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Trigger factors and mechanisms in migraine

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CHAPTER 1

GENERAL INTRODUCTION



CLINICAL FEATURES OF MIGRAINE

Migraine is a severe paroxysmal neurovascular disorder and considered a major cause of disability by the World Health Organisation^{1,2}. The duration of a migraine attack is between 4 to 72 hours³ and a full blown attack consists of four phases: premonitory, aura, headache and recovery^{4,5}. The premonitory phase can last up to 24 hours and consists of a wide range of symptoms, such as mood disturbances, autonomic symptoms and concentration problems. The prevalence of premonitory symptoms is unclear and ranges from 8%⁶ to 80%⁷ in a clinic based sample. The second phase is the aura phase. Approximately 33% of migraine patients report aura symptoms during an attack⁸ which mostly consist of visual or sensory phenomena⁹. Headache is the third part of an attack and for many patients the most prominent phase. The typical headache during a migraine attack is moderate to severe, unilateral, pounding and aggravates during physical activity. The headache is accompanied by nausea, vomiting and phono/photophobia (Table 1). The final phase of a migraine attack is the recovery phase consisting of symptoms that are similar to the premonitory phase⁷. The clinical presentation of a migraine attack can differ within and between migraine patients⁹.

EPIDEMIOLOGY AND ATTACK SUSCEPTIBILITY

The one year prevalence of migraine in the Netherlands is 25% in women and 7.5% in men⁸ and in the USA the one year prevalence is 17.2% in women and 6% in men¹⁰. Everybody can have a migraine attack, but it is the recurrence of attacks that is abnormal¹¹. A patient is considered a migraine patient only after five MO attacks or two MA attacks according to the IHS criteria³. Attack frequency varies between and within patients and the occurrence of a migraine attack is the result of a misbalance between susceptibility and trigger factors¹². Migraine susceptibility is strongly influenced by genetic factors¹³ and prophylactic treatment¹⁴. Up to now three genes have been identified in familial hemiplegic migraine which is a subtype of migraine with aura¹⁵⁻¹⁷. Whether these genes are involved in the common types of migraine is unknown^{18,19}. Besides genetic factors, prophylactic drugs have shown to alter susceptibility for migraine. Beta-blockers and anti-epileptic drugs are first choice, however, their efficacy is rather limited¹⁴.

Table 1 IHS diagnostic criteria for migraine with and without aura

1.1 Migraine without aura		_____ regel 1
A. At least 5 attacks fulfilling criteria B–D		_____ regel 2
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)		_____ regel 3
C. Headache has at least two of the following characteristics:	1. unilateral location	_____ regel 4
	2. pulsating quality	_____ regel 5
	3. moderate or severe pain intensity	_____ regel 6
	4. aggravation by or causing avoidance of routine physical activity (eg, walking or	_____ regel 7
	1. nausea and/or vomiting	_____ regel 8
D. During headache at least one of the following:	2. photophobia and phonophobia	_____ regel 9
E. Not attributed to another disorder		_____ regel 10
		_____ regel 11
1.2 Migraine with aura		_____ regel 12
A. At least 2 attacks fulfilling criteria B–D		_____ regel 13
B. Aura consisting of at least one of the following, but no motor weakness:	1. fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)	_____ regel 14
	2. fully reversible sensory symptoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)	_____ regel 15
		_____ regel 16
C. At least two of the following:	1. homonymous visual symptoms and/or unilateral sensory symptoms	_____ regel 17
	2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes	_____ regel 18
		_____ regel 19
D. Headache fulfilling criteria B–D for 1.1 <i>Migraine without aura</i> begins during the aura or follows aura within 60 minutes		_____ regel 20
		_____ regel 21
E. Not attributed to another disorder		_____ regel 22
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TRIGGER FACTORS FOR MIGRAINE

A trigger for migraine is any factor that on exposure or withdrawal leads to the development of a migraine attack.²⁰ An extensive list of factors has been proposed as possible trigger factors for migraine (Table 2). Observational questionnaire studies often suggest strong associations between possible trigger factors and migraine which rarely is confirmed by prospective studies and experimental trials. Using questionnaires

regel 1 _____ it is easy to reach a large number of patients, however associations are mainly based
regel 2 _____ on retrospective data and should be regarded as hypothesis generating²¹. On the other
regel 3 _____ hand experimental studies mainly focus on one factor at the time. In the next section,
regel 4 _____ possible trigger factors will be grouped into six categories: food products, stress, female
regel 5 _____ hormones, atmospheric, pharmacological and other factors.

A) Food products

regel 6 _____
regel 7 _____ The occurrence of migraine is often linked to the intake of certain food products and
regel 8 _____ migraine has been described as food allergy²². Despite many studies, the association
regel 9 _____ between food products and migraine remains unclear. Based on retrospective
regel 10 _____ questionnaires a long list possible migraine triggering products has been formulated
regel 11 _____ (Table2). Among the most frequently mentioned products are alcohol (including
regel 12 _____ wine), cheese, chocolate as well as withdrawal of caffeine and missing a meal.²³⁻³⁰
regel 13 _____ Furthermore, several diet elimination studies suggest a positive association between
regel 14 _____ food and migraine.^{22,31-33} On the other hand, experimental provocation studies are less
regel 15 _____ positive. Red wine provoked migraine in 9 out of 11 migraine patients who were pre-
regel 16 _____ selected on being sensitive for red wine.³⁴ Chocolate triggered migraine in 5 out of
regel 17 _____ 12 "chocolate sensitive" migraine patients³⁵, whereas in a second study the headache
regel 18 _____ response after chocolate did not differ from placebo³⁶. Tyramine 200mg has also been
regel 19 _____ tested in a provocation study in 80 migraine patients and there was no difference in the
regel 20 _____ occurrence of headache between tyramine and placebo.³⁷ Prospective studies in which
regel 21 _____ the intake of food and the occurrence of migraine attacks are scored independently
regel 22 _____ using electronic diaries to prevent retrospective data entries are missing.
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B) Stress

regel 25 _____ Although no clear definition of stress exists³⁸, it has been linked to a whole range
regel 26 _____ of diseases including multiple sclerosis³⁹, asthma⁴⁰ and risk factors for cardiovascular
regel 27 _____ disease.⁴¹ In migraine, both mental and physical stressors are frequently reported as
regel 28 _____ trigger factor. In retrospective questionnaire studies between 30.5% and 81.8% of
regel 29 _____ patients reported psychosocial stressors as trigger factor, whereas between 15.5% and
regel 30 _____ 43.1% of patients identified physical stressors as possible trigger factor (Table 2). Also
regel 31 _____ prospective studies using diaries suggest a positive association between mental stress
regel 32 _____ and migraine.^{42,43} However, this seemingly apparent association between stress and
regel 33 _____ migraine is difficult to replicate in observational and experimental studies using biological
regel 34 _____ stress parameters such as cortisol and cardiovascular parameters. In experimental studies
regel 35 _____ no difference was found in cardiovascular response between the migraine attack and
regel 36 _____ the inter-ictal state.^{44,45}
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Table 2 Potential trigger factors for migraine.

	Trigger factor	Response rate* Range (%)	
Food products ^{24-30,119}	Various food items	10 – 36	
	Missing a meal	0.9 – 55.8	
	Chocolate	0 – 22.5	
	Wine	1.4	
	Alcohol	20	
	Dairy products	18.5	
	Caffeine (withdrawal)	6.4	
Atmospheric ^{24-29,120}	Weather changes	6.9 – 52.3	
	Sunlight exposure	4.2 – 38	
	Altitude/ hypoxia		
	Chinook winds		
Stress ^{24-30,121}	Smoking	2 – 26	
	Psychosocial	30.5 – 81.8	
	Physical	15.5 – 43.1	
Female Hormones ^{24-30,122}	Vacation and travel	8 – 54.6	
	Menstruation	20.7 – 53.5	
Pharmacological	Nitroglycerin ^{55,56,78,116,123-129}	20 -83%	
	Sildenafil ⁵⁸	83	
	Dipyridamole ¹³⁰	50	
	Histamine ⁶⁴	50	
	M-chlorophenylpiperazine ⁵⁹	53	
	Calcitonin gene related peptide ⁶¹	33.3	
	Acetazolamide ⁶⁵	Not tested in RCT	
	Prostaglandine E1 ⁶⁸	Not tested in RCT	
	Reserpine ⁶⁹	Not tested in RCT	
	Calcineurin inhibitors ⁷⁰	Not tested in RCT	
	Polidocanol foam ⁷¹	Not tested in RCT	
	Other	Sleep (lack or excess) ⁷²	31 – 52.4
		Visual stimulation ⁷³	
Cerebral angiography ⁷²			
Sexual activity ⁷⁴		0 – 11	
	Use of personal computer ²⁴	6.6	

*Response rate are based on findings in questionnaire studies, prospective diary studies or experimental provocation studies.

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C) Female hormones

Based on clinical arguments there is a strong association between female hormones and the occurrence of migraine attacks. The life time prevalence of migraine is 3 times higher in females compared to males⁸, between 20.7% and 53.5% of females reported an association between menstruation and migraine (Table 2) and there is a decrease in migraine frequency during pregnancy.⁴⁶ In a study of 40 female migraine patients, the incidence of migraine attacks was inversely associated with urinary oestrogen concentration across the menstrual cycle. There was no association between migraine and urinary concentrations of progestogens.⁴⁷

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D) Atmospheric

Weather changes have also been linked to a wide variety of medical diseases⁴⁸ including migraine.⁴⁹ Retrospective questionnaires showed that between 6,9% and 52,3% of migraine patients identify weather changes as possible trigger factor (Table 2). In contrast three prospective studies, combining objective weather data from meteo institutes with information from headache diaries or visits to the emergency room for migraine, showed no positive associations.⁵⁰⁻⁵² Only one study found a positive relation between weather changes and the occurrence of headache in 77 migraine patients.⁵³ Furthermore there is a large discrepancy between what patients think and what can be objectified. For instance a positive association between Chinook winds and migraine attacks was suggested by 88% of 34 migraine patients, whereas an objective correlation could only be found in 21% of patients.⁵⁴ Experimental studies including atmospheric parameters are limited in number.

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E) Pharmacological

Nitroglycerin (NTG) is frequently used in migraine provocation studies (Table 2). The clinical response after NTG (0.5 micrograms/kg/20min) consists of an immediate type headache during infusion and a delayed headache attack after 5 to 6 hours which fulfils the criteria of migraine without aura in 20% to 83% of patients (Table 2). Migraine patients without aura might be more susceptible to nitroglycerin than patients with aura.^{55,56} Sildenafil (Viagra) is a highly selective phosphodiesterase type 5 inhibitor used to treat patients with erectile dysfunction⁵⁷ and in migraine susceptible patients Viagra has shown to provoke delayed migraine attacks in 10 out of 12 patients.⁵⁸ A third drug shown to provoke migraine is m-chlorophenylpiperazine (mCPP). Migraine attacks were triggered in 10 out of 19 migraine patients (53%) in a randomized controlled trial.⁵⁹ Also in a study including patients with bulimia and anorexia nervosa, mCPP triggered severe headache 28 out of 52 patients (54%).⁶⁰ Calcitonin gene related

peptide (CGRP) is a vasoactive peptide that is increased during spontaneous migraine attacks⁶¹. In turn, infusion of CGRP triggers migraine in 3 out of 9 susceptible migraine patients.⁶² The neurotransmitter histamine has also shown to trigger moderate to severe throbbing headache in migraine susceptible patients⁶³ fulfilling the criteria for migraine in 50% of the migraine patients.⁶⁴ Besides aforementioned drugs, several others drugs might be capable of triggering migraine, but they are up to now never been tested in a formal randomized controlled trial (RCT). Acetazolamide (Diamox), a carbonic anhydrase inhibitor, is both used to provoke and to treat migraine. Oral administration of acetazolamide (14.3 mg/kg) in 20 migraine patients caused migraine headache accompanied by photophobia, phonophobia and nausea after 1 to 8 hours.⁶⁵ The number of patients fulfilling the criteria for migraine was not specified in this study. In contrast, diamox (500 to 750 mg daily) has also been used as treatment in migraine and it might be effective in the acute treatment of migraine aura status.⁶⁶ Furthermore, diamox (500mg) has been tested as prophylaxis for migraine in 53 patients and was not effective.⁶⁷ And finally prostaglandine E1⁶⁸, reserpine⁶⁹, calcineurin inhibitors (eg, cyclosporine and tacrolimus) ⁷⁰ and polidocanol foam⁷¹ might be able to provoke migraine attacks in susceptible patients.

F) Other possible trigger factors

Sleep (lack or excess) and fatigue are frequently associated with migraine attacks (Table 2). Also in a prospective diary study the quality of sleep seemed to be negatively associated with the occurrence of migraine attacks.⁷² Visual stimulation has been used to trigger migraine in a fMRI study.⁷³ Two (out of 10) migraine patients with aura experienced a typical migraine aura and 8 (out of 12) experienced migraine headache within 7.3 minutes after provocation. Whether these headache episodes fulfilled migraine criteria was not described. Cerebral angiography using contrast agent has shown to induce headache in 15 (out of 45) patients after 2 hours.⁷² In four patients (8.8%) symptoms fulfilled criteria for migraine without aura. Sexual activity has also been associated with a wide range of positive as well as negative effects, including headache and migraine (Table 1). There is even a sub classification for "preorgasmic" and "orgasmic" headache.³ In a group of 51 patients with "headache associated with sexual activity" co morbidity with migraine was 25%.⁷⁴ Whether it is just physical stress causing headache or something extra during sexual activity is not known. The use of personal computer (PC) is a rather new factor and identified as possible trigger factor in 6.6% of Japanese migraine patients.²⁴ This factor has not been included in other questionnaire studies or experimental trials.

PATHOPHYSIOLOGY OF A SPONTANEOUS MIGRAINE ATTACK

Activation of the trigeminovascular system is pivotal during the headache phase of a migraine attack⁷⁵. The mechanism causing activation of the trigeminovascular system remains to be elucidated^{12,76}. Several mechanisms might be involved in the initiation of a migraine attack. A) Cortical spreading depression (CSD) is a steady depolarization of neuroglial membranes and is the pathophysiological mechanism underlying migraine aura¹². A long-lasting blood flow change in meningeal arteries have been observed after CSD depending on trigeminal and parasympathetic activation⁷⁷. B) Vasodilatation of cerebral and meningeal arteries might activate trigeminal nerves. Vasoactive substances such as nitroglycerin can trigger migraine in susceptible patients⁷⁸ and triptans may exert their anti-migraine effect through vasoconstriction of cranial blood vessels⁷⁵. C) Neurogenic inflammation caused by vasoactive peptides released from the trigeminal nerve or other sources such as blood have shown to activate and sensitize meningeal perivascular nerve ending causing activation of the trigeminovascular system⁷⁹ and possible disruption of the blood-brain barrier⁸⁰. D) Nociceptive information from the trigeminal nerve is modulated in the brainstem⁸¹. Activation of brainstem area's, such as the peri-aqueductal grey, has been shown during spontaneous and provoked migraine attacks^{82,83}. E) The occurrence of premonitory symptoms (such as fluid retention, sleep problems and food craving) prior to the onset of headache suggest involvement of the hypothalamus.^{84,85} Hypothalamic activation has also been shown in other trigeminal neuralgias, such as cluster headache⁸⁶. For further information on the pathophysiology of migraine please read some excellent reviews that have been published recently^{12,75,79,87}.

MECHANISM OF ACTION OF TRIGGER FACTOR IN MIGRAINE: STRESS, HYPOXIA AND NITROGLYCERIN

As presented, there are many (potential) trigger factors for migraine all with a different mechanism of action. Since it is not feasible to study all we will focus on three trigger factors: mental stress, normobaric hypoxia and nitroglycerin. The study of trigger factor mechanisms may provide further insight into the first phases of a migraine attack

A) Stress and the autonomic nervous system during migraine

Mental stressors are commonly perceived as important trigger factors by both patients and physicians⁸⁸, although direct evidence for this claim is lacking. In retrospective questionnaire studies, up to 62% of migraine patients reported that psychosocial stress

was an important trigger-factor for their attacks^{25,29,89}, but patients have a tendency to overestimate stress on retrospective measures⁹⁰. In cross-sectional studies, migraine patients were found to have elevated plasma levels of cortisol, an indicator for stress, both outside a migraine attack compared to healthy volunteers⁹¹ and during attacks compared to the inter-ictal phase⁹². Stress-provocation studies, involving mental and physical stressors, have suggested sympathetic and parasympathetic changes in migraine patients outside attacks compared to healthy volunteers⁹³⁻⁹⁶. However, experimental prospective studies examining whether stress-related biological changes are actually temporally related to the onset of migraine attacks, are lacking. We therefore performed a prospective, longitudinal ambulatory study, assessing perceived stress and objective stress-related biological changes in the four days prior to an impending migraine attack (chapter 2).

B) Hypoxia and blood brain barrier dysfunction

Hypoxia might also be a trigger factor for migraine. Firstly, acute exposure to high altitude may induce acute mountain sickness (AMS), which is characterized by headache, insomnia, dizziness, lassitude, fatigue and gastrointestinal symptoms such as anorexia, nausea, or vomiting in an unacclimatized person who has recently reached an altitude above 2500 m⁹⁷. Up to one third of subjects with acute AMS also fulfill the criteria for migraine^{3,98,99}. Secondly, chronic exposure to high altitude is associated with an increased migraine prevalence^{100,101} and thirdly, sumatriptan is an established drug for the acute treatment of migraine⁷⁵, and was also shown to be effective in some studies in AMS^{102,103}. In chapter 3 we have tested whether normobaric hypoxia may trigger migraine attacks in migraine patients under experimental conditions. Hypoxia has many biological effects and one of the mechanisms involved in the pathophysiology of AMS is disruption of the BBB causing cerebral edema⁹⁷. In severe cases of AMS there are clear signs of vasogenic edema as shown by MRI¹⁰⁴. Also in migraine disruption of the BBB has been suggested¹⁰⁵. Whether hypoxia causes cerebral edema in mild cases of AMS (resembling migraine) is unclear. This question was studied in chapter 4.

C) Nitroglycerin and changes in cerebral blood flow

Nitroglycerin is an exogenous donor of nitric oxide¹⁰⁶, which is involved in central pain mechanism¹⁰⁷ and regulation of cerebral blood flow¹⁰⁸. Infusion of NTG has shown to increase the diameter of the middle cerebral artery¹⁰⁹ and meningeal media artery¹¹⁰ as well as to decrease blood flow velocity in the internal carotid artery and middle cerebral artery¹¹¹⁻¹¹³. The effects of NTG on cerebral blood flow are caused either through the release of CGRP from the trigeminal nerve^{114,115} or via a direct effect on vascular smooth

regel 1 _____ muscle cells in blood vessels¹⁰⁶. Infusion of NTG results in immediate type headache
regel 2 _____ in >80% of migraine patients and <20% in healthy volunteers¹¹⁶. A delayed migraine
regel 3 _____ attack is observed several hours after infusion of NTG in approximately 60% to 80%
regel 4 _____ of migraine patients and very rarely in healthy volunteers without a family history of
regel 5 _____ migraine^{55,78,116}. Whether there is a difference in cerebrovascular response to NTG
regel 6 _____ between migraine patients and healthy controls is unclear. One study suggested an
regel 7 _____ increased cerebrovascular response during NTG infusion in migraine patients¹¹⁷, whereas
regel 8 _____ in a second study no increased response was observed.¹¹⁸ This will be studied in chapter
regel 9 _____ 6. In the same provocation study (chapter 7) we have studied cerebrovascular changes
regel 10 _____ (both blood vessel diameters and blood flow) during the provoked migraine attack.

AIMS OF THIS THESIS

regel 11 _____
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regel 15 _____ As discussed there are many potential trigger factors for migraine. We have chosen
regel 16 _____ to study three (potential) trigger factors: mental stress, normobaric hypoxia and
regel 17 _____ nitroglycerin. The following aims for this thesis were defined:

- regel 18 _____
regel 19 _____ 1. To assess the prevalence of premonitory symptoms in a clinic based sample of migraine
regel 20 _____ patients and to study a potential overlap between premonitory symptoms and trigger
regel 21 _____ factors (chapter 1).
- regel 22 _____
regel 23 _____ 2. To assess both subjective and objective stress related parameters during the
regel 24 _____ development of a spontaneous migraine attack (chapter 2).
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regel 26 _____ 3. To test normobaric hypoxia as a trigger factor for migraine in migraine susceptible
regel 27 _____ patients and to compare the response to nitroglycerin (chapter 3).
- regel 28 _____
regel 29 _____ 4. To test whether normobaric hypoxia caused cerebral edema in healthy volunteers
regel 30 _____ (chapter 4).
- regel 31 _____
regel 32 _____ 5. To develop a method to measure vasodilatation in cranial blood vessels as small as
regel 33 _____ the middle meningeal artery in healthy volunteers and migraine patients using magnetic
regel 34 _____ resonance angiography (chapters 5 and 6).
- regel 35 _____
regel 36 _____ 6. To assess the initial vascular response to nitroglycerin in migraine as a predictor for
regel 37 _____ the development of a provoked migraine attack (chapter 6).
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7. To assess vasodilatation in cranial blood vessels during a provoked migraine attack (chapter 7).

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