The migraine triad: chronification, depression, and medication overuse

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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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and:

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

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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

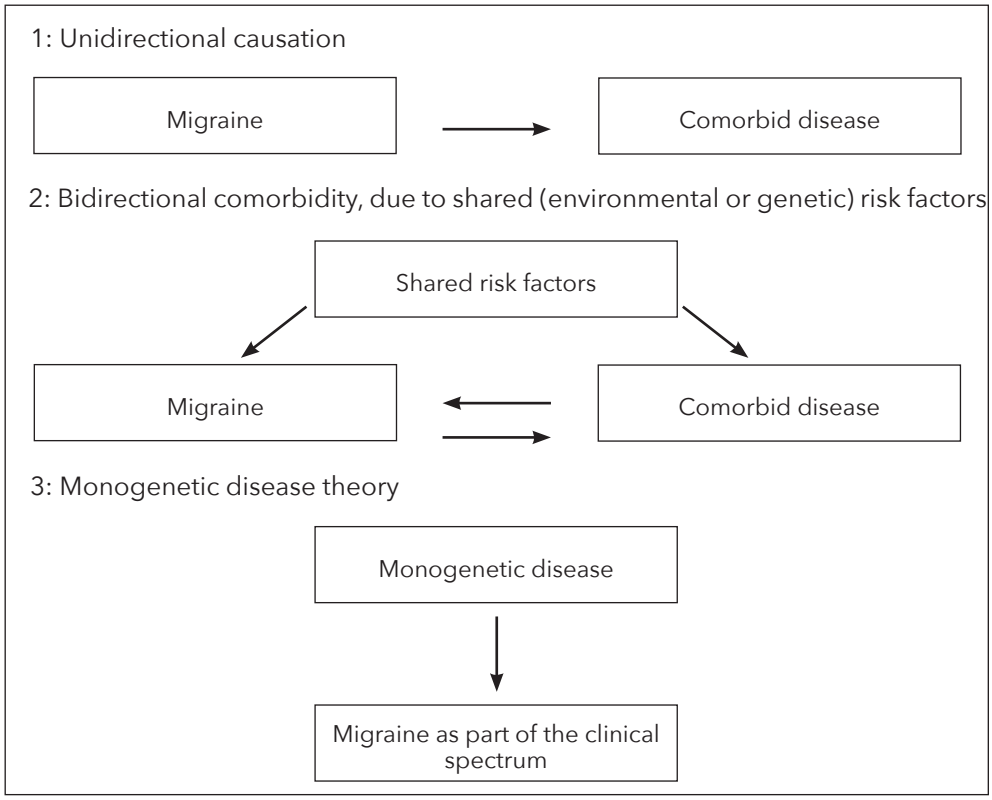
The interpretation of comorbidity is not always simple. In fact, true comorbidity can be caused by different mechanisms (figure 1). The first mechanism is that there is a unidirectional causation, which states simply that migraine may be a risk factor for another disease. In this case, it would be predicted 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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