Erling Tronvik

Migraine, blood pressure and the renin- angiotensin system

Thesis for the degree of Philosophiae Doctor

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Norwegian University of Science and Technology
Faculty of Medicine
Department of Neuroscience

NTNU
Norwegian University of
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Migrene, blodtrykk og renin- angiotensin systemet

Renin-angiotensin systemet spiller en viktig rolle i reguleringen av blodtrykk i ulike deler av kroppen. Systemet finnes også i hjernen hvor det er involvert i en rekke funksjoner. Formålet med denne avhandlingen var å se om medikamenter som påvirker renin- angiotensin systemet også kunne være effektive som migreneforebyggende behandling, og om det var forskjeller mellom migrenepasienter og friske kontroller i gener for ulike komponenter i renin- angiotensin systemet. For å kaste lys over mekanismene for den gunstige effekten av enkelte blodtrykksmedisiner ved migrene ønsket vi også å se på sammenhengen mellom blodtrykk og migrene i befolkningen, samt å studere i nærmere detalj eventuelle fysiologiske avvik i blodtrykksreguleringen hos migrenepasienter.

Hovedfunn i avhandlingen:

1. Atacand (candesartan) er effektivt som forebyggende behandling mot migrene.
2. Det er ingen sammenheng mellom angiotensin-konverterende enzym (ACE) genotype og migrene, og ACE genotype kunne ikke brukes til å forutsi den migreneforebyggende effekten av Atacand.
3. Høyt systolisk blodtrykk og pulstrykk er assosiert med redusert forekomst av ikke- migrenøs hodepine og migrene hos voksne i den generelle befolkningen.
4. Spontan barorefleksensitivitet og hjerteratevariabilitet var økt hos unge, kvinnelige migrenepasienter (uten aura) sammenlignet med friske alders-matchede kontroller.

Contents

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List of papers

Paper I

Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA. 2003;289:65-9.

Paper II

Tronvik E, Stovner LJ, Bovim G, White LR, Gladwin AJ, Owen K, Schrader H. Angiotensin- converting enzyme gene insertion/deletion polymorphism in migraine patients. BMC Neurol. 2008;8:4.

Paper III

Tronvik E, Stovner LJ, Hagen K, Holmen J, Zwart JA. High pulse pressure protects against headache: prospective and cross-sectional data (HUNT study). Neurology. 2008;70:1329-36.

Paper IV

Nilsen KB, Tronvik E, Sand T, Gravdahl GB, Stovner LJ. Increased baroreflex sensitivity and heart rate variability in migraine patients. Submitted for publication.

Summary

Background and objectives

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure (BP) in different parts of the body. This system is also widely distributed in the brain where it is involved in several processes. The aims of this dissertation were to explore whether drugs affecting the RAS could be valuable in migraine prophylaxis, and whether differences existed between migraine patients and healthy controls in genes for different components of the renin- angiotensin system. To shed light on the mechanisms of the favourable effect of several antihypertensives in migraine, we wished to explore in detail possible physiological differences in the regulation of BP in migraine patients.

Studies

A randomized, double-blind crossover study was performed in 60 patients to determine the effect of candesartan compared to placebo in migraine prophylaxis. The number of headache days were reduced by 26% in the treatment period with candesartan compared to the placebo period. For migraine hours the reduction was 36%. There was no association between antimigrainous effect and the lowering of the BP.

The angiotensin- converting enzyme (ACE) gene insertion/deletion polymorphism was determined by polymerase chain reaction (PCR) in 347 patients with migraine and 403 healthy controls. No significant difference between patients with migraine and controls was found with regard to angiotensin- converting enzyme genotype.

Cross-sectional and prospective data from two large epidemiological surveys (HUNT-1 and HUNT-2) were analyzed to look at the association between BP and headache. Groups with high systolic BP and pulse pressure had lower prevalences of nonmigrainous headache or migraine in an adult population.

Baroreflex sensitivity and heart rate variability were measured in 16 women with migraine without aura and compared to 14 age-matched controls. Spontaneous baroreflex sensitivity and heart rate variability were increased in the migraine patients.

Abbreviations

ACE – Angiotensin- converting enzyme

ACE-I – angiotensin- converting enzyme inhibitor

ANG II – angiotensin II

ARB – angiotensin II receptor blocker

BP – blood pressure

BRS - baroreflex sensitivity

CGRP – calcitonin gene-related peptide

CRH – corticotrophin-releasing hormone

DBP – diastolic blood pressure

GABA – amma amino butyric acid

HF – high frequency

HUNT-1 - Nord-Trøndelag Health survey 1984-86

HUNT-2 - Nord-Trøndelag Health survey 1995-97

iNOS – inducible nitric oxide synthase

LF – low frequency

MAP – mean arterial pressure

MMP3 - matrix metalloproteinase -3

MTHFR – methylenetetrahydrofolate reductase

NF-kappaB – nuclear factor-kappaB

NN-interval – normal-to-normal beat interval

NO – nitric oxide

NTS – nucleus tractus solitarius

PAG – periaquaductal grey matter

PCR - polymerase chain reaction

PP – pulse pressure

RAS - renin angiotensin system

RMSSD – root mean square of successive NN-intervals

RVLM – rostral ventrolateral medulla

SBP – systolic blood pressure

SDNN – standard deviation of successive NN-intervals

SP - substance P

VLF – very low frequency

Migraine, blood pressure and the renin-angiotensin system

1. Historical background

Dating back to 7000 BC, skulls have been found bearing man made holes (called trepanation) presumably done for medical reasons which may have included the treatment of headache in order to release demons and evil spirits from the head (1). Even as late as 1660, the famous Dr. William Harvey recommended trepanation to a patient with what appears to have been intractable migraine. The Ebers Papyrus (2), dating back to about 1200 BC, mentions migraine, neuralgia, and shooting head pains. Following the instructions on the papyrus, the Egyptians would firmly bind a clay crocodile holding grain in its mouth to the head of the patient. Hippocrates (400 BC) may have been the first to describe the clinical symptoms of migraine. In the Hippocratic books he describes a shining light, usually in the right eye, followed by violent pain beginning in the temples and eventually reaching the entire head and neck area. The term "migraine' itself is derived from the Greek word hemicrania (1).

2. Migraine pathophysiology

Migraine is a common neurological disorder characterized by recurrent attacks of disabling headache accompanied by nausea/vomiting, photo- and phonophobia. Some of the patients also experience transient focal neurological symptoms prior to the headache (migraine with aura).

The pathophysiology of migraine is still not completely understood but this condition is considered to be a neurovascular disorder where there is an activation of the socalled "trigeminovascular complex" in genetically disposed subjects (3). The cause of this activation is still debated but it may involve sterile meningeal neurogenic

inflammation secondary to cortical spreading depression and/or dysfunction of brain-stem pathways that normally modulate sensory input (4). Important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, nucleus locus ceruleus, nucleus raphe magnus and the periaquaductal grey matter (PAG) (4). During a migraine attack calcitonin gene-related peptide (CGRP) and substance P (SP) are released from sensory nerve endings (5) and these transmitters are thought to sensitize trigeminal neurons to convey nociceptive signals to the brain stem (6).

3. Migraine prophylactic medication

Two types of migraine drug therapy exists; acute and prophylactic. Acute medication is taken when the attack has started and aims at treating the head pain and other symptoms. Prophylactic medication is taken every day and aims at reducing the frequency and/or intensity of the attacks. Recent evidence also suggests that this type of treatment enhances the patient's response to acute migraine therapies, and it may hopefully also reduce the likelihood of developing chronic daily headache (7). Migraine prophylactic treatment may be indicated if the patient experiences more than 2-3 severe migraine attacks per month. Other factors that count in favour of prophylactic treatment are long or severe attacks, insufficient effect or troublesome adverse effects of acute medication, overuse of acute medication, or if there are co-morbid conditions for which the preventative drug may have a beneficial effect. Each prophylactic drug should be tried for at least 2-3 months at a sufficient dose while keeping a headache diary for evaluation of efficacy. Success is generally defined as 50% reduction in attack frequency, a significant decrease in attack duration or improved response to acute medication (7). About one third of migraineurs fulfil the criteria for use of prophylactic treatment, according to epidemiological studies, but

only 3-13% of patients do actually use this kind of treatment (8). One of the reasons for this may be lack of efficacy or the adverse effects associated with this type of long-term treatment.

Substances used for migraine prophylactic treatment include certain antihypertensive drugs (propranolol, flunarizine), antiepileptic drugs (valproate, topriamate) and antidepressant drugs (amitriptyline). The exact mode of action of these drugs in migraine is unknown, and several of them have side-effects that for many patients are not compatible with long-term use.

4. Blood pressure and the baroreflex system

Blood pressure (BP) is a measure of the force applied to the walls of the arteries as the heart pumps blood through the body. The pressure is determined by the force and amount of blood pumped, and the size and flexibility of the arteries. BP is continually changing depending on activity, temperature, diet, emotional and physical state, posture, and medication use. BP is usually represented by two values. The systolic arterial pressure is defined as the peak pressure in the arteries, which occurs at the beginning of the cardiac cycle; the diastolic arterial pressure is the lowest pressure which is present in the resting phase of the cardiac cycle. BP is also characterized by its pulsatile and steady components. The pulsatile component, estimated by pulse pressure (PP) (systolic BP minus the diastolic BP), represents BP variation during the cardiac cycle and is affected by left ventricular ejection fraction, arterial stiffness, early pulse wave reduction, and heart rate. The steady component, estimated by mean arterial pressure (MAP), is a function of left ventricular contractility, heart rate, and

vascular resistance and elasticity averaged over time. MAP is defined as 1/3 systolic blood pressure (SBP) + 2/3 diastolic blood pressure (DBP).

Short-term regulation of arterial pressure involves arterial baroreceptors (Figure 1) exerting a chronotropic effect on the heart and regulating sympathetic outflow. A lowering of the BP leads to a reduction in impulses sent from the baroreceptors thorough the glossopharyngeal and vagus nerves to the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla. This leads to decreased output from the vagus nerve to the sinus node, resulting in increased heart rate. A second efferent pathway is mediated by central projections from the NTS to presympathetic neurons in the rostral ventrolateral medulla (RVLM) resulting in sympathetic inhibition, leading to increased vascular resistance (9).

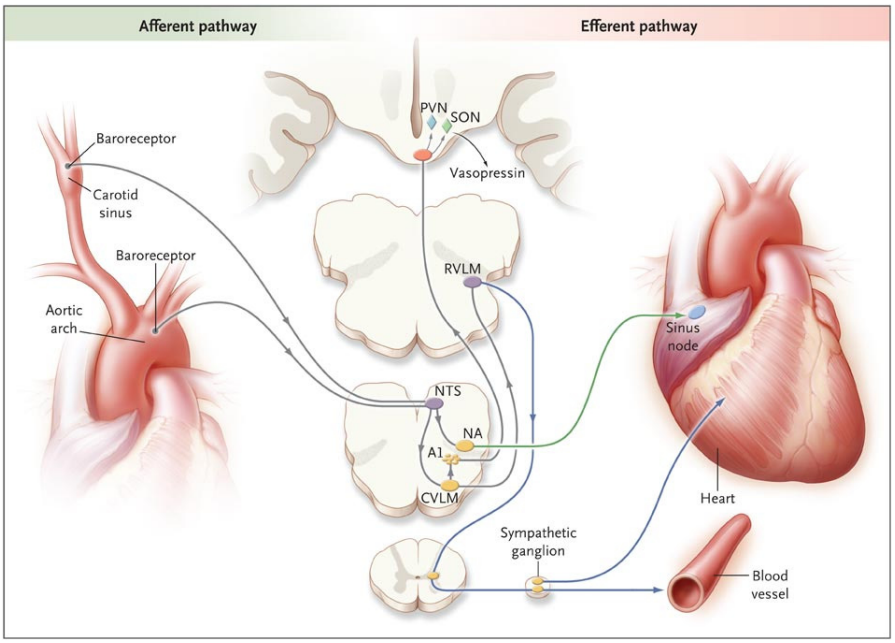

Figure 1: Freeman R. Clinical practice. Neurogenic orthostatic hypotension. N Engl J Med. 2008;358:615-24 (PVN = paraventricular nucleus. SON = supraoptic nucleus. RVLM = Rostral ventrolateral medulla. NTS = Nucleus tractus solitarius. NA = Nucleus ambiguous. A1 = A1 cell group. CVLM = Caudal ventrolateral medulla.)

In addition there is strong evidence that arterial baroreceptors, through afferents terminating in the NTS, may modulate cerebral blood flow through direct connections with pontine parasympathetic neurons (10). The baroreflex sensitivity (BRS) is a measure of the effectiveness of the baroreflex system. BRS is defined as pulse interval variations when the SBP changes, i.e. the slope of linear regression of RR intervals on the electrocardiogram versus SBP. Different factors influence BRS in the healthy population, including sex, age, BP, heart rate, body mass index, arterial stiffness, blood glucose and insulin levels, physical fitness and medication (11).

5. Hypertension associated hypalgesia

Hypertension--associated hypalgesia is a phenomenon that was first reported in 1979. Increasing the BP pharmacologically in rats reduced their avoidance reaction following a mildly aversive trigeminal nucleus stimulus (12). This effect was not seen in rats with denervated baroreceptors. In another study (13) occlusion of rat abdominal aorta proximal to the renal arteries resulted in both increased BP and antinociception, while occlusion distal to the renal arteries had neither of these effects. A neurophysiological investigation even detected attenuation in spinal nociceptive transmission in hypertensive rats (14). Later, studies have shown a reduced perception of painful stimuli in hypertensive human individuals (15, 16). There is evidence that stimulation of the baroreflex arch due to increased BP may inhibit pain transmission at both spinal and supraspinal levels, possibly due to an interaction of the centres modulating nociception and cardiovascular reflexes in the brainstem (17). Within the central nervous system, the baroreflex influences several important sites in pain modulation, and it has been demonstrated that a substantial number of PAG neurons and neurons in the nucleus raphe magnus are excited by pharmacologically induced changes in BP (12, 18). In addition, stimulation of the NTS, which is the terminal site of baroreceptor afferent fibers, induces antinociception (15). The nucleus reticularis gigantocellularis in the medulla oblongata may also be an important site in BP-related nociceptive modulation, and angiotensin III, a peptide derived from angiotensin II (Ang II), is thought to act as a transmitter here (19).

6. The relationship between blood pressure and migraine

For many years it was assumed that hypertension might be a cause of headache. Studies supporting this connection were published and the pulsating characteristic of some headaches and the introduction of β-blockers in migraine prophylactic treatment may further have supported this view (20, 21). However, this observation may be an example of admission rate bias (Berkson's bias) as hypertension and headache are common medical disorders and consulting the doctor for one of the disorders may give a higher likelihood of detecting the other condition. Later, epidemiological studies showing no relationship between headache and high BP were published (22, 23), and in the International Classification of Headache Disorders II it is stated that mildly or moderately elevated BP is not a cause of headache (24). This was confirmed in 2002 by prospective data from a large unselected population in Norway (The Nord-Trøndelag Health Study – HUNT) on 22 685 adults, and this study even indicated that high systolic and diastolic pressures might be associated with reduced risk of non-migrainous headache 11 years later. For migrainous headache no clear association was found (25). A prospectively planned cohort study from Brazil (26) with 1763 hypertensive patients demonstrated a negative association between SBP and headache prevalence, a positive association between DBP and headache and a negative association between pulse pressure (PP) and headache. Another group has also demonstrated that in 1174 adults those with normal BP complained of migraine more frequently than participants with high BP (27). In a French population of 1373 subjects, migraine patients had lower SBP and lower PP than controls (28). In accordance with this a population-based study from Iceland with 21 537 subjects found that individuals with migraine had lower PP, lower SBP and higher DBP than

controls (29). This inverse relation is not restricted to headache (30) but seems to be as valid for pain in other parts of the body.

However, in favour of the hypothesis that hypertension causes migraine, one may cite the large meta-analysis of 94 randomized placebo-controlled trials of different antihypertensive drugs in which headache was registered as an adverse event, demonstrating a preventive effect on headache (31). It is also a fact that many, but not all, antihypertensive drugs have a well established place in migraine prophylactic therapy. Hence, the relationship between BP and headache is not well understood and deserves further scrutiny.

7. The cerebral renin angiotensin system

Since it was discovered in 1898, the renin-angiotensin system (RAS) was thought to be a hormonal system by which the kidney influences systemic cardiovascular regulation. In the classic model, renin, excreted by the kidneys, cleaves angiotensinogen from the liver into angiotensin I. This decapeptide is then cleaved into Ang II by angiotensin-converting enzyme (ACE) which is abundant in the pulmonary endothelium. Ang II has two receptors, AT1 and AT2 which are expressed in many cardiovascular and other tissues (32).

Later it was discovered that injecting Ang II into the general circulation also elicited effects in the central nervous system (33). Ang II does not cross the blood brain barrier, and AT1 and AT2 receptors responding to circulating Ang II were discovered in the circumventricular organs lacking a normal blood brain barrier (34), and later in

cerebrovascular endothelial cells. In addition several local tissue Ang II systems have been discovered in numerous organs, including the brain (35). These systems appear to be regulated independently of peripheral Ang II (36). In the brain all components of the classical RAS , such as angiotensinogen, renin, ACE, Ang II and the AT1 and AT2 receptors, are present.

Ang II is involved in many important processes in the brain. It influences cerebrovascular flow, the production of nitric oxide (NO) and the release of hormones (vasopressin and oxytocin). It increases sympathetic nervous activity and acts as a potent vasoconstrictor. Blockade of the AT1 receptor has also been shown to reverse cerebrovascular inflammation and can possibly decrease vulnerability to cerebral ischemia (37).

8. The angiotensin system in migraine

8.1 Clinical evidence

In 1981, after the ACE inhibitors (ACE-Is) had become available as antihypertensives, it was known that circulating opioids (particularly enkephalins) were metabolized by enkephalinase and ACE (38). This provided the motivation for the group of Sicuteri to study the effect of ACE-Is on 35 patients suffering from idiopathic headaches (ophthalmic migraine [4], common migraine [16] and mixed headache [15]). Essential hypertension was present in 11 of the patients. All patients were treated with an ACE-I (captopril) for periods lasting from 1 to 6 months (39). An initial dose of 25 mg was increased to 100 mg within a week. The subjects had

previously used different migraine prophylactic agents with variable effect. Of the 35 patients, 23 reported a 50% or more headache reduction on captopril.

In 1995, a small open study by Bender (40) explored the use of the ACE-Is enalapril (most) or lisinopril (some) in 17 patients with migraine. The medication was given once daily in doses from 10 to 25 mg for a period of 3 months to 3 years. 10 patients reported a marked effect on their headache, in six the effect was moderate, and in one there was only a slight effect.

In 2001, a double-blind, randomized, placebo-controlled crossover study of an ACE-I (lisinopril) (41) was published by doctors from the department of Neurology in Trondheim, including 60 patients who suffered from migraine according to the diagnostic criteria of the International Headache Society. In the per-protocol analysis of 47 patients hours with headache, days with headache, days with migraine, and headache severity index were significantly reduced (by 20, 17, 21 and 20%, respectively) in the lisinopril period compared to the placebo period. The number of days with migraine was reduced by at least 50% for active treatment compared to placebo in 14 participants, and for active treatment compared to the run-in period in 17 patients. The intention-to-treat analysis supported the difference in favour of lisinopril for the primary endpoints. With respect to the side-effects, there was markedly more cough, dizziness and tendency to faint in the active period than in the placebo period.

In 2006, an open-label study (42) examined the effect of the Angiotensin II receptor blocker (ARB), olmesartan, in 24 subjects aged 27 to 76 with either hypertension or

prehypertension and migraine. They were treated with 10 to 40 mg of olmesartan for at least 3 months, and endpoint data were collected by asking the patients about the frequency and severity of their headache. Patients reported an 82.5% average reduction in the frequency of migraine attacks and a 45% average reduction in the severity of migraine attacks. The only side-effects registered were dizziness and presyncope. There were no serious adverse events and no patients had to be withdrawn from the study due to intolerance to the drug.

8.2 Clinical indirect evidence

In 2002 a meta-analysis of 27 randomized, placebo-controlled trials on ARBs in hypertension looked at headache as an adverse event (43). In the 12 110 patients the overall risk of headache was about 30% lower in the group receiving ARBs compared with those taking placebo.

In 2003 1537 elderly hospitalized patients diagnosed with hypertension were asked about headache after they had received nitrates during the hospital stay (44). Patients using ACE-Is had a 56% reduced risk of headache compared to those using other types of antihypertensives, even though the BP reduction was the same in both groups.

In 2004 a large pharmacological database provided information about the consumption of specific migraine-abortive drugs (ergotamine or a triptan) before and after patients started receiving treatment with an ACE-I, an ARB or a diuretic (45). The patients using ACE-Is or ARBs showed a significant reduction in the consumption of migraine-abortive drugs compared to those using diuretics. If the

antihypertensive treatment was stopped, the use of migraine-abortive drugs increased again in those who had received ACE-Is or ARBs, but not in those who had used diuretics.

8.3 Genetic evidence

Migraine is a multifactorial disorder with both environmental and genetical components. It is today generally accepted that both migraine with and without aura have a considerable genetic component, but whether they share a common genetic cause is still unknown (46).

In 2000, an Italian group examined the frequency of polymorphisms of the ACE gene in 302 patients with migraine without aura compared to 201 healthy controls (47). The human ACE gene locus occurs with either an insertion (I) or a deletion (D) allele, resulting in three genotypes: II, ID and DD. In the migraine patients the ACE-DD polymorphism occurred more often (48%) than in the control population (37%). The frequency of migraine attacks was also greater (2.1 attacks per week on average) in patients with the DD genotype than in those with the ID genotype (1.5 attacks on average per week). No difference was found in the duration of migraine attacks, and plasma ACE was increased in patients with the ACE-DD genotype.

In 2005, a Japanese study (48) with 54 patients suffering from migraine with aura, 122 patients with migraine without aura, 78 with tension-type headache and 248 healthy controls showed the DD genotype to be more prevalent among the migraine with aura patients.

In 2005, an Australian group found evidence that the methylenetetrahydrofolate reductase (MTHFR) TT genotype and the ACE (ID/DD) genotypes act in combination to increase susceptibility to migraine (OR 2.18) (49). The C677T mutation in the MTHFR gene has previously been shown to be a risk factor for migraine (50). Two hundred and seventy migraine patients with and without aura were compared to 270 healthy controls and no difference in genotype or allele frequencies was found.

In 2005, a Taiwanese study (51) with 240 migraine patients and 200 healthy controls found no difference in genotype or allele frequencies between the groups. Stratification by gender, however, showed more of the DD genotype in male migraineurs. No difference in headache frequency or duration was found.

In 2007, a Turkish group investigated ACE genotypes and matrix metalloproteinase -3 (MMP-3) genotypes in 59 migraine patients with aura, 109 without aura, 10 with basilar migraine and two with complicated migraine (52). The control croup consisted of 210 healthy individuals. ACE is a bivalent dipeptidyl carboxyl metalloproteinase and given that it shares ancestry with MMP-3 they were both examined.
The frequencies of 5A5A genotypes of the MMP-3 and D-allele of ACE were elevated while the 6A allele of MMP-3 and II genotype of ACE were decreased in migraine patients compared to controls.

8.4 Physiological and biochemical evidence

In animal studies conflicting results have been found concerning the role of the RAS in nociception. In different studies ARBs and ACE-Is have been found to both

promote and prevent pain transmission. Ang II injected directly into the cerebral ventricles has been shown to both antagonize morphine-induced antinociception (53) and to produce an analgesic effect that can be blocked by naloxone (54). Similarly, ARBs and ACE-Is may both block and promote cerebral antinociception (55, 56). In one study (57) injecting Ang II into the periaquaductal grey area of rats resulted in antinociceptive effects that could be reversed by an ARB administered simultaneously into the same area. However, ARBs and ACE-Is administered daily by mouth have produced antinociceptive effects, whereas no such effect was obtained with a single dose (58). Perhaps this may indicate that long-term administration results in an improved penetration of the blood brain barrier.

SP and CGRP are both vasoactive neuropeptides thought to be involved in the neurogenic inflammation that may be present during migraine attacks. A Japanese study (59) examined the levels of these transmitters in addition to ACE which is known to degrade SP. Forty-one patients suffering from migraine with aura, 54 without aura and 52 healthy controls were included and only interictal measurements were performed. Levels of CGRP and SP were higher in both migraine with and without aura patients while the ACE level was higher in the migraine with aura group. In migraine with aura patients there was a positive correlation between SP level and ACE activity. This is the opposite tendency of what would be expected if increased ACE activity leads to increased degradation of SP, and the results of this study may indicate that ACE is involved in migraine pathophysiology.

A hypothesis that mast cells activating the RAS may contribute to migraine has also been proposed (60). Mast cells in the meninges are located perivascularly where

several triggers may lead to degranulation (61). This may result in meningeal irritation, vascular dilatation and stimulation of nociceptive nerve endings of the trigeminal nerve (60). Ang II is known to enhance mast cell degranulation (62) and there is also evidence that mast cells are capable of releasing renin and increase local production of Ang II (63). Stress is a main trigger for migraine attacks, and one explanation for this may be that stress can induce mast cell degranulation intracranially by release of corticotrophin-releasing hormone (CRH) (64).

In addition to mast cell degranualation, there are several ways in which Ang II may contribute to neurogenic inflammation. Nuclear factor-kappaB (NF-kappaB) is cytoplasmic transcription factors that are associated with increased expression of inducible nitric oxide synthase (iNOS), a mediator of the inflammatory response associated with migraine attacks (65, 66). These transcription factors are activated by Ang II and prevented by ARBs and ACE-Is (67, 68). Ang II has also been shown to increase oxidative stress in the central nervous system by inducing production of superoxide (69). Oxidative stress has been associated with migraine, and a migraine prophylactic agent, flunarizine, has been found effective in limiting the oxidative reactions occurring in migraine sufferers (70). Endothelin-1, a potent vasodilator possibly linked to migraine pathophysiology, is also stimulated by Ang II (71). CGRP, which is released from activated trigeminal neurons during a migraine attack is perhaps one of the most important mediators in migraine pathophysiology known today. Two selective CGRP antagonists have also been shown effective in the treatment of migraine attacks (72). Ang II can stimulate the release of CGRP (73) and can therefore possibly be involved in maintenance of the migraine attack.

The central sensitization theory of migraine proposes that altered processing of sensory input in the brainstem, could account for many of the features of migraine. The N-methyl-D-aspartate (NMDA) receptor is important for the central sensitization process and there is evidence that ARBs, by blocking the AT1 receptor, may increase the stimulation of the AT2 receptor, resulting in AT2 receptor-mediated inhibition of NMDA signalling in neuronal cells (74). Theoretically this might reduce induction of central sensitization in migraine (75).

9. Premises for and methods of the studies in this thesis

9.1 Methodology of the candesartan study

A randomized, double-blind placebo controlled study is the gold standard to measure the effect of a drug. In the candesartan study, a cross-over design was chosen to obtain sufficient statistical power in a relatively small study which could be feasible in a single centre. Sixty migraine patients aged 18 to 65 years with 2 to 6 migraine attacks per month were recruited mainly from newspaper advertisements. After a 4-week single-blind placebo run-in period to verify the frequency of attacks, patients were randomized to either 12 weeks of candesartan 16 mg daily or placebo. The patients then entered a 4-week wash-out period before they crossed over so that those having received active medication in the first treatment period received placebo in the second, and vice versa.

9.2 Headache biobank of the Norwegian National Headache Centre

The main purpose of the Norwegian National Headache Centre is to generate and spread knowledge of the different headache disorders. In order to do so most

effectively and to provide material for this thesis, a headache biobank was established in 2004. The reason for including patient material in a biobank is to ensure that the collection, management and destruction of the material is handled in an ethical way. In the headache biobank all patients with one or more headache diagnoses verified by a neurologist are eligible for inclusion. From each participant 10 ml of blood is collected and stored in 5 different containters frozen at -80 degrees Celsius. In addition a registration form containing information about the features of the patient's headache is filled out. Material from this biobank was used in the ACE polymorphism study. Genetic analyses were performed in UK (AstraZeneca R&D Genetics) and at the lab of Neurobiology, St.Olavs Hospital.

9.3 The North-Trøndelag Health Study (HUNT)

Epidemiology is the study of how often diseases occur in different groups of people and why. The advantage of using data from the HUNT study to investigate the relationship between BP and headache was the large and unselected population, the use of validated diagnoses and the availability of both cross-sectional and prospective data.

The North-Trøndelag Health Study (Norwegian acronym is HUNT), one of the world's largest epidemiological surveys, was performed in the Norwegian county of North-Trøndelag, which has a total population of 126 000, 92 566 of which are above the age of 20.

The first study, HUNT-1, was conducted between 1984 and 1986, mainly focusing on BP and diabetes. Inhabitants aged 20 and older were invited to participate, and of 85

100 eligible subjects, 77 310 (91%) answered the questionnaire, attended a medical examination and had their BP measured.

HUNT-2, a more comprehensive follow-up of HUNT-1, was performed between 1995 and 1997. 64 560 (70%) of 92 566 invited subjects participated and 51 353 (56%) who attended a medical examination had their BP measured and responded to a headache questionnaire. Diagnoses obtained were validated (76).

9.4 Measurements of baroreflex sensitivity (BRS) and heart rate variability (HRV)

The measurements were performed in the department of Neurology and Clinical Neurophysiology, St.Olavs Hospital.

Heart rate variability (HRV) and BRS are used to assess the activity in the autonomic nervous system. HRV is a measure of the tonic autonomic heart rate control, whereas BRS measures the dynamic autonomic heart rate control (77). The RR-interval in the ECG is the time measured between two heartbeats. HRV refers to the beat-to-beat alterations in heart rate. Prior to analysis of a time period, ectopic beats will have to be removed and the rate interpolated. A statistical mapping of normal-to-normal beat intervals (NN-intervals) can be performed with different techniques. Spectral analysis with Fourier transformation (frequency domain technique) enables calculation of total power which is the variability of the NN-intervals in the frequency band 0- 0.40 Hz. In addition, high frequency (HF 0.15- 0.40 Hz), low frequency (LF 0.04- 0.15 Hz) and very low frequency (VLF 0- 0.04 Hz) bands can be calculated. These different parts of the spectra give information about the activity of the autonomic nervous system, as only the parasympathetic nervous system is able to generate the rapid

changes of heart rate in the HF band. In the LF band both the parasympathetic and sympathetic nervous systems are able to alter the heart frequency (77). The VLF is influenced by many other factors (chemoreceptors etc). Another way of calculating HRV is by use of the time-domain technique. This is a mapping of the NN-intervals using the standard deviation of successive NN-intervals (SDNN) or the root mean square of successive NN-intervals (RMSSD).

BRS is defined as change in RR-interval as a result of change in BP and is measured in ms/mmHg. If the SBP increases with 1 mmHg and the RR-interval is increased with 10 ms, the BRS is 10 ms/mmHg. To calculate BRS, series with at least 3 successive heart beats in which the SBP either increases or decreases are detected. Then the correlation coefficient for the regression line between the systolic pressures and the RR-intervals is calculated, and the BRS is the average of several such correlation coefficients (78).

10. Discussion

For headache research, it always helps having a professor with migraine in your department. Most drugs used for migraine prevention have been discovered by serendipity or educated guesses, and professor Harald Schrader made the connection when he used lisinopril for treating his hypertension and discovered that this migraine disappeared. He then tried it out on a few patients with excellent response. As lisinopril proved valuable in migraine prevention (41), the question was whether direct blockade of the receptor of the major RAS effector (Ang II) could provide better effect. This elicited my interest in the RAS, both as a main regulatory system for BP, but most importantly as an independent modulatory system for processes in

the brain. This lead us to explore the connection between the RAS, migraine and BP with clinical, genetic, epidemiological and neurophysiological investigations.

10.1 Candesartan in migraine prophylaxis

Alleviating the burden of migraine allows sufferers to live normal lives, unhindered by the disability and considerable discomfort associated with the condition. It may also offer important socioeconomic benefits (79) by reducing headache-related absenteeism from the workplace. In migraine prevention it is desirable that medicines are efficient and well tolerated, but unfortunately current prophylactic drugs do not meet these demands.

Using the ARB candesartan we demonstrated for the first time efficacy of this drug in migraine prophylaxis. Direct comparison of results between the candesartan study and studies with other migraine prophylactics is difficult to perform due to differences in design and endpoints. Our study was also conducted with a crossover design providing placebo- subtracted results, which gives a more conservative estimate of the real effect than most other studies that have a parallel group design, reporting differences from baseline. The efficacy of candesartan was, however, of the same order of magnitude as reported in previous studies (80-84). The number of adverse events in the treatment period was similar to that in the placebo period, which is in accordance with the good tolerability profile shown in other studies on candesartan used as an antihypertensive agent (85). In addition to its good efficacy and tolerability in our study it has the advantage of being administered just once daily.

The mechanism of effect is not known, but as mentioned in the Background section, there are many ways in which the cerebral RAS may act in modulating pain. A direct blockade of AT1 receptors in the brain is possible. There may also be a direct effect on the peripheral BP, but this seems less likely since there was no association between response to the drug and degree of BP reduction. In light of the epidemiological findings that high BP is associated with less headache, it is an interesting hypothesis that the drug, by lowering the BP, triggers reflex mechanisms to counteract the hypotensive stimulus, and that these mechanisms in some unknown way can improve the headache.

In order to evaluate the long term effect of candesartan in migraine prophylaxis a questionnaire was sent one year after completion of the study to the 18 responders and they were also asked to keep a headache diary for one month (Not published data). 13 responded and no reminder was sent. Of these 10 were still using candesartan and 9 of these completed the one-month headache diary. A total of 29 headache days were reported during follow-up, and in the one-month placebo run-in period the same patients reported 62 headache days. This may give an indication that candesartan may be effective in preventing migraine for at least a period of 1-2 years.

10.2 ACE I/D polymorphism in migraine

After having found an effect of drugs influencing the RAS it was natural to ask whether migraine might be due to some derangement in this system, and possibly the genes involved in its various components. The ACE gene consists of either an insertion (I) allele or a deletion (D) allele forming three possible genotypes: II, ID and DD. Several studies have looked at the association between the ACE gene and

migraine (47-49, 51, 52), but the results are not consistent. Some association between these genes and migraine have been found only in subgroups based on diagnostic subtype and sex. Our study is the largest performed with more than 700 patients and controls, but no association was found in a Norwegian population. For the subgroup "migraine without aura", one study had a larger patient sample (47). Even though our study has > 80% power to detect an association of the same magnitude, a relationship between the DD-polymorphism and migraine cannot be completely ruled out. However, the fact that other studies (48, 49, 51) also were negative for this subgroup, makes such an association less likely. The studies were done in different ethnic populations (Norwegian, Italian, Japanese, Taiwanese, Australian) that may display different genotypic patterns.

We also wanted to investigate whether the ACE I/D polymorphism might predict clinical response to either lisinopril or candesartan in migraine prophylaxis. In order to be clinically relevant, we decided that at least 75-100% of the responders would have to have a specific genotype. If this turned out to be the case, genotyping could be an alternative to trying out the drugs for two to three months. However, we found no clinically significant predictive value of ACE genotype.

10.3 Blood pressure and headache

Like candesartan, several of the drugs used for migraine prophylaxis have a BP-lowering effect (31). It was therefore of interest to investigate the relationship between headache and BP, and we used data from one of the world's largest epidemiological surveys, the HUNT study. High systolic and high pulse pressure turned out to be associated with a decreased prevalence of non-migrainous headache

and migraine, and the use of antihypertensive medication tended to weaken this relationship.

Against this background it may seem to be a paradox that many antihypertensive medicines, which lower both the BP and PP, are effective in migraine prophylaxis. One possible explanation is that hypertension may mediate antinociception in general whereas antihypertensive drugs may influence migraine specific mechanisms (e.g. acting directly on neuronal activity in the CNS). A lower degree of central sensitization has also been demonstrated in healthy subjects in response to pain in those with elevated resting BP level, indicating that high BP has a protective effect against central sensitization (86). Another possibility is that migraine symptoms are reduced through mechanisms indirectly related to the effects on BP. One such indirect mechanism may be change in BRS.

Several interesting observations may support the results in this thesis. BP can be divided into different components and it is well established that for the same level of MAP, different patterns of PP may be observed (87, 88). PP showed the most consistent inverse association with headache prevalence, and the fact that the pulsatile component is more prominent (increased PP) after the age of 55 (87) may help explain why headache prevalence decreases after this age. Another interesting observation in support of our results is that PP is significantly higher (89) and the BRS greatly reduced (> 40%) in the second and third trimester of normotensive pregnant women (90). This may contribute to the fact that the majority of pregnant migraine sufferers will note significant improvement in their headaches during the second and third trimesters.

10.4 The baroreflex system and migraine

To evaluate the role of the baroreflex in migraine under normal conditions, we measured BRS and HRV in 16 female migraine without aura patients and 14 age-matched healthy female controls. Even in this small material we found an increased spontaneous BRS as well as increased HRV in the migraineurs. Increased BRS is associated with lower systolic or pulse pressure (91, 92), which is exactly what was found in the subjects with headache in the HUNT-study. This indicates that increased BRS may be the reason why patients with migraine (and possibly other painful conditions) in general have a lower SBP and PP than those without pain. The high BRS may be another manifestation of the generalized increased sensitivity (e.g. photo- and phonophobia) seen in migraine patients.

11. Hypothesis

11.1 Conclusion

Based on the present and previous studies it is tempting to present a hypothesis about the relation between migraine, BP and the RAS. This hypothesis can be summarized in a few statements:

1) Migraineurs have a generalized increased sensitivity to stimuli, both light, sound, odours, touch and bodily movements. This is particularly exacerbated during attacks, but it is also to some degree present outside attacks.
2) Increased BRS may be another manifestation of increased generalized sensitivity.

3) According to the phenomenon of hypertension-associated analgesia (17), high BRS and low BP is associated with more pain, which is in concordance with the results found in our studies.
4) In light of known functional links between key areas in the midbrain and brainstem contributing to both pain modulation and autonomic control, it is not unlikely that 1), 2) and 3) describe interrelated components in a complex feedback system, making it hard to determine that one is the cause of another.
5) The cerebral RAS may be important for the system described in 4). In addition to being one of the main regulatory systems for maintaining BP, it influences several factors that are central in migraine pathophysiology like cerebrovascular flow, cerebral inflammation processes, the secretion of neuropeptides and production of NO. AT1 and AT2 receptors have also been found in brainstem areas involved in pain modulation and autonomic functions. In incompletely known ways the cerebral RAS therefore may mediate the relation between BP and pain sensitivity.
6) ARBs may have a beneficial effect in migraine because they
    a. Act on cerebral Ang II receptors (AT1 and/or AT2) thereby influencing pain modulation in the CNS.
    b. Induce hypotension resulting in baroreceptor stimulation which can influence pain perception.
7) Neither the migraine itself nor the effect of the ARBs is related to differences between migraineurs and non-migraineurs in ACE genotype.

11.2 Weaknesses of the hypothesis

It is a weakness that only two placebo-controlled, randomized studies on drugs influencing the RAS have been conducted, one for an ARB and one for an ACE-I. More studies are needed to confirm the effect of these drug classes in migraine prophylaxis.

An important problem for part of the hypothesis is that some antihypertensives do not seem to work in migraine (e.g. diuretics, betablockers with partial agonist activity). If 6b of our hypothesis is correct, one would believe that all antihypertensives should be effective to some degree.

Also, it is a problem that, although both baroreflex modulation and hypertension are known to have an antinociceptive effect (93, 94), the effect of antihypertensive drugs on BRS is not clear. Both increase and decrease in BRS have been reported (95-97). In addition, we found HRV to be increased in migraine patients, but other papers report conflicting results (both decreased and enhanced HRV) (98-101).

As to the point 7 in the hypothesis, one may object that although we did not find any difference between migraineurs and controls with regard to ACE genes there are many other components of the RAS that may be different in migraine patients. This can be clarified through other genetic studies (e.g AT1 receptor genes etc.)

12. Future prospects

Further studies on the mechanisms underlying the relation between migraine, BP and the RAS are warranted. The effect of candesartan should be confirmed and

preferentially be compared to one of the first-line migraine prophylactic agents (e.g betablocker). In addition, the influence of the brain RAS in migraine should be investigated further. The main effect of Ang II on BP is mediated by blockade of the AT1 receptor, but pharmacological manipulation of other parts of the RAS like the AT2 receptors, renin or the active metabolites of Ang II (angiotensin 1-7, angiotensin III and angiotensin IV) could give further insight into its effect on migraine. Further exploration of the genetic components of the RAS like AT1 receptor genes, may also provide valuable information. Measuring BRS and HRV before and after treatment with an ARB could make clear whether these drugs exert their effect through the baroreflex system. Use of ARBs in other headache disorders or other chronic pain conditions could further provide insight into how much of the effect is migraine-specific.

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Angiotensin-converting enzyme gene insertion/deletion polymorphism in migraine patients

Erling Tronvik*[1,2], Lars J Stovner[1,2], Gunnar Bovim[2], Linda R White[1,2], Amanda J Gladwin[3], Kathryn Owen[3] and Harald Schrader[1,2]

Address: [1]Department of Neurosciences, Norwegian University of Science and Technology, Trondheim, Norway, [2]Department of Neurology and Clinical Neurophysiology, University Hospital of Trondheim, Trondheim, Norway and [3]AstraZeneca, R&D Genetics, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK

Email: Erling Tronvik* - Erling.Tronvik@ntnu.no; Lars J Stovner - Lars.Stovner@ntnu.no; Gunnar Bovim - Gunnar.Bovim@ntnu.no; Linda R White - Linda.White@ntnu.no; Amanda J Gladwin - Amanda.Gladwin@astrazeneca.com; Kathryn Owen - Kathryn.Owen@astrazeneca.com; Harald Schrader - Harald.Schrader@ntnu.no

* Corresponding author

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Abstract

Background: The main objective of this study was to investigate the angiotensin converting enzyme (*ACE*) genotype as a possible risk factor for migraine (both with and without aura) compared to controls. We also wanted to examine whether a clinical response to an ACE inhibitor, lisinopril, or an angiotensin II receptor blocker, candesartan, in migraine prophylaxis was related to *ACE* genotype.

Methods: 347 migraine patients aged 18–68 (155 migraine without aura (MoA), 187 migraine with aura (MwA) and 5 missing aura subgroup data) and 403 healthy non-migrainous controls > 40 years of age were included in the study. A polymerase chain reaction (PCR) was performed on the genomic DNA samples to obtain the *ACE* insertion (I)/deletion(D) polymorphisms.

Results: No significant differences between migraine patients and controls were found with regard to *ACE* genotype and allele distributions. Furthermore, there was no significant difference between the controls and the MwA or MoA subgroups.

Conclusion: In our sample there is no association between *ACE* genotype or allele frequency and migraine. In addition, *ACE* genotype in our experience did not predict the clinical response to lisinopril or candesartan used as migraine prophylactics.

Background

Two small open studies reported an improvement of the headache in migraine patients using an angiotensin-converting enzyme (ACE) inhibitor [1,2]. Indirectly, a beneficial effect of angiotensin II receptor blockers (ARB's) on headache is shown in a meta-analysis on side effects reported in placebo controlled trials including over 12 000 patients [3]. Two randomized, placebo controlled studies conducted by our research group have evidence for efficacy of an ACE inhibitor (lisinopril) and an ARB (candesartan) in migraine prophylaxis [4,5]. This and other evidence points in the direction of involvement of the renin-angiotensin system (RAS) in migraine pathophysi-

ology. (For further discussion on possible mechanisms see reference [6]).

The human angiotensin converting enzyme (*ACE*) gene consists of either an insertion (I) allele or a deletion (D) allele forming three possible genotypes: II, ID or DD. Many studies have suggested an association between the *ACE-D* allele and cardiovascular diseases [7]. For migraine an Italian (Paterna) [8], an Australian (Lea) [9], and a Japanese (Kowa) [10] study has demonstrated different results regarding whether an association between the *ACE* polymorphisms and this condition exists (Table 1).

The objectives of the present study were two-fold. Firstly we wanted to examine whether a beneficial effect in the above mentioned migraine prophylactic studies [4,5] could be predicted by *ACE* genotype, a question that has also been raised in a recent publication [11]. Secondly we wanted to investigate the *ACE* genotype as a possible risk factor for migraine with (MwA) and without (MoA) aura in a Norwegian population.

Methods

Included in the study were 347 migraine patients aged 18–68 (155 MwA, 187 MoA and 5 missing aura subgroup data, based on ICHD-2 criteria [12]) and 403 healthy non-migrainous controls > 40 years of age. The migraineurs were recruited partly from the lisinopril [4] (n = 49) and candesartan [5] (n = 59) studies, and the remaining group (n = 239) from the outpatient clinic of the Department of Neurology, Trondheim University Hospital. The patients and the controls were recruited from the same area and only subjects with Nordic ethnic background were included. The diagnosis was confirmed by an experienced clinical neurologist. Responder status in the candesartan and lisinopril studies was defined as a reduction in days with headache of at least 50% in the treatment period compared to the placebo period. Non-responders were the subjects not defined as responders and with both genotype and response data available. No patients were included in both the lisinopril and candesartan studies. The control group was recruited in collaboration with the Department of Immunology and Transfusion Medicine and criteria for inclusion were no present or former history of migraine or other types of chronic headaches, no history of epilepsy or of hypertension in need of medical treatment, and age > 40 years (since status as "non-migraineur" cannot be determined with relative certainty before this age). No direct interview was made in the control group, but the participants filled out a questionnaire to determine eligibility for participation. In addition to not having migraine the control group was required to have no other headache condition and less than one headache day per month.

The migraine group had a mean age of 41 years (standard deviation (SD): ± 12 years) and consisted of 268 women and 79 men. Median age of migraine onset was 16 years

Table 1: *ACE* genotype and allele distributions among controls and migraine patients in different studies

		Genotypes			Alleles	
	N	**DD(%)**	**ID(%)**	**II(%)**	**D(%)**	**I(%)**
Controls						
Tronvik	403	92 (26.6)	204 (50.6)	107 (22.8)	388 (48.1)	418 (51.9)
Paterna (ref 8)	201	75 (37.3)	101 (50.3)	25 (12.4)	251 (62.4)	151 (37.6)
Lea (ref 9)	244	76 (31.1)	122 (50.0)	46 (18.9)	274 (56.1)	214 (43.9)
Kowa (ref 10)	248	31 (12.5)	114 (46.0)	103 (41.5)	176 (35.5)	320 (64.5)
Migraine						
Tronvik	347	78 (22.5)	186 (53.6)	83 (23.9)	342 (49.3)	352 (50.7)
Paterna	302	146 (48.3)	129 (42.7)	27 (9.0)	421 (69.7)	183 (30.3)
Lea	250	77 (30.8)	142 (56.8)	31 (12.4)	296 (59.2)	204 (40.8)
Kowa	176	33 (18.7)	86 (48.9)	57 (32.4)	152 (43.2)	200 (56.8)
MwA subgroup						
Tronvik	155	34 (21.9)	87 (56.1)	34 (21.9)	155 (50.0)	155 (50.0)
Paterna	NA	NA	NA	NA	NA	NA
Lea	151	48 (31.8)	85 (56.3)	18 (11.9)	181 (59.9)	121 (40.1)
Kowa	54	14 (25.9)*	26 (48.2)	14 (25.9)	54 (50.0)*	54 (50.0)
MoA subgroup						
Tronvik	187	43 (23.0)	96 (51.3)	48 (25.7)	182 (48.7)	192 (51.3)
Paterna	302	146 (48.3)*	129 (42.7)	27 (9.0)	421 (69.7)	183 (30.3)
Lea	99	29 (29.3)	57 (57.6)	13 (13.1)	115 (58.1)	83 (41.9)
Kowa	122	19 (15.6)	60 (49.2)	43 (35.2)	98 (35.2)	146 (59.8)

* Reported significant finding for genotype or allele frequencies

and median attack frequency was 4.0 attacks per month. In the control group with 233 women and 170 men, mean age was 50 years (SD: ± 7 years).

311 of the samples were genotyped by AstraZeneca, R&D Genetics, UK, and 439 samples were genotyped at the Department of Neurology, Trondheim University Hospital, Norway.

Genomic DNA preparation and polymerase chain reaction (PCR) analysis

DNA was extracted from peripheral EDTA-blood stored at -80°C. The D and I alleles were identified on the basis of PCR amplification of the respective fragments from intron 16 of the *ACE* gene. The oligonucleotide primers [13,14] used (MedProbe) were sense (forward): 5' CTGGAGACCACTCCCATCCTTTCT 3' and antisense (reverse): 5' GATGTGGCCATCACATTCGTCAGAT 3'. Amplification was performed with 0.5 μmol of each primer. The PCR product was a 191 bp fragment in the absence, and a 479 bp fragment in the presence of the insertion. Homozygous D alleles were confirmed using the insertion-specific primer 5' TTTGAGACGGAGTCTCGCTC 3'.

Part of the samples (n = 311) were amplified using a thermal cycler and the products separated on 2% agarose gel. The remaining samples (n = 439) were analyzed using a LightCycler instrument (Roche). Amplification conditions for the first method were 1.2 mM $MgCl_2$, 1 U AmpliTaq Gold, 200 μM dNTPs and 5 μL DNA template in a total reaction volume of 25 μL, enzyme activation at 94°C for 20 min, denaturation at 94°C for 1 min, annealing at 58°C for 1 min and extension at 72°C for 2 min for a total of 32 cycles. Samples analyzed by LightCycler used the FastStart DNA Master SYBR Green 1 mix, which includes Taq DNA polymerase (Roche Diagnostics), plus 3 mM $MgCl_2$, and 2 μL DNA template, in a total reaction volume of 20 μL with enzyme activation at 95°C for 10 min, denaturation at 95°C for 10 s, annealing at 50°C for 5 s, and elongation at 72°C for 15 s, for a total of 35 cycles. The fluorescence intensity of the double-strand specific SYBR Green I is directly proportional to the amount of PCR product formed. Melting curves indicated the respective melting temperatures of the 191 bp and 479 bp fragments to be 84.5°C and 91.8°C respectively, with samples from heterozygotes displaying a peak at both temperatures. Reaction products were confirmed on 2% agarose gel. The ratio between cases and controls was the same for both methods of analysis and blinded control experiments in 10 random patients analysed by the first method were confirmed by the second method.

Statistical analysis

Observed genotype count was used to calculate genotype and allele frequencies for the *ACE I/D* polymorphism. The expected genotype proportions were calculated and compared to the observed proportions according to the Hardy-Weinberg law. The significance level was set at $p < 0.05$. For comparison between groups we used the χ^2 test with one or two degrees of freedom. To compare means (age of debut, frequency of migraine/headache) we used one-way ANOVA. Statistical analysis were performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Power calculation for the association between *ACE* polymorphisms and migraine was performed with the method described by Altman with correction for unequal sample sizes [15]. For the association between *ACE* polymorphisms and drug response, we performed a one sample two tailed test with alpha = 0.05.

Ethics

The study was approved by the regional committee for ethics in medical research, and by the Norwegian data inspectorate. All subjects included gave a written informed consent.

Results

The observed genotypes in the control population did not deviate significantly from the Hardy-Weinberg equilibrium (p = 0.98). With regard to the genotype and allele distributions, no significant differences between migraine patients and controls were detected, even though the *ACE-D* allele tended to be more frequent (p = 0.058) among responders than non-responders in the candesartan group (Table 2). Furthermore, there was no significant difference between the controls and the MwA or MoA subgroups, nor between responders and non-responders to lisinopril and candesartan, and no difference was detected when stratifying by sex. Within the migraine group differences in genotype could not explain the presence of aura (n = 342, missing data = 5, p = 0.64), of coexisting tension-type headache among migraineurs (n = 343, missing data = 4, p = 1.0), differences in age of debut (n = 342, missing = 5, p = 0.69) or frequency of migraine (n = 342, missing = 5, p = 0.52) or in headache frequency as recorded in the placebo period in the candesartan study (n = 56, missing = 3, p = 0.77).

Frequencies of the genotypes and alleles for the different studies are presented in Table 1. There are large differences in genotypes and alleles among the controls. E.g. the II genotype varies between 12.4 and 41.5 and the D-allele between 35.5 and 62.4%.

Discussion

In the present Norwegian sample, there is no difference in *ACE* genotype or allele frequency in a migraine group compared to a control group. Associations between *ACE* polymorphism and migraine reported in other studies are not consistent and have been detected in different diag-

Table 2: *ACE* genotype and allele distributions among controls and migraine patients in a Norwegian population

		Genotypes			Alleles	
	N	**DD(%)**	**ID(%)**	**II(%)**	**D(%)**	**I(%)**
Controls	403	92 (26.6)	204 (50.6)	107 (22.8)	388 (48.1)	418 (51.9)
Migraine	347	78 (22.5)	186 (53.6)	83 (23.9)	342 (49.3)	352 (50.7)
MwA subgroup	155	34 (21.9)	87 (56.1)	34 (21.9)	155 (50.0)	155 (50.0)
MoA subgroup	187	43 (23.0)	96 (51.3)	48 (25.7)	182 (48.7)	192 (51.3)
Lisinopril responders	12	2 (16.7)	6 (50.0)	4 (33.3)	10 (41.7)	14 (58.3)
Lisinopril non-responders	37	10 (27.0)	16 (43.2)	11 (29.7)	36 (48.6)	38 (51.4)
Candesartan responders*	18	7 (38.9)	9 (50.0)	2 (11.1)	23 (63.9)	13 (36.1)
Candesartan non-responders*	38	8 (21.1)	18 (47.4)	12 (31.6)	34 (44.7)	42 (55.3)
Responders combined	30	9 (30.0)	15 (50.0)	6 (20.0)	33 (55.0)	27 (45.0)
Non-responders combined	75	18 (24.0)	34 (45.3)	23 (30.7)	70 (46.7)	80 (53.3)

* Response data available in 56 of 59 genotyped

Allele and genotype frequency distributions are not significantly different for any diagnostic groups (migraine, MwA, MoA) vs controls, or for responders vs non-responders ($p > 0.05$).

nostic or sex categories. The results of these studies are shown in Table 1. In addition a recently published study from Taiwan found no differences in *ACE* allelic frequencies between migraine patients and controls, but stratified by gender the DD frequency was significantly lower in male migraineurs than controls (not included in Table 1 because only the abstract was published in the English language) [16]. Findings that the DD genotype is more frequent in MoA [8] and MwA [10] or less frequent in male migraineurs [16] are not supported by our data. Our population which is the largest to date used to study the relationship between *ACE* polymorphism and migraine (MoA and MwA) should have >80% power to detect an association of the same magnitude as in the study by Paterna et al [8]. Our study also did not find a relationship between *ACE* genotype and response to prophylactic drugs influencing the RAS. The allele frequency in the responders versus non-responders in the candesartan group had a p-value of 0.058 and with low numbered groups the risk of a false negative result is present.

The purpose of looking at the association between responders in the two clinical trials and *ACE* genotype was not to detect a small theoretical association, in which case this subgroup analyses would be underpowered, but to see whether there was an association so strong that it would be valuable in clinical use predicting response in migraine – prophylactic treatment. That is whether it would be clinically beneficial to use *ACE* genotype to predict whether the patient would respond to the drug or not. Our opinion is that in order for an association to be clinical valuable at least 75–100% of responders to a migraine-prophylactic drug should have a specific *ACE*-genotype. The power of our study to measure a percentage of 75% DD among the candesartan responders with the control population as reference is > 80%.

A limitation of the study is that the control group was not directly interviewed increasing the risk of migraineurs self-reporting themselves as non-migraineurs and thereby increasing the risk of type II errors. In order to minimize this problem participants in the control group were required to have no other headache condition and less than one headache day per month.

Population stratification refers to differences in allele frequencies between cases and controls due to systematical differences in ancestry rather than in the association of genes with disease [17,18]. There are large differences in the frequencies of the *ACE*-alleles in different populations (Table 1). Hence, due to the problem with population stratification we did not find it meaningful to perform a statistical analysis of the merged data of all these studies. This might have been misleading also because the way diagnosis were made, both of migraineurs and controls, may differ somewhat between the studies.

Conclusion

There was no difference in *ACE* genotype distribution between a migraine and a control population in our material. Our study also indicates that *ACE* genotyping will not be a valuable tool for predicting clinical response of drugs influencing the angiotensin system in headache treatment. It is, however, important that these findings should be confirmed in other studies with more patients and among different ethnic groups.

Abbreviations

RAS, renin-angiotensin system; ACE, angiotensin converting enzyme; MoA, migraine without aura; MwA, migraine with aura; ARB's, angiotensin II receptor blockers.

Competing interests

Co-authors Amanda Gladwin and Katryn Owen are AstraZeneca staff.

No disclosures from the rest of the authors.

Authors' contributions

ET, LJS, GB, LRW and HS were involved in designing the study. AG, KO and LRW were responsible for the genotyping. ET and LJS conducted the statistical analyses. All authors were involved in either drafting the manuscript or revising it.

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40. Kjell-Arne Rein: THE EFFECT OF EXTRACORPOREAL CIRCULATION ON SUBCUTANEOUS TRANSCAPILLARY FLUID BALANCE.
41. Arne Kristian Sandvik: RAT GASTRIC HISTAMINE.
42. Carl Bredo Dahl: ANIMAL MODELS IN PSYCHIATRY.

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43. Torbjørn A. Fredriksen: CERVICOGENIC HEADACHE.
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47. Johan C. Ræder: PREMEDICATION AND GENERAL ANAESTHESIA IN OUTPATIENT GYNECOLOGICAL SURGERY.
48. M. R. Shalaby: IMMUNOREGULATORY PROPERTIES OF TNF-α AND THE RELATED CYTOKINES.
49. Anders Waage: THE COMPLEX PATTERN OF CYTOKINES IN SEPTIC SHOCK.
50. Bjarne Christian Eriksen: ELECTROSTIMULATION OF THE PELVIC FLOOR IN FEMALE URINARY INCONTINENCE.
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55. Eva Hofsli: TUMOR NECROSIS FACTOR AND MULTIDRUG RESISTANCE.
56. Helge S. Haarstad: TROPHIC EFFECTS OF CHOLECYSTOKININ AND SECRETIN ON THE RAT PANCREAS.
57. Lars Engebretsen: TREATMENT OF ACUTE ANTERIOR CRUCIATE LIGAMENT INJURIES.
58. Tarjei Rygnestad: DELIBERATE SELF-POISONING IN TRONDHEIM.
59. Arne Z. Henriksen: STUDIES ON CONSERVED ANTIGENIC DOMAINS ON MAJOR OUTER MEMBRANE PROTEINS FROM ENTEROBACTERIA.
60. Steinar Westin: UNEMPLOYMENT AND HEALTH: Medical and social consequences of a factory closure in a ten-year controlled follow-up study.
61. Ylva Sahlin: INJURY REGISTRATION, a tool for accident preventive work.
62. Helge Bjørnstad Pettersen: BIOSYNTHESIS OF COMPLEMENT BY HUMAN ALVEOLAR MACROPHAGES WITH SPECIAL REFERENCE TO SARCOIDOSIS.
63. Berit Schei: TRAPPED IN PAINFUL LOVE.
64. Lars J. Vatten: PROSPECTIVE STUDIES OF THE RISK OF BREAST CANCER IN A COHORT OF NORWEGIAN WOMAN.

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65. Kåre Bergh: APPLICATIONS OF ANTI-C5a SPECIFIC MONOCLONAL ANTIBODIES FOR THE ASSESSMENT OF COMPLEMENT ACTIVATION.
66. Svein Svenningsen: THE CLINICAL SIGNIFICANCE OF INCREASED FEMORAL ANTEVERSION.

67. Olbjørn Klepp: NONSEMINOMATOUS GERM CELL TESTIS CANCER: THERAPEUTIC OUTCOME AND PROGNOSTIC FACTORS.
68. Trond Sand: THE EFFECTS OF CLICK POLARITY ON BRAINSTEM AUDITORY EVOKED POTENTIALS AMPLITUDE, DISPERSION, AND LATENCY VARIABLES.
69. Kjetil B. Åsbakk: STUDIES OF A PROTEIN FROM PSORIATIC SCALE, PSO P27, WITH RESPECT TO ITS POTENTIAL ROLE IN IMMUNE REACTIONS IN PSORIASIS.
70. Arnulf Hestnes: STUDIES ON DOWN´S SYNDROME.
71. Randi Nygaard: LONG-TERM SURVIVAL IN CHILDHOOD LEUKEMIA.
72. Bjørn Hagen: THIO-TEPA.
73. Svein Anda: EVALUATION OF THE HIP JOINT BY COMPUTED TOMOGRAMPHY AND ULTRASONOGRAPHY.

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74. Martin Svartberg: AN INVESTIGATION OF PROCESS AND OUTCOME OF SHORT-TERM PSYCHODYNAMIC PSYCHOTHERAPY.
75. Stig Arild Slørdahl: AORTIC REGURGITATION.
76. Harold C Sexton: STUDIES RELATING TO THE TREATMENT OF SYMPTOMATIC NON-PSYCHOTIC PATIENTS.
77. Maurice B. Vincent: VASOACTIVE PEPTIDES IN THE OCULAR/FOREHEAD AREA.
78. Terje Johannessen: CONTROLLED TRIALS IN SINGLE SUBJECTS.
79. Turid Nilsen: PYROPHOSPHATE IN HEPATOCYTE IRON METABOLISM.
80. Olav Haraldseth: NMR SPECTROSCOPY OF CEREBRAL ISCHEMIA AND REPERFUSION IN RAT.
81. Eiliv Brenna: REGULATION OF FUNCTION AND GROWTH OF THE OXYNTIC MUCOSA.

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82. Gunnar Bovim: CERVICOGENIC HEADACHE.
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84. Bjørn Naume: IMMUNOREGULATORY EFFECTS OF CYTOKINES ON NK CELLS.
85. Rune Wiseth: AORTIC VALVE REPLACEMENT.
86. Jie Ming Shen: BLOOD FLOW VELOCITY AND RESPIRATORY STUDIES.
87. Piotr Kruszewski: SUNCT SYNDROME WITH SPECIAL REFERENCE TO THE AUTONOMIC NERVOUS SYSTEM.
88. Mette Haase Moen: ENDOMETRIOSIS.
89. Anne Vik: VASCULAR GAS EMBOLISM DURING AIR INFUSION AND AFTER DECOMPRESSION IN PIGS.
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91. Kjell Å. Salvesen: ROUTINE ULTRASONOGRAPHY IN UTERO AND DEVELOPMENT IN CHILDHOOD.

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92. Nina-Beate Liabakk: DEVELOPMENT OF IMMUNOASSAYS FOR TNF AND ITS SOLUBLE RECEPTORS.
93. Sverre Helge Torp: *erb*B ONCOGENES IN HUMAN GLIOMAS AND MENINGIOMAS.
94. Olav M. Linaker: MENTAL RETARDATION AND PSYCHIATRY. Past and present.
95. Per Oscar Feet: INCREASED ANTIDEPRESSANT AND ANTIPANIC EFFECT IN COMBINED TREATMENT WITH DIXYRAZINE AND TRICYCLIC ANTIDEPRESSANTS.
96. Stein Olav Samstad: CROSS SECTIONAL FLOW VELOCITY PROFILES FROM TWO-DIMENSIONAL DOPPLER ULTRASOUND: Studies on early mitral blood flow.
97. Bjørn Backe: STUDIES IN ANTENATAL CARE.
98. Gerd Inger Ringdal: QUALITY OF LIFE IN CANCER PATIENTS.
99. Torvid Kiserud: THE DUCTUS VENOSUS IN THE HUMAN FETUS.
100. Hans E. Fjøsne: HORMONAL REGULATION OF PROSTATIC METABOLISM.
101. Eylert Brodtkorb: CLINICAL ASPECTS OF EPILEPSY IN THE MENTALLY RETARDED.
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103. Unni Syversen: CHROMOGRANIN A. Phsysiological and Clinical Role.

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104. Odd Gunnar Brakstad: THERMOSTABLE NUCLEASE AND THE *nuc* GENE IN THE DIAGNOSIS OF *Staphylococcus aureus* INFECTIONS.
105. Terje Engan: NUCLEAR MAGNETIC RESONANCE (NMR) SPECTROSCOPY OF PLASMA IN MALIGNANT DISEASE.
106. Kirsten Rasmussen: VIOLENCE IN THE MENTALLY DISORDERED.
107. Finn Egil Skjeldestad: INDUCED ABORTION: Timetrends and Determinants.

108. Roar Stenseth: THORACIC EPIDURAL ANALGESIA IN AORTOCORONARY BYPASS SURGERY.
109. Arild Faxvaag: STUDIES OF IMMUNE CELL FUNCTION *in mice infected with* MURINE RETROVIRUS.

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110. Svend Aakhus: NONINVASIVE COMPUTERIZED ASSESSMENT OF LEFT VENTRICULAR FUNCTION AND SYSTEMIC ARTERIAL PROPERTIES. Methodology and some clinical applications.
111. Klaus-Dieter Bolz: INTRAVASCULAR ULTRASONOGRAPHY.
112. Petter Aadahl: CARDIOVASCULAR EFFECTS OF THORACIC AORTIC CROSS-CLAMPING.
113. Sigurd Steinshamn: CYTOKINE MEDIATORS DURING GRANULOCYTOPENIC INFECTIONS.
114. Hans Stifoss-Hanssen: SEEKING MEANING OR HAPPINESS?
115. Anne Kvikstad: LIFE CHANGE EVENTS AND MARITAL STATUS IN RELATION TO RISK AND PROGNOSIS OF CANCER.
116. Torbjørn Grøntvedt: TREATMENT OF ACUTE AND CHRONIC ANTERIOR CRUCIATE LIGAMENT INJURIES. A clinical and biomechanical study.
117. Sigrid Hørven Wigers: CLINICAL STUDIES OF FIBROMYALGIA WITH FOCUS ON ETIOLOGY, TREATMENT AND OUTCOME.
118. Jan Schjøtt: MYOCARDIAL PROTECTION: Functional and Metabolic Characteristics of Two Endogenous Protective Principles.
119. Marit Martinussen: STUDIES OF INTESTINAL BLOOD FLOW AND ITS RELATION TO TRANSITIONAL CIRCULATORY ADAPATION IN NEWBORN INFANTS.
120. Tomm B. Müller: MAGNETIC RESONANCE IMAGING IN FOCAL CEREBRAL ISCHEMIA.
121. Rune Haaverstad: OEDEMA FORMATION OF THE LOWER EXTREMITIES.
122. Magne Børset: THE ROLE OF CYTOKINES IN MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO HEPATOCYTE GROWTH FACTOR.
123. Geir Smedslund: A THEORETICAL AND EMPIRICAL INVESTIGATION OF SMOKING, STRESS AND DISEASE: RESULTS FROM A POPULATION SURVEY.

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124. Torstein Vik: GROWTH, MORBIDITY, AND PSYCHOMOTOR DEVELOPMENT IN INFANTS WHO WERE GROWTH RETARDED *IN UTERO*.
125. Siri Forsmo: ASPECTS AND CONSEQUENCES OF OPPORTUNISTIC SCREENING FOR CERVICAL CANCER. Results based on data from three Norwegian counties.
126. Jon S. Skranes: CEREBRAL MRI AND NEURODEVELOPMENTAL OUTCOME IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN. A follow-up study of a geographically based year cohort of VLBW children at ages one and six years.
127. Knut Bjørnstad: COMPUTERIZED ECHOCARDIOGRAPHY FOR EVALUTION OF CORONARY ARTERY DISEASE.
128. Grethe Elisabeth Borchgrevink: DIAGNOSIS AND TREATMENT OF WHIPLASH/NECK SPRAIN INJURIES CAUSED BY CAR ACCIDENTS.
129. Tor Elsås: NEUROPEPTIDES AND NITRIC OXIDE SYNTHASE IN OCULAR AUTONOMIC AND SENSORY NERVES.
130. Rolf W. Gråwe: EPIDEMIOLOGICAL AND NEUROPSYCHOLOGICAL PERSPECTIVES ON SCHIZOPHRENIA.
131. Tonje Strømholm: CEREBRAL HAEMODYNAMICS DURING THORACIC AORTIC CROSSCLAMPING. An experimental study in pigs.

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132. Martinus Bråten: STUDIES ON SOME PROBLEMS REALTED TO INTRAMEDULLARY NAILING OF FEMORAL FRACTURES.
133. Ståle Nordgård: PROLIFERATIVE ACTIVITY AND DNA CONTENT AS PROGNOSTIC INDICATORS IN ADENOID CYSTIC CARCINOMA OF THE HEAD AND NECK.
134. Egil Lien: SOLUBLE RECEPTORS FOR **TNF** AND **LPS**: RELEASE PATTERN AND POSSIBLE SIGNIFICANCE IN DISEASE.
135. Marit Bjørgaas: HYPOGLYCAEMIA IN CHILDREN WITH DIABETES MELLITUS
136. Frank Skorpen: GENETIC AND FUNCTIONAL ANALYSES OF DNA REPAIR IN HUMAN CELLS.
137. Juan A. Pareja: SUNCT SYNDROME. ON THE CLINICAL PICTURE. ITS DISTINCTION FROM OTHER, SIMILAR HEADACHES.

138. Anders Angelsen: NEUROENDOCRINE CELLS IN HUMAN PROSTATIC CARCINOMAS AND THE PROSTATIC COMPLEX OF RAT, GUINEA PIG, CAT AND DOG.
139. Fabio Antonaci: CHRONIC PAROXYSMAL HEMICRANIA AND HEMICRANIA CONTINUA: TWO DIFFERENT ENTITIES?
140. Sven M. Carlsen: ENDOCRINE AND METABOLIC EFFECTS OF METFORMIN WITH SPECIAL EMPHASIS ON CARDIOVASCULAR RISK FACTORES.

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141. Terje A. Murberg: DEPRESSIVE SYMPTOMS AND COPING AMONG PATIENTS WITH CONGESTIVE HEART FAILURE.
142. Harm-Gerd Karl Blaas: THE EMBRYONIC EXAMINATION. Ultrasound studies on the development of the human embryo.
143. Noèmi Becser Andersen:THE CEPHALIC SENSORY NERVES IN UNILATERAL HEADACHES. Anatomical background and neurophysiological evaluation.
144. Eli-Janne Fiskerstrand: LASER TREATMENT OF PORT WINE STAINS. A study of the efficacy and limitations of the pulsed dye laser. Clinical and morfological analyses aimed at improving the therapeutic outcome.
145. Bård Kulseng: A STUDY OF ALGINATE CAPSULE PROPERTIES AND CYTOKINES IN RELATION TO INSULIN DEPENDENT DIABETES MELLITUS.
146. Terje Haug: STRUCTURE AND REGULATION OF THE HUMAN UNG GENE ENCODING URACIL-DNA GLYCOSYLASE.
147. Heidi Brurok: MANGANESE AND THE HEART. A Magic Metal with Diagnostic and Therapeutic Possibilites.
148. Agnes Kathrine Lie: DIAGNOSIS AND PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION IN CERVICAL INTRAEPITELIAL NEOPLASIA. Relationship to Cell Cycle Regulatory Proteins and HLA DQBI Genes.
149. Ronald Mårvik: PHARMACOLOGICAL, PHYSIOLOGICAL AND PATHOPHYSIOLOGICAL STUDIES ON ISOLATED STOMACS.
150. Ketil Jarl Holen: THE ROLE OF ULTRASONOGRAPHY IN THE DIAGNOSIS AND TREATMENT OF HIP DYSPLASIA IN NEWBORNS.
151. Irene Hetlevik: THE ROLE OF CLINICAL GUIDELINES IN CARDIOVASCULAR RISK INTERVENTION IN GENERAL PRACTICE.
152. Katarina Tunòn: ULTRASOUND AND PREDICTION OF GESTATIONAL AGE.
153. Johannes Soma: INTERACTION BETWEEN THE LEFT VENTRICLE AND THE SYSTEMIC ARTERIES.
154. Arild Aamodt: DEVELOPMENT AND PRE-CLINICAL EVALUATION OF A CUSTOM-MADE FEMORAL STEM.
155. Agnar Tegnander: DIAGNOSIS AND FOLLOW-UP OF CHILDREN WITH SUSPECTED OR KNOWN HIP DYSPLASIA.
156. Bent Indredavik: STROKE UNIT TREATMENT: SHORT AND LONG-TERM EFFECTS
157. Jolanta Vanagaite Vingen: PHOTOPHOBIA AND PHONOPHOBIA IN PRIMARY HEADACHES

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158. Ola Dalsegg Sæther: PATHOPHYSIOLOGY DURING PROXIMAL AORTIC CROSS-CLAMPING CLINICAL AND EXPERIMENTAL STUDIES
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160. Christina Vogt Isaksen: PRENATAL ULTRASOUND AND POSTMORTEM FINDINGS – A TEN YEAR CORRELATIVE STUDY OF FETUSES AND INFANTS WITH DEVELOPMENTAL ANOMALIES.
161. Holger Seidel: HIGH-DOSE METHOTREXATE THERAPY IN CHILDREN WITH ACUTE LYMPHOCYTIC LEUKEMIA: DOSE, CONCENTRATION, AND EFFECT CONSIDERATIONS.
162. Stein Hallan: IMPLEMENTATION OF MODERN MEDICAL DECISION ANALYSIS INTO CLINICAL DIAGNOSIS AND TREATMENT.
163. Malcolm Sue-Chu: INVASIVE AND NON-INVASIVE STUDIES IN CROSS-COUNTRY SKIERS WITH ASTHMA-LIKE SYMPTOMS.
164. Ole-Lars Brekke: EFFECTS OF ANTIOXIDANTS AND FATTY ACIDS ON TUMOR NECROSIS FACTOR-INDUCED CYTOTOXICITY.
165. Jan Lundbom: AORTOCORONARY BYPASS SURGERY: CLINICAL ASPECTS, COST CONSIDERATIONS AND WORKING ABILITY.
166. John-Anker Zwart: LUMBAR NERVE ROOT COMPRESSION, BIOCHEMICAL AND NEUROPHYSIOLOGICAL ASPECTS.
167. Geir Falck: HYPEROSMOLALITY AND THE HEART.

168. Eirik Skogvoll: CARDIAC ARREST Incidence, Intervention and Outcome.
169. Dalius Bansevicius: SHOULDER-NECK REGION IN CERTAIN HEADACHES AND CHRONIC PAIN SYNDROMES.
170. Bettina Kinge: REFRACTIVE ERRORS AND BIOMETRIC CHANGES AMONG UNIVERSITY STUDENTS IN NORWAY.
171. Gunnar Qvigstad: CONSEQUENCES OF HYPERGASTRINEMIA IN MAN
172. Hanne Ellekjær: EPIDEMIOLOGICAL STUDIES OF STROKE IN A NORWEGIAN POPULATION. INCIDENCE, RISK FACTORS AND PROGNOSIS
173. Hilde Grimstad: VIOLENCE AGAINST WOMEN AND PREGNANCY OUTCOME.
174. Astrid Hjelde: SURFACE TENSION AND COMPLEMENT ACTIVATION: Factors influencing bubble formation and bubble effects after decompression.
175. Kjell A. Kvistad: MR IN BREAST CANCER – A CLINICAL STUDY.
176. Ivar Rossvoll: ELECTIVE ORTHOPAEDIC SURGERY IN A DEFINED POPULATION. Studies on demand, waiting time for treatment and incapacity for work.
177. Carina Seidel: PROGNOSTIC VALUE AND BIOLOGICAL EFFECTS OF HEPATOCYTE GROWTH FACTOR AND SYNDECAN-1 IN MULTIPLE MYELOMA.

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178. Alexander Wahba: THE INFLUENCE OF CARDIOPULMONARY BYPASS ON PLATELET FUNCTION AND BLOOD COAGULATION – DETERMINANTS AND CLINICAL CONSEQUENSES
179. Marcus Schmitt-Egenolf: THE RELEVANCE OF THE MAJOR hISTOCOMPATIBILITY COMPLEX FOR THE GENETICS OF PSORIASIS
180. Odrun Arna Gederaas: BIOLOGICAL MECHANISMS INVOLVED IN 5-AMINOLEVULINIC ACID BASED PHOTODYNAMIC THERAPY
181. Pål Richard Romundstad: CANCER INCIDENCE AMONG NORWEGIAN ALUMINIUM WORKERS
182. Henrik Hjorth-Hansen: NOVEL CYTOKINES IN GROWTH CONTROL AND BONE DISEASE OF MULTIPLE MYELOMA
183. Gunnar Morken: SEASONAL VARIATION OF HUMAN MOOD AND BEHAVIOUR
184. Bjørn Olav Haugen: MEASUREMENT OF CARDIAC OUTPUT AND STUDIES OF VELOCITY PROFILES IN AORTIC AND MITRAL FLOW USING TWO- AND THREE-DIMENSIONAL COLOUR FLOW IMAGING
185. Geir Bråthen: THE CLASSIFICATION AND CLINICAL DIAGNOSIS OF ALCOHOL-RELATED SEIZURES
186. Knut Ivar Aasarød: RENAL INVOLVEMENT IN INFLAMMATORY RHEUMATIC DISEASE. A Study of Renal Disease in Wegener's Granulomatosis and in Primary Sjögren's Syndrome
187. Trude Helen Flo: RESEPTORS INVOLVED IN CELL ACTIVATION BY DEFINED URONIC ACID POLYMERS AND BACTERIAL COMPONENTS
188. Bodil Kavli: HUMAN URACIL-DNA GLYCOSYLASES FROM THE UNG GENE: STRUCTRUAL BASIS FOR SUBSTRATE SPECIFICITY AND REPAIR
189. Liv Thommesen: MOLECULAR MECHANISMS INVOLVED IN TNF- AND GASTRIN-MEDIATED GENE REGULATION
190. Turid Lingaas Holmen: SMOKING AND HEALTH IN ADOLESCENCE; THE NORD-TRØNDELAG HEALTH STUDY, 1995-97
191. Øyvind Hjertner: MULTIPLE MYELOMA: INTERACTIONS BETWEEN MALIGNANT PLASMA CELLS AND THE BONE MICROENVIRONMENT
192. Asbjørn Støylen: STRAIN RATE IMAGING OF THE LEFT VENTRICLE BY ULTRASOUND. FEASIBILITY, CLINICAL VALIDATION AND PHYSIOLOGICAL ASPECTS
193. Kristian Midthjell: DIABETES IN ADULTS IN NORD-TRØNDELAG. PUBLIC HEALTH ASPECTS OF DIABETES MELLITUS IN A LARGE, NON-SELECTED NORWEGIAN POPULATION.
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195. Ulrik Wisløff: CARDIAC EFFECTS OF AEROBIC ENDURANCE TRAINING: HYPERTROPHY, CONTRACTILITY AND CALCUIM HANDLING IN NORMAL AND FAILING HEART
196. Øyvind Halaas: MECHANISMS OF IMMUNOMODULATION AND CELL-MEDIATED CYTOTOXICITY INDUCED BY BACTERIAL PRODUCTS
197. Tore Amundsen: PERFUSION MR IMAGING IN THE DIAGNOSIS OF PULMONARY EMBOLISM

198. Nanna Kurtze: THE SIGNIFICANCE OF ANXIETY AND DEPRESSION IN FATIQUE AND PATTERNS OF PAIN AMONG INDIVIDUALS DIAGNOSED WITH FIBROMYALGIA: RELATIONS WITH QUALITY OF LIFE, FUNCTIONAL DISABILITY, LIFESTYLE, EMPLOYMENT STATUS, CO-MORBIDITY AND GENDER
199. Tom Ivar Lund Nilsen: PROSPECTIVE STUDIES OF CANCER RISK IN NORD-TRØNDELAG: THE HUNT STUDY. Associations with anthropometric, socioeconomic, and lifestyle risk factors
200. Asta Kristine Håberg: A NEW APPROACH TO THE STUDY OF MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT USING MAGNETIC RESONANCE TECHNIQUES

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201. Knut Jørgen Arntzen: PREGNANCY AND CYTOKINES
202. Henrik Døllner: INFLAMMATORY MEDIATORS IN PERINATAL INFECTIONS
203. Asta Bye: LOW FAT, LOW LACTOSE DIET USED AS PROPHYLACTIC TREATMENT OF ACUTE INTESTINAL REACTIONS DURING PELVIC RADIOTHERAPY. A PROSPECTIVE RANDOMISED STUDY.
204. Sylvester Moyo: STUDIES ON STREPTOCOCCUS AGALACTIAE (GROUP B STREPTOCOCCUS) SURFACE-ANCHORED MARKERS WITH EMPHASIS ON STRAINS AND HUMAN SERA FROM ZIMBABWE.
205. Knut Hagen: HEAD-HUNT: THE EPIDEMIOLOGY OF HEADACHE IN NORD-TRØNDELAG
206. Li Lixin: ON THE REGULATION AND ROLE OF UNCOUPLING PROTEIN-2 IN INSULIN PRODUCING ß-CELLS
207. Anne Hildur Henriksen: SYMPTOMS OF ALLERGY AND ASTHMA VERSUS MARKERS OF LOWER AIRWAY INFLAMMATION AMONG ADOLESCENTS
208. Egil Andreas Fors: NON-MALIGNANT PAIN IN RELATION TO PSYCHOLOGICAL AND ENVIRONTENTAL FACTORS. EXPERIENTAL AND CLINICAL STUDES OF PAIN WITH FOCUS ON FIBROMYALGIA
209. Pål Klepstad: MORPHINE FOR CANCER PAIN
210. Ingunn Bakke: MECHANISMS AND CONSEQUENCES OF PEROXISOME PROLIFERATOR-INDUCED HYPERFUNCTION OF THE RAT GASTRIN PRODUCING CELL
211. Ingrid Susann Gribbestad: MAGNETIC RESONANCE IMAGING AND SPECTROSCOPY OF BREAST CANCER
212. Rønnaug Astri Ødegård: PREECLAMPSIA – MATERNAL RISK FACTORS AND FETAL GROWTH
213. Johan Haux: STUDIES ON CYTOTOXICITY INDUCED BY HUMAN NATURAL KILLER CELLS AND DIGITOXIN
214. Turid Suzanne Berg-Nielsen: PARENTING PRACTICES AND MENTALLY DISORDERED ADOLESCENTS
215. Astrid Rydning: BLOOD FLOW AS A PROTECTIVE FACTOR FOR THE STOMACH MUCOSA. AN EXPERIMENTAL STUDY ON THE ROLE OF MAST CELLS AND SENSORY AFFERENT NEURONS

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216. Jan Pål Loennechen: HEART FAILURE AFTER MYOCARDIAL INFARCTION. Regional Differences, Myocyte Function, Gene Expression, and Response to Cariporide, Losartan, and Exercise Training.
217. Elisabeth Qvigstad: EFFECTS OF FATTY ACIDS AND OVER-STIMULATION ON INSULIN SECRETION IN MAN
218. Arne Åsberg: EPIDEMIOLOGICAL STUDIES IN HEREDITARY HEMOCHROMATOSIS: PREVALENCE, MORBIDITY AND BENEFIT OF SCREENING.
219. Johan Fredrik Skomsvoll: REPRODUCTIVE OUTCOME IN WOMEN WITH RHEUMATIC DISEASE. A population registry based study of the effects of inflammatory rheumatic disease and connective tissue disease on reproductive outcome in Norwegian women in 1967-1995.
220. Siv Mørkved: URINARY INCONTINENCE DURING PREGNANCY AND AFTER DELIVERY: EFFECT OF PELVIC FLOOR MUSCLE TRAINING IN PREVENTION AND TREATMENT
221. Marit S. Jordhøy: THE IMPACT OF COMPREHENSIVE PALLIATIVE CARE
222. Tom Christian Martinsen: HYPERGASTRINEMIA AND HYPOACIDITY IN RODENTS – CAUSES AND CONSEQUENCES
223. Solveig Tingulstad: CENTRALIZATION OF PRIMARY SURGERY FOR OVARAIN CANCER. FEASIBILITY AND IMPACT ON SURVIVAL

224. Haytham Eloqayli: METABOLIC CHANGES IN THE BRAIN CAUSED BY EPILEPTIC SEIZURES
225. Torunn Bruland: STUDIES OF EARLY RETROVIRUS-HOST INTERACTIONS – VIRAL DETERMINANTS FOR PATHOGENESIS AND THE INFLUENCE OF SEX ON THE SUSCEPTIBILITY TO FRIEND MURINE LEUKAEMIA VIRUS INFECTION
226. Torstein Hole: DOPPLER ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION
227. Vibeke Nossum: THE EFFECT OF VASCULAR BUBBLES ON ENDOTHELIAL FUNCTION
228. Sigurd Fasting: ROUTINE BASED RECORDING OF ADVERSE EVENTS DURING ANAESTHESIA – APPLICATION IN QUALITY IMPROVEMENT AND SAFETY
229. Solfrid Romundstad: EPIDEMIOLOGICAL STUDIES OF MICROALBUMINURIA. THE NORD-TRØNDELAG HEALTH STUDY 1995-97 (HUNT 2)
230. Geir Torheim: PROCESSING OF DYNAMIC DATA SETS IN MAGNETIC RESONANCE IMAGING
231. Catrine Ahlén: SKIN INFECTIONS IN OCCUPATIONAL SATURATION DIVERS IN THE NORTH SEA AND THE IMPACT OF THE ENVIRONMENT
232. Arnulf Langhammer: RESPIRATORY SYMPTOMS, LUNG FUNCTION AND BONE MINERAL DENSITY IN A COMPREHENSIVE POPULATION SURVEY. THE NORD-TRØNDELAG HEALTH STUDY 1995-97. THE BRONCHIAL OBSTRUCTION IN NORD-TRØNDELAG STUDY
233. Einar Kjelsås: EATING DISORDERS AND PHYSICAL ACTIVITY IN NON-CLINICAL SAMPLES
234. Arne Wibe: RECTAL CANCER TREATMENT IN NORWAY – STANDARDISATION OF SURGERY AND QUALITY ASSURANCE

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235. Eivind Witsø: BONE GRAFT AS AN ANTIBIOTIC CARRIER
236. Anne Mari Sund: DEVELOPMENT OF DEPRESSIVE SYMPTOMS IN EARLY ADOLESCENCE
237. Hallvard Lærum: EVALUATION OF ELECTRONIC MEDICAL RECORDS – A CLINICAL TASK PERSPECTIVE
238. Gustav Mikkelsen: ACCESSIBILITY OF INFORMATION IN ELECTRONIC PATIENT RECORDS; AN EVALUATION OF THE ROLE OF DATA QUALITY
239. Steinar Krokstad: SOCIOECONOMIC INEQUALITIES IN HEALTH AND DISABILITY. SOCIAL EPIDEMIOLOGY IN THE NORD-TRØNDELAG HEALTH STUDY (HUNT), NORWAY
240. Arne Kristian Myhre: NORMAL VARIATION IN ANOGENITAL ANATOMY AND MICROBIOLOGY IN NON-ABUSED PRESCHOOL CHILDREN
241. Ingunn Dybedal: NEGATIVE REGULATORS OF HEMATOPOIETEC STEM AND PROGENITOR CELLS
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