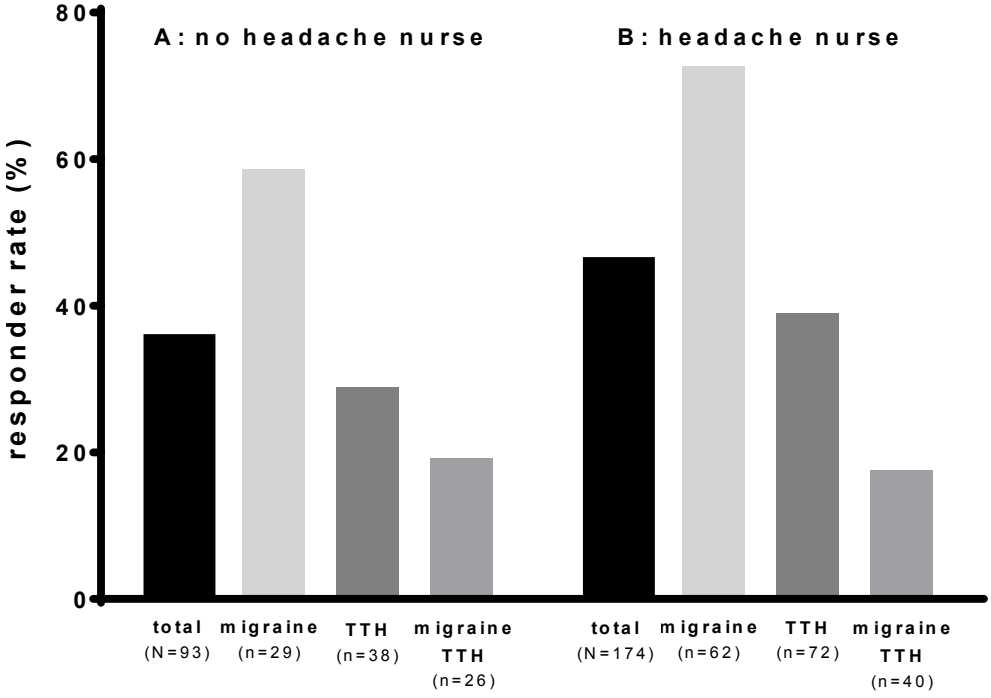
MOH= Medication Overuse Headache
TTH = Tension-Type Headache



[1]*New outpatients:* New patients at the LUMC outpatient headache clinic
[2]*Excluded:* No medication overuse ([2a] n=645 [2b] n=893); Age < 18 years ([2a] n=1 [2b] n=3); No withdrawal therapy ([2a] n=21 [2b] n=35); Withdrawal therapy elsewhere ([2a] n=27 [2b] n=45)
[3]*Diagnosis MOH and advice is to withdraw medication:* [3a] without support by a headache nurse; [3b] with support by a headache nurse
[4]*Excluded:* Patient is not willing to start withdrawal ([4a] n=5 [4b] n=13); Unsuccessful withdrawal ([4a] n=15 [4b] n=24); Lost to follow-up ([4a] n=44 [4b] n=31)
[5]*Successful withdrawal*: 2-3 months medication- and caffeine-free period.
[6]*Excluded:* No migraine, TTH or combination ([6a] n=1 [6b] n=2); Missing data on primary headache, number of headache days or caffeine use ([6a] n=5 [6b] n=9)

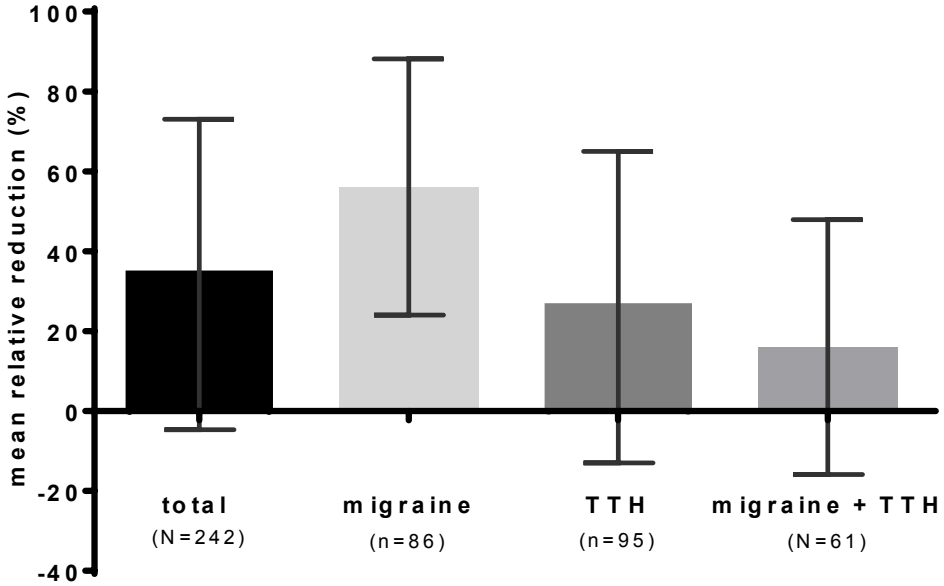
Figure 2: The responder rate, defined as the percentage of patients with a ≥ 50% reduction in headache days, following medication withdrawal with and without support by a headache nurse, subdivided by diagnosis (N = 267).

Responder rate group A (no headache nurse) = 35.5%, responder rate group B (headache nurse) = 46.0% (x^2 test, p = 0.098)



TTH = tension-type headache

Figure 3: The mean relative reduction in headache days of successfully withdrawn patients and subdivided by diagnosis. (n = 242, due to missing data in 25 patients, one-way ANOVA: $p < 0.001$)



Error bars display standard deviations

TTH = Tension-Type Headache

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7
CHAPTER

Candidate gene association study searchingfor genetic factors invloved in migraine chronification

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Cephalalgia 2015 May;35(6):500-7
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Abstract

Introduction
Chronic migraine (CM) is at the severe end of the clinical migraine spectrum, but its genetic background is unknown. Our study searched for evidence that genetic factors are involved in the chronification process.

Methods
We initially selected 144 single nucleotide polymorphisms (SNPs) from 48 candidate genes, which we tested for association in two stages: the first stage encompassed 262 CM patients, the second investigated 226 patients with high-frequency migraine (HFM). Subsequently, SNPs with *p*-values <0.05 were forwarded to the replication stage containing 531 patients with CM or HFM.

Results
Eight SNPs were significantly associated with CM and HFM in the two-stage phase. None survived replication in the third stage.

Discussion
We present the first comprehensive genetic association study for migraine chronification. There were no significant findings. Future studies may benefit from larger, genome-wide data sets or should use other genetic approaches to identify genetic factors involved in migraine chronification.

Introduction

According to the ICHD-III beta classification criteria, a clinical diagnosis of chronic migraine (CM) is made when a patient has 15 or more days with headache per month of which at least eight days have features of migraine headache (or that are described by the patient as migraine and are relieved by migraine-specific medication). (1) CM is at the severe end of the clinical migraine spectrum with a substantially decreased quality of life and increased disability, and is strongly associated with depression, medication overuse, and/or cutaneous allodynia. (2, 3) The reported prevalence of CM is estimated to be around 0.5% to 2.0%. (4, 5) Recently, several genome-wide association studies (GWAS) have identified a dozen susceptibility gene variants and loci for episodic migraine, but until now no studies have focused on identifying genetic risk factors for CM. (6-8)

It is debatable whether it is meaningful to make a strict distinction between episodic and chronic migraine because headache frequency in patients varies from month to month and the thresholds of 15 headache days and eight migraine days, while practical, are arbitrary. (9) Genetic studies in rarer complex disease subtypes, such as CM, are particularly challenging as collecting sufficiently large numbers of well-characterized patients is difficult. Therefore, we decided to also include a group of patients with high-frequency migraine (HFM) that suffer from headache on 10 to 14 days per month, with half or more days meeting the criteria for migraine.

The aim of this study was to obtain evidence for association of variants in genes, acting in pathways possibly implicated in the chronification process of migraine as well as relevant secondary hits from GWA studies, with chronification of migraine. In total, 144 SNPs selected based on literature and previous studies were tested in a three-stage design.

Methods

Participants and design of the genetic association study

Participants included in our study were patients diagnosed with either chronic migraine (CM) or high frequency migraine (HFM), and healthy control individuals. Migraine diagnoses were based on ICHD criteria. A three-stage genetic association study was performed (Figure 1). The discovery stage included 262 CM patients and 2,879 control individuals (all patients came from the CHROMIG study (Spain) or the LUMINA study (The Netherlands)). In this stage, all 144 SNPs (in 48 genes) were tested. The selected markers filled one or more of the following criteria: i) SNPs had been positively associated to migraine and not replicated in other migraine

candidate gene association studies; ii) the corresponding genes had already been implicated in mechanisms relevant to the chronification of migraine; or iii) SNPs were identified as secondary findings in previous migraine GWA studies. In the second stage, all SNPs of the first stage that showed a p-value <0.05 were tested in a further 226 patients diagnosed with HFM vs. the same 2,879 controls (patients again came from Spain or The Netherlands). In the third stage, SNPs with p-values <0.05 in the first two stages were tested for replication in 531 patients with CM or HFM (all patients came from the CHROMIG study, Spain, the LUMINA study, The Netherlands or the HUNT study, Norway). In this stage, 2,491 different control individuals from the three countries were tested.

Gene and SNP selection

We designed a candidate-gene association study focusing on genes that are likely associated with migraine or migraine comorbidities and may act as risk factors for migraine progression. To date, many association studies have been performed to identify genetic factors that confer susceptibility to common migraine (10, 11). We selected genetic variants that had been studied in Caucasian populations, especially those which were only studied once. According to these criteria, a total number of 42 SNPs in 26 genes were selected. These genes were related to: i) ion metabolism transport (*CACNB2* and *KCNB2* (12), *STX1A* (13), *EDN1, EDNRA* and *EDNRB*) (14-16); ii) dopamine (*DBH*) (17) and serotonin metabolism (*HTR2B*) (18); iii) hormonal metabolism (*ESR1*) (19-23); iv) vascular disease (*IL-9, KCNK17, LRP1, MMP12, MTHFD1, NOS3, SCNN1A, TGFB1* and *TNF*) (24-26); v) autonomous nervous system dysfunction (*GNAS1* and *KCNJ1*) (27, 28); vi) stress-response (*BDNF*) (29); vii) and psychiatric disorders related genes, specially associated with anxiety and depression syndrome (*COMT, CRY1, VIPR2*, *RGS2*, *SCN9A* and *WFS1*) (30-33). In addition, we selected candidate genes that encode molecules known to play an important role in migraine pathophysiology but had not been studied before in candidate gene association studies for migraine. In more detail, 37 TagSNPs were selected from CEU Hapmap data using a tagger pairwise tool with r^2>0.8 (Haploview tool) that code for calcitonin-gene related peptide (*CALCA*) and its CGRP-receptor subunits (*CALCRL* and *RAMP1*). The pituitary adenylatecyclase-activating polypeptide (*PACAP*), a neuroexcitatory peptide released to periaqueductal gray matter during neurogenic inflammation, encoded by the *ADCYAP1* gene, and its receptor, encoded by *ADCYAP1R1*, were also investigated with 17 tagSNPs. *ESR1* and *ESR2,* but not *GPR30* estrogen receptors, have been previously studied in relation to migraine, so we included *GPR30*, which encodes a multi-pass membrane protein that binds estrogen. Fractalkine, a chemokine that has been associated with neuroprotection (*CX3CL1* gene), and its receptor (*CX3CR1*) were chosen as candidate genes with six tagSNPs(34). We also focused on two molecules that had previously been reported in a microarray study as probable migraine with aura biomarkers, namely alpha-phodrin (*SPTAN1)* and

hippocalcin-like protein (*HPCAL1)* (35). The former is a cytoskeletal protein of the spectrins family and the latter is a member of neuron-specific calcium binding protein family and is involved in neuronal signaling in the central nervous system. Two tagSNPs in both genes were genotyped. A tagSNP in peripherin (*PRPH*), a cytoskeletal protein localized in neurons of the peripheral nervous system , the expression of which has been associated with *GPR30*, was also studied (36). Finally, eight tagSNPs in a gene involved in circadian rhythm and metabolism regulation (*CLOCK*) were added to the panel. Overall, 77 non-previously studied gene variants in 12 genes were selected.

Finally, 25 polymorphisms extracted from the list of secondary top hits in the analysis of the first migraine GWAS (6) that was carried out by our International Headache Genetics Consortium (IHGC) were included. The list included fifteen intergenic SNPs and 10 variations that were located in gene coding regions (*ACSL5, C4Orf22, DCC, INSIG2, OPCML, OR9Q1, RELN, SMYD3, STAMBPL1* and *TRPM8*). In summary, 119 SNPs were genotyped in 38 candidate genes, as well as 25 additional SNPs from GWAS data.

Cohorts

Spanish CM and HFM patients were recruited at the Headache Unit of the Vall d'Hebron University Hospital (Barcelona). Patients with CM were diagnosed by a clinical interview and physical examination by a headache specialized neurologist, according to the ICHD-III beta classification. (1) HFM was diagnosed when patients suffered from headache on 10 to 14 days per month, from which half or more days fulfilled the criteria for migraine. Healthy controls were blood donors. Exclusion criteria for this control population were migraine, a positive family history for migraine and any type of severe or recurrent headache in first-degree relatives.

Dutch CM and HFM patients were available from the well-defined, web-based LUMINA population (Leiden University Migraine Neuro Analysis program) (www.lumc.nl/hoofdpijn). Details of this study are described elsewhere. (37) Migraine was diagnosed according to the ICHD-III beta criteria. (1) CM was diagnosed when patients suffered from migraine and indicated that they experienced severe headache on 15 or more days per month. HFM was diagnosed when patients suffered from migraine and indicated that they experienced severe headache on 10-14 days per month. Control samples for the discovery phase were part of the population-based Rotterdam Study. (38) Control samples for the replication phase were collected via a Dutch blood bank.

The Norwegian patients were recruited from the population-based HUNT-2 (1995-97) and HUNT-3 (2006-08) studies, in which all inhabitants (age ≥20 years) of the Nord-Trøndelag county of Norway were invited to participate. (39, 40) Migraine

was diagnosed based on a modified version of the most recent ICHD criteria at the time of each study, and this questionnaire-based headache classification has been validated by interview diagnoses. (39, 40) Migraineurs reporting headache on 7 or more days per month were classified as HFM, and those reporting headache on 15 or more days per month were classified as CM. Controls were recruited from the same two studies, and participants fulfilling criteria for migraine were excluded from the control population.

Genotyping

Spanish cohorts

Venous blood samples of subjects that fulfilled inclusion criteria were collected in EDTA tubes and conserved at -80ºC until DNA extraction. DNA was extracted from blood lymphocytes at the *Centre de RegulacióGenòmica* (CRG, Barcelona, Spain) with the Chemagen® extraction kit (Perkin Elmer, Germany) and at the *Departament de Genètica* (Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain) by a standard salting out procedure. (41) Quantity and quality of DNA samples were controlled spectrophotometrically with NanoDrop ND1000 (Nanodrop, Wilmington, DE, USA).Genotyping of SNPs in the discovery sample set was performed with VeracodeGoldenGate technology (Illumina, CRG, Barcelona, Spain). For the replication phase, an additional 70 CM and HFM patients and 394 controls were recruited under the same criteria and procedures that were used for the discovery sample. Blood sampling and DNA extraction were performed in the same way. Genotyping was performed with a Taqman® SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA) using the 7900HT Sequence Detection System (SDS, Applied Biosystems) in 384-well plates and following the manufacturer's protocol.

Dutch cohort

Peripheral blood samples were collected in EDTA tubes. Subsequently, DNA was isolated using a standard salting out method. Genotyping of the samples had been previously performed as part of two genome-wide association studies for common migraine. (6, 7) Genotyping of the replication cohort was performed with a Taqman® SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA). A standard PCR reaction was carried out using the TaqMan Universal PCR Master Mix. Genotyping clusters were analysed using the Lightcycler LC-480 machine and LightCycler®480 1.5.0 software, version 1.5.0.39 (Roche Applied Science, Penzberg, Upper Bavaria, Germany) in 384-well plates following the manufacturer's protocol.

Norwegian cohorts

DNA from all Norwegian samples was extracted from blood using two kits: Autopure Kit (Qiagen, Duesseldorf, Germany) and Masterpure Kit (Medinor, Oslo, Norway), both based on a salting out procedure.Quantity and quality of DNA samples were controlled regularly by monitoring every eighth sample spectrophotometrically with NanoDrop ND1000 and ND8000 (Nanodrop). Genotyping of the replication cohort was performed with a Taqman® SNP Genotyping Assay (Applied Biosystems). A standard PCR reaction was carried out using the TaqMan Universal PCR Master Mix. Genotyping clusters were analyzed using the Lightcycler LC-480 machine and LightCycler®480 1.5.0 software, version 1.5.0.39 (Roche Applied Science, Penzberg, Germany) in 384-well plates following the manufacturer's protocol. A part of the Norwegian sample for replication had previously been genotyped with the Illumina 670k platform, as part of a genome-wide association study of migraine (8), and was used for *in silico* replication for the current study. We used the Illuminus calling algorithm, with the following filters for genotyped SNPs: minimum call rate per SNP and per individual (0.97), Hardy-Weinberg equilibrium p-value higher than 1.00E-06 and MAF>0.01. For those SNPs that were not directly genotyped, imputation was performed with Impute v.2.1.2 in a standardized pipeline, using HapMap2 data from CEU population as the reference panel.

Statistical analyses

We performed power calculations for all three steps of our design, assuming an additive model, an effect allele frequency of 0.20 and effect sizes ranging from 1.2-1.4. We added the outcome of these power calculations to the supplementary information. Statistical analyses were performed using PLINK v1.07 (42) and SNPTEST v2.2.0. (43) GTOOL v0.7.5 was used to combine different cohorts. First, the entire panel of SNPs was tested for the Hardy-Weinberg equilibrium (HWE) for each cohort considering $p<0.05$ as the threshold. Then, both allele and genotype frequencies were compared between cases and controls, considering additive, genotypic (co-dominance), dominant and recessive models. Subsequently, a meta-analysis was performed using GWAMA v2.1. For all analyses, the threshold for statistical significance was defined as a p-value below 0.05. Approval was obtained from local medical ethics committees and written informed consent was obtained from all participants.

Results

For this study, 144 SNPs in genes already implicated in migraine or that had surfaced as interesting secondary hits in GWA studies (see Supplementary Data) were used in a three-stage association design (Figure 2). In the first stage, SNPs were tested in 262 patients with CM vs. 2,879 control individuals. Nominal significant associations (p-value <0.05) were obtained for 30 SNPs (see also Supplemental Table 2). These 30 SNPs were taken forward to the second stage with 226 patients with HFM and the same control data set, where eight SNPs showed a nominally significant association; rs5742912 (in *SCNN1A*), rs3792603 (in *CLOCK*), rs2956 (in *CALCA*), rs858745 (in *CALCRL*), rs302680 (in *RAMP1*), rs2267730 and rs2299908 (in *ADCYAP1R1*), and rs217693 which is an intergenic SNP. These eight SNPs were taken forward to the replication stage and were genotyped in three replication cohorts from Spain (70 patients with CM or HFM and 394 controls), The Netherlands (210 patients with CM or HFM and 896 controls), and Norway (162 patients with CM or HFM and 495 controls).The availability of GWA data allowed testing of seven of the eight SNPs in 89 additional Norwegian patients with CM or HFM and 706 controls. Subsequently, a combined meta-analysis of the association results from these replication cohorts with 531 patients with CM or HFM and 2,491 controls was performed but showed no statistically significant associations.

Discussion

Here we present the first comprehensive genetic association study in chronic and high-frequent migraineurs testing 144 SNPs from 48 genes in 1,019 patients with chronic or high frequency migraine, without significant associations. Patient numbers in each cohort were relatively small, largely because of the rarity of chronic migraine, which makes it difficult to collect large enough patient samples. As (chronic) migraine is a complex genetic disorder, it is likely that multiple genetic variants, each with relatively small effect, contribute to disease susceptibility, suggesting that large numbers of patients and controls are needed to reach sufficient power to detect a genetic association. We attempted to address this challenge in two ways. First, to increase overall numbers, we decided not t only to include chronic migraine patients, but also high frequency migraineurs, as we consider the cut off values for a diagnosis of chronic migraine rather arbitrary and instead favour the idea that migraine chronification has a broader spectrum with respect to the number of headache days.(9) Second, by selecting only candidate genes (and SNPs therein) we reduced the massive correction for multiple testing that is needed for unbiased genome wide association approaches. Considering the negative results, our approach may still have had insufficient statistical power or we may have selected SNPs irrelevant to migraine chronification. As even large international collaborations, such as the International Headache Genetics

Consortium (IHGC), have difficulties to collect large enough cohorts of well-characterized patients with chronic and high frequency migraine, we feel that studies like ours will probably remain underpowered in the immediate future. We are working in the International Headache Genetic Consortium on unifying the criteria to select patients so that future studies will be able to count on larger and better phenotyped cohorts.

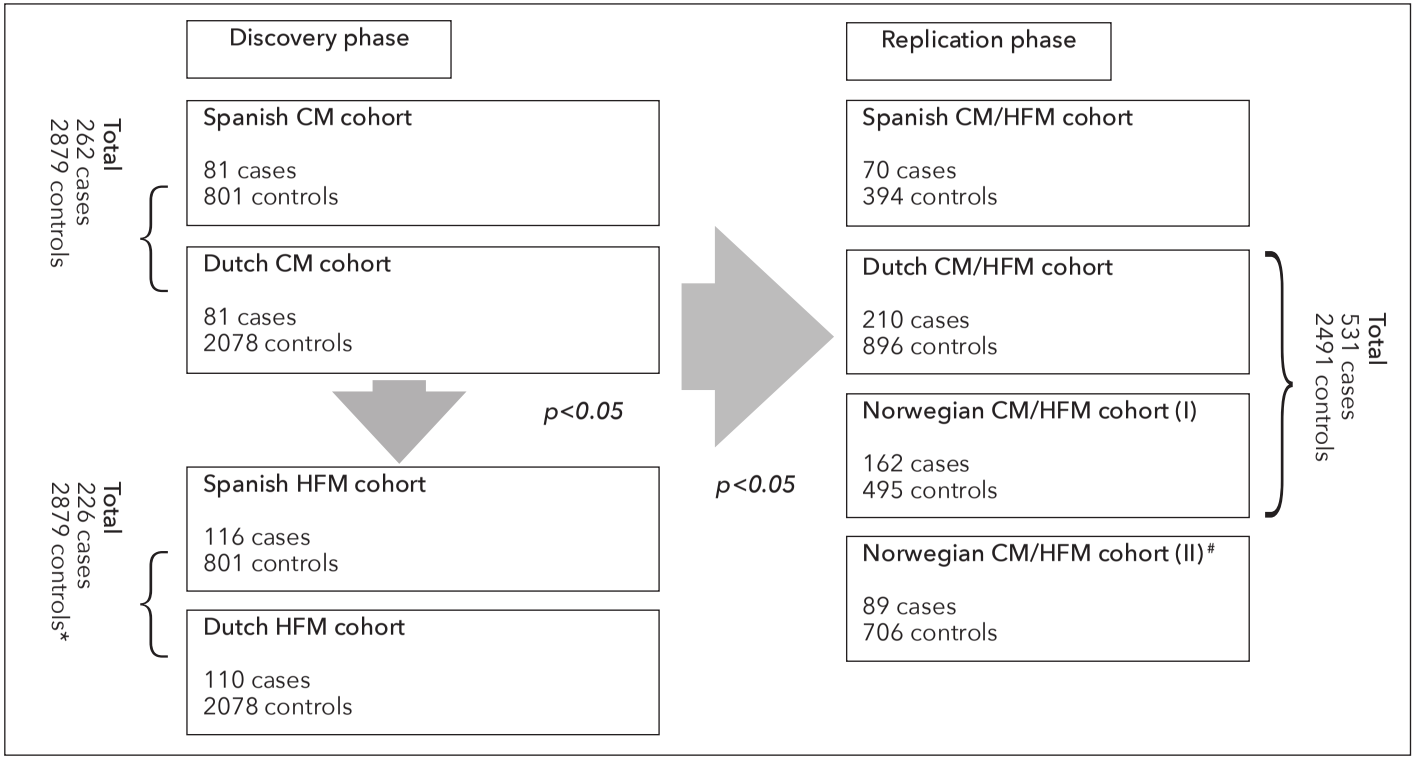
Chronic migraine is severely disabling and difficult to manage, as affected patients experience substantially more-frequent headaches, comorbid pain and affective disorders, and fewer pain-free intervals, than do those with episodic migraine. (4) Furthermore, the relationship of chronic migraine with cutaneous allodynia has been investigated, indicating that cutaneous allodynia is a clear risk factor for migraine chronification. (3) Different models have been proposed to explain this relationship. Further investigations in the basic mechanisms of cutaneous allodynia, and its relationship with migraine chronification, could lead to new potential genes which should be studied in future designs.

Clinical and genetic studies have shown that migraine is a multifactorial disorder with complex interaction between multiple predisposing genetic and modulating non-genetic factors. GWAS have identified 13 gene variants pointing, among others, at pathways involved in glutamatergic neurotransmission and synaptic function. (8) Translating results from GWAS to pathophysiological mechanisms, however, remains one of the biggest challenges in molecular biology as gene effect sizes are small and their interactions are complex.

We suggest that for future designs it is relevant to consider the outcome of withdrawal from medication, as the vast majority of CM patients is (over)using acute headache medication. In this study, we did not have sufficient data to include this aspect in the analysis. However, future studies would benefit from subdividing chronic migraineurs into patients responsive to withdrawal therapy and returning to episodic migraine after withdrawal of their medication, and patients in which such withdrawal has no or less effect on attack frequency. Lastly, although the problem of statistical power will remain problematic in association studies for chronic and high frequent migraine, we would like to put forward that perhaps other genetic approaches are more fruitful in detecting genes and pathways involved in chronic migraine, such as gene expression studies, epigenetic studies or the analysis of rare variants.

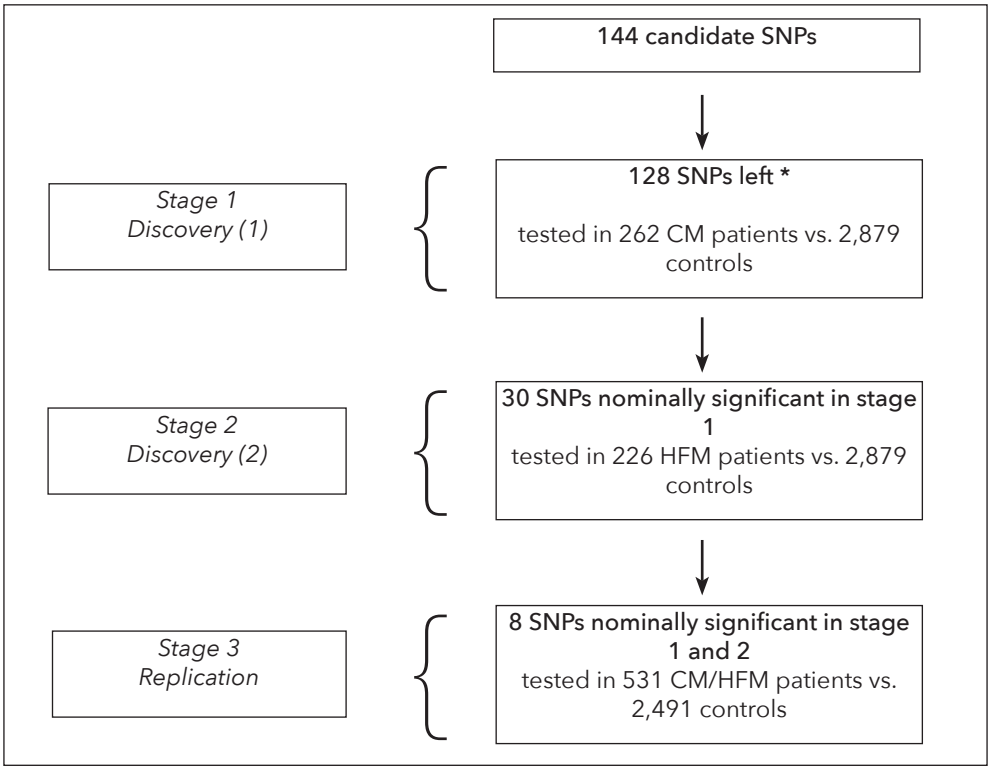
Figures and tables

Figure 1: Three-stage gene association cohort study design



*In stages 1 and 2, the same group of 2879 controls was used.
The second Norwegian cohort was previously genotyped as part of a GWAS (5). This cohort was used for *in silico* replication in the present study. The other cohorts in stage 3 were genotyped using a *Taqman* genotyping assay.

Figure 2: SNP selection study flow



* 16 SNPs excluded due to genotyping failure, low HWE, or low rate of successful genotypes.
Nominally significant: $p < 0.05$

Table 1: Results of the replication phase (stage 3)

General SNP information					Stage 1	Stage 2	Stage 3				
					Discovery phase (CM)	Discovery phase (HFM)	Replication phase (CM/HFM)				
SNP	*Chr.(position)*	*Gene*	*Ref. allele*	*Alt. allele*	*p-value*	*p-value*	*p-value*	*OR (95% CI)*	*Cohorts (N)*	*Samples (N)*	*Effects*
rs5742912	12 (6458350)	*SCNN1A*	G	A	0.035	0.003	0.31	0.872 (0.672-1.132)	3	2,108	-/?/-/-
rs3792603	4 (56302058)	*CLOCK*	G	A	0.006	0.004	0.69	1.024 (0.911-1.151)	4	2,943	-/+/-/+
rs217693	14 (62402801)	intergenic	G	A	0.045	0.019	0.10	0.911 (0.816-1.018)	4	2,930	-/-/-/-
rs2956	11 (14989121)	*CALCA*	T	A	<0.001	0.029	0.90	0.993 (0.895-1.102)	4	2,967	-/+/+/+
rs858745	2 (188216807)	*CALCRL*	T	C	<0.001	0.004	0.12	1.129 (0.971-1.313)	4	2,925	+/+/+/+
rs302680	2 (238791396)	*RAMP1*	G	A	0.040	0.010	0.89	1.009 (0.887-1.147)	4	2,937	+/-/-/+
rs2267730	7 (31122630)	*ADCYAP1R1*	T	C	0.043	0.036	0.36	0.956 (0.868-1.052)	4	2,845	-/+/+/-
rs2299908	7 (31138096)	*ADCYAP1R1*	G	A	0.026	0.046	0.34	0.946 (0.843-1.061)	4	2,871	-/-/+/-

Genomic position in basepairs according to Build 37.
Ref. allele, Reference allele; Alt. allele, Alternative allele; OR, odds-ratio; CI, confidence interval.
Stage 1 included 262 CM cases and 2879 controls, stage 2 included 226 HFM cases and 2879 controls (same controls as stage 1), stage 3 included 531 CM/HFM cases and 2491 controls
Effects: Direction of individual effects in the four replication cohorts, depicted in the following order: *Spanish CHROMIG (Taqman) / Norwegian HUNT (in silico) / Norwegian HUNT (Taqman) / Dutch LUMINA (Taqman).* (+) risk addition; (-) risk reduction; (?) not calculated (due to missing data).

Supplemental Information

Supplemental table 1: power calculations
Stage 1:

MAF	Prevalence of CM	RR	Cases	Controls	Power (alpha 0.05)
0.2	0.02	1.2	262	2,879	39%
0.2	0.02	1.25	262	2,879	54%
0.2	0.02	1.3	262	2,879	69%
0.2	0.02	1.4	262	2,879	90%

Stage 2:

MAF	Prevalence of HFM	RR	Cases	Controls	Power (alpha 0.05)
0.2	0.07	1.2	226	2,879	35%
0.2	0.07	1.25	226	2,879	49%
0.2	0.07	1.3	226	2,879	63%
0.2	0.07	1.4	226	2,879	85%

Stage 3:

MAF	Prevalence of CM/HFM	RR	Cases	Controls	Power (alpha 0.05)
0.2	0.09	1.2	531	2,491	73%
0.2	0.09	1.25	531	2,491	79%
0.2	0.09	1.3	531	2,491	91%
0.2	0.09	1.4	531	2,491	99%

MAF= minor allele frequency
CM/HFM= chronic/high frequency migraine patients
RR= Relative Risk

Supplementary table 2: SNPs that showed nominal association (p-value <0.05) in the CM cohort and were subsequently tested in the HFM cohort

Gene	SNP	Alternative allele	Reference allele	MAF CM (N=262)	MAF HFM (N=226)	MAF controls (N=2,879)	Association test (CM/ HFM)	CM uncorrected p-value	HFM uncorrected p-value
GPR30	rs3808353	A	G	0.130	0.140	0.150	Gen/Gen	0.035	0.62
SCNN1A	rs5742912	G	A	0.036	0.048	0.035	Add/Add	0.023*	0.003*
COMT	rs4680	G	A	0.517	0.467	0.464	Rec/Rec	0.005	0.67
TNF	rs1800750	A	G	0.048	0.031	0.024	Add/Add	<0.001	0.33
CLOCK	rs3792603	G	A	0.279	0.200	0.246	Rec/Dom	0.006*	0.004*
STX1A	rs941298	A	G	0.262	0.274	0.315	Add/Add	0.014	0.063
EDNRA	rs1801708	A	G	0.331	0.299	0.306	Rec/Rec	0.012	0.94
TRPM8	rs17862920	T	C	0.074	0.088	0.106	Add/Add	0.022	0.236
intergenic	rs10888075	T	G	0.204	0.153	0.146	Add/Add	<0.001‡	0.66
intergenic	rs7753655	G	A	0.250	0.287	0.298	Add/Add	0.015	0.67
intergenic	rs217693	A	G	0.242	0.256	0.209	Dom/Add	0.045*	0.019*
intergenic	rs8060725	A	C	0.311	0.288	0.281	Rec/Rec	0.028	0.75
intergenic	rs1374111	G	A	0.382	0.367	0.334	Dom/Rec	0.014	0.051
CALCA	rs2956	A	T	0.570	0.484	0.435	Add/Add	<0.001‡*	0.029*
CALCRL	rs858745	T	C	0.213	0.190	0.156	Rec/Rec	<0.001‡*	0.004*
	rs17464221	T	C	0.333	0.317	0.304	Rec/Rec	0.045	0.97
RAMP1	rs302679	G	T	0.225	0.215	0.199	Rec/Rec	0.029	0.062
	rs302680	G	A	0.179	0.170	0.151	Rec/Rec	0.040*	0.010*
	rs302673	A	G	0.391	0.347	0.344	Dom/Dom	0.008	0.76
	rs6741923	C	G	0.328	0.280	0.280	Rec/Rec	0.003	0.39
	rs7578855	C	T	0.406	0.387	0.377	Rec/Rec	0.014	0.27
	rs6746771	G	A	0.122	0.080	0.085	Add/Add	0.004	0.71
	rs6717794	G	A	0.351	0.291	0.312	Dom/Dom	0.009	0.26
	rs4663804	T	C	0.363	0.443	0.412	Dom/Dom	0.007	0.41
	rs895572	C	T	0.502	0.425	0.447	Rec/Rec	0.001	0.70
	rs1080519	T	C	0.256	0.192	0.222	Rec/Rec	0.001	0.65
ADCYAP1R1	rs17723231	T	C	0.287	0.261	0.251	Add/Add	0.027	0.55
	rs2249714	T	C	0.343	0.314	0.334	Rec/Rec	0.031	0.42
	rs2267730	T	C	0.432	0.430	0.471	Rec/Add	0.043*	0.036*
	rs2299908	A	G	0.232	0.179	0.223	Rec/Dom	0.026*	0.046*

*Statistically significant in both discovery sets. ‡Corrected *p*-value <0.05.
Genomic position in basepairs according to Build 37.
CM: chronic migraineurs; HFM: high-frequency migraineurs; MAF: Minor Allele Frequency.
Association model analysis: Gen (genotypic); Dom (dominant); Rec (recessive); Add (additive).

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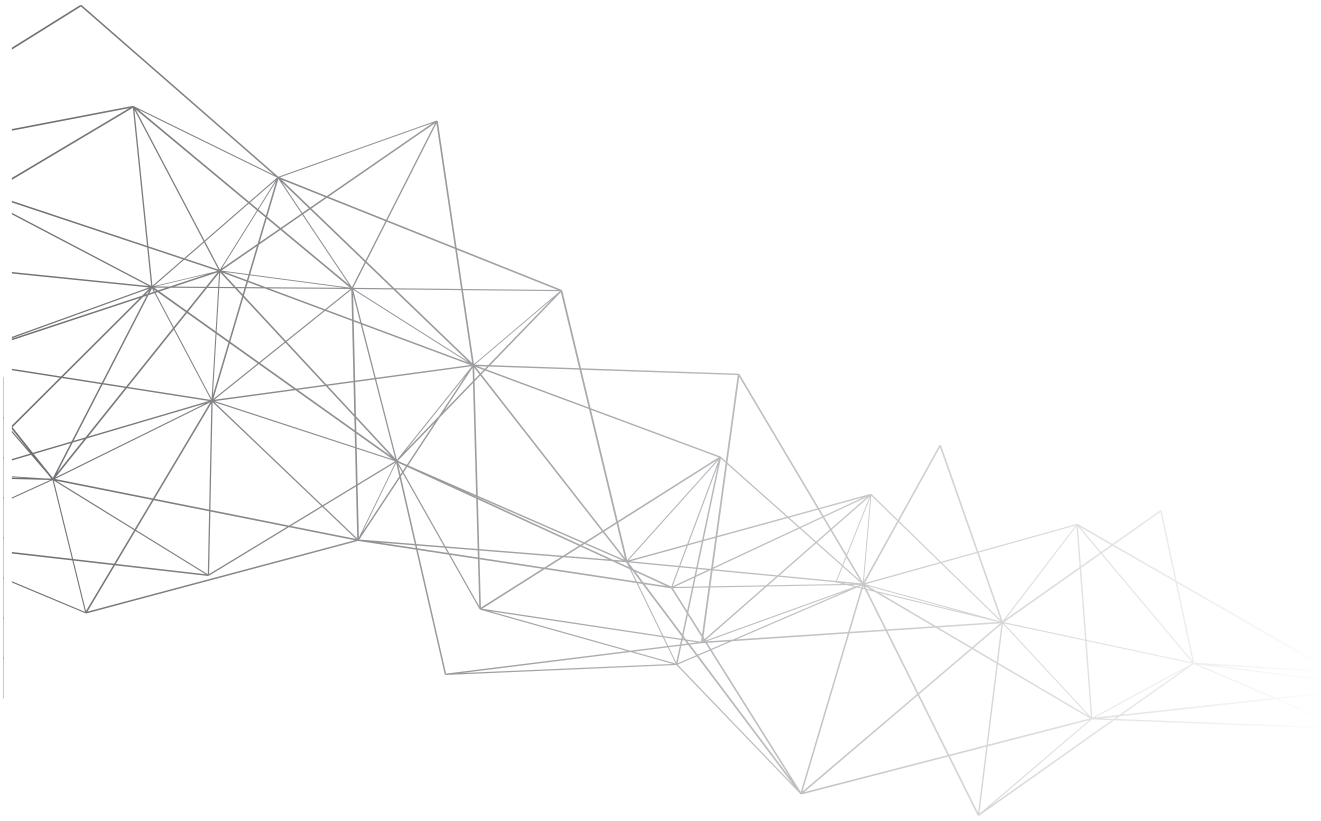
8 CHAPTER

Cluster headache and depression



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Neurology 2016 Nov 1;87(18):1899-1906
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Abstract

Objectives
As cluster headache (CH) is often referred to as 'suicide headache', we wanted to assess the prevalence of depression in cluster headache patients, and to investigate determinants of depression such as sleep disturbances.

Methods
In a cross-sectional, web-based, validated questionnaire study among 462 well-defined CH patients and 177 controls, we diagnosed CH according to the International Classification of Headache Disorders (ICHD-III). We assessed depression using the Hospital Anxiety and Depression Scale (HADS-D) and the Center for Epidemiologic Studies Depression scale (CESD) with supplementary questions to assess lifetime depression. Data were analysed with logistic and linear regression models.

Results
Lifetime depression showed almost three times higher odds in CH patients (n=462) than controls (n=177) (OR 2.77, 95% CI 1.70-4.51). Chronic (n=67) vs. episodic (n=394) patients had a higher prevalence of lifetime depression and more sleeping problems. Current depression was associated with having active attacks (last attack < 1 month) (adjusted p=0.02), but no effect remained after correction for sleep disturbances.

Conclusion
Cluster headache is associated with an almost three times increased odds of lifetime depression. Current depression is highly prevalent in patients with active disease, in part related to sleep disturbances due to current nocturnal attacks.

Introduction

Cluster headache (CH) is a highly disabling headache disorder, typically represented by frequently recurring attacks of 15-180 minutes of unilateral, peri-orbital, excruciating pain associated with ipsilateral facial autonomic features and restlessness. (1) Nocturnal sleep-related attacks are highly prevalent, with 75% of all attacks starting between 9:00 pm and 10:00 am, leading to impaired sleep quality and quantity. (2) In about 85% of patients, headache attacks cluster in periods of several weeks to months, interspersing with attack-free periods of several months to years (episodic CH); in the remaining patients, long attack-free periods are absent (chronic CH). (1, 3, 4) The lifetime prevalence of CH is about one in 1000 with a male to female ratio is 4.3). (4, 5) Related to the low prevalence, many patients are diagnosed only after many years. (6, 7) The reduction of quality of life, social functioning, and socioeconomic status can be enormous in CH patients (depending on subtype, number of cluster periods, attack frequency, and response to treatment). (8)

Patients portray the excruciating pain of a cluster headache attack as being worse than any other pain they have ever experienced. The extreme nature of the pain has earned CH the title 'suicide headache'. Suicidal tendencies have been reported in 25-55% of patients. (9-11)

CH shows several clinical, therapeutical and pathophysiological similarities to migraine, another episodic headache disorder. Prospective long-term follow-up studies in patients with migraine and in patients with depression have shown that the risk of depression is increased in patients with migraine and *vice versa* the risk of migraine is increased in patients with depression. (12, 13) Such bidirectional comorbidity suggests shared underlying pathophysiological, possibly genetic mechanisms for both episodic brain conditions. (14, 15) Furthermore, many CH patients have a lack of sleep due to nocturnal attacks, potentially contributing to depressive symptoms. Previous small studies investigated the relationship between cluster headache and depression, but did not use specific and structured questionnaires for establishing a diagnosis of CH or depression. (10, 16, 17) We therefore wanted to assess whether depression is also a comorbid condition in CH. To this end we interviewed 462 well-characterized CH patients from the Leiden University Cluster Headache Analysis programme (LUCA) using validated questionnaires, and compared the results with those of 177 non-headache controls. Secondarily, we wanted to identify CH specific characteristics that are associated with depression.

Methods

Participants and study design

The present study was conducted as part of the LUCA project (Leiden University Cluster headache Analysis programme), the details of which have been reported elsewhere. (18) In brief, using a dedicated website and two validated web-based screening and diagnostic questionnaires, with a specificity of 88% to diagnose CH according to the International Classification of Headache Disorders (ICHD-III beta) criteria, (1) Dutch speaking persons between 18 and 80 years of age from The Netherlands were invited to participate in research on CH. A clinically confirmed diagnosis of cluster headache by a physician was available for 94% of the LUCA population. (18) For the remaining 6%, no clinically confirmed diagnosis was available, for instance because they never consulted a doctor. The questionnaires included, in addition to diagnostic questions, also questions regarding demographic factors, use of acute and prophylactic headache medications, and CH attack frequency. The CH questionnaire primarily was validated for the ICHD-II criteria for cluster headache. (18, 19) Recently, however, new ICHD-III criteria have been published, which have been shown to have no differences to the validity of the CH questionnaire. (20) Therefore, our diagnoses fulfil the ICHD-III criteria for CH.

Non-headache individuals willing to participate had to pass a screening questionnaire online via the research website. If this screening questionnaire did not show any indication for having migraine, cluster headache, chronic tension type headache or medication overuse headache, individuals were sent a subsequent in depth questionnaire. This second questionnaire again assessed possible headache complaints, together with demographic variables. Only individuals that fulfilled both the criteria of 'non-headache' in the screening and in depth questionnaire were considered eligible controls and were approached for this questionnaire study. Healthy controls were also sent web-based questionnaires on symptoms of (lifetime) depression, sleeping problems and demographic characteristics, identical to the questionnaires that were sent to the CH patients.

All patients diagnosed with CH and controls received an invitation to participate in a questionnaire with questions on symptoms of lifetime depression and sleeping problems. For all questionnaires, non-responders received two e-mail reminders. Participants without the needed internet skills were able to fill out the questionnaires on paper.

Standard Protocol Approvals, registrations, and patient consents

The LUCA and depression studies were approved by the Medical Ethics Committee of the Leiden University Medical Center. All participants provided written informed consent.

Measures

The extended CH questionnaire included questions which allowed to divide between chronic (no attack-free periods of more than one month) and episodic (attack-free periods) CH, and to indicate whether the CH was 'active' (last attack < 1 month ago) or the participant was 'attack-free' (last attack > 1 month ago). For episodic CH patients questions were asked on the mean frequency of attacks during the start-up phase, the bout and the recovery phase. Also, the mean duration of the remission phase was asked. For chronic CH patients the mean number of attacks per day was asked. We defined four groups of patients: 1) episodic active; 2) episodic attack-free; 3) chronic active; 4) chronic attack-free. The latter group is considered to be treated successfully for their chronic CH, although a return to episodic CH ('secondary episodic' CH) cannot be excluded. In order to be able to adjust for potential confounding effects of demographic variables and addictive behaviour, questions were asked on gender, age, marital status, ethnicity, education, body mass index (BMI), smoking, caffeine use and alcohol consumption.

Lifetime depression was measured as a dichotomous variable. We used validated cut-off scores for the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) and the Centre for Epidemiologic Studies Depression scale (CESD), in combination with a previously used and published algorithm for depression and an additional question on depression diagnoses in the past: [HADS-D ≥ 8, or CES-D ≥ 16, or use of antidepressants with as indication a depression, or having had the diagnosis depression in the past]. (14, 15, 21, 22) Both CH patients and controls filled out the same depression questionnaires, whereas the CH patients filled out additional questions on current headache status at the time of the depression questionnaire.

To correct for a potential confounding effect of sleep disorders, the Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep disturbances over the past month. The PSQI is designed to measure the quality and patterns of sleep in the past month and contains 19 self-rated questions, with a global scoring range of 0 to 21. Higher scores denote a poorer sleep quality. (23) Scores are also allowed to be dichotomized, with a score of >5 defining 'poor sleepers'. CH patients and controls filled out the same questionnaire.

Statistical method

We reported baseline characteristics as mean ± standard deviation (SD) or percentages. Differences in means between CH and control groups were tested with 2-sided independent samples *t*-tests. Differences in proportions were tested by x^2 tests. We conducted a univariate logistic regression model to test the crude association between the presence of CH and the odds of being depressed. Analyses were rerun, adjusting for gender, age, education and BMI (model 1), and additively adjusting for PSQI-score (model 2). Results were reported as odds ratios with 95% confidence intervals and corresponding *p*-values. Secondarily, baseline characteristics of the different CH subtypes (episodic/chronic, and active/attack-free) were reported as mean ± SD or percentages. We tested differences in means between CH subgroups with one-way ANOVAs or independent samples *t*-tests. Differences in proportions were tested using x^2 tests. A univariate linear regression model was conducted to test the crude association between the CH status (active/attack-free) and the score on the HADS-D depression questionnaire. Here also, analyses were rerun, adjusting for gender, age, education and BMI (model 1), for subtype (chronic/episodic) (model 2) and for PSQI-score (model 3). Subsequently, we investigated associations with current antidepressant use and current lithium use in an additional model. Results were reported as unstandardized regression coefficients (B) with 95% confidence intervals and corresponding *p*-values. For all analyses *p*-values of <0.05 were considered to indicate statistical significance. We performed all analyses by SPSS 17.0 (SPSS inc., IBM, USA).

Results

Study flow and descriptives

The total study flow is shown in figure 1. All eligible persons with CH within the LUCA database (n=528) received a depression questionnaire (mean age ± SD: 48.8 ± 11.7), of which ultimately 467 returned questionnaires (88.4% response rate). The primary analysis was conducted in 462 participants with CH, because of missing demographic data in 5 patients. Responders (n = 462) did not differ from non-responders (n = 66) for age or gender. The secondary analysis was conducted in 461 participants with CH because of missing attack frequency data in one subject. Of the 252 controls in the LUCA database (mean age ± SD: 45.0 ± 14.3), n=177 (70.2%) filled out a depression questionnaire. Responders (n=177) were slightly older than non-responders (n=75), (46.6 years *v.* 41.3 years; p = 0.006), but did not differ in gender (supplementary tables e-1, e-2. e-3).

Descriptive data for participants with CH and non-headache controls are shown in Table 1. The 462 CH participants differed on several variables from the 177 healthy

controls. CH participants more often were males and married, were slightly older, had a lower educational level and slightly higher BMI, smoked substantially more pack years, and tended to use more caffeine. Furthermore, they showed increased scores on depression and anxiety scales and were more likely to report increased use of antidepressants, having received a diagnosis of depression in the past and experiencing sleeping problems.

The association between CH, depression and sleep disturbances

Participants with CH scored higher on all different subscales of the depression questionnaires, more often had lifetime depression and more often used or had used antidepressants (table 1). They also scored higher on the PSQI questionnaire (indicating worse sleep quality), and more often could be qualified as 'poor sleeper'. As shown in table 2 and figure e-1, the logistic regression analyses of the association between CH and the odds of depression showed in the crude model, an odds ratio of 4.17 compared with controls. This effect remained largely unchanged when adjusted for the covariates gender, age, education and BMI (OR 4.08). After adjustment for PSQI-score, the odds ratio remained increased (OR 2.77).

Baseline comparison of CH subtypes

CH participants (n=461) were divided in the following groups: 1) episodic active (n=106); 2) episodic attack-free (n=288); 3) chronic active (n=58); 4) chronic attack-free (n=9). Differences in alcohol use, duration of attack-free periods, time to last attack and all different depression and sleep subscales were observed. In general, participants with chronic CH had more symptoms of depression, and worse sleep quality, when compared to participants with episodic CH (table 3).

The association between active CH and current depression

As shown in table 4 and figure e-2, participants with active CH scored 1.81 points higher on the current depression questionnaire (HADS-D) than attack-free CH patients. This effect remained after adjustment for covariates gender, age, education and BMI (model 1). After adjustment for CH subtype (episodic or chronic), the effect decreased (B -1.02) (model 2). After adjustment for PSQI score (model 3), no effect remained (B -0.04). These results indicate an association between the current activity of CH and current depression, with involvement of current sleep disturbances.

Determinants of depression in CH patients

As shown in table 4, model 3, determinants of current depression in CH participants were: a lower educational level, having chronic CH and a higher PSQI sum score. Use of lithium might indicate more severe cluster headache (as it may be prescribed as a second line prophylactic treatment), more severe depression (as it may be prescribed as an additive to antidepressants if other treatments fail), or both. Additional analyses of current use of lithium indeed showed an association with depression scores, without changing the *p*-values for the other determinants. Subsequent analyses with current antidepressant use showed an association with depression scores, without changes in the significance of *p*-values of the other determinants.

Discussion

This is a large study on the prevalence of depression in a large sample of patients with cluster headache (CH).

CH patients had three times higher odds for depression than controls. Patients with active or chronic CH had higher depression scores than patients with CH who were attack free. Our finding that CH is associated with increased prevalence of depression is well in line with results from earlier smaller studies which, however, did not use specific and structured questionnaires for CH and depression. (10, 16, 17) Considering that depression is more prevalent among women and that there were proportionally much fewer women in the cluster headache sample than in the control group, the increased prevalence of depression in cluster headache is even more striking.

We can only speculate on why CH patients have increased prevalence of depression. As 85% of participants with CH had nocturnal attacks, lack of sleep might have been a contributing factor. Despair and stress because of relentlessly recurring pain attacks is another possible factor. Finally, hypothalamic dysfunction may offer a good explanation as depression (24), sleep disorders (25) and CH (26-28) have been associated with both functional and structural changes in this part of the brain. Epidemiological associations with depression have been described for a range of neurological disorders, in particular those associated with chronic pain. (29) Whether and to what extent the underlying mechanisms are similar remains to be studied.

Depression in cluster headache patients is at least partially explained by poor sleep quality. The odds ratio for depression dropped from 4.17 to 2.77 after adjustment for sleep disturbances. Current attacks of cluster headache was associated

with current depression, but this effect disappeared after adjustment for sleep disturbances. Participants were not wrongly considered as depressed due to sleeping problems, as the HADS questionnaire, in contrast to other instruments that measure depressive symptoms, contains no questions about this issue. It seems more likely that CH, depression and sleeping disturbances are intertwined. There is evidence that sleeping problems can be a risk factor for depression (30), and sleeping problems in cluster headache patients are caused by CH attacks that typically occur at night.

Another striking and clinically potentially relevant finding of our study was that, in all likelihood, depression was considerably underdiagnosed and undertreated in cluster headache patients. Only 23/133 (17%) of the 133/462 (28%) participants with cluster headache who fulfilled the loose criterion for current depression (HADS-D ≥ 8) and only 14/56 (25%) of the 56/462 (12%) participants who fulfilled the stricter criterion for current depression (HADS-D ≥ 11) were treated with antidepressants.

Our data suggest that current attacks are associated with increased symptoms of depression, and worse sleep quality. Therefore, we may conclude that unsuccessful treatment of cluster headache is associated with poor outcomes: depression and sleeping problems. This underlines the importance of adequate treatment for cluster headache. Suicidal thoughts are frequently reported in patients with cluster headache and could be related to the higher frequency of depression. (10, 11) Unfortunately we have no information on suicidal thoughts in our study population, but this would be an important topic for future research.

In patients with migraine, comorbid depression is a risk factor for migraine chronification. (15, 31, 32) Interestingly, in the present study, participants with chronic CH scored substantially higher on all depression subscales than those with episodic CH. However, due to the cross-sectional nature of our study, we cannot distinguish between cause and consequence. Likewise, we cannot determine whether depression and CH show bidirectional comorbidity. This would require long-term, prospective follow-up studies which are challenging because of the low incidence and prevalence of CH.

Strengths of our study include the large sample size for such a rare condition, the use of validated diagnostic questionnaires for CH (18) and the detailed information on depression. Head trauma has been associated with both depression and, in a few cases, cluster headache. (33, 34) The evidence for a causal relationship between head trauma and cluster headache is, however, limited and the relation, if any, seems rare. We therefore believe that the lack of information on a history of head trauma is unlikely to have affected the results. Possible limitations of our study are that our LUCA population is predominantly Dutch/Caucasian, of relatively

young age, recruited via the internet, and on average well-educated. We therefore cannot extrapolate our studies to other ethnic groups or populations from different socio-economic backgrounds. Also, in line with previous epidemiological studies, participants with CH more frequently were male and heavy smokers than non-CH controls. (5, 11) It seems unlikely that these differences have materially affected the results, as we adjusted all analyses for these differences. Another possible limitation is that depression was measured with questionnaires which are not specifically designed to diagnose clinical depression in individuals. However, we used validated cut-off values, which should provide a reliable differentiation between depressive and non-depressive persons. (21, 22) Cluster headache patients showed increased anxiety which might have contributed to the increased comorbid prevalence of depression. Unravelling the exact role of anxiety should be a topic of future research. Lastly, due to the cross-sectional character of this study no firm conclusion could be drawn regarding the direction of the comorbidity.

Early detection of comorbid depression in cluster headache may be important to prevent suicide in this unbearably painful primary headache disorder. Longitudinal bidirectional follow-up studies, although challenging, will be necessary to investigate the relationship in time between CH and depression, to answer the question on causal relationship.

Figure 1 : total study flow

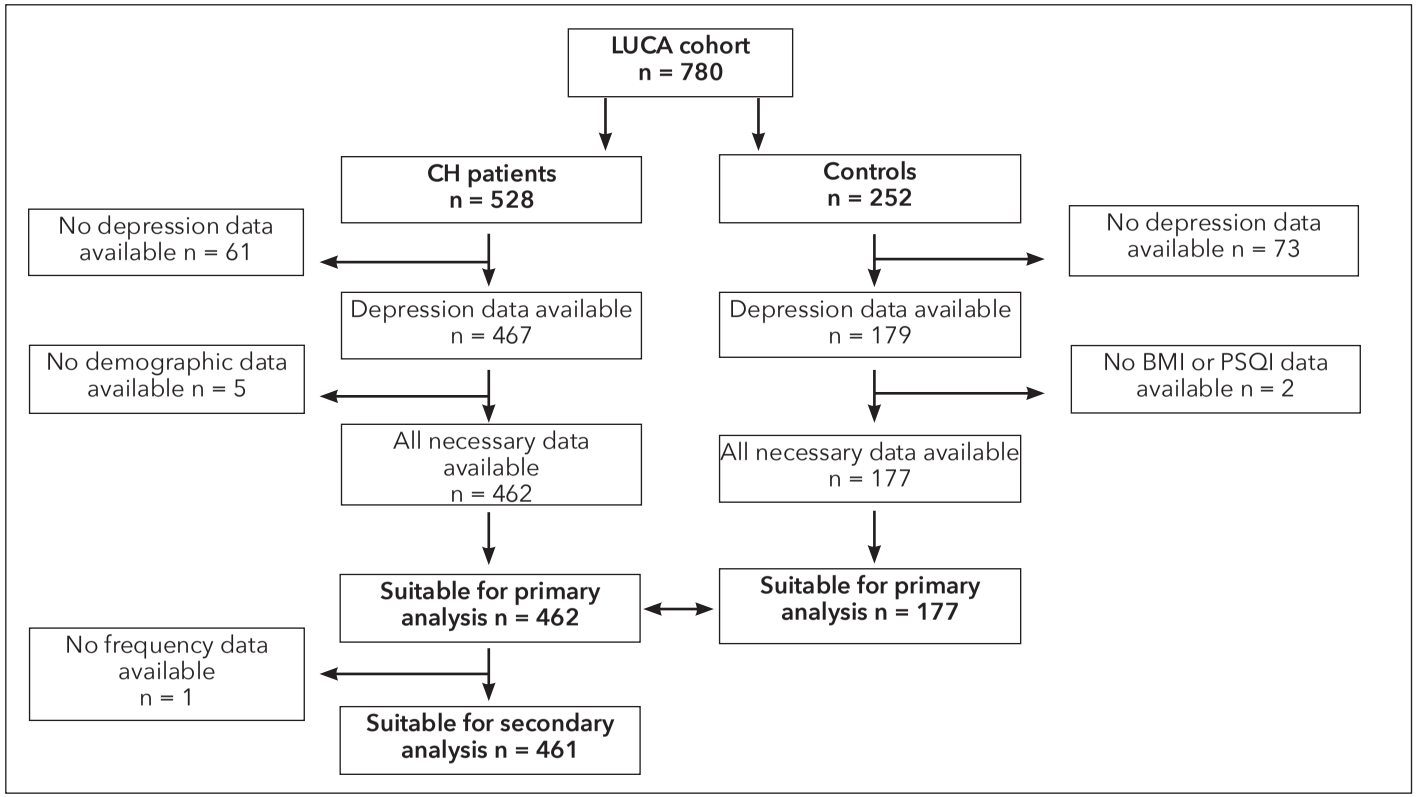

Table 1: Baseline characteristics of study population and comparison between 462 CH patients and 177 controls.

	CH patients (n=462)	Controls (n=177)	p-value
Gender (% male)	73.4%	44.6%	**<0.001**
Age (years)	49.2 ± 11.3	46.6 ± 14.3	**0.03**
Marital status			**0.006**
% single	12.8%	20.3%	
% cohabiting	15.6%	22.6%	
% married	66.2%	53.1%	
% divorced / widowed	5.4%	4.0%	
Education (years)	13.0 ± 3.3	14.2 ± 3.5	**<0.001**
BMI (kg/m^2)	25.4 ± 3.6	24.1 ± 2.8	**<0.001**
Packyears	18.6 ± 16.8	4.8 ± 8.4	**<0.001**
Caffeine (units per day)	6.6 ± 2.8	5.5 ± 2.5	**<0.001**
Alcohol (units per week)	7.6 ± 9.4	6.9 ± 7.6	0.28
HADS total score	10.8 ± 7.8	5.8 ± 5.2	**<0.001**
HADS-D score	5.3 ± 4.3	2.6 ± 2.9	**<0.001**
HADS-A score	5.6 ± 4.2	3.3 ± 2.9	**<0.001**
CESD score	11.5 ± 10.2	5.3 ± 6.2	**<0.001**
Ever antidepressants (% yes)	22.5%	10.2%	**<0.001**
Current antidepressants (% yes)	7.8%	2.3%	**0.01**
Ever diagnosis depression (% yes)	16.7%	8.4%	**0.007**
Lifetime depression (% yes)	43.9%	15.8%	**<0.001**
PSQI score	6.3 ± 3.9	4.2 ± 2.8	**<0.001**
Poor sleeper (% yes)*	58.4%	37.3%	**<0.001**

CH, Cluster Headache; BMI, Body Mass Index; HADS, Hospital Anxiety and Depression Scale (D: depression scale; A: anxiety scale); CES-D, Centre for Epidemiologic Studies Depression Scale; PSQI, Pittsburgh Sleep Quality Index. Values are percentages or means ± SD. P-values depicted in bold indicate a statistical significant difference, using x^2 tests and independent samples t-tests appropriately.

* Poor sleeper defined as PSQI-score >5

Table 2: Logistic associations between CH and lifetime depression in 462 participants with CH and 177 controls.

	OR	95% CI	p-value
Univariate association	**4.17**	**2.68 – 6.50**	**<0.001**
Model 1 *Adjusted for gender, age, education, BMI*	**4.08**	**2.56 – 6.49**	**<0.001**
Model 2 *Additively adjusted for sleep disturbances*	**2.77**	**1.70 – 4.51**	**<0.001**

Data are Odds Ratios (OR) with 95% confidence intervals and p-values. Model 1 was adjusted for gender, age, education and BMI. Model 2 was additively adjusted for PSQI-score. Values depicted in bold indicate statistical significant results.

Table 3: Baseline characteristics of 461 people with CH and comparison between 4 different subtypes

	Episodic (n=394)		Chronic (n=67)		p-value
	Active (n=106)	Attack-free (n=288)	Active (n=58)	Attack-free (n=9)	
Gender (% female)	31.1%	23.3%	32.8%	33.3%	0.25
Age (years)	48.2 ± 12.1	50.1 ± 11.1	47.5 ± 10.8	44.8 ± 9.8	0.16
Marital status					0.23
% single	19.8%	9.7%	10.3%	33.3%	
% cohabiting	16.0%	15.6%	15.5%	11.1%	
% married	59.4%	68.8%	69.0%	55.6%	
% divorced / widowed	4.7%	11.1%	5.2%	0.0%	
Education (years)	12.9 ± 3.4	13.1 ± 3.4	12.5 ± 3.0	12.9 ± 3.2	0.60
BMI (kg/m^2)	25.1 ± 3.9	25.5 ± 3.4	25.6 ± 4.2	27.4 ± 4.4	0.29
Packyears	19.3 ± 17.9	18.3 ± 16.7	18.7 ± 16.1	18.8 ± 13.3	0.97
Caffeine (units per day)	6.6 ± 2.9	6.7 ± 2.8	6.1 ± 2.5	5.9 ± 2.1	0.41
Alcohol (units per week)	7.2 ± 9.1	8.2 ± 8.9	5.0 ± 8.3	13.2 ± 22.4	**0.03**
Number of attacks per day in CCH patients	.	.	2.9 ± 3.5	1.5 ± 2.4	0.32
Number of attacks per day (start-up phase)	1.1 ± 1.4	0.9 ± 1.0	.	.	0.13
Number of attacks per day (bout)	3.3 ± 2.8	3.3 ± 2.4	.	.	0.90
Number of attacks per day (recovery phase)	1.0 ± 1.4	0.9 ± 1.0	.	.	0.53
Duration attack-free period (years)	0.7 ± 0.9	1.9 ± 2.5	.	.	**<0.001**
Time to last attack (years)	0.03 ± 0.05	1.9 ± 3.3	0.01 ± 0.01	5.6 ± 8.3	**<0.001**
HADS total score	11.5 ± 7.8	9.6 ± 7.0	15.0 ± 9.4	15.3 ± 9.6	**<0.001**
HADS-D score	5.6 ± 4.2	4.6 ± 3.8	7.9 ± 5.5	7.2 ± 4.5	**<0.001**
HADS-A score	5.8 ± 4.3	5.1 ± 3.9	7.1 ± 4.9	8.1 ± 5.6	**0.002**
CESD score	12.7 ± 9.7	9.8 ± 9.4	17.5 ± 11.9	14.8 ± 14.7	**<0.001**
Lifetime depression (% yes)	51.9%	37.5%	63.8%	33.3%	**0.001**
Ever antidepressants (% yes)	28.3%	18.4%	31.0%	33.3%	0.05
Current antidepressants (% yes)	9.4%	6.3%	13.8%	0.0%	0.17
PSQI score	7.5 ± 3.9	5.2 ± 3.3	9.0 ± 4.5	7.8 ± 5.1	**<0.001**
Poor sleeper (% yes)	75.5%	46.5%	82.8%	77.8%	**<0.001**

BMI, Body Mass Index; CCH, Chronic CH; ECH, Episodic CH; HADS, Hospital Anxiety and Depression Scale (D: depression scale; A: anxiety scale); CES-D, Centre for Epidemiologic Studies Depression Scale; PSQI, Pittsburgh Sleep Quality Index. Active,

last attack ≤1 month; Attack-free, no attacks for > 1 month. Values are percentages or means ± SD. P-values depicted in bold indicate a statistical significant difference, using x^2 tests and independent samples t-tests appropriately.

Table 4: Linear associations between CH status (active / attack-free) and current depression (HADS-D scores) in 461 participants with CH.

	B	95% CI	p-value
Univariate association			
CH status (attack free vs. active)	**-1.81**	**-2.62 - -1.00**	**<0.001**
Model 1			
CH status (attack free vs. active)	**-1.74**	**-2.54 - -0.94**	**<0.001**
Gender (female vs. male)	-0.26	-1.15 – 0.62	0.56
Age	-0.006	-0.04 – 0.03	0.73
Years of education	**-0.25**	**-0.37 - -0.13**	**<0.001**
BMI	0.05	-0.06 – 0.15	0.39
Model 2			
CH status (attack free vs. active)	**-1.02**	**-1.89 - -0.14**	**0.02**
Gender (female vs. male)	-0.31	-1.19 – 0.56	0.48
Age	-0.003	-0.04 – 0.03	0.88
Years of education	**-0.24**	**-0.35 - -0.13**	**<0.001**
BMI	0.03	-0.07 – 0.14	0.56
CH subtype (chronic vs. episodic)	**2.27**	**1.08 – 3.45**	**<0.0**
Model 3			
CH status (attack free vs. active)	-0.04	-0.86 - 0.79	0.93
Gender (female vs. male)	-0.76	-1.56 - 0.05	0.07
Age	-0.004	-0.04 - 0.03	0.82
Years of education	**-0.17**	**-0.27 - -0.06**	**0.002**
BMI	0.04	-0.06 - 0.14	0.40
CH subtype (chronic vs. episodic)	**1.49**	**0.39 - 2.58**	**0.008**
PSQI sumscore	**0.47**	**0.37 – 0.57**	**<0.001**
Subsequent analyses:*			
Current lithium use	**1.35**	**0.26 – 2.45**	**0.02**
Current use of antidepressants	**2.50**	**1.17 – 3.82**	**<0.001**

Data are unstandardized regression coefficients (B) with 95% confidence intervals and p-values. Model 1 was adjusted for gender, age, education and BMI. Model 2 was additively adjusted for CH subtype (chronic/episodic). Model 3 was additively adjusted for PSQI-score. Values depicted in bold indicate statistical significant results.

* Subsequent (separate) analyses with current lithium use and current use of antidepressants showed no changes in the significance of the other determinants.

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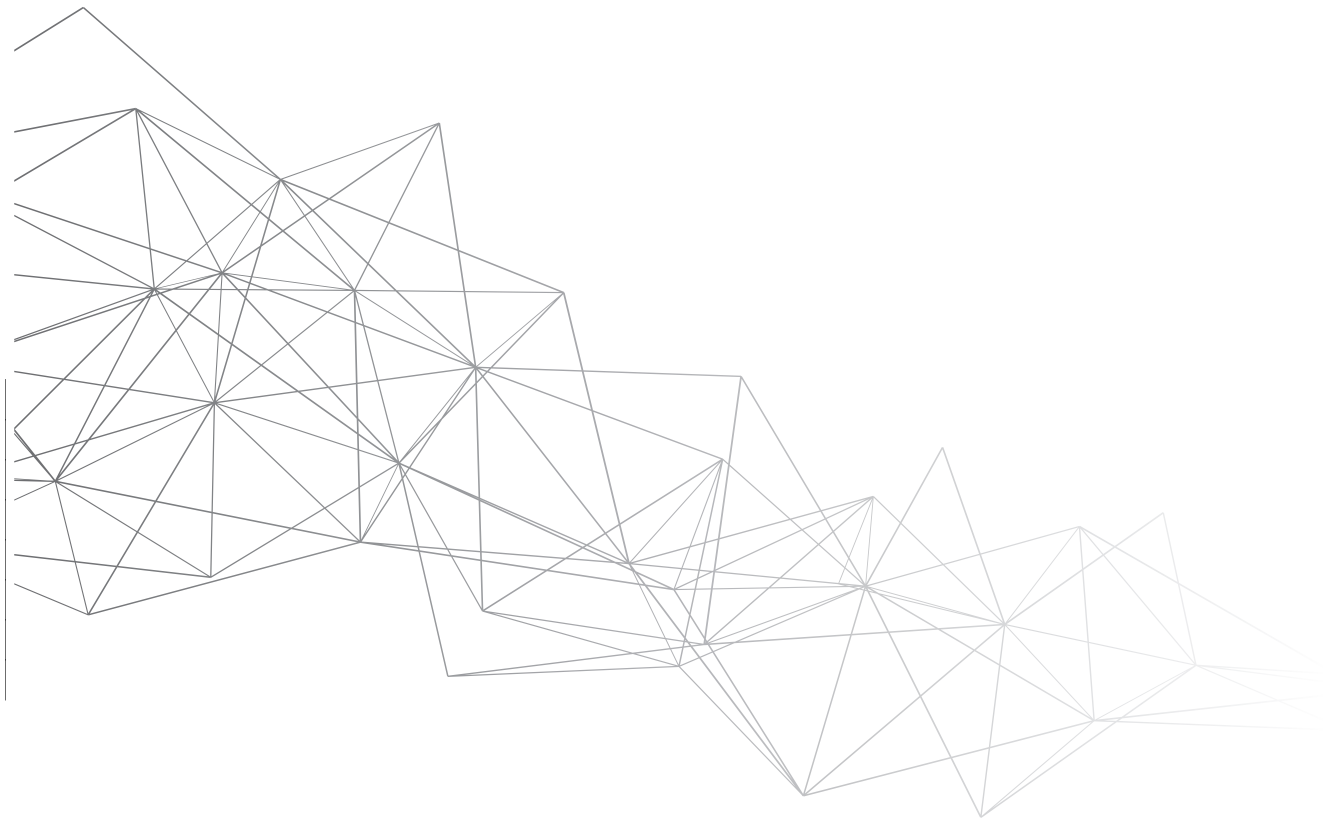
9 CHAPTER | Summary and general discussion



9.1 Summary

In **chapter 1** I provide a general introduction in the topic of this thesis. It describes epidemiology, criteria, pathophysiology, genetics and treatment of migraine and depression, and also migraine chronification and the role of medication overuse. Furthermore, an introduction in comorbidity of both diseases is given, focusing on what we know already, and specific remaining questions to be answered in this thesis.

In **chapter 2**, I describe that 45% of migraineurs fulfilled the criteria for lifetime depression. A high migraine attack frequency and the presence of cutaneous allodynia were migraine specific factors associated with an increased prevalence of depression. Furthermore, being a poor sleeper, female gender, high BMI, being single, smoking, and a low alcohol consumption were general determinants of depression in our population. This study identified allodynia, in addition to high migraine attack frequency, as a new migraine specific factor associated with depression.

In **chapter 3** I essay that cutaneous allodynia was highly prevalent in our migraineurs: 70% reported allodynia during migraine attacks. Allodynia was associated with the presence of depression, and also with female gender, low age at onset, and high migraine attack frequency. Analysis of the longitudinal data showed that allodynia was an independent predictor for increase in migraine frequency.

In **chapter 4**, I show that hemiplegic migraine patients had increased odds for lifetime depression compared with controls. Use of acute anti-migraine medication was associated with lifetime depression.

In **chapter 5**, I describe that migraine patients differed significantly from healthy controls on all 3 dimensions of affective disorders: lack of positive affect, somatic arousal, and negative affect. For the lack of positive affect and negative affect dimensions, migraine patients were predominantly similar to a 'past psychopathology' group. For the somatic arousal dimension, migraine patients scores were more comparable with a 'current psychopathology' group.

Chapter 6 provides evidence that successful withdrawal from medication overuse was significantly higher in the group supported by a headache nurse than in the group without support. Support by a headache nurse was not associated with response (≥ 50% reduction in headache days after successful withdrawal). The underlying headache primary headache diagnosis, determined after withdrawal, was significantly correlated with response (with increased response in the group with underlying migraine, when compared with the group with tension type headache).

I describe a study in **chapter 7** which aimed to search for evidence that genetic factors are involved in the chronification process of migraine. No loci survived replication, which left us without significant findings.

In **chapter 8** I show that 44% of cluster headache patients fulfilled the criteria for lifetime depression. Chronic vs. episodic patients had a higher prevalence of lifetime depression and more sleeping problems. Current depression was associated with having active attacks, but no effect remained after correction for sleep disturbances.

9.2 General Discussion and future perspectives

9.2.1 Clinical determinants of depression in migraine patients

A broad range of studies, with mostly cross-sectional and sparsely longitudinal designs, have been published on the topic of migraine and depression. (1-14) **Chapter 2** showed that our population of migraine patients was comparable to other studies with respect to the prevalence of lifetime depression (varying from 20% to 60%). The quality of migraine characterization and depression characterization, however, has in most of the previous studies been moderate, if not poor. A major strength of our study, and a clear difference with most earlier published studies, is the extensive characterization of patients. We could show clear associations with a large number of determinants. This detailed information on clinical and socio-demographic variables allowed for specific subsequent studies, with broad opportunities for statistical adjustment to prevent bias. The question could be raised whether the found association might be the artefact of our definitions. A part of the comorbidity between migraine and affective disorders could be due to overlapping symptomatology, as some of the characteristic features of migraine attacks, such as nausea, loss of energy, anhedonia, and sleep disturbances, could lead to misclassification of depressive disorder in migraine patients. However, the association of migraine and depression is still present when questionnaires focusing on the non-somatic aspects of depression are applied, such as the Hospital Anxiety and Depression Scale. (15) Furthermore, the robust trend in published literature on the issue of migraine and depression is that, irrespective the extensiveness of the depression characterization, all studies show an association. In our opinion, this strongly suggests that we have confirmed a real association between 2 genuine disorders.

9.2.2 High migraine attack frequency is associated with depression

We identified migraine frequency to be associated with depression (**chapter 2**), which confirmed findings from two other studies with poor characterization of

depression. (16) (17) The direction of this causation in our study remained unclear due to its cross-sectional character. We addressed this problem in **chapter 3**. There we showed that lifetime depression at baseline was associated with an increase in migraine days over a median follow-up period of 2 years. These findings confirm that depression is a risk factor for migraine chronification.

9.2.3 Genetic factors involved in migraine and depression

As it remains unclear which specific genetic factors are involved in the increased liability to migraine and depression (11, 18), we performed a GWAs study to identify shared genetic factors for migraine and depression (not presented in this thesis). A total of 1450 migraine patients of our LUMINA cohort had migraine and depression, of which GWAs data was obtained for 598 patients. A GWAs study was performed for these patients and combined with GWAs data of three additional cohorts in a meta-analysis for migraine and depression. This resulted in 4 peaks (loci) that reached the threshold of suggestive significance. The study included a total amount of 1700 cases and 5600 controls. Four study samples were made available for replication, and 20 SNPs located in these four top loci were genotyped in these cohorts using the Sequenom technique. Unfortunately, we could not replicate our initial findings. The negative outcome in our first GWAs on migraine and depression is less surprising in view of findings in GWAs studies of depression, where only the latest GWAs in June 2016 provided first evidence of genetic factors in depressive symptoms in large amounts of cases. (19) Regardless, our approach to test migraine and depression combined (as an endophenotype) may yield more positive results, although the challenge seems considerable. To increase power, we increased our sample size by adding new cohorts to our discovery sample. Additional GWAs for migraine and depression are currently being performed. Hitherto we have not been able to present or definitely refute evidence from genetic studies that migraine and depression share an aetiological basis.

9.2.4 Cutaneous allodynia is associated with migraine chronification

The study described in **chapter 2** was the first to identify cutaneous allodynia as a determinant of lifetime depression in migraineurs. The prevalence of allodynia in our study is in line with all previous studies on allodynia in migraine (ranging from 50% to 80%). (20) Migraine, depression and allodynia are intertwined, and allodynia plays an important role in the migraine triad of chronification, depression, and medication overuse. As cutaneous allodynia is considered a clear marker for a central sensitization process of the brain, (21) this finding could shed new light on the pathophysiological mechanisms behind the relationship between migraine chronification and depression.

Chapter 3 shows that recurrent migraine with cutaneous allodynia probably leads to a decreased threshold for subsequent migraine attacks. A possible explanation may be that repetitive activation of trigeminovascular neurons and of modulatory pain pathways may lead to impairment of function or neuronal cell damage in brain areas involved in migraine generation. This might lead to decreased thresholds for activation, leading to chronification of migraine. (20, 22) Another concept is that of nociception-induced plasticity, suggesting that kindling and related models of neuroplasticity can be used to describe ways in which exposure to a noxious stimulus may, under certain conditions, lead to a permanently sensitized state, and to chronification of pain. (23)

The finding that repeated migraine attacks increase the susceptibility for subsequent attacks, which may also lead to structural and functional changes within pain pathways, could in the future also be validated in wild type mice and our transgenic knock-in migraine mouse models that harbour human pathogenic mutations for familial hemiplegic migraine. (24-26) These mice exhibit increased neuronal calcium influx and glutamatergic neurotransmission, resulting in lowering of the induction-threshold for cortical spreading depression and an increase of the frequency of cortical spreading depression. By repeating induced cortical spreading depression, it could be determined whether there is a critical window for chronification. Daily administration of analgesics or triptans could possibly induce a state comparable to medication overuse headache. Study designs with an experimentally evoked anhedonic depressive-like status could investigate the relationship between anhedonia and sensitivity for cortical spreading depression. Measurements of cutaneous allodynia have been performed before in mice, and could be associated with the sensitivity for cortical spreading depression. Altogether, mouse models could provide supporting evidence and new insights about the relationship between migraine chronification, cutaneous allodynia, and depression.

9.2.5 Dimensions of affective disorders in migraine patients

Not only migraine, but also several other somatic disorders (like diabetes, obesity, and cardiovascular disease) show increased associations with the somatic-affective dimension rather than cognitive-affective symptoms of affective disorders, as described in **chapter 5.** (27-30) Therefore, it has often been hypothesized that the association between a somatic disease and depression is primarily through the somatic-affective dimension of depression, the so-called somatic depression. (31, 32)

One might argue that we did not find a comorbidity between migraine and depression, but between migraine and 'feeling unwell', as a consequence of the somatic disease. We would however like to object to this argumentation. First, the

source papers for the relationship between migraine and depression have been for years the longitudinal studies of Breslau et al. (1, 2) These papers describe not only an increased risk of first onset depression in migraine patients, but also *vice versa* an increased risk of first onset migraine in patients with a depression. This argues against depressed feelings following (frequent) migraine attacks. Furthermore, **chapter 5** clearly shows that the symptom profile of affective disorders in migraine patients differs from healthy controls for all three dimensions of the MASQ-D30 questionnaire, not only for the somatic arousal dimension. Therefore, our study shows that affective disorders in migraine patients cannot be fully explained by somatic depression or overlapping symptomatology.

Our study shows an even stronger comorbidity between migraine and symptoms of anxiety, than between migraine and symptoms of depression per se. This is particularly interesting, since most studies hitherto focused on the comorbidity between migraine and depression, whilst the comorbidity of migraine and anxiety is a largely unexplored area. Our study shows that anxiety arousal might be the corresponding component, but the underlying mechanism should be further investigated.

9.2.6 Depression in hemiplegic migraine

Our finding from **chapter 4** that the lifetime prevalence of depression in patients with hemiplegic migraine compares to the prevalence found in migraineurs with and without aura (**chapter 2**), fits well with the hypothesis that hemiplegic migraine is part of the migraine spectrum. (33) Probably the same pathophysiological mechanisms play a role in the comorbidity of depression with migraine with and with aura at the one hand, and hemiplegic migraine at the other.

The genes involved in hemiplegic migraine may, directly or indirectly, make patients more susceptible to depression (**chapter 4**). Hitherto three genes have been identified for hemiplegic migraine. FHM1 is caused by missense mutations in *CACNA1A* on chromosome 19p13. (34) FHM2 is caused by missense mutations in *ATP1A2* on chromosome 1q23. (35) FHM3 is caused by missense mutations in *SCN1A* on chromosome 2q24. (36) The functional effects of FHM1, FHM2 and FHM3 gene mutations all predict increased levels of glutamate in the synaptic cleft. Clinical data also suggest the involvement of the glutamatergic system in the pathophysiology of depression. (37) Proton magnetic resonance spectroscopy (^{1}H-MRS) data suggest alterations to glutamatergic concentrations in several brain areas, whereas post-mortem studies indicate alterations in NMDA receptor subunit expression in patients with major depressive disorder. The finding that depression is highly prevalent in patients with hemiplegic migraine contributes to the evidence that the glutamatergic system might be involved in the pathophysiology

of depression. It would be interesting to study the role of ion channels encoded by *CACNA1A*, *ATP1A2* and *SCN1A* in large cohorts with comorbid depression and common forms of migraine.

9.2.7 Genetic factors involved in chronic migraine

An important drawback of focusing on subgroups of patients, as we did in **chapter 7** with chronic and high-frequent migraine, is that the number of available patients decreases. Thus, to increase homogeneity, we had to sacrifice statistical power. Although we collaborated in the International Headache Genetics Consortium, the patient numbers were relatively small, largely because of the rarity of chronic migraine and poor clinical characterization of migraineurs in other cohorts. Considering the negative results of the study, our approach may have had insufficient statistical power, or we may have selected SNPs irrelevant to migraine chronification. If the problem of statistical power will remain problematic, we would like to put forward that perhaps other genetic approaches will be more fruitful in detecting genes and pathways involved in chronic migraine, such as gene expression studies, epigenetic studies or the analysis of rare variants.

9.2.8 Depression in cluster headache

The marked relationship of depression and sleep disturbances in cluster headache (**chapter 8**) adds to the hypothesis that hypothalamic dysfunction plays a role, as depression, sleep disorders and cluster headache have all been associated with both functional and structural changes in this part of the brain. (38-42) Interestingly, depression scores were increased in patients with chronic cluster headache, when compared with patients with episodic cluster headache. This reminds of the relationship between depression and migraine chronification, as described in **chapters 2** and **3**. However, due to the cross-sectional nature of our study, we could not distinguish between cause and consequence. Likewise, we could not determine whether depression and cluster headache show bidirectional comorbidity. It could still be possible that the pain in cluster headache is thus severe, that depression is an almost unavoidable consequence – an argument supported by the fact that a stronger association was found for chronic cluster headache. The necessary long-term, prospective follow-up design for a study to prove bidirectional comorbidity (1, 2), will be challenging because of the low prevalence of cluster headache. Longitudinal studies within a cluster headache population could shed more light on the process of cluster headache chronification, and its relation with depression, cutaneous allodynia and sleep disturbances. Further research should also focus on the pathophysiological background of the interactions between cluster headache, sleep disturbances, chronification of disease, and depression. Comparable to migraine, cutaneous

allodynia might provide clues to pathophysiological processes involved in this comorbidity. Genetic analyses could either way contribute, with consideration of the limitations that rare diseases involve, in particular a lack of statistical power to detect genetic variants with a small effect.

9.2.9 The treatment of medication overuse headache

Psychological phenomena play an important role in patients with chronic headache or high headache related disability. They are more prone to use unsuitable coping mechanisms, score low on pain acceptance and high on catastrophizing scales, and experience a low internal pain control. (43-45) Interestingly, in patients with migraine, pain control and self-management can be improved by cognitive behavioural therapy. (46) It seems likely that all these elements play a role in successful withdrawal with support of a headache nurse (**chapter 6**). Further research, specifically focusing on cognitive-behavioural interventions before and during withdrawal, might further improve the success rate of withdrawal therapy.

Over the last few years a shift has occurred in the approach of patients with medication overuse. Traditionally, it was advised to withdraw patients from their overused medication before starting any prophylactic agent. Randomised trials in chronic migraine with topiramate and onabotulinum toxin A, however, contributed significantly to the debate whether, and when detoxification is necessary in the treatment of medication overuse headache. (47-51) In our opinion, it would be interesting to study whether Onabotulinum toxin A could be effective for patients who do not respond to withdrawal therapy, or whether Onabotulinum toxin A could mitigate the process of medication withdrawal.

9.2.10 A critical discussion of the methodology

An important part of the analyses in this thesis was carried out with material from two large databases we have compiled over the course of years: the LUMINA migraine population (52) and the LUCA cluster headache population. (53) The LUMINA database started in 2008 as a web-based method to include migraine patients in several research projects, but first and foremost in our genetic data collection project. The LUCA database, including cluster headache patients, started a few years later, using the same methodology and technical infrastructure as LUMINA. During the years, an increasing number of satellite projects was added to the LUMINA and LUCA databases, meaning that participants received additional requests for questionnaires, biochemical research, Magnetic Resonance Imaging and –Spectroscopy studies, migraine attack provocation studies, and even a clinical trial on the effect of Onabotulinum Toxin A in the treatment of chronic migraine. Collection of a healthy control population started years after the first migraine patients were included. Also, data collection via our outpatient clinic was introduced into the LUMINA project.

As described, the primary focus of the LUMINA database had always been the collection of DNA samples from migraine patients, in order to be able to participate with considerable numbers of samples in the International Headache Genetics Consortium. This meant that the database was not optimally equipped for epidemiological research questions. We unfortunately had to go back to our patients with additional questionnaires a few times, thereby decreasing the adherence of our population, and decreasing the numbers of eligible patients.

Another consideration regarding the LUMINA and LUCA databases is the question whether the use of these kinds of database for a range of different clinical questions is allowed by the rules of statistics. Conservative voices might argue that only 1 pre-defined question could be answered using such a database, with a number of included patients calculated beforehand using a power calculation. Probably they will state that for every new question, a correction for multiple comparison should be introduced in the analyses, to reduce the risk of a false positive result to 5% (the type-I error). The exact count of the number of tests however, remains a difficult issue. Should we count all statistical tests regarding a specific issue, or all tests in one chapter of this thesis, or all tests ever performed within the LUMINA database during its lifetime? According to the well-known epidemiologist Rothman, 'the policy of not making adjustments for multiple comparisons is preferable because it will lead to fewer errors of interpretation when the data under evaluation are not random numbers but actual observations on nature', whereas a basic premise of empirical research is that nature follows a regular law, and an expected order, that may be studied through observations. (54) We have concluded that, if the hypothesis is strictly defined in advance, with one primary outcome measure and at most a few secondary outcome measures, and a statistical plan has been designed which is followed exactly during the analyses, without extensive post-hoc sub-group analyses, no correction for multiple testing is needed if it were only for the fact that several papers arise from one and the same database. LUMINA and LUCA are both progressively growing databases, with new patients entering almost on a daily basis. As a consequence, future research questions will be answered in a (partially) different population. It is needless to say that the extent of both databases allows for more than one research question. Lastly, research questions in LUMINA and LUCA are most of the time not fully independent, which makes strict correction for multiple testing (i.e. following the Bonferroni correction) a too conservative choice.

Although we previously described the LUMINA population as a clinical based cohort, we now feel that it is better to describe it as a 'well-defined, web-based migraine population'. In fact, it is a mix of clinical based and population based participants, because of the collection via our website. In the LUMINA population 70% used triptans. Compared to other countries this may seem high but in the Netherlands and some Scandinavian countries the use of triptans in population

based studies is amongst the highest. Furthermore, 87% was previously diagnosed with migraine by a physician, 26% is currently seen by a neurologist, 43% by a general practitioner. The remaining 31% is not seen by a neurologist or a general practitioner. This proves that the LUMINA population contains the full range of migraine patients.

For the LUCA population, a clinically confirmed diagnosis of cluster headache by a physician was available for 94%. For the remaining 6%, no clinically confirmed diagnosis was available, for instance because they never consulted a doctor. Still, for cluster headache it is almost impossible to collect a population based cohort, because of the low prevalence.

Lastly, we would not use our algorithm for lifetime depression in our daily psychiatric practice, whereas we think that the eye of the experienced and evidence-based working clinician is the only guarantee for reliable depression diagnoses. In clinical practice it is most important to combine symptoms, as presented by the patients, with the archetypical presentation of depression as we want to observe in our psychiatric examination, and which thereafter might fit into our classification system as a ´DSM-5 defined depression'. Clearly, the use of self-report questionnaires could never replace this kind of diagnostic finesse. Nevertheless, we would like to defend our depression definition as an accurate measurement for purposes of scientific research, knowing that extensive psychiatric examination is impracticable if the primary purpose of the project is to collect thousands of patients for genetic research.

9.2.11 Clinical implications of our findings

Chapter 2 and **chapter 3** show clear involvement of cutaneous allodynia in the triad of migraine chronification, depression, and medication overuse. Clinically, central sensitization causes refractoriness to acute treatment. (21) Thus, allodynia has consequences for disease progression and treatment, and it should lead to an increased awareness of comorbidity of migraine and depression, and of risk of chronification of migraine. As described in **chapter 3**, the clinical findings from this study correspond with the pathophysiological mechanism of CA. The underlying mechanism of migraine and allodynia is activation of the trigeminovascular neurons. (55) The activation of the trigeminovascular pathway contributes: i) to the headache phase of the migraine attack by sensitization of peripheral trigeminovascular neurons innervating the meninges; ii) to the cephalic allodynia by sensitization of second-order neurons in the spinal trigeminal nucleus (in the medullary dorsal horn) that receive input form the meninges, scalp and facial skin; and iii) to the development of extracephalic allodynia by third-order neurons in the posterior thalamic nuclei which receive input form meninges, facial and body skin. (55) Importantly, once established, sensitization of second order

trigeminovascular neurons becomes activity independent, and maintains itself in the absence of sensory input later on. (55) The activity-independent form is the consequence of neurotransmitter and neuromodulator induced activation of multiple intracellular signalling pathways. Activity-independent sensitization develops slowly over several hours and lasts for a prolonged period of time. (56) This has important clinical implications, as late treatment with triptans during an attack is unsuccessful when this independent activity has occurred. (21) Finding out which critical thresholds are exceeded before central sensitization occurs will potentially lead to new medications preventing sensitization.

The high prevalence of depression in our HM cohort, described in **chapter 4**, also may have clinical implications. HM patients should be screened for depression, and migraine prophylactics such as flunarizine or topiramate which may provoke depressive symptoms should perhaps be prescribed with caution in HM patients with active depression. (57)

Previous studies suggest that patients with (chronic) headache or high headache related disability, are more prone to use unsuitable coping mechanisms (43), score low on pain acceptance (44) and high on catastrophizing scales, and experience a low internal pain control. (45) In patients with migraine, pain control and self-management can be improved by behavioural therapy. (46) We hypothesize that contact with a headache nurse (**chapter 6**) influences the above-mentioned factors and thus will help patients to endure the withdrawal period. With the support of a headache nurse, comprising only one face-to-face contact and a median of three contacts by telephone, 75% of patients with medication overuse headache succeed to undergo a highly cost-effective outpatient withdrawal therapy, which is easily implemented in general neurology practice.

Our data from **chapter 8** suggest that current cluster headache attacks are associated with increased symptoms of depression, and worse sleep quality. Therefore, we may conclude that unsuccessful treatment of cluster headache is associated with poor outcomes: depression and sleeping problems. This underlines the importance of adequate treatment for cluster headache. Another striking and clinically potentially relevant finding of our study was that, in all likelihood, depression is considerably underdiagnosed and undertreated in cluster headache patients. Early detection of comorbid depression in cluster headache may be important to prevent suicide in this unbearably painful primary headache disorder.

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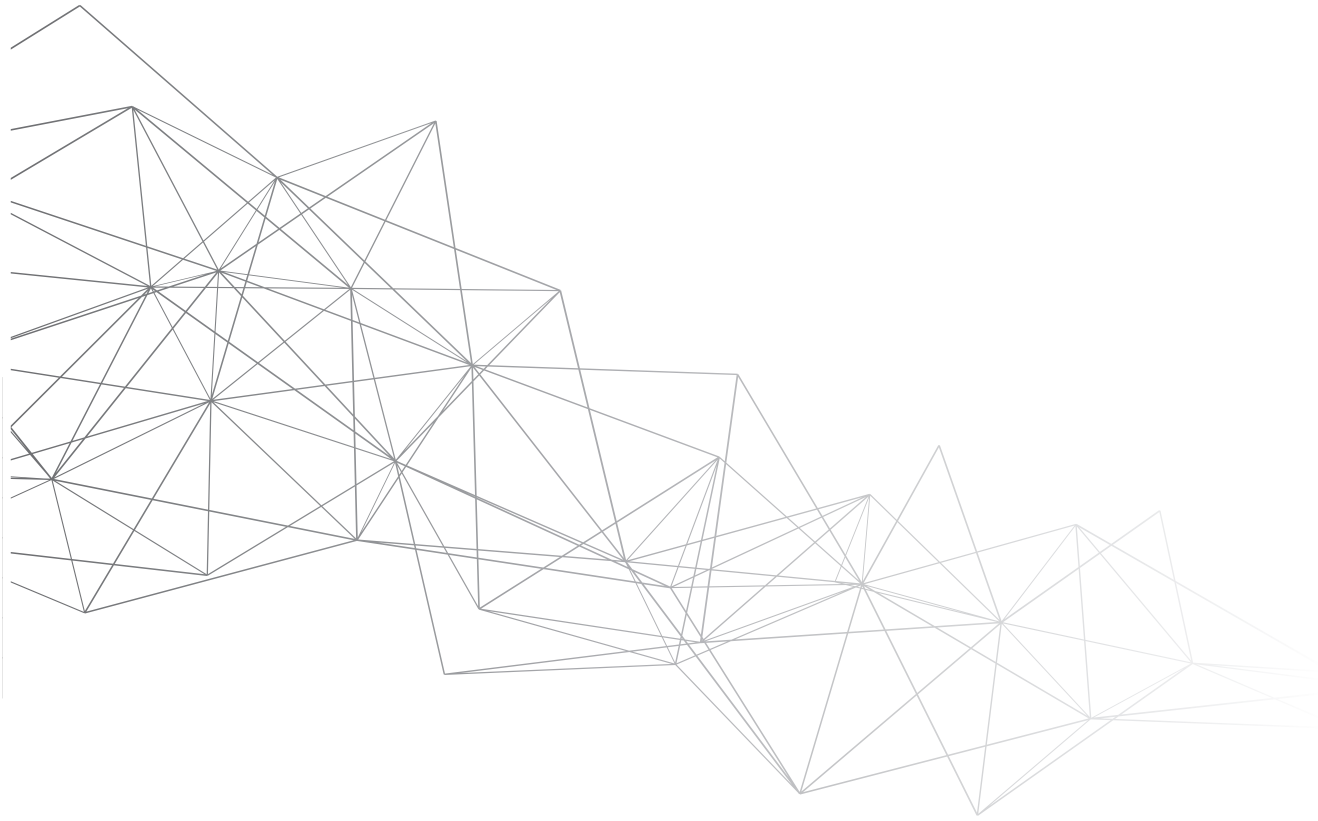
10 CHAPTER

Nederlandse samenvatting
List of publications
Curriculum Vitae en Dankwoord



Nederlandse samenvatting

Hoewel voorheen al onderzoek is verschenen naar verschillende onderdelen van de migrainedriehoek: chronificatie, depressie, en medicatieafhankelijkheid, waren er nog altijd ontbrekende stukken van de puzzel. Dit proefschrift onderzocht verschillende aspecten van deze driehoeksrelatie, waarbij wij ons richtten op:

- klinische determinanten van depressie in migrainepatiënten (**hoofdstuk 2 en 3**),
- de associatie van depressie met migraine aanvalsfrequentie, zowel in dwarsdoorsnede onderzoek (**hoofdstuk 2**) als in longitudinale studieopzet (**hoofdstuk 3**),
- de rol van allodynie van de huid in zowel de comorbiditeit met depressie alsook migraine chronificatie (**hoofdstuk 2 en 3**),
- symptoomdimensies van affectieve stoornissen in migrainepatiënten, in vergelijking met personen zonder migraine met en zonder affectieve aandoeningen (**hoofdstuk 5**),
- de comorbiditeit van depressie in hemiplegische migraine, als een monogenetisch migraine fenotype (**hoofdstuk 4**),
- genetische factoren die betrokken zijn bij migraine chronificatie (**hoofdstuk 7**),
- de comorbiditeit van depressie in clusterhoofdpijn, als een ernstige episodische primaire hoofdpijnvorm anders dan migraine (**hoofdstuk 8**), en
- de behandeling van medicatieafhankelijke hoofdpijn.

De meest opmerkelijke bevindingen worden samengevat in dit hoofdstuk.

Hoofdstuk 1 biedt een algemene introductie in het onderwerp van dit proefschrift. Epidemiologie, criteria, pathofysiologie, genetica, en behandeling van zowel migraine als depressie worden beschreven, alsook migraine chronificatie en de rol van medicatieafhankelijkheid. Voorts voorziet het hoofdstuk in een introductie over de comorbiditeit van migraine met depressie, wat we daarover al weten, en specifieke overblijvende vragen die in dit proefschrift behandeld zullen worden.

In **hoofdstuk 2** wordt de comorbiditeit van migraine met depressie bestudeerd in onze LUMINA populatie, inclusief de identificatie van migraine specifieke factoren die betrokken zijn bij deze associatie. In een groep met 2533 migrainepatiënten, voldeden er 1137 (45%) aan de criteria voor lifetime depressie. Een hoge migraine aanvalsfrequentie en de aanwezigheid van huidallodynie bleken migraine specifieke factoren geassocieerd met een toegenomen prevalentie van depressie. Verder waren slecht slapen, het vrouwelijk geslacht, een hoge BMI, alleenstaand zijn, roken, en een lage alcoholconsumptie algemene determinanten van depressie in onze populatie. Deze studie identificeerde allodynie, in aanvulling op een hoge

aanvalsfrequentie, als een nieuwe migraine specifieke factor geassocieerd met depressie.

Hoofdstuk 3 beschrijft een studie onder 2331 migrainepatiënten uit de LUMINA populatie, waarbij we onderzoek deden naar huidallodynie (de gewaarwording van pijn als reactie op een niet-pijnlijke prikkel op de normale huid), in een longitudinale studieopzet. Allodynie wordt beschouwd als een klinische aanduiding voor centrale sensitizatie. We onderzochten of allodynie in migrainepatiënten een voorspeller kon zijn voor migraine chronificatie. Allodynie bleek, naar verwachting, hoogprevalent in onze migraineurs: 70% gaf aan allodynie te hebben tijdens migraineaanvallen. Allodynie bleek geassocieerd met de aanwezigheid van depressie (OR 1.52, 95% BI 1.26-1.84), alsook met het vrouwelijk geslacht, een lage leeftijd bij aanvang van de migraine, en een hoge migraine aanvalsfrequentie. Analyse van de longitudinale data liet zien dat allodynie een onafhankelijke voorspeller is voor een toename in het aantal migrainedagen gedurende een mediane follow-up duur van 2 jaar.

Als monogenetisch subtype is Hemiplegische Migraine (HM) een meer homogeen model om migraine pathofysiologie te bestuderen dan migraine subtypes met een complexer genetische achtergrond (zoals migraine met en zonder aura). Zodoende presenteren we in hoofdstuk 4 een cross-sectionele studie onder 89 goed gedefinieerde HM patiënten en 235 gezonde controles. HM patiënten vertoonden een verhoogde odds voor lifetime depressie (OR 3.73, 95% BI 2.18-6.38) in vergelijking met controles. Het gebruik van acute anti-migraine medicatie was geassocieerd met lifetime depressie.

In hoofdstuk 5 beschrijven we een studie waarin we voor het eerst een onderscheid maken naar symptoomdimensies van het affectieve stoornissen spectrum in een grote hoeveelheid migrainepatiënten. Hierbij worden 3174 migrainepatiënten uit de LUMINA populatie vergeleken met 561 gezonde controles, 1129 patiënten met huidige psychopathologie, en 477 patiënten met psychopathologie in het verleden, alle afkomstig van de NESDA populatie. Gebruikmakend van de MASQ-30 vragenlijst werden depressieve symptomen dimensioneel gemeten, waarbij werd gefocust op 3 symptoomdomeinen: het gebrek aan positief affect, somatische opwinding, en negatief affect. Migrainepatiënten verschilden significant van gezonde controles op alle 3 dimensies. Voor het gebrek aan positief affect en de negatief affect dimensie waren migrainepatiënten vergelijkbaar met de groep patiënten met psychopathologie in het verleden. Voor de dimensie somatische opwinding waren de scores van migrainepatiënten veel meer vergelijkbaar met de groep patiënten met huidige psychopathologie.

Hoofdstuk 6 beschrijft een retrospectieve gecontroleerde follow-up studie in 406 patiënten met medicatieafhankelijke hoofdpijn, met als doel vast te stellen

of de ondersteuning van een hoofdpijnverpleegkundige bij de behandeling van medicatieafhankelijke hoofdpijn, en om determinanten van respons op ontwenningsbehandeling te bestuderen. De percentages voor succesvol afkicken waren significant hoger in de groep die door een hoofdpijnverpleegkundige werd begeleid dan in de groep zonder begeleiding (73.1% vs. 60.7%, p=0.008), wat werd bevestigd in multivariate analyse (OR 1.73, 95 BI 1.11-2.71, p=0.016). Ondersteuning door een hoofdpijnverpleegkundige was niet geassocieerd met respons (een reductie van 50% of meer in het aantal hoofdpijndagen, na succesvol afkicken). De onderliggende primaire hoofdpijndiagnose, vastgesteld na afkicken, was significant gecorreleerd met respons (met een sterkere respons in de groep met onderliggend migraine, dan in de groep met onderliggend spanningshoofdpijn).

Om voor het eerst inzicht te verwerven in de genetische achtergrond van chronische migraine, beschrijven we in **hoofdstuk 7** een studie waarvan het doel was om te zoeken naar bewijs dat genetische factoren betrokken zijn bij het chronificatieproces van migraine. Na selectie van 144 *single nucleotide polymorphisms* (SNPs) uit 48 kandidaatgenen, testten we voor een associatie in twee stappen: de eerste stage bevatte 262 chronische migrainepatiënten, de tweede stage 226 patiënten met hoog-frequente migraine. Acht SNPs waren significant geassocieerd met zowel chronische migraine als hoog-frequente migraine. Geen van deze SNPs overleefde echter de replicatiefase, waardoor deze studie geen significante resultaten opleverde.

We wilden onderzoeken of de associatie van hoofdpijnaanvallen met depressie specifiek was voor migraine. Omdat clusterhoofdpijn verscheidene klinische, therapeutische en pathofysiologische overeenkomsten vertoont met migraine, en studies betreffende de comorbiditeit van clusterhoofdpijn met depressie ontbraken, bleef de vraag over of depressie tevens comorbide was met clusterhoofdpijn. **Hoofdstuk 8** beschrijft dat 44% van de 462 clusterhoofdpijn patiënten uit de LUCA populatie voldoet aan de criteria voor lifetime depressie (OR 2.77, 95% BI 1.70-4.51). Chronische (n=67) vs. episodische (n=394) patiënten hadden een hogere prevalentie van lifetime depressie en meer slaapproblemen. Huidige depressie was geassocieerd met huidige aanvallen (laatste aanval minder dan 1 maand geleden) (gecorrigeerde p=0.02), maar dit effect verdween na correctie voor slaapproblemen.

List of publications

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Curriculum vitae

Mark Louter was born in Moerkapelle on August 24, 1982. After finishing athenaeum at the Driestar College (Gouda) in 2000, he started Medical School at Leiden University. During his medical study he performed a scientific internship under supervision of dr. G.M. Terwindt, performing a 10-year follow-up study on patients with Sporadic Hemiplegic Migraine. After finishing his clinical rotations he achieved his medical degree in 2009. He started working as a researcher in training at the departments of Neurology and Psychiatry of the Leiden University Medical Centre. His research, supervised by prof. Michel Ferrari (neurologist), dr. Gisela Terwindt (neurologist) and prof. Frans Zitman (psychiatrist), focused on the comorbidity of migraine with depression, and the involvement of medication overuse and chronification of migraine in this comorbidity. In June 2013 Mark started his training in Psychiatry at the Leiden University Medical Centre and GGZ Rivierduinen, under supervision of prof. Roos van der Mast and drs. Frank Huismans. He is currently working as resident in Psychiatry at 'De Viersprong', a psychotherapeutic centre for patients with severe personality disorders in Bergen op Zoom.

Dankwoord

Mijn dank gaat eerst en vooral uit naar Gisela Terwindt, die mij in meer dan 10 jaar tijd zowel wetenschappelijk-inhoudelijk als persoonlijk heeft begeleid en gevormd. Michel Ferrari, dank voor de plaats in je gerenommeerde onderzoeksgroep, waar ik als toekomstig psychiater me toch altijd op mijn plek heb gevoeld. Ik dank Frans Zitman voor zijn relativerende aanwezigheid op afstand, als psychiatrisch geweten van dit proefschrift.

De patiënten die deelnamen aan de verschillende vormen van onderzoek die hebben geleid tot de publicaties in dit proefschrift, wil ik danken voor hun bijdrage aan kennis over de migrainedriehoek. Zonder bereidwillige patiënten, die keer op keer vragenlijsten kregen in te vullen, of bloed lieten afnemen, of in welke vorm ze dan ook hebben bijgedragen, was dit proefschrift niet tot stand gekomen. Ik ben hen daarvoor zeer erkentelijk.

De kamer- en ganggenoten van de K5, met name Ron van Oosterhout en Ronald Zielman, ben ik dankbaar voor prachtige jaren, waarin spanning en ontspanning, wetenschappelijk en profaan, elkaar in een prettig tempo opvolgden. Samenwerken op wetenschappelijk gebied heeft geleid tot veel gezamenlijke publicaties, waarvoor in het bijzonder dank aan Anine Stam, Boukje de Vries, Antonette Smelt, Ron van Oosterhout, Poldi Wilbrink, Nadine Pelzer en Gerthe Veen. Wetenschapsstagestudenten hebben gedurende mijn gehele onderzoeksperiode een belangrijke bijdrage geleverd aan de dataverzameling, waarvoor dank. Met veel plezier kijk ik ook terug op het voorbereiden en uitvoeren van de CHARM trial, met Gisela Terwindt, Mark Kruit, Dennis Kies en Judith Pijpers. Jennifer Trouerbach wil ik danken voor de samenwerking op de hoofdpijnpolikliniek, zowel in het kader van de wetenschap als de patiëntenzorg.

Tijdens mijn opleiding tot psychiater is er veel tijd geweest om wetenschappelijk werk te kunnen verzetten, met dank aan mijn opleider Roos van der Mast. Zij is in de afgelopen jaren meer dan wie ook inspirerend en vormend geweest voor de manier waarop ik het vak van psychiater wil uitoefenen. Frank Huismans, Bert van Hemert, Joost Fransen en Ineke Gras, dank voor de manier waarop jullie mij hebben geholpen na te denken over mijn toekomst. Martijn van Noorden, je bent een continue factor geweest sinds mijn eerste binnenkomst op de afdeling Psychiatrie in 2008. Dank voor je begeleiding bij wetenschap en kliniek, maar ook op persoonlijk vlak.

Hanneke, we delen geloof, hoop en liefde, en dat is goed. Het maakt me gelukkig dat we in de jaren die achter ons liggen beiden met toewijding, plezier en passie konden werken aan wat ons inspireert. Emma, Hugo en Marcus: *Geluk is langzaam naar beneden gaan en daar zitten wachten op stappen, tussen muren bedekt met tekeningen: vaders, moeders, kinderen, tafel, huis, voorgoed aan het ontbijt. En ik was één van hen* (R. Kopland, 'Er moeten toch mensen wonen' uit: Verzamelde gedichten, 2006).