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Clinical Characteristics and Pathophysiological Mechanisms of Familial Migraine with and without Aura

by
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Academic Dissertation

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, referred to in the text by their Roman numerals (I-VI):

I Kallela M, Wessman M, Färkkilä M. Validation of a migraine-specific questionnaire for use in family studies. European Journal of Neurology. In press.

II Kallela M, Wessman M, Färkkilä M, Palotie A, Koskenvuo M, Honkasalo M-L, Kaprio J. Clinical characteristics of migraine in a population-based twin sample: similarities and differences between migraine with and without aura. Cephalalgia 1999;19:151-158.

III Kallela M, Wessman M, Färkkilä M, Palotie A, Koskenvuo M, Honkasalo M-L, Kaprio J. Clinical characteristics of migraine-concordant monozygotic twin pairs. Acta Neurologica Scandinavica 1999;100:254-259.

IV Kallela M, Wessman M, Färkkilä M, Havanka H, Palotie A. Familial migraine with and without aura: clinical characteristics and co-occurrence. Submitted.

V Hovatta I, Kallela M, Färkkilä M, Peltonen L. Familial migraine: exclusion of the susceptibility gene from the reported locus of familial hemiplegic migraine on 19p. Genomics 1994;23:707-709.

VI Kallela M, Färkkilä M, Saijonmaa O, Fyhrquist F. Endothelin in migraine patients. Cephalalgia 1998;18:329-332.

ABBREVIATIONS

ANS	autonomic nervous system
ATP	adenine triphosphate
ß-blockers	ßeta-adrenoreceptor-blockers
Ca^{2+}	calcium
CACNA1A	the gene for a subunit of a P/Q-type calcium channel, related to FHM
CADASIL	cerebral autosomal dominant arteriopathy with stroke-like episodes and leukoencephalopathy
CGRP	calcitonin-gene related peptide
Cl^-	chloride
cM	centiMorgan
CT	computed tomography
DHE	dihydroergotamine
DNA	deoxyribonucleic acid
DRD2	dopamine receptor D_2
DZ	dizygotic
ET-1	endothelin-1
FHM	familial hemiplegic migraine
fMRI	functional magnetic resonance imaging
$FMSQ_{FS}$	Finnish Migraine-Specific Questionnaire for Family Studies
$FMSQ_0$	original version of the Finnish Migraine-Specific Questionnaire
$FMSQ_{TW}$	Finnish Migraine-Specific Questionnaire for Twin Studies
5-HT	5-hydroxytryptamine, serotonin
ICH	intracerebral haemorrhage
IHS	International Headache Society
ISA	intrinsic sympathomimetic activity
K^+	potassium
LC	locus coeruleus
LOD	logarithm of odds
MELAS	mitochondrial encephalopathy with lactic acidosis and stroke-like episodes
MRI	magnetic resonance imaging
mtDNA	mitochondrial deoxyribonucleic acid
MZ	monozygotic
Na^+	sodium
NO	nitric oxide
NOTCH3	the gene for CADASIL
NR	nucleus ruber, red nucleus
NRD	nucleus raphe dorsalis, dorsal raphe nucleus
NSAIDs	nonsteroidal anti-inflammatory drugs
PCR	polymerase chain reaction
PET	positron emission tomography
SAH	subarachnoid haemorrhage
SD	standard deviation
SN	substantia nigra
TIA	transient ischemic attack

Abbreviations of the questionnaire-based diagnoses

Eqv	migraine aura without headache, migraine equivalent
HA	headache (no migraine)
MA	migraine with aura or migraine with and without aura
MU	migraine with unclassified aura
MwA	migraine with aura
MwA+MwoA	migraine with and without aura
MwoA	migraine without aura
NO_{MIG}	no migraine (headache can be present)
NoHA	a subject with no headache (or migraine)

1. INTRODUCTION

The recent progress of molecular genetics has widened horizons in many fields of medicine. In 1993 the first genetic locus was linked to a migraine disorder, familial hemiplegic migraine (FHM) (1), a rare autosomal dominant form of migraine with aura. Later the gene, *CACNA1A*, was identified and shown to code for one of the subunits of a voltage-dependent calcium (Ca^{2+}) channel (2). This has stimulated research on migraine pathophysiology and many new discoveries are anticipated in the next few years.

Perhaps the most important lesson of the FHM-breakthrough was that hereditary migraine, also on a broader scale, might be a disease caused by mutations in ion channels, a 'channelopathy' (3, 4). Ion channels are important functional units of all cells, having special importance in the central nervous system. They modify, among other things, neuronal excitability (5, 6). Migraine patients are known to be 'sensitive' to many internal and external triggers (7, 8) and some of this hyperexcitability could well be caused by dysfunctional ion channels (9). The uncovering of FHM has provided new insight into the mechanisms leading to a migraine attack. This will hopefully also lead to new modalities for the treatment of migraine in the future. Especially new prophylactic medications are eagerly waited for.

In the current treatment of migraine, the big step forward has been the development of the 'triptans' (10-12) *i.e.* migraine-specific drugs, which have improved the life of many patients, especially those with the most severe attacks (13). The target of the triptans, the serotonin system, is well known for its role in pain transmission (14) in which ion channels have an integral modifying role. There could well be clinically important secrets in the connection between the two recent success stories in the migraine world, and patients and clinicians alike are eagerly waiting for what is to come.

Much work is needed to make progress in the trail from genetics to the clinic, or *vice versa*. The gap from the ion channel to the patient is wide. In Finland a systematic clinical project was started in 1993 to secure enough power for molecular genetic analysis to locate new predisposing liability genes for migraine. Hundreds of patients have been studied, families recruited and blood samples collected. Additional work has been done to pinpoint possible candidate genes for the molecular geneticists. Ion channels are obvious choices, but there are others, too. Migraine is, after all, a neurovascular disorder (15) and vascular mechanisms should not be overlooked (16). Endothelin-1 (ET-1), a potent vasoconstrictor first connected to migraine by Färkkilä and colleagues in 1992 (17), is one of the many candidate genes related to the regulation of vascular tone during migraine attacks. ET-1 has been associated with vasospastic disorders (18) and could well modify attack characteristics, especially during the aura phase of migraine.

The present study points out clinical observations on hereditary migraine in Finland during the first years of the project. The eventual goal of the study is to identify predisposing genes for migraine with and without aura. It is hoped that the study will help to better understand migraine pathophysiology and subsequently to develop new migraine treatments.

2. REVIEW OF THE LITERATURE

2.1. Definitions and criteria of migraine

The current understanding is that migraine is a neurovascular disorder (15) characterised by neuronal aura symptoms and vascular headache. Since 1988 migraine is defined by the criteria set by the Headache Classification Committee of the International Headache Society (IHS) (19). According to the criteria migraine with aura is an "idiopathic, recurring disorder manifesting with attacks of neurological symptoms unequivocally localizable to cerebral cortex or brain stem, usually gradually developed over 5-20 minutes and usually lasting less than 60 minutes. Headache, nausea and/or photophobia usually follow neurological aura symptoms directly or after a free interval of less than an hour. The headache usually lasts 4-72 hours, but may be completely absent". Correspondingly migraine without aura is an "idiopathic, recurring headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, photo- and phonophobia". Table 1 presents the current classification and Table 2 the diagnostic criteria. These criteria have been a major improvement for migraine research (20, 21) and have been shown to perform adequately both in science and in the clinic (22, 23). Perhaps the best proof for the usefulness of the criteria is that the triptans, migraine-specific drugs, have been shown to perform equally well in different countries in multicentre, multinational, double-blind studies using these criteria (11, 13, 21). Thus it seems that study populations meeting the criteria have been uniform across countries and continents.

Table 1. International Headache Society Classification of Migraine (reference 19)

1. MIGRAINE

- 1.1 Migraine without aura
- 1.2 Migraine with aura
  - 1.2.1 Migraine with typical aura
  - 1.2.2 Migraine with prolonged aura
  - 1.2.3 Familial hemiplegic migraine
  - 1.2.4 Basilar migraine
  - 1.2.5 Migraine aura without headache
  - 1.2.6 Migraine with acute onset aura
- 1.3 Ophthalmoplegic migraine
- 1.4 Retinal migraine
- 1.5 Childhood periodic syndromes that may be precursors to or associated with migraine
  - 1.5.1 Benign paroxysmal vertigo of childhood
  - 1.5.2 Alternating hemiplegia of childhood
- 1.6 Complications of migraine
  - 1.6.1 Status migrainosus
  - 1.6.2 Migrainous infarction
- 1.7 Migrainous disorder not fulfilling above criteria

2.2. Clinical characteristics of migraine with and without aura

The current IHS criteria describe well the major features of migraine aura and headache (Table 2).

2.2.1. Migraine aura

The migraine aura is exceptionally diverse and is thoroughly analysed by Liveing and later by Sacks (24, 25). According to the IHS, migraine aura consists of homonymous visual disturbances, hemisensory symptoms, hemiparesis or dysphasia, or their combinations. Gradual development, duration under one hour and complete reversibility are characteristic (19). Russell and Olesen, in 1996,

Table 2. International Headache Society Criteria for Migraine with and without Aura [19]

1.1 Migraine without aura

A. At least 5 attacks fulfilling 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 intensity (inhibits or prohibits daily activities)
   4. Aggravation by walking stairs or similar routine physical activity
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
E. At least one of the following:
   1. History, physical- and neurological examinations do not suggest a secondary cause of headache
   2. History and/or physical- and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations
3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

1.2 Migraine with aura

A. At least 2 attacks fulfilling B
B. At least 3 of the following 4 characteristics:
   1. One or more fully reversible aura symptoms indicating focal cerebral cortical - and/or brain stem dysfunction
   2. At least one aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession
   3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased
   4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura)
C. Same as 1.1.E, see above

found that in the general population migraine aura is visual in 99%, sensory in 31%, aphatic in 18% and includes motor disturbances in 6% of the patients. “The typical visual aura starts as a flickering, uncolored, zigzag line in the centre of the visual field and affects the central vision. It gradually progresses towards the periphery of one hemifield and often leaves a scotoma. The typical sensory aura is unilateral, starts in the hand, progresses towards the arm and then affects the face and the tongue. The typical motor aura is half-sided and affects the hand and arm”(26).

2.2.2. Migraine headache

The same Danish group has studied the prevalence of IHS-defined features of migraine headache in the general population (Table 3) (27). The table summarises perhaps the most thoroughly studied characteristics of the headache phase of IHS-defined migraine published so far. Migraine headache is usually moderate or severe and lasts the whole day, sometimes two to three days. It is typically unilateral, pulsating, and associated with nausea, photophobia and phonophobia. Physical activity usually makes it worse, and often the patient has to lie down during the attack. In severe attacks the patient may vomit repeatedly. The usual notion is that the headache is identical in migraine with and without aura (28, 29).

2.2.3. Migraine attack

While aura and headache are the hallmarks of migraine, the migraine attack can be seen in a broader sense. Sacks describes five stages in a typical migraine attack: initial excitement (caused by a provocative stimulus), a state of engorgement (prodromal symptoms), a state of prostration (attack itself with headache), a state of resolution (when the attack ends either abruptly or gradually) and a state

Table 3. Prevalence of IHS Charateristics of Headache in Migraineurs by Russell and Colleagues [27]

Headache characteristic	Migraine without aura		Migraine with aura	
	Men (%) N=197	Women (%) N=145	Men (%) N=92	Women (%) N=64
Frequency	100,0	100,0	100,0	100,0
Duration	99,0	99,3	65,2	79,4
Severity	100,0	100,0	90,2	93,8
Pulsating quality	84,8	79,0	78,3	75,4
Location unilateral	48,2	64,3	55,4	64,1
Physical activity	98,0	95,8	87,0	80,0
Nausea	85,8	88,9	70,7	81,5
Vomiting	41,6	49,3	37,0	44,6
Photophobia	92,4	92,4	82,6	90,8
Phonophobia	78,7	85,4	64,1	78,5

The figures represent the proportion of patients (%) meeting the particular criteria defined by the International Headache Society (IHS). N=number of patients

of rebound (state of well-being after the attack) (30). Selby has described migraine as "a drama in three acts", the acts being premonitory symptoms, aura followed by headache and finally attack termination with a "hangover" (31). Blau (32) has also emphasised the dynamic nature and different phases of migraine. Premonitory symptoms may occur hours to a day or two before a migraine attack (with aura or without aura) (19). They usually consist of hyperactivity, hypoactivity, depression, craving for special foods, repetitive yawning and similar atypical symptoms. Typical 'hangover' symptoms after the attack include physical and mental fatigue, subdued and depressed mood, impaired concentration, reduced physical activity, and yawning (33).

2.3. Familial hemiplegic migraine (FHM)

Recent progress in molecular genetics has emphasised the importance of the clinical characteristics of FHM. According to the current classification (see Table 1) FHM is an autosomal dominant form of migraine with aura (19). As in migraine with aura, homonymous visual disturbances, hemisensory symptoms, hemiparesis or dysphasia, or combinations of these, are typical. Gradual development, duration under one hour, and complete reversibility are characteristic of the aura which is associated with headache. Families with strikingly identical and sometimes long-lasting attacks have been described (19). Table 4 presents the IHS criteria of the entity. In addition to migraine aura and headache, some patients have episodic or progressive ataxia as part of their symptomatology (34-36). Thus, the clinical characteristics of FHM and the more common forms of migraine (with and without aura) are far from identical. On the other hand, in FHM families there are also patients with these common forms of migraine, and FHM patients can also have attacks of "non-hemiplegic migraine" (36). It has been hypothesised that FHM can be seen as a model for studying migraine with and without aura. Patients with FMH would thus represent the most severe phenotype of these entities and could assist greatly in uncovering their pathophysiology (36).

2.4. Diagnosing migraine

Migraine is currently diagnosed according to the IHS criteria (19). The criteria represent the expert opinion of acknowledged clinicians on what is characteristic of migraine.

Table 4. International Headache Society Criteria for Familial Hemiplegic Migraine [19]

Description: Migraine with aura including hemiparesis and where at least one first degree relative has identical attacks

Diagnostic criteria:

A. Fulfils criteria for migraine with aura

B. The aura includes some degree of hemiparesis and may be prolonged

C. At least one first degree relative has identical attacks

The criteria have been shown to be exhaustive and valid in clinical practice (37, 38). There are naturally also other ways to define migraine (39, 40) and the IHS criteria have also been criticised (41). Clearly, in clinical practice, patients may have attacks that are difficult to categorise strictly according to the criteria. In all cases, regardless of the diagnostic criteria applied, the diagnosis is made by a trained physician based on clinical examination and a clinical interview. The diagnosis can also be made based on migraine-specific questionnaires in situations where a visit to the physician can not be arranged or is impractical.

2.4.1. Clinical diagnosis

The only method that formally fulfills the IHS criteria for diagnosing migraine is a face-to-face interview and a clinical examination performed by a neurologist (42). Besides the history given by the patient, there is no clinical, laboratory, radiological or other study or test that assists in the diagnosis. Thus the clinical experience and practical skills of the physician are the most essential diagnostic tools in diagnosing migraine.

2.4.2. Questionnaire-based diagnosis

In numerous epidemiological studies, migraine has been diagnosed based on the patient's replies to questionnaires. Diagnosing diseases with self-administered questionnaires has both advantages and disadvantages, compared to a clinical interview. Self-administered questionnaires are usually inexpensive, able to reach remote populations, allow for reflexion and search for information, put little pressure on participation, have no interviewer effect, and can bring up better information to sensitive questions (43). On the other hand, the questionnaires must be short and highly structured, there are few possibilities for detecting misunderstandings, non-linear data collection is difficult, response rates are often low, and there is no guarantee of getting a response from the proper person (43). Questionnaires on headache and migraine have been validated by comparing self-administered questionnaires with clinical examinations as the 'golden standard'. Table 5 presents predictive values and agreement (kappa-value) rates between questionnaire-based and clinical interview-based diagnoses of selected validation studies (44-52). The studies differed in their methodology and can not be compared directly, but they do give an overview of the validity of the different questionnaires used. It is especially important to choose the study population of validation studies correctly. Agreement may tend to be overestimated in studies based on interviews of clinical samples instead of using random samples of the population (52). On the other hand, the final evaluation of validity and reliability of any questionnaire is how it performs in the population for which it is designed for (43). Thus, questionnaires for the general population should be validated in the general population and questionnaires for the clinical patient in the clinic. As shown in Table 5, and also in other studies (53, 54), with a proper design and study population, migraine can be diagnosed reliably with a questionnaire.

The well-specified and simple nature of the current IHS criteria will also guide in the development of questionnaires. Despite this, some studies have revealed major flaws in questionnaire-based diagnosing (44, 53, 55). The main obstacles have been poor response rates (55), inability to differentiate subgroups of migraine (53) and difficulties in differentiating different forms of headache (44). To overcome these deficiencies, Olesen has proposed a procedure in which the migraine diagnosis, in large epidemiological studies, starts with a screening questionnaire, followed by a telephone interview, and finally a definite diagnosis is established after a face-to-face interview and a neurological examination (42).

2.5. Epidemiology of migraine

The literature dealing with the epidemiology of migraine is substantial. Table 6 presents selected observations concerning migraine prevalence and incidence.

2.5.1. Prevalence

Migraine is a very common disorder. With the modern criteria, life-time prevalence for any type of migraine in the general population is about 10% for men and 25% for women (49, 56). Life-time prevalence is roughly 5% for migraine with aura and 10% for migraine without aura. Both types of migraine are overrepresented in females, and more so in migraine without aura (28, 57). Ulrich and colleagues studied life-time prevalence of migraine in twins in the general population (58). The prevalence for migraine with aura was 8% for women and 7% for men. For migraine without aura the corresponding figures were 19% for women and 7% for men.

Table 5. Conditional Probabilities and Agreement Between Questionnaire-based and Clinical Interview-based Diagnoses of Migraine in the Literature

Author	Respondents N	Sensitivity	Specificity	Negative predictive value	Postitive predictive value	Kappa (95% CI)
Rasmussen, Denmark, 1991 [44]	712	0,51	0,92	0,93	0,50	0,43 (0,32-0,54)
Galiano, Spain, 1994 [47]	34	1,0	0,94	1,0	0,90	0,71
Pereira-Monteiro, Portugal, 1992 [45]	205	0,41	0,92	0,84	0,59	0,37 (0,20-0,55)
Lainez, Spain, 1994 [46]	316	0,34	0,86	0,75	0,51	0,22 (0,10-0,32)
Wong, Hong Kong, 1995 [48]	101			0,73	0,86	0,56 (0,36-0,76)
Russell, Denmark, 1995 [49]	727			0,89	0,93	0,77 (0,71-0,83)
Sakai, Japan, 1996 [50]	102	0,80	0,96	0,98	0,67	0,56
Hayran, Turkey, 1999 [51]	294	0,68	0,91	0,95	0,53	0,52
Hagen, Norway, 2000 [52]	167	0,69	0,89	0,78	0,84	0,59 (0,47-0,71)

N=number of respondents, CI=confidence interval

The same migraine patient can suffer from both migraine with and without aura. A common estimate is that 3/4 of all migraine patients have migraine without aura, 1/3 migraine with aura and up to 1/3 have both migraine with and without aura (4). One-year prevalences in Denmark are also shown in Table 6 (59).

2.5.2. Incidence

The age of onset is younger for men than for women and the first symptoms of migraine with aura occur at a younger age than of migraine without aura. Table 6 summarises the peak age- and gender-specific incidences from USA (60).

Table 6. Epidemiology of Migraine

Type of migraine:	Lifetime prevalence (%)	
	women	men
Migraine, any	25	10
Migraine with aura	8	7
Migraine without aura	19	7
Women:		
	One-year prevalence (%)	Mean age of population (years)
Migraine with aura	11	46.0
Migraine without aura	5	43.7
Women with:	Peak incidence per 1000 person-years	Age (years)
Migraine with aura	14,1	12-13
Migraine without aura	18,9	14-17
Men:		
	One-year prevalence (%)	Mean age of population (years)
Migraine with aura	2	49.5
Migraine without aura	3	42.3
	Peak incidence per 1000 person-years	Age (years)
Migraine with aura	6,6	5
Migraine without aura	10,0	10-11

References: 28, 49, 56–60

2.6. Differential diagnosis of migraine

The migraine has to be differentiated from disorders presenting with neurological aura-like symptoms or headache as part of their symptomatology.

2.6.1. Migraine aura

The differential diagnosis of migraine aura concerns mainly cerebrovascular diseases and epilepsy (61). The differentiation depends on a thorough history which pays attention to the recurring nature and duration of migraine aura. Familiarity with the complexity and sequence of migraine aura will also help in the differential diagnosis (62).

Migraine is essentially a recurring condition, as underlined also by the IHS criteria (Table 2) (19). While one aura does not make a migraineur, recurrent auras do. This is especially important in acute situations; the first migraine aura should always be studied carefully to rule out secondary (and dangerous) vascular causes of migraine-like symptoms.

The migraine aura typically 'builds up', expands and migrates in the visual field lasting 5-20 minutes (19). If the symptoms are sudden, exclusively negative and maximal instantly at onset, vascular events other than migraine should be suspected. When the patient is elderly or has vascular risk factors, caution is recommended as well (63). Convulsions and loss of consciousness are not usually part of migraine, and if such symptoms appear, epilepsy should be ruled out (25). Epileptic phenomena are usually much more abrupt than the gradually spreading migraine aura (25).

Migraine aura is characterised by its complex and diverse nature. The sequence of migraine is part of the complexity and helps to differentiate migraine from many other conditions. Various visual, sensory, motor, speech and balance disturbances can be present at the same time or follow each other. They are usually both positive (*i.e.* zigzag lines) and negative (hemianopia). If a combination of premonitory, aura, headache and postdromal phases repeatedly follow each other in sequence, the diagnosis of migraine is secure (32, 62).

Some rare neurological disorders also have to be considered in the differential diagnosis. Aura-like symptoms very similar, if not identical, to migraine aura are part of the MELAS (64, 65) and the CADASIL syndromes (66) (MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; CADASIL = cerebral autosomal dominant arteriopathy with stroke-like episodes and leucoencephalopathy). If there is suspect family history or additional clinical characteristics (accompanying strokes, depression, dementia) these entities should be ruled out with appropriate studies. Magnetic resonance imaging (MRI) is clearly the best neuroradiological examination when migraine is only one component of the spectrum of symptoms (67, 68). Also symptoms associated with amyloid angiopathy can resemble migraine aura (69), and if this condition is clinically suspected (typical characteristics are intracerebral haemorrhages (ICH), strokes or transient ischemic attacks (TIAs), dementia) neuroradiology with MRI is indicated (70).

2.6.2. Migraine headache

Headache is usually the primary complaint that brings a migraineur to visit a physician. This can be challenging for the physician because migraine can resemble a vast number of conditions presenting with headache. Table 7 shows some of the most important disorders listed by Campbell and Sakai (61).

In acute cases migraine has to be distinguished from vascular headaches secondary to cerebrovascular diseases. Subarachnoid haemorrhage (SAH) is the most important differential diagnostic entity (71). Contrary to SAH migraine is a recurrent disorder. Thus, until several attacks (five according to the

criteria) have occurred, SAH should be ruled out appropriately (adequate history and clinical examination; computed tomography (CT) and cerebrospinal fluid analysis, when indicated). ICH (72, 73), ischemic stroke (74), carotic dissection (75) and sinus thrombosis (76) are also important differential diagnostic possibilities in emergency situations.

If the headache is chronic, lasting weeks to months, migraine has to be differentiated from tension-type headache (77), analgesic abuse and many secondary headaches (61). Again adequate history and clinical examination usually lead to correct diagnosis. The features most predictive of migraine, when compared to tension type-headache, are nausea, photophobia, phonophobia, and exacerbation by physical activity (78). If there are focal symptoms (not meeting the aura criteria), or signs in neurological examination neuroradiology is indicated (79), with contrast enhanced CT or preferably with MRI. If the neurological status is normal with no anamnestic focal symptoms the yield of neuroradiology in this clinical setting is minimal (80).

2.7. Pathophysiology of migraine

The key elements in migraine pathophysiology are theories explaining how the attacks start, where the 'migraine generators' reside, what causes the migraine aura and migraine headache, and why the aura so often leads to a headache.

2.7.1. Attack onset

Migraine has been considered as a state of neuronal hyperexcitability relating to both

Table 7. Causes of Headache in the Differential Diagnosis of Migraine [61]

Cerebrovascular disorders	Nonvascular intracranial disorders	Chemical, metabolic, endocrine abnormalities	Cranium, neck, eyes, and nose	Other
Transient ischemic attacks	Beningn intracranial hypertension	Nitrites, nitrates	Arnold-Chiari malformation	Epilepsy
Cerebral infarction	Low CSF pressure	Other vasodilatators	Cervical spine abnormalities	Trauma
Cerebral haemorrhage	Intracranial neoplasm	Hypoxia	Purulent sinuitis	Other primary headaches
Subarachnoid haemorrhage		Hypoglycemia	Sinus and base of skull neoplasms	Fever
Intracranial hematoma		Dialysis	Glaucoma, refractive errors	Systemic disease
Intracranial aneurysm and AVM		Hypercarbia	Tolosa-Hunt syndrome	
Arterial dissection carotid or vertebral			Raeder's syndrome	
Venous thrombosis				
Arterial hypertension				
Cranial vasculitis				

CSF=cerebrospinal fluid, AVM=arteriovenous malformation

genetic and environmental factors (81, 82). It is believed that anyone can have a migraine attack, but only migraineurs are liable to recurrent attacks (4, 83). There is evidence that the brainstem with its wide connections is at the heart of migraine. Diener and colleagues have been able to show activation of brainstem centres with positron emission tomography (PET) during migraine attacks without aura. The 'migraine generator' is hypothesised to be located in these centres (84, 85). The serotonergic *nucleus raphe dorsalis (NRD)* and the noradrenergic *locus coeruleus* (*LC*) are anatomically very near these activation centres described by Diener and coworkers and they are currently considered as "the brainstem centres of migraine" (85). These centres could play a role both in the onset of attacks and in their prolongation. The application of electrodes (to treat intractable pain) near these centres can cause migraine-like headaches in patients with no history of migraine (86). These centres have extensive connections in the central nervous system, and when activated, are thought to lower the threshold for an attack (87-89). The occipital lobes (where the visual aura is generated) seem most vulnerable to this brainstem-driven hypersensitivity (90, 91). In addition, both *NRD* and *LC* have well established connections with the hypothalamus which may account for premonitory symptoms (yawning, craving for food, thirst) before the main attack (92, 93). Genetic factors (such as gender) form the basis underlying these hypersensitive brainstem pathways, but any factor, inherited or acquired, that affects the network at different time points can change the probability for attack onset (factors such as stress, emotional state, menstrual cycle, pregnancy, medications, alcohol, *etc*.). For example, stress, a common provoker of migraine, can activate the brainstem via the orbitofrontal cortex, and thus set the attack in motion (83). Along with the unstable aminergic pathways, many factors have been hypothesised to contribute to the migraine-related 'hypersensitivity': *e.g.* mitochondrial defects (94), magnesium deficiency (95), dysfunctional ion channels (2, 96), increased membrane instability (82, 97), central sensitisation of trigeminal fibers (98). Many of the listed mechanisms are more likely contributory than exclusive and together form the multifactorial basis of migraine.

2.7.2. Migraine aura

Migraine aura is believed to be caused by a phenomenon similar to "spreading depression" described by Leao already in 1944 (99, 100). The phenomenon, an innate feature of the rodent brain, is believed to occur also in humans (101). It could represent the expression of neuronal hyperexcitability related to migraine. According to this theory, when the human cortex is activated, a wave of neuronal excitation, followed by depression, starts to spread along the cortex and manifests itself clinically as migraine aura (102, 103). Many unspecific events and causes can put this phenomena in motion and start an attack. The occipital cortex is especially sensitive to spreading depression, which would explain why visual fortification spectra is the hallmark of migraine (81, 104). Neuronal phenomena are followed by vascular changes (105-107) causing "spreading oligemia" (108-110), and in exceptional circumstances even ischemia, leading rarely to strokes (111, 112).

2.7.3. Migraine headache

After the migraine attack is underway, the 'vascular' headache of migraine usually supervenes. The part of the trigeminal nerve innervating cranial vasculature is at the heart of the theory, explaining the migraine headache (15). This trigeminovascular system, when activated (*e.g.* by spreading depression), causes the blood vessels in the dura mater to dilatate and neuropeptides to be released locally along the vessels. These peptides cause further vasodilatation resulting in additional peptide release, and even-

tually this vicious circle keeps the headache going (113). Of the neuropeptides, calcitonin-gene related peptide (CGRP), has been shown to be elevated in the jugular blood of migraine patients during the attacks (114, 115) and it is a likely cause of this trigeminus-driven 'neurogenic inflammation' in the blood vessels of migraineurs (116).

The trigeminoparasympathetic reflex is another vasodilatating pathway thought to be central in migraine (15). The afferent limb of this arc is the trigeminal nerve, and the efferent limb the facial/greater superficial petrosal nerve of the parasympathetic nervous sytem.

In the periphery nitric oxide (NO), produced locally by the pulsating vessels, may function as the common final pathway in the initiation and maintenance of migraine headache (117). Endothelin-1 (ET-1), a potent vasoconstrictor, has been shown to be elevated early during migraine attacks, and is a potential modulator of attacks (17, 118). On the other hand, both a NO synthase inhibitor and an ET-1 antagonist (bosentan) have failed in the treatment of migraine attacks (119, 120).

2.7.4. Why aura leads to headache

The relationship between aura and how it leads to headache has been difficult to explain. The current theory is that spreading depression depolarises sensory nerve fibres of the trigeminovascular system and sets up a painful sterile inflammatory state around the artery (105). Recently it has been hypothesised that Ca^{2+} signals from the cortical parenchyma may be transmitted to the pia-arachnoid by gap-junction communication or extracellular movement of adenine triphosphate (ATP), and that this could induce some of the neurovascular changes in migraine (121). In addition, recent studies with functional magnetic resonance imaging (fMRI) have shown aura-related activation of brainstem centres *nucleus ruber* (*NR*) and *substantia nigra* (*SN*). Aura-induced dysfunction of these centres could then play a role during migraine headache and headache-associated symptoms (nausea, vomiting, dysautonomia) (122). Thus the connection between migraine aura and headache has been hypothesised to be both local (aura-induced trigeminovascular neurogenic inflammation) and central (dysfunction of brainstem centres).

2.7.5. Autonomic nervous system in migraine

The autonomic nervous system (ANS) is clearly involved in the migraine cascade with symptoms such as nausea and vomiting, among others. Sacks has seen the whole migraine attack as characterised by "protracted parasympathetic tonus", preceded and followed by opposite sympathetic activation (123). Welch stressed the importance of the sympathetic, noradrenergic arm of the autonomic nervous system (83). Havanka-Kanniainen proposed that both sympathetic and parasympathetic dysfunction are in play (124). The complex nature of the migraine attack and various symptoms that can be related to the ANS make studies difficult to interpret and firm conclusions regarding the pathophysiology of migraine related to the ANS are still elusive.

2.7.6. Serotonin in migraine

Serotonin (5-HT) has long been implicated in migraine pathophysiology (125, 126) and currently the most effective migraine drugs, the triptans, have been shown to work through 5-HT mechanisms (10). 5-HT may play a role in both vascular and neuronal aspects of migraine. As a neurotransmitter, 5-HT is predominantly inhibitory (127) and modulates pain perception in the brainstem (128). It is also vasoactive and can both constrict or dilatate blood vessels, depending on the circumstances (vessel tone, diameter,

vascular bed, species, administration route) (129). Migraine has been seen as a chronic systemic 5-HT deficiency, which predisposes patients to painful headache attacks (130). The triptans work by stimulating the 5-HT system. The serotonin $5\text{-HT}_{1D/ß}$ receptors (10) are specific targets for the triptans. The $5\text{-HT}_{1ß}$ receptor mediates mainly vasoconstriction while the 5-HT_{1D} receptor reduces pain transmission in the trigeminal nerve (131, 132). 5-HT has wide spread effects also outside the central nervous system. Serotonin-packed platelets have long been implicated in migraine pathophysiology (126). Most likely the abnormalities observed in the platelets (overall and enzyme activity, serotonergic function, cell signaling) are secondary in the migraine cascade (133, 134), but they might still be important in the rare instances when migraine has caused a stroke (134, 135).

2.7.7. Dopamine in migraine

Although the current research focus has been on 5-HT, also dopaminergic effects are likely to have an important modulating role in migraine. Many migraine symptoms can be considered dopaminergic (yawning, nausea, vomiting) and dopamine antagonists are widely used in the treatment of migraine (136). Recently, activation of the dopaminergic *substantia nigra (SN)* (along with another brain stem centre, *nucleus ruber (NR*) has been observed during migraine attacks with fMRI (122, 137). The role of the dopaminergic system in migraine needs further clarification. Lance and Goadsby have concluded that available information, in 1998, points to dopamine deficiency with supersensitivity of dopamine receptors (89) in migraine.

2.8. Treatment of migraine

The treatment of migraine can be divided into acute and prophylactic treatments. Acute (abortive) treatment is used to stop migraine during the attacks, and prophylactic (preventive) treatment attempts to decrease attack frequency. The emphasis of this review is on the medications widely used in Finland (Table 8).

Table 8. Commonly Prescribed Migraine Medications in Finland

Acute treatment	Prophylactic treatment
ASA	ß- blockers:
Paracetamol	propranolol
NSAIDs	metoprolol
Triptans:	bisoprolol
sumatriptan	Amitriptyline
naratriptan	Valproate
zolmitriptan	Verapamil
rizatriptan	
Ergotamine	

ASA=aspirin

NSAIDs=nonsteroidal anti-inflammatory drugs

2.8.1. Acute treatment

The acute treatment of migraine is tailored to the individual patient (138). If simple oral analgesics (aspirin (139, 140) or paracetamol) are efficient, they are widely used (141, 142). Nonsteroidal anti-inflammatory drugs (NSAIDs, *e.g.* ibuprofen (143, 144), tolfenamic acid (145, 146), naproxen sodium (147) are a therapeutic option if simple analgesics do not work (148). The addition of metoclopramide increases efficacy and oral absorption (149-151). If needed, alternative routes of administration should be considered to bypass gastroparesis and vomiting associated with migraine. The rectal, nasal or parenteral routes might thus be preferable to the oral (79, 142). Adequate dosing of analgesics or NSAIDs is important (152).

If these measures are not adequate, migraine-specific triptans, suma- (153-155), nara- (156), zolmi- (157), riza- (158), or eletriptan (159, 160), are widely used (141). These drugs have proven to be a major advance in the treatment of migraine in the past few years. Subcutaneous sumatriptan has a success rate of about 80% within one hour and 86% within two hours in clinical trials (161-163). Oral preparations (suma-, nara-, zolmi-, riza- and eletriptan) have success rates of about 60% in clinical trials (13). Sumatriptan is available and effective also as intranasal spray (164) and rectal suppositories (165).

The use of ergotamine (141) has been reduced after triptans became available, but they are still preferred by an important minority of patients (166). Dihydroergotamine (DHE) is also used to treat severe migraine attacks in some countries (167, 168).

2.8.2. Prophylactic treatment

ß-adrenoreceptor-blockers (ß-blockers) propranol and metoprolol (169, 170) and the antiepileptic sodium valproate (171) have been shown to be effective in migraine prevention, and are considered widely as first line therapy for migraine prophylaxis (4, 172, 173). Besides propranolol and metoprolol, other ß-blockers can also be used (174). The intrinsic sympathomimetic action (ISA) of some ß-blockers seems to reduce therapeutic efficacy, and preparations without ISA should thus be used (141).

Antidepressant amitriptyline has also shown efficacy (175) and is widely used in Finland: it is supposed to work because it effectively treats tension-type headache, and decreases also concurrent migraine attacks (4).

The efficacy of antiserotonin drugs (methysergide and pizotifen) and calcium antagonists (flunarizine) has also been proven, and they are used in some countries, as are NSAIDs (176).

2.8.3. National guidelines for management of migraine

Recently some national guidelines for management of migraine have been published (148, 177, 178). These guidelines have been formulated to state general principles of treatment in order to improve quality of care and allow for informed decision making by both physicians and patients. Corresponding Finnish guidelines are also expected to be published shortly.

2.9. Genetics of migraine

2.9.1. Historical perspective

It has been known for centuries that migraine tends to run in certain families, and many studies have addressed the inheritance of migraine. Still there is no consensus on the mode of inheritance of the common types of migraine, migraine with and without aura (179). There are several reasons for this. Firstly, migraine is so prevalent (59) that it might occur in several family members just by chance. Secondly, variable definitions of migraine have been used because there is no

simple 'marker' for migraine and the diagnostic criteria have changed from time to time (19, 39, 40, 180). The family studies are also demanding in that all family members should be interviewed directly, migraine with and without aura should be accurately differentiated, and population-based cohorts should be used instead of clinical patients (181).

2.9.2. Family studies

Two population-based studies have addressed the heredity of migraine using the current IHS criteria and making a distinction between migraine with and without aura (181, 182). Based on these studies, Russell and colleagues concluded that migraine is a hereditary disease, that migraine with and without aura are distinct entities, and that migraine with aura is largely or exclusively determined by genetic factors, whereas also environmental factors are important in migraine without aura. Peroutka and Howell studied 255 patients who had migraine without aura according to the IHS criteria, and found that in 91% at least one of the parents had IHS migraine (183). This can be taken to suggest a dominant mode of inheritance. It is likely that a syndrome as diverse as migraine is not inherited in any simple way (179) and, indeed, segregation studies of migraine have pointed to multifactorial inheritance (184).

2.9.3. Twin studies

Several twin studies have supported a strong genetic component for migraine. Merikangas reviewed twin studies comparing monozygotic (MZ) and dizygotic (DZ) twins, and concluded that about 50% of the predisposition to migraine can be considered hereditary (179). Table 9 summarises probandwise concordance rates and heritability figures from seven large population-based twin studies (185-190). In a recent twin study involving MZ and DZ twins raised together and apart, Ziegler *et al.* came up with an estimate of 52% (191), which is probably the best heritability estimate of migraine to date.

Table 9. Population-based Twin Studies of Migraine

Population sample	Author	IHS	Migraine type	Probandwise concordance		Heritability
				MZ	DZ	
USA	Corey et al. (1991) [185]	-	Migraine	0.35	0.17	0.36
Norway	Corey et al. (1991) [185]	-	Migraine	0.32	0.18	0.28
Sweden	Larsson (1995) [186]	+	Migraine	0.48	0.31	0.39-0.58
Australia	Merikangas et al. (1994) [187]	+	Migraine	0.44	0.24	0.36
Finland	Honkasalo et al. (1995) [188]	-	Migraine	0.28	0.12	0.34-0.51
Denmark	Gervil et al. (1999) [190]	+	MwoA	0.43	0.31	0.61
Denmark	Ulrich et al. (1999) [189]	+	MwA	0.34	0.12	0.65

MwoA=migraine without aura, MwA=migraine with aura, IHS+=a study using the IHS criteria for migraine, IHS=a study using other criteria, MZ=monozygotic, DZ=dizygotic

2.9.4. Molecular genetic studies

In recent years, molecular genetic studies have provided new and important information on the pathophysiology of migraine. Gene loci relevant to migraine have been found in chromosomes 19, 1, 11 and X (Table 10). Mitochondrial DNA (mitochondrial deoxyribonucleic acid, mtDNA) has also been studied.

In 1993 the gene for FHM was linked to chromosome 19 (1) and in 1996 the first gene for FHM was found (2). The gene, *CACNA1A*, codes for a subunit (alfa 1A subunit) of a calcium channel (P/Q type voltage sensitive Ca^{2+} channel) and this discovery has evolved theories of migraine as a 'chanellopathy' (4, 192), along with other neurological 'paroxysmal' episodic maladies such as hyperkalemic periodic paralysis (Na^+ channel affected), hypokalemic periodic paralysis (Ca^{2+} channel), episodic ataxia 1 (K^+ channel) and 2 (Ca^{2+} channel), spinocerebellar ataxia 6 (Ca^{2+} channel), benign neonatal familial convulsions (K^+ channel), congenital myotonia (Cl^- channel), congenital paramyotonia (Na^+ channel) and malignant hyperthermia (Ca^{2+} channel) (192).

In association analyses, the *CACNA1A* gene has also been connected to migraine with and without aura (96). In addition, Nyholt and colleagues have been able to link typical migraine in an Australian family to chromosome 19p13, but evidence for genetic heterogeneity was also discovered (193).

Linkage of FHM to chromosome 1 has been observed by two groups (194, 195). The gene (or genes) has not yet been identified. The nearby calcium channel genes are among the most studied candidate genes.

However, there are FHM families not linked to either chromosome 19 or 1, and thus at least a third gene locus for FHM exists (194).

Heterogeneity is also very likely for the more common entities, migraine with and without aura (193, 196). The female preponderance of migraine could suggest involvement of the X-chromosome in migraine. Indeed, Nyholt and colleagues have found, in two large multigenerational migraine pedigrees, significant excess allele sharing of Xq in typical familial migraine (196). Peroutka and colleagues reported overrepresentation of *DRD2 IC allele* of the D2 dopamine receptor gene in chromosome 11 in patients

Table 10. Molecular Genetics of Migraine

	FHM	Migraine with and without aura	"Dopaminergic" migraine	CADASIL	MELAS
Chromosome 19	*CACNA1A* [2]	*CACNA1A (association)* [96]		*NOTCH3* [97]	
Chromosome 1	Unknown gene in 1q21-31 [194-195]				
Chromosome X		Xq (association) [196]			
Chromosome 11		*DRD2 (association)* [197]	*DRD2 (association)* [198]		
Mitochondrial DNA					point mutations [65]

FHM=familial hemiplegic migraine, CADASIL=cerebral autosomal dominant arteriopathy with stroke-like episodes and leukoencephalopathy, MELAS=mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, *CACNA1A*=the gene for a subunit of a P/Q-type calcium channel, *NOTCH3*=the gene for CADASIL *DRD2*=the gene for dopamine receptor D_2, q=long arm of a chromosome

with migraine with aura (197). In Sardinia, Del Zompo and colleagues demonstrated a positive association between allele 1 of the same dopamine receptor gene in migraineurs with both yawning and nausea during the attacks (198). Dopaminergic candidate genes have thus also been in the spotlight.

Syndromes in which migraine is one component of a wider spectrum of symptoms include CADASIL and MELAS. CADASIL is characterised by ischemic strokes, vascular dementia, mood disorders, severe depression, and migraine with aura (199, 200). In 1996 a *NOTCH3* gene was identified in the CADASIL critical region (97). The function of this gene is unknown, but it may have something to do with the development of neuronal synapses (201). Why CADASIL patients can also have migraine with aura-like symptoms is unknown at the present time. A broad spectrum of clinical syndromes is associated with mutations in mtDNA. Virtually all patients with MELAS suffer from migraine-like attacks. It is possible that at least in some families migraine might be caused or modified by mitochondrial defects (65).

2.9.5. Comorbidity

Migraine has been associated with many hereditary diseases and syndromes (202). The similarities with epilepsy are obvious, but a firm genetic conclusion on this relationship can not yet be drawn (202). It is noteworthy that several epilepsy syndromes have recently been shown to be 'chanellopathies' (5). Suspected comorbidity of migraine with psychiatric and psychological problems is also well known (203). The involvement of serotonin both in depression, anxiety and migraine is interesting also from the genetic point of view (179, 204). There is a rare but clinically important association between migraine and stroke, especially in young women (112). The pathophysiological mechanisms underlying this comorbidity remain to be clarified.

By far the most usual disorder associated with migraine is tension-type headache (37). This combination is extremely common especially in specialised headache clinics (205, 206). Such patients present regularly with very frequent, even daily, headaches and susceptibility to medication overuse (205, 207). Regular comorbidity of migraine and tension-type headache has been detected also in random, non-clinical, populations (208, 209). Despite the common co-occurrence, the entities are widely considered to be pathophysiologically distinct (210, 211). On the other hand, some scientists consider migraine and tension-type headache to represent different ends of a shared headache continuum (212-215). Migraine patients with severe attacks would be on one end of the continuum, and patients suffering from tension-type headache characterised by milder attacks on the other end. Pathophysiological and genetic mechanisms underlying the comorbidity of migraine and tension-type headache and the occasional transformation of migraine into complex chronic headache syndromes (207) still remain for the most part to be resolved. Mechanisms related to central sensitisation could play a role in such instances (98, 216).

3. AIMS OF THE STUDY

The present study is part of the Finnish Migraine Gene Project, which aims to locate predisposing genes for migraine in the Finnish population. The specific aims of this study were:

1. To develop a questionnaire for use in twin and family studies of migraine (Studies I, II)

2. To study possible differences in clinical characteristics of migraine with and without aura in a population-based cohort of twins (Study II)

3. To evaluate whether migraine is identical in both co-twins of migraine-concordant monozygotic twin pairs (Study III)

4. To study the clinical characteristics and co-occurrence of migraine with and with out aura in Finnish migraine families (Study IV)

5. To study whether familial migraine with typical migraine with and without aura is linked to the locus of Familial Hemiplegic Migraine on chromosome 19p13 (Study V)

6. To investigate the potential role of endothelin-1 in migraine pathophysiology (Study VI)

4. THE PRESENT STUDY

4.1. General remarks

The present work consists of six clinical studies, four of which (Studies I-IV) focus on migraine symptomatology, one on a candidate gene locus (Study V), and one study is biochemical (Study VI). All studies were conducted at the Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland, in 1993-1999. The linkage analysis for Study V was performed at the Department of Human Molecular Genetics, National Public Health Institute, Helsinki, Finland, and the biochemical analysis of ET-1 for Study VI at the Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland. All studies were approved by the Ethics Committee of the Department of Neurology, and the participants gave their written informed consent for the studies, according to the Declaration of Helsinki.

4.2. Diagnostic categories

The studies used the IHS-defined categories of migraine with two exceptions. First, in the questionnaire-based studies (Studies II,III, IV), for the patients having attacks with aura and headache, in which headache fulfilled the IHS criteria but aura did not, migraine with unclassified aura category (MU), rather than migraine without aura (MwoA), was used. Second, in Studies II-III and V-VI the patients having aura in every attack and the patients getting attacks with and without aura were classified as MA. In the family study (Study IV) the IHS criteria were applied fully, and the patients with both kinds of attacks were differentiated from the patients with exclusively aural attacks. In Study IV also patients having migraine aura without headache, migraine equivalent (Eqv), were differentiated from other patients with aura. The corresponding diagnostic categories and abbreviations are thus (see also Table 11):

Table 11. Abbreviations of the Diagnostic Migraine Categories in the Studies

	Migraine equivalent (aura without headache)	Migraine with aura (aura always)	Migraine with and without aura	Migraine with aura not meeting the IHS criteria	Migraine without aura
Study I ($FMSQ_{TW}$)	MA	MA	MA	MU	MwoA
Study II	MA	MA	MA	MU	MwoA
Study III	MA	MA	MA	MU	MwoA
Study V	MA	MA	MA	MU	MwoA
Study VI	MA	MA	MA	MU	MwoA
Study I ($FMSQ_{FS}$)	Eqv	MwA	MwA+MwoA	MU	MwoA
Study IV	Eqv	MwA	MwA+MwoA	MU	MwoA

The MA category includes patients with IHS migraine with aura (including migraine equivalents) and patients with migraine with and without aura, $FMSQ_{TW}$=the Finnish Migraine Specific Questionnaire for Twin Studies, $FMSQ_{FS}$=the Finnish Migraine Specific Questionnaire for Family Studies.

• Migraine aura without headache: Eqv (Study I, IV)
• Migraine with aura: MwA (Studies I, IV)
• Migraine with and without aura: MwA+MwoA (Studies I, IV)
• Migraine with aura, or, migraine with and without aura: MA (*i.e.* patients with exclusively aural attacks, or, patients who have both aural and non-aural attacks) (Studies I, II, III, V, VI)
• Migraine with unclassified aura: MU (all Studies)
• Migraine without aura: MwoA (all Studies)
• Headache not meeting the IHS criteria for migraine: HA (Study II)
• Patients without migraine (headache can be present): NO_{MIG} (Study I)
• Patients with no headache (or migraine): NoHA (Study II)

4.3. Development and principles of study questionnaires

The original version of the Finnish Migraine-Specific Questionnaire ($FMSQ_o$) was used in Study V, in 1993. The questionnaire was then systematically developed in collaboration with a panel of neurologists, molecular geneticists and epidemiologists. Experience from various migraine studies along with feedback from migraine patients attending an outpatient neurologic clinic helped to improve the questionnaire further. The patients were asked to complete the questionnaire and to give suggestions for improvement. The feedback received was then discussed with a panel of neurologists in debriefing sessions, and the questionnaire was modified accordingly. An upgraded version of the questionnaire, the Finnish Migraine-Specific Questionnaire for Twin Studies ($FMSQ_{TW}$) (Appendix 1), was completed in 1996 and used in Studies II, III and experience from these studies led to further improvements, and the final version of the questionnaire, the Finnish Migraine-Specific Questionnaire for Family Studies ($FMSQ_{FS}$) (Appendix 2).

The questionnaire was developed on the basis of the criteria of the IHS (19). Particular attention was paid to aura description. A brief description of the most characteristic visual aura (hemianopia, scotoma, fortification spectra, photopsia, visual blurring) was given in the questionnaire. The patients could then indicate which of these best described their aura. In addition, they were asked to describe the aura in their own words. The percentage of migraine attacks with visual aura was recorded. Other types of aura recorded were sensory, motor, hemisensory and hemiparetic, as well as vertigo and speech disturbances. Particular attention was again paid to the patient's descriptions of these. Questions relating to headache and other aspects of migraine (premonitory symptoms, provoking and relieving factors, hormonal influences, diurnal variation in the onset of attacks, and associated autonomic-nervous-system symptoms) were included. The patients were asked whether they experienced different kinds of headache attacks and, if so, how they differed from one another. The efficacies of different medications were recorded, paying special attention to the triptans. The overall health of each respondent was determined from the responses to questions on major illnesses and health problems. Family histories relating to migraine and stroke were also recorded.

The presence or absence of the IHS-defined characteristics of migraine headache and aura were noted in questionnaire replies, and the patients were categorised according to the criteria (Table 2). No uncertain diagnosis was approved in the case of incompletely filled questionnaires. In all uncertain cases, a clinical interview (by telephone or during a visit to the clinic) was arranged.

4.4. Validation of the study questionnaires (Studies I, II)

Two separate questionnaires were analysed and validated during the course of the studies: the $FMSQ_{TW}$ and $FMSQ_{FS}$.

4.4.1. The Finnish Migraine-Specific Questionnaire for Twins ($FMSQ_{TW}$)

4.4.1.1. Subjects and methods

Consecutive migraine patients attending an outpatient neurologic clinic in Helsinki, Finland, were invited to take part in the validation study of $FMSQ_{TW.}$ Patients were recruited until 10 were clinically diagnosed as having migraine with aura and 10 migraine without aura (Table 12, Study I). The patients were asked to complete the questionnaire later at home. The questionnaire diagnosis was undertaken on the basis of the questionnaire replies by a neurologist unaware of the clinical diagnosis reached. Agreement between the two sets of diagnoses was compared.

4.4.2. The Finnish Migraine-Specific Questionnaire for Family Studies ($FMSQ_{FS}$)

4.4.2.1. Subjects and methods

The $FMSQ_{FS}$ was validated in two parts. The first part analysed the questionnaire presented to clinical migraine patients. One hundred consecutive clinically diagnosed migraine patients attending an outpatient neurologic clinic in Helsinki, Finland, were invited to participate (Table 12, Study I). These 100 patients completed the questionnaire at home. The questionnaire diagnosis was undertaken on the basis of the questionnaire replies by another neurologist unaware of the clinical diagnosis reached. Agreement between the two sets of diagnoses was compared.

In the second part, consecutively identified families with a strong family history of migraine (= 4 migraineurs in the family) were involved. Family members, migraineurs or non-migraineurs, were asked to complete the questionnaire and mail it to one of the study neurologists. One hundred consecutively returned questionnaires were analysed; the corresponding family members were also included. A migraine diagnosis was made on the basis of the questionnaire replies. The 100 participants were then contacted by telephone for a clinical interview. All telephone interviews were made by the same neurologist. Based on these interviews, migraine was diagnosed in accordance with the IHS criteria. The neurologist was unaware of the questionnaire diagnosis reached at the time of the telephone contacts. Agreement between the two sets of diagnoses was compared.

Table 12. Subjets in the Studies

Study	Patient number N	Gender F/M	Female to male ratio F:M	Age of participants years mean (SD, range)
Study I	214	174F/40M	4.4	39.8 (16.4, 6-80)
Study II	805	670F/135M	5.0	44.9 (6.5, 36-68)
Study III	102	92F/10M	9.2	44.5 (7.2, 36-68)
Study IV	1000	730F/230M	3.2	43.1 (18.2, 6-91)
Study V	61	32F/29M	1.1	50.0 (20.0, 9-89)
Study VI	31	29F/2M	14.5	42.0 (9.3, 23-56)

N=number of patients, F=female, M=male, SD=standard deviation

4.5. Clinical characteristics of migraine in a population-based twin sample and in migraine-concordant monozygotic twin pairs (Studies II, III)

4.5.1. Subjects and methods

The twin studies are based on the older part of the Finnish Twin Cohort (217), which consists of same-sexed Finnish twins born before 1958 and alive in 1967. The twins have been followed up with questionnaires in 1975, 1981 and 1990. The 1981 and 1990 questionnaires formed the basis, and all twins who had a set diagnosis of migraine or self-reported headache with a frequency greater than once a month were listed. There were altogether 865 pairs concordant for these criteria. Twins born before 1930, deceased since the 1990 study, living abroad, or speaking Swedish as their mother tongue, or taking part in a parallel hypertension study, were not included. This reduced the available twin pairs to 509 (Tables 12-13). $FMSQ_{TW}$ was mailed to these 1018 individuals. The clinical characteristics of migraine were analysed on the basis of the questionnaire replies. 248 twins with undiagnostic or incompletely filled questionnaires were contacted by telephone by a study neurologist to define the diagnosis. In Study III only those MZ twin pairs (51 pairs) in which both co-twins were subsequently diagnosed as having migraine were analysed further.

4.5.1.1. Ascertainment of zygocity of the twins (Study III)

The zygosity of all twins in the Finnish Twin Cohort was originally determined with a questionnaire method (218). To further test the questionnaire method employed, all MZ (zygosity based on questionnaire) aura-discordant twin pairs (pairs with one MA and one MwoA twin, MA-MwoA pairs, altogether 12 pairs) were genotyped. This was done with five highly polymorphic fluorescence labeled DNA markers which were D2S1790, D7S1805, D12S1045, D17S928, and D19S246 (from the set of the Cooperative Human Linkage Center). EDTA blood samples were collected, and genomic DNA extracted by standard procedures (219). The markers were analysed using PCR (Polymerase Chain Reaction) and gelelectrophoresis by ALFexpress (Pharmacia Biotech, Uppsala, Sweden).

4.6. Familial migraine with and without aura (Study IV)

4.6.1. Subjects

In the family study consecutively identified families with at least four members who were affected by migraine were analysed. The families were recruited from patients attending two headache clinics in Helsinki and Kemi,

Table 13. Compilation of the Participating Twins in the Studies II and III

Twins from the Finnish Twin Cohort	Individual twins N	Twin pairs N
All twins in the older part of the Finnish Twin Cohort	34000+	17000+
Concordant for the incluson criteria	1730	865
Concordant and available for the study	1018	509
Returned the study questionnaire	805 (79.1%)	349 (68.6%)
MZ and returned the study questionnaire	239 (78.6%)	107 (70.4%)

MZ=monozygotic, N=number of twins or twinpairs, response rates in parentheses, the older part of the Finnish Twin Cohort consists of the same-sexed Finnish twins born before 1958 and alive in 1967 (over 17000 twin pairs)

Finland. Two neurologists were in charge of the recruitment. When a member of the family, *i.e.* the index case, was clinically diagnosed by a neurologist as suffering from migraine, he or she contacted all the other members of the family believed to suffer from migraine and asked whether they would be willing to participate in the study. If at least three possible migraineurs were willing to take part, the $FMSQ_{FS}$ was mailed to each of them, and to their parents and siblings. The participants were then recruited until 1000 first family members had been diagnosed as having migraine based on the returned questionnaires (Table 12, Study III). At this time point altogether 210 migraine families had participated in the study.

4.6.2. Methods

The clinical characteristics of migraine were analysed on the basis of the questionnaire replies. Four clinical indices were calculated, reflecting migraine symptoms and severity. The indices are based on the clinical experience of the neurologists involved in the Finnish Migraine Gene Project and are intended to assist in the clinical analysis of migraine patients. They are not intended to be used in clinical practice. The indices enable quantitative analysis of migraine characteristics and assist in comparisons between different subtypes of migraine.

1. The aura index is designed to reflect the occurrence of migraine aura throughout the life-time of the patient. The index can range from 0 (no aura) to 50 (for details see Table 14).

2. The index for IHS headache is designed to reflect how precisely the IHS headache criteria were met. One point was given for each variable defined in the IHS classification (headache frequency, headache duration, unilateral headache, pulsating headache, moderate or severe intensity, aggravation of headache by physical activity, nausea, vomiting, photophobia, phonophobia). The index (sum of the given points) is referred to as the 'IHS score'. The index can range from 0 (no IHS variable identifiable) to 10 (all IHS variables identifiable).

3. The index for characteristics associated with migraine is designed to reflect the occurrence of symptoms typically associated with migraine but not included in the IHS criteria. The symptoms considered specific for migraine were given two points, and more unspecific migraine related symptoms one point. Two points were given for each of the following premonitory symptoms: craving for food, yawning, stereotypical mood change and exceptional tiredness already before the attacks. One point was given for provocation of an attack by stress, by missing a meal, by ingestion of alcohol, chocolate, cheese, or specifically of red wine. One point was given for each of paleness during an attack, goose

Table 14. The Aura Index

Type of aura:	**Points**
Any visual	2
Fortification spectra	6
Scotoma	6
Photopsia	4
Speech	4
Sensory	1
Motor	1
Hemisensory	3
Hemiparetic	4
Aura frequency:	
1	1
2-10	5
> 10	10
Aura spread	3
Aura duration > 1 min	3
Aura < 60 min before headache	3
Maximum total	50

The total sum of scored points gives the aura index score

pimples during an attack, feeling cold during an attack, sweating during an attack, and tachycardia or bradycardia during an attack. The index (sum of points given) can range from 0 (no feature present) to 20 (all features present).

4. The index for overall severity of migraine is designed to reflect the life-time burden of migraine in relation to the patient in question (Table 15). Variables relating to aura are omitted from the index. The index for overall severity of migraine can range from 0 to 50.

4.7. Linkage analysis of four typical migraine families (Study V)

4.7.1. Subjects

Ten clinically diagnosed migraine patients with a positive family history of migraine were selected for the molecular genetic study. The migraines of the index cases were responsive to the treatment with sumatriptan, at the time a novel $5HT_{1D}$-like receptor agonist (10). Family information was collected initially from the description of the clinically studied index case, after which the questionnaire ($FMSQ_o$) was sent to all members of the family, regardless of whether they had been classified as affected or non-affected on the basis of the information from the index case. All responding family members were then classified as migraineurs or non-migraineurs based on the IHS criteria. For further genetic analysis, four families with the highest number of affected individuals were selected (Table 12, Study V; Figure 1).

4.7.2. Methods

Four polymorphic microsatellite markers (D19S216, D19S221, D19S226, and D19S215) were analysed to see whether four migraine families with typical IHS migraine would show linkage to the FHM locus on 19p13. All of the markers were chosen from Genethon's amplifiable marker map (220). EDTA-blood samples from all available family members were collected, and genomic DNA extracted by standard procedures (219). The markers were analysed using PCR and polyacrylamide gelelectrophoresis. PCR reactions were performed in multiwell microtitration plates for 28 cycles as described previously (221). One of the primers was labeled at the 5' end using ^{32}P-g ATP. The amplified fragments were size-analysed by 5% denaturing polyacrylamide gel (221).

Table 15. The Index for Migraine Severity

Number of lifetime attacks:	**Points**
> 100	12
50-100	8
10-50	4
5-10	2
< 5	1
Headache severity:	
unbearable	10
severe	8
moderate	4
mild	1
Headache duration:	
> 72 hours	8
2-72 hours	5
< 4 hours	2
Nausea	3
Vomiting	3
Photophobia	3
Phonophobia	3
Aggravation by stress	2
Aggravation by missing a meal	2
Not able to work	4
Maximum total:	50

The total sum of scored points gives the migraine severity score

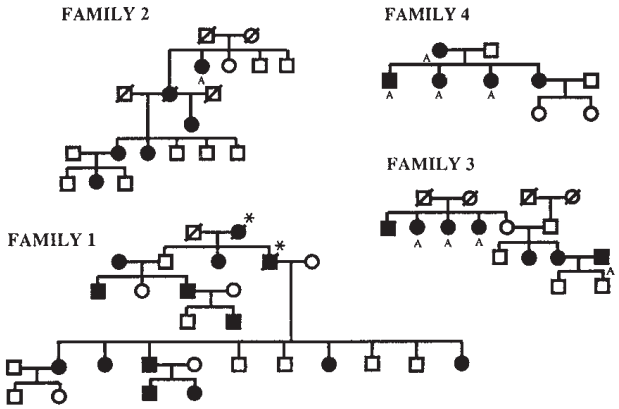


Figure 1. Pedigrees of the four migraine families analysed

Affected individuals are indicated by filled symbols, deceased individuals with probable migraine by asterisks. Patients suffering from migraine with aura are indicated by an A. □=male, ○=female, /=deceased

Two point and multipoint linkage analyses were carried out using the MLINK, ILINK, and LINKMAP options of the LINKAGE package (222). The allele frequencies for all markers were calculated from the founders and married-in members of the families. Segregation of the trait was performed with the ILINK option of the LINKAGE package. The likelihood was maximised over penetrance with the disease gene frequency of 0.08. ILINK provided a penetrance of 0.436 for homozygous disease gene carriers, 0.574 for heterozygotes, and 0.001 for homozygous nondisease gene carriers. This model closely resembles an autosomal dominant inheritance pattern. For the linkage analyses, we constructed three age-dependent penetrance classes based on the age of onset in our family material. For individuals under 19 years, 20-29 years, and over 30 years, penetrances of 0.35, 0.50, and 0.70 were used, respectively. The phenocopy frequency of 0.024 was used for all age groups. The maximum penetrance of 0.70 was adopted since the ILINK result is an average for all age groups. With these values the population frequency of genetically affected individuals would be 0.108, the frequency of phenocopies 0.020, and the population frequency of all affected individuals 0.128. The phenocopy frequency was set that high because two families (1 and 3, Figure 1) had one married-in migraineur.

4.8. Levels of endothelin-1 in migraine (Study VI)

4.8.1. Subjects

To study ET-1 in migraine, 31 clinically diagnosed migraine patients were chosen (Table 12, Study VI). All the participants had 1-6 migraine attacks per month at the time of the study. Patients with a history of opiate, psychotropic drug, alcohol or ergotamine abuse were excluded, as were patients with hypertension (diastolic blood pressure > 95 mmHg), ischemic heart disease or other manifestations of arteriosclerosis. All patients had also a positive family history of migraine.

4.8.2. Methods

Endothelin-1 (ET-1) was measured during and between the migraine attacks. The ictal values were taken as soon as possible after the beginning of an untreated migraine at-

tack; 22 samples, with a mean time of delay of 4.9 hours (SD 4.2, range 0.8-14.0) were examined. All patients had by definition moderate or severe headache when the blood samples were taken. Interictal samples from 18 patients were taken at least 72 hours after the last migraine attack. Both ictal and interictal values were recorded for 9 patients.

The blood samples were drawn, with the patients supine, from the cubital vein. Plasma was separated from blood drawn into tubes containing Na_2EDTA. The plasma was frozen and stored immediately at -20 °C until assayed for ET-1. Control plasma samples were obtained similarly from 76 ambulatory, healthy subjects (41 men, 35 women).

All plasma samples were purified by Bondelut C18-OH analytical columns (Analytichem. International, Harbor City, USA). One millilitre of plasma was acidified with 4% acetic acid and subjected to columns prewashed with methanol and distilled water. The columns were then washed with distilled water and absorbed peptide eluded with 40% ethanol in 4% acetic acid. The eluted fraction was lyophilised and subjected to ET-1 radioimmunoassay, which was performed as described earlier (223) using synthetic ET-1 (Peptide Institute, Barnet, UK) and ET antiserum generated in rabbits with ET-1 coupled to glutaraldehyde to keyhole limpet hemocyanin (Sigma, St.Louis, LA, USA) as an immunogen. The antiserum showed 100% cross-reaction with ET-2 and ET-3 (human; Peninsula, London, UK). The antiserum showed < 0.1% cross-reaction with the 20-50, 74-91, 171-201 sequences of preproendothelin (Peptide Institute), with big endothelins 1-38 and 22-38 (human; Peninsula), ANP 1-28 (human; Peninsula), angiotensin II (Schwarz-Mann, St. Louis, LA, USA), and arg-vasopressin (Ferring, Malmö, Sweden).

4.9. Statistical analyses

In Studies I-IV and VI the data were recorded and analysed with StatView 4.5 and 5.0 software packages (Abacus Concepts, Inc., Berkeley, CA, USA, 1996). Additionally, in analyses of agreement (Study I), StatXact-4 for windows software package was used (Cytel Software Corporation, MA, USA, 1999). In Study V LINKAGE package (222) was used. In the questionnaire-based studies (Studies II, III, IV), statistical analyses were undertaken for those who had responded to the particular question, missing data was not analysed.

In Study I, for validation of $FMSQ_{FS}$, weighted Cohen's kappa statistic was used to test the observed agreement, corrected for chance (224), between the clinical and questionnaire diagnosis (step I) and between the telephone interview and the questionnaire (step II). A value of > 0.75 was set to indicate strong agreement.

In Studies II and III (the twin studies) unpaired analysis of variance using Fisher's PLSD post hoc test was used to compare the age of the twins between the diagnostic categories. The Chi-squared test and Fisher's exact test were used for categorical data. The Mann-Whitney U-test or Kruskal-Wallis one-way analysis of variance were used for ordered categories. An alpha level of 0.05 was used to indicate statistical significance. Bonferroni/Dunn correction was used for multiple comparisons.

In Study IV (the family study) analyses of variance using Fisher's PLSD post hoc test and the Chi-squared test were employed in relation to continuous variables (the clinical indices) and category variables (the IHS variables, prodromal symptoms, provoking factors, autonomic-nervous-system symptoms), respectively. An alpha level of 0.05 was used.

In Study V (the linkage study) LOD (logarithm of odds) score cutoff values of 3 and –2 were used to show and to exclude linkage, respectively.

In Study VI 95% confidence intervals were calculated for the ET-1 values and differences between the ET-1 values at different time points.

5. RESULTS

5.1. Validation of study questionnaires (Studies I-II)

The questionnaires were validated by comparing agreement between the questionnaire-based and interview-based diagnoses.

5.1.1. The Finnish Migraine-Specific Questionnaire for Twins ($FMSQ_{TW}$)

A correct migraine diagnosis could be made for all the 20 participating migraine patients purely by means of the questionnaire. Two patients with migraine without aura would have been classified as MU according to the questionnaire. One had vague sensory symptoms with headache which, judging by the clinical interview and using the IHS criteria, were not migraine aura. The other patient had had only one IHS aura during her life-time and thus did not fulfill the IHS frequency criterion for migraine with aura.

5.1.2. The Finnish Migraine-Specific Questionnaire for Family Studies ($FMSQ_{FS}$)

The first stage of $FMSQ_{FS}$ validation compared the questionnaire-based diagnoses to the clinical diagnoses reached by the study neurologist. The association between these two sets is shown in Table 16 (Stage I).

All 100 migraine patients were diagnosed as suffering from migraine on the basis of their replies to the questionnaire. In two cases, a distinction between MwA and MwA+MwoA proved impossible based on the $FMSQ_{FS}$. Corresponding conditional probabilities relating to the questionnaire are shown in Table 17. Results are also shown with the non-IHS category MU omitted or recategorised as MwoA. Weighted Cohen's

Table 16. Association Between the Clinical and the Questionnaire Diagnoses

Stage I	MwA (Q)	MwA+MwoA (Q)	MU (Q)	MwoA (Q)	Total
MwA (CL)	7	1	0	0	8
MwA+MwoA (CL)	2	45	8	0	55
MwoA (CL)	0	0	15	20	35
Total	9	46	23	20	98

Stage II	MwA (Q)	MwA+MwoA (Q)	MU (Q)	MwoA (Q)	NO_{MIG} (Q)	Total
MwA (CL)	17	2	0	0	0	19
MwA+MwoA (CL)	3	20	4	0	0	27
MwoA (CL)	0	0	8	14	1	23
NO_{MIG} (CL)	0	0	0	0	25	25
Total	20	22	12	14	26	94

MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura, NO_{MIG}=no migraine, CL=the clinical diagnosis, Q=the questionnaire-based diagnosis

Table 17. Validation Stage 1: Conditional Probabilities of the $FMSQ_{FS}$ for Different Types of Migraine

A. Non-IHS questionnaire category MU omitted

	MwA	MwA + MwoA	MwoA
Sensitivity	0.88	0.96	1.0
Specificity	0.97	0.96	1.0
False positive rate	2/9	1/46	0/20
False negative rate	1/66	2/29	0/55
Positive predictive value	0.78	0.98	1.0
Negative predictive value	0.98	0.93	1.0

B. MU subjects re-categorised as MwoA

	MwA	MwA + MwoA	MwoA
Sensitivity	0.88	0.82	1.0
Specificity	0.98	0.98	0.87
False positive rate	2/9	1/46	8/43
False negative rate	1/89	10/52	0/55
Positive predictive value	0.78	0.98	0.81
Negative predictive value	0.99	0.81	1.0

The $FMSQ_{FS}$-based diagnosis is compared with diagnosis reached on the basis of a telephone interview by a neurologist, MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MwoA=migraine without aura, $FMSQ_{FS}$=the Finnish Migraine-Specific Questionnaire for Family Studies

Table 18. Validation Stage 2: Conditional Probabilities of the $FMSQ_{FS}$ for Different Types of Migraine

A. Non-IHS category MU omitted

	MwA	MwA + MwoA	MwoA	NO_{MIG}
Sensitivity	0.89	0.83	0.93	1.0
Specificity	0.95	0.97	1.0	0.98
False positive rate	3/20	2/22	0/14	1/26
False negative rate	2/63	4/61	1/69	0/57
Positive predictive value	0.85	0.91	0.0	0.96
Negative predictive value	0.97	0.93	0.99	0.0

B. MU subjects re-categorised as MwoA

	MwA	MwA + MwoA	MwoA	NO_{MIG}
Sensitivity	0.89	0.74	0.61	1.0
Specificity	0.96	0.97	1.0	0.99
False positive rate	3/20	2/22	0/14	1/26
False negative rate	2/74	7/72	9/80	0/68
Positive predictive value	0.85	0.91	1.0	0.96
Negative predictive value	0.97	0.90	0.89	1.0

The $FMSQ_{FS}$-based diagnosis is compared with diagnosis reached on the basis of a telephone interview by a neurologist, MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MwoA=migraine without aura, NO_{MIG}=no migraine, $FMSQ_{FS}$=the Finnish Migraine-Specific Questionnaire for Family Studies

Table 19. Validation Stage 2: Differences Between Diagnoses Reached on the Basis of the Telephone Interview and Diagnoses Reached on the Basis of Responses to the $FMSQ_{FS}$

Patient	Age (years)	Telephone-interview-based diagnosis	Questionnaire-based diagnosis	Reason for difference in diagnosis
Female	67	MwA (TI)	MwA+MwoA (Q)	Patient recall imprecise
Female	54	MwA (TI)	MwA+MwoA (Q)	Patient regularly wakes up with migraine
Female	46	MwA+MwoA (TI)	MwA (Q)	Patient recall imprecise
Female	29	MwA+MwoA (TI)	MwA (Q)	Patient recall imprecise
Male	71	MwA+MwoA (TI)	MwA (Q)	Patient regularly wakes up with migraine
Female	45	MwA+MwoA (TI)	MU (Q)	Patient failed to report all features of aura in Q
Female	46	MwA+MwoA (TI)	MU (Q)	Patient failed to report all features of aura in Q
Female	41	MwA+MwoA (TI)	MU (Q)	Patient failed to report all features of aura in Q
Female	30	MwA+MwoA (TI)	MU (Q)	Patient failed to report all features of aura in Q
Female	63	MwoA (TI)	NO_{MIG} (Q)	Patient failed to report all features of headache in Q
Female	32	MwoA (TI)	MU (Q)	Patient reported unspecified visual symptoms
Female	23	MwoA (TI)	MU (Q)	Patient reported unspecified visual symptoms
Female	33	MwoA (TI)	MU (Q)	Patient reported unspecified visual symptoms
Female	50	MwoA (TI)	MU (Q)	Patient reported unspecified visual symptoms
Female	24	MwoA (TI)	MU (Q)	Patient reported unspecified sensory symptoms
Male	32	MwoA (TI)	MU (Q)	Patient reported unspecified sensory symptoms
Female	40	MwoA (TI)	MU (Q)	Patient had migraine aura only once
Female	65	MwoA (TI)	MU (Q)	Patient recall imprecise

$FMSQ_{FS}$ = the Finnish Migraine-Specific Questionnaire for Family Studies, MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura, NO_{MIG}=no migraine, TI=telephone interview, Q=questionnaire

kappa statistic for the agreement is 0.94 (95% confidence interval 0.88-1.00; a value > 0.75 indicates strong agreement) if MU cases were omitted. When the patients in the MU category were recategorised as MwoA subjects, the corresponding value of weighted kappa is 0.86 (95% confidence interval 0.77-0.94).

In the second stage of validation, 100 consecutive patients who had returned the questionnaire were contacted by telephone to compare the questionnaire- and telephone-interview-based diagnoses. 94 of the 100 could be reached. Sixty-seven (71.3%) were women and 27 (28.7%) men. Mean age was 44.6 years (SD 18.0, range 6-80 years).

The association between the telephone interview and the questionnaire is shown in Table 16 (Stage II). The specificity of the questionnaire for migraine was 0.96 (25/26), and sensitivity was 0.99 (67/68). Corresponding conditional probabilities relating to the questionnaire and subtypes of migraine are shown in Table 18. The results are again shown with the non-IHS category MU either omitted or recategorised as MwoA. Weighted Cohen's kappa statistic for this agreement is 0.97 (95% confidence interval 0.95-0.99), if the MU cases were omitted. When patients in the MU category were recategorised as MwoA subjects, the corresponding value of weighted kappa is 0.96 (95% confidence interval 0.93-0.98).

Table 19 presents all participants (18 subjects) whose diagnoses were not exactly the same based on the questionnaire and the telephone interview. Also reasons for the discrepancies are suggested.

5.2. Clinical characteristics of migraine in a population-based twin sample (Study II)

Clinical characteristics of migraine were analysed on the basis of the questionnaire replies. 805 of the 1018 possible participants returned the questionnaire (response rate 79.1%). This included 349 twin pairs, of which both co-twins returned the questionnaire (pairwise response rate 68.6%). The mean age of the subjects was 44.9 years (SD 6.5, range 36-68 years).

5.2.1. Characteristics of migraine in individual co-twins

5.2.1.1. Distribution of diagnostic categories

The participants were placed into the study categories based on their questionnaire replies or the telephone interview (248 individuals). Of all the analysed individual co-twins, 39.9% (321 individuals) were categorised as MA, 7.2% as MU, 20.6% as MwoA (166 individuals), 18.5% as HA, and 13.8% as NoHA.

The mean age was 45.2 (SD 6.6, range 36-62) for MA, 45.3 (SD 7.3, range 36-68) for MU, 44.0 (SD 5.9, range 36-62) for MwoA, 45.2 (SD 6.7, range 36-62) for HA and 44.8 (SD 6.0, range 36-62) for NoHA. None of these differences between ages was statistically significant. Men were significantly more likely to be diagnosed as NoHA compared to women (21.5% vs. 12.2%, p=0.0069). Women were more likely to be MwoA, but the difference did not reach statistical significance (21.8% vs. 14.8%, p=0.068). All other diagnostic categories were evenly distributed between the genders, also MA (women 40.0% vs. men 39.3%).

5.2.1.2. Characteristics of aura

Of the 321 MA twins, 98.4% reported visual phenomena, 7.8% motor, 28.0% sensory, and 5.3% speech disturbances as their aura. Visual aura was hemianopia in 31.2% of the twins, scintillating scotoma in 57.3%, photopsia in 42.1%, and blurring of vision in 34.0%.

Table 20. Headache Characteristics of the Twins with Migraine with Aura (MA) and Migraine without Aura (MwoA)

		All twins		p	MA twins		p	MwoA twins		p
		MA (%) N=321	MwoA (%) N=166		Women (%) N=268	Men (%) N=53		Women (%) N=146	Men (%) N=20	
Lifetime frequency of headache	5-10	7.5	4.8		6.3	13.2		4.8	5.0	
	10-49	41.1	39.8		40.7	43.4		41.1	30.0	
	≥ 50	50.8	54.2		52.2	43.4		52.7	65.0	
Duration of headache (h)	< 4	15.3	0		12.7	28.3		0	0	
	4-24	60.1	73.5	< 0.01	60.4	58.4	< 0.01	69.9	100	< 0.05
	24-72	20.2	26.5		22.4	9.4		30.1	0	
	≥ 72	1.9	0		1.9	1.9		0	0	
Location of headache	Unilateral	67.3	57.8	< 0.05	70.1	52.8	< 0.05	58.2	55.0	
Quality of headache	Pulsating	73.5	75.9		77.6	52.8	< 0.001	77.4	65.0	
Intensity of headache	Mild	1.6	0		0.4	7.5		0	0	
	Moderate	27.2	31.9		26.2	32.1	< 0.05	34.9	10.0	
	Severe	53.1	53.6		53.9	49.1		50.7	75.0	
	Unbearable	17.5	13.9		18.7	11.3		13.7	15.0	
Physical activity	Worsened by	70.4	72.3		72.4	60.4		73.3	65.0	
Associated symptoms of headache	Nausea	82.6	92.8	< 0.01	84.0	75.5		91.8	100.0	
	Vomiting	42.1	44.0		44.0	32.1		42.5	55.0	
	Photophobia	83.8	74.1	< 0.05	84.7	79.2		75.3	65.0	
	Phonophobia	57.9	59.0		60.4	45.3	< 0.05	61.6	40.0	

MA=migraine with aura, MwoA=migraine without aura, h=hours; N=number of twins (individuals); only values p <0.05 shown % refers to the percentage of twins with the particular headache characteristic

Table 21. Distribution of the Study Diagnoses in Monozygotic (MZ) and Dizygotic (DZ) Twin Pairs

	All twin pairs (N=349)		MZ pairs (N=107)		DZ pairs (N=223)	
	N	%	N	%	N	%
MA-MA	66	18.9	20	18.7	41	18.4
MA-MwoA	49	14.0	12	11.2	35	15.7
MwoA-MwoA	22	6.3	6	5.6	15	6.7
MU-MA	16	4.6	4	3.7	10	4.5
MU-MU	7	2.0	4	3.7	2	0.9
MU-MwoA	12	3.4	5	4.7	7	3.1
HA-MA	48	13.8	19	17.8	27	12.1
HA-MU	6	1.7	0	0	6	2.7
HA-MwoA	30	8.6	10	9.3	18	8.1
HA-HA	13	3.7	6	5.6	7	3.1
HA-No HA	13	3.7	4	3.7	8	3.6
NoHA-MA	39	11.2	9	8.4	29	13.0
NoHA-MU	3	0.9	0	0	3	1.3
NoHA-MwoA	17	4.9	5	4.7	12	5.4
NoHA-No HA	8	2.3	3	2.8	3	1.3

HA=headache; MA=migraine with aura; MwoA=migraine without aura; MU=migraine with unclassified aura; NoHA=no headache; MA-MA=both twins have MA; MA-MwoA=one twin has MA the other MwoA; etc., N=number of pairs. There were 19 twin pairs of unkown zygosity

5.2.1.3. IHS characteristics of headache

IHS characteristics of headache were compared in MA and MwoA twins to determine possible differences (Table 20). The duration of headache was more often brief in MA compared with MwoA (Mann-Whitney U-test p=0.007; in MwoA headache lasts over four hours, by definition). Headache was significantly more often unilateral (p=0.039) and associated with photophobia (p=0.010) in MA, whereas nausea was more frequent in MwoA (p=0.002). Women with MA had significantly longer (p=0.001) and more severe attacks (p=0.046), and their headache was more often unilateral (p=0.014), pulsating (p=0.0004), and they experienced more phonophobia (p=0.041) than the men with MA. There was less variability between the genders in MwoA, but women had longer attacks (p=0.029).

5.2.2. Characteristics of migraine in twin pairs

5.2.2.1. Concordance of diagnostic categories

Of all the 349 twin pairs, 18.9% were concordant for MA (MA-MA pairs) and 6.3% for MwoA (MwoA-MwoA pairs). If a twin had MA, the risk for the co-twin also having MA was 0.47, and the corresponding figures were 0.28 for MU, 0.29 for MwoA, 0.21 for HA and 0.18 for NoHA. There were no significant differences between MZ and DZ twins in concordance for the study diagnoses. A complete distribution of the diagnoses in all the 349 twin pairs is presented in Table 21.

5.3. Clinical characteristics of migraine in migraine-concordant monozygotic twin pairs (Study III)

The clinical characteristics of migraine in these MZ migraine-concordant twin pairs were analysed on the basis of the questionnaire replies. There were altogether 51 MZ migraine-concordant pairs (*i.e.* each co-twin returned the questionnaire and was subsequently diagnosed as having MA, MU or MwoA).

5.3.1. Distribution of diagnostic categories

Of the 102 MZ twins, 56 (54.9%) were diagnosed as MA, 17 (16.7%) as MU and 29 (28.4%) as MwoA. The mean age of the MZ twins was 44.5 years (SD 7.2, range 36-68). It was 44.8 (SD 7.4, range 36-62) for MA, 46.2 (SD 9.7, range 37-68) for MU, and 43.5 (SD 4.7, range 36-52) for MwoA. None of these differences between ages was statistically significant. 46 pairs were female, five male (female to male ratio 9.2:1).

5.3.2. Diagnostic categories in twin pairs

In the 51 MZ migraine-concordant twin pairs, if one twin had MA, the risk for the co-twin to have MA as well was 0.71, the corresponding figures being 0.47 for MU and 0.41 for MwoA. There were 12 MZ twin pairs discordant for the main migraine subtypes, MA and MwoA (MA-MwoA pairs). Of these pairs, 11 were female, 1 male. The distribution of the study diagnoses differed significantly from evenly distributed expected values, p=0.0064 (Table 22). MA-MA, MwoA+MwoA, MU-MU were the pairs that were observed more frequently than expected.

5.3.3. Characteristics of aura

In the twin pairs concordant for MA (MA-MA pairs, altogether 40 individuals) 40/40 cases (100%) reported visual auras. One (2.5%) had motor and 11 (27.5%) sensory symptoms as an aura. 16 (40.0%) had negative scotoma or hemianopia, 28 (70.0%) fortification spectra, 13 (32.5%) photopsia and 13 (32.5%) visual blurring. In the one subject with motor symptoms the aura was not hemiparesis. In three individuals the sensory symptoms were of clearly spreading hemisensory nature. Two had speech disturbances as an aura.

5.3.4. The IHS characteristics of headache

Headache characteristics in the MA and MwoA categories were compared. Also individuals in diagnostically different twin pairs, *i.e.* MA-MA, MA-MwoA or MwoA-MwoA pairs, were similarly compared (Table 23).

The MA twins had significantly more short-lived headache attacks (<4 hours, p=0.014) and more photophobia (p= 0.032), while the MwoA twins had more nausea (p=0.025). The headache of the MA twins in the MA-MA pairs did not differ significantly from the headache of the MwoA twins in the MwoA-MwoA pairs in any respect (frequency, severity, duration, associated features, *etc.*). The MA twins in the MA-MA pairs had significantly more photophobia than the MwoA twins in the MA-MwoA pairs (p=0.023). The MA twins in the MA-MwoA pairs had more often unilateral headache compared to their MA counterparts in the MA-MA pairs (p=0.037). The MA twins did not differ significantly from the MwoA co-twins in any respect within the MA-MwoA pairs. The MA co-twins in the MA-MwoA pairs had significantly more often unilateral and pulsating headache than the MwoA co-twins in the MwoA-MwoA pairs (p=0.009 for unilateral headache and p=0.047 for pulsating headache). The MwoA twins in the MA-MwoA and MwoA-MwoA pairs did not differ significantly from one another. Life-time frequency of headache, overall duration of headache and intensity of headache did not differ significantly between any of the diagnostic groups.

Concordance of the different aura and headache features was also compared (Table 24). The distribution of unilateral headache differed significantly between the groups (p=0.033). The MA-MwoA pairs had significantly more often unilateral headache when compared separately to both the other groups (p=0.043 in comparison with the MA-MA pairs and p=0.025 in comparison with the MwoA-MwoA pairs). Corrected with the

Table 22. Distribution of the Study Diagnoses in the 51 Migraine Concordant Monozygotic Twin Pairs

	N	%
MA-MA	20	39.2
MA-MwoA	12	23.6
MwoA-MwoA	6	11.8
MU-MA	4	7.8
MU-MU	4	7.8
MU-MwoA	5	9.8

N=number of twin pairs, MA=migraine with aura, or migraine with and without aura, MwoA=migraine without aura, MU=migraine with unclassified aura, MA-MA pair=both co-twins have MA, MA-MwoA=one co-twin has MA and the other MwoA, etc.

Table 23. Headache Features in the Monozygotic Migraine Concordant Co-twins

Headache variables		All MA twins	All MwoA twins	MA twins in MA-MA pairs	MA twins in MA-MwoA pairs	MwoA twins in MA-MwoA pairs	MwoA twins in MA-MwoA pairs
		% of twins N=56	% of twins N=29	% of twins N=40	% of twins N=12	% of twins N=12	% of twins N=12
Lifetime frequency of headache	5-10	7.1	3.4	7.5	0.0	0.0	0.0
	10-49	42.9	37.9	47.5	25.0	33.3	33.3
	≥50	50.0	58.6	45.0	75.0	66.7	66.7
Duration of headache (h)	< 4	17.9	0.0	17.5	16.7	0.0	0.0
	4-24	55.4	75.9	60.0	41.7	58.3	83.3
	24-72	23.2	24.1	20.0	33.3	41.7	16.7
	≥ 72	1.8	0.0		0.0	8.3	0.0
Unilaterality	Unilateral	66.1	55.2	55.0	91.7	75.0	33.3
Pulsating quality	Pulsating	85.7	72.4	80.0	100.0	83.3	66.7
Intensity of headache	Mild	1.8	0.0	0.0	8.3	0.0	0.0
	Moderate	17.9	20.7	22.5	8.3	25.0	25.0
	Severe	55.4	62.1	55.0	58.3	66.7	58.3
	Unbearable	23.2	17.2	20.0	25.0	8.3	16.7
Physical activity	Worsened by	75.0	65.5	77.5	66.7	66.7	58.3
Associated symptoms of headache	Nausea	83.9	100.0	80.0	91.7	100.0	100.0
	Vomiting	41.1	51.7	37.5	50.0	50.0	50.0
	Photophobia	83.9	62.1	82.5	83.3	50.0	58.3
	Phonophobia	55.4	55.2	55.0	50.0	66.7	41.7

MA=Migraine with aura, MwoA=Migraine without aura, MA-MA pair=both co-twins have MA, MA-MwoA pair=one co-twin has MA and the other MwoA, MwoA-MwoA pair=both twins have MwoA, h=hours, N=number of co-twins (individuals), % refers to the percentage of twins with the particular headache characteristic, ⌜⌝ = Chi-square or Fisher's exact test $p < 0.05$

Table 24. Distribution of Clinical Characteristics in Migraine with Aura (MA) and Migraine without Aura (MwoA) Concordant and Aura Discordant Monozygotic (MZ) Twin Pairs

Aura or headache characteristics	MA concordant MZ pairs N=20			Aura discordant MZ pairs N=12			MwoA concordant MZ pairs N=6		
	Neither twin with the characteristic	Discordant for the characteristic	Concordant for the characteristic	Neither twin with the characteristic	Discordant for the characteristic	Concordant for the characteristic	Neither twin with the characteristic	Discordant for the characteristic	Concordant for the characteristic
Type of aura:									
Any visual aura	0	0	20		Not applicable			No aura	
Hemianopia or scotoma	9	6	5		Not applicable			No aura	
Fortification spectra	0	12	8		Not applicable			No aura	
Photopsia	10	7	3		Not applicable			No aura	
Blurring of vision	9	9	2		Not applicable			No aura	
Hemiparesis	20	0	0		Not applicable			No aura	
Hemisensory aura	17	2	1		Not applicable			No aura	
Speech disturbance	20	0	0		Not applicable			No aura	
Characteristics of headache:									
Over 50 lifetime attacks	6	10	4	1	5	6	0	4	2
Duration of headache 4-72 h	2	4	14	0	3	9	0	0	6
Unilateral headache	4	10	6	0	4	8	3	2	1
Pulsating headache	2	4	14	0	2	10	0	4	2
Moderate or severe headache	0	1	19	0	1	11	0	0	6
Aggravation by physical activity	1	7	12	2	4	6	1	3	2
Associated symptoms:									
Nausea	2	4	14	0	1	11	0	0	6
Vomiting	9	7	4	4	4	4	2	2	2
Photophobia	1	5	14	2	4	6	1	3	2
Phonophobia	6	6	8	3	4	5	3	1	2

N=number of twin pairs, MA=migraine with aura, or migraine with and without aura, MwoA=migraine without aura. Discordant pairs differ significantly from the concordant pairs in unilateral headache (Mann-Whitney U-test, $p<0.05$)

Bonferroni/Dunn method for multiple comparisons, the difference remains significant between MA-MwoA and MwoA-MwoA.

5.3.5. Ascertainment of zygocity of twins

All aura-discordant twin pairs (MA-MwoA pairs) were genotyped to confirm their zygocity as MZ. Zygocity was confirmed as MZ in all 12 pairs (verifying the validity of the previously used questionnaire).

5.4. Clinical characteristics of familial migraine with and without aura (Study IV)

Clinical characteristics of familial migraine were analysed on the basis of the questionnaire replies. Of the 1000 consecutive migraine sufferers who had returned the questionnaire, 730 were women, 270 men. 94 of the patients (60 women, 34 men) failed to indicate whether they suffered from both MwA and MwoA, so an unambiguous study diagnosis was therefore possible in the case of 906 subjects who were analysed further.

5.4.1. Age of the patients

The mean ages of the patients in the diagnostic categories were 53.0 (SD 11.6, range 19-74) years for Eqv, 41.0 (SD 17.0, range 9-84) years for MwA, 44.4 (SD 16.8, range 8-87) years for MwA+ MwoA, 42.1 (SD 18.5, range 6-90) years for MU and 40.6 (SD 19.2, range 5-90) years for MwoA. The mean age of the Eqv subjects was statistically significantly greater than in the other categories ($p=0.001$ in relation to MwA subjects, $p=0.012$ in relation to MwA+MwoA subjects, $p=0,002$ in relation to MU subjects, and $p=0.0004$ in relation to MwoA subjects). The mean age of the MwA+MwoA subjects was significantly higher than of the MwoA subjects ($p=0.012$). No other difference between the categories was significant. The observed statistical age differences between the study categories, although statistically significant, are not considered clinically relevant in a questionnaire-based study.

5.4.2. Distribution of the diagnostic categories

Participants were placed into the study categories based on the questionnaire replies or the clinical interview (182 individuals). Of the 906 analysed patients, 29 (3.2%) were diagnosed as Eqv, 102 as MwA (11.1%), 373 as MwA+MwoA (40.6%), 186 as MU (20.3%) and 216 as MwoA (23.5%) (Figure 2). The distribution of the diagnoses differed significantly between women and men ($p<0.0001$). Men were more likely to be diagnosed as MwA or MwoA and women as MwA+MwoA.

5.4.3. Characteristics of aura

Table 25 shows the occurrence of different types of migraine aura among the patients, and the values calculated for the aura indices. The mean aura index was 33.0 (SD 9.0) for MwA, and 30.0 (SD 9.0) for MwA+MwoA. The aura index was statistically significantly higher in MwA subjects than in MwA+MwoA subjects ($p=0.0003$). Figure 3 shows the occurrence of the visual aura in the patients. Aura in the MU category does not meet the IHS criteria, and the MU patients were thus not analysed.

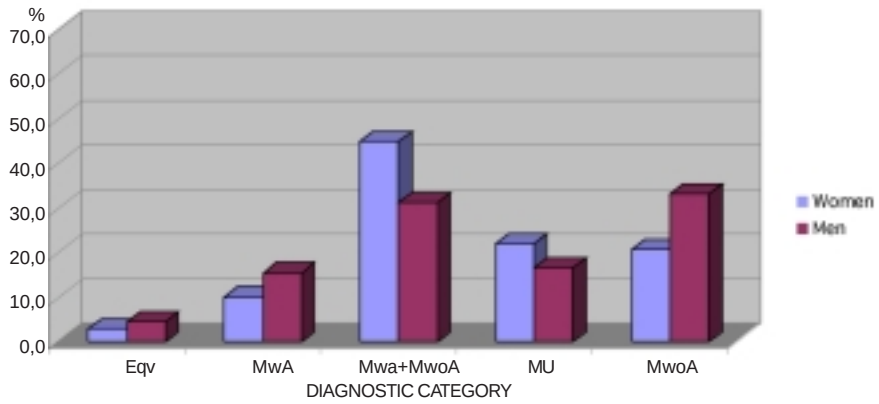


Figure 2. Distribution of Diagnostic Migraine Categories in Study IV

Eqv=migraine equivalent, MwA=migraine with aura, Mwa+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura

Table 25. Clinical Characteristics of Familial Migraine: Migraine Aura

	MwA (%) N=102	MwA+MwoA (%) N=373	MU (%) N=186
Type of aura:			
Any visual aura	100.0	99.7	60.8
Hemianopia	68.6	53.1	7.0
Scintillating scotoma	73.5	65.1	7.5
Photopsia	47.1	55.0	23.7
Blurring of vision	52.9	48.0	31.7
Speech disturbance	45.1	37.8	25.3
Any sensory aura	52.0	44.8	33.9
Any motor aura	28.4	26.0	10.2
Hemisensory aura	43.1	37.5	19.9
Hemiparetic aura	25.5	22.8	7.5
	MwA	MwA+MwoA	MU
Aura index:			
Index score, total (SD)	33.0 (9.0)	30.0 (9.0)	9.8 (7.4)
Index score, women (SD)	34.1 (9.2)	30.5 (9.2)	10.2 (7.5)
Index score, men (SD)	31.0 (9.5)	27.9 (7.9)	8.1 (6.9)

MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura, N=number of patients, SD=standard deviation, % refers to the percentage of patients with the particular aura characteristic

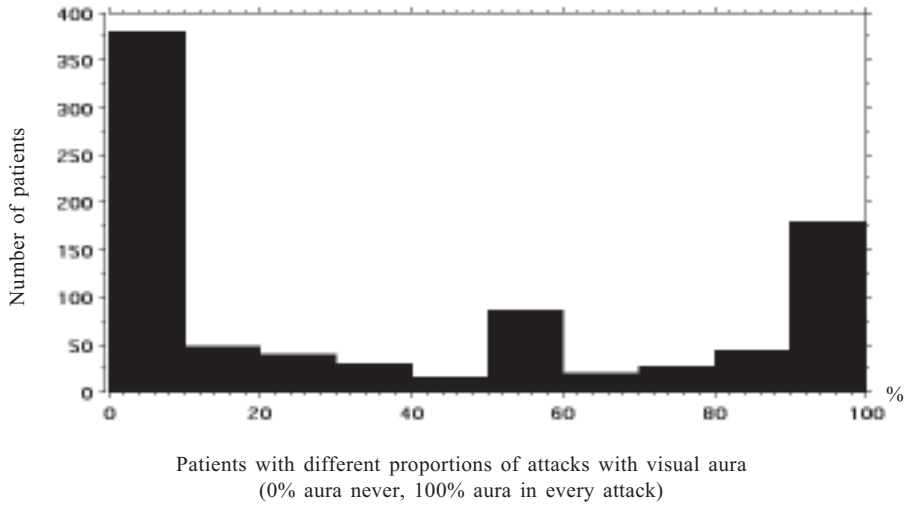


Figure 3. Migraine Patients with Visual Aura in Finnish Migraine Families (Study IV)

5.4.4. IHS characteristics of headache

Tables 26 and 27 show the IHS variables of headache. The p values relate to distribution variables between the four diagnostic categories. The categories were not compared pair-wise. The mean IHS score was 7.1 (SD 2.4) for MwA, 8.3 (SD 1.6) for MwA+MwoA, 7.9 (SD 1.6) for MU, and 7.4 (SD 1.5) for MwoA. The mean IHS score was statistically significantly higher for MwA+MwoA than for MwA ($p<0.0001$), MU ($p=0.0063$) and MwoA ($p<0.0001$). The mean IHS score was also significantly higher for MU than for MwA ($p=0.0003$) or MwoA ($p=0.002$). The mean IHS score for MwA and MwoA did not differ significantly.

5.4.5. Migraine-associated features

Table 28 shows variables which are unrelated to the IHS criteria, but are often described by migraine sufferers. The distribution of these variables differed significantly between the four diagnostic categories. The Eqv category was not analysed. Again, no pair-wise comparisons were undertaken. The mean value of the index of migraine-associated characteristics was 4.7 (SD 3.9) for MwA, 7.4 (SD 3.8) for MwA+MwoA, 6.5 (SD 3.7) for MU and 5.0 (SD 3.0) for MwoA. Data on 2 patients were missing. The indices were therefore calculated for 875 patients. The difference between MwA +MwoA and the other categories was statistically significant ($p<0.0001$ compared with MwA, 0.0036 with MU and <0.0001 with MwoA). MU had statistically significantly more migraine-associated features than MwA ($p<0.0001$) and MwoA ($p<0.0001$). The difference between MwA and MwoA was not statistically significant.

Table 26. Clinical Characteristics of Familial Migraine: Distribution of IHS Characteristics of Headache within Study Categories

	MwA (%) N=102	MwA+MwoA(%) N=373	MU (%) N=186	MwoA (%) N=216	p
Lifetime frequency of migraine attacks					
< 5	7,8	0,5	0,0	0,0	
5-10	14,7	4,8	7,0	6,9	
10-50	21,6	21,7	25,3	23,6	< 0,0001
50-100	22,5	23,1	23,1	26,9	
> 100	30,4	47,2	39,2	36,1	
(data missing)	(2.9)	(2.7)	5.4)	(6.5)	
Duration of typical migraine attacks					
< 4 hours	32,4	12,9	10,2	19,4	
4-72 hours	60,8	79,4	79,0	75,9	< 0,0001
> 72 hours	4,9	7,5	8,1	2,3	
(data missing)	(2.0)	(0.3)	(2.7)	(2.3)	

MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura, N=number of patients, SD=standard deviation, % refers to percentage of patients with the characteristic, p-value refers to distribution between the four migraine categories, no pair-wise comparisons have been undertaken.

Table 27. Clinical Characteristics of Familial Migraine: Distribution of IHS Characteristics of Headache within Study Categories

	MwA (%) N=102	MwA+MwoA (%) N=273	MU (%) N=186	MwoA (%) N=216	p
Unilateral headache	63,7	75,3	67,7	56,5	< 0,0001
Pulsating headache	64,7	77,7	69,9	63,0	< 0,0001
Headache intensity unbearable	34,3	41,0	37,6	25,0	< 0,0001
Headache intensity severe	34,3	43,7	40,3	49,5	
Headache intensity moderate	20,6	13,7	21,0	23,6	
Headache intensity mild	6,9	0,8	0,5	0,9	
Aggravation by physical activity	66,7	78,6	77,4	73,6	< 0,05
Associated nausea	70,6	86,3	83,3	81,5	< 0,0001
Associated vomiting	49,0	58,4	55,9	48,6	< 0,0001
Associated photophobia	83,3	93,6	82,3	76,9	< 0,0001
Associated phonophobia	73,3	83,4	74,7	64,8	< 0,0001

MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura, % refers to percentage of patients with the characteristic, N=number of patients p-value refers to distribution between the four migraine categories, no pair-wise comparisons have been undertaken

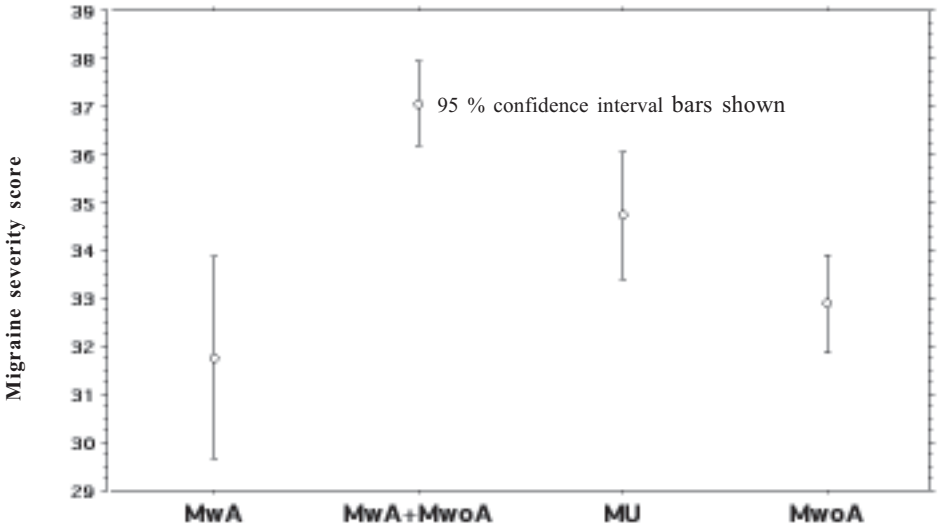
Data was missing for unilateral headache in 2.9% of patients in the MwA category, MwA+MwoA 0.3%, MU 1.6%, MwoA 0.5%; for pulsating headache: MwA 2.9%. MwA+MwoA 0 %, MU 1.6%, MwoA 0.9%; for headache intensity: MwA 3.9%, MwA+MwoA 0.8%, MU 0.5%, MwoA 0.9%; for aggravation by physical activity: MwA 21.6%, MwA+MwoA 12.3%, MU 16.7%, MwoA 17.6%; for nausea: MwA 2.0%, MwA+MwoA 0%, MU 0%, MwoA 0.5%; for vomiting: MwA 2.0%, MwA+MwoA 0%, MU 0.5%, MwoA 0%; for photophobia: MwA 2.0%, MwA+MwoA 0%, MU 1.6%, MwoA 0%; for phonophobia: MwA 2.0%, MwA+MwoA 0%, MU 1.6%, MwoA 0%

Table 28. Clinical Characteristics of Familial Migraine: Distribution of Associated Features of Migraine within Study Categories

	MwA (%) N=102	MwA+MwoA (%) N=372	MU (%) N=186	MwoA (%) N=321	P-value
Prodromal symptoms:					
Craving for food	7.8	18.0	13.4	5.1	<0.0001
Yawning	21.6	41.9	34.9	25.5	<0.0001
Stereotypical mood change	19.6	31.2	22.0	12.0	<0.0001
Unusual tiredness	33.3	51.6	53.2	38.0	<0.0001
Provoking factors:					
Stress	73.5	90.6	76.3	76.4	< 0.0001
Missing a meal	46.1	73.2	74.7	66.7	< 0.0001
Alcohol	30.4	55.6	45.7	38.4	< 0.0001
Periods	36.4	55.3	46.3	40.6	< 0.0001
Chocolate	9.8	14.2	8.6	4.2	< 0.0001
Cheese	5.9	9.1	5.9	3.7	< 0.01
Redwine	6.9	7.5	3.2	2.3	< 0.001
Symptoms related to activation on ANS:					
Paleness	54.9	79.1	72.0	65.3	< 0.0001
Goose pimples	32.4	41.0	36.6	29.2	< 0.0001
Feeling cold	21.6	27.9	28.0	22.2	< 0.01
Sweating	4.9	13.9	14.0	9.3	< 0.01
Tachycardia	20.6	37.5	27.4	17.1	< 0.0001
Bradycardia	3.9	8.6	10.2	3.2	< 0.01

MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura, ANS=Autonomic nervous system, IHS=International Headache Society, % refers to percentage of patients with the characteristic, P-value refers to distribution between the four migraine categories, N=number of patients

Data was missing in < 2% of questionnaires for each presented migraine characteristic, except in 8.4% of questionnaires for provocation of attacks by alcohol (10.8% in MwA, 5.6% in MwA+MwoA, 11.8% in MU and 6.5% in MwoA)



MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine unclassified aura, MwoA=migraine without aura

Figure 4. The index Score for Migraine Severity

Table 29. Clinical Characteristics of Familial Migraine: the Clinical Indices

	MwA		MwA+MwoA		MwoA	
	women	men	women	men	women	men
	mean (SD)		mean (SD)		mean (SD)	
The aura index	34.1 (8.7)	31.0 (9.5)	30.5 (9.2)	27.9 (7.9)	0	0
The index for IHS-headache	7.2 (2.4)	6.8 (2.5)	8.5 (1.5)	7.5 (1.7)	7.5 (1.5)	7.1 (1.5)
The migraine-associated-characteristics index	5.4 (4.3)	3.4 (2.7)	7.9 (3.6)	5.5 (3.8)	5.2 (3.0)	4.6 (3.2)
The migraine severity index	32.4 (10.2)	30.6 (11.1)	37.8 (8.3)	34.2 (8.5)	33.5 (7.2)	31.7 (7.3)

MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura, SD=standard deviation. The aura index and the index for IHS-headache could be calculated for all 102 MwA, 373 MwA+MwoA and 216 MwoA patients; The migraine associated-characteristics-index for 102 MwA, 371 MwA+MwoA and 216 MwoA patients (data missing for 2 patients in these categories) The migraine severity index for 98 MwA, 363 MwA+MwoA and 202 MwoA patients (data missing for 30 patients)

5.4.6. Overall migraine severity

The mean migraine severity index was 31.8 (SD 10.5) for MwA, 37.1 (SD 8.4) for MwoA+MwoA, 34.7 (SD 8.9) for MU and 32.9 (SD 7.2) for MwoA (Figure 4). Data on 38 patients in these categories were missing, the indices were calculated for 839 patients. The Eqv category was not analysed. The mean migraine severity index was statistically significantly higher for MwA+MwoA than for MwA ($p<0.0001$), MU ($p=0.0031$) and MwoA ($p<0.0001$) (95% confidence intervals are shown in Figure 4). The index was also statistically significantly higher for MU than for MwA ($p=0.0059$) or MwoA (0.0361). The migraine severity index did not differ significantly between MwA and MwoA. Table 29 shows all clinical indices in the family study.

5.5. Linkage analysis of four typical migraine families (Study V)

Linkage analysis was performed in four Finnish migraine families (Figure 1) to study whether these families were linked to the reported FHM locus on 19p13 (1).

The pairwise linkage data are shown in Table 30. All of the markers displayed LOD scores of <-2 at a recombination fraction of 0.0. The exclusion map of the chromosomal region based on the multipoint analyses of four markers flanking the FHM locus is given in Figure 5. Altogether a region of 50 cM (centiMorgans) could be excluded (LOD score <-2) as the migraine locus in the four Finnish families studied. For 'affecteds only' analysis, all penetrances were divided by 1000 and pair-wise lod scores were calculated. All of the markers resulted in negative lod scores (Table 30).

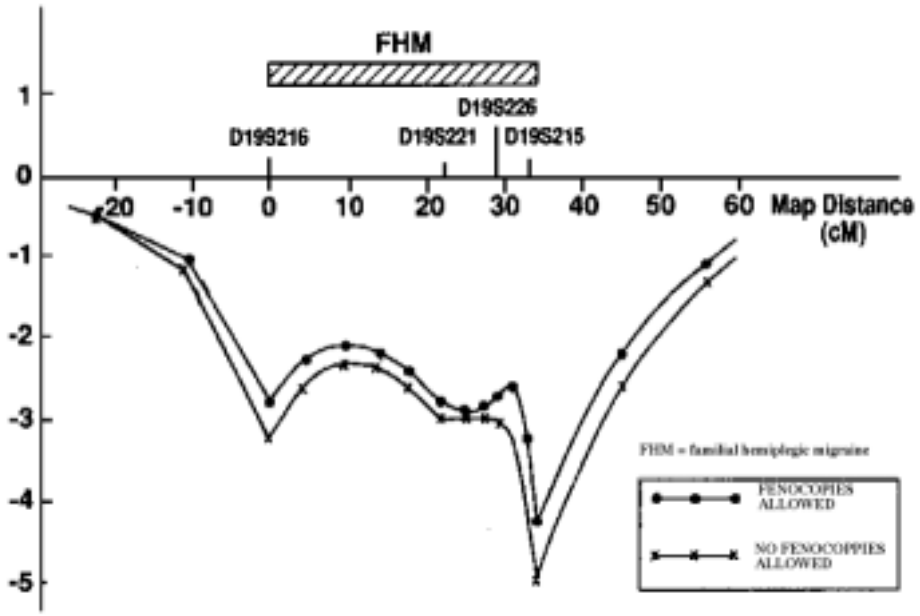


Figure 5. Exclusion Map of the FHM region in Four Finnish Migraine Families

Table 30. Pairwase Linkage Data for Chromosome 19 Markers

Locus		Recombination fraction				
		0.00	0.05	0.10	0.20	0.30
D19S216	Family 1	−0.63	−0.12	0.09	0.22	0.17
	Family 2	−1.13	−0.54	−0.34	−0.15	−0.06
	Family 3	−0.60	−0.41	−0.30	−0.16	−0.08
	Family 4	0.10	0.08	0.06	0.03	−0.00
	Total	−2.26	−0.99	−0.48	−0.07	−0.00
	AOM*	−0.55	−0.39	−0.27	−0.14	−0.06
D19S221	Family 1	−1.64	−1.28	−0.98	−0.53	−0.25
	Family 2	−0.05	−0.02	−0.00	0.01	0.01
	Family 3	−0.37	−0.29	−0.23	−0.14	−0.06
	Family 4	−0.35	−0.31	−0.26	−0.15	−0.07
	Total	−2.41	−1.91	−1.48	−0.81	−0.37
	AOM	−0.79	−0.64	−0.51	−0.31	−0.15
D19S226	Family 1	−1.60	1.08	−0.72	−0.31	−0.11
	Family 2	−1.15	0.07	0.08	0.10	0.08
	Family 3	−0.52	−0.37	−0.25	−0.11	−0.04
	Family 4	−0.43	−0.36	−0.28	−0.16	−0.07
	Total	−2.49	−1.74	−1.18	−0.48	−0.13
	AOM	−0.42	−0.27	−0.15	0.01	0.07
D19S215	Family 1	−0.73	−0.58	−0.46	−0.29	−0.16
	Family 2	−1.13	−0.78	−0.56	−0.28	0.11
	Family 3	−0.32	−0.25	−0.19	−0.11	−0.05
	Family 4	−0.29	−0.24	−0.18	−0.08	−0.02
	Total	−2.47	−1.85	−1.39	−0.75	−0.33
	AOM	−1.05	−0.80	−0.61	−0.33	−0.15

* Affecteds only model.

5.6. Levels of endothelin-1 in migraine (Study VI)

Ictal and interictal ET-1 values were measured to study possible differences between ictal and interictal states in the migraineurs, and to compare migraine patients with healthy control subjects.

The mean interictal ET-1 value was 5.3 pg/ml (SD 1.8) and ictal value 6.4 pg/ml (SD 3.9). The mean acute (blood sample taken = 2 h after onset of attack) ET-1 was 8.4 (SD 3.5) and subacute (sample taken later during attack) 5.0 (SD 3.6). The difference between the interictal values of the migraineurs and the control subjects was 1.5 pg/ml (95% confidence interval 0.8 to 2.2). The change between interictal and ictal values for patients with both values (n = 9, ET-1 ictal - ET-1 interictal) was -1.7 pg/ml (95% confidence interval -3.5 to 0.2). The difference between mean acute and interictal values was 3.1 pg/ml (95% confidence interval 1.0 to 5.2). Table 31 summarises the main results. Gender differences in ET-1 were not analysed because there were only two men in the study. For reference, in our laboratory the mean plasma ET-1 of healthy subjects is 3.8 pg/ml (SD 1.3; n = 76, age 21-54, range 0.7 - 5.5 pg/ml, no sex differences).

During the migraine attacks ET-1 value depended on the time elapsed from the start of the attack to the time of sampling (Figure 6). The highest values were detected during the first two hours after the start of an attack. There was no significant difference in ET-1 values in patients with moderate or severe headache. Only two patients had aura during their attack and thus attacks with and without aura could not be compared. The acute ET-1 value was 11.0 pg/ml in both patients with aura.

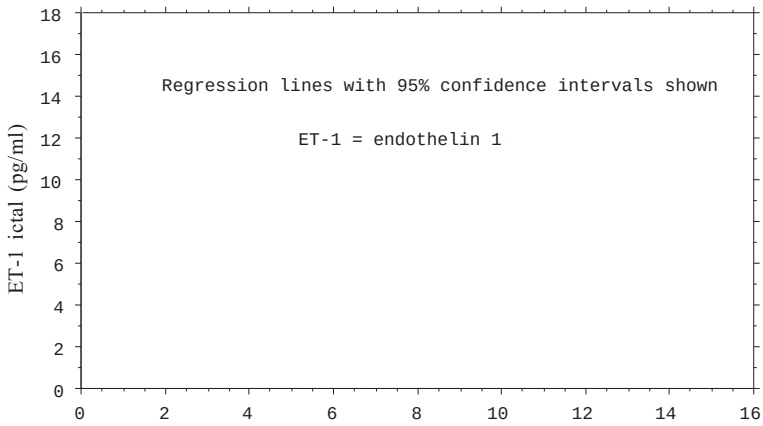


Figure 6. Endothelin-1 Values in the Course of a Migraine Attack

Table 31. Levels of Endothelin-1 (ET-1) in Migraine Patients

Ictal and interictal ET-1 values in migraine	Number of subjects	Mean pg/ml	SD	Std. Error	95% confidence interval pg/ml
ET-1 interictal	18	5.3	1.8	0.4	4,4 to 6,2
ET-1 ictal	22	6.4	3.9	0.8	4,7 to 8,1
ET-1 control	76	3.8	1.3	0.2	3,5 to 4,1
ET-1 acute	9	8.4	3.5	1.2	5,7 to 11,1
ET-1 subacute	13	5.0	3.6	1.0	2,8 to 7,1
ET-1 interictal - ET-1 control	means compared	1.5			0,8 to 2,2
ET-1 ictal - ET-1 interictal (paired)	9	-1.7	2.4	0.8	-0,2 to -3,5
ET-1 acute - ET-1 interictal (means)	means compared	3.1			1.0 to 5,2
ET-1 acute - ET-1 subacute (means)	means compared	3.5			0,3 to 6,7

Acute=blood sample taken=2 h from attack onset, subacute= blood sample taken later during attack, SD=standard deviation, Std.Error=standard error

5.7. Summary of clinical characteristics of familial migraine (Studies II-IV)

The results of Studies II, III and IV are compared in Figures 7-10. Figure 7 compares the diagnostic categories, Figures 8-9 the characteristics of migraine aura, and Figure 10 the characteristics of migraine headache.

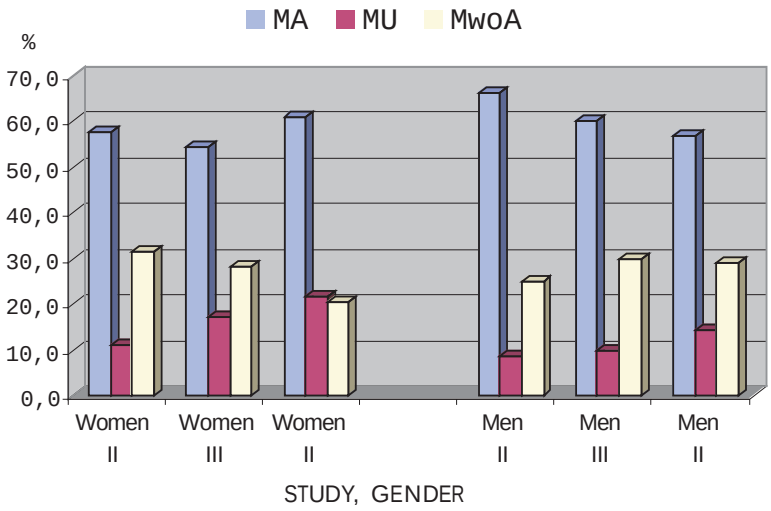


Figure 7A. Distribution of the Diagnostic Migraine Categories in Studies II–IV

MA=migraine with aura, or migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura

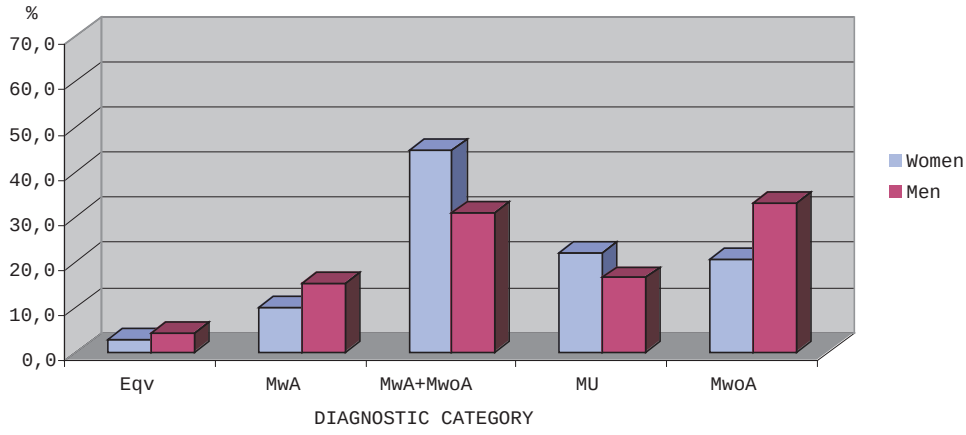


Figure 7B. Distribution of the Diagnostic Migraine Categories in Study IV

Eqv=migraine equivalent, MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MU=migraine with unclassified aura, MwoA=migraine without aura

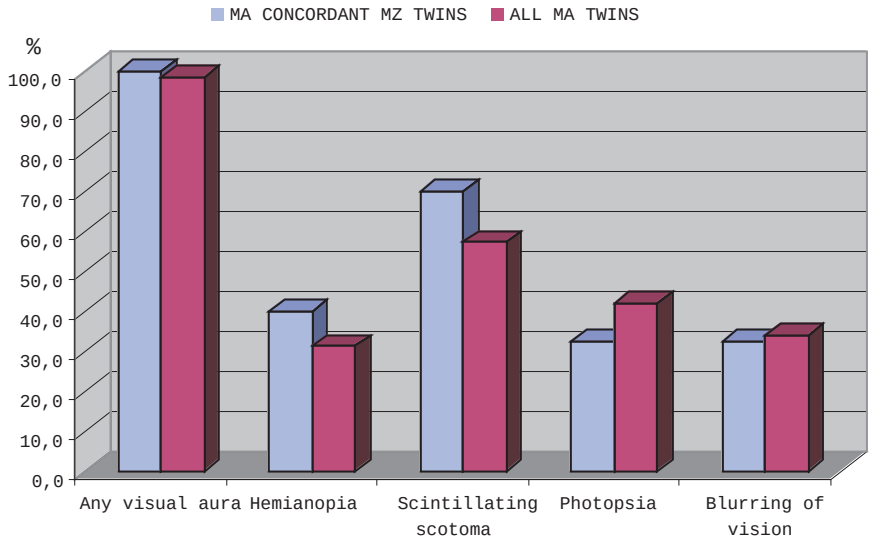


Figure 8A. Visual Aura in Finnish Twins Suffering from MA in Studies II and III

MA=migraine with aura, or migraine with and without aura, MZ=monozygotic

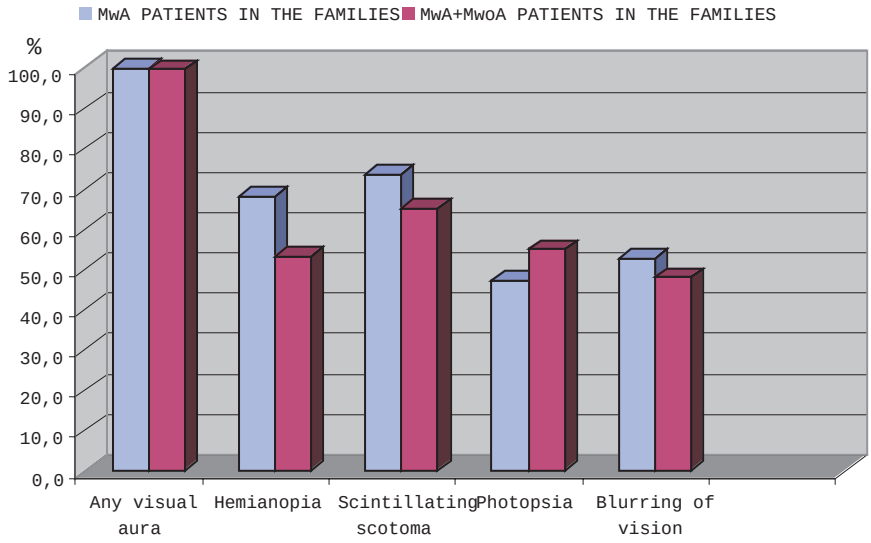


Figure 8B. Visual Aura in Patients with MwA or MwoA+MwoA in Finnish Migraine Families in Study IV

MA=migraine with aura, MwA+MwoA=migraine with and without aura

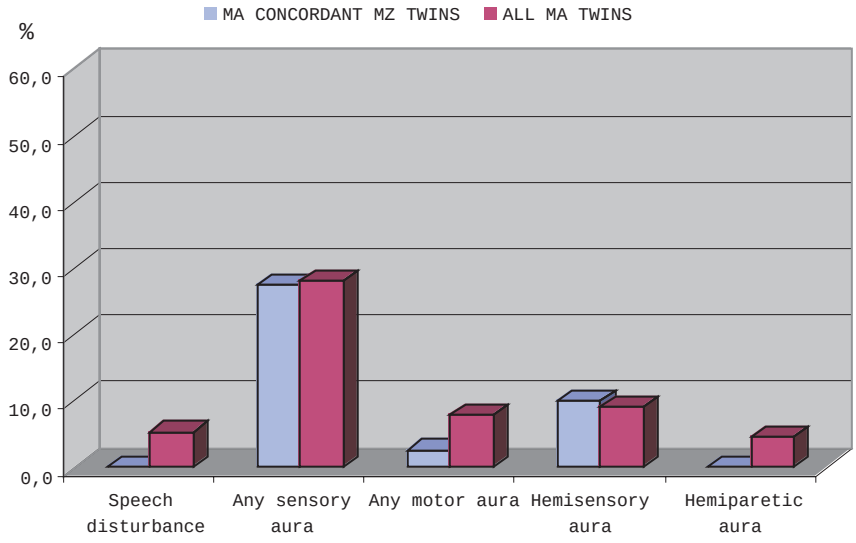


Figure 9A. Speech, Sensory and Motor Type of Aura in Finnish Twins Suffering from MA in Studies II and III

MA=migraine with aura, or migraine with and without aura, MZ=monozygotic

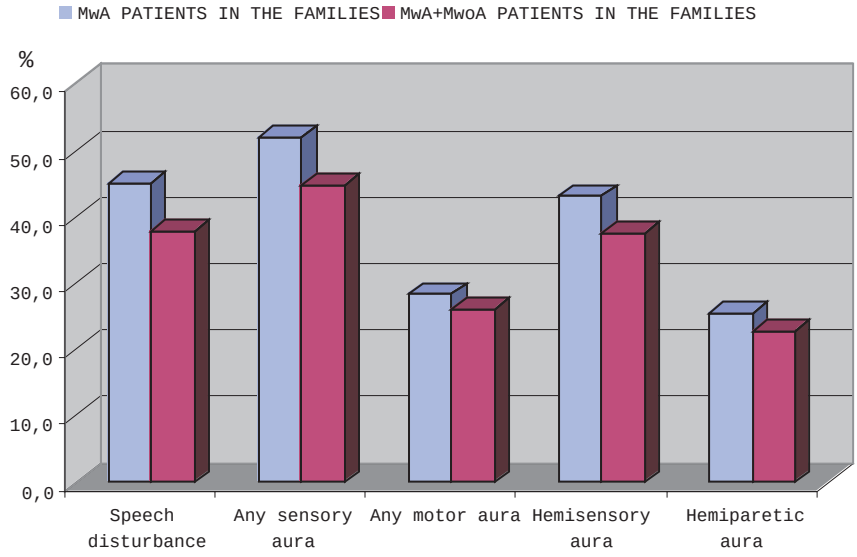


Figure 9B. Speech, Sensory and Motor Type of Aura in Patients with MwA or MwA+MwoA in Finnish Migraine Families in Study IV

MwA=migraine with aura, MwA+MwoA=migraine with and without aura

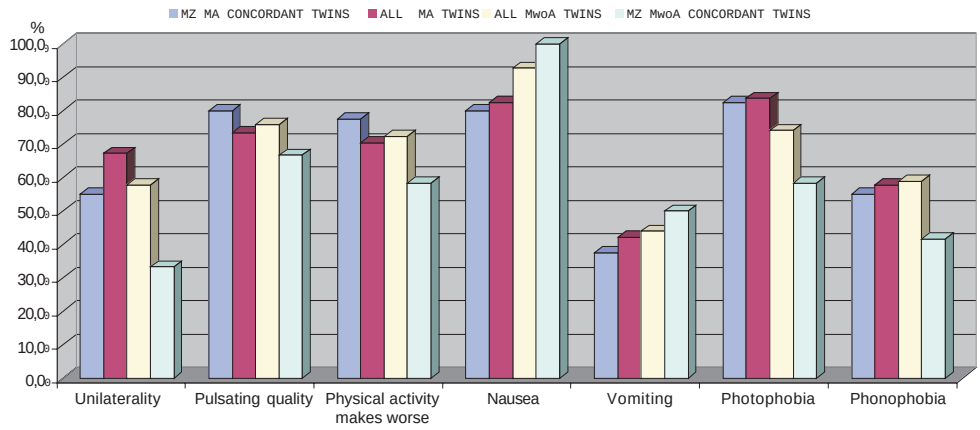


Figure 10 A. The IHS Characteristics of Headache in Finnish Twins Suffering from MA or MwoA in Studies II and III

MA=migraine with aura, or migraine with and without aura, MwoA=migraine without aura, MZ=monozygotic

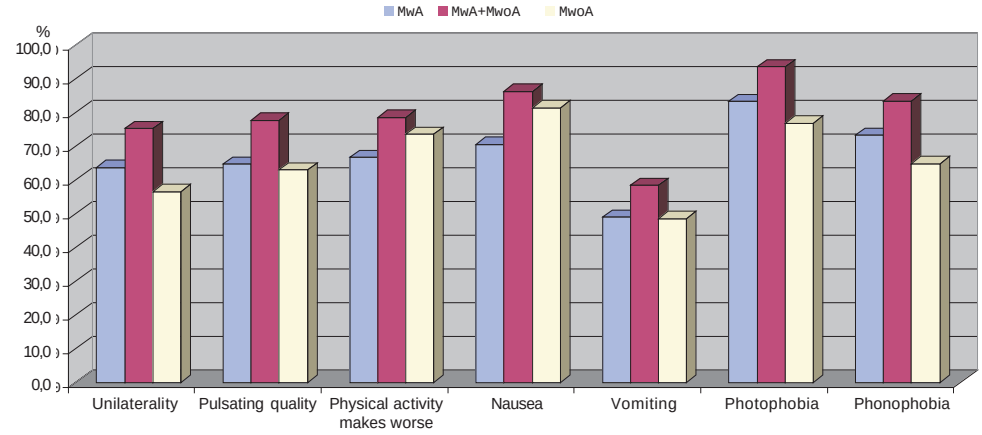


Figure 10 B. The IHS Characteristics of Headache in Finnish Migraine Families in Study IV

MwA=migraine with aura, MwA+MwoA=migraine with and without aura, MwoA=migraine without aura

Figure 10. The IHS Characteristics of Headache in Finnish Twins (Studies II, III) and Migraine Families (Study IV)

Clinical features of migraine headache as a function of zygosity and diagnosis:
a) Upper figure, left hand side: genetically identical twin pairs concordant for migraine with aura (MA). Right hand side: corresponding pairs with migraine without aura (MwoA).
b) Lower figure, left hand side: patients in Finnish migraine families with exclusively migraine without aura (MwoA), MwA+MwoA: patients with both aural and non-aural migraine attacks.

6. DISCUSSION

Since the discovery of the FHM gene (1, 2) molecular genetic research on migraine has been extensive. FHM, a relatively distinct clinical entity, has been shown to be genetically heterogenous with at least three different genes involved (225). The complexities of the FHM teach important lessons for studies involving the more common forms of migraine, migraine with and without aura. Genetically different types of migraine, although each meeting the current criteria for migraine, are likely to exist. This means that meticulous clinical analysis looking for subgroups of migraine is required before molecular genetic analyses can be undertaken. The number of patients and blood samples needed to locate additional liability genes for migraine can be expected to be very high. Methods that allow cost-effective participation of hundreds of patients is required, making office-based studies impractical. Thirdly, while a random search for migraine genes can be expensive and frustrating, a candidate gene approach is another relevant strategy for the studies: in the breakthrough study of FHM, the co-localization of the *CADASIL* gene in the same chromosome, speeded up the molecular genetic process (1). Thus, studies involving possible candidate genes are important.

These three topics are addressed in the present work. Tools for conducting cost-effective diagnoses of migraine are created, clinical characteristics of migraine in Finnish twins and Finnish migraine families are analysed, and studies concerning the FHM gene *(CACNA1A)* and ET-1 as possible candidate genes for migraine with and without aura are carried out.

The $FMSQ_{TW}$ and the $FMSQ_{FS}$

Careful clinical planning and validation of the diagnostic tools and methods to be used is a necessity in any medical project. Both the disease under study and the projected study population have to be accounted for. In the present studies development of the questionnaires and their pretesting were done in close collaboration with the migraine patients and their family members. The participants were asked to take active part in the process. This helped to translate the questions into the language of the study population and avoided many possible misunderstandings and inaccuracies. These pretesting methods have been shown to add accuracy to questionnaire data (226). Subsequent validation studies showed that the work paid off with the questionnaire-based diagnoses having excellent agreement with the clinical interview-based diagnoses in the projected target population, migraine families (Table 18). Earlier Rasmussen and colleagues have strongly, and justifiably, criticised the validity of questionnaire data in headache research (44, 59). Their conclusion was that migraine can be ruled out with a questionnaire but that all other results have to be interpreted with care (44). The major difficulty has been poor response rates (44). In the present studies, the response rates (75-80 % in the twin studies) are good and demonstrate that, although quite extensive, the questionnaires have been well accepted by the study population.

The diagnostic categories of the study

The IHS has succeeded well in its effort to standardise operational criteria for migraine all over the world (23, 38). Also in the present study the IHS classification was found to be practical, and most participants could be classified according to the criteria. The use of the non-IHS category MU, migraine with unclassified aura, throughout the present work is necessary for several reasons. It is

often difficult, even in a direct interview, to assimilate the various experiences and descriptions given by patients concerning aura and aura-like symptoms. Some pain-associated features can easily be incorrectly classified as aura, and some important aspect may be forgotten or ignored by the patient or the physician. To help in relation to this distinction the MU category was added for patients with such unclassifiable, but potentially important, symptoms. Woods *et al.* (1994) used positron emission tomography (PET) to study a patient during an attack of migraine without aura with unspecified visual symptoms, and found spreading oligemia (109), which is widely thought to be consistent with migraine aura (227) and should not exist in migraine without aura (228). Thus the IHS criteria might be too restrictive and in some cases result in a pathophysiologically unsatisfactory classification placing a patient with migraine with aura into the migraine-without-aura category. For genetic linkage studies, the high specificity of the migraine diagnosis is more important than high sensitivity. Indeed, the specificity figures of $FMSQ_{FS}$ are excellent (Table 18) and the application of the MU category will further assist in differentiating between migraine with and without aura.

The study population, Finnish twins and migraine families

The chosen setting of two distinct target populations allows one to study, and compare, migraine in the general population, and in a more clinical cohort, the migraine families. The Finnish Twin Cohort (217), from which the studied twins come from, is representative of the isolated population of Finland, and as such provides an exceptional opportunity for genetic studies of migraine (229). In analysing the twin data (Studies II and III) some important aspects related to patient selection have to be emphasised. Twin pairs (MZ, DZ, or of unknown zygocity) concordant for a headache problem were included in the studies. Thus, the traditional method of comparing MZ twins to DZ does not apply: both the MZ and DZ twin pairs were similarly selected to begin with, thus abolishing possible zygocity-based differences. This selection strategy was chosen to cost-effectively identify sibling pairs for future molecular genetic studies, and, what is important for the present work, this strategy does not impair observations on clinical characteristics of migraine in the population-based twins. Especially the rare MZ MA-MA and MwoA-MwoA pairs can be considered to be interesting when hereditary migraine is discussed. Another matter related to patient selection is that twins taking part in a parallel hypertension study were not included. While this probably does not affect the presented clinical characteristics of migraine, in the future molecular genetic studies the omission could have consequences, especially in relation to the vascular aspects of migraine, and it thus has to be accounted for.

In the family study, index cases were selected from consecutive migraine patients attending two outpatient neurological clinics. Patients with an exceptionally prominent family history of migraine were chosen, regardless of their aura status, or other characteristics of their attacks. Thus, no bias towards MwA or MwoA exists due to the selection method. Subsequently all first degree relatives of the index case were included in the study. While the index cases are probably biased towards having severe migraine, their family members are not, which makes the data more balanced. Overall, the presented migraine families can thus be considered to represent well typical familial migraine in Finland.

Clinical characteristics of familial migraine in Finland

In all the presented studies, clinical analysis naturally relies heavily on the IHS criteria. The criteria are applied and explored both in relation to aura and headache. Despite this,

other features of migraine are not forgotten, especially Study IV pays attention to several migraine-associated features not defined by the IHS. Figures 7-10 summarize the key observations during the studies.

Distribution of diagnostic study categories in familial migraine

More than half of all patients with familial migraine (altogether 1545 individuals, Studies II–IV) had migraine with aura (the MA, MwA, MwA+MwoA categories). This is much more than the usual notion that 15% of all migraine patients have migraine with aura, and even more than the one third referred in a recent review by Ferrari (4). Thus, in familial migraine, aura is much more prevalent than usually believed. This is in agreement with the view that the hereditary component in migraine with aura is stronger than in migraine without aura (181). Another key observation concerning migraine with aura is that the frequency distribution of patients with different proportions of attacks with aura is clearly not a normal distribution (Figure 3). On the contrary, opposite ends of the spectrum stand out. Thus patients with exclusively migraine with aura and exclusively migraine without aura can be identified. This is also in agreement with previous literature. Population-based epidemiological studies have for years underlined the importance of differentiating migraine with aura from migraine without aura (58, 59, 230).

Also differences between genders have been observed (Figure 2). Men belong relatively more often to the pure MwA or MwoA categories than do women. Women have more often both kinds of attacks, and thus belong to the MwA+MwoA category. This observation could have implications for future studies. Families with men migraineurs having solely MwA or MwoA could be easier to find than families with female migraineurs belonging always to the same category. This could assist in sorting out families into more homogenous groups and reduce genetic heterogeneity. It is possible that in the future migraine classification will be based on the underlying molecular genetic predisposition, and the clinical importance of detailed family history of migraine will increase.

Migraine aura

The occurrence of the different aura symptoms in familial migraine (Figures 8-9) is essentially similar to that described by Russell and Olesen in a population-based clinical study using the IHS criteria (26). As expected visual aura and fortification spectra are the hallmarks of migraine with aura. This is true also for the rare MZ MwA-concordant twin pairs, which can in a way be taken to present pure hereditary migraine with aura. Russell and Olesen found that speech disturbance, sensory and motor aura were present in 31, 18 and 6 % of migraineurs, respectively. The figures from the present study are not comparable, because questionnaire data can not be compared to a clinical interview regarding these aura symptoms. Despite this, the obvious difference between twins and family members is interesting (Figures 8-9). Twins from a sample representing the general population (Studies II and III) report clearly less speech, sensory and motor manifestations than the family members in the questionnaires. This suggests differences between clinical (all index cases of families had contacted a neurologist for advice regarding their migraine) and population-based migraine (the twins were included regardless of whether they had contacted a doctor regarding their migraine). Of note is also that none of the MwA-concordant MZ twins had hemiparetic symptoms. Thus, if one surveys a population-based twin registry in search of monozygotic twin pairs concordant for IHS migraine, one ends up with typical migraine with visual aura, but with no hemiparetic symptoms. Also hemisensory symptoms are very rare. This might suggest that typical IHS migraine with aura is distinct from FHM, and the proposed pathophysiological similarity of

FHM and migraine with aura (96) needs to be re-evaluated.

The presented observations have pathophysiological implications. Scintillating scotoma, not hemiparesis, is the characteristic feature in familial migraine. Scintillating spreading scotoma with positive and negative features can also be considered the best extrapolation to represent spreading depression in patients. Molecular genetic studies of a large sample of patients or sibling pairs (or families if possible) with typical build up of the IHS fortification spectra will be one of the next steps in the analysis of the significance of spreading depression in migraine. Clearly, twin pairs concordant for this characteristic can be identified. Among the many possible candidate genes underlying the spreading migraine aura in humans, there could be genes coding for connexin proteins, which are subunits of gap-junctions (231) and have also been associated with spreading depression (231, 232) and, at least in theory, with induction of neurovascular changes responsible for the pain in migraine (121).

Migraine headache

Figure 10 summarises observations regarding migraine headache in familial migraine. There is a clear trend in the distribution of unilateral headache, nausea, vomiting and photophobia in the twin pairs. Genetically identical MZ subjects in MA concordant twin pairs are relatively more characterised by unilateral headache and photophobia. Correspondingly, patients in MZ twin pairs concordant for MwoA have more nausea. Clinically, in terms of diagnosis and treatment, the differences shown are probably not important, but pathophysiologically they merit attention. For example, in terms of molecular genetic analysis, subgroups with MwA with prominent photophobia and strictly unilateral headache and MwoA with prominent nausea can be targeted when typical migraine with and without aura, respectively, are analysed. In Sardinia, a subgroup of patients with prominent nausea (and yawning) has already been associated with a dopamine receptor gene *(DRD2)* (198). A similar trend (unilateral headache and photophobia in MwA and nausea in MwoA) can be seen in the families, but the difference is not so clear. In addition the MwA+MwoA category clearly stands out in having the most typical migraine headache in all respects. In light of these differences, it was unfortunate that the twin questionnaire did not differentiate MwA from MwA+MwoA. This shortcoming will be corrected in an extension study of the family members of MwA- and MwoA-cordordant twin pairs.

Comorbidity of migraine with and without aura

The key observation in the family study was that patients with MwA+MwoA differed in their attack characteristics from both their pure MwA and MwoA counterparts. They are the ones with several attacks and numerous associated features (Table 28).

This is not surprising, compared to the MwA patients, because the IHS criteria define only the aura phase and many patients with mild headache fulfill the criteria for IHS migraine with aura. What is surprising, is that the headache of the MwA+MwoA patients is also more typical than of the MwoA subjects, who were diagnosed entirely based on the IHS-defined characteristics of vascular headache. Thus, the complete migraine (32, 233) does not belong to either of the pure types, *i.e.* MwA or MwoA, but to those with both kinds of attacks.

This suggests that the relationship of migraine with and without aura could be expressed as a continuum, shown in Figure 11. This theory would also explain some of the differences in opinion between clinicians and epidemiologists on the comorbidity of migraine with and without aura (234, 235). Thus, in clinical populations, MwA+MwoA patients with severe attacks stand out, while in population-based studies, MwA and MwoA patients are easily identified.

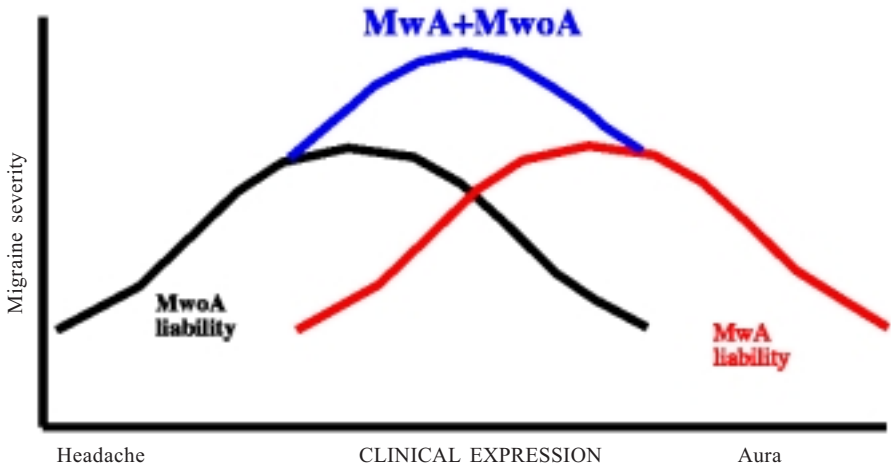


Figure 11. Hypothesis: Comorbidity of Migraine with and without Aura

MwA=Migraine with aura, MwA+MwoA=Migraine with and without aura, MwoA=Migraine without aura

This relates also to the main result of the twin studies, the migraine-subtype-discordant monozygotic twin pairs. It can be hypothesised that these twins, in the migraine spectrum of Figure 11, would be located between MwA+MwoA and MwoA patients. Thus, genetic predisposition would be intermediate for the aura, and environmental or acquired factors would eventually decide whether attacks with aura should appear, with the co-twins differing in these influences despite their identical genotype.

Exclusion of the FHM locus as a predisposing locus in four Finnish migraine families

In study V we applied methods that test if the locus identified on chromosome 19p would contribute to the more common forms of familial migraine with and without aura. The linkage analyses resulted in negative LOD scores (< -2). These exclusion results are, however, highly dependent on the assumption, that the disease is due to a single major gene with dominant inheritance. In complex diseases the affection status is probably caused by many interacting genes. Therefore we performed also affecteds only analysis, where only affected individuals have influence on linkage data. Also these analyses resulted in negative LOD scores. Thus, according to our results there is less than 1:100 chance that the 19p13 region, linked to FHM, is involved in migraine in our four families. Consequently, it seems that locus heterogeneity exists between different types of migraine.

These results reinforced our clinical notion that a difference between FHM and migraine with and without aura actually exists also genetically. Secondly, the diverse distribution of migraine with and without aura in these families helped to guide the development of the eventual study questionnaire, in which much attention is paid to differentiate between migraine with and without aura.

ET-1 in migraine patients

The recent migraine research has focussed especially on the neuronal mechanisms (93), partly ignoring the vascular side and nerve-blood vessel interaction of migraine. NO (117) and ET-1 (17, 118) are molecules that could well mediate some vascular aspects of migraine. Both are vasoactive and have been shown to influence the membrane potential of cerebral blood vessels (236, 237), which in turn influences the vascular tone. The vascular tone of cerebral vessels, at a given point of time, could well affect the temporal sensitivity of the vasculature to the migraine generator residing in the brain stem (85). Thus, the central activation (brainstem, hypothalamus) could be modified markedly by the periphery.

The original report on ET-1 changes in migraine came from Finland (17). The results of the present study confirm the observation that ET-1 levels are elevated early during migraine attacks (17, 118) and, in addition, interictal values in migraineurs are higher than in normal controls. This suggest that ET-1 might be involved both in the predisposition to migraine (elevated interictal values), and in the characteristics of the attacks (elevated acute values). The relationship between migraine aura and ET-1, a potent vasoconstrictor, is naturally interesting in regard to the old vasoconstriction-vasodilatation hypothesis of migraine (16) and in regard to the observed high ET-1 values early after onset of migraine in the present study. On the other hand, it has been shown that bosentan, an ET-1 antagonist, is not effective in migraine (119) and, furthermore, ET-1 does not seem to be involved in spreading depression (238). Despite these reports, several aspects make further studies of ET-1 appealing. In the present study two subjects had aura before ET-1 was measured, and both had very high (11.0 pg / ml) values. It could well be that the presence of aura would explain these high values.

In addition, as Studies II-IV have shown, patients with MwA, MwA+MwoA and MwoA are clinically distinct and should be defined and compared also in studies dealing with ET-1. This was not done in the present study. ET-1 could well be hypothesised to be relatively more important in migraine with aura, and thus make up some of the spectrum presented in Figure 11. In addition, ET-1 could have at least a modifying role in some special situations related to migraine. In antiphospholipid syndrome, also associated with migraine (239, 240), elevated ET-1 levels have been shown to correlate with arterial thrombosis and strokes (241). Thus, ET-1 could be one of the factors that occasionally contribute to migraine-related strokes (111).

However, ET-1 is only one of many factors that affect cerebral vascular tone (242) at a given time point. Especially the temporal interplay of the potent vasodilator NO and the vasoconstrictor ET-1 is interesting in the discussion on migraine pathophysiology. Comparison of serially taken ET-1 and NO values in attacks with and without aura between a statistically adequate number of pure MwA and MwoA patients could be one of the next steps in the evaluation of the eventual importance of ET-1 in migraine pathophysiology.

Future considerations

The clinical characteristics of familial migraine in Finland, presented here, will serve as the foundation for molecular genetic studies of migraine in the future. Clearly, in the study population, migraine with aura dominates over migraine without aura, suggesting indirectly a stronger inherited component to migraine with aura. Thus, migraine with aura will be targeted in extension studies. The MZ-migraine-concordant twin pairs show that, in addition to genes, also acquired factors modify the basic migraine characteristics; genetically identical twin pairs concordant for migraine but discordant for aura can be identified. These environmental confounding influences have to be accounted for also in genetic studies. The presented data indi-

cate that migraine with and without aura are different entities, but with very frequent co-occurrence. The relationship between the entities seems to be more of a continuum than a clear-cut difference. Based on this, the correct distinction between patients with migraine with aura and migraine without aura is essential when predisposing genes for migraine are sought. The presented linkage data indicate that genetic heterogeneity exists between FHM and migraine with and without aura. The common forms of migraine are likely of multifactorial origin. One of many candidate genes that could have an impact on the clinical characteristics and differences between migraine with and without aura is ET-1.

The overall conclusion reached here is that familial migraine is a diverse syndrome with both clinical and genetic heterogeneity. It is likely that several subgroups of migraine, such as FHM, can be identified within IHS-defined migraine with and without aura. It is likely that pathophysiological and genetic mechanisms will differ between these subgroups. It appears that one has to move from studying groups of patients to studying groups of families with very stereotypical migraine throughout the whole family before new predisposing genes for migraine can be identified. This demands large population-based studies with accurate case ascertainment and detailed analysis of migraine. The combined use of national twin registries and validated migraine-specific questionnaires can greatly assist in the clinical analysis of migraine before molecular genetic methods will take the next step forward.

7. SUMMARY AND CONCLUSIONS

This thesis presents clinical observations on familial migraine in Finland during the first years of the Finnish Migraine Gene Project. The eventual goal of the project is to identify predisposing genes for migraine with and without aura.

Two questionnaires, developed for the analysis of familial migraine, the Finnish Migraine-Specific Questionnaire for Twin Studies ($FMSQ_{TW}$) and the Finnish Migraine-Specific Questionnaire for Family Studies ($FMSQ_{FS}$), were validated by comparing the questionnaire-based diagnoses to the diagnoses based on a clinical interview. All 20 migraine patients taking part in the validation study of $FMSQ_{TW}$ were correctly diagnosed as migraineurs. In the validation study of $FMSQ_{FS}$, agreement between the $FMSQ_{FS}$-based and clinical interview-based migraine diagnoses was 0.97 (Cohen's weighted kappa). The sensitivity of $FMSQ_{FS}$ for migraine was 0.99, and specificity 0.96.

Clinical characteristics of migraine were analysed in 321 twins suffering from migraine with aura, or migraine with and without aura, (MA) and 166 twins suffering from migraine without aura (MwoA) using a combination of a mailed questionnaire and telephone interview. Unilateral headache ($p<0.05$) and photophobia ($p<0.05$) were more typical for migraine with aura, while nausea was more typical for migraine without aura ($p<0.05$). Also the duration of headache in migraine without aura was longer than in migraine with aura ($p<0.01$). There was no statistically significant difference in the age of onset, menstrual provocation or prodromal symptoms between MA and MwoA.

Clinical characteristics of migraine were analysed in 51 migraine-concordant monozygotic (MZ) twin pairs using a validated mailed questionnaire. All 20 pairs with MA were concordant for visual aura and 19 for moderate or severe headache intensity, while all 6 pairs with MwoA were concordant for headache duration of 4 to 24 hours, moderate or severe headache intensity, and nausea. The 12 mixed pairs (one twin with MA and the other with MwoA) had more often unilateral and pulsating headache compared to both the MA and the MwoA pairs. All in all, individual MA twins had more photophobia ($p<0.05$) and MwoA twins more nausea ($p<0.05$).

Clinical characteristics and co-occurrence of migraine with aura (MwA) and migraine without aura (MwoA) were determined in 1000 migraine patients belonging to 210 Finnish migraine families, using the $FMSQ_{FS}$. 906 patients were able to indicate whether they suffered from migraine with aura (MwA), migraine with and without aura (MwA+MwoA) or MwoA, and were analysed further. Of these patients, 3.2% had experienced migraine aura without headache (Eqv), 11.1% MwA, 40.6% MwA+MwoA, 23.5% MwoA and 20.3% migraine with aura-like symptoms not meeting the IHS criteria. The MwA+MwoA patients had statistically significantly more severe attacks, more typical headache and more prodromal symptoms than the MwA or the MwoA subjects.

Four polymorphic microsatellite markers (D19S216, D19S221, D19S226, and D19S215) were analysed to study whether four migraine families with typical IHS migraine would show linkage to the FHM locus on 19p13. All of the markers displayed LOD scores < -2 at a recombination fraction of 0.0. Also 'affected only' analysis resulted in negative LOD scores. Thus, it is highly unlikely that the 19p13 region is involved in migraine in these four typical migraine families.

The plasma levels of ET-1 (endothelin-1) in 31 migraine patients were studied during and between migraine attacks. The mean interictal and ictal values were 5.3 pg/ml (SD1.8) and 6.4 pg/ml (SD 3.9), respectively. The ictal values were markedly elevated at the beginning of the migraine attack and declined to interictal or even a lower level later

in the course of an attack. The interictal values of migraineurs were significantly higher than those of control subjects. Only two of the patients had an aural attack, ET-1 in these attacks was high (11.0 pg/ml).

Recalling the specific aims of the present study, the results can be summarised as follows:

1. The Finnish Migraine-Specific Questionnaire for Twins ($FMSQ_{tw}$) and the Finnish Migraine-Specific Questionnaire for Family Studies ($FMSQ_{FS}$) were valid and practical for use in the twin and family studies of migraine.

2. There are differences in the clinical characteristics of migraine between migraine with and without aura. The headache phase in migraine with aura is shorter and does not always fulfill the IHS criteria for migraine headache. Unilateral headache and photophobia are relatively more typical for migraine with aura, while nausea is more typical for migraine without aura. Migraine with aura predominates in the population-based cohort.

3. Co-twins of migraine-concordant monozygotic twin pairs can have different types of migraine. Differences in clinical characteristics between twins with and without aura are not determined entirely by genes.

4. Migraineurs of Finnish migraine families had frequently both migraine with and without aura. The co-occurrence of both types was most usual in the migraineurs with the most severe attacks.

5. Familial migraine in the studied families was not linked to the FHM locus in 19p13, suggesting genetic locus heterogeneity in migraine with and without aura.

6. The interictal values of ET-1 in migraineurs were higher than in normal controls. The levels of ET-1 increased even further early during the migraine attacks. The liability to migraine and attack characteristics could be modified by ET-1. The ET-1 gene can be considered one of the candidate genes for migraine, and particularly for migraine with aura.

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APPENDIX 1.

QUESTIONS CONCERNING THE IHS CRITERIA OF HEADACHE

How long do your headache attacks last without medication (usually):

1 less than 4 hours
2 4-24 hours
3 24-72 hours
4 over 72 hours

How long do your headache attacks last with medication (usually):

1 less than 4 hours
2 4-24 hours
3 4-72 hours
4 over 72 hours

What is the quality of headache during the attacks (usually):

1 pain is on one side
2 pain is on both sides

1 it is pulsating / throbbing
2 it is steady

1 it is mild
2 it is moderate
3 it is severe
4 it is unbearable

Can you work / take care of your tasks during the attacks:

1 yes 2 no

How does physical effort affect headache: (for example climbing stairs, busy walking or such normal activity)

1 makes it worse
2 makes it milder
3 has no effect / can not say

During your attacks, do you have:

1 nausea
2 vomiting
3 sensitivity to light
4 sensitivity to sound
5 visual disturbances
6 one sided sensory numbness or motor weakness

QUESTIONS CONCERNING THE IHS CRITERIA OF VISUAL AURA:

[Questions concerning hemiparetic or hemisensory symptoms were asked in the same way]

Preceding the attacks, do you have.

1 visual disturbances lasting several minutes (for example zigzag patterns, clear double vision, repeatedly flashing lights, deficiency in your visual fields)
2 difficulties to speak
3 one sided sensory numbness or motor weakness

If you have experienced visual disturbances preceding the attack, is it:

1 Deficiency in your visual fields
2 scintillating zigzag pattern
3 sparks, stars in your visual field
4 blurring, undulating vision
5 other visual disturbance:

How fast does this symptom develop and how long does it last:

1 it is at it's worst or maximum intensity in less than 1-2 minutes
2 it worsens or spreads over 4 minutes

1 it lasts less than one minute
2 it lasts less than one hour, but over a minute
3 it last over an hour

1 it disappears fully in 24 hours
2 it does not disappear fully

How are visual disturbances and headache connected in time:

1 headache follows the symptoms in less than one hour
2 headache follows the symptoms later
3 headache and the symptoms occur at the same time
4 headache comes first
5 no headache occurs

How many headache attacks with these kind of aura symptoms (symptoms preceding the attacks) have you had during your lifetime:

1 one
2 2 or more
3 over ten

Please explain in your own words all the symptoms preceding headache:

APPENDIX 2. The Finnish Migraine-Specific Questionnaire for Family Studies ($FMSQ_{FS}$)

Dear addressee!

A study has been started in Meilahti Hospital which aims to investigate the hereditary nature of migraine. This way the knowledge of migraine will be improved and as there will be more information, improved medication and treatments can be developed for the symptoms of those with migraine.

There is a person in your family having migraine and therefore we would like you to participate in our study regardless of whether or not you have migraine.

The study is in two parts:

1. You are requested to fill in and return the questionnaire (a pre-paid and pre-addressed return envelope is enclosed)

2. You are requested to visit your own health centre or private doctor for a blood test. A referral to a blood test will be enclosed to the questionnaire (the health centre will know from the referral which tests they should do) We request that you contact your private doctor or health centre before you go to the blood test.

Naturally, the study is absolutely confidential. You will be informed of the results when the study is completed.

Should you have any questions about the study, please contact:

Markus Färkkilä
Docent
Physician in charge of the research

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Helsinki University Central Hospital (HUCH)/
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PLEASE ANSWER THE FOLLOWING QUESTIONS ABOUT HEADACHE AND MIGRAINE

- THE QUESTIONS CONCERN ALL THE HEADACHES YOU HAVE HAD DURING YOUR LIFE

- PLEASE ANSWER EVEN IF YOU NO LONGER HAVE HEADACHES

- PLEASE ANSWER ACCORDING TO THE INSTRUCTIONS ON THE NEXT PAGE EVEN IF YOU HAVE NEVER HAD ANY HEADACHES

QUESTIONNAIRE FOR THE GENEALOGICAL STUDY OF MIGRAINE:
Name: .....
Date of birth: .....
Address: .....
Telephone: ..... **Work:** .....
E-mail: .....

Who is the relative, who asked you to participate in the study:

.....

In what way are you related?

.....

Which one of the following describes your state in relation to headaches best

- **I have hardly any headaches at all and there have not been headaches before either ( )**
- **I have headaches (or have had headaches) sometimes ( )**
- **My head often feels strange and heavy like there was pressure inside ( )**
- **I have a headache approximately once a month ( )**
- **I have headaches weekly ( )**
- **I have a headache almost every day ( )**

If you do not have headaches and have not really had them before, please go straight to section 24

Please answer the following questions, however, if YOU HAVE DISTURBING HEADACHES, OR HAVE HAD DISTURBING HEADACHES AT LEAST SOMETIMES.

1. I would estimate that I have had headaches during my life:

Possible childhood headaches are also included, please check the most appropriate alternative

Never **( )**

(please move on to section 24)

less than 5 **( )**
5-10 **( )**
10-50 **( )**
50-100 **( )**
more than 100 **( )**

2. At the moment, I have headaches:

for 15 days a month or less **( )**
for over 15 days a month **( )**

3. Without medication, the headaches (usually) last:

Or if you always take medication, how long would you estimate they would last without medication

less than 4 hours **( )**
4-72 hours **( )**
more than 72 hours **( )**

"Without medication, a headache typical of me lasts (or lasted) for":

If you always take medication for the headache, please give an estimate of how long you would think it would last without medication

With medication, the headaches (usually) last:

less than 4 hours **( )**
4-72 hours **( )**
more than 72 hours **( )**

The longest continuous period that the headaches have lasted is:

_____
days

The shortest headaches last:

_____
hours

4. The ache is (usually):

one-sided	( )
throbbing or pounding	( )
"the ache is throbbing to he beat of the hearth"	
steady	( )
some other kind, what: _____	( )

5. The intensity of the headaches is (usually):

mild	( )
moderate	( )
severe	( )
unbearable	( )

On a scale of 1 to 10 the headaches are (usually):

_____

0 = no headache, 10 = the most severe headache imaginable

Are you usually capable of working / going to school during the headaches:

the headaches prevent working / going to school entirely	( )
the headaches clearly make working /going to school more difficult	( )
the headaches do not impede with working / going to school significantly	( )
I cannot say	( )

6. Does the ache ever change from one side to another (if it is one-sided)

yes ( ) no ( )

7. How does physical exercise (e.g. climbing up stairs or a similar normal exercise) affect the headaches:

makes them worse	( )
does not affect	( )
makes them better	( )
I cannot say	( )

8. Do the headaches (at least sometimes) involve:

nausea	( )
vomiting	( )
sensitivity to light	( )
sensitivity to sounds	( )

9. Do you see ”after images” in connection with the headaches as you close your eyes:

yes ( ) no ( )

10. Which one of the features of the headache bothers you the most (do not choose more than one feature):

the throbbing of the headache	( )
the intensity of the headache	( )
the nausea and / or vomiting associated with the headaches	( )
the sensitivity to light and /or sounds associated with the headaches	( )
otherfactor,what? _____	( )

If necessary, please explain in more detail:

_____
_____
_____
_____
_____
_____

11. Are the headaches (at least sometimes) preceded by:

- **VISUAL DISTURBANCE** yes ( ) no ( )

  (e.g. serrate optical phenomenon, pronounced double vision, recurring flashes of light, flashing lights or colours, visual field defect)

- **SPEECH DIFFICULTY** yes ( ) no ( )

  .....

- **SENSORY DISTURBANCE OF THE LIPS OR TONGUE**

  (e.g. TINGLING OR NUMBNESS)

  yes ( ) no ( )

- **ONE-SIDED SENSORY DISTURBANCE** yes ( ) no ( )

  (e.g. TINGLING OR NUMBNESS) in the face+arm or arm+leg or face+arm+ leg)

  .....

- **ONE-SIDED MUSCULAR WEAKNESS** yes ( ) no ( )

  (e.g. in the face+arm or arm+leg or face+arm+leg)

  .....

- **SENSORY DISTURBANCE OF ALL 4 EXTREMITIES** yes ( ) no ( )

- **MUSCULAR WEAKNESS IN ALL 4 EXTREMITIES** yes ( ) no ( )

  .....

- **VERTIGO** yes ( ) no ( )

  (the world is spinning, seems clearly to be moving)

  yes ( ) no ( )

12. Are the headaches repeatedly preceded by: some of the following symptoms, which indicate to you that the headaches are coming, even though your head does not hurt yet?

Unusual HYPERENERGY ( )

RESTLESSNESS, DIFFICULTY OF CONCENTRATION ( )

"CRAVING" FOR A CERTAIN FOODSTUFF ( )
e.g. chocolate, other sweets etc.
Please explain in more detail:
.....
.....

Unusual feeling of THIRST ( )
Unusually frequent YAWNING ( )
Clear change of MOOD ( )
repeatedly in the same way
Depression ( )
Nervousness ( )
Irritation, ill temper ( )
Good mood
Please explain in more detail: ( )
.....
.....

Difficulty in FOCUSING THE EYES ( )
Pronounced, unusual TIREDNESS, POWERLESSNESS ( )
"dead beat", "dead-tired" before the headaches
SENSITIVITY TO LIGHT (before the headaches) ( )
SENSITIVITY TO SOUND (before the headaches) ( )

FEELING OF COLD, FREEZING
SWEATING, COLD SWEAT
FEELINGS IN THE NECK
e.g. pain, stiffness, tension, etc.
Please explain in more detail:
.....
.....
OTHER PRODORMAL SYMPTOM yes ( ) no ( )
Another symptom is:
.....
.....
None of the above ( )

13. Do the headaches ever involve:

Visual disturbance IN BOTH EYES:	**( )**
AT THE SAME TIMES	
Tinnitus	**( )**
Hearing loss	**( )**
Ear ache	**( )**
Pressure in the ears, blocked ears	**( )**
Other ear symptom	**( )**
Whatkind	
Vertigo, "the world is spinning like a merry-go-round"	**( )**
Other kind of dizziness	**( )**
Clumsiness of hands	**( )**
Objects keep falling from the hands	**( )**
Clumsiness of feet	**( )**
Disturbance of balance, uncertainty of walking	**( )**
Double vision	**( )**
Difficulties in swallowing	**( )**
Stiffness or numbness of the tongue	**( )**
Numbness of the pharynx	**( )**
Fits of fainting and unconsciousness	**( )**
Fever	**( )**
Confusion	**( )**
None of the above	**( )**

14. Can the following factors trigger the headaches:

Menstruation ( )
Alcohol ( )
Certain food or a beverage (what?) ( )
.....
Not eating ( )
Forgetting to eat a snack ( )

Physical exercise ( )
Stress ( )
Relieving of stress
e.g. weekend, beginning of holiday ( )

(Even a mild) injury to the head, "banging one's head" ( )

Sleeping too long ( )
Staying up, lack of sleep ( )
Change of the climate ( )
Please explain in more detail:
.....
.....

Heat, e.g. hot weather, sauna ( )
Coldness, e.g. cold weather ( )
A bright or a flashing light
Please explain in more detail:
.....
.....

A certain scent or smell ( )
Please explain in more detail:
.....
.....

Does another factor trigger the head aches often (which?)
.....
.....

None of the above ( )

15. The headache can be alleviated by:

An easy run ( )
Lying down ( )
Turning off the lights ( )
Another factor, which? ( )
.....
.....

16. Hormonal factors affecting the headaches (for women):

Beginning of menstruation:

increased the headaches ( )
decreased the headaches ( )
had no effect ( )

Menstruation has not started yet ( )

During the last two trimesters of pregnancy the headaches:

got better ( )
got worse ( )
no effect ( )

I have not been pregnant ( )
If necessary, please explain in more detail:
.....
.....

The effect of the cessation of menstruation (menopause):

alleviated the headaches ( )
made the headaches worse ( )
had no effect ( )

Menstruation has not ended yet ( )

The effect of contraceptive pills

alleviated the headaches ( )
made the headaches worse ( )
had no effect ( )

I have never taken contraceptive pills ( )

17. Do the headaches often start:

- early in the morning ..... ( )

- in the morning ..... ( )
- before noon ..... ( )

- afternoon ..... ( )
- in the evening ..... ( )

- in the night ..... ( )
- There is no clear connection with the start of the headaches to the above ( )
- in connection with menstruation ( )

18. Do the headaches involve:

- Abdominal pain ( )
- Diarrhoea ( )
- Constipation ( )
- Flatulence ( )
- Paleness ( )
- "Goose bumps" ( )
- Fingers turn "white" ( )
- Facial flushing ( )
- Dizziness when getting up ( )
- Everything goes black before the eyes when getting up ( )
- Skin feels dry ( )
- Feeling of cold, freezing ( )
- Sweating, cold sweat ( )
- Palpitation ( )
- Slow heartbeat ( )
  (pulse is slower than normal)
- Nose "gets blocked" or "is running" ( )
- Tears are "dripping" from the eyes ( )
- Mouth turns dry ( )
- Eyes feel dry ( )
- Clear feeling of malaise ( )
- Clear feeling of weakness ( )

None of the above ( )

19. How old were you when the headaches started:

younger than 5 years ( )
younger than 10 years ( )
younger than 15 years ( )
younger than 20years ( )
20-30 years ( )
30-40 years ( )
40-50 years ( )
older than 50 years ( )

How old approximately _____ years old
please do not hesitate to state the age according to your best recollection

20. Has any event in your life (or an equivalent experience) Increased your headaches significantly

going to school ( )
studying ( )
working ( )
marriage ( )
birth of the children ( )
divorce ( )
serious illness ( )
head injury ( )
meningitis ( )
other, what? ( )

_____

_____

serious illness of a family member ( )
certain medication, what? ( )

_____

_____

None of the above ( )

PLEASE DESCRIBE BRIEFLY THE MOST TYPICAL FEATURES OF YOUR HEADACHES

1 _____

_____

2 _____

_____

3 _____

_____

DO YOU HAVE MORE THAN ONE TYPE OF HEADACHE?

YES ( )
NO ( )

PLEASE EXPLAIN IN MORE DETAIL

_____

_____

_____

_____

_____

HAS YOUR DOCTOR/PHYSICIAN DIAGNOSED YOU TO HAVE MIGRAINE?

YES ( )
NO ( )

I DO NOT KNOW ( )

HAVE YOU EVER HAD AN MRI OF THE BRAIN PERFORMED?

YES ( )
NO ( )

I DO NOT KNOW ( )

IF YES, WHERE AND WHEN WAS IT PERFORMED?

_____

_____

_____

21. Medication:

Which medicine is the most efficient on your headaches:
(please underline the efficient medicinal products, 2 lines under the most efficient one)

- Panadol, Para-Suppo, Para-Tabs
- Acetard, Acetylsalic., Alka-Selzer, Asapor, Aspirin, Disperin, Primaspan, Migpriv

- Diclometin, Diclomex, Trabona, Voltaren
- Brufen, Bucal, Burana, Ibumetin, Ibusal, Nurofen, Dexit
- Confortid, Indocal, Indocid, Indometin, Inmetsin
- Ketocal, Ketofen, Ketomex, Ketorin, Orudis
- Alpoxen, Miranax, Naprometin, Naprosyn, Naproxen, Nycopren, Pronaxen

- Dacam, Felden, Pirom
- Clotam, Tolfen
- Clinoril, Donobid, Novalgin, Ponstan, Surgamyl, Tilcotil, Toradol

- Norflex, Robaxin, Trancopal
- Dolan, Lobac, Metsapal, Muscotal, Norgesic, Robaxisal, Somadril

- Aspam, Dolopam, Dolorin
- Indalgin, Panacod, Staralgin, Symptomal
- Anervan, Cafergot, Trimigrin
- Klotriptyl, Limbitrol, Noritren, Saroten, Triptyl
- Imigran, Migmax
- Zomig, Naramig, Maxalt
- some other product, which one:
.....

22. Targeted drugs for migraine:

Have you ever taken Imigran® or Migmax® for migraine?

yes ( ) no ( )

Did you take:

- a tablet of 50 mg ( )
- a tablet of 100 mg ( )
- nasal spray ( )
- injection ( )
- suppository ( )
- I do not remember ( )

Would you say that the effect was:

Excellent ..... ( )
.....

Good ..... ( )
.....

Moderate ..... ( )
.....

Poor ..... ( )

Please explain in more detail

.....

.....

Did the medication have side effects? yes ( ) no ( )

If yes, what were they like?

.....

.....

Have you ever taken Zomig®-, Naramig® or Maxalt® for migraine?

yes ( ) no ( )

What was the effect of Zomig® like .....
.....

What was the effect of Naramig® like .....
.....

What was the effect of Maxalt® like .....
.....

Please explain in more detail

.....

.....

Is one of these new drugs for migraine clearly better than the others for you?

yes ( ) no ( )

Please explain in more detail .....

.....

23. Has prophylactic medication for migraine ever been tried on you?

YES ( )
NO ( )

I DO NOT KNOW ( )

IF IT HAS BEEN TRIED, PLEASE TELL WHICH MEDICATION AND WHAT ITS EFFECT WAS LIKE:

E.G. BETA-BLOCKER, CALCIUM ANTAGONIST, AMITRITYLINE, VALPROATE, ACETAZOLAMIDE, ETC. (E.G. PROPRAL®, EMCONCOR®, KLOTRIPTYL MITE®, SAROTEN®, DEPRAKINE®, ABSENOR®, DIAMOX®, ÖDEMIN®, ETC.)

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

24

The following pages deal with the neurological symptoms of migraine, so called aura. They are often connected with headache, most commonly precede it but can also occur without the ache.

In case you have not had visual disturbance, sensory disturbance, muscular weakness or speech difficulties of this kind, you can go straight to section 29.

However, please glance through the next pages to see if you recognise any of the symptoms. Some of them are do not always associated with migraine.

If you have had any of these symptoms during your life, please answer the questions in the next pages.

25. IS VISUAL DISTURBANCE AN AURA SYMPTOM IN AT LEAST SOME OF THE HEADACHES?

(a prodormal aura symptom precedes the headaches but it can sometimes occur simultaneously with the headaches). PLEASE CHECK THE APPROPRIATE ALTERNATIVES:

*** VISUAL FIELD DEFECT ( )**
*** Flashing "serrate phenomenon" ( )**
***"SPARKS", "STARS" in the visual field ( )**
the colour of the sparks is:
.....
*** BLURRING OF VISION, WAVING in the visual field ( )**
• OTHER VISUAL DISTURBANCE, what: .....

which:

- is at its worst / strongest right away (less than 1-2 minutes) ( )
- gets worse / expands after more than 4 minutes ( )
- lasts for less than a minute ( )
- lasts for more than a minute but less than 60 minutes ( )
- lasts for more than 60 minutes ( )

- the symptom goes away entirely ( )
- does not go away entirely ( )

- headaches follow the symptom within 60 minutes ( )
- headaches do not follow the symptom until later ( )
- headaches and symptom occur simultaneously ( )

- headaches precede the symptom ( )

Headaches with prodormal symptoms such as these you have had in your life:

- once ( )
- 2-5 ( )
- 5-10 ( )
- 10-50 ( )
- 50-100 ( )
- more than 100 ( )

Visual disturbance occurs in about ____ % of the headaches

Visual disturbance does not always involve headaches at all ( )

Please explain with your own words what the visual disturbance is like:
THE VISUAL DISTURBANCE INTENDED HERE ARE VISUAL FIELD DEFECTS, SERRATE OPTICAL PHENOMENA, "SPARKS", "STARS", ETC. MERE SENSITIVITY TO LIGHT DOES NOT HAVE TO BE REPORTED HERE.

_____
_____
_____
_____
_____
_____

Would you say that your migraines involve visual disturbance:

Always ( )
Most of the time ( )
In about half of the cases ( )
Every now and then ( )
Never ( )

IF ALL ATTACKS DO NOT INVOLVE VISUAL DISTURBANCE:

Is the headache associated with visual disturbance similar to the headache in migraine attacks without visual disturbance?

The headaches are similar whether there were prodormal symptoms or not:
Yes ( )

The headache is different depending on the occurrence of prodormal symptoms:
Yes ( )

Do you ever have headaches involving nausea or pronounced sensitivity to light with out the said visual disturbance:
Yes ( ) **No** ( )

If necessary, please explain with your own words, how the headaches differ indifferent kind of attacks:

_____
_____
_____

26. IS UNILATERAL PARESIS (MUSCULAR WEAKNESS) AN AURA SYMPTOM IN AT LEAST SOME OF THE HEADACHES:

(a prodormal aura symptom precedes the headaches but it can sometimes occur simultaneously with the headaches).

Yes ( ) **Never ( )**

IF YES, IS THE PARALYTIC SYMPTOM:

A. ON ONE SIDE OF THE FACE **( )**

("one half of the face is hanging")

HAS ANYONE EVER MADE A REMARK ON ONE SIDE OF THE FACE HANGING DURING THE HEADACHES?

YES ( ) **NO ( )**

B. IN THE FACE AND IN THE UPPER LIMB OF THE SAME SIDE **( )**

IS THE WEAKNESS OF THE UPPER LIMB EVER SO STRONG THAT COMPRESSIVE FORCE IS CLEARLY REDUCED DURING THE HEADACHES?

YES ( ) **NO ( )**

IS THE WEAKNESS OF THE UPPER LIMB EVER SO STRONG THAT THE ARM CAN COT BE HELD UP NORMALLY DURING THE HEADACHES?

YES ( ) **NO ( )**

C. IN THE EXTRIMITIES OF THE SAME SIDE (ARM+LEG) **( )**

IS THE WEAKNESS OF THE OTHER LEG EVER SO STRONG THAT YOU ARE NOT ABLE TO WALK NORMALLY OR THAT YOU WALK WITH A LIMP DURING THE HEADACHES?

YES ( ) **NO ( )**

Paralytic symptoms such as these associated with headaches you have had in your life:

- **once** **( )**
- **2-5** **( )**
- **5-10** **( )**
- **10-50** **( )**
- **50-100** **( )**
- **more than 100** **( )**

IMPORTANT: Please describe with your own words what kind of paralytic symptoms you have or have had and how long the paresis lasts:

_____

_____

_____

27. IS A CLEAR UNILATERAL SENSORY DISTURBANCE, NUMBNESS, TINGLING AN AURA SYMPTOM IN AT LEAST SOME OF THE HEADACHES:

Yes ( ) **Never ( )**

IF YES, IS THE SENSORY DISTURBANCE:

A. ON ONE SIDE OF THE FACE **( )**

("one side of the face turns numb", "tingles")

B. IN THE FACE AND THE UPPER LIMB OF THE SAME SIDE **( )**

C. IN THE EXTRIMITIES OF THE SAME SIDE (ARM+LEG) **( )**

HOW LONG DOES THE NUMBNESS (OR TINGLING) LAST USUALLY?

- **LESS THAN A MINUTE** **( )**
- **MORE THAN 4 MINUTES** **( )**
- **DOZENS OF MINUTES** **( )**
- **HOURS** **( )**
- **DAYS** **( )**
- **I CANNOT SAY** **( )**

DOES THE NUMBNESS (OR TINGLING) EVER OCCUR BEFORE THE HEADACHES

YES ( ) **NO ( )**

DOES THE NUMBNESS EVER SPREAD SLOWLY FROM THE ARM UP TO THE UPPER ARM AND FACE, OR DOWN FROM THE FACE TO THE ARM?

YES ( ) **NO ( )**

SENSORY DISTURBANCE symptoms such as these associated with headaches you have had in your life:

- **once** **( )**
- **2-5** **( )**
- **5-10** **( )**
- **10-50** **( )**
- **50-100** **( )**
- **more than 100** **( )**

IMPORTANT: Please describe in your own words what the sensory disturbance is like:

_____

_____

_____

_____

28. IS PRONOUNCED SPEECH DISTURBANCE AN AURA SYMPTOM IN AT LEAST SOME OF THE HEADACHES:

Yes ( ) Never ( )

IF YES, WHAT IS THE SPEECH DISTURBANCE LIKE?
The speech is difficult to form, "the tongue is stiff", "the speech gobbles"
yes ( ) no ( )
Has such as speech difficulty ever involved pronounced weakness of one arm
yes ( ) no ( ) I can not tell ( )
Words are forgotten, words and sentences come out wrong, "the speech is double Dutch"
yes ( ) no ( )
Has such as speech difficulty ever involved clear weakness of one arm
yes ( ) no ( ) I can not tell ( )
Headaches involving pronounced speech difficulty you have had in your life:
- once
- 2-5 ( )
- 5-10 ( )
- 10-50 ( )
- 50-100 ( )
- more than 100 ( )
Please describe with your own words:

_____
_____

HAVE YOU EVER BEEN IN A HOSPITAL OR AT THE DOCTOR BECAUSE OF THESE SYMPTOMS OF PARALYTIC, SENSORY OR SPEECH DISTURBANCES?

Yes ( ) no ( )

If yes, please explain in more detail:

_____
_____

29

29.A. Family History:

Do (did) your parents have migraine:
Mother …… yes ( ) no ( ) I do not know ( )

Father …… yes ( ) no ( ) I do not know ( )

Do (did) your siblings have migraine:
No ( ) I do not know ( )
Yes ( )
Who: .....
.....
.....
.....
.....

How many brothers and sisters do you have:
…… sisters …… brothers

Do (did) your children have migraine:
No ( ) I do not know ( )
Yes ( )
Who: _____
_____
_____
_____
_____

How many children do you have: Sons .....
Daughters .....
Does (did) your spouse have migraine:
No ( ) I do not know ( ) No Spouse ( )
Yes( )
Who: .....
.....
.....
.....
.....

29.B. Family History

Have your parents, siblings or children had
paralytic symptoms:

No ( ) Who: .....
Yes ( ) .....
At what age did the paralytic symptoms appear?
.....

Have your parents, siblings or children had
dementia or pronounced memory disturbances:

No ( ) Who: .....
Yes ( ) .....
At what age did the symptoms appear?
.....

Have your parents, siblings or children had
unusual tremor:

No ( ) Who: .....
Yes ( ) .....
At what age did the symptoms appear?
.....

Have your parents, siblings or children had
disturbance of balance or unusual clumsiness or has any of them been in a wheel chair:

No ( ) Who: .....
Yes ( ) .....
At what age did the symptoms appear?
.....

Have your parents, siblings or children had
epilepsy or seizures:

No ( ) Who: .....
Yes ( ) .....
At what age did the symptoms appear?
.....

30. Previous illnesses:

Do you have or have you had:

- Stroke (or cerebral infarction ( )
- Intracerebral haemorrhage ( )
- Other cerebral circulatory disorder ( )
  of what
  kind: _____
- Epilepsy ( )
- Seizure ( )
- Fit of unconsciousness ( )
- Fever convulsion as a child ( )
- Hypertension ( )
- Myocardial infarction ( )
- Symptomatic heart disease ( )
- Cardiac insufficiency ( )
- Atrial fibrillation ( )
- Other cardiac arrhythmia ( )
- Ménièr's disease ( )
- Eye disease ( )
  which: .....
- Diabetes ( )
  which: .....
- Cancer ( )
  which: .....
- Rheumatic condition ( )
  which: .....
- Allergy or atopy: ( )
  which one : .....
- Mental disorder ( )
  - Depression, severe depression ( )
  - Anxiety disorder that needed treatment ( )
  - Panic disorder ( )
  - Insomnia ( )
  - Other, which: ..... ( )
- High cholesterol level ( )
- High triglyceride level ( )
- Do you have or have you had some other significant illness: ( )
  which: .....

None of the above ( )

31. Other factors:

Yes ( ) no ( )

Have you been taking contraceptive pills?

for how long:

.....

Do you have a tendency to snore loudly? Yes ( ) no ( )

this is asked because snoring sometimes causes headache

Do you smoke? Yes ( ) no ( )

since when and how much:

.....

.....

How much alcohol do you use:

I hardly use any alcohol at all ( )

Wine: about ..... glasses a week

Beer: about ..... bottles of medium strength beer a week

Beer: about .....bottles of strong beer a week

Liquor: .....drinks a week

Does alcohol cause symptoms of hangover to you: (headache, nausea, etc.)

Extremely easily ( )

Easily ( )

Not particularly easily ( )

Hardly at all ( )

How often do you have disturbing headache in connection with fever (e.g. common flu)

Always ( )

Often ( )

Sometimes ( )

Hardly ever ( )

32. Your latest blood pressure value was

..... / ..... mmHg

(systolic / diastolic)

You do not remember but you were told it was :

high ..... yes ( ) no ( )

low ..... yes ( ) no ( )

normal ..... yes ( ) no ( )

33. Do you fingers easily turn white in the cold

..... **yes ( ) no ( )**

Do phenomena ever occur where your fingers first turn white, then turn blue and finally red

..... **yes ( ) no ( )**

Do you have or have you had a tendency for travel sickness

yes ( ) no ( )

Please explain in more detail:

.....

.....

Do you have or have you ever had fits of vertigo

yes ( ) **no ( )**

Please explain in more detail:

.....

.....

34. Places of Birth:

What is your place of birth:

.....

.....

What is your mother's place of birth:

.....

.....

What is your father's place of birth:

.....

.....

What are your grandparents' places of birth:

maternal grandmother:

.....

.....

maternal grandfather:

.....

.....

paternal grandmother:

.....

.....

paternal grandfather:

.....

.....

36. NEUROLOGICAL SYMPTOMS:

THIS SECTION IS ESSENTIAL FOR THE STUDY!!!!!

NEUROLOGICAL SYMPTOMS ASSOCIATED WITH MIGRAINE ARE AMONG OTHERS:

• VISUAL DISTURBANCE: SERRATE OPTICAL PHENOMENA, DEFECTS OF VISUAL FIELD, HOLES IN THE VISUAL FIELD, ETC.

• SENSORY DISTURBANCE: UNUSUAL TINGLING OR NUMBNESS IN THE TONGUE, PHARYNX, FACE OR UNILATERAL TINGLING OR NUMBNESS IN THE EXTREMITIES OR BODY.

• HEARING IMPAIREMENT: WHISTLING OF THE EAR, PRONOUNCED MOMENTARY IMPAIREMENT OF ACCURACY OF HEARING, ETC.

• CHANGES IN THE SENSE OF SMELL

• SYMPTOMS OF PARESIS OR MUSCULAR WEAKNESS

• SPEECH DISTURBANCE

• VERTIGO

• DOUBLE VISION

• DIFFICULTY TO SWALLOW

• OTHER SYMPTOM YOU FIND IMPORTANT

IF YOU HAVE HAD SYMPTOMS MENTIONED ABOVE OR EQUIVALENT TO THEM, PLEASE DESCRIBE THEM WITH YOUR OWN WORDS, IF YOU HAVE NOT ALREADY DONE SO:

• VISUAL DISTURBANCE:

• SENSORY DISTURBANCE:

• HEARING IMPAIREMENT:

• PARALYTIC SYMPTOMS:

• SPEECH DIFFICULTIES

• DIZZINESS:

Please explain in more detail what the dizziness is like: e.g. uncertainty while walking, rotative or spinning, etc.

• SOME OTHER SYMPTOM CLEARLY ASSOCIATERD WITH YOUR HEADACHES IS:

36. HAVE SYMPTOMS SIMILAR TO THE ONES MENTIONED ABOVE OCCURED WITHOUT THE HEADACHES?

THESE IMPORTANT SYMPTOMS WERE AMONG OTHERS:

• VISUAL DISTURBANCE: SERRATE OPTICAL PHENOMENA, DEFECTS OF VISUAL FIELD, HOLES IN THE VISUAL FIELD, ETC.

• SENSORY DISTURBANCE: UNUSUAL TINGLING OR NUMBNESS IN THE TONGUE, PHARYNX, FACE OR UNILATERAL TINGLING OR NUMBNESS IN THE EXTREMITIES OR BODY.

• HEARING IMPAIREMENT: WHISTLING OF THE EARS, PRONOUNCED MOMENTARY IMPAIREMENT OF ACCURACY OF HEARING, ETC.

• CHANGES IN THE SENSE OF SMELL
• SYMPTOMS OF PARESIS OR MUSCULAR WEAKNESS
• SPEECH DISTURBANCE
• VERTIGO
• DOUBLE VISION
• DIFFICULTY TO SWALLOW
• OTHER SYMPTOM YOU FIND IMPORTANT

YES ( ) NO ( )

IF YES, PLEASE CIRCLE THE APPROPRIATE ALTERNATIVE AND, IF NECESSARY, EXPLAIN IN MORE DETAIL:

37. SEVERE HEADACHES:

IN ALL, I WOULD ESTIMATE THAT I HAVE HAD SEVERE HEADACHES IN MY LIFE:

POSSIBLE CHILDHOOD HEADACHES ARE ALSO INCLUDED
PLEASE CHECK THE MOST APPROPRIATE ALTERNATIVE

NEVER	**( )**
LESS THAN 5	**( )**
5-10	**( )**
MORE THAN 10	**( )**
MORE THAN 50	**( )**
MORE THAN 100	**( )**

HEADACHES INVOLVING VISUAL DISTURBANCE (AURA) I HAVE HAD:

POSSIBLE CHILDHOOD HEADACHES ARE ALSO INCLUDED
PLEASE CHECK THE MOST APPROPRIATE ALTERNATIVE

NEVER	**( )**
1	**( )**
2-5	**( )**
5-10	**( )**
MORE THAN 10	**( )**
MORE THAN 50	**( )**
MORE THAN 100	**( )**

How would you advise us to improve this questionnaire?

Blood Test Included in the Study:

You will find a referral to a blood test in the envelope you received. You will have no costs of the blood test. You can go to the blood test to a private doctor or a health centre. (In Tampere region, the health centre will not take the blood test, so go to a private doctor instead).

All the necessary information can be found in the referral, you only need to give the referral to the personnel of the laboratory.

(the referral explains how the blood test should be taken, where the laboratory should send it to and where to direct the bill)

After you have filled in the form, you can close it in the return envelope.

Thank you very much!