Trigger factors and mechanisms in migraine

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CHAPTER 1

GENERAL INTRODUCTION

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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 hours[3] 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 attack[8] which mostly consist of visual or sensory phenomena[9]. 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 phase[7]. The clinical presentation of a migraine attack can differ within and between migraine patients[9].

Epidemiology and attack susceptibility

The one year prevalence of migraine in the Netherlands is 25% in women and 7.5% in men[8] and in the USA the one year prevalence is 17.2% in women and 6% in men[10]. Everybody can have a migraine attack, but it is the recurrence of attacks that is abnormal[11]. A patient is considered a migraine patient only after five MO attacks or two MA attacks according to the IHS criteria[3]. Attack frequency varies between and within patients and the occurrence of a migraine attack is the result of a misbalance between susceptibility and trigger factors[12]. Migraine susceptibility is strongly influenced by genetic factors[13] and prophylactic treatment[14]. Up to now three genes have been identified in familial hemiplegic migraine which is a subtype of migraine with aura[15-17]. 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 limited[14].

Table 1 IHS diagnostic criteria for migraine with and without aura

1.1 Migraine without aura	
A. At least 5 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 characteristics:	1. unilateral location 2. pulsating quality 3. moderate or severe pain intensity 4. aggravation by or causing voidance of routine physical activity (*eg*, walking or
D. During headache at least one of the following:	1. nausea and/or vomiting 2. photophobia and phonophobia
E. Not attributed to another disorder	
1.2 Migraine with aura	
A. At least 2 attacks fulfilling criteria B–D	
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) 2. fully reversible sensory symptoms including positive features (*ie*, pins and needles) and/or negative features (*ie*, numbness)
C. At least two of the following:	1. homonymous visual symptoms and/or unilateral sensory symptoms 2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes	
E. Not attributed to another disorder	

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

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it is easy to reach a large number of patients, however associations are mainly based on retrospective data and should be regarded as hypothesis generating[21]. On the other hand experimental studies mainly focus on one factor at the time. In the next section, possible trigger factors will be grouped into six categories: food products, stress, female hormones, atmospheric, pharmacological and other factors.

A) Food products

The occurrence of migraine is often linked to the intake of certain food products and migraine has been described as food allergy[22]. Despite many studies, the association between food products and migraine remains unclear. Based on retrospective questionnaires a long list possible migraine triggering products has been formulated (Table2). Among the most frequently mentioned products are alcohol (including wine), cheese, chocolate as well as withdrawal of caffeine and missing a meal.[23-30] Furthermore, several diet elimination studies suggest a positive association between food and migraine.[22,31-33] On the other hand, experimental provocation studies are less positive. Red wine provoked migraine in 9 out of 11 migraine patients who were pre-selected on being sensitive for red wine.[34] Chocolate triggered migraine in 5 out of 12 "chocolate sensitive" migraine patients[35], whereas in a second study the headache response after chocolate did not differ from placebo[36]. Tyramine 200mg has also been tested in a provocation study in 80 migraine patients and there was no difference in the occurrence of headache between tyramine and placebo.[37] Prospective studies in which the intake of food and the occurrence of migraine attacks are scored independently using electronic diaries to prevent retrospective data entries are missing.

B) Stress

Although no clear definition of stress exists[38], it has been linked to a whole range of diseases including multiple sclerosis[39], asthma[40] and risk factors for cardiovascular disease.[41] In migraine, both mental and physical stressors are frequently reported as trigger factor. In retrospective questionnaire studies between 30.5% and 81.8% of patients reported psychosocial stressors as trigger factor, whereas between 15.5% and 43.1% of patients identified physical stressors as possible trigger factor (Table 2). Also prospective studies using diaries suggest a positive association between mental stress and migraine.[42,43] However, this seemingly apparent association between stress and migraine is difficult to replicate in observational and experimental studies using biological stress parameters such as cortisol and cardiovascular parameters. In experimental studies no difference was found in cardiovascular response between the migraine attack and the inter-ictal state.[44,45]

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	
	Smoking	2 – 26
Stress[24-30,121]	Psychosocial	30.5 – 81.8
	Physical	15.5 – 43.1
	Vacation and travel	8 – 54.6
Female Hormones[24-30,122]	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 males[8], 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]

D) Atmospheric

Weather changes have also been linked to a wide variety of medical diseases[48] 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.

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 dysfunction[57] 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 attacks[61]. 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 patients[63] 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 E1[68], reserpine[69], calcineurin inhibitors (eg, cyclosporine and tacrolimus) [70] and polidocanol foam[71] 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 attack[75]. 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 aura[12]. A long-lasting blood flow change in meningeal arteries have been observed after CSD depending on trigeminal and parasympathetic activation[77]. B) Vasodilatation of cerebral and meningeal arteries might activate trigeminal nerves. Vasoactive substances such as nitroglycerin can trigger migraine in susceptible patients[78] and triptans may exert their anti-migraine effect through vasoconstriction of cranial blood vessels[75]. 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 system[79] and possible disruption of the blood-brain barrier[80]. D) Nociceptive information from the trigeminal nerve is modulated in the brainstem[81]. Activation of brainstem area's, such as the peri-aquaductal 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 headache[86]. 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 physicians[88], 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 measures[90]. 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 volunteers[91] and during attacks compared to the inter-ictal phase[92]. Stress-provocation studies, involving mental and physical stressors, have suggested sympathetic and parasympathetic changes in migraine patients outside attacks compared to healthy volunteers [93-96]. 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 m [97]. 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 migraine [75], 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 edema[97]. In severe cases of AMS there are clear signs of vasogenic edema as shown by MRI[104]. Also in migraine disruption of the BBB has been suggested[105]. 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 oxide[106], which is involved in central pain mechanism[107] and regulation of cerebral blood flow[108]. Infusion of NTG has shown to increase the diameter of the middle cerebral artery[109] and meningeal media artery[110] as well as to decrease blood flow velocity in the internal carotid artery and middle cerebral artery[111-113]. 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

muscle cells in blood vessels[106]. Infusion of NTG results in immediate type headache in >80% of migraine patients and <20% in healthy volunteers[116]. A delayed migraine attack is observed several hours after infusion of NTG in approximately 60% to 80% of migraine patients and very rarely in healthy volunteers without a family history of migraine[55,78,116]. Whether there is a difference in cerebrovascular response to NTG between migraine patients and healthy controls is unclear. One study suggested an increased cerebrovascular response during NTG infusion in migraine patients[117], whereas in a second study no increased response was observed.[118] This will be studied in chapter 6. In the same provocation study (chapter 7) we have studied cerebrovascular changes (both blood vessel diameters and blood flow) during the provoked migraine attack.

Aims of this thesis

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

1. To assess the prevalence of premonitory symptoms in a clinic based sample of migraine patients and to study a potential overlap between premonitory symptoms and trigger factors (chapter 1).

2. To assess both subjective and objective stress related parameters during the development of a spontaneous migraine attack (chapter 2).

3. To test normobaric hypoxia as a trigger factor for migraine in migraine susceptible patients and to compare the response to nitroglycerin (chapter 3).

4. To test whether normobaric hypoxia caused cerebral edema in healthy volunteers (chapter 4).

5. To develop a method to measure vasodilatation in cranial blood vessels as small as the middle meningeal artery in healthy volunteers and migraine patients using magnetic resonance angiography (chapters 5 and 6).

6. To assess the initial vascular response to nitroglycerin in migraine as a predictor for the development of a provoked migraine attack (chapter 6).

7. To assess vasodilatation in cranial blood vessels during a provoked migraine attack (chapter 7).