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Arkink, E.B.

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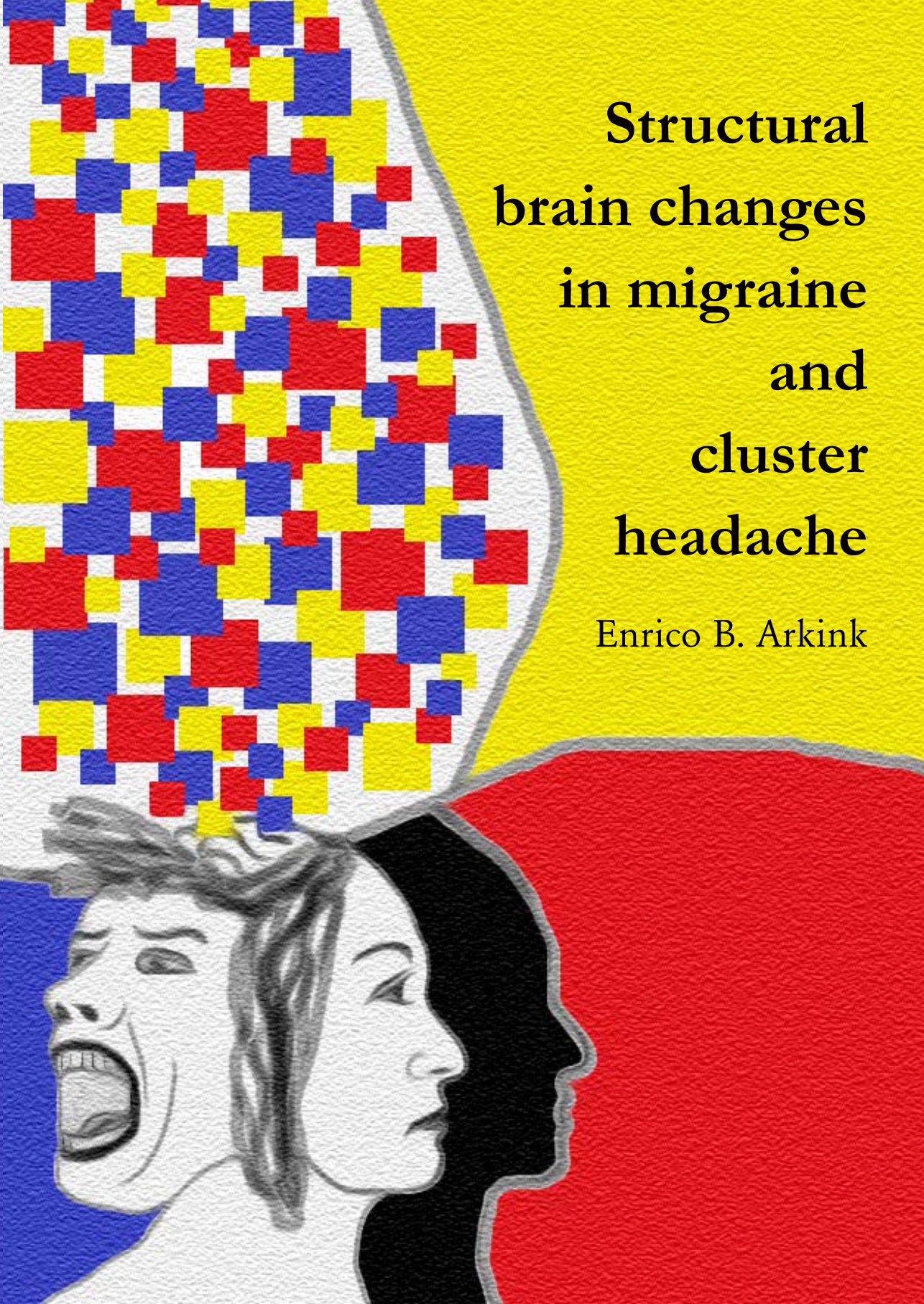

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Enrico B. Arkink

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Promotores:
Prof. dr. M.A. van Buchem
Prof. dr. M.D. Ferrari

Copromotor:
Dr. M.C. Kruit

Leden promotiecommissie:
Prof. dr. G.M. Terwindt
Prof. dr. G.J. Blauw
Dr. I. Ronen
Prof. dr. B.K. Velthuis (Universitair Medisch Centrum Utrecht)
Prof. dr. M.W. Vernooij (Erasmus Medisch Centrum, Rotterdam)

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General introduction and outline

Headache is a very frequent symptom in everyday life, with active headache disorders occurring in approximately 46% of the adult population.[1] Primary headache syndromes compromise up to 98% of all headaches.[2] The most well-known of primary headache syndromes are tension-type headache, migraine and cluster headache. In spite of the high total prevalence of primary headache syndromes, and despite their high impact on quality of life and activities of daily living, for a long time there has been little public recognition of their impairing character. [3] Migraine was listed only as the 19th global cause of disability by the World Health Organization (WHO) in the *Global Burden of Disease Survey 2000*.[4] This has proven to be an underestimation; in the *Global Burden of Disease Survey 2010*, migraine ranked 8th,[5] while in the same survey in 2013 it rose to 6th position[6] and in the 2017 survey, migraine was even considered the 2nd cause of disability worldwide after low back pain.[7] This is mainly due the fact that migraine affects quality of life during peak years of productivity. Migraine alone is responsible for about 2.9% of the total of number of years that are lived with any disability.[5]

Even though headache disorders nowadays receive increasing attention from medical professionals, patients remain underdiagnosed and undertreated.[3] Different from most other neurological disorders, headache affects those in their workable years of live. Consequently, the financial cost to society due to lower productivity and untailored health-care utilization are enormous in comparison to the expenses necessary for adequate headache treatment.[3] In a 2008 report by the Dutch Central Bank, direct costs associated with migraine (medications, medical assistance seeking) have been estimated above € 250 million per annum for The Netherlands alone. Indirect costs to Dutch society, including lost productivity, are estimated to be over € 1.5 billion annually.[8] With a one-year prevalence of migraine of over 16% in a population (2010) of about 10.2 million people, residing in The Netherlands aged 20-65 years,[9;10] associated costs per Dutch migraine patient may add up to approximate € 1060 per annum.

Primary headache symptomatology

Two types of primary headache have been subject of research for this thesis, namely migraine and cluster headache. After tension-type headache, migraine is the second most prevalent primary headache syndrome, with a lifetime prevalence of 33% in females and 13% in males.[9] It is a mul-

tifactorial neurovascular disorder characterised by recurrent attacks of moderate to severe, often unilateral pulsating headache lasting 4 to 72 hours, accompanied by nausea, vomiting, photophobia and phonophobia. A combination of these symptoms is required to make a definite diagnosis.[11] In up to a third, transient focal neurological phenomena precede or accompany the headache phase in all or part of the migraine attacks. These aura symptoms almost always include visual disturbances (>90%).[11] Less frequent aura symptoms are sensory phenomena and speech disturbances (mainly aphasia).[11] Different transient aura symptoms often follow each other in succession, with each symptom progressing over minutes and possibly lasting up to 60 minutes. Patients with migraine with aura should have had at least two attacks with aura during their lifetime. For the more frequent migraine without aura, five attacks are required.

Compared to migraine, cluster headache is a rather rare headache syndrome with a one-year prevalence of 0.6-3.8‰.[12] Together with the even less frequent paroxysmal hemicrania and short lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), it is considered a trigeminal autonomic cephalalgia. Cluster headache attacks are typically characterized by frequent, highly disabling attacks of severe unilateral headache accompanied by ipsilateral features of facial autonomic dysfunction. In typical cases, attacks may last 15-180 minutes and may occur up to 8 times per day. About 85% of patients have an *episodic* form in which attacks come in periods of several weeks to months alternating with periods of several months to years with complete freedom of attacks. In the remaining 15% with a *chronic* form of cluster headache, attacks continue to reoccur over very long periods, usually many years, without attack-free periods. Despite its low prevalence, the severity and rhythmicity of cluster headache strongly influence the patient's life and surroundings.

Associations with vascular disease and role of structural neuroimaging in primary headache disorders

In the past decades, extensive research has been conducted on patients with primary headache syndromes. Fundamental research, electrophysiological experiments and functional and structural neuroimaging studies have been performed to broaden our understanding of their underlying

pathogenesis. Despite all the information revealed by these studies, the exact mechanisms responsible for these episodic headache disorders are still unclear.

Whereas migraine has been considered for quite some time a bothersome, but harmless disorder without long-term consequences for the brain, numerous studies have linked migraine to cerebrovascular and other cardiovascular disease. First of all, migraine has been described as the cause of ischemic stroke in a number of case reports. According to the International Classification of Headache Disorders (ICHD) of the International Headache Society, a diagnosis of migrainous cerebral infarction can be established in known migraineurs with aura when one or more aura symptoms in an attack typical of previous attacks persist for >60 minutes and neuroimaging reveals characteristics in a relevant area compatible with ischemic stroke, and when other causes of stroke have been ruled out.[11] True migrainous infarcts however are very rare and likely to be overdiagnosed.[13]

A second association between migraine and cerebrovascular disease can be found in conditions in which migraine is a symptom of the underlying vascular disease. In several genetic and acquired vasculopathies including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL), retinal vasculopathy with cerebral leukodystrophy and systemic manifestations (RVCL-S) and Sneddon's syndrome, migraine is a prominent part of the phenotype.[14;15] Different types of cerebrovascular damage can be found in sufferers of these syndromes. These vasculopathies may share pathophysiologic mechanisms with migraine, and thereby suggest that cerebrovascular damage is vasculopathy-related in subgroups of migraine.

A third observation linking migraine to cerebrovascular disease is that migraineurs more often have an unfavourable cardiovascular risk profile, putting them at increased risk of vascular disease.[16-18] For instance, migraineurs might have higher cholesterol levels or raised systolic and diastolic blood pressure in comparison with non-migraineurs, or may suffer of diabetes more often.[17;18] However, apart from an increased prevalence of vascular risk factors, migraine itself, specifically migraine with aura, has consistently been designated as an independent risk factor for

ischemic and haemorrhagic stroke.[19-22] Migraine is also increasing the risk of claudication, ischemic coronary heart disease and cardiovascular death[18;23-26] and raises the chances of undergoing coronary revascularization procedures.[26] The underlying mechanisms responsible for increasing the risk of these cerebro- and cardiovascular events need to be elucidated. Apart from already mentioned more adverse risk profile in migraineurs, other pathophysiological mechanisms responsible for this susceptibility, may include impaired cerebrovascular reactivity, compromised arterial compliance, endothelial dysfunction, and hypercoagulability.[27] Other than an increased risk of clinical stroke, migraine is also associated with a higher prevalence of different types of subclinical brain lesions. In two population-based magnetic resonance imaging (MRI) studies, patients with migraine with aura were shown to be at increased risk of subclinical infarcts in the posterior circulation territory.[28;29] Other subgroups of migraineurs were found to be at independently increased risk of supratentorial white matter hyperintensities (WMHs)[28;30] and infratentorial hyperintensities.[31]

Besides these detectable changes on conventional MRI images, numerous studies applying sophisticated MRI post-processing techniques such as morphometric analyses measuring global or regional brain volumes, diffusion-weighted imaging evaluating the diffusivity of water molecules within cerebral tissue and magnetisation transfer imaging assessing microstructural brain tissue integrity have detected widespread changes within the structure of the brain of migraineurs.[32-35] These changes, mainly found in areas involved in nociceptive and somatosensory processing, may be the consequence of repetitive migraine attacks[32] and could provide a disease biomarker, potentially aiding in recognizing those patients with complicated migraine subtypes that most likely respond to customised treatment or in providing the migraineurs an appropriate prognosis.[34;35]

Nevertheless, many of these structural changes, especially those in pain processing areas, might not be specific to migraine. In similar studies performed in cluster headache patients, grey matter volume changes were found in similar areas involved in nociception and behavioural and emotional responses to pain.[36-39] However, brain structure in cluster headache has scarcely been studied so far.

Scope and outline of the thesis

The primary goal of this thesis is to identify structural changes in the brain and surrounding structures in migraine and cluster headache, to provide new insights into primary headache, in their symptomatology and possible consequences.

In **Chapter 2**, we present a previously unreported early 18th-century description of cluster headache, which illustrates the impact of this headache disorder on a patient's life centuries ago, and stresses the necessity for unravelling the pathophysiology of cluster headache. **Chapter 3** focuses on structural brain changes in cluster headache patients. The primary objectives of this study include to assess whether structural changes were present in the hypothalamus, or in other brain areas in patients with typical episodic and chronic cluster headache, and whether these changes are specific to typical cluster headache, or whether they can also be found in other episodic headache syndromes such as probable cluster headache, chronic paroxysmal hemicrania and migraine. In **Chapter 4**, we assess the structure and dimensions of the cavernous sinus in typical cluster headache patients, to test the hypothesis that a constitutionally or acquired narrowed cavernous sinus might predispose individuals to cluster headache.

Chapter 5 describes the results of a voxel-based morphometry study in the population-based Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study. For this study, we compare brain structure of migraineurs from the general population voxel-wise with controls. In **Chapter 6**, we use magnetization transfer ratio to the microstructural brain tissue integrity in migraineurs from the CAMERA study to see whether brain structure is altered beyond visible subclinical white matter hyperintensities and infratentorial infarcts as seen on MRI. We also investigate whether microstructural brain tissue is altered before white matter hyperintensities become detectable on conventional MRIs.

For **Chapter 7**, we study MRIs of participants to the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) to evaluate whether cerebral microbleeds are more prevalent in elderly migraineurs, compared to elderly controls. **Chapter 8** describes the prevalence of infratentorial

hyperintensities in this same population, as well their relationship with migraine and other cardiovascular risk factors. We also assess their prognostic value regarding overall mortality. In **Chapter 9** we investigate whether carotid artery endothelial stress might contribute to the occurrence of white matter lesions in migraine patients from the PROSPER study.

Chapter 10 provides a summary of the results of this thesis, with a general discussion and suggestions for future research neuroimaging possibilities in primary headache disorders.

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2

An early 18th century case description of cluster headache

E.B. Arkink

M.A. van Buchem

J. Haan

M.D. Ferrari

M.C. Kruit

Cephalalgia 2010; 30:1392-1395

Abstract

We present a previously unreported early 18th-century description of cluster headache by the English antiquary Abraham de la Pryme (1671–1704) initially attributed to hydrophobia (rabies).We will also give a short overview of other descriptions of cluster and cluster-like headache in historical literature.

Case description

In 1702, Abraham de la Pryme published on "A Remarkable Case of the Hydrophobia" in the Royal Society's *Philosophical Transactions*.[1] The report is about his brother's dog and her whelps which had all succumbed to rabies in 1695. One of his brother's servants, an apprentice of about 14 years of age, was seized with headache shortly after caring for the dogs, together with other servants. He developed a fever and characteristic features of rabies, including and behavioural alterations before ultimately passing away. De la Pryme also mentions another servant who was afflicted by headache shortly after the death of the whelps:

> "They being thus dead, were soon forgot, until that about 3 Weeks after, my Brother's Servant, a most strong laborious Man, that had frequently put his Fingers into the Whelp's Mouth, began to be troubled now and then with an exceeding acute Pain in the Head, sometimes once, sometimes twice a Day, so very vehement that he was forc'd to hold his Head with both his Hands, to hinder it from riving in two, which Fits commonly held him about an Hour at a time; in which his Throat would contract, as he said, and his Pulse tremble, and his Eyes behold every thing of a fiery red Colour. Thus was he tormented for a whole Week together, but being of a strong Constitution, and returning to his Labour in every Interval, he sweat and wrought it off, without any Physic."

Abraham de la Pryme, an English antiquary born January 15, 1671 in Hatfield, South Yorkshire, and of Flemish and French Huguenot ancestry, kept a diary from the age of 12 until his death in 1704, *Ephemeris vitae, or a diary of my own life, containing an account likewise, of the most observa-*

ble and remarkable things that I have taken notice of from my youth up hitherto. He studied at St. John's College in Cambridge from 1690 and in addition to the usual classical and philosophical studies, he concentrated on natural history, chemistry and magic until he received his degree of Bachelor of Arts in 1694.[2] At Cambridge, he was a contemporary of Sir Isaac Newton, whom he described as "a very learned man" and as "an excellent mathematician, philosopher, divine, etc." He was the author of the first history of the city of Hull and several scientific papers of his were published in the Royal Society's *Philosophical Transactions*. This ultimately led to his election as fellow of the Royal Society. His diary was published in 1870.[3]

De la Pryme ascribed the servants' disease symptoms to rabies because of the close relationship they had had to the dogs. Moreover, as de la Pryme wrote about his experiences only seven years later, recall bias may have contributed as well. Rabies can indeed cause a wide range of neurological symptoms, including quite frequently headache. Rabies-associated headache tends to be more of a continuous character and often precedes the acute neurological syndrome.[4] De la Pryme notes that the first time the second-mentioned servant had his headache attacks was about three weeks after the death of the whelps. The incubation period of rabies most commonly is between 20 and 60 days with a range from 10 days to a year.[4] He did not mention other specific symptoms than recurrent headache attacks. Intermittent "contraction of the throat" during the headache attacks is unlikely to be due to hydrophobia. De la Pryme stressed that the servant was cured spontaneously without receiving any medication. This makes it most unlikely that the man had suffered from rabies and that the headache attacks had been a consequence of this disease. Even to date, rabies remains a fatal disease in many once clinical symptoms have become manifest or is associated with long-lasting neurological features.[5-7] The chances of a man surviving rabies in the late 17th century, without any lingering symptoms, are therefore negligible.

De la Pryme's attribution of the headache to rabies can still be considered as progressive, however. In the 17th century, superstition was still manifest in a large part of the population, with de la Pryme being a prime example, especially at younger age. It is therefore remarkable that he thought that an infectious disease caused the "devilish headache" he had observed.

The pattern of the headache attacks, once or twice a day and their duration of an hour without lasting symptoms are suggestive of cluster headache. Although a cluster period of one week is relatively short, episodic cluster headache bouts can, at the lower end of the scale, last for periods as short as a week;[8] even minibouts (bouts shorter than of one week) have been described.[9]
Unfortunately, de la Pryme, who had hardly any medical training, did not mention the localization of the headaches, and used non-medical prosaic and metaphoric descriptions. "The riving in two" might be interpreted as hemicrania, although it could also indicate the severity of the pain. The passage "his Eyes behold every thing of a fiery red Colour" most likely points to de la Pryme's observation of reddening of the eyes (a probable accompanying cranial autonomic symptom), but theoretically could also describe the very rare symptom of erythropsia (abnormality of vision in which all objects appear in a red tint). Clear (other) secondary symptoms, such as lacrimation, ptosis, miosis and rhinorrhea, remain unnoticed, unreported or absent. Despite the lack of a clear description of secondary symptoms, we believe De la Pryme witnessed a one-week long episode of cluster headache and that this is the oldest description of cluster headache in English literature.

Discussion

Cluster headache and paroxysmal hemicrania were conceptualized in the 20th century as separate entities. Bing, Harris and Horton[10-14] contributed to the concept of cluster headache in the first half of that century, while the term *paroxysmal hemicrania* was introduced by Sjaastad and Dale only a few decades ago.[15;16] Together with the very infrequent short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT), these three headache types are often collectively referred to as trigeminal autonomic cephalalgias.
Historical reports of possible trigeminal autonomic cephalalgias are, probably due to the rarity of these disorders, scarce. Descriptions suggestive of cluster headache date back to the 17th century, when the Dutch physician Nicolaes Tulp (the main physician seen in Rembrandt's paint "The Anatomy Lesson") published his *Observationes medicae* in 1641. He described the headache history of an Amsterdam merchant of Flemish origin, Isaack van Halmale (1577/1578–1641), who, in the beginning of the summer, "was afflicted with a very severe headache, occurring and disappear-

ing daily on fixed hours", with headache attacks rarely lasting longer than two hours. Although the details are insufficient to meet today's criteria for episodic cluster headache of the International Headache Society (IHS),[17] cluster headache is a highly probable diagnosis.[18]

The only other known 17th century description of a possible trigeminal autonomic cephalalgia was published by the English doctor and founding member of the Royal Society Thomas Willis. He was one of the first to distinguish continuous from intermittent headaches and described in his *De anima brutorum* (1672) "a venerable matron" who was afflicted with severe recurrent daily headaches, occurring every afternoon around 4 o'clock, for about five weeks.[19]

Whereas Tulp's observation is currently regarded as the earliest case of cluster headache, the first description of a patient meeting today's IHS criteria for episodic cluster headache is by the Dutch physician Gerard van Swieten, court physician of Mary Therese of Austria.[20] He discussed in his *Commentaria in Hermanni Boerhaave aphorismos de cognoscendis et curandis morbis* (1745) the medical cases of his teacher, the famous professor Herman Boerhaave at Leiden University. He described a middle aged man, who suffered from a peculiar left-sided headache that occurred every day at the same hour. This headache lasted a few hours and was accompanied by reddening and tearing of the left eye.

Besides these three cases, a dozen of general descriptions and case histories in both medical and non-medical literature, like diaries, have been reported in the past decades that are suggestive of periodical, hemicranial headaches that could be diagnosed as cluster headache or paroxysmal hemicrania. A 35-year old German female patient in Johann Christoph Ulrich Oppermann's *Dissertatio medica inauguralis de hemicrania horologica* (1747) suffered from excruciating daily headache attacks that lasted fifteen minutes. This case of clockwise headache ("hemicrania horologica") is currently regarded as the earliest account of (chronic) paroxysmal hemicrania by some,[21] but not by all.[22;23] Additional possible pre-20th-century cases and descriptions of cyclical headaches suggestive of cluster headache were published, among others, by the Italian professor Giovanni Battista Morgagni (1761),[24] the English physicians Robert Whytt (1764) and Marshall Hall (1836),[24] the German neurologists Moritz Heinrich Romberg (1840),[25] and Albert Eulen-

berg (1871),[26] and self-reported by the German physician Johann Valentin Müller (1813)[27] and the English vicar Robert Francis Kilvert (1840-1879).[28]

Tulp and Van Swieten both originally published their case histories in Latin, the language which was most common in medical literature until the 19th century; Tulp translated his *Observationes medicae* into Dutch as soon he discovered it had been translated inadequately by others. Willis, the first Englishman publishing about periodical headaches, wrote in Latin as well. In English medical literature, the oldest description of a hemicranial headache suggestive of cluster headache so far was published by the Edinburgh professor Robert Whytt, who, like Van Swieten, was a pupil of Boerhaave's. He wrote about periodical headaches in his manuscript *On the nature, causes, and cure of those disorders which are commonly called nervous, hypochondriac or hysteric* published in 1764.[24]

It probably is a matter of time until other cases of cluster headache, perhaps even older than those described by Tulp, Willis and de la Pryme, will be found in historical medical or non-medical literature. The overwhelming nature of disorders now known as trigeminal autonomic cephalalgias may have inspired more historical authors to describe headache patients suffering from these disorders. New innovations like Google Book Search, a service of Google that allows searching the full text of old digitized books, may help us in this search. It has already been suggested that, as the use of Latin in medicine became obsolete after the 1820s, the limited knowledge of classic Latin and Greek languages possessed by today's doctors hinders a systematic search of old medical texts, which is needed for recovering historical descriptions of headache syndromes.[20] However, the case by de la Pryme underlines, that not only the medical observations of historical physicians should be critically reviewed for descriptions of headache, but that other texts and diaries, even in currently used languages, might still provide us with information on the existence and nature of trigeminal autonomic cephalalgias in earlier centuries.

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3

The anterior hypothalamus in cluster headache

E.B. Arkink

N. Schmitz

G.G. Schoonman

J.A. van Vliet

J. Haan

M.A. van Buchem

M.D. Ferrari

M.C. Kruit

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Abstract

Objective:

To evaluate the presence, localization, and specificity of structural hypothalamic and whole brain changes in cluster headache and chronic paroxysmal hemicrania (CPH).

Methods:

We compared T1-weighted magnetic resonance images of subjects with cluster headache (episodic n=24; chronic n=23; probable n=14), CPH (n=9), migraine (with aura n=14; without aura n=19), and no headache (n=48). We applied whole brain voxel-based morphometry (VBM) using two complementary methods to analyze structural changes in the hypothalamus: region-of-interest analyses in whole brain VBM, and manual segmentation of the hypothalamus to calculate volumes. We used both conservative VBM thresholds, correcting for multiple comparisons, and less conservative thresholds for exploratory purposes.

Results:

Using region-of-interest VBM analyses mirrored to the headache side we found enlargement ($p<0.05$, small volume correction) in the anterior hypothalamic gray matter in subjects with chronic cluster headache compared to controls, and in all participants with episodic or chronic cluster headache taken together compared to migraineurs. After manual segmentation, hypothalamic volume (mean±SD) was larger ($p<0.05$) both in subjects with episodic (1.89±0.18 ml) and chronic (1.87±0.21 ml) cluster headache compared to controls (1.72±0.15 ml) and migraineurs (1.68±0.19 ml). Similar but non-significant trends were observed for participants with probable cluster headache (1.82±0.19 ml; $p=0.07$) and CPH (1.79±0.20 ml; $p=0.15$). Increased hypothalamic volume was primarily explained by bilateral enlargement of the anterior hypothalamus. Exploratory whole brain VBM analyses showed widespread changes in pain-modulating areas in all subjects with headache.

Interpretation:

The anterior hypothalamus is enlarged in episodic and chronic cluster headache and possibly also in probable cluster headache or CPH, but not in migraine.

Introduction

Cluster headache is a relatively rare headache syndrome typically characterized by frequent, highly disabling attacks of 15-180 minutes of intense, unilateral headache accompanied by ipsilateral features of facial autonomic dysfunction.[1] In *episodic* cluster headache (≈85% of patients), attacks come in periods of several weeks to months, alternating with complete attack-free periods of several months to years. In *chronic* cluster headache, attacks continue to recur without intermittent attack-free periods for at least a year.[2] In *probable* cluster headache, attacks fulfill all but one of the diagnostic criteria for cluster headache, usually by lasting longer than 3 hours.[2;3] Chronic paroxysmal hemicrania (CPH) is very similar to cluster headache except for shorter attack duration (2-30 minutes), much higher attack frequency (up to 30 per day), and often excellent response to indomethacin. Both cluster headache and CPH belong to the trigeminal autonomic cephalalgias (TACs).[4]

The etiology of cluster headache is unknown. The circadian timing of the attacks, the circannual clustering of attacks typically during autumn and spring, and the hormonal changes during attacks all point at involvement of the hypothalamus,[5;6] in particular the suprachiasmatic nucleus, the endogenous biological clock.[5;7] Studies using functional magnetic resonance imaging (MRI) and positron emission tomography have suggested hypothalamic activation during attacks of cluster headache.[8-11] One highly cited MRI-study using voxel-based morphometry (VBM) found increased gray matter volume of the posterior inferior hypothalamus in cluster headache patients,[12] but this could not be confirmed in four other studies.[13-16] These latter studies, however, did find structural changes in brain areas which are structurally or functionally connected with the hypothalamus[17;18] and which are involved in emotional handling and nociception and other types of sensory processing.[13-16]

In the present study we wanted to assess (i) whether there are structural changes in the hypothalamus of subjects with typical episodic and chronic cluster headache; (ii) whether there are structural changes in other brain areas in these subjects; and (iii) whether these changes are specific to typical cluster headache or can also be found in other episodic headache disorders such as probable cluster headache, CPH, and migraine (which is not a TAC). To this end, we applied

state-of-the art whole brain VBM using two complementary methods to assess structural hypothalamic changes: region-of-interest analyses in whole brain VBM, and manual segmentation of the hypothalamus.

Methods

Study population

We included 112 subjects with either episodic (n=25), chronic (n=27) or probable (n=16) cluster headache, CPH (n=9), or migraine with (n=16) or without aura (n=19). Patients were diagnosed by two experienced headache experts (GGS, JAvV) according to the diagnostic criteria (2nd edition) of the International Headache Society.[1] All patients also fulfilled the 3rd edition of the diagnostic criteria (2). Subjects with episodic cluster headache were in remission for at least three months. Participants with probable cluster headache fulfilled all but one of the diagnostic criteria for typical cluster headache: in n=13, the attack duration was longer than 180 minutes, and in n=3, autonomic symptoms and a sense of restlessness or agitation were absent. For comparison, 50 otherwise healthy volunteers (recruited by advertisement) without a history of headache were included as control subjects. The local medical ethics committee approved the study and all subjects gave written informed consent.

Neuroimaging and image post processing

Structural 3D T1-weighted turbo field echo brain images (repetition /echo time of 7.4/3.4 ms; 160 axial 1.0 mm continuous slices) were acquired using a 1.5 Tesla MRI system (NT-ACS, Philips, Best, The Netherlands). All MRIs were checked for structural brain abnormalities (including confluent white matter hyperintensities; small, punctate white matter hyperintensities were not considered an exclusion criterion) or artifacts that could interfere with further automatic image post-processing.

Voxel-based morphometry

To localize regional volumetric gray and white matter differences between patient groups and controls, MR images were processed with voxel-based morphometry (VBM), applying dif-

feomorphic anatomical registration exponentiated lie algebra (DARTEL; using default parameters),[19] in SPM8 (Statistical Parametric Mapping, Wellcome-Department of Cognitive Neurology, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm) on a MATLAB platform (The MathWorks Inc., Natick, MA, USA; version 7.5). The VBM-DARTEL procedure involved (i) segmentation of MR images into gray matter, white matter, and cerebrospinal fluid, (ii) creation of a DARTEL template derived from nonlinear deformation fields for the aforementioned segmentation procedure, and (iii) registration of all individual deformations to this DARTEL template. This registration step included modulation, which preserved the absolute amount of local gray and white matter volumes in spatially normalized images by scaling by Jacobian determinants (i.e. a correction for the distance over which a voxel had to be stretched or compressed to fit into standard space). Finally, (iv) modulated normalized gray and white matter segments were smoothed with an isotropic 8 mm full width at half maximum Gaussian-kernel for statistical comparison.

Assessment of hypothalamic volumes

Using FSLView v3.0 (http://www.fmrib.ox.ac.uk/fsl/), hypothalami (including mammillary bodies) were segmented manually in the original MR images blinded for diagnosis, by one rater (E.B.A.), using a validated segmentation procedure with predefined borders described in detail elsewhere.[20] The anterior border of the hypothalamus is formed by the lamina terminalis. At this level, the upper and lower borders of the hypothalamus are demarcated by the anterior commissure and the optic chiasm. The medial border is demarcated by the third ventricle, and laterally the hypothalamus approximates the substantia innominata. Slightly more caudally, additional borders are formed by the fornix and the genu of the internal capsule. The infundibular stalk forms the inferior margin of the hypothalamus in this area. Further posteriorly, the upper border is formed by the posterior limb of the internal capsule and the telodiencephalic fissure. In mediolateral direction the hypothalamus lies between the third ventricle and the posterior limb of the internal capsule, approximating the globus pallidus. The posterior part of the hypothalamus, including the mammillary bodies, was segmented using the third ventricle, the telodiencephalic fissure, the mammillothalamic tract and the cerebral exterior as delineations. Hypothalamic volumes were calculated for comparison between groups. Applying intraclass correlation coefficient,

both intrarater (0.84, assessed by segmenting hypothalami in ten brains twice) and interrater reliability (0.82, assessed by segmenting ten hypothalami by a second rater) was good. To localize differences between controls and subjects with headache, segmented hypothalami were registered to the Montreal Neurological Institute (MNI) standard template provided in FSL using the 12-parameter linear registration algorithm of FLIRT.[21]

Statistical analyses

Voxel-based morphometry

A general linear model was used to compare gray and white matter segments voxelwise between the six groups of subjects with headache and controls, implementing age, sex and total parenchymal volume as covariates. Total parenchymal volume was chosen instead of total intracranial volume because of faulty segmentations of cerebrospinal fluid in some subjects. Total parenchymal and intracranial volume can be used interchangeably in VBM analyses because of their strong correlation.[22] As expected, hypothalamic volume was smaller with increasing age and larger with increasing total parenchymal volume (exploratory analysis at $p<0.001$, uncorrected for multiple comparisons, data not shown). Sex was included to adjust for sex-related differences, but regional grey matter volume in and surrounding the hypothalamus was not different between males and females (exploratory analysis at $p<0.001$, uncorrected for multiple comparisons). Although smoking may influence trigeminal pain processing on supraspinal and brainstem levels, it did not influence our statistical model substantially and was therefore not included. Possible interactions between the covariates did not affect the statistical model and were not included either. To exclude false positives in non-gray or non-white matter tissue, voxelwise comparisons were masked with explicit optimal threshold masks created using the SPM Masking Toolbox.[23] Statistical comparisons were thresholded at $p<0.05$, corrected for multiple comparisons (family-wise error, FWE), which is standard in neuroimaging data.[24] For additional exploratory whole-brain analyses, statistical parametric maps were subsequently thresholded at $p<0.001$, uncorrected for multiple comparisons, with a minimal cluster size of 100 voxels. The locations of significant voxels were identified using two detailed atlases in consensus.[25;26]

Based on our a priori hypothesis, we applied small volume corrections (pFWE-SVC<0.05, no cluster size threshold) applied in a region encompassing the complete hypothalamus with wide margins (x=[-12 12], y=[6 -18], z=[0, -20]) to compare headache patient groups to non-headache controls, and in addition, compare all subjects with typical cluster headache versus controls and versus all migraineurs. Some researchers believe that mirroring of hemispheres is essential for neuroimaging studies in TACs to preclude false negatives,[27] as cluster headache and CPH are lateralized disorders. The effect of mirroring in VBM-DARTEL analyses is unknown, however. When using the standard procedure, an asymmetrical study-specific DARTEL template is created upon the asymmetrical MNI template.[28] Therefore, mirroring hemispheres (even before creating the study-specific DARTEL template) may introduce non-existing structural differences in stereotactic space because of hemispheric asymmetry, causing false positives to occur. Therefore, we only report results from mirrored and unmirrored analyses for the ROI analyses of the hypothalamic region. For these lateralized analyses, MRIs of subjects with predominantly right-sided headaches during attacks were mirrored in the midline, as if all participants effectively had left-sided headache attacks.

Other statistical analyses

The Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA; version 16.0.2) was used for statistical analysis. To compare demographic, clinical and headache characteristics, one-way ANOVA (for continuous variables) and chi-squared tests (for categorical variables) were applied. For comparison of hypothalamic volumes, linear regression models were corrected for age, sex, and total intracranial volume (estimated with SIENAX[29] part of FSL[30]) with diagnoses included as an independent variable. Possible interactions between the covariates did not affect regression models and were not included. Additional analyses investigating the influence of perceived headache side, headache history and attack frequency were carried out. Standardized regression coefficients (β values) representing the relative contribution of headache diagnosis to the linear regression models and corresponding p-values were calculated.

Results

Study sample

Eleven subjects were excluded (n=7 with episodic [n=1], chronic [n=4] and probable [n=2] cluster headache; n=2 with migraine with aura and n=2 controls) because of incomplete MRI acquisition (n=3), MRI artifacts (n=4) or unexpected structural brain abnormalities (n=4; all outside of the hypothalamus region) as these might have affected further automatic image post-processing. Table 3.1 summarizes the demographic, clinical and specific headache characteristics of the included subjects in each diagnostic group (n=151). Sex was unevenly distributed, reflecting the normal sex distribution of the disorders. Current smoking was more prevalent in subjects with cluster headache or migraine with aura. Other demographic and clinical characteristics were similar across the diagnostic groups.

Hypothalamus

Voxel-based morphometry

In mirrored ROI analyses, locally increased gray matter volume in the anterior hypothalamus was observed when comparing participants with chronic cluster headache to controls (ipsilateral to headache side; T 3.80; Z 3.70; cluster of 34 voxels, pFWE-SVC=0.021) and when comparing all subjects with typical cluster headache to migraineurs (contralateral to headache side; T3.61; Z 3.52; cluster of 37 voxels, pFWE-SVC=0.036) (Figure 3.1), but not in other subanalyses. In unmirrored analyses, hypothalamic gray matter volume did not differ between non-headache controls and subjects with cluster headache or any of the other headache groups either.

Manual segmentation

Bilateral hypothalamic volumes were larger in subjects with cluster headache compared to controls (standardized β=0.253; p=0.003) and migraineurs (standardized β=0.272; p=0.009), both for episodic cluster headache (p=0.009 [standardized β=0.212] versus controls; p=0.015 [standardized β=0.228] versus migraineurs) and chronic cluster headache (p=0.021 [standardized β=0.184] versus controls; p=0.030 [standardized β=0.199] versus migraineurs).

Table 3.1 Subject characteristics (n=151)

		Trigeminal autonomic cephalalgias					Migraine			
	Controls n=48	Total CH n=47	eCH n=24	cCH n=23	pCH n=14	CPH n=9	Total n=33	MA n=14	MO n=19	p-value
Demographic										
Female	30 (63%)	8 (17%)	4 (17%)	4 (17%)	8 (57%)	6 (67%)	31 (94%)	13 (93%)	18 (95%)	0.000
Age	47 (12)	47 (9)	45 (9)	48 (9)	50 (10)	48 (9)	47 (8)	47 (9)	47 (8)	0.840
Headache characteristics										
Predominant headache side:										
Left	-	24 (51%)	11 (46%)	13 (57%)	7 (50%)	1 (11%)	6 (18%)	2 (14%)	4 (21%)	-
Right	-	23 (49%)	13 (54%)	10 (44%)	7 (50%)	8 (89%)	12 (36%)	4 (29%)	8 (42%)	-
Bilateral	-		-	-	-	-	15 (45%)	8 (57%)	7 (37%)	-
Number of attacks (/day for TACs, /month for migraine)	-	3.6 (2.9)	3.8 (3.5)	3.4 (1.8)	2.6 (1.9)	14.0 (6.6)	2.7 (1.7)	2.5 (1.2)	2.8 (1.9)	-
Headache history (in years)	-	15 (10)	16 (12)	14 (9)	19 (10)	15 (7)	28 (13)	28 (10)	29 (15)	-
Other clinical characteristics										
Systolic blood pressure (mmHg)	134 (18)	136 (13)	136 (13)	137 (13)	135 (15)	146 (17)	133 (21)	133 (17)	134 (17)	0.577
Diastolic blood pressure (mmHg)	88 (13)	87 (8)	88 (8)	87 (8)	86 (11)	89 (12)	86 (12)	85 (13)	87 (11)	0.942
Hypertension	6 (13%)	10 (21%)	5 (21%)	5 (22%)	5 (36%)	4 (44%)	6 (18%)	3 (21%)	3 (16%)	0.292
Current smoker	7 (15%)	35 (74%)	17 (71%)	18 (78%)	8 (57%)	1 (11%)	7 (21%)	6 (43%)	1 (5%)	0.000
Ever smoker	25 (52%)	43 (91%)	21 (88%)	22 (96%)	13 (93%)	5 (56%)	19 (58%)	11 (79%)	8 (42%)	0.000
Number of cigarettes (or equivalent) per day	14 (10)	20 (13)	14 (8)	26 (15)	18 (7)	3 (-)	12 (8)	13 (8)	3 (-)	0.021
Ever use of (medication) treatment										
Triptans	-	37 (79%)	17 (71%)	20 (87%)	13 (93%)	6 (67%)	30 (91%)	12 (86%)	18 (95%)	-
Ergotamine	-	11 (23%)	3 (13%)	8 (35%)	3 (21%)	2 (22%)	14 (42%)	6 (43%)	8 (42%)	-
Indomethacin	-	2 (4%)	0 (0%)	2 (9%)	0 (0%)	9 (100%)	2 (6%)	2 (14%)	0 (0%)	-
Lithium	-	10 (21%)	2 (8%)	8 (35%)	1 (7%)	1 (11%)	0 (0%)	0 (0%)	0 (0%)	-
Verapamil	-	32 (68%)	13 (54%)	19 (83%)	6 (43%)	5 (56%)	0 (0%)	0 (0%)	0 (0%)	-
Oxygen	-	16 (34%)	8 (33%)	8 (35%)	6 (43%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-

For continuous variables denotation is mean (SD); for categorical variables denotation is number (%); CH: cluster headache; eCH: episodic CH; cCH: chronic CH; pCH: probable CH; CPH: chronic paroxysmal hemicrania; MA: migraine with aura; MO: migraine without aura. P-values for one-way ANOVA in continuous variables, for chi-squared test in categorical variables between controls and headache subtypes.

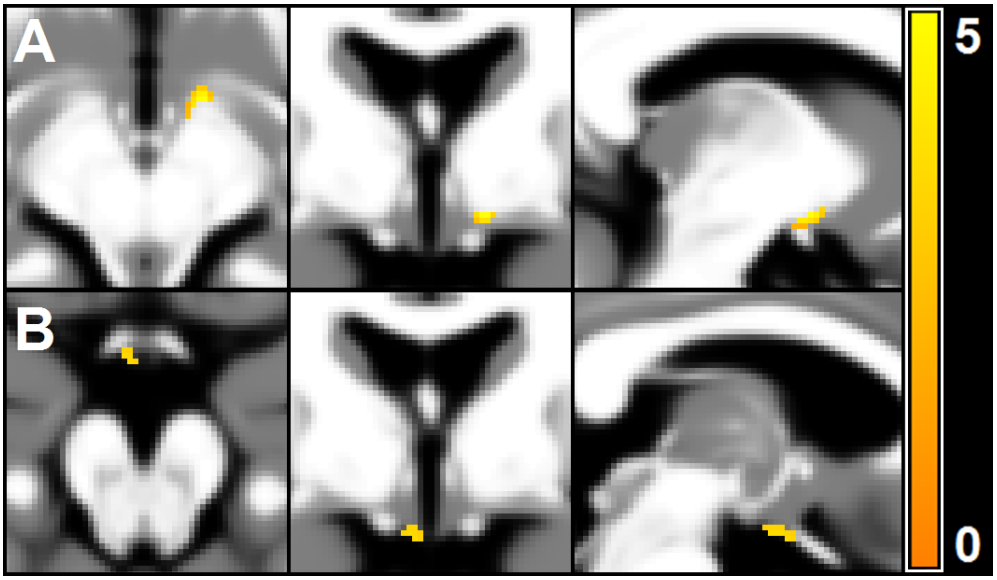

Figure 3.1 Results of region-of-interest voxel-based morphometry analyses. Axial, coronal and sagittal images (left to right) zoomed in on the area around the hypothalamus showing focal increases in anterior hypothalamic gray matter volume when comparing subjects with chronic cluster headache to controls (row A, ipsilateral to headache side, T 3.80, Z 3.70, cluster of 34 voxels, pFWE-SVC=0.021, x -10/y -3/z -8) and when comparing participants with cluster headache to migraineurs (row B, contralateral to headache side, T3.61, Z 3.52, cluster of 37 voxels, pFWE-SVC=0.036, x 3/y -3/z -15). Images displayed in radiological convention (left side of the image is right side of the brain).

Also when analysing only males with cluster headache (n=39) compared to male controls (n=18), hypothalamic volume was larger (standardized β=0.328, p=0.015 [episodic cluster headache: standardized β=0.319, p=0.026; chronic cluster headache: standardized β=0.280, p=0.046]). In the small group of females with cluster headache (n=8) compared to female controls (n=30), volumes were not significantly larger (standardized β=0.114, p=0.297). The volume differences did not lateralize after stratification by usual headache side (data not shown). Hypothalamic volumes were not significantly larger in the smaller subgroups of subjects with probable cluster headache (p=0.071 [standardized β=0.132] versus controls; p=0.065 [standardized β=0.144] versus migraineurs) and CPH (p=0.152 [standardized β=0.101] versus controls; p=0.131 [standardized β=0.111] versus migraineurs). Between groups with CPH or episodic, chronic and probable cluster headache there were no statistically significant differences in hypothalamic volume (p>0.584 for every comparison).

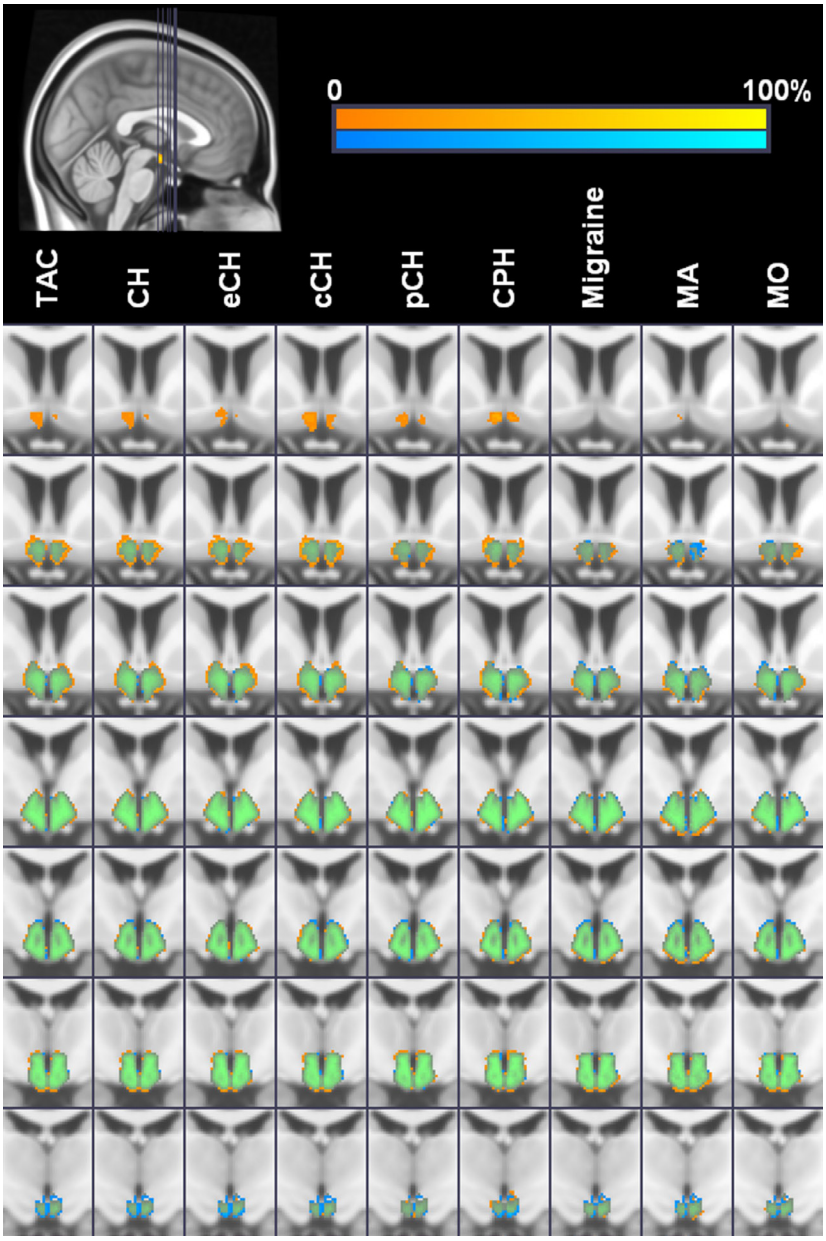

Figure 3.2 Results of manual segmentation. Mean hypothalami in subjects with headache (TAC: trigeminal autonomic cephalalgia; CH: cluster headache; eCH: episodic CH; cCH: chronic CH; pCH: probable CH; CPH: chronic paroxysmal hemicrania; MA: migraine with aura; MO: migraine without aura; in yellow/orange) and control subjects (in blue) projected on top of each other (overlap in green). Images displayed in radiological convention with from top-to-bottom coronal slices through the hypothalamus (from anterior to posterior) as displayed on sagittal slice.

Table 3.2 Mean volume in millilitres of manually segmented hypothalami

		Trigeminal autonomic cephalalgias						Migraine	
	Controls	Total	CH	eCH	cCH	pCH	CPH	Total	MA	MO
	n=48	n=70	n=47	n=24	n=23	n=14	n=9	n=33	n=14	n=19
Total	1.72 (0.15)	1.85 (0.20)[a,b]	1.88 (0.20)[a,b]	1.89 (0.18)[a,b]	1.87 (0.21)[a,b]	1.82 (0.19)	1.79 (0.20)	1.68 (0.19)	1.68 (0.18)	1.65 (0.19)
Left	0.88 (0.08)	0.95 (0.11)[a,b]	0.97 (0.11)[a,b]	0.97 (0.10)[a,b]	0.96 (0.11)[a]	0.95 (0.11)	0.93 (0.12)	0.87 (0.10)	0.87 (0.09)	0.86 (0.11)
Right	0.83 (0.07)	0.90 (0.10)[a,b]	0.90 (0.10)[a,b]	0.91 (0.09)[a,b]	0.91 (0.10)[a,b]	0.88 (0.09)	0.86 (0.08)	0.81 (0.09)	0.82 (0.09)	0.79 (0.08)

[a]p<0.05, compared to controls; [b]p<0.05, compared to migraineurs. CH: cluster headache; eCH: episodic CH; cCH: chronic CH; pCH: probable CH; CPH: chronic paroxysmal hemicrania; MA: migraine with aura; MO: migraine without aura.

When all participants with typical and probable cluster headache and CPH were considered one group of subjects with different forms of TACs (n=70), the hypothalamic volume was larger than in non-headache controls (standardized β=0.252; p=0.002) and migraineurs (standardized β=0.269; p=0.006). Hypothalamic volume was larger in male subjects with TACs (n=48), compared to controls (n=18; standardized β=0.289, p=0.014), and also in female subjects with TACs (n=22) compared to female controls (n=30; standardized β=0.212, p=0.064) and migraineurs (n=31; standardized β=0.289, p=0.026). Hypothalamic volume was not significantly related to disease duration (in years) (standardized β=0.153; p=0.181) or attack frequency (standardized β=0.219, p=0.228). After normalization by registration of the segmented hypothalamic volumes to standard space, qualitative analysis revealed that the volume differences between subjects with cluster headache, migraineurs and controls were present in the whole hypothalamus, but most prominent in the anterior part of the hypothalamus (Figure 3.2). No differences were found between migraineurs and controls (Table 3.2).

Whole brain voxel-based morphometry

In whole brain analyses, gray matter volume was decreased in subjects with migraine without aura in the right lingual gyrus (p=0.035, FWE-corrected). Other increases and decreases in gray and white matter that were found when applying less stringent thresholds (p<0.001, uncorrected for multiple comparisons, minimal cluster size 100 voxels) are presented in Table 3.3 and 3.4.

Table 3.3 Voxel-based morphometry: increases and decreases in gray matter volume in subjects with headache, compared to control subjects (p<0.001, uncorrected for multiple comparisons, cluster extend threshold 100 voxels)

	BA	L/R	DARTEL coordinates			k_E	Z-score
			x	y	z		
Gray matter increases							
Episodic cluster headache							
-	-	-	-	-	-	-	-
Chronic cluster headache							
Middle frontal gyrus	8	L	-42	15	43	285	3.69
Probable cluster headache							
Middle frontal gyrus	10	L	-26	54	-7	226	3.99
Chronic paroxysmal hemicrania							
Precuneus, parietal lobe	19	L	-3	-76	37	401	4.31
Parahippocampal gyrus	30	L	-12	-37	-10	427	4.08
Superior parietal lobule	7	R	12	-50	62	443	3.94
Cuneus, occipital lobe	17	L	-11	-83	7	215	3.43
Parahippocampal gyrus	28	L	-19	-17	-18	124	3.42
Migraine with aura							
Inferior occipital gyrus	18	R	32	-93	-4	174	3.70
Migraine without aura							
-	-	-	-	-	-	-	-
Gray matter decreases							
Episodic cluster headache							
Putamen	-	R	29	-13	-10	457	3.78
Middle temporal gyrus	37	R	55	-41	-8	265	3.71
Chronic cluster headache							
-	-	-	-	-	-	-	-
Probable cluster headache							
Amygdala	-	R	21	-9	-10	216	3.55
Superior frontal gyrus	8	R	6	25	50	304	3.42
Chronic paroxysmal hemicrania							
-	-	-	-	-	-	-	-
Migraine with aura							
Medial frontal gyrus	8	R	3	22	43	1205	4.42
Migraine without aura							
Lingual gyrus	18	R	19	-83	-3	520	4.61[a]
Postcentral gyrus	2	L	-35	-26	40	730	4.05
Postcentral gyrus	3	R	44	-20	53	641	3.95
Anterior cingulate cortex	32	R	7	23	-7	197	3.61
Angular gyrus	39	R	35	-66	27	207	3.30

BA: Brodmann area; L:left; R:right; k_E:cluster size. [a]p<0.05, family-wise error-corrected.

Discussion

By using two complementary MRI post-processing techniques, we found that the *anterior* part of the hypothalamus is bilaterally enlarged in typical episodic and chronic cluster headache, and possibly also probable cluster headache and CPH. In migraine, another episodic (but non-TAC)

Table 3.4 Voxel-based morphometry: increases and decreases in white matter volume in subjects with headache, compared to control subjects (p<0.001, uncorrected for multiple comparisons, cluster extend threshold 100 voxels)

	L/R	DARTEL coordinates			k_E	Z-score
		x	y	z		
White matter increases						
Episodic cluster headache						
Medial frontal WM	R	14	41	7	133	3.31
Chronic cluster headache						
-	-	-	-	-	-	-
Probable cluster headache						
Precuneal WM	R	8	-54	48	349	3.93
Anterior cingulate WM	R	9	32	2	319	3.34
Frontal WM	L	-24	47	3	144	3.24
Chronic paroxysmal hemicrania						
-	-	-	-	-	-	-
Migraine with aura						
-	-	-	-	-	-	-
Migraine without aura						
-	-	-	-	-	-	-
White matter decreases						
Episodic cluster headache						
-	-	-	-	-	-	-
Chronic cluster headache						
Parietal WM	R	22	-41	54	146	3.46
Probable cluster headache						
-	-	-	-	-	-	-
Chronic paroxysmal hemicrania						
Precentral gyral WM	R	48	-14	32	438	3.64
Cerebellar WM	R	13	-69	-34	160	3.34
Migraine with aura						
Cingulate WM	R	9	21	39	272	4.09
Migraine without aura						
Precentral gyral WM	R	34	-22	52	399	3.64

L: left; R:right; k_E: cluster size.

headache syndrome, we did not find changes in hypothalamic volume compared to controls. We were unable to identify structural changes in brain areas other than the hypothalamus that might distinguish between typical cluster headache and the other episodic headache syndromes. Implications, relevance and validity of these findings are discussed below.

Several nuclei in the anterior part of the hypothalamus might explain the larger hypothalamic

volumes in typical cluster headache. Functional disturbances of the suprachiasmatic nucleus, the endogenous biological clock, might cause the striking circadian and circannual rhythms of cluster headache attacks and periods.[31] Another anteriorly located hypothalamic nucleus, the paraventricular hypothalamic nucleus, has been suggested to modulate or trigger TACs by mediating the regulation of nociceptive and autonomic input.[32] Several processes affecting the local MRI T1-signal may explain the increase in gray matter volume. These include an increase in the number or size of neurons or glial cells, increases in synaptic plasticity, fluid shifts between intra- and extracellular space due to homeostatic imbalance, and presence of gliosis. High-field MRI, MR spectroscopy, and molecular imaging studies are probably better suited to differentiate between these possible causes.

We have been the first to use manual segmentation to study volume changes in the hypothalamus in typical cluster headache. This showed a major limitation of VBM; even with mirrored ROI-VBM-analyses we were almost unable to detect the bilateral enlargement of the (anterior) hypothalamus in participants with typical cluster headache revealed by manual segmentation. Perhaps these volume changes were too widespread or too small to be picked up by state-of-the art VBM. The region of the hypothalamus is characterized by large T1-signal intensity differences in a relatively small volume of brain tissue which makes this delicate area extra susceptible to effects of normalisation and smoothing procedures in VBM, leading to loss of information.

Our findings suggest the possibility of false negative findings of previous VBM studies in cluster headache negative for structural change in the hypothalamus (13-16).
In line with these 'negative' studies however, we could not reproduce the previously reported increased volume of the posterior inferior hypothalamus in cluster headache (12) with either one of the two complementary post-processing techniques. The sample size in our study was sufficiently large for obtaining stable results in neuroimaging studies (n=15-20)[33;34] and we, therefore, believe that the statistical power to reproduce earlier findings of increased posteroinferior hypothalamic volume should have been sufficient.[12] Moreover, we did find changes but in a different area of the hypothalamus. In general, differences in methodology may explain why VBM-studies in cluster headache found different (positive and negative) results, including accurate evaluation of MR and

post-processed images for structural abnormalities and artefacts,[12;14] the use of registration algorithms superior[19] to those used in earlier studies[12;14] and differences in smoothing, modulation, covariate implementation in statistical models and statistical thresholding.

We were not able to confirm previous findings of structural changes in the *posterior* hypothalamus with our complementary manual delineation of the hypothalamus either. We might accidentally not have included this area in our manual segmentation procedure, because the posterior border of the hypothalamus is much more difficult to delineate than the anterior part, even on high-resolution T1-weighted images. An alternative explanation for non-inclusion is that the area of structural hypothalamic changes as reported in cluster headache,[12] is located in the midbrain tegmentum rather than in the posterior hypothalamus.[35]

Our study has some limitations. First, to obtain patient and control groups that are truly matched is a major challenge in cluster headache research. Consequently, sex was unequally distributed between headache patient groups, which might suggest that this interfered with our main results, as previously larger regional hypothalamic volumes were found in men compared to women.[36]

However, we were unable to detect an effect of sex in the hypothalamus in our VBM analyses. Moreover, manually segmented hypothalamic volumes were also larger when comparing male subjects with cluster headache with male controls, which affirms that our results were not majorly affected by this unequal sex distribution. We cannot exclude that regional grey matter volume has been influenced by the use of prophylactic medical treatment, such as lithium,[37] or by history of smoking,[38] although we are unaware of any effect of these agents on regional hypothalamic volume.

Second, the patient groups with probable cluster headache and CPH were quite small, and the changes in hypothalamic volume failed to reach statistical significance in these subgroups, probably due to lack of power. Our current findings however do suggest that enlargement of the anterior hypothalamus is not specific to cluster headache, but might also apply to other TACs. This should be confirmed in future studies also including episodic paroxysmal hemicrania and

short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT).

In line with previous studies, we found plasticity changes in cortical gray matter and connecting white matter pathways which might be due to repetitive pain[27] or behavioural and emotional responses to pain.[39] These changes are not specific to TACs, as they are also found in migraine. To prevent obscuration by plasticity changes in a maladaptive pain modulatory network, future studies searching for structural brain changes that are specific for episodic headache syndromes might benefit from implementing only patients who recently developed headache symptoms. Drug naivety in these patients may be an additional advantage, as it is unknown in what way acute or prophylactic drug treatment in headache patients influences neuroplasticity.

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4

The cavernous sinus in cluster headache - a quantitative structural magnetic resonance imaging study

E.B. Arkink
G.G. Schoonman
J.A. van Vliet
H.S. Bakels
M.A.M. Sneeboer
J. Haan
M.A. van Buchem
M.D. Ferrari
M.C. Kruit

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Abstract

Background:

It has been hypothesized that a constitutionally narrow cavernous sinus might predispose to cluster headache. Cavernous sinus dimensions, however, have never been assessed.

Methods:

In this case-control study, we measured the dimensions of the cavernous sinus, skull base, internal carotid, and pituitary gland with high-resolution T2-weighted MRI in 25 episodic, 24 chronic and 13 probable cluster headache patients, 8 chronic paroxysmal hemicrania patients, and 22 headache-free controls. Dimensions were compared between groups, correcting for age, sex, and transcranial diameter.

Results:

On qualitative inspection, no relevant pathology or anatomic variants previously associated with cluster headache or chronic paroxysmal hemicranias were observed in the cavernous sinus or paracavernous structures. The left-to-right transcranial diameter at the temporal fossa level (mean ± SD) was larger in the headache groups (episodic cluster headache: 147.5 ± 7.3 mm, $p=0.044$; chronic cluster headache: 150.2 ± 7.3 mm, $p<0.001$; probable cluster headache: 146.0 ± 5.3 mm, $p=0.012$; and CPH: 145.2 ± 9.4 mm, $p=0.044$) compared with controls (140.2 ± 8.0 mm). After adjusting for transcranial diameter and correcting for multiple comparisons, there were no differences in the dimensions of the cavernous sinus and surrounding structures between headache patients and controls.

Conclusion:

Patients with cluster headache or chronic paroxysmal hemicrania had wider skulls than headache-free controls but the proportional dimensions of the cavernous sinus were similar.

Introduction

Trigeminal autonomic cephalalgias (TACs) such as cluster headache and paroxysmal hemicrania are characterized by recurrent, severe, short-lasting attacks of unilateral headache accompanied by ipsilateral facial autonomic symptoms.[1,2] Both forms of TACs may present either in an *episodic* form, characterized by periods of several weeks to months during which many attacks occur alternating with attack-free periods of several months to years, or a *chronic* form, in which attacks continue recurring without (long) attack free periods. In *probable* cluster headache, patients fulfil all but one of the diagnostic criteria for cluster headache.[2]

The cavernous sinus has been put forward as a possible key area in the pathophysiology of cluster headache.[3] Trigeminal nociceptor excitation might initiate cavernous sterile inflammation and trigeminal-parasympathetic cavernous internal carotid artery vasodilatation,[4] which could obliterate cavernous venous outflow. Such processes might compress the internal carotid sympathetic plexus, and thereby explain the unilateral headache, parasympathetic discharge, and sympathetic dysfunction during cluster headache attacks.[4;5]

It has been suggested that a narrow cavernous sinus, either constitutionally or acquired due to structural lesions, might predispose an individual to cluster headache.[6-8] Here we present the first study assessing the structure and dimensions of the cavernous sinus with high-resolution magnetic resonance imaging (MRI) in cluster headache and chronic paroxysmal hemicrania.

Materials and methods

Subjects

In total, 98 subjects with episodic (n=25), chronic (n=25) or probable (n=15) cluster headache, chronic paroxysmal hemicrania (n=8), or without a history of headache (n=25) took part in the study. Patients were diagnosed at the Department of Neurology by two experienced headache experts (GGS, JAvV) according to the International Classification of Headache Disorders, 2nd edition (ICHD-2).[9] All patients also fulfilled the criteria of the International Classification of

Headache Disorders, 3rd edition (beta version) (ICHD-3-beta).[2] Subjects with probable cluster headache fulfilled all but one of the ICHD-2 and ICHD-3-beta diagnostic criteria for cluster headache (attack duration >180 minutes, n=12, absence of autonomic symptoms, n=3).[2;9;10] The local medical ethics committee of Leiden University Medical Center approved the study and all subjects gave written informed consent.

MRI acquisition and analysis

Whole-brain 3D T1-weighted turbo field echo (repetition time (TR)/echo time (TE) of 7.4/3.4 ms; 160 axial 1.0-mm continuous slices; 260-mm field of view (FOV); acquisition matrix 256; flip angle 8°), combined proton density and T2-weighted fast spin echo (TR/TE of 3000/(27/120) ms; 48 axial 3-mm continuous slices; 220-mm FOV; acquisition matrix 256 x 220) and fluid-attenuated inversion recovery images (FLAIR, TR/TE 8000/100 ms; inversion time 2000 ms; 48 axial 3-mm continuous slices; 220-mm FOV; acquisition matrix 256 x 191) were acquired at a 1.5-Tesla Philips Medical System Scanner (NT-ACS, Philips, Best, The Netherlands) to exclude relevant gross pathology outside the cavernous sinus region. Further, high-resolution T2-weighted spin echo images of the sellar region (TR/TE 2000/120 ms; 80 axial 1.0-mm slices; 0.5-mm slice overlap; 200 mm FOV; acquisition matrix 256x256; 0.78x0.78-mm pixel resolution; flip angle 90˚) were obtained. For obtaining measurements, these images were reoriented with image contrast at comparable levels using multiplanar reformation (MPR) in Vitrea (Vital Images Inc., Plymouth, MN, USA). Correct orientation was defined as having the optic chiasm as a horizontal line and the pituitary gland with the caudal part of the infundibulum in the same coronal slide, with all structures positioned as symmetrically as possible.

An experienced neuroradiologist (MCK), who was blinded for headache diagnosis and clinical data, systematically read all of the available images of the brain and cavernous sinus on a radiological viewing station to identify structural abnormalities of anatomic structures in the brain, sella, cavernous sinus, or surrounding skull base.

For quantitative analyses, reoriented images were interpreted by two observers (HSB, MAMS, both blinded to all clinical data). The quantitative analysis consisted of 13 measurements in

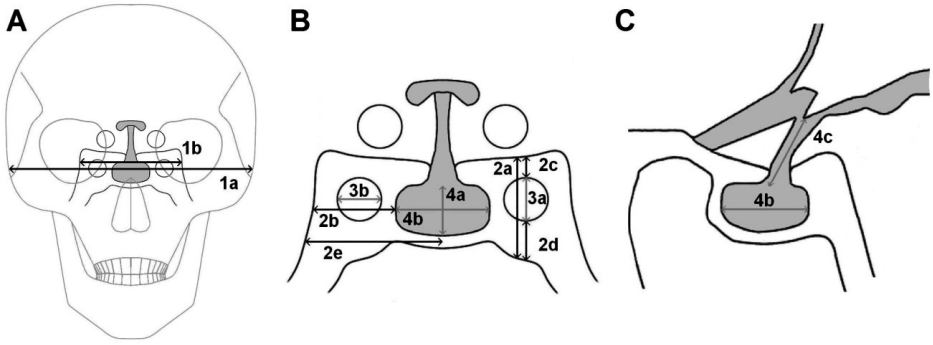
coronal and sagittal view (see Figure 4.1). As a reference, the transcranial (left-to-right) diameter was measured in coronal plane at temporal fossa level (at the level of the carotid arteries) (1a). Another skull base measure entailed the diameter of the sellar compartment (1b). In the cavernous sinus cranial-caudal (2a), medial-lateral (2b), supracarotid (2c), subcarotid (2d) and midline-inferolateral (2e) diameters were measured. Further measurements included left-to-right (3a) and cranial-caudal (3b) internal carotid artery (ICA) diameters, cranial-caudal (4a) left-to-right (4b),

and anterior-posterior (4c) diameters of the pituitary and the length of infundibulum (4d). Cavernous sinus and ICA diameters were measured bilaterally. Pituitary volume was estimated after left-to-right, anterior-posterior and cranial-caudal pituitary diameters, applying Cavalieri's principle in the following equation:[11]

$$\text{pituitary volume} = \left({}^{4}/_{3} \text{ x } \left[\frac{\text{left}\rightarrow\text{right}}{2}\right] \text{x } \left[\frac{\text{anterior}\rightarrow\text{posterior}}{2}\right] \text{x } \left[\frac{\text{cranial}\rightarrow\text{caudal}}{2}\right]\right) \qquad (10.1)$$

We mirrored all left and right measurements of patients with predominant left-sided headache as if they had right-sided headache. For main analyses, cavernous sinus dimensions ipsilateral to the headache in TAC patients were compared with the mean of left and right cavernous sinus dimensions in controls. As approximately 14% of subjects with cluster headache experience side shifts

Figure 4.1 Measured dimensions of the skull (**A**) and of cavernous sinus and surrounding structures in coronal (**B**) and sagittal (**C**) view. Digit-letter combinations correspond with those used in Table 2 and 3 and are fully explained in the "materials and methods"- section.



or contralateral attacks,[12;13] we performed sub-analyses for those subjects who only had experienced strictly unilateral headache during their disease history. As sex is a main predictor for transcranial diameter (with males having larger skull sizes compared with females), and sex was unequally distributed among subject groups, we also performed sex-stratified sub-analyses.

Statistical analyses

Statistical Package for Social Science (version 16.0; SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. In order to assess inter- and intra-rater reproducibility, each measurement was obtained by both raters or twice by the same rater in 20 subjects and intra-class correlation coefficients (ICCs) were calculated. All ICCs lay in the range of 0.57-0.97 (see Supplementary Table 4.1 for exact ICCs), indicating fair to excellent reproducibility for all measurements.[14] Multiple linear regression models controlling for sex, age and skull diameter (as a correction for head size) were applied for all measurements to compare headache patients with controls. The association between headache diagnosis and transcranial diameter at temporal fossa level was determined by a linear regression model controlling for sex and age. P-values <0.05 were considered significant. Despite the explorative nature of this study, in addition, we corrected p-values for multiple comparisons using Benjamini and Hochberg false-discovery rate (FDR) correction.[15]

Results

Of the 98 study subjects, four were excluded because of insufficient MRI quality (probable cluster headache n=1; controls n=3). Two subjects were left out of the analysis because of comorbid multiple sclerosis (chronic cluster headache n=1; probable cluster headache n=1). The demographic characteristics of the remaining 92 subjects are depicted in Table 4.1 and the observed incidental and pathologic structural abnormalities on MRI in Table 4.2. None of the subjects had clinically relevant structural abnormalities in the region of the cavernous sinus, skull base, or surrounding anatomical structures.

Table 4.1 Demographic characteristics of subjects included in analyses

		Cluster headache				
	Controls n=22	Total n=49	Episodic n=25	Chronic n=24	Probable CH n=13	CPH n=8
Demographic characteristics						
Female sex	12 (55%)	9 (18%)	4 (16%)	5 (21%)	8 (62%)	5 (65%)
Age (years)	43±13	47±9	45±9	49±9	51±9	48±10
Currently smoking	4 (18%)	37 (76%)	18 (72%)	19 (79%)	7 (54%)	1 (13%)
Headache characteristics						
Predominant headache:						
Left side	-	24 (49%)	11 (44%)	13 (54%)	7 (54%)	0 (0%)
Right side	-	25 (51%)	14 (56%)	11 (46%)	6 (46%)	8 (100%)
No. of attacks per day	-	3.6±2.8	3.8±3.4	3.2±1.9	2.4±1.8	12.7±5.9
Headache history (years)	-	15±10	16±12	14±9	19±10	15±8
Criterion missing for IHS diagnosis of cluster headache						
Attack length > 180 minutes	-	-	-	-	10 (77%)	-
No autonomic symptoms	-	-	-	-	3 (23%)	-

Mean ± SD for continuous, number (%) for categorical variables. CH: cluster headache; CPH: chronic paroxysmal hemicrania

Table 4.2 Incidental and pathologic findings on MR imaging of subjects included in analyses

Structural abnormality	Group	Sex	Age	Remark
small lacunar infarct caudate nucleus	chronic CH	male	53	ipsilateral to perceived headache side
bilateral cerebellar infarct-like lesions	control	male	55	
empty sella	probable CH	male	51	
Rathkes cleft cyst	episodic CH	male	35	
pituitary cyst	control	female	38	most likely Rathkes cleft cyst, differential diagnosis cystic microadenoma
developmental venous anomaly	probable CH	female	51	contralateral to perceived headache side
Tornwaldt (nasopharyngeal) cyst	CPH	female	47	

CH: cluster headache; CPH: chronic paroxysmal hemicrania.

Table 4.3 summarizes the mean group dimensions of the skull base, cavernous sinus, and neighbouring structures for participants with or without headache. The left-to-right transcranial diameter at the temporal fossa level (mean ± SD) was larger in all headache groups (episodic cluster headache: 148 ± 7 mm, p=0.044; chronic cluster headache: 150 ± 7 mm, p<0.001; probable cluster headache: 146 ± 5 mm, p=0.012; and CPH: 145 ± 9 mm, p=0.044) compared

Table 4.3 Dimensions of the cavernous sinus and neighbouring structures of cluster headache and chronic paroxysmal hemicrania patients and headache-free controls

	Controls (n=22)	Cluster headache			Probable CH (n=13)	CPH (n=8)
		Total (n=49)	Episodic (n=25)	Chronic (n=24)		
Skull base measures						
1a Transcranial	140.2±8.0	148.8±7.4*	147.5±7.3*	150.2±7.3*	146.0±5.3*	145.2±9.4*
1b Sellar compartment	29.6±2.7	31.9±3.3	32.0±3.0	31.9±3.7	31.3±3.9	29.7±3.7
Cavernous sinus measures						
2a Cranial-caudal	12.3±1.7	12.7±2.8	12.2±3.0	12.8±2.5	11.6±2.9	10.8±2.0
2b Medial-lateral	8.7±1.4	9.3±1.9	9.5±1.8	9.2±1.8	8.6±2.0	9.1±1.9
2c Supracarotid	2.0±1.1	2.7±1.9	3.1±1.6*	2.2±1.6	2.4±2.1	2.0±1.5
2d Subcarotid	3.3±1.1	3.6±1.7	3.4±1.6	3.6±1.4	3.0±0.9	3.3±1.4
2e Midline-inferolateral	15.2±1.3	16.2±2.1	16.4±1.8	16.0±2.0	16.5±2.3	15.6±2.1
Internal carotid artery measures						
3a Cranial-caudal	3.8±0.7	4.2±0.7	4.1±0.6	4.3±0.7	4.1±0.7	3.9±0.8
3b Left-to-right	4.6±0.6	4.7±0.9	4.5±0.7	5.0±0.9	4.7±0.6	4.2±0.7
Pituitary measures						
4a Cranial-caudal	5.0±1.3	4.5±1.1	4.4±1.1	4.7±1.2	5.2±1.9	4.7±1.0
4b Left-to-right	13.3±2.0	13.6±2.0	13.4±2.4	13.7±1.7	15.4±2.3*	12.7±2.3
4c Anterior-posterior	10.5±1.3	11.1±1.2	11.1±1.0	11.1±1.4	11.0±1.3	10.8±1.6
4d Length infundibulum	8.1±2.4	8.2±2.1	8.0±1.5	8.4±2.6	7.1±1.8	9.0±2.5
Pituitary volume (mm^3)	120.9±50.6	114.2±37.1	110.3±33.2	118.2±41.2	148.2±61.3	105.6±31.3

All measurement in millimetres, unless stated otherwise; denotation in means ± SDs; values for controls are means of left & right measurements, for TACs measurements ipsilateral to the headache side; number-letter combinations correspond to those used in Figure 1; *p<0.05, multiple regression analysis controlling for sex and age, uncorrected for multiple comparisons. CH: cluster headache; CPH: chronic paroxysmal hemicrania

with controls (140 ± 8 mm). Sex-stratified analyses showed this larger left-to-right transcranial diameter in both female and male headache patients. The ipsilateral supracarotid diameter of the cavernous sinus was larger in episodic cluster headache patients (3.1 ± 2.0) compared with controls (2.0 ± 1.1, p=0.046) but not in other headache patients. The left-to-right pituitary diameter was larger in probable cluster headache patients (15.4 ± 2.3), compared with controls (13.3 ± 2.0, p=0.013), but pituitary volumes did not differ between patients with TACs and headache-free controls. Other measures of the cavernous sinus or its surrounding structures did not differ from those of controls.

Similar results were found when leaving out those headache subjects who experienced side shifts or contralateral attacks at some point in their disease history (n=13 (episodic cluster headache

n=3, chronic cluster headache n=6, probable cluster headache n=2, chronic paroxysmal hemicrania n=2), 19%). In addition, in the subset of subjects who never experienced side shifts or contralateral attacks, a larger midline-inferolateral diameter of the cavernous sinus (17.4 ± 2.3) was found in probable cluster headache compared with controls (15.2 ± 1.3, p=0.016).

Discussion

This is the first study using high-resolution MRI to specifically assess the aspect and dimensions of the cavernous sinus in cluster headache and chronic paroxysmal headache.

Despite the acquisition of high-resolution T2-weighted 1.5-T MRI, we did not find pathological lesions in the cavernous sinus or its neighbouring structures as have been previously associated with TACs,[8] which is in line with a previous study using conventional sequences at 0.5-T and 1.5-T magnetic resonance systems.[7] However, we cannot exclude though that structural abnormalities would have shown up using a more extensive MRI protocol including gadolinium-enhanced T1-weighted images of the sellar region and magnetic resonance angiography of intracranial and cervical vasculature.

We failed to find any evidence of a constitutionally narrow cavernous sinus region in these TACs, even when combining the results for all 49 (episodic and chronic) cluster headache patients together, which would provide 90% power for demonstrating a 15% difference in cavernous sinus diameter at alpha=0.05 versus controls. Our results did not change when leaving out subjects who experienced side shifts or contralateral attacks at some point in their disease history.

Subjects with cluster headache and chronic paroxysmal hemicrania did have a wider skull size than headache-free controls. Although an explanation for this finding remains purely speculative, it seems to be in accordance with observations of so-called leonine facial features in cluster headache as described several decades ago.[16]

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5

Volumetric brain changes in migraineurs from the general population

I.H. Palm-Meinders*

E.B. Arkink*

H. Koppen*

S. Amlal

G.M. Terwindt

L.J. Launer

M.A. van Buchem

M.D. Ferrari**

M.C. Kruit**

*shared first authors; ** shared last authors

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Abstract

Objective:

To assess volumetric brain changes in migraineurs from the general population in comparison with controls.

Methods:

Structural brain changes in migraineurs from the general population-based MRI Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA)-2 observational cohort study were assessed by state-of-the-art voxel-based morphometry. T1-weighted MR images of 84 migraineurs (52 with aura; 32 without aura) and 35 headache-free controls were evaluated. Regional volumes were compared voxel-wise, corrected for age, sex and total intracranial volume, using region-of-interest and whole-brain analyses.

Results:

In region-of-interest analyses, migraineurs showed decreased grey matter volume in the visual areas V3 and V5 of the right occipital cortex compared to controls ($p<0.05$, family-wise error correction). Post-hoc analyses revealed that similar changes were present irrespective of migraine aura status, disease activity (>1 year attack-free [inactive] versus ≥1 attack within the last year [active] and attack frequency [≤1 [low] versus ≥1 attack/month [high]). In exploratory whole-brain analyses ($p<0.001$, uncorrected for multiple comparisons) we identified additional structural differences in migraineurs in other cortical and subcortical areas, including white matter tracts, that are particularly involved in visual processing.

Conclusions:

Migraineurs from the general population showed small volumetric brain changes, mainly in cortical areas involved in visual motion processing, compared to controls. The presence of morphological changes irrespective of the presence of migraine aura or disease activity suggests that migraine with and without aura share common pathophysiological pathways and suggests that these changes are (partially) irreversible or might have been present throughout life.

Introduction

Despite many studies investigating structural changes in migraine,[1;2] it remains unclear whether, how, and to what extent migraine affects brain morphology.

Voxel-based morphometry (VBM) is an automated, unbiased, method for voxel-by-voxel comparison of grey and white matter density and volume.[3] Several groups have reported VBM grey matter changes in migraine, particularly volume decreases in pain-transmitting and pain-processing areas.[4-10] Other groups employed surface-based morphometry and found cortical thinning in areas involved in nociception[11] and cortical thickening in the somatosensory cortex[12] and visual motion processing areas.[11;13] Cortical surface area was increased in regions involved in executive functioning and visual motion processing while it was decreased in pain-processing areas.[11]

There is, however, ongoing discussion on: (i) the relevance, specificity and generalizability of these findings; (ii) the possible causes (e.g. changes in metabolism, neurotransmitter levels, or functional processing of sensory information); (iii) possible reversibility; and (iv) whether these changes are a cause or a consequence of migraine.[1;2] The earlier study samples were relatively small and primarily included migraineurs from headache clinics who were likely to be affected more severely than average, overusing acute anti-headache medications and suffering from comorbid (psychiatric) diseases which may affect brain architecture.[1;2;9;14-16] Finally, these VBM and surface-based morphometry studies did not always account for the increased risk of subclinical brain lesions that are more prevalent among migraineurs.[17;18]

We assessed cerebral grey and white matter volumes of migraineurs from the general population by applying state-of-the-art VBM while minimizing the potential influence of the various confounders reviewed above.

Materials and methods

Participants

Participants originated from the CAMERA-2 study (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis), a nine-year follow-up study on brain changes in participants with migraine and controls from the general population. Characteristics of the study population and the assessment of migraine have been described in detail elsewhere.[18] In short, participants with migraine (diagnosed according to International Headache Society-criteria[19]) and age- and sex-matched controls were evaluated by standardized interview, physical, and neurological examination, and brain MR imaging. The brain MR imaging protocol included a 3D T1-weighted sequence (Maastricht research center only because of technical reasons), suitable for VBM analysis, in 128 participants. Characteristics of participants scanned with (Maastricht) and without (Doetinchem) this sequence were comparable. Nine enrolled participants were excluded because of large brain infarcts (n=3) or movement artifacts (n=6), leaving n=119 participants (69% female; mean age 57 years; migraine with aura n=52, migraine without aura n=32, and controls n=35) for VBM analysis. Small, punctate white matter hyperintensities (WMHs) as frequently observed in participants with migraine[17] were not considered an exclusion criterion. None of the included participants had large, confluent WMHs.

Standard protocol, approvals, registrations, and patient consents

The study protocol was approved by the institutional review boards and all participants gave written informed consent prior to participation.

Magnetic Resonance Imaging

Structural whole brain 3D T1-weighted fast field echo images (repetition/echo time 8.6/4.6 ms; 140 sagittal 1.0 mm continuous slices; 256 mm field of view; acquisition matrix 256; acquisition voxel size 1x1x1 mm) were acquired on a 1.5T scanner (ACS-NT; Philips Medical System, Best, The Netherlands). In addition, combined proton density and T2-weighted fast spin-echo (repetition/echo time 3000/27-120 ms) and fluid-attenuated inversion recovery (FLAIR; repeti-

tion/echo/inversion time 8000/100/2000 ms) sequences were acquired to check images for structural abnormalities and to assess white matter hyperintensities and infarcts.

Voxel-based morphometry

One observer (M.C.K.) who was blinded for participant characteristics and diagnosis visually screened all MRIs for artifacts and gross structural abnormalities that might interfere with further post-processing. MRIs were processed using VBM, applying diffeomorphic anatomical registration exponentiated lie algebra (DARTEL)[20], with default parameters in SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, United Kingdom, http://www.fil.ion.ucl.ac.uk/spm) on a MATLAB platform (The MathWorks Inc., Natick, Massachusetts; version 7.4), to localise regional differences in grey and white matter volume. The DARTEL algorithm is considered as a better inter-subject registration than normalisation algorithms in previous SPM versions.[21] The VBM-DARTEL procedure included (i) checking the location of the anterior commissure in raw MRIs, (ii) segmentation into grey matter, white matter, and cerebrospinal fluid using the standard SPM8 segmentation algorithm, (iii) creation of a DARTEL template derived from non-linear deformation fields for the aforementioned segmentation procedure, and (iv) registration of all individual deformations to the DARTEL template. This registration step included modulation, which preserved the absolute amount of local grey and white matter volumes in spatially normalised images by scaling by Jacobian determinants, i.e. a correction for the distance over which a voxel had to be stretched or compressed to fit into standard space. Subsequently, (v) modulated normalised grey and white matter segments were smoothed with an 8 mm full width at half maximum isotropic Gaussian-kernel for statistical comparison.

Statistical analyses

Statistical Package for Social Science (SPSS Inc., Chicago, IL, USA; version 17.0) was used for independent sample t-tests (normally distributed continuous variables), Mann-Whitney U tests (non-normally distributed continuous variables) and Fisher's exact tests (categorical variables) to compare baseline characteristics between participants with migraine and controls. Voxel-based morphometry analyses included region-of-interest (ROI) grey matter analyses and whole-brain

grey and white matter analyses. Grey and white matter segments were compared voxelwise between (subgroups of) participants with migraine and controls, by creating general linear models including all participants with implementation of age, gender, and total intracranial volume as covariates. To exclude false positives in non-grey or non-white matter tissue, voxelwise comparisons were masked with explicit optimal threshold grey and white matter masks created using the SPM Masking Toolbox.[22]

Region-of-interest analyses

Based on results from previous VBM and surface-based morphometry studies,[2;6;11;13;23] ROI grey matter analyses were carried out in the prefrontal, insular, anterior cingulate, somatosensory and occipital cortex (visual motion processing areas V3 and V5), the thalamus and the brainstem (dorsolateral pons and periacqueductal gray). For these ROIs, Montreal Neurologic Institute (MNI) coordinates were extracted from the literature.[24-29] Participants with migraine were compared to controls by applying small volume corrections ($p_{FWE\text{-}SVC}<0.05$) by centering a 10-mm sphere around these MNI coordinates. In case of significant findings, post-hoc analyses were performed to assess whether these changes, as found in comparing participants with migraine with controls, were similar in subgroups of participants with migraine. For these post-hoc analyses, the average volume of grey matter per voxel in significant ROI clusters were obtained for each individual and compared between controls and migraine subgroups using general linear regression models correcting for main effects of age, gender and total intracranial volume and all its possible interactions. Subgroups of migraineurs were based on aura status (with or without aura), disease activity (>1 year free of attacks [inactive] vs. at least 1 attack within the last year [active]) and attack frequency (≤1 [low] or >1 attack/month [high] within the past 12 months). In these post-hoc analyses, $p<0.05$ was considered significant.

Whole brain analyses

For whole brain analyses comparing grey and white matter between migraineurs and controls, statistical parametric maps were thresholded at a significance level of $p<0.05$, corrected for multiple comparisons using random field theory (family-wise error), which is the standard to control

for multiple testing in neuroimaging data.[30] In case of significant findings, post-hoc analyses similar to ROI-analyses were to be performed.

As this is the first VBM-study investigating a population-based sample of participants with migraine with a minimum of comorbid factors, we deemed it justified to perform additional exploratory whole brain analyses at a less stringent significance level of $p<0.001$, uncorrected for multiple comparisons and minimal cluster sizes of 20 voxels.

Localization of region-of-interest and whole brain VBM findings

The location of the most significant voxel in ROI and whole brain VBM clusters of grey and white matter volume differences were determined using two detailed atlases in consensus.[31;32] To ascertain whether changes in white matter between participants with migraine and controls were not due to the occurrence of WMHs, the locations of VBM changes were compared to the location of WMHs. WMHs were segmented semi-automatically as hyperintense lesions on proton density, T2 and FLAIR images using QBrain as described in detail elsewhere.[18] Lesion maps were created per participant and registered to MNI152-space. Probability maps, depicting the chance for participants to have a lesion in a specific area, were created for the participants with migraine and controls included in the VBM analyses. Finally, these lesion maps were registered to the study-specific DARTEL space using a 12-parameter affine linear registration.

Results

Participants in the migraine group were slightly older than the controls (57.8 vs 54.6 years, $p=0.05$), particularly those with migraine with aura (58.2 vs. 54.6, $p=0.04$). No other differences were found for the demographic characteristics of participants with migraine and those of controls (Table 5.1).

Region-of-interest analyses

In ROI analyses (Figure 5.1), grey matter volumes ($p_{FWE\text{-}SVC}<0.05$, family wise error, small volume correction) were smaller in the V3 ($p_{FWE\text{-}SVC}=0.025$; x 26/y -87/z 22) and MT+/V5 ($p_{FWE\text{-}SVC}=0.031$; x 38/y -76/z 11) areas of the right occipital gyrus of participants with migraine com-

pared to those of controls. In post-hoc analyses migraine subgroups displayed roughly the same pattern of grey matter volume decrease in these areas, compared to controls (Table 5.2). However, in migraineurs with inactive disease (attack-free for more than one year) , compared to controls, there was a decrease in average grey matter volume per voxel in the V3 area, but not in the MT+/V5 area . Decrease of grey matter volume in the MT+/V5 was more pronounced in migraineurs with active disease and high attack frequency; this was not the case for the V3 area. No differences were found between migraineurs and controls for the other ROIs (prefrontal, insular, anterior cingulate, somatosensory and, the thalamus and the brainstem).

Table 5.1 Characteristics of CAMERA VBM study participants

			Migraineurs		
	Total (n=119)	**Control (n=35)**	**All (n=84)**	**MO (n=32)**	**MA (n=52)**
Age, mean (SD), years	56.9 (8.0)	54.6 (7.8)	57.8* (8.0)	57.1 (7.7)	58.3* (8.2)
Female, No. (%)	82 (69%)	25 (71%)	57 (68%)	21 (66%)	36 (69%)
Low education†, No. (%)	60 (50%)	17 (49%)	43 (51%)	17 (53%)	26 (50%)
Body mass index, mean (SD)	25.5 (3.3)	26.0 (3.2)	25.2 (3.3)	24.6 (2.8)	25.6 (3.6)
Hypertension‡, No. (%)	35 (29%)	9 (26%)	26 (31%)	8 (25%)	18 (35%)
History of stroke‡, No. (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Current medication, No. (%)					
Prophylactics	N/A	N/A	2 (2%)	0	2 (4%)
Abortive treatment	N/A	N/A	48 (57%)	16 (50%)	32 (62%)
Triptans	N/A	N/A	12 (14%)	4 (13%)	8 (15%)
Ergotamines	N/A	N/A	2 (2%)	1 (3%)	1 (2%)
Total intracranial volume, mean (SD), liter	1.12 (0.11)	1.14 (0.12)	1.12 (0.11)	1.12 (0.10)	1.11 (0.12)
DWMH volume, median (IQR), milliliter	0.06 (0-0.35)	0.06 (0-0.35)	0.08 (0-0.36)	0.06 (0-0.35)	0.11 (0-0.39)
Right-handed, No. (%)	102 (86%)	31 (89%)	71 (85%)	29 (91%)	42 (81%)
Migraine attacks per year#, median (IQR)	N/A	N/A	9 (6-18)	10 (6-24)	9 (6-18)
Migraineurs with high attack frequency#, No. (%)	N/A	N/A	32 (38%)	12 (38%)	20 (39%)
Active disease*, No. (%)	N/A	N/A	50 (60%)	15 (47%)	35 (67%)

MA=migraine with aura, MO=migraine without aura, DWMH=deep white matter hyperintensity, SE=standard error, IQR=interquartile range, No.=number, N/A=not applicable. *p<0.05 (all pairs of groups tested)
† Low education indicates primary school or lower vocational education
‡ Hypertension and history of stroke were self-reported, based on a previous physician's diagnosis
# High migraine attack frequency defined as on average ≥1 attack per month in the last year before examination
* Active disease defined as ≥1 attack within the last year before examination

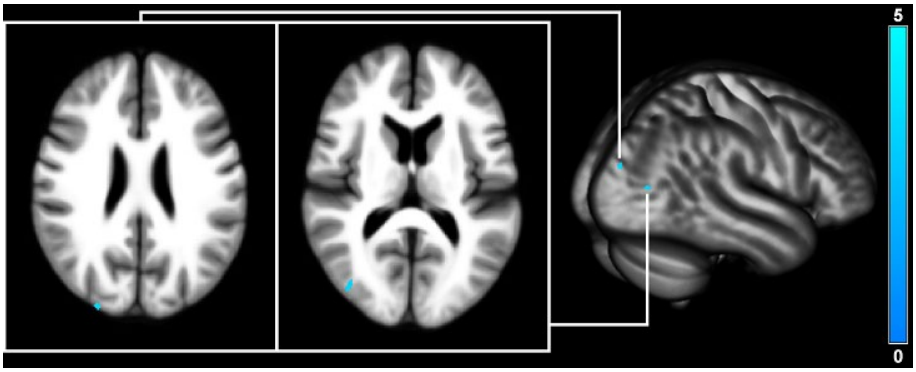

Figure 5.1 Grey matter volume decreases in V3 and V5 areas in migraineurs compared to controls. Axial slices (left) and volume rendering (right) of grey matter volume decreases in V3 (left panel) and V5 areas (right panel) in region-of-interest analyses between migraineurs and controls. Color bar represent Z-values. Pictures depicted in radiological convention.

Table 5.2 Post-hoc analyses based on region-of-interest (ROI) analyses comparing migraineurs, migraine subgroups and controls

	V3	p*	p†	V5	p*	p†
Controls (n=35)	0.416 (0.074)			0.385 (0.089)		
Migraine (n=84)	0.366 (0.063)	<0.001		0.327 (0.074)	0.001	
MA (n=32)	0.370 (0.067)	<0.001	0.60	0.325 (0.073)	<0.001	0.84
MO (n=52)	0.360 (0.057)	<0.001		0.330 (0.076)	0.003	
Active (n=50)	0.359 (0.066)	<0.001	0.38	0.315 (0.068)	<0.001	0.04
Inactive (n=34)	0.376 (0.059)	0.01		0.345 (0.078)	0.06	
HF (n=32)	0.352 (0.061)	<0.001	0.28	0.299 (0.058)	<0.001	0.002
LF (n=52)	0.373 (0.064)	0.003		0.344 (0.077)	0.03	

Values represent the mean grey matter volume per voxel in significant ROI clusters (small volume correction [p_{FWE}<0.05]) comparing migraineurs and controls; denotation mean (standard deviation).
p*=p-value for comparing migraine and migraine subgroups to controls; p†=p-value for comparing migraine sub-groups to each other. MA=Migraine with aura; MO=Migraine without aura; active migraine= at least 1 attack within the last year; HF=High migraine attack frequency; and LF=Low attack frequency (cutoff at 'high' is >1 attack per month in the year before examination).

Whole brain analyses

In whole brain analyses, no differences were found in grey or white matter when comparing migraineurs to controls ($p<0.05$, uncorrected for multiple comparisons).

Exploratory whole brain analyses ($p<0.001$, cluster extend threshold 20 voxels, uncorrected for multiple comparisons) confirmed smaller grey matter volumes in the right occipital gyrus of patients with migraine compared to controls as already found with ROI grey matter analyses. In addition, these analyses demonstrated: (i) larger grey matter volumes in the left angular, right middle temporal, left precentral and right superior frontal gyrus, and the left lateral geniculate nucleus; (ii) smaller grey matter volumes in the uvula of the left cerebellum; and (iii) smaller white matter volumes bilaterally in the occipital lobe and the stria medullaris of the thalamus, and unilaterally in the left frontal lobe (Table 5.3). These regional decreases in white matter volume did not correlate with deep white matter hyperintensities (Figure 5.2). Increased white matter volumes were not observed.

Discussion

In this population-based assessment of volumetric changes in the migraine brain, we found decreased grey matter volume in the visual areas V3 and V5 of the extrastriate cortical areas of the right occipital gyrus (Brodmann area 19) in migraineurs compared to controls. Migraine subgroups (i.e. migraine with or without aura, active or inactive disease, low or high attack frequency) displayed roughly the same pattern of differences in these areas as compared to controls. In exploratory whole brain analyses, we identified structural differences in other cortical and subcortical areas that are particularly involved in sensory processing.

Our findings of decreased grey matter volume in the visual motion processing areas V3 and V5 of the occipital gyrus are in line with previous VBM findings.[5] They seem to contradict the reported cortical thickening in visual processing areas in participants with migraine as assessed with SBM, though.[11;13] This apparent discrepancy might, however, be explained by the fact that local grey matter volume is not only defined by thickness of the cortex but also by other parameters such as

Table 5.3 Increases and decreases in grey and white matter between migraineurs vs. controls (exploratory whole-brain analyses)

	BA	L/R	DARTEL coordinates			k_E	Z-score
			x	y	z		
Grey matter increases							
Angular gyrus[1]	39	L	-50	-61	17	432	3.92
Precentral gyrus[2]	6	L	-51	-1	31	58	3.87
Middle temporal gyrus[3]	21	R	54	-32	-6	65	3.52
Superior frontal gyrus[4]	9	R	8	53	28	39	3.45
Lateral geniculate nucleus[5]	N/A	L	-21	-27	-5	27	3.33
Grey matter decreases							
Occipital gyrus[6]	19	R	26	-87	22	34	3.47
Cerebellum, uvula[7]	N/A	L	-14	-43	-42	68	3.44
Middle occipital gyrus[8]	19	R	38	-76	11	44	3.39
White matter increases							
-	-	-	-	-	-	-	-
White matter decreases							
Occipital white matter[1]	N/A	R	29	-78	15	173	4.48
Occipital white matter[2]	N/A	R	15	-80	10	386	4.24
Stria medullaris of thalamus[3]	N/A	R	5	-8	9	90	4.06
Stria medullaris of thalamus[4]	N/A	L	-3	-13	5	44	3.91
Occipital white matter[5]	N/A	R	42	-69	20	23	3.77
Occipital white matter	N/A	R	27	-86	14	105	3.64
Occipital white matter[6]	N/A	L	-22	-70	15	457	3.64
Occipital white matter[7]	N/A	L	-9	-85	5	30	3.34
Frontal white matter[8]	N/A	L	-34	16	19	30	3.23

BA=Brodmann area, L=left, R=right, k_E=cluster size, N/A=not applicable; $p<0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels; number 1-8 represent axial slices in Figure 5.2, grey matter (upper two rows) and white matter (lower two rows)

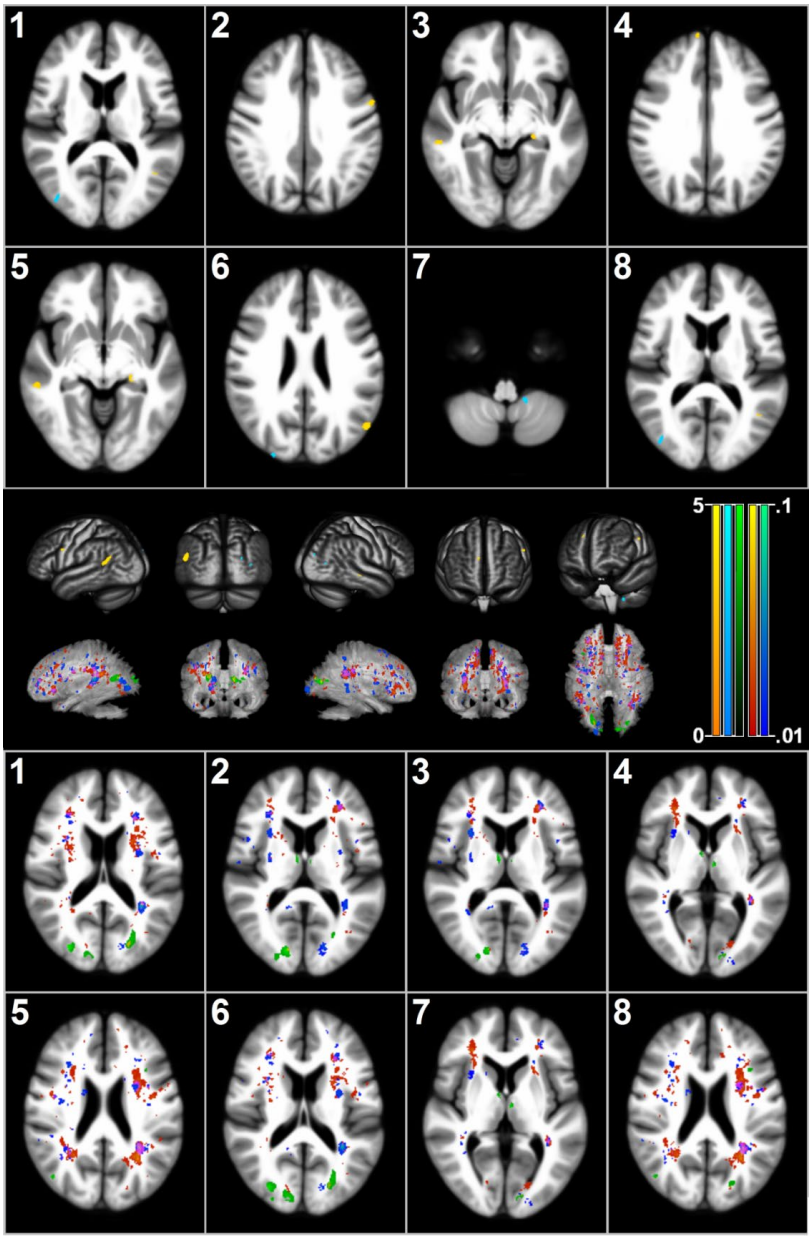

Figure 5.2 Increases and decreases in grey and white matter between migraineurs vs. controls (exploratory whole-brain analyses). Volume rendering images and axial slices of increases (yellow) and decreases (light blue) in grey matter and of decreases (green) in white matter between migraineurs vs. controls ($p<0.001$, uncorrected for multiple comparisons, cluster extend threshold 20 voxels). Axial slices correspond with numbers 1-8 in table 3 for grey matter (two upper rows) and white matter (two bottom rows). Decreases in white matter are shown in relation to deep white matter hyperintensities in migraineurs (red) and controls (dark blue). Color bars represent Z-values (0-5) or probability of voxels being deep white matter hyperintensities (1-10%). Pictures depicted in radiological convention.

cortical folding patterns and total surface area of the cortex. Structural changes in cortical visual (motion) processing areas might be related to hyperexcitability (i.e. increased cortical responses ofthe visual cortex to intense, repetitive or long-lasting stimulation),[33] to distorted cerebral metabolic homeostasis or to changes in local neurotransmitter compositions.[34;35] Whether such changes are inherited, congenital, or acquired remains to be determined. Changes in cortical responsiveness might explain well-known clinical symptoms of participants with migraine such as increased sensitivity to visual (light), auditory (sound) and tactile stimuli (allodynia). These might also relate to lack of habituation to repeated visual stimulation[36] and interictal deficits in visual motion processing[37;38] in migraine with and without aura. Cortical spreading depression, the electrophysiological correlate of migraine aura, might also be due to cortical hyperexcitability[39;40] and may begin in visual motion processing areas.[41] We found alterations in the right visual cortex only, which may relate to asymmetries in abnormal visual function as suggested by asymmetric visual evoked potentials in interictal migraineurs with aura.[42;43]

Participants with migraine who had not experienced migraine attacks in the year before MR scanning (with most being attack-free for over 5 years) still showed changes in the right occipital gyrus (V3 area) compared to healthy controls. Therefore, these changes appear to be irreversible, at least partially, or may have existed throughout life. Grey matter volume decrease in the visual area V5 was more pronounced in active migraineurs and those participants with a high attack-frequency which suggests that these volume decrease may (in part) be attack-related. As no differences were found for these areas between migraineurs with and without aura, these changes appear to be independent from presence of aura symptoms.

In exploratory whole brain analyses, next to cortical areas involved in visual processing, we found increased grey matter volume in the lateral geniculate nucleus in migraineurs compared to controls. This thalamic structure processes visual input from the optic chiasm to the primary visual cortex[44] and is, like the cortical areas found in ROI analyses, associated with visual motion processing.[45] The lateral geniculate nucleus is also thought to attenuate light perception in the absence of visual contrast[46] and has been suggested to play a role in photophobia in migraine.[47] Previous studies already described an altered structure[13] of this nucleus and increased oxygen metabolism after visual stimulation.[39]

We found bilateral volume decrease in the occipital white matter adjacent to visual processing cortical areas. Previously, with diffusion tensor imaging,[13;48] reduced fractional anisotropy was found in white matter tracts in the middle temporal area[13] and optic radiation tracts of participants with migraine,[48] possibly due to increased axonal diameter.[13;48] However, our results of decreased white matter volume make less myelination due to abnormal maturation or axonal loss a more likely explanation.

Theoretically, white matter changes as identified with VBM might be caused by WMHs which are known to be more prevalent in migraine.[17;18] WMHs show a drop in MR T1-signal due to gliosis and appear as relatively grey areas and therefore may be falsely classified by VBM segmentation tools as grey matter, despite their location in the deep white matter. However, the white matter decreases we found in the visual pathways did not co-localize with WMHs (Figure 5.2).

Although previous studies notably described differences in areas known to be primarily involved in pain processing,[4-6;8-10;12;49] these areas were less prominent in our study. Apart from differences in image acquisition and post-processing, and statistical thresholding, the major strength of our study is that the migraineurs from the CAMERA-cohort have had less frequent exposure to pain compared to the participants from headache clinics in the other studies, who tend to suffer from more severe migraines. A recent study explicitly found no alterations in cortical structures of areas involved in visual processing in migraine patients with visual aura.[4] Again, differences in participant characteristics, numbers of participants, and post-processing methods could explain the discrepancy of findings across publications. Previous studies showed that adaptive remodeling due to chronic pain might be reversible and disappear shortly after adequate therapy.[2;50] We showed that part of (cortical) grey matter changes were still present long after the last migraine attack.

Our study also has limitations. Despite a reasonably large sample size, we were not able to find differences, corrected for multiple comparisons, in whole brain grey or white matter when comparing migraineurs to controls. Therefore, precaution should be taken in interpreting the results of the exploratory whole brain analyses. Moreover, we did not adjust analyses for use or even overuse of prophylactic or acute migraine medications. Only 2% of the sample used prophylac-

tics, which did not allow for robust (sub)analyses. Although half of the migraineurs used abortive treatment, the large variety in type and dose of medications precluded sensible analyses. Moreover, abortive medication strongly correlates with attack frequency and this may have been a confounding factor for any differences related to attack frequency. Nevertheless, both participants with high and low attack frequency showed similar patterns of grey matter volume change in cortical visual motion processing areas, suggesting that acute migraine medication was not of major influence.

Further, in general, it is difficult to translate VBM changes to specific alterations at microscopic level as the technique is strongly depending on local T1 MRI signal intensity which is influenced by local tissue composition, including number and size of neurons, configuration of the extracellular space, presence of specific compounds (like iron, myelin, and neurotransmitters), homeostatic balance, and actual macro- and microvascular perfusion. Because whole brain T1 weighted images could be acquired only in the CAMERA-2 MRI study and not also in the 9-year earlier CAMERA-1 baseline study, we could not study changes over time. Moreover, the cross-sectional design of our study precludes analysis of whether the observed structural brain changes are a cause or a consequence of migraine.

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6

Microstructural white matter changes preceding white matter hyperintensities in migraine

E.B. Arkink
I.H. Palm-Meinders
H. Koppen
J. Milles
B. van Lew
L.J. Launer
P.A.M. Hofman
G.M. Terwindt
M.A. van Buchem
M.D. Ferrari
M.C. Kruit

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Abstract

Objective:

We used magnetization transfer imaging (MTI) to assess white matter tissue integrity in migraine, to explore whether white matter microstructure was more diffusely affected beyond *visibile* WMHs, and to explore whether focal *invisible* microstructural changes precede *visible* focal WMHs in migraineurs.

Methods:

We included 137 migraineurs (79 with aura, 58 without aura) and 74 controls from the CAMERA study, a longitudinal population-based study on structural brain lesions in migraine patients, who were scanned at baseline and at a 9-year follow-up. To assess microstructural brain tissue integrity, baseline magnetization transfer ratio (MTR)-values were calculated for whole brain white matter. Baseline MTR-values were determined for areas of normal appearing white matter that had progressed into MRI-detectable WMHs at follow-up and compared to MTR-values of contralateral NAWM.

Results:

MTR-values for whole brain white matter did not differ between migraineurs and controls. In migraineurs, but not in controls, normal appearing white matter that later progressed to WMHs at follow-up had lower mean MTR (mean [SD]: 0.354 [0.009] versus 0.356 [0.008], p=0.047) at baseline as compared to contralateral white matter.

Conclusions:

We did not find evidence for widespread microstructural white matter changes in migraineurs compared to controls. However, our findings suggest that a gradual or stepwise process might be responsible for evolution of focal invisible microstructural changes into focal migraine-related visible WMHs.

Introduction

We previously identified migraine as a risk factor for subclinical focal deep white matter hyperintensities (WMHs).[1;2] The etiology of these lesions remains to be clarified.

In migraineurs, diffuse invisible white matter changes may be present that extend beyond the visible focal WMHs on conventional MRI. Magnetization transfer imaging (MTI) is an MRI technique that provides quantitative information on microstructural tissue integrity. MTI detects structural changes both in areas with abnormal signal intensity on conventional MRI and in normal-appearing brain tissue.[3;4] Magnetization transfer ratio (MTR) values reflect the proportion of exchange between free water protons and water protons bound to macromolecules (f.i. myelin, proteins, and cell membrane molecules). Reduced MTR-values suggest lower macromolecular content or microscopic edema, indicating microstructural changes.[5] Brain parenchyma in migraineurs has scarcely been studied with MTI[6-8] and indeed suggested migraine-related focal microstructural damage in some studies.[6;7] However, another study found no difference in MTR for whole brain and normal-appearing white matter (NAWM) in migraineurs compared to controls.[8] These findings may have been biased by investigating more severe migraine phenotypes. Hence, we examined whole-brain white matter integrity in migraineurs from the general population.

The 9-year follow-up data of the CAMERA study revealed that the WMHs in female migraineurs were progressive also in those who no longer had migraine activity during follow-up.[2] Whether WMHs in migraineurs develop acutely or in progressive way needs further assessment. Therefore, we investigated whether baseline MTR might reveal invisible brain changes in NAWM at sites that had changed to visible WMHs at follow-up.

Methods

Study population

Participants were included from the Maastricht subpopulation of the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) 1 and 2 studies, a longitudinal population-based MRI study on structural brain lesions in migraine patients. Characteristics of the study population and the assessment of migraine have been described in detail elsewhere.[1;2;9] The original participants of the CAMERA-1 study included 295 well-characterized migraineurs and 140 controls, divided into two subpopulations from the Dutch cities of Doetinchem and Maastricht. The Maastricht subpopulation of this study consisted of 213 participants (n=80 migraine with aura, n=58 migraine without aura, n=75 controls). For 211 of these 213 participants, the MR imaging protocol included MTI at baseline. The participants included in current analyses were more likely to smoke than those participants who were excluded because of missing MTI data (Table 6.1). Further demographics and clinical characteristics were comparable between groups. A total of 128 participants of the original Maastricht subpopulation (n=55 migraine with aura, n=35 migraine without aura, n=38 controls) participated in CAMERA-2, a 9-year follow-up study.[2] Reasons for participants not to participate in CAMERA-2 included inability to recontact the participant due to relocation, loss to civil registry information, no interest, inability to visit the research center, claustrophobia, non-neurological illness and death. The MR imaging protocol did not include MTI at follow-up.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the Leiden University Medical Center ethics committee. All participants gave written informed consent.

Magnetic Resonance Imaging

Fast field echo MTI images (TR 106 ms, TE 5.9 ms, 28 axial 5 mm slices, 256x256 acquisition matrix, field of view 220 mm, flip angle 12º, in-plane resolution 0.86x0.86 mm) were acquired on a 1.5T MRI scanner (Philips Gyroscan Intera ACS-NT, Best, the Netherlands) at baseline. MTI comprised two consecutive sequences, one without (M0) (resulting in proton density

Table 6.1 Baseline characteristics of included & excluded CAMERA-1 study participants for current MTR substudy

	Included (n=211)	Excluded (n=224)
Migraine	137 (65)	158 (71)
With aura	79 (37)	82 (36)
Age, years	48.8 (7.7)	47.9 (7.6)
Female	146 (69)	171 (76)
Low education †	113 (54)	114 (51)
Body mass index, kg/m^2	25.2 (4.4)	24.9 (3.9)
Blood pressure, mmHg		
Systolic	134.0 (18.0)	134.7 (17.4)
Diastolic	90.9 (10.5)	91.5 (9.3)
Hypertension	80 (38)	87 (39)
Diabetes	1 (0.5)	3 (1)
Smoking		
Ever	151 (72)	136 (61)*
Current	82 (39)	63 (28)*
Pack years	13.0 (15.3)	7.5 (10.2)*
Cholesterol, mmol/l	5.25 (0.94)	5.37 (0.99)
HDL cholesterol, mmol/l	1.37 (0.35)	1.44 (0.42)
Medication (migraineurs only) §		
Prophylactics	9 (7)	3 (2)
Abortive treatment		
Triptans	14 (10)	8 (5)
Ergotamines	9 (7)	9 (6)
Migraine disease duration, years	23.6 (11.6)	23.2 (12.0)
Migraine attacks per year #	17.5 (20.5)	15.2 (14.6)
Migraineurs with high attack frequency #	60 (44)	76 (48)

Excluded participants included the Doetinchem subpopulation (n=222) and those participants from the Maastricht subpopulation that did not undergo MTI (n=2)
Mean (SD) for continuous, number (%) for categorical variables. N/A=not applicable
*p<0.05 (one-way ANOVA (or non-parametric test in case of skewed distribution) for continuous, Fisher exact test for categorical variables)
† Low education indicates primary school or lower vocational education
§ Ever use of medications
# Mean number of lifetime migraine attacks; high migraine attack frequency defined as mean ≥1 attack per month

contrast) and one with (Ms) radiofrequent saturation pulse (1100 Hz upfield of H2O resonance). In addition, dual echo T2 (TR 3000 ms, TE 27-120 ms, echo train length 10) and fluid-

attenuated inversion recovery (FLAIR) (TR 8000 ms, TE 100 ms, inversion time 2000 ms, echo train length 19) images were acquired to check images for structural abnormalities and to be able to segment WMHs at baseline and after a 9-year follow-up, using the same MRI scanner and protocols.

Image post processing

MTI data were post-processed using FSL (FMRIB Software Library, FMRIB Center, Oxford, United Kingdom)[10] and ELASTIX.[11] First, M0 images were linearly registered to the Ms images using FLIRT.[12] Non-brain tissue was removed from M0 images using BET;[13] a binary mask created in this processing step was applied to remove non-brain tissue from Ms images. The MTR was then calculated by the equation (M0-Ms)/M0. The MTR images were linearly registered to the MNI152 (Montreal Neurological Institute) stereotactic standard space implemented in FSL using FLIRT again. To optimize image registration in the white matter around the ventricles, these normalized MTR images were registered to MNI152 space once again using standard parameters in ELASTIX. The MNI152 template was segmented into gray matter, white matter and cerebrospinal fluid binary masks using FAST.[14] MTR histogram parameters (mean and normalized peak height) were retrieved for white matter for all participants by overlaying the binary masks on the normalized MTR images. The mean MTR reflects the average MTR in a region-of-interest (i.e., white matter in this case). The peak height of the MTR histogram shows the number of voxels with the most common MTR value and reflects the uniformity of the underlying voxels in terms of MTR-values. As the peak height depends on the total number of voxels, normalized peak height is calculated by dividing the number of voxels with the most common MTR by the total number of voxels in the region-of-interest. To decrease influence of extreme outliers, only MTI measures within 3 standard deviations of the mean were included in the statistical analysis.

To study the baseline MTR of brain tissue that developed into WMHs at follow-up, supratentorial WMHs were segmented semi-automatically as hyperintense lesions on PD, T2 and FLAIR images both at baseline and follow-up using QBrain 1.1.[2] As we had a particular interest in the development of deep WMHs, which were more prevalent and more progressive in (female)

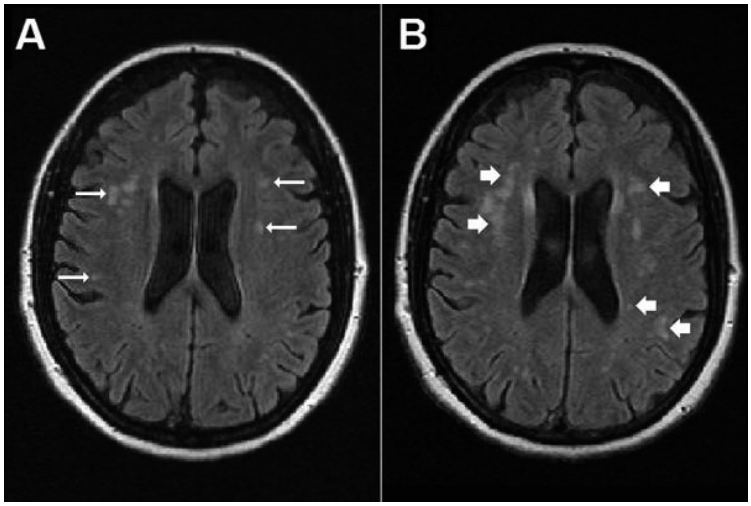

Figure 6.1 Example of deep white matter intensities at a similar level on FLAIR images of one participant showing DWMHs at baseline (A, long thin arrows) and progressive and new DWMHs at follow-up (B, short thick arrows)

migraineurs in CAMERA-2,[2] we differentiated between deep and periventricular WMHs. WMHs attached to the lateral ventricles were classified as periventricular WMHs. For follow-up analyses, we included all study participants with deep WMH progression, defined as increase in size or number of WMHs, or both (Figure 6.1). Segmented deep WMHs at baseline and at follow-up were registered to normalized MTR-images in MNI152 space using FLIRT. Mean MTR was computed for deep WMHs at baseline and for tissue that had progressed to deep WMH at follow-up. As deep WMHs often occur as asymmetric, punctate lesions, we considered that white matter contralateral to the deep WMHs could serve as NAWM for within-participant comparisons. MTR-values of this contralateral white matter were computed by per slice mirroring deep WMH maps about the sagittal axis.

Statistical analyses

Demographic characteristics were compared applying one-way ANOVAs (normal distribution), non-parametric tests (skewed distribution) and Fisher's exact tests (Statistical Package for Social Science 20.0, SPSS Inc., Chicago, IL, USA). The primary analysis of MTR histogram parameters of whole brain white matter and NAWM comprised the comparison between migraineurs, migraine subgroups and controls for the whole population that underwent MTI (n=211) using gen-

eral linear models adjusting for age, sex, hypertension, diabetes, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and body mass index (BMI).[15]

To decrease the effect of possible misregistration between conventional T2 and MTI images, which is theoretically largest for the smallest WMHs, paired sample t-tests comparing mean MTR of deep WMHs and contralateral NAWM were weighted for the deep WMH volume. Mean MTR of deep WMHs was also compared between migraine (subgroups) and controls using general linear models adjusting for age, sex, hypertension, diabetes, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and BMI. P-values <0.05 were considered statistically significant. An explorative subanalysis was performed for subgroups of migraineurs based on disease activity (>1 year free of attacks [inactive] vs at least 1 attack within the last year [active]).

Results

MTI data at baseline were available for 137 migraineurs (n=79 with aura; n=58 without aura) and 74 controls. Demographics and clinical characteristics were similar between migraineurs and controls, except for a higher BMI in migraineurs (25.7 [4.8]; mean [SD]) versus controls (24.3 [3.3], p=0.02; Table 6.2), particularly in migraineurs with aura (26.2 [5.1], p=0.005).

Whole brain analyses

Mean MTR and normalized MTR peak height in baseline whole brain white matter (including areas with WMHs at baseline and follow-up) and NAWM (excluding areas with WMHs at baseline and follow-up) did not differ between migraineurs (or subgroups of migraine patients) and controls (Table 6.3).

Focal WMHs analyses

At 9-year follow-up, 49 migraineurs (29 MA, 20 MO) and 19 controls had increased deep WMH volume due to new or progressive lesions (Table 6.3). In migraineurs, areas that had undergone transition to deep WMHs at follow-up had lower baseline mean MTR (0.354 [0.009] vs 0.356 [0.008], p=0.047), compared to their own contralateral white matter. This contralateral difference was not seen in controls. Baseline MTR in areas that had progressed to WMHs at

Table 6.2 Baseline (CAMERA-1) characteristics of CAMERA MTR study participants

	Control (n=74)	Migraineurs		
		All (n=137)	With aura (n=79)	Without aura (n=58)
Age, years	48.4 (8.0)	49.0 (8.0)	49.9 (8.0)	47.7 (8.0)
Female	49 (67)	97 (70)	54 (67)	43 (74)
Low education †	37 (50)	61 (37)	33 (42)	28 (48)
Body mass index, kg/m^2	24.3 (3.3)	25.7 (4.8)*	26.2 (5.1)*	24.9 (4.4)
Blood pressure, mmHg				
Systolic	135.7 (17.7)	133.1 (18.1)	134.3 (18.0)	131.4 (18.4)
Diastolic	91.0 (9.6)	90.9 (10.9)	91.3 (10.9)	90.3 (11.1)
Hypertension ‡	25 (34)	55 (40)	32 (41)	23 (40)
Diabetes	0 (0)	1 (1)	0 (0)	1 (2)
Smoking				
Ever	56 (76)	95 (69)	54 (68)	41 (71)
Current	34 (46)	48 (35)	24 (30)	24 (41)
Pack years	14.9 (17.1)	12.0 (14.2)	11.9 (15.5)	12.3 (12.2)
Cholesterol, mmol/l	5.22 (0.94)	5.26 (0.94)	5.22 (0.96)	5.32 (0.92)
HDL cholesterol, mmol/l	1.40 (0.36)	1.35 (0.35)	1.36 (0.34)	1.34 (0.37)
Medication §				
Prophylactics	N/A	9 (7)	7 (9)	2 (3)
Abortive treatment				
Triptans	N/A	14 (10)	10 (13)	4 (7)
Ergotamines	N/A	9 (7)	5 (6)	4 (7)
Migraine disease duration, years	N/A	23.6 (11.6)	24.7 (11.6)	22.0 (11.7)
Migraine attacks per year #	N/A	17.5 (20.5)	17.1 (22.4)	18.2 (17.9)
Migraineurs with high attack frequency #	N/A	60 (44)	33 (42)	27 (47)

Mean (SD) for continuous, number (%) for categorical variables. N/A=not applicable

*p<0.05 (one-way ANOVA (or non-parametric test in case of skewed distribution) for continuous, Fisher exact test for categorical variables)

† Low education indicates primary school or lower vocational education

‡ Hypertension was defined as a systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure of ≥95 mm Hg or use of antihypertensive drugs during CAMERA-1

§ Ever use of medications

Mean number of lifetime migraine attacks; high migraine attack frequency defined as mean ≥1 attack per month

follow-up was not lower than in contralateral white matter in subgroups of active (0.354 [0.008] vs 0.356 [0.009], p=0.12) and inactive (0.353 [0.011] vs 0.356 [0.006], p=0.21) migraineurs. At the sites of deep WMHs present at baseline, mean MTR was lower in migraineurs compared to controls (0.355 [0.008] vs 0.358 [0.012], p=0.048). Baseline mean MTR of areas that progressed to WMHs at follow-up in migraineurs (0.354 [0.009]) was not significantly lower than in similar areas in controls (0.357 [0.010]; p=0.08).

Discussion

In this study using MTI in migraineurs from the general population we found no significant differences in baseline whole brain white matter MTR-values between migraine patients and controls.

Thus, in contrast to four studies using diffusion-weighted MRI[16;17] and MTI,[6;7] but in line with another MTI study,[8] compared to controls, we did not find evidence for more diffuse microstructural changes in the white matter of migraineurs from the general population. A possible explanation might be that compared to the clinic-based patients in previous studies, our participants likely had less severe migraine. They also were less exposed to the potentially confounding effects of prophylactic and abortive medications and concomitant anxiety and depressive disorders, factors that might influence brain architecture as well.[18;19]

In migraineurs we found that mean MTR at baseline was significantly lower in normal appearing areas on conventional T2-weighted images on baseline that progressed to deep WMHs at 9-year follow-up. This suggests the presence of focal occult microstructural alterations or damage in brain tissue integrity prior to the appearance of visible deep WMHs on conventional T2-weighted MRI. This difference was not obviously explained by differences between migraineurs that had active migraine and those with inactive disease (with most being attack-free for >5 years), which is in line with our previous findings of WMHs being progressive in female migraineurs regardless of disease activity.[2] Although the nature of these microstructural changes remains elusive, our findings do suggest that deep WMHs in migraine develop gradually or

Table 6.3 *Volumes and MTR histogram parameters for whole brain white matter, deep white matter hyperintensities and contralateral deep white matter*

		Controls (n=74)	Migraine		
			All (n=137)	With aura (n=79)	Without aura (n=58)
Whole brain white matter (including WMHs at baseline and follow-up)					
Mean MTR		0.349 (0.006)	0.350 (0.006)	0.351 (0.006)	0.350 (0.006)
MTR NPH		0.184 (0.019)	0.185 (0.019)	0.185 (0.018)	0.184 (0.020)
NAWM (excluding WMHs at baseline and follow-up)					
Mean MTR		0.349 (0.006)	0.349 (0.006)	0.350 (0.006)	0.349 (0.006)
MTR NPH		0.183 (0.018)	0.182 (0.018)	0.182 (0.018)	0.182 (0.019)
DWMH volume, median (range), ml					
Baseline		0.04 (0.00-0.80)	0.07 (0.00-0.77)	0.06 (0.00-0.77)	0.09 (0.00-0.55)
9-y Follow-up		0.24 (0.01-1.56)	0.36 (0.00-4.16)	0.36 (0.01-4.16)	0.36 (0.00-2.55)
Progression/new		0.22 (0.00-1.01)	0.31 (0.00-3.42)	0.26 (0.01-3.42)	0.31 (0.00-2.00)
DWMH and cDWM at baseline					
		n=17 of 74	n=50 of 137	n=30 of 79	n=20 of 58
Mean MTR	*DWMH*	0.358 (0.012)	0.355 (0.008)*	0.356 (0.008)	0.353 (0.008)
	cDWM	0.354 (0.006)	0.354 (0.006)	0.354 (0.006)	0.354 (0.007)
Progressive/new DWMH and cDWM between baseline and follow-up					
		n=19 of 38	n=49 of 90	n=29 of 55	n=20 of 39
Mean MTR	*DWMH*	0.357 (0.010)	0.354 (0.009)†	0.353 (0.011)	0.354 (0.006)
	cDWM	0.356 (0.007)	0.356 (0.008)†	0.356 (0.008)	0.355 (0.008)

MTR=magnetization transfer ratio; NPH=normalized peak height; NAWM=normal appearing white matter, DWMH=deep white matter hyperintensity; cDWM=contralateral deep white matter; averages (SD) per group; *=p<0.05 general linear models comparing migraine (subgroups) vs. controls; †=p<0.05 DMWH vs. cDWM, paired-samples t-test

stepwise, possibly due to complex interplay of electrophysiological and vascular phenomena. We may only speculate about underlying pathophysiology. Cortical hyperexcitability is thought to lower the threshold for cortical spreading depression in migraine. This cortical spreading depression, possibly triggered by ischemic events, leads to a phase of self-expanding oligemia,[20] which may trigger the release of pro-inflammatory and prothrombotic substances. Together with preexistent modulating factors as an increased cardiovascular risk profile, circulating substances associated with vascular impairment, and dysfunctional endothelium,[21] this may ultimately contribute to a state of (chronic) ischemia, leading to axonal loss, demyelination or gliosis, appearing as WMHs on conventional MRI.

Our study was underpowered so we cannot exclude the possibility that WMHs in control participants may develop in a similar gradual or stepwise manner. After all, 50% of controls that participated in the follow-up study had progressive white matter lesions in the same follow-up period as well, compared to 54% in migraineurs. In some controls these white matter lesions may have

been preceded by similar MTR differences as seen in migraineurs. However, it should also be mentioned that the average increase in lesion load was (non-significantly) lower in controls, further decreasing the possibility to find similar MTR changes. Since MTR is not homogeneous throughout the white matter due to local differences in myelination,[3] differences in distribution of deep WMHs between migraine and controls may explain why we found lower mean MTR in deep WMHs at baseline in migraineurs compared to controls. In a previous study based on the whole CAMERA-2 study population indeed showed that WMHs were more diffusely distributed in female migraineurs compared to controls, also affecting subcortical white matter in upper frontal regions.[2] Alternatively, microstructure within WMHs in migraineurs might also just be more severely affected than in controls. Further, we cannot exclude that MTR-values might have decreased even further after our baseline measurement, as MTR changes may show evolution in time.

Nevertheless, the MTR changes in our and older migraine studies[8] are mild compared to those found in, for instance, multiple sclerosis[8] or elderly subjects.[22;23] This might explain why deep WMHs are not associated with clinically relevant cognitive decline in migraine.[2]

Thus, despite being visible, these WMHs only show minor changes in microstructural integrity in migraineurs and may thus well be clinically insignificant. Therefore, when incidentally discovered on conventional MRI, they may be no reason for alarm. Our findings that migraine is not accompanied by occult extensive white matter disease might provide further reassurance for migraineurs and their physicians.

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7

Infratentorial microbleeds: another sign of microangiopathy in migraine

E.B. Arkink
G.M. Terwindt
A.C. de Craen
J. Konishi
J. van der Grond
M.A. van Buchem
M.D. Ferrari
M.C. Kruit
on behalf of the PROSPER Study Group

Stroke 2015; 46: 1987-1989

Abstract

Background and purpose:

Migraine is a risk factor for clinical stroke and for subclinical white matter hyperintensities and infratentorial infarcts. These subclinical are linked to small-vessel pathology. Cerebral microbleeds (CMBs) are another biomarker of small-vessel disease but have not yet been studied in migraine.

Methods:

Identification of CMBs in 63 migraineurs (25 with aura/35 without aura/3 unknown aura status) and 359 controls (aged, 73-85 years) from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) magnetic resonance imaging study. We assessed the modifying role of migraine in the co-occurrence of CMBs, infarcts, and white matter hyperintensity-load.

Results:

Infratentorial microbleeds were more prevalent in migraine without aura patients than in controls (14% vs. 4%). Prevalence of other CMBs, infarcts and WMHs did not differ between groups. Migraineurs with CMBs had more often infarcts than controls with CMBs (65% vs. 43%). In comparison with controls with infarcts, migraineurs with infarcts had more commonly CMBs (55% vs. 30%).

Conclusions:

Migraine, notably without aura, is associated with infratentorial CMBs at older age. Furthermore, CMBs and infarcts co-occur more often in migraine than in controls. This supports the hypothesis of small vessel involvement in migraine pathophysiology.

Introduction

Migraine affects ≤33% of women and ≤13% of men during lifetime,[1] and independently increases the risk of ischemic and hemorrhagic stroke.[2] On magnetic resonance imaging (MRI), migraineurs more often have cerebellar infarcts, supratentorial and infratentorial white matter hyperintensities (WMHs),[3] suggesting involvement of small cerebral blood vessels in migraine. Cerebral microbleeds (CMBs) are another hallmark of small vessel disease.[4;5] However, their prevalence has not yet been studied in migraine. Here, we evaluate whether CMBs are more common in lifetime migraineurs, and whether they are more likely to co-occur with other vascular brain lesions in migraine, investigating whether microangiopathy might explain migraine-related cerebrovascular disease.

Methods

Subjects were from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) MRI study, a placebo-controlled trial assessing effects by pravastatin on cardiovascular disease.[6] In 544 of 554 subjects (aged, 73-85 years), lifetime migraine diagnosis was based on a previously used and validated questionnaire[1] and checked by migraine experts (G.M.T., M.C.K.), addressing all International Headache Society criteria.[7] Validation in twenty migraineurs and six controls resulted in 95% sensitivity and 100% specificity. The institutional review board approved the study. All subjects gave written informed consent.

CBMs were scored[8] (E.B.A. and J.K.) blinded for diagnosis on T2*-weighted images from a 1.5T MRI system. Due to incomplete acquisition and MRI-artifacts, CMB detection was not feasible in 27 of 554 subjects. Because of known increased vulnerability of the posterior fossa in migraine,[3] we a priori differentiated between lobar, basal ganglia and infratentorial CMBs. Interobserver reliability was excellent for the detection of any (κ=0.87), lobar (κ=0.85), basal ganglia (κ=0.95), and infratentorial CMBs (κ=0.94).

Cortical, lacunar, and infratentorial infarcts were scored. WMHs were segmented automatically

using validated software. WMH-volumes above the 80th percentile were classified as high WMH-load.

Inter-rater agreement was assessed using Cohen κ. Demographics were compared with Fisher exact and t-tests (SPSS 20.0.0, Chicago, IL, USA). Subclinical lesion prevalences were compared with logistic regression models adjusting for age, sex, hypertension, diabetes mellitus, smoking status, high-density lipoprotein and low-density lipoprotein cholesterol levels, antithrombotics use (factors previously associated with CMBs[8]) and pravastatin allocation, giving odds ratios (ORs) with 95% confidence intervals.

Results

In 506 subjects with available MRI, lifetime migraine was diagnosed in 63 (12%; men 7% and women 19%); 359 were controls; 67 subjects with severe headache history did not fully meet migraine criteria (probable/possible migraine; Figure 7.1).

Prevalence of sex, hypertension and smoking differed between migraineurs and controls (Table 7.1). Migraineurs with aura had higher total cholesterol and low-density lipoprotein levels compared with controls. Other characteristics did not differ between groups.

Overall CMB prevalence did not differ between migraineurs (29%), migraine with aura (24%), migraine without aura (31%), and controls (24%; Table 7.2). Infratentorial CMBs were more

Figure 7.1 Flow chart of included and excluded subjects.

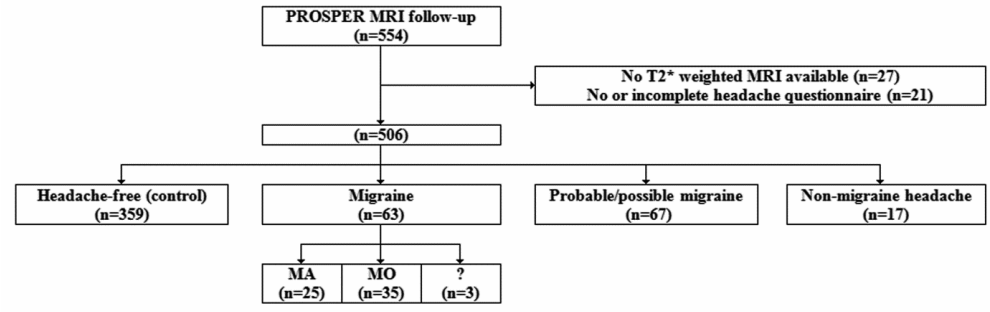

Table 7.1 Demographics

	Controls n=359	Migraine		
		Total n=63	With aura n=25	Without aura n=35
Female sex	130 (36)	43 (68)*#	18 (72)*#	23 (66)*#
Age	77.0±3.2	77.8±3.2	77.9±3.3	77.8±3.3
Blood pressure:				
systolic (mmHg)	157±22	157±21	156±17	159±23
diastolic (mmHg)	85±11	87±13	86±11	90±14
Body mass index (kg/m²)	26.6±3.6	26.5±3.8	26.9±4.0	26.4±3.8
Total cholesterol (mmol/L)	5.7±0.8	5.9±0.9	6.1±0.7*	5.7±0.9
HDL (mmol/L)	1.2±0.3	1.3±0.3	1.3±0.2	1.3±0.3
LDL (mmol/L)	3.9±0.7	4.0±0.7	4.2±0.6*	3.8±0.8
Triglycerides (mmol/L)	1.5±0.7	1.5±0.6	1.6±0.6	1.4±0.7
Current smoking	83 (23)	6 (10)*	3 (12)	2 (6)*
History of:				
hypertension	212 (59)	53 (84)*	19 (76)*	33 (94)*
diabetes	52 (14)	8 (13)	3 (12)	5 (14)
Pravastatin use	164 (46)	37 (59)	16 (64)	20 (57)
Antithrombotics use				
aspirin	110 (31)	21 (33)	13 (37)	7 (28)
anticoagulants	15 (4)	2 (2)	0 (0)	2 (6)

Mean±SD, number (%); HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein; *p<0.05 compared with controls; #the higher proportion of women reflects the normal sex distribution of migraine.

prevalent in migraineurs without aura versus controls (14% versus 4%; p=0.048).When the 67 subjects with probable/possible migraine were included in the migraine group (10% versus 4%; p=0.02) or in the control group (14% versus 5%; p=0.09), similar figures were seen.

Infratentorial CMBs were more prevalent in subjects with migraine and hypertension (11% versus 2%; OR 6.1 [1.5-25]; p=0.01) or migraine and diabetes (25% versus 4%; OR 7.5 [1.4-41]; p=0.02), compared with control subjects without hypertension or diabetes, respectively. However, neither hypertension (5% versus 2%; OR 2.6 [0.7-9.6]; p=0.14) nor diabetes (2% versus 4%; OR 0.4 [0.1-3.5]; p=0.44) increased the odds for infratentorial CMBs in controls significantly.

Overall (31% versus 35%) and infratentorial (14% versus 13%) infarct prevalence and high WMH-load (23% versus 19%) was similar in migraineurs and controls, although there was a

trend for high WHM-load in migraineurs without aura (32% versus 19%, p=0.06). Cerebral infarcts were more prevalent in migraineurs (irrespective of aura status) with CMBs versus controls with CMBs (65% vs. 43%; p=0.05). Migraineurs with infarcts versus controls with infarcts more often had lobar (55% versus 26%; p<0.01), infratentorial (25% versus 5%; p=0.01), and overall CMB prevalence (55% versus 30%; p=0.03). Compared with controls, migraineurs more often had co-occurrence of infarcts and CMBs than only one of these types of brain lesions (42% versus 21%; p=0.02).

Table 7.2 Microbleeds by lifetime migraine status and location

	Controls n=359	Migraine		
		Total n=63	With aura n=25	Without aura n=35
Average CMBs	2.5±3.2	3.5±6.5	1.3±0.5	4.9±8.1
Any CMB				
Prevalence	86 (24%)	18 (29%)	6 (24%)	11 (31%)
Unadjusted OR (95%CI)	1.0 (ref)	1.3 (0.7-2.3)	1.0 (0.4-2.6)	1.5 (0.7-3.1)
Adjusted OR (95%CI)		1.2 (0.6-2.2)	1.0 (0.4-2.8)	1.2 (0.5-2.7)
Lobar CMB				
Prevalence	71 (20%)	16 (25%)	6 (24%)	9 (26%)
Unadjusted OR (95%CI)	1.0 (ref)	1.4 (0.7-2.6)	1.3 (0.5-3.3)	1.4 (0.6-3.1)
Adjusted OR (95%CI)		1.5 (0.8-3.0)	1.6 (0.6-4.2)	1.4 (0.6-3.3)
Basal ganglia CMB				
Prevalence	18 (5%)	4 (6%)	0 (0%)	4 (11%)
Unadjusted OR (95%CI)	1.0 (ref)	1.3 (0.4-3.9)	n.a.	2.4 (0.8-7.7)
Adjusted OR (95%CI)		0.8 (0.2-2.6)	n.a.	1.2 (0.4-4.3)
Infratentorial CMB				
Prevalence	14 (4%)	6 (10%)	1 (4%)	5 (14%)
Unadjusted OR (95%CI)	1.0 (ref)	2.6 (1.0-7.0)	1.0 (0.1-8.0)	4.1 (1.4-12.2)*
Adjusted OR (95%CI)		2.2 (0.7-6.6)	0.9 (0.1-8.3)	3.3 (1.0-11.0)*

Mean±SD, number (%) and OR (odds ratio; 95%CI) *p<0.05; ref=reference; n.a.= not applicable

Discussion

Lifetime migraine, in particular without aura, was an independent risk factor for infratentorial CMBs, a hallmark of small-vessel disease. CMBs and infarcts co-occur more often in migraine than in controls.

CMBs point at a hemorrhage-prone vasculopathy and result from disruption of the endothelial layer of small vessels. Endothelial dysfunction seems a mechanism involved in migraine pathophysiology.[9] Infratentorial CMBs are linked to hypertension,[8] and migraineurs in our study indeed had more frequently unfavorable cardiovascular risk profiles, as reported by others.[10] Notwithstanding, our data suggest that migraine plays an additive and/or independent role in developing infratentorial CMBs, a finding that together with reports on cerebellar infarcts and infratentorial hyperintensities,[3] stresses the vulnerability of the infratentorial microvasculature in migraineurs.

We could not reproduce higher prevalences of infarcts and WMHs as found in younger migraineurs in other studies, likely because of a lack of power, as well as the effect of migraine might have been obscured by prevalent cardiovascular risk factors in current participants. Recall bias in this elderly population and strict migraine criteria possibly explain the lower prevalence of migraine compared with the literature.[1] Applying less strict criteria (including probable/possible migraine) did however not change our results. The relatively small number of cases precluded further post hoc analyses or investigating the effect of attack or aura frequency, activity, duration, chronicity and life course of migraine.

In summary, migraine without aura is associated with higher prevalence of infratentorial CMBs. CMBs and infarcts co-occur more often in migraine than in controls. Small-vessel disease might underlie migraine-associated cerebrovascular damage in at least a subgroup of migraineurs. This should be confirmed in larger populations of elderly migraineurs.

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8

Infratentorial hyperintensities and associated risk of mortality in an elderly cohort

E.B. Arkink
G.M. Terwindt
G.J. Blauw
J. van der Grond
M.A. van Buchem
M.D. Ferrari
M.C. Kruit
on behalf of the PROSPER Study Group

Submitted

Abstract

Objective:

To assess associations of infratentorial hyperintensities (IHs) with cardiovascular risk factors, migraine, and other lesion types and to investigate whether their presence is predictive of mortality.

Methods:

We examined the prevalence and severity of IHs in 545 participants of the MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). After study completion, mortality of study participants was followed-up. Logistic regression models assessed associations between IHs, cardiovascular risk factors, migraine, and other neuroimaging characteristics. Cox proportional hazard models evaluated overall mortality risk associated with IHs.

Results:

Higher age, smoking, and lower body mass indices correlated with the presence and severity of IHs. Overall, migraine did not increase the risk of IHs. However, male migraineurs had more severe IHs (odds ratio (OR) 2.50, 95% confidence interval (95%CI) 1.01-6.15) than male controls. IHs correlated with the presence of lacunar (OR 2.02, 95%CI 1.34-3.07) and infratentorial OR 2.04, 95%CI 1.23-3.40) infarcts, supratentorial white matter hyperintensity load (OR 3.61, 95%CI 2.31-5.65) and enlarged Virchow-Robin spaces. Participants with severe, confluent IHs had an increased risk of death (hazard ratio 1.85, 95%CI 1.21-2.88) compared to those without IHs.

Conclusions:

Higher age, smoking, lower body mass indices and -in males only- migraine predispose for IHs. The co-occurrence of IHs with other ischemic markers of small vessel disease suggests that IHs share common pathophysiological pathways. Higher mortality among participants with IHs makes their identification on MRI potentially clinically relevant.

Introduction

On T2-weighted brain magnetic resonance imaging (MRI) scans, infratentorial hyperintensities (IHs) are focal or diffuse lesions in the cerebellar white matter, cerebellar peduncles, and brainstem, mostly located in the pons.[1] IHs are relatively unknown, underrecognized and only scarcely investigated. This is in great contrast with supratentorial white matter hyperintensities (WMHs), that are strongly associated with aging and chronic conditions, such as hypertension and diabetes, leading to white matter injury through microvascular, inflammatory, and metabolic mechanisms.[2-5]

IHs were present in 23-48% of patients with clinical manifestations of atherosclerosis, vascular dementia and stroke.[6-8] In these cases, IHs correlated with age and the presence of supratentorial leukoaraiosis, atrophy and lacunar cerebral infarcts,[7;8] suggesting that IHs are also due to small vessel disease.[7;9] In a population-based study we reported that migraine was associated with higher prevalence and higher rate of progression of IHs, independent from age, sex and cardiovascular determinants.[1]

It is unknown whether in elderly people migraine is still associated with an increased prevalence of IHs. More in general, to our knowledge, data on prevalence and associations of IHs in the elderly general population are largely lacking. Although pontine hyperintensities were associated with poor clinical outcome after supratentorial ischemic stroke,[8] it is unknown if IHs are predictive of mortality in the general elderly population.

We evaluated the presence, severity, and associated neuroimaging characteristics of IHs in an elderly population with or at risk of vascular disease. We determined which risk factors correlated with IHs, with a particular interest for migraine. Further, we investigated the prognostic value of IHs regarding overall mortality.

Methods

Study population

Participants were included from the MRI substudy of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a placebo-controlled trial studying risk reduction by pravastatin of cardiovascular and cerebrovascular disease in elderly participants at risk.[10]

Follow-up MRI scans were available in 545 of 646 participants included at baseline (aged 73-85 years at follow-up); the remaining participants were incapable of undergoing MRI scans due to illness or death, MRI contraindications, technical issues, loss to follow-up or informed consent withdrawal. For subanalyses in migraineurs, in 535/545 participants lifetime migraine status was evaluated using a previously used and validated questionnaire[11] and checked by migraine experts (G.M.T., M.C.K.), addressing International Headache Society criteria.[12] Validation of this questionnaire in a separate elderly cohort of 20 migraineurs and 6 headache-free controls resulted in 95% sensitivity and 100% specificity.

Mortality of study participants was continuously followed-up after study completion. The cut-off date for determining mortality was February 10, 2014, which was up to 12.9 years after follow-up MRI.

Standard protocol approvals, registrations, and patient consents

The institutional review board approved the study. All participants gave written informed consent. All consenting participants were enrolled from May 2, 1998 onwards.

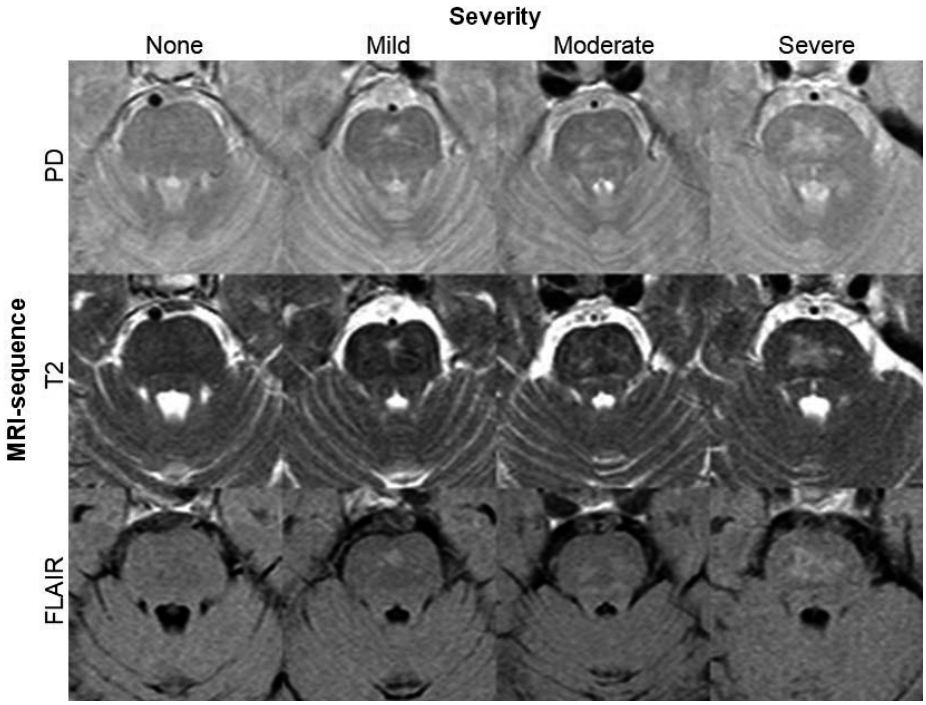
MRI acquisition and scoring of neuroimaging characteristics

T2-weighted, proton density-weighted, fluid-attenuated inversion recovery (FLAIR), and T2*-weighted images were acquired at a 1.5 T MRI system (NT-ACS, Philips, Best, the Netherlands). One rater (E.B.A.), blinded for clinical information, scored IHs. These were defined as non-lacunar hyperintense lesions on T2-weighted and proton density-weighted images. We further differentiated between pontine and cerebellar hyperintensities, and we graded severity of IHs

(0=none, 1=mild (single punctate), 2=moderate (multiple punctate, beginning confluent), 3=severe (large confluent)), similar to the Fazekas scale for deep white matter lesions (see Figure 8.1).[13]

Cerebral infarcts (supracortical (cortical, lacunar), infratentorial),[14;15] cerebral microbleeds (lobar, basal ganglia, infratentorial)[16] and enlarged Virchow-Robin spaces (VRS) (semioval center, basal ganglia, subinsular, mesencephalon)[17] were scored using previously established criteria. VRS were differentiated from lacunar infarcts based on size, location, (longitudinal) shape and the absence of a surrounding high signal intensity rim on FLAIR images. Pontine and cerebellar parenchymal defects isointense to CSF on all sequences were differentiated from IHs and VRS and classified as infratentorial infarcts. Due to incomplete acquisition and MRI artifacts, microbleed detection was not feasible in 20/545 participants.

Figure 1 Examples of IHs Proton density-weighted (PD, upper row), T2-weighted (middle row) and FLAIR (bottom row) MR images at the midpontine level showing examples of no (1st column), mild (2nd column), moderate (3rd column) and severe (4th column) IHs



Supratentorial WMHs were segmented automatically as hyperintensities in T2-weighted, proton density-weighted and FLAIR images using Software for Neuro-Image Processing in Experimental Research (SNIPER).[18] WMH volumes above the 80th percentile were classified as high WMH-load.[19] Intracranial and brain parenchyma volume were also calculated with SNIPER. Atrophy was calculated using the formula: atrophy (%)=([intracranial volume-brain parenchyma volume]/[intracranial volume])x100%.

Statistics

We calculated the predictive value of established cardiovascular risk factors for the presence and severity of IHs using univariate binary and ordinal logistic regression analyses, respectively (SPSS 20.0.0, Chicago, IL, USA). Then, multivariate binary and ordinal logistic regression analyses were performed taking into account all these cardiovascular determinants in one model. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to identify effect direction of each determinant. P-values <0.05 were considered significant. To study the effect of migraine, these initial analyses were repeated for a subgroup with all controls and definite migraineurs, including migraine as an additional cardiovascular risk factor. Additional explorative analyses were performed differentiating between migraine with and without aura. Based on previous reports of sex differences in the relationship between migraine and cerebrovascular damage,[20] we also a priori stratified between male and female migraineurs.

The association between IHs and other types of cerebrovascular damage was assessed using univariate binary (prevalence) and ordinal (severity) logistic regression analyses.

We calculated Kaplan-Meier survival curves for overall mortality for no, mild, moderate and severe IHs. Cox proportional hazard models were applied to estimate the risk of overall mortality associated with IHs, adjusting for age, sex, body mass index and current smoking (model 1), additional cardiovascular determinants (systolic and diastolic blood pressure, cholesterol and triglyceride levels, alcohol consumption, and history of hypertension/diabetes/myocardial infarction/stroke or transient ischemic attack; model 2) and, in addition to model 2, other types of neuroimaging characteristics (presence of any cerebral infarcts, microbleeds and/or high WMH-load; model 3). Hazard ratios (HRs) with 95% CIs were calculated.

Results

The prevalence of IHs was 42% (40% pontine, 6% cerebellar; n=235). These IHs were mild in n=73 (13%), moderate in n=123 (23%), and severe in n=39 (7%). Main predictors for prevalence and severity of IHs were higher age, smoking, and lower body mass index (Table 8.1).

Lifetime migraine was diagnosed in 66/535 participants (12%; men 6%, women 19%). Of these, 26 had migraine with aura, 37 migraine without aura, and in 3 participants aura status was uncertain. In total 371 participants served as controls. In the remaining 98 participants, data was missing, other types of headache were diagnosed or severe headache history did not fully meet migraine criteria ('probable/possible migraine'). Comparison of the demographics showed that migraineurs were more often female (70% versus 36%; p<0.001; reflecting the normal sex distribution of migraine), had more often hypertension (82% versus 59%; p<0.001) and consumed less alcohol (5.03±6.50 versus 7.78±8.97; p=0.016) than controls (Table 8.2). Further, migraineurs without aura were less likely to smoke (8% vs 23%; p=0.036) while migraineurs with aura had higher total cholesterol levels (6.07±0.76 vs 5.71±0.84; p=0.039), compared to controls.

Lifetime migraine was not an independent predisposing factor compared to controls, neither for prevalence (47% in migraine vs 42% in controls) nor for severity of IHs (Table 8.3). Prevalence and severity of IHs did not differ in subgroups of migraine with and without aura compared to controls either. Male migraineurs however had more frequent (65% vs 39%, univariate analysis) and more severe IHs (univariate and multivariate analysis) than male controls. Migraine was not an independent predictor of IHs in females.

The presence of cerebral infarcts was associated with a higher presence (43% vs 27%) and severity (p<0.001) of IHs. IHs were particularly associated with lacunar and infratentorial infarcts, but not with cortical infarcts (Table 8.4). High WMH-load was associated with a higher presence (31% vs 11%) and severity (p<0.001) of IHs as well. Higher VRS scores in any location also strongly correlated with higher prevalence and severity of IHs. Microbleeds and atrophy were not associated with IHs in this cohort.

Table 8.1 Comparison of cardiovascular risk factors for prevalence and severity of IHs

	All participants	IHs prevalence		IHs severity			Prevalence (logistic regression)		Severity (ordinal regression)	
	n=545	None n=310	Any n=235	Mild n=73	Moderate n=123	Severe n=39	Univariate	Multivariate	Univariate	Multivariate
Age (years)	77.2±3.2	76.9±3.1	77.7±3.2	77.9±3.3	77.5±3.2	78.3±3.2	1.08 [1.03-1.14]*	1.09 [1.03-1.16]*	1.08 [1.03-1.14]*	1.08 [1.02-1.14]*
Female sex	236 (43)	128 (42)	108 (46)	29 (40)	56 (46)	23 (59)	1.19 [0.84-1.67]	1.22 [0.80-1.85]	1.26 [0.91-1.74]	1.33 [0.90-1.97]
Current smoker	114 (21)	55 (18)	59 (25)	15 (21)	34 (28)	10 (26)	1.55 [1.03-2.35]*	1.83 [1.09-3.06]*	1.57 [1.06-2.31]*	2.02 [1.25-3.27]*
Hypertension	344 (63)	199 (64)	145 (62)	38 (52)	81 (66)	26 (67)	0.90 [0.63-1.28]	1.23 [0.77-1.95]	0.99 [0.71-1.39]	1.43 [0.92-2.23]
Diabetes	91 (17)	57 (18)	34 (14)	12 (16)	14 (11)	8 (21)	0.75 [0.47-1.19]	0.92 [0.55-1.54]	0.77 [0.49-1.21]	0.93 [0.57-1.51]
Myocardial infarction	67 (12)	41 (13)	26 (11)	7 (10)	17 (14)	2 (5)	0.82 [0.48-1.38]	0.89 [0.47-1.71]	0.81 [0.49-1.35]	0.98 [0.52-1.82]
Stroke/TIA	87 (16)	49 (16)	38 (16)	11 (15)	20 (16)	7 (18)	1.03 [0.65-1.63]	0.81 [0.45-1.47]	1.05 [0.68-1.64]	0.89 [0.51-1.57]
Vascular disease	234 (43)	132 (43)	102 (43)	34 (47)	55 (45)	13 (33)	1.03 [0.73-1.46]	1.22 [0.73-2.02]	0.98 [0.70-1.35]	1.13 [0.70-1.82]
Systolic blood pressure (mmHg)	157.5 ±21.8	158.5 ±21.4	156.1 ±22.2	156.3 ±22.1	155.2 ±20.1	158.9 ±28.3	0.99 [0.99-1.00]	0.99 [0.98-1.01]	1.00 [0.99-1.00]	1.00 [0.99-1.01]
Diastolic blood pressure (mmHg)	85.9±11.0	86.4±11.0	85.2±11.1	84.9±10.7	85.6±11.0	84.6±12.3	0.99 [0.98-1.01]	1.00 [0.98-1.02]	0.99 [0.98-1.01]	1.00 [0.98-1.02]
Body mass index (kg/m^2)	26.7±3.6	27.1±3.6	26.1±3.5	26.1±3.4	26.2±3.5	25.4±3.8	0.92 [0.88-0.97]*	0.93 [0.88-0.98]*	0.92 [0.88-0.97]*	0.93 [0.88-0.98]*
Total cholesterol (mmol/l)	5.8±0.9	5.8±0.9	5.7±0.8	5.8±0.8	5.8± 0.9	5.6±0.8	0.97 [0.80-1.19]	0.94 [0.75-1.18]	0.95 [0.78-1.14]	0.89 [0.72-1.11]
Triglyceride (mmol/l)	1.5±0.7	1.5±0.7	1.4±0.6	1.6±0.7	1.4±0.6	1.4±0.6	0.83 [0.64-1.07]	0.90 [0.67-1.19]	0.79 [0.62-1.02]	0.87 [0.66-1.15]
Alcohol (units/week last month)	6.7±8.3	7.1±8.4	6.3±8.2	7.2±9.2	6.2±8.2	5.0±5.4	0.99 [0.97-1.01]	0.99 [0.97-1.02]	0.90 [0.78-1.03]	0.99 [0.97-1.01]

Mean±SD; number (%); *p<0.05

Table 8.2 Demographics for migraine patients and headache-free controls

	All n=545	Controls n=371	Migraine		
			Total n=66	MA n=26	MO n=37
Age (years)	77.3± 3.2	77.0±3.2	77.8±3.1	77.9±3.2	77.8±3.2
Female sex	236 (43)	134 (36)	46 (70)†	19 (73)†	25 (68)†
Current smoker	114 (21)	85 (23)	8 (12)	4 (15)	3 (8)*
Hypertension	344 (63)	219 (59)	54 (82)†	19 (73)	34 (92)†
Diabetes	91 (17)	57 (15)	8 (12)	3 (12)	5 (14)
Myocardial infarction	67 (12)	50 (13)	7 (11)	3 (12)	4 (11)
Stroke/TIA	87 (16)	58 (16)	11 (17)	3 (12)	8 (22)
Vascular disease	234 (43)	168 (45)	26 (39)	10 (38)	15 (41)
Blood pressure:					
systolic (mmHg)	157.5±21.8	157.2±21.3	156.5±21.4	156.8±17.5	158.2±23.7
diastolic (mmHg)	85.9±11.0	85.3±10.7	87.1±12.5	85.2±10.6	89.4±13.5
Body mass index (kg/m^2)	26.7±3.6	26.7±3.8	26.5±3.8	27.1±4.0	26.4±3.7
Total cholesterol (mmol/l)	5.8±0.9	5.7±0.8	5.9±0.9	6.1±0.8*	5.7±0.9
Triglycerides (mmol/l)	1.5±0.7	1.5±0.7	1.5±0.6	1.6±0.6	1.4±0.7
Alcohol (units/week last month)	6.7±8.3	7.8±9.0	5.0±6.5*	5.5±7.8	4.7±5.5

Mean±SD, number (%); TIA=transient ischemic attack; MA=migraine with aura; MO=migraine without aura; Independent samples T-test for continuous (except for alcohol consumption; Mann-Whitney U test used), Fisher's exact test for categorical variables and comparing migraine or migraine subgroups to controls; *p<0.05, †p<0.001. Figures of migraine subgroups do not sum up to total due to uncertainty about subclassification in some migraineurs.

The mean follow-up duration for determining mortality was 9.2(±3.7) years after follow-up MRI scan. In this period, 348 of 545 participants (64%; 170 with IHs) had deceased. Figure 8.2 shows the corresponding Kaplan-Meier survival curve for these participants. The presence of any IH independently increased the risk of mortality after correction for age, sex, body mass index and smoking, additional cardiovascular risk factors, and other neuroimaging characteristics (HR 1.32, 95% CI 1.03-1.64). Those participants with severe (large, confluent) IHs were at highest risk (HR 1.87, 95% CI 1.21-2.88; model 3) (Table 8.4). When comparing migraineurs and controls, similar survival curves were found for the association between infratentorial hyperintensities and mortality (no significant differences between groups).

Table 8.3 Associations between IHs and other neuroimaging characteristics

	IHs prevalence		IHs severity			Prevalence (binary logistic regression)	Severity (ordinal logistic regression)
	None n=310	Any n=235	Mild n=73	Moderate n=123	Severe n=39		
Infarcts	84 (27)	100 (43)	25 (34)	56 (46)	19 (49)	1.98 [1.38-2.84]†	2.04 [1.44-2.86]†
Cortical	35 (11)	31 (13)	9 (12)	15 (12)	7 (18)	1.19 [0.71-1.99]	1.23 [0.76-2.01]
Lacunar	50 (11)	66 (28)	15 (21)	37 (30)	14 (36)	2.02 [1.34-3.07]†	2.12 [1.44-3.12]†
Infratentorial	29 (9)	41 (17)	9 (12)	22 (18)	10 (26)	2.04 [1.23-3.40]*	2.18 [1.37-3.48]*
Microbleeds	66 (22)	61 (27)	18 (26)	33 (28)	10 (28)	1.33 [0.89-1.99]	1.31 [0.89-1.93]
Lobar	53 (18)	51 (23)	13 (19)	30 (25)	8 (22)	1.38 [0.90-2.12]	1.40 [0.93-2.10]
Basal ganglia	14 (5)	10 (4)	2 (3)	6 (5)	2 (6)	0.92 [0.42-2.20]	1.05 [0.47-2.30]
Infratentorial	16 (5)	12 (5)	4 (6)	3 (3)	5 (14)	1.01 [0.47-2.18]	1.14 [0.55-2.36]
VRS: semioval center							
None	165 (53)	101 (43)	33 (45)	50 (41)	18 (46)	reference	reference
<5 on either side	81 (26)	72 (31)	21 (29)	40 (33)	11 (28)	1.45 [0.97-2.17]	1.42 [0.97-2.09]
=>5 on either side	64 (21)	62 (26)	19 (26)	33 (27)	10 (26)	1.58 [1.03-2.43]*	1.53 [1.02-2.30]*
VRS: basal ganglia							
Substantia innominata only, <5 on either side	46 (15)	14 (6)	4 (5)	8 (7)	2 (5)	reference	reference
Substantia innominata only, =>5 on either side	33 (11)	10 (4)	3 (4)	5 (4)	2 (5)	1.00 [0.39-2.52]	1.00 [0.40-2.49]
Lentiform nucleus, <5 on either side	77 (25)	41 (17)	17 (23)	20 (16)	4 (10)	1.75 [0.86-3.55]	1.63 [0.82-3.27]
Lentiform nucleus, 5-9 on either side or <5 in the caudate nucleus	63 (20)	44 (19)	18 (25)	20 (16)	6 (15)	2.30 [1.13-4.67]*	2.13 [1.06-4.26]*
Lentiform nucleus, =>10 on either side and <5 in the caudate nucleus	63 (20)	73 (31)	23 (32)	39 (32)	11 (28)	3.81 [1.92-7.57]†	3.54 [1.82-6.90]†
Lentiform nucleus, =>10 on either side and =>5 in the caudate nucleus	28 (9)	53 (23)	8 (11)	31 (25)	14 (36)	6.22[2.93-13.21] †	6.95 [3.41-14.20] †
VRS: subinsular							
None	76 (25)	44 (19)	15 (21)	24 (20)	5 (13)	reference	reference
<5 on either side	124 (40)	77 (33)	27 (37)	37 (30)	13 (33)	1.07 [0.67-1.72]	1.08 [0.69-1.71]
=>5 on either side	110 (35)	114 (49)	31 (42)	62 (50)	21 (54)	1.79 [1.14-2.82]*	1.83 [1.18-2.84]*
VRS: mesencephalon	131 (42)	131 (56)	41 (56)	66 (54)	24 (62)	1.72 [1.22-2.42]*	1.67 [1.20-2.32]*
High WMH-load	35 (11)	74 (31)	15 (21)	38 (31)	21 (54)	3.61 [2.31-5.65]†	3.97 [2.66-5.92]†
Atrophy (%)	27.35 ±3.04	27.10 ±3.78	27.60 ±3.99	26.85± 3.43	27.39 ±3.91	0.99 [0.94-1.04]	1.01 [0.97-1.06]

Mean±SD; number (%); *p<0.05, †p<0.001; VRS=Virchow Robin spaces; WMH=white matter hyperintensity

Discussion

The most surprising finding of this study is that IHs are associated with higher mortality, independent of cardiovascular risk factors and other types of cerebrovascular damage. We identified increasing age, smoking and low body mass index as the main predictors of IHs. Where previously migraine was identified as a risk factor for progressive IHs in younger participants irrespective of sex, in this elderly cohort migraine only increased the risk of IHs in male participants. IHs strongly correlated with the presence of high supratentorial WMH-load, lacunar and infratentorial infarcts, and VRS, which suggests that IHs are another hallmark of small vessel disease.

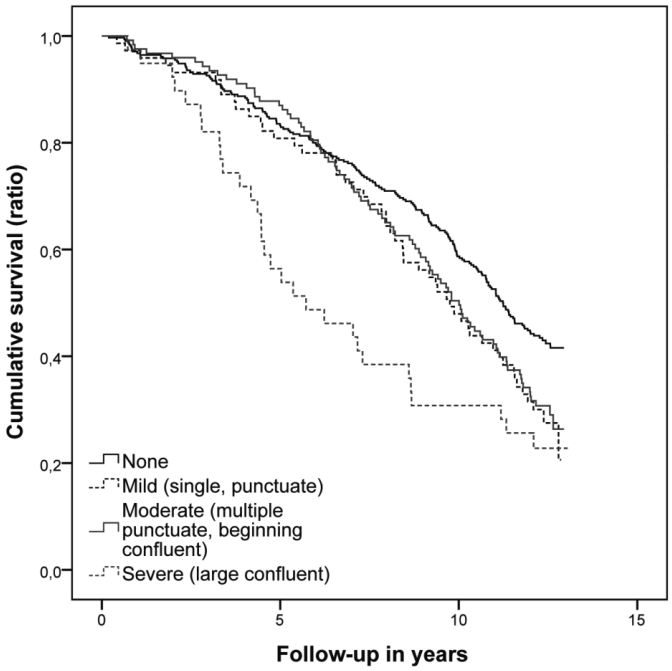
A major strength of this study is that we studied a considerably large population-based study sample to examine IHs and their associations with cardiovascular risk factors and other types of cerebrovascular damage.[7;8] We could confirm age as a risk factor[7] and we could add smoking and lower body mass index as predisposing factors. Although a lower body mass index has also been reported as a predisposing factor for subclinical cerebral infarction[21-23] and supratentorial WMH-load,[24] this finding seems counterintuitive. An explanation for this increased risk of subclinical cerebrovascular damage may be the "obesity paradox": a lower body mass index might indicate malnutrition, for instance due to (chronic) medical or psychogeriatric conditions or drug abuse. Furthermore, more obese participants in our population may have received more aggressive medical treatment in the past as they were recognized at increased risk of vascular disease.[25]

Table 8.4 Risk of mortality associated with presence and severity of IHs

		Model 1		Model 2		Model 3
	d/n	HR (95% CI)	d/n	HR (95% CI)	d/n	HR (95% CI)
No IHs	178/310	1.00 (reference)	178/310	1.00 (reference)	173/301	1.00 (reference)
Any IH	170/235	1.36 [1.10-1.68]*	170/235	1.46 [1.17-1.82]†	162/224	1.32 [1.05-1.64]*
Mild IHs	53/73	1.32 [0.97-1.80]	53/73	1.37 [1.00-1.88]*	50/69	1.33 [0.97-1.81]
Moderate IHs	87/123	1.27 [0.98-1.64]	87/123	1.38 [1.06-1.80]*	84/119	1.22 [0.93-1.60]
Severe IHs	30/39	1.90 [1.28-2.82]*	30/39	2.17 [1.44-3.26]†	28/36	1.85 [1.21-2.88]*

d/n=deceased/total number of participants; HR=hazard ratio; CI=confidence interval; corrected for age, sex, smoking and body mass index (model 1), other cardiovascular risk factors (model 2) and other types of cerebral damage (model 3); *p<0.05, †p<0.001.

Figure 8.2 Kaplan-Meier survival curve in relation to IH severity; depicted are participants with no (black solid line), mild (black dotted line), moderate (grey solid line) and severe (grey dotted line) IHs



Similarly, participants in our study may also have been treated adequately for other traditional risk factors that strongly correlate with supratentorial WMH-load, such as hypertension and diabetes. This might explain why we did not find an association of these determinants with IHs. Hence, the increased risk of vascular disease also represents a limitation of our study and results might therefore not be generalizable to the entire population.

Previously, IHs were associated with the presence of supratentorial leukoaraiosis, supratentorial atrophy and lacunar cerebral infarcts.[7;8] Therefore, it has been proposed that they are also the consequence of small vessel disease.[7;9] The high prevalence of IHs in small vessel diseases like CADASIL (in up to 100% in those older than 50 years of age) supports this notion.[26] Hypoperfusion in border zones between different vascular territories in the pontine and cerebellar areas has been suggested to contribute to this process.[7;27;28] In the current study, we found strong correlations of IHs with high supratentorial WMH-load, lacunar and infratentorial infarcts, that

all can be considered ischemic markers of cerebral small vessel disease.[29] Despite these associated neuroimaging characteristics, we were unable to associate IHs to cerebral microbleeds, a hemorrhagic marker of microangiopathy, possibly because our study lacked sufficient power. However, it has also been suggested that distinct inflammatory pathways may underlie ischemic and hemorrhagic cerebrovascular MRI markers in small vessel disease.[29] Thus, an alternative explanation for a weaker association between IHs and microbleeds might be that they are the result of different inflammatory cascades causing endothelial cell dysfunction and damage. Future research should clarify whether the inflammatory pathways associated with ischemic lesions in small vessel disease can be related to IHs as well.

In spite of the high prevalence of other cardiovascular risk factors in our elderly population, the more unfavorable cardiovascular risk profiles in migraineurs, and the relatively small number of migraine cases, lifetime migraine still independently increased the severity of IHs in males. Together with the higher risk of subclinical cerebellar infarcts[19] and infratentorial microbleeds,[30] these data again suggest that migraine modifies the risk of infratentorial cerebrovascular damage. Due to recall bias and by using strict migraine criteria we likely underdiagnosed the prevalence of migraine compared to literature.[11] The consequential small number of migraine cases disallowed us to assess effects of attack frequency, activity, duration, and chronicity of migraine, which is another limitation of our study. Anyhow, our findings again suggest that migraine should be added to the known risk factors for cerebrovascular small vessel disease. Moreover, it suggests that migraine should not be disregarded as a risk factor for cerebrovascular damage in elderly male participants. In previous studies, particularly women, and not men, with migraine were at increased risk of subclinical brain lesions.[20] Moreover, female migraineurs are at higher risk of ischemic stroke compared to male patients.[31] The reason for this discrepancy is unclear. Previous population-based studies may have been underpowered to measure effects in men, whereas our study may have lacked sufficient power to detect differences in female migraineurs. Moreover, other cardiovascular risk factors might have obscured the role of migraine in our female population, as the association between migraine and cardiovascular risk is especially increased in young women.[32]

The association between infratentorial hyperintensities and mortality makes their identification on MRI potentially clinically relevant. Unfortunately, the individual causes of death were not available for all deceased participants at the chosen study end point and thus, we were not able to differentiate between overall, cardiovascular and stroke-related mortality like in previous observations in this cohort.[33] Therefore we could not verify whether the increased mortality in participants with infratentorial hyperintensities can be ascribed to cardiovascular and cerebrovascular events, as reasonably might be expected in this cohort of elderly individuals with or at increased risk of vascular disease. Future studies should tackle this issue to identify patients at increased risk of these mortality causes, as they might benefit most from close cardiovascular risk monitoring and preventive medical care.

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MRI evaluation of the relationship between carotid artery endothelial shear stress and brain white matter lesions in migraine

E.S. Hoogeveen
E.B. Arkink
J. van der Grond
A.J.M. de Craen
M.A. van Buchem
M.D. Ferrari
G.M. Terwindt
M.C. Kruit
on behalf of the PROSPER Study Group

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Abstract

Although white matter lesions are frequently detected in migraine patients, underlying mechanisms remain unclear. Low carotid artery endothelial shear stress has been associated with white matter lesions. We aimed to investigate the association between carotid artery endothelial shear stress and white matter lesions in migraine. In 40 elderly migraine patients (n=29 females, 75 years [SD 3]) and 219 controls (n=80 females, 74 years [SD 3]) from the PROSPER-MRI study, carotid artery endothelial shear stress was estimated on 1.5T gradient-echo phase contrast MRI. White matter lesion volumes were calculated from structural MRI scans. Analyses were adjusted for age, sex, cardiovascular risk factors and cardiovascular disease. Migraine patients had lower mean endothelial shear stress compared to controls (0.90 [SD 0.15] versus 0.98 [SD 0.16] Pa; P=0.03). The association between mean endothelial shear stress and white matter lesion volume was greater for the migraine group than control group (P for interaction=0.05). Within the migraine group, white matter lesion volume increased with decreasing endothelial shear stress (β=-0.421; P= 0.01). In conclusion, migraine patients had lower endothelial shear stress which was associated with higher WML volume.

Introduction

Migraine is a common, multifactorial, neurovascular disorder characterized by recurrent attacks of headache accompanied with autonomic nervous system dysfunctions and, in one third of patients, aura symptoms.[1] The prevalence of brain white matter lesions (WMLs) is increased in migraine patients, which has not been explained by traditional cardiovascular risk factors or atherosclerosis.[2-5] Some studies suggested that endothelial or arterial dysfunction might predispose individuals to brain WMLs.[6;7]

Endothelial shear stress is an important regulator of endothelial function and is defined as the tangential force exerted on the endothelial cells by viscous blood flow. Sufficiently high endothelial shear stress is essential for endothelial homeostasis as it optimizes endothelial structure and function by inducing the release of agents with antithrombotic and anti-inflammatory properties.[8] In contrast, low or highly fluctuating endothelial shear stress has a deleterious effect on the endothelium by decreasing nitric oxide (NO) and increasing endothelin-1 levels.[9] Low endothelial shear stress also induces endothelial apoptosis, endothelial cell shape transformation and promotes sub-endothelial accumulation of low-density lipoprotein cholesterol.[10;11] Previously, low endothelial shear stress in the carotid arteries has been associated with cerebrovascular pathology such as brain WMLs.[12-17]

In the present study, we aimed to evaluate whether migraine is associated with reduced carotid artery endothelial shear stress. Moreover, we aimed to explore the association between carotid artery endothelial shear stress and WML volume in migraine.

Material and methods

Study design and participants

Data were obtained from the baseline measurements of the PROSPER MRI substudy, a large randomized controlled trial assessing the benefits of 40-mg pravastatin daily on vascular outcomes, of which the design has been described in detail elsewhere.[18;19] At baseline (before start of the study medication) 554 participants were enrolled in the MRI substudy of whom 329 underwent MRI of both the internal carotid arteries and cranium. Of these 329 participants, 40 had migraine, 219 had no history of headache (controls). The remaining 70 participants were

excluded because of missing or incomplete (n=13) headache questionnaire, presence of non-migraine headaches (n=11) or migraine-like headache (n=46). All participants refrained from smoking for at least 90 minutes before examinationThe institutional review board of the Leiden University Medical Center approved the protocol for the MRI study. The study was conducted in accordance with the Declaration of Helsinki (1983). All participants gave written informed consent and agreed with future retrospective analyses.

Migraine status

Lifetime migraine status, defined as current or past migraine, was assessed by trained research nurses using validated headache questionnaires (sensitivity 95%; specificity 100%),[20] according to classification of the International Headache Society criteria of 2004.[21] All subjects also fulfilled the new criteria of 2013.[1] Two migraine experts evaluated all questionnaires and decided on the final diagnosis.

MRI measurements

Flow measurements in the internal carotid arteries were performed on a 1.5-Tesla MRI platform (Gyroscan ACS-NT 15; Philips Medical Systems) using a gradient echo phase-contrast technique (repetition time 14.7 ms; echo time 9.1 ms; flip angle 7.5°; slice thickness 5 mm; matrix 256x154; field of view 250 x 188 mm; and velocity encoding 100 cm/sec and one number of signal averages), in the plane perpendicular to the vessel, 40 mm from the carotid bifurcation. Retrospective cardiac triggering by means of a peripheral pulse unit was applied, resulting in 16 phases over a cardiac heart cycle. The images were analyzed using the software package FLOW® (Division of Image Processing, LKEB, Department of Radiology, Leiden University Medical Center).[22,23] With this semi-automatic method, the vessel has to be identified manually, after which the delineation of the vessel is established automatically.

Calculation of endothelial shear stress

Velocity profiles were approximated by a previously described 3-dimensional paraboloid method.[24] Endothelial shear stress was calculated:

$$\text{Endothelial shear stress} = \mu \cdot \text{shear rate}$$

$$\text{Shear rate} = \text{Vmax} \cdot \sqrt{(2\pi \cdot \text{Vmax}/Q)}$$

Where μ represents the blood viscosity, Q the blood flow volume, and Vmax the maximum velocity over the cross section of the vessel. Blood viscosity and its shear thinning properties were modeled using the Carreau-Yasuda model, individually adjusted for hematocrit:

$$\mu = 2.2 + (22 - 2.2) \cdot (1 + (0.11 \cdot \text{shear rate})^{0.644})^{(\text{hematocrit}-1)/0.644}$$

Endothelial shear stress during the 16 phases of one cardiac cycle were clustered into early (4-6), mid (7-9) and late diastolic (10-12) and peak systolic (15-0) endothelial shear stress.[16] The average endothelial shear stress during the cardiac cycle was defined as mean endothelial shear stress. Figure 9.1 shows an example of endothelial shear stress during the cardiac cycle and illustrates how the cardiac phases were subdivided. Measurements from both internal carotid arteries were averaged.

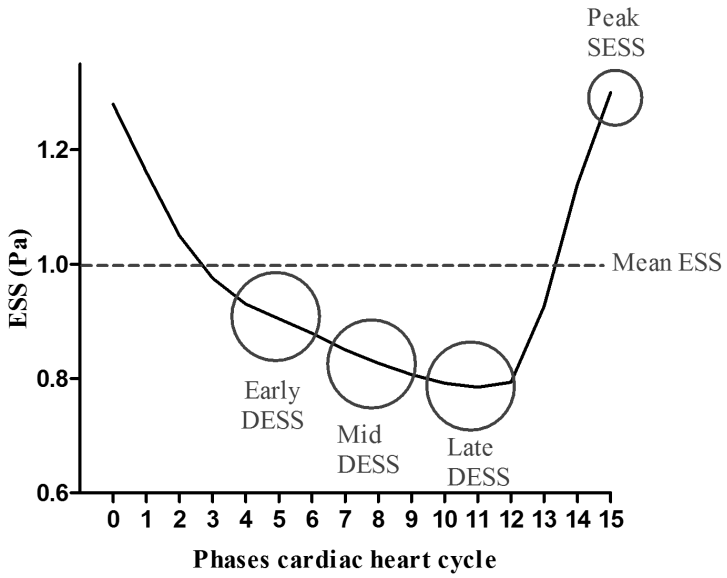

Figure 9.1 Endothelial shear stress during one cardiac cycle. Abbreviations: DESS=diastolic endothelial shear stress, ESS= endothelial shear stress, SESS=systolic endothelial shear stress

Brain white matter lesions

WMLs were assessed using in-house-developed semi-automated software which is described in detail elsewhere.[25] Briefly, WMLs were defined as regions being hyperintense on both proton density-weighted MRI and T2-weighed MRI. Infratentorial WMLs were excluded. The automatically generated WMLs maps were edited and reviewed by a trained rater with 20 years of neuroradiological experience, blinded to subject identity and diagnosis. WMLs were divided into periventricular or deep WMLs, depending on their connection to the lateral ventricles.

Statistical analysis

Data are presented as mean ± SD or as number (percentage). Baseline characteristics were compared between the groups using a Students t test for continuous variables and a Chi square test for categorical variables. Distributions of continuous variables were examined for normality and logarithmically transformed when appropriate (total WMLs, deep WMLs, periventricular WMLs). Median (interquartile range) are reported for original values of variables that were logarithmically transformed.

Generalized linear models were used and corrected for age, sex, smoking, systolic blood pressure, diastolic blood pressure, serum cholesterol, history of hypertension, history of diabetes mellitus and history of vascular disease. Associations between mean internal carotid artery endothelial shear stress with WML volumes were additionally adjusted for total intracranial volume. Regression lines between mean endothelial shear stress and WML volumes were compared in subjects with and without migraine by adding an interaction term (presence of migraine x mean endothelial shear stress) to the models. Z-values were calculated for standardization of variables. The association of mean endothelial shear stress and WML volumes in migraine patients and controls are presented as standardized Betas with corresponding P-values. Analyses were performed before and after stratification by sex, based on earlier observations of increased risk of WMLs only among female migraine patients.[3] For all analyses, SPSS software was used (IBM SPSS Statistics for Windows, Version 23.0 Armonk, NY: IBM Corp.). Statistical significance was defined as a two tailed $P<0.05$, and $P<0.1$ for interaction terms.

Table 9.1 Baseline characteristics of study participants (n=259)

	Migraine N=40	Control N=219	*P*-value
Age, y	74.8 ± 3.1	74.4 ± 3.2	0.47
Female	29 (73)	80 (37)	<0.001
Body mass index, kg/m^2	26.5 ± 4.0	26.5 ± 3.6	0.96
Systolic blood pressure, mm Hg	157 ± 18	157 ± 22	0.87
Diastolic blood pressure, mm Hg	87 ± 12	85 ± 11	0.17
Total cholesterol, mmol/L	5.9 ± 0.9	5.7 ± 0.9	0.41
Low-density lipoprotein, mmol/L	4.0 ± 0.8	3.9 ± 0.8	0.58
High-density lipoprotein, mmol/L	1.3 ± 0.3	1.2 ± 0.3	0.28
Current smoking	5 (13)	44 (20)	0.26
History of hypertension	34 (85)	134 (61)	0.004
History of diabetes mellitus	6 (15)	34 (16)	0.93
History of vascular disease[a]	15 (38)	100 (46)	0.34
Anti-hypertensive use			
Diuretics	17 (43)	59 (27)	0.047
ACE inhibitors	16 (40)	64 (29)	0.18
Beta blockers	8 (20)	75 (34)	0.08
Calcium channel blockers	7 (18)	52 (24)	0.39
Anti-thrombotics use			
Aspirin	14 (35)	69 (32)	0.66
Anti-coagulants	1 (3)	10 (5)	0.55
Migraine diagnosis			
With aura, n (%)	16 (40)	N.A.	N.A.
Without aura, n (%)	21 (53)	N.A.	N.A.
Doubt about aura status, n (%)	3 (8)	N.A.	N.A.
Internal carotid arteries			
Flow (mL/min)	190.2 ± 39.7	195.7 ± 37.4	.40
Maximum velocity (cm/s)	24.7 ± 3.8	26.2 ± 4.5	.05
Blood viscosity (mPa·s)	5.2 ± 0.5	5.3 ± 0.5	.30

Values are n (%) or mean ± SD.
[a] Any of stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction, peripheral arterial disease surgery or amputation for vascular disease more than 6 months before study entry

Results

Table 9.1 shows the characteristics of the migraine and control group. In the migraine group, females were overrepresented (73% vs 37%, P<0.001), reflecting the normal sex predilection of migraine in women. Migraine patients more often had a history of hypertension (85% vs 61%, P=0.004), and consequently the use of diuretics was higher in the migraine group compared with controls (43% vs 27%, P=0.047). Use of other antihypertensive and anti-thrombotic medication was similar between the groups.

Table 9.2 Internal carotid artery endothelial shear stress in migraine patients and controls

	Migraine	Control	*P*-value
All	n=40	n=219	
Mean ESS	0.90 ± 0.15	0.98 ± 0.16	**.03**
Early Diastolic ESS	0.85 ± 0.14	0.92 ± 0.15	**.04**
Mid Diastolic ESS	0.77 ± 0.12	0.83 ± 0.13	**.04**
Late Diastolic ESS	0.73 ± 0.14	0.79 ± 0.12	**.04**
Peak Systolic ESS	1.17 ± 0.19	1.31 ± 0.24	**.01**
Female	n=29	n=80	
Mean ESS	0.88 ± 0.15	0.97 ± 0.16	**.03**
Early Diastolic ESS	0.83 ± 0.13	0.90 ± 0.15	**.04**
Mid Diastolic ESS	0.75 ± 0.12	0.82 ± 0.13	**.02**
Late Diastolic ESS	0.71 ± 015	0.77 ± 0.12	**.04**
Peak Systolic ESS	1.14 ± 0.20	1.29 ± 0.25	**.02**
Male	n=11	n=139	
Mean ESS	0.96 ± 0.12	0.99 ± 0.15	.84
Early Diastolic ESS	0.90 ± 0.13	0.93 ± 0.15	.84
Mid Diastolic ESS	0.84 ± 0.13	0.84 ± 0.13	.87
Late Diastolic ESS	0.79 ± 0.09	0.80 ± 0.12	.93
Peak Systolic ESS	1.24 ± 0.17	1.32 ± 0.24	.62

Abbreviations: ESS =endothelial shear stress.
Data are presented in Pascal (Pa) with means ± SD. *P*-values are adjusted for age, sex, smoking, systolic blood pressure, diastolic blood pressure, serum cholesterol, history of hypertension, history of diabetes mellitus and history of vascular disease. Bold values represent significant results ($P<0.05$)

Endothelial shear stress

After adjustment for age, sex and cardiovascular risk factors and disease, mean, diastolic and systolic endothelial shear stress was significantly lower in the migraine group as compared to the control group (all P<0.05) (Table 9.2). Stratified analyses by sex showed significantly lower mean, diastolic and systolic endothelial shear stress in the female migraine patients compared to female control subjects. Although in males the same trend was shown, this did not reach statistical significance (Table 9.2).

WMLs

In migraine patients, median (interquartile range) total WML volume was 1.65 (0.7-5.6) mL, deep WML was 0.66 (0.1-1.2) mL, and periventricular WML was 1.22 (0.4-4.2) mL. In control subjects, median (interquartile range) total WML was 1.32 (0.4-5.3) mL, deep WML was 0.30 (0.09-1.3) mL, and periventricular WML was 0.95 (0.2-4.0) mL. Median WML

volumes were thus higher in migraine patients compared to control subjects, although not statistically significant (all P>0.05). Stratification by sex similarly revealed no differences in WML volume between migraine patients and controls (all P>0.05).

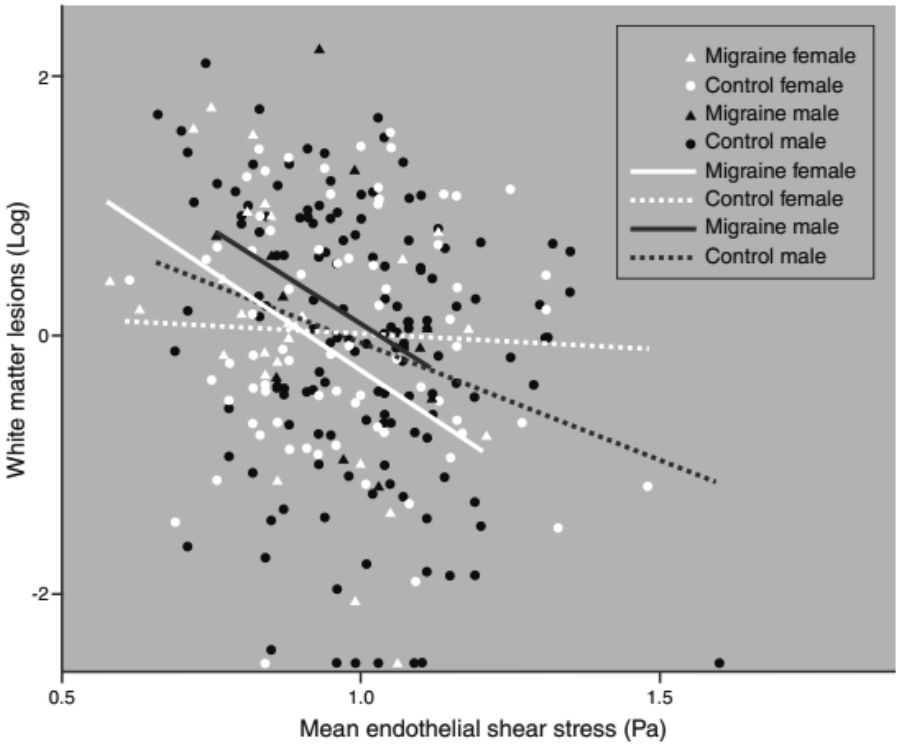

Figure 9.2 Scatterplot between mean endothelial shear stress and total white matter lesions showing regression lines for the migraine and control group, stratified by sex.

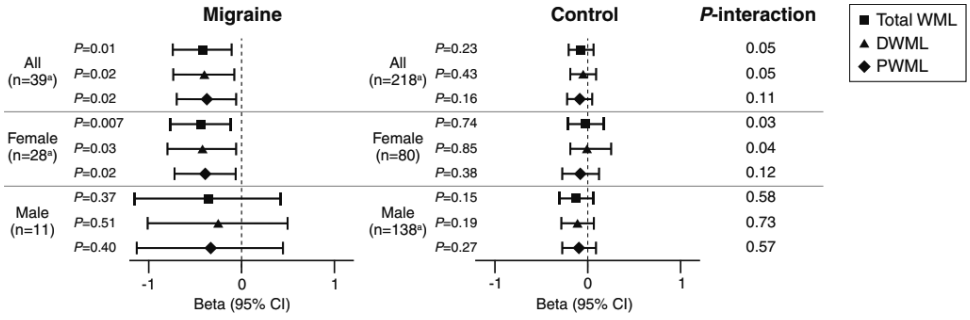

Figure 9.3 Associations between endothelial shear stress and white matter lesions, stratified by sex. Abbreviations: WML= white matter lesions, DWML= deep white matter lesions, PWML= periventricular white matter lesion. The associations as standardized beta with 95% confidence intervals (CI) between mean endothelial shear stress and white matter lesion volumes in migraine patients and controls, stratified by sex. [a] For these analyses, one female migraine patient and one male control were excluded, because of missing total intracranial volume measurements.

We compared the slope of the regression lines between mean endothelial shear stress and WML volumes in migraine patients and controls (Figure 9.2). Figure 9.3 shows the associations between endothelial shear stress and WML volumes in migraine patients and controls as standardized beta coefficients with 95% confidence intervals. The observed significant interaction effects (P<0.1) indicate that the influence of endothelial shear stress on total and deep WML volumes was greater for the migraine group than the control group. Within the migraine group, decreasing endothelial shear stress was associated with increasing total WML volume (β=-0.421; P=0.01), deep WML volume (β =-0. 407; P=0.02) and periventricular WML volume (β=-0.378; P=0.02). In the control group, associations did not reach statistical significance. Stratified analyses showed that these effects were only visible among females (Figure 9.3).

Discussion

In this study, we demonstrate that migraine patients have lower carotid artery endothelial shear stress compared to controls. Furthermore, in migraine patients, a lower endothelial shear stress was associated with higher WML volume. This provides new insights in the well-known associations between migraine and brain WMLs.

Low endothelial shear stress is associated with endothelial dysfunction.[8;26] In line with the current finding of lower endothelial shear stress in migraine patients, some previous studies that assessed peripheral vascular reactivity in response to physiologic or pharmacologic stimuli in migraine patients suggested impaired endothelial-dependent vascular reactivity.[27] Moreover, biochemical alterations, indicating changes in endothelial activation, have also been reported,[28] and studies evaluating peripheral arterial function in migraine are pointing at increased stiffness or reduced compliance of the arterial system.[27] Recently, women suffering from migraine with aura showed higher levels of circulating endothelial microparticles, a surrogate for endothelial dysfunction.[29]

Present findings of decreased carotid artery endothelial shear stress in migraine invite to speculate on the nature of the relationship. We have to note that, as this was a cross-sectional study, we cannot determine the direction of the associations between migraine and the decreased carotid

artery endothelial shear stress. Low endothelial shear stress has deleterious effects on the endothelium by decreasing NO and increasing endothelin-1 levels.[9] Possibly, shear stress induces endothelial changes on the capillary level that directly modifies neuronal and astrocytic function. This hypothesis has been derived from observations in rodents showing that NO deprivation lowered the threshold for a cortical spreading depression, the assumed pathophysiological correlate of the migraine aura.[30-32] This suggests connections between the neuronal and astrocytic network and the vascular tree and may provide an explanation for the found associations between reduced endothelial shear stress (and endothelial dysfunction) in migraine. Another possibility is that migraine-related risk factors predispose to decreased endothelial shear stress. Hypertension was indeed more prevalent in the current group of migraine patients. Nevertheless, the adjustment of our findings for vascular risk factors and diseases (smoking, blood pressure, serum cholesterol, history of hypertension, history of diabetes mellitus and history of vascular disease) did not influence the results. Therefore, we find it less likely that these common cardiovascular risk factors have driven the found association. Lastly, migraine has been proposed as a systemic vascular disorder characterized by a (chronic, probably slight) pro-inflammatory, pro-coagulatory or otherwise vasculopathic state.[33] Such chronic conditions could predispose to a gradual development of vascular wall changes in migraine patients, which finally may lead to unfavorable hemodynamics, including lower endothelial shear stress. This may be only measurable at older age.

The finding of increased WML volume with decreasing endothelial shear stress has been described previously in the PROSPER study.[16] In the present study, we observed significant interaction effects indicating that the influence of endothelial shear stress on development of WML is greater for the migraine group compared to the control group. In the control group, we could no longer demonstrate a significant effect between endothelial shear stress and WMLs. It seems plausible that in the earlier PROSPER study the association was notably driven by migraine. Vasculopathic changes of the intracranial microvasculature, possibly leading to changed compliance,[34] are likely a direct cause of brain WMLs. Possibly, a combination of decreased endothelial shear stress (resulting in endothelial dysfunction) and local neurovascular changes during migraine attacks such as activation of the clotting system[35] and neurogenic inflammation,[36] affect the vulnerable

small deep penetrating arteries in migraine patients and result in higher burden of WMLs in these patients.

A limitation of this study is the cross-sectional design. As a result, we cannot determine the direction of the association between migraine, carotid artery endothelial shear stress and brain WMLs. Therefore, future studies are warranted to determine whether the associations represent a causal relationship. Another limitation is the study population which consists of elderly migraine patients at increased risk for cardiovascular disease. This may hamper generalization of our findings to the general migraine population. In accordance with previous studies,[2;3;5] we found that migraine patients had higher WML volume load compared to migraine-free controls, although this did not reach statistical significance. This is likely because of limited statistical power and, in addition, the older age and high cardiovascular disease burden of our study population may have obscured migraine effects. We only assessed migraine diagnosis and no other headaches. Consequently, we were not able to assess whether the found association of endothelial shear stress with WMLs was specific for migraine or whether this was also present for other types of headache, as was suggested in a previous study.[37] Although the differences between females and males in our study highlight that sex-differences possibly play a role in the pathophysiology of migraine, it must be stated that our sample size is likely too small for a proper analysis of male migraine patients (n=11), also visualized by the broad confidence intervals of the associations (Figure 9.3). Moreover, our sample size was too small to evaluate migraine with and without aura as separate groups.

In conclusion, we showed that migraine patients were associated with decreased carotid artery endothelial shear stress when compared to migraine-free controls and that migraine patients with lower carotid artery endothelial shear stress were associated with higher WML volumes. This reduced carotid artery endothelial shear stress may predispose patients with migraine to development of WMLs. Elucidating the relationship between endothelial shear stress and WMLs may lead to a better understanding of the pathophysiologic mechanism underlying the increased risk of WMLs in migraine patients.

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10

Summary, discussion and conclusions

Summary

The primary objective of this thesis was to investigate in what way the brain is structurally different in cluster headache and migraine, to gain further understanding of the symptomatology, underlying pathophysiology and possible harmful effects of these conditions. To this purpose, we used both conventional and advanced MRI techniques with state-of-the-art post-processing techniques to detect both macrostructural as well as microstructural changes in both headache disorders.

In **Chapter 2**, we presented an early 18th century observational report on a patient likely suffering of cluster headache. It is an illustration of the general usefulness to review historical research data. First, in this specific case, it provided information on the existence and nature of trigeminal autonomic cephalalgias in earlier centuries. We notice that theories about the aetiology of primary headache syndromes have evolved over centuries, and that sometimes today we have returned to the original theories from decades or even longer ago.[1] Secondly, previously disregarded observations and theories on the pathophysiological processes may help to understand current research findings, and can be the base for future research.[2] Thirdly, review of historical findings may also explain the origin of incorrect hypotheses. For instance, the theory that migraine has a pure vascular pathophysiology, appeared to be based on inconsistent study results by Harold Wolff and his colleagues.

In **Chapter 3** we aimed to identify structural brain changes in patients with cluster headache by way of acquiring high-resolution T1-weighted images and applying voxel-based morphometry (VBM). In several ways, we were unable to reproduce a previous highly cited study finding that the posterior inferior hypothalamus ought to have an increased volume in cluster headache patients. Instead, we observed changes in another area of the hypothalamus. By applying a region-of-interest VBM analysis and a complementary manual segmentation of the hypothalamus we found bilateral increases in global hypothalamic volume in typical cluster headache patients compared to controls and migraineurs. These volume increases were mainly localized in the anterior part of the hypothalamus. Hypothalamic nuclei that can be responsible for the volume increase include the suprachiasmatic nucleus and the paraventricular nucleus. The suprachiasmatic nucleus is considered to be the endogenous biological clock and may be linked to circadian and circan-

nual rhythms that characterize cluster headache attacks and periods. The paraventricular nucleus is thought to provoke or modulate cluster headache attacks due to its role in the regulation of nociceptive and autonomic input.[3] Nonetheless, no definite conclusions regarding the nature of this increase in hypothalamic volume can be drawn from this research. The anatomic assessment of brain structure with MRI is highly depending on T1 signal intensity differences, and these can be caused by, for instance, changes in number or size of neurons, fluid shifts between intra- and extracellular space and gliosis. Differentiation between processes that can influence these changes is not possible with T1-weighted MRI alone. For a better understanding of these processes we need to know what happens at a molecular level, thus requiring multimodal molecular imaging techniques combining for instance MRI and positron emission tomography (PET). Another concern brought forward by our results is the fact that VBM did not detect the more global structural changes in the small area of the hypothalamus. This might explain why previous studies failed to pinpoint morphometric changes in this brain region. VBM seems thus less sensitive for analysis of smaller structures, resulting in false negative results.

In **Chapter 4**, we investigated whether cluster headache was associated with a constitutionally or acquired narrowed cavernous sinus as it has been suggested previously that this might predispose individuals to this type of primary headache. We used high-resolution MRI images to study the cavernous sinus region, but found no evidence, neither for structural lesions in this region nor for smaller dimensions of the cavernous sinus. Instead, we found that patients with cluster headache and chronic paroxysmal hemicrania had wider skulls than headache-free controls, which might be in accordance with observations of so-called leonine facial features in cluster headache as described several decades ago.

In **Chapter 5**, using VBM we identified structural changes, particularly in the V3 and V5 visual areas of the occipital cortical grey matter, in migraineurs from the large population-based sample of the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) study. Similar changes were present in both migraine with and without aura, and changes in the V3 visual area were present independent of disease activity or attack frequency. Some of these changes were still present in patients who had not experienced migraine attacks for several years, suggesting that they are irreversible or may have existed throughout life rather than representing neuroplasticity changes (i.e. changes in the structure and organisation of the brain due to its ability to

adapt to external stimuli, such as for instance repetitive pain episodes due to recurrent migraine attacks). We further showed that subcortical grey (lateral geniculate nucleus) and white matter structures (white matter tracts) may also be altered in migraineurs in comparison to control subjects. The majority of these cortical and subcortical areas seem to be involved in processing visual stimuli. By using these subjects taken from the general population, we minimized potential sources of bias, such as comorbidities and medication overuse, which are likely to have influenced the results of previous VBM studies performed in migraineurs recruited at specialized headache centres.

Chapter 6 describes the results of our study using magnetization transfer imaging to assess white matter tissue integrity in migraineurs from the CAMERA study. We did not find diffuse microstructural white matter changes in migraine. We however also examined the integrity of the white matter in areas that transitioned from normal appearing white matter tissue to T2-visible white matter hyperintense lesions at a 9-year follow-up. We detected that magnetization transfer ratio values were decreased in these white matter areas at baseline, indicating microstructural changes being present. This suggests that occult brain tissue integrity changes are present before they become visible on T2-weighted MRI as white matter hyperintensities, which implies a chronic, systemic disease process might be responsible for their occurrence.

A hallmark of cerebral small vessel disease, cerebral microbleeds, has not been previously studied in migraine. In **Chapter 7**, we assessed the prevalence of cerebral microbleeds in the elderly participants of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Migraine, especially without aura, was an independent risk factor for infratentorial microbleeds. Together with the earlier findings of increased risk of cerebellar infarcts in migraine, this further points at the infratentorial microcirculation as a potential endangered brain area in migraine.[4;5] Cerebral microbleeds and infarcts co-occurred more often in migraine than in control participants, which further suggests that small-vessel disease might underlie migraine-associated cerebrovascular damage at least in a subset of migraineurs.

For **Chapter 8**, we investigated the prevalence and severity of infratentorial hyperintensities, i.e. T2-hyperintense lesions in the pons and cerebellar white matter, and assessed their associations with cardiovascular risk factors and other types of cerebrovascular damage. In the PROSPER-

study cohort mentioned earlier, higher age, smoking, and lower body mass indices correlated with more frequent and more severe infratentorial hyperintensities. In this population, male migraineurs were at increased risk of this particular type of cerebrovascular damage. This is remarkable, as in previously studied populations, only female migraineurs were found to be at increased risk of supratentorial white matter lesions. The presence of infratentorial hyperintensities was also associated with prevalence of lacunar and infratentorial infarcts, and supratentorial white matter lesion load. This indicates that infratentorial hyperintensities represent another ischemic hallmark of cerebral small vessel disease. We also discovered that subjects with severe confluent hyperintensities in the posterior fossa in this elderly population were twice as likely to die within the follow-up period compared to those without infratentorial hyperintensities. Although we were unable to relate this increased mortality risk to specific death causes, it seems reasonable to assume that this increased hazard ratio is related to cardiovascular (and possibly more specific, stroke-related) death. Future studies should clarify these assumptions and if this would be the case, subjects with infratentorial hyperintensities might benefit from rigorous cardiovascular monitoring and intervention, making the identification of these infratentorial hyperintensities on MRI clinically relevant.

Chapter 9 describes another study based on the PROSPER-cohort that examined in what migraineurs differed from headache-free controls regarding endothelial shear stress, which ensures endothelial homeostasis by exerting tangential force on the endothelium by viscous blood flow. A decrease in endothelial shear stress causes impairment of endothelial structure and function, which may predispose to cerebrovascular damage. In this study, we discovered that carotid artery endothelial shear stress is decreased in migraineurs compared to controls, supporting the widespread hypothesis that migraine is associated with endothelial dysfunction. Moreover, lower carotid artery endothelial shear stress correlated with higher total and deep white matter lesion load in migraineurs, especially females with this condition, but not in headache-free control subjects. This suggests that endothelial shear stress contributes to the development of white matter lesions.

General discussion

Structural and functional brain changes in primary headaches

Complexity of the disorders

The complex nature of primary headache syndromes makes the unravelling of its underlying aetiology difficult. In the past two decades, numerous structural and functional neuroimaging studies have tried to analyse the brain of subjects with primary headache syndromes. Most of these studies have been investigating migraine,[1] but also cluster headache has been studied widely with neuroimaging.[6] Despite the vast number of studies, which all together aid towards our increased understanding of the biological concepts underlying migraine and cluster headache, it is challenging to get a thorough overview of the vast amount of structural and functional changes that have been described in these conditions. Structural and functional neuroimaging studies so far pinpointed a vast number of anatomical (sub)structures of the brain that are supposed to be involved in the pathophysiology of migraine and cluster headache. The clinical picture of migraine includes altered processing of different types of sensory input. Structural changes have been ascribed to all kinds of symptoms caused by dysfunction of the trigeminal nociceptive, visual, auditory, olfactory and vestibular systems.

Interpretation of voxel-based morphometry results

One of the main goals of this thesis was to further explore structural brain changes in two different primary headache disorders (migraine and cluster headache), to increase our understanding in their aetiology, symptomatology as well as effects on brain tissue. We have merely succeeded in our mission. While VBM analyses identified "structural changes" in the brains of both migraine and cluster headache patients that could be linked to pathophysiological concepts in both diseases, the exact nature and role of these changes in these pathophysiological processes require further elucidation. VBM depends strongly on the signal intensity in the T1 images, and we have to keep in mind that the signal intensity is influenced by several factors and processes at a microscopic level, that could be anatomical but also functional. VBM-findings in grey or white matter volume may thus point at different (patho)physiological and metabolic processes, leading to changes in

for instance compounds in intra- and extracellular space, homeostatic balance, and perfusion. Hence, the results of our studies represent a mere starting point for future imaging studies.

The hypothalamus and the brainstem: revisited structures in primary headaches

One of the structures with revived heighted interest in both structural and functional imaging studies is the hypothalamus. This structure was previously pinpointed as the main modulator or even pacemaker in attacks of cluster headache and similar trigeminal autonomic cephalalgias.[7-11] Recent studies using $H_2{}^{15}O$-PET however also showed hypothalamic activation in migraine, both in the prodromal phase in nitroglycerin-induced attacks and during the (spontaneous) headache phase.[12;13] In a recently published study, one subject with migraine was scanned for 30 consecutive days using fMRI.[14] Authors demonstrated altered hypothalamic activity as a response to trigeminal nociceptive stimulation in the 24 hours before onset of the migraine attack, as well as altered functional coupling between the hypothalamus, spinal trigeminal nuclei (particularly in the preictal phase) and the dorsal rostral pons (during the ictal phase).[14] Therefore, although the locations of hypothalamic activation were quite distinct and more posterior in trigeminal autonomic cephalalgias,[7-9;11] involvement of the hypothalamus seems not to be specific for trigeminal autonomic cephalalgias, as the hypothalamus is also involved in migraine. The hypothalamus consists of a subset of nuclei that have various functions and that are entangled in a number of autonomic, metabolic and endocrine regulatory processes and physiological events controlling hunger, thirst, arousal, sleep-wake cycle and circadian rhythms. It even is involved in pain processing.[1] It may therefore serve as major mediator or trigger in part of symptomatology in both migraine and cluster headache. Unfortunately, current imaging methods are not capable of clearly distinguishing between the different hypothalamic nuclei, but with technological advancement leading to better signal-to-noise ratio, spatial and temporal resolution it may become possible to demonstrate involvement of distinct subsets of hypothalamic nuclei in different primary headache syndromes in the near future.

Better imaging quality may also be beneficial in studying the brainstem in migraine, whose activation is thought to be specific for migraine pathophysiology.[15] The dorsal rostral pons has traditionally been considered the generator of migraine attacks.[14] In a patient with both cluster headache and migraine, activation of the dorsal rostral pons was only seen in migraine attacks.[16] This

activation seems to be ipsilateral to the headache side,[17] and may be present as early as in the premonitory phase.[12] In this phase of a migraine attack, spinal trigeminal nuclei in the midbrain show reduced activation after trigeminal nociceptive stimulation,[18] but also activation of the ventral tegmental area in the floor of the midbrain and the periaqueductal grey matter were observed.[12] This shows that numerous small brainstem substructures are involved in migraine (and probably also other primary headache syndromes). For optimal localization of the structures involved, better spatial resolution is required. Further, a high temporal resolution is necessary in functional studies to clearly identify the role of brainstem substructures during various moments of the migraine attack cycle (or the attack cycle in other primary headache syndromes).

Confounding and patient selection

Neuroimaging studies investigating primary headache syndromes so far tend to fail to take into account a major confounder that is shared by all these disorders, in their designs: head pain. By only investigating one type of primary headache syndrome, the specificity of findings remains unclear, as structural or functional changes may be the consequence of repetitive nociceptive input and the autonomic, endocrine, behavioural and emotional responses to this unpleasant experience. Therefore, it is elusive which neuroimaging results should be considered of utter importance in unravelling the biological events underlying primary headache disorders. Inclusion of subjects with other (primary) headache syndromes, as we did in our VBM study in cluster headache patients (Chapter 3), might solve this limitation.

Another real quagmire in primary headache neuroimaging is patient selection. Next to previously mentioned neuroplasticity changes due to repetitive pain, subjects with primary headache syndromes tend to suffer from comorbid (psychiatric) diseases that might affect brain structure. Further, the effect of prophylactic and acute medication that headache patients use on brain plasticity is unknown. Such eventual confounding factors might be eliminated by examining younger, relatively medication-naive subjects without comorbidities shortly after being diagnosed with a primary headache disorder, as they have experienced fewer repetitive brain attacks that might have changed the brain's structure.

Multiphasic & sequential imaging

However, apart from these obscuring factors, the fact that migraine is such a heterogeneous, multifactorial disorder with interindividual variances in cyclicity and consequential symptomatology may be of even greater significance. For instance, migraine is characterized by different attack phases (premonitory, aura, headache, postdromal and interictal phases), that show significant overlap between phases. It should be clear at which point in the migraine cycle subjects are being imaged. For instance, functional blood oxygen level dependent (BOLD) MRI-responses in the spinal trigeminal nuclei during nociceptive stimulation varied in different phases of a migraine attack in one study.[18] It is very likely that similar phase-dependent functional (and therefore also structural) signal changes can be expected elsewhere in the brain that vary due to the cycling behaviour of primary headache syndrome attacks. As a lot of structural and functional imaging studies in the recent past may not have sufficiently taken into account this oscillating behaviour of signal changes, they might have failed on identifying changes that might reflect the increased subject's brain susceptibility to succumb to new headache attacks. It is therefore crucial to image primary headache patients at the same time point within their attack cycles. Moreover, neuroimaging studies in primary headache may benefit from sequential imaging; previously mentioned primary headache attack-related oscillating changes in function or structure might then be detected more easily. Sequential imaging may also facilitate studying the postdromal phase, in which patients recover from their headache attack, to which little attention has been given so far in neuroimaging studies. However, even when fully taking into account the importance of scanning all subjects at the similar points within an attack cycle, one should be aware of the fact that, next to the effects of primary headache syndromes, there are physiological, circadian oscillations in normal biological processes including sleep that affect synaptic plasticity as well.[19-22] To make things even more complex, primary headache syndromes tend to have a thorny interplay with these biological circadian rhythms.[1;23] As it will be impossible to completely eliminate these physiological confounders, scanning patients at the same moment in their attack cycle becomes even more important. This might be especially true for functional studies that make use of techniques with limited ability of performing repeated measurements, such as, for instance, dynamic susceptibility contrast MRI.[24] Therefore, the high inter- and intra-individual variance in cerebral hemodynamics might benefit most from developing imaging techniques such as arterial spin-labelling MRI

which might give us the opportunity to monitor cerebral blood flow changes non-invasively with sufficient spatial and temporal resolution.[24]

Next to these attack phases, there is a huge variation in type, degree and duration of associated symptoms, with for example transient focal neurologic deficits (aura) occurring in only up to a third of migraineurs. Profound knowledge about associated symptomatology should be acquired in primary headache patients that are included in imaging studies. By investigating clearly predefined different subgroups of migraineurs and cluster headache patients one might discover which neuronal mechanisms make subjects susceptible for developing a headache attack, and also for developing its associated symptomatology. For instance, it is unclear why some migraine patients develop a headache without preceding aura, some others do during or immediately after an aura, whereas in some migraineurs typical aura symptoms are not accompanied or followed by headache of any kind. These aforementioned patients with "migraine sans migraine" do not show activation and sensitization of their trigeminovascular pathways in the brainstem and the diencephalon, but the exact pathway responsible for activation of these brain structures in migraine with headache is unclear.[25;26] Comparison of headache patient groups only differing in one subset of symptoms may be helpful in identifying the brain structures mediating or triggering this symptomatology.

Multimodal neuroimaging in primary headache

Preferably, future imaging studies should apply multimodal imaging methods to unravel the physiological or metabolic processes underlying changes in grey and white matter structure. When thinking of multimodal imaging, one should of course think of combining conventional MRI methods, including T1- and T2-weighted sequences, with functional MRI methods including diffusion-weighted imaging, perfusion-weighted imaging, arterial spin labelling, resting-state functional connectivity studies, and MR spectroscopy, which has already been performed in the past years.[1] The resulting combination of both structural and function information may – on a voxelwise or on a more region-of-interest based comparison between subgroups – provide clues on the underlying neuronal, vascular and metabolic mechanisms occurring in different brain areas during various moments within the attack cycle of primary headache syndromes. Recent advances in MRI technology result in images with better signal-to-noise ratio at higher resolution, provid-

ing images with unprecedented anatomical detail.[27] This high anatomical resolution is crucial for differentiating between small brain nuclei and other delicate brain areas to better understand their function and their role in associated brain networks in primary headache patients. Recent technical developments also offer the possibility of combining high-resolution MR imaging with other imaging modalities, such as positron emission tomography (PET). Whereas this latter modality was previously mainly used to study metabolism and perfusion in the migraine brain, other technical possibilities, such as the assessment of receptor binding status, have rather been unexplored in migraine and other headache syndromes. For instance, a recent study used PET with 11C-flumazenil, a ligand selectively binding to the γ-aminobutyric acid $(GABA)_A$-receptor, to study the function of this receptor in the brain in subjects with familial hemiplegic migraine type 1 (FHM1) and spinocerebellar ataxia type 6 (SCA6) associated with the CACNA1A gene mutation.[28] The results of this study showed reduced 11C-flumazenil binding in the cerebellum of both FHM1 and SCA6 patients and in the temporal cortex of FHM1 patients. One could consider experiments using similar PET ligands in conventional migraine, although $GABA_A$-receptors constitute only one subtype of the receptors involved in the complex process of modulation of trigeminovascular nociceptive transmission in migraine.[1] The number of radioligands available for PET is however vastly growing and currently, PET ligands for glutamate,[29] serotonin[30] and orexin[31;32]-receptors are available as well. Metabolic brain mapping will be a challenge due to the heterogeneous, multifactorial character of primary headache syndromes, particularly migraine. Similar difficulties were seen in using molecular imaging techniques in depression,[33] a disorder with quite some similarities and, not to mention, a high comorbidity with migraine. Another major challenge in primary headache neuroimaging research using PET will remain the spatial and temporal resolution of this technique. The former problem of spatial resolution thwarts the anatomical localization of changes in metabolism or receptor binding, but this might be overcome by using hybrid imaging at a PET-MRI-system, allowing for simultaneous high-resolution conventional MRI to provide anatomical detail. Such a system might also allow for simultaneous, dual-modality metabolic imaging with PET and MR spectroscopy.[34] The usage of these different modalities in combination may allow for a proper characterization of the processes that cause increases and decreases in grey and white matter volume as seen in current VBM and surface-based morphometry (SBM) methods.

Migraine and cerebrovascular damage

Next to the previously discussed microstructural changes, another part of this thesis focused on visually detectable structural changes on MRI in primary headache syndromes, with the main interest in cerebrovascular damage to the migraine brain. In the current thesis we found evidence for migraine to be related to different consequences of small vessel disease, although associations were sometimes only present in subgroups of migraineurs. For instance, male migraineurs were at higher risk of having infratentorial hyperintensities.

Gene expression data: the next step in associating migraine and cerebrovascular damage?

Previous studies found an increased risk of supratentorial white matter lesions in female migraine patients, but not in male migraineurs.[35] This suggests that the development of cerebrovascular damage in migraine is multifactorial, influenced by both gender, genetic and environmental factors, such as for instance hormonal changes. Recently, genetic loci that were associated with migraine in genome-wide association studies were integrated with gene expression data of the normal adult brain from the Allen Human Brain Atlas to identify brain regions, cell types and pathways involved in migraine pathophysiology.[36] Migraine-associated genes were found to be enriched in modules that show involvement in cortical neurotransmission, metabolic, mitochondrial and oligodendrocyte function, suggesting that these play a pivotal role in the development of migraine. Likewise, it would be interesting to know whether patterns of cerebrovascular damage in grey and white matter coincide with gene expression data, as this might hint at specific mono- or oligogenic conditions causing vasculopathies that underlie both migraine symptomatology and brain lesions in subgroups of migraineurs.

The number of rare, inherited cerebral small vessel diseases with migraine as a major symptom that often also have extracerebral, systemic manifestations has been steadily growing over the past years, as is seen in for instance the disease recently redefined "retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations" or RVCL-S.[37;38] This condition has clinically been under-recognized and misdiagnosed in previous years and has only received recognition very recently. It is very likely that similar underdiagnosed conditions are present amongst the population currently treated for "general" migraine. Associating cerebrovascular damage patterns with gene expression data may also explain why some migraineurs, or why specific brain regions, such

as the posterior fossa, are more susceptible for developing particular types of cerebrovascular damage. The other way around, in case migraine-associated genes might also be related to brain lesions, their expression profile may lead to the discovery of cerebrovascular damage that may have gone undetected so-far; if genes are expressed in particular brain areas, one might become more aware of the cerebrovascular damage in those areas.

Migraine: need for ultra-high field strength MRI?

In this light, it will also be important to acquire MR images with high spatial resolution on an ultra-high field strength of 7T, allowing for instance for easy detection of cerebral microinfarcts,[39] as these might have been underrecognized in migraineurs up till now. Cortical microinfarcts were detected in patients with cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a disease with migraine with aura as a major symptom, only a few years ago.[40] These microinfarcts are another hallmark of small vessel disease and might be more prevalent in migraineurs. Particularly also cerebellar microinfarcts should be mentioned in this matter, as these might not be secondary to low flow in between arterial perfusion territories, but rather represent the end-result of occlusion of small end-arteries in the cerebellum.[41] High resolution MR images of the cerebellum might show whether these cerebellar microinfarcts are associated with migraine as well, as other types of small vessel disease in the posterior fossa that were discussed previously in this thesis. Next to a better detection of cortical and cerebellar microinfarcts, imaging at 7T may also improve insights in other aspects of small vessel disease, such as the anatomy of small arteries at 3D time-of-flight MR angiography and venous anatomy, hemosiderin and iron deposits on T2*-weighted sequences.[39] Thus, scanning at higher field strengths with greater anatomical detail may show better the consequences of small vessel disease in migraineurs and may help to identify migraineurs that are at increased risk of these types of cerebrovascular damage.

Migraine and cerebrovascular reactivity

Small vessel disease affects the structure and function of small cerebral vessels, such as arteries, arterioles, capillaries and sometimes venules.[42] Different mechanisms may contribute to both hemorrhagic and ischemic markers of small vessel disease. These include for instance changes in

endothelial function, aggregations of platelets and inflammatory responses. These processes may lead to impaired cerebrovascular reactivity, the response of cerebral blood vessels to react to vaso-active stimuli. Particular advanced imaging methods may aid in understanding the underlying pathophysiology of microangiopathy in migraineurs, by assessing this cerebrovascular reactivity. In recent years, MRI with BOLD and arterial spin labelling has increasingly been used to measure cerebrovascular reactivity in response to a stimulus, for instance carbon dioxide.[43] Using such techniques in migraineurs may increase our understanding about the relationship between migraine, small vessel disease and cerebrovascular damage.

Conclusion

In summary, primary headache syndromes are associated with macrostructural as well as microstructural brain changes. Some of these brain changes may be congenital, some may represent reversible or irreversible neuroplastic changes as a response of the brain to adapt to external stimuli and others should be considered as brain damage associated with these primary headache syndromes. Cluster headache patients have larger anterior hypothalamic volumes and wider skulls, observations that oppose previous neuroimaging findings and pathophysiological theories. Migraine is associated with microstructural changes in particularly visual processing areas in both cortical and subcortical grey matter and in white matter tracts connecting these structures. These changes might in part be irreversible or may have existed throughout life. Some migraineurs are also at increased risk of visually detectable changes on MRI, such as infratentorial microbleeds and, in male migraineurs, infratentorial hyperintensities. The underlying etiology of these types of cerebrovascular damage remains elusive and is probably the consequence of a multifactorial process.

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Samenvatting, discussie en conclusies

Samenvatting

Het hoofddoel van dit proefschrift was om te onderzoeken op welke wijze de hersenen structureel verschillen in clusterhoofdpijn en migraine, om zo verdere kennis te vergaren over symptomatologie, onderliggende pathofysiologie en mogelijk schadelijke effecten van deze aandoeningen. Hiertoe gebruikten we naast conventionele ook geavanceerde MRI-technieken met moderne hedendaagse beeldverwerkingstechnieken om zowel macrostructurele als microstructurele veranderingen in de beide hoofdpijnaandoeningen op te sporen.

In **Hoofdstuk 2** presenteerden wij een vroeg 18e-eeuwse beschrijving van een patiënt die vermoedelijk leed aan clusterhoofdpijn. Het illustreert de algemene zin om oog te hebben voor historische onderzoeksgegevens. Allereerst, in dit specifieke geval, gaf de casus informatie over het bestaan en het karakter van zogenaamde trigeminale autonome cefalalgieën in vroegere tijden. Ideeën over de etiologie van primaire hoofdpijnsyndromen hebben zich in de loop der tijden ontwikkeld. Thans bestaat soms de noodzaak terug te grijpen op originele theorieën van tientallen jaren oud of van zelfs langer geleden.[1] Ten tweede kunnen eerder genegeerde waarnemingen en theorieën over pathologische processen ons soms helpen om de onderzoeksresultaten van heden ten dage te begrijpen en kunnen zij zo de basis vormen voor toekomstig wetenschappelijk onderzoek.[2] Ten derde kan een herbeoordeling van historische bevindingen soms de oorsprong van onjuiste hypotheses verklaren. De theorie dat een primair probleem met de hersenbloedvaten verantwoordelijk zou zijn voor migraine bleek bijvoorbeeld gebaseerd op inconsistente onderzoeksresultaten van Harold Wolff en zijn collega's.[1]

In **Hoofdstuk 3** beoordeelden we de structuur van de hersenen van patiënten met clusterhoofdpijn door voxel-gebaseerde morfometrie ("voxel-based morphometry", VBM) toe te passen op hoge resolutie anatomische T1-gewogen MRI-beelden. Op verschillende manieren waren wij niet in staat om de bevinding uit een eerder veelvuldig geciteerd onderzoek, waarbij gevonden werd dat het inferoposterieure gedeelte van de hypothalamus een groter volume had, te reproduceren. In plaats daarvan ontdekten wij veranderingen in een ander gedeelte van de hypothalamus. Door het toepassen van een VBM-analyse in een gebied van interesse en een aanvullende handmatige segmentatie van de hypothalamus vonden wij een beiderzijdse toename in het volume van de hypothalamus. Deze volumetoename was hoofdzakelijk gelokaliseerd in het voorste gedeelte van

de hypothalamus. Hypothalamuskernen die verantwoordelijk kunnen zijn voor deze volumetoename zijn de nucleus suprachiasmaticus en de nucleus paraventricularis. De nucleus suprachiasmaticus wordt beschouwd als de innerlijke biologische klok en is gelieerd aan circadiaanse en jaarlijkse ritmes die clusterhoofdpijnaanvallen en –perioden karakteriseren. De nucleus paraventricularis wordt gezien als de mogelijke initiator of modulator van hoofdpijnaanvallen vanwege zijn rol in de regulatie van nociceptieve en autonome input.[3] Desalniettemin kunnen uit deze studie geen definitieve conclusies worden getrokken ten aanzien van de aard van de volumetoename in de hypothalamus. Het nauwkeurig bepalen van hersenstructuur middels MRI is sterk afhankelijk van T1-signaalintensiteitsveranderingen en deze kunnen bijvoorbeeld worden veroorzaakt door veranderingen in het aantal of de grootte van neuronen, verschuivingen van vloeistof tussen de intra- en extracellulaire ruimte en gliose. Onderscheid tussen de verschillende processen die het signaal kunnen beïnvloeden is niet mogelijk door middel van alleen T1-gewogen MRI. Voor een beter begrip van deze processen moeten we weten wat er gebeurt op moleculair niveau. Daarvoor zijn multimodale moleculaire beeldvormende technieken noodzakelijk, die bijvoorbeeld MRI en positronemissietomografie (PET) combineren. Een andere zorg die door onze resultaten wordt gebaard is dat VBM er niet in slaagde de meer globale structurele veranderingen in het kleine gebied van de hypothalamus vast te stellen. Mogelijkerwijs verklaart dit waarom vorige studies er niet in slaagden om morfometrische veranderingen in dit hersengebied te detecteren. VBM lijkt dus minder sensitief voor de analyse van kleinere structuren, wat kan leiden tot foutnegatieve resultaten.

In **Hoofdstuk 4** onderzochten wij of clusterhoofdpijn geassocieerd is met een aangeboren of verworven nauwere sinus cavernosus. Eerder werd gesuggereerd dat dit zou predisponeren voor dit type hoofdpijn. We gebruikten MRI met hogeresolutiebeelden om het gebied van de sinus cavernosus te onderzoeken, maar we vonden noch aanwijzingen voor structurele afwijkingen in dit gebied, noch voor kleinere afmetingen van de sinus cavernosus. Daarentegen vonden we dat patienten met clusterhoofdpijn en chronische paroxysmale hemicranie bredere schedels hadden dan hoofdpijnvrije controleproefpersonen, hetgeen in overeenstemming zou kunnen zijn met observaties van zogenaamde leeuwengezichtstrekken die enkele decennia geleden in clusterhoofdpijnpatienten werden beschreven.

In **Hoofdstuk 5** ontdekten we met behulp van VBM structurele veranderingen, vooral in de V3 en V5 visuele gebieden van de occipitale corticale grijze stof, bij migrainepatiënten uit de gewone populatie afkomstig uit het "Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA)"-cohort. Vergelijkbare veranderingen waren aanwezig bij zowel migraine met als zonder aura en veranderingen in het V3 visuele gebied waren aanwezig onafhankelijk van ziekteactiviteit of aanvalsfrequentie. Enkele van deze veranderingen waren nog steeds aanwezig terwijl patiënten al meerdere jaren geen aanvallen meer hadden ervaren. Dit suggereert dat deze veranderingen onherstelbaar zijn of dat ze gedurende het gehele leven hebben bestaan. Neuroplasticiteitsveranderingen (dat wil zeggen veranderingen in de structuur en organisatie van de hersenen als gevolg van hun capaciteit om zich aan te passen aan uitwendige stimuli, zoals herhaaldelijke episodes van pijn ten gevolge van terugkerende migraineaanvallen) lijken daar een minder waarschijnlijke verklaring. Verder toonden we aan dat ook subcorticale grijze stof (het corpus geniculatum laterale) en wittestofbanen anders in samenstelling zijn bij migrainepatiënten in vergelijking met controleproefpersonen. De meerderheid van deze corticale en subcorticale gebieden lijken te zijn betrokken bij de verwerking van visuele prikkels. Door gebruik te maken van deze proefpersonen, afkomstig uit de algemene populatie, wisten wij mogelijke oorzaken van statistieke vertekening (bias), zoals comorbiditeit en overgebruik van geneesmiddelen, te minimaliseren. Deze oorzaken van bias hebben vermoedelijk de resultaten van eerdere VBM-studies beïnvloed, aangezien veel eerdere studies werden uitgevoerd in gespecialiseerde hoofdpijncentra met migrainepatiënten met ernstiger klachten in vergelijking met de door ons bestudeerde gemiddelde migrainepatiënt uit de algemene bevolking..

In **Hoofdstuk 6** beschreven we de resultaten van onze studie met magnetisatie-transfer- beeldvorming om de integriteit van witte stof in migrainepatiënten uit de CAMERA-studie te beoordelen. Wij vonden geen wijdverspreide microstructurele wittestofveranderingen in migraine. We onderzochten echter ook de integriteit van witte stof in gebieden die in een tijdsbestek van 9 jaar van normaal uitziende witte stof veranderden in op T2-gewogen MRI-beelden zichtbare, hyperintense wittestoflaesies. We stelden vast dat de magnetisatie-transfer-ratio (MTR)-waarden in deze wittestofgebieden waren verlaagd, wat duidt op microstructurele veranderingen ter plaatse, terwijl deze gebieden op conventionele MRI nog als normale witte stof oogden. Dit suggereert dat structurele hersenveranderingen aanwezig zijn alvorens zij zichtbaar worden als wittestofhyperintensi-

teiten op T2-gewogen MRI. Dit zou kunnen betekenen dat een chronische systeemziekte verantwoordelijk is voor het optreden van deze hersenlaesies.

Cerebrale microbloedingen, een karakteristieke eigenschap van cerebrale microangiopathie (dat wil zeggen een aandoening van de kleinste hersenvaten), zijn nooit eerder onderzocht in migraine. In **Hoofdstuk 7** onderzochten we de prevalentie van cerebrale microbloedingen in de oudere deelnemers aan de "PROspective Study of Pravastatin in the Elderly at Risk (PROSPER)"-studie. Migraine, voornamelijk migraine zonder aura, was een onafhankelijke risicofactor voor infratentoriële microbloedingen. Samen met eerdere bevindingen van een verhoogd risico op cerebellaire infarcten bij migraine wijst dit opnieuw op mogelijke fragiliteit van de kleine hersenvaten in de fossa posterior.[4;5] Cerebrale microbloedingen en infarcten komen ook vaker voor bij migrainepatiënten dan bij controleproefpersonen, wat verder bewijs vormt voor een mogelijke rol voor microangiopathie bij in ieder geval een subpopulatie van migrainepatiënten voor wat betreft de ontstaanswijze van aan migraine gerelateerde cerebrovasculaire schade.

Voor **Hoofdstuk 8** onderzochten we de prevalentie en ernst van infratentoriële hyperintensiteiten, dat wil zeggen T2-hyperintense laesies in de pons en cerebellaire witte stof. We onderzochten hun associaties met cardiovasculaire risicofactoren en andere soorten cerebrovasculaire schade. In het cohort van de eerder genoemde PROSPER-studie bleken hogere leeftijd, roken en een lagere body mass index te correleren met het vaker voorkomen van en een grotere ernst aan infratentoriele hyperintensiteiten. Mannelijke migrainepatiënten hadden in deze populatie een verhoogd risico op dit specifieke type cerebrovasculaire schade. Dit is opmerkelijk, aangezien in eerder onderzochte populaties alleen vrouwelijke migrainepatiënten een verhoogd risico op supratentoriële wittestoflaesies hadden. De aanwezigheid van infratentoriële hyperintensiteiten bleek ook geassocieerd met de prevalentie van lacunaire en infratentoriële infarcten en de hoeveelheid supratentoriële wittestofschade. Dit lijkt erop te wijzen dat ook infratentoriële hyperintensiteiten een kenmerk van ischemische cerebrale microangiopathische schade vormen. Verder ontdekten we in deze oudere populatie dat personen met ernstige, confluerende infratentoriële hyperintensiteiten een twee keer zo hoge kansverhouding hadden om in de follow-upperiode te overlijden dan diegenen zonder hyperintensiteiten in de fossa posterior. Hoewel we door een gebrek aan data niet in staat waren dit verhoogde mortaliteitsrisico aan specifieke doodsoorzaken te relateren, ligt het voor de hand dat deze verhoogde *hazard ratio* samenhangt met cardiovasculaire doodsoorzaken

(en mogelijkerwijs, meer specifiek, beroerte). Toekomstige studies moeten deze aannames proberen te bevestigen en als dit inderdaad het geval is, zouden diegenen met infratentoriële hyperintensiteiten baat kunnen hebben bij rigoureuze cardiovasculaire monitoring en interventie, waardoor het herkennen van deze infratentoriële hyperintensiteiten op MRI klinisch relevant wordt.

Hoofdstuk 9 beschreef een andere studie gebaseerd op het PROSPER-cohort. Voor deze studie onderzochten we op welke wijze migrainepatiënten verschilden van hoofdpijnvrije controleproefpersonen met betrekking tot endotheliale *shear stress*. Deze shear stress garandeert endotheliale homeostase door met behulp van een viskeuze bloedstroom een tangentiële kracht op het endotheel uit te oefenen. Een verlaagde endotheliale shear stress heeft negatieve uitwerkingen op de structuur en functie van het endotheel, hetgeen kan predisponeren voor cerebrovasculaire schade. In deze studie ontdekten wij dat de endotheliale shear stress in de halsslagaderen was verlaagd in migrainepatiënten in vergelijking met controleproefpersonen, wat ondersteuning biedt aan de wijdverbreide hypothese dat migraine is geassocieerd met endotheliale dysfunctie. Verder correleerde een lagere endotheliale shear stress in de halslagaderen met hogere totale wittestofschade en diepewittestofschade bij migrainepatiënten, vooral bij vrouwen met deze aandoening, maar niet bij hoofdpijnvrije controleproefpersonen. Dit suggereert dat endotheliale shear stress een rol speelt in de ontwikkeling van wittestoflaesies.

Algemene discussie

Structurele en functionele hersenveranderingen in primaire hoofdpijnsyndromen

Complexiteit van de aandoeningen

De complexe aard van primaire hoofdpijnsyndromen maakt het lastig de onderliggende etiologie te ontrafelen. In de afgelopen twee decennia zijn ontelbare studies met structurele en functionele beeldvorming van de hersenen uitgevoerd in personen met primaire hoofdpijnsyndromen. De meeste van deze studies onderzochten migraine,[1] maar ook clusterhoofdpijn is uitgebreid onderzocht met beeldvorming van de hersenen.[6] Al deze studies tezamen hebben bijgedragen aan een verbeterd begrip van de biologische concepten die ten grondslag liggen aan migraine en clusterhoofdpijn. Desalniettemin is het ondanks dit grote aantal studies zeer uitdagend om een grondig overzicht te krijgen van de grote hoeveelheid structurele en functionele hersenveranderingen die

zijn toegeschreven aan deze aandoeningen. Structurele en functionele beeldvorming van de hersenen identificeerde tot dusverre een aanzienlijk aantal anatomische (sub)structuren van de hersenen die betrokken zouden zijn in de pathofysiologie van migraine en clusterhoofdpijn. Het klinische beeld van migraine omvat onder andere een veranderde verwerking van verschillende soorten sensorische stimuli. Structurele veranderingen zijn toegeschreven aan allerlei symptomen, veroorzaakt door dysfunctie van trigeminale nociceptieve, visuele, auditieve, olfactorische en vestibulaire systemen.

Interpretatie van voxel-gebaseerde morfometrieresultaten

Een van de belangrijke doelen van dit proefschrift was om verder onderzoek te doen naar structurele hersenveranderingen in twee verschillende primaire hoofdpijnsyndromen (migraine en cluster hoofdpijn) om zo ons begrip van deze aandoeningen met betrekking tot de etiologie, de symptomen en de effecten op het hersenweefsel te vergroten. Wij zijn ten dele geslaagd in onze missie. VBM-analyses identificeerden "structurele veranderingen" in de hersenen van zowel patiënten met migraine als patiënten met clusterhoofdpijn die kunnen worden gelinkt aan pathofysiologische concepten in deze beide aandoeningen. De exacte aard en rol van deze veranderingen in die pathofysiologische processen moeten echter nog worden opgehelderd. VBM is sterk afhankelijk van signaalintensiteitsveranderingen op T1-gewogen beelden. De signaalintensiteit wordt beïnvloed door verschillende, zowel anatomische als fysiologische, factoren en processen op microscopisch niveau. VBM-verschillen in grijze en witte stof kunnen dus het gevolg zijn van verschillende (patho)fysiologische en metabole processen die bijvoorbeeld leiden tot veranderde samenstellingen in intra- en extracellulaire ruimte, homeostatisch evenwicht en perfusie. Derhalve vormen de resultaten van onze studies vooral een startpunt voor verder beeldvormend wetenschappelijk onderzoek.

De hypothalamus en de hersenstam: structuren met hernieuwde aandacht in primaire hoofdpijnsyndromen

Een van de structuren die recentelijk hernieuwde interesse heeft gewekt in zowel structurele als functionele beeldvormende onderzoeken is de hypothalamus. Deze structuur is in het verleden aangewezen als de belangrijkste modulator of wellicht zelfs initiator van aanvallen van cluster-

hoofdpijn en soortgelijke trigeminale autonome cefalalgieën.[7-11] Recente studies die gebruik maakten van $H_2{}^{15}O$-PET toonden echter ook verhoogde hypothalame activiteit aan bij met behulp van nitroglycerine geïnduceerde migraineaanvallen, zowel in de prodromale fase als gedurende de (spontane) hoofdpijnfase.[12;13] In een recent gepubliceerd onderzoek werd een persoon met migraine dertig opeenvolgende dagen gescand met functionele MRI (fMRI).[14] De onderzoekers demonstreerden veranderde activiteit in de hypothalamus in reactie op trigeminale pijnstimulatie in de 24 uur voorafgaand aan de migraineaanval, als ook veranderingen in de verbindingen tussen hypothalamus, de spinale trigeminale nuclei (vooral in de pre-ictale fase) en het dorsorostrale deel van de pons (gedurende de aanvalsfase).[14] Daarom, hoewel de locatie van hypothalame activatie eigenlijk wel meer naar posterieur gelegen is in trigeminale autonome cefalalgieën dan in migraine,[7-9;11] lijkt betrokkenheid van de hypothalamus niet specifiek voor deze trigeminale autonome cefalalgieën, aangezien de hypothalamus ook verwikkeld is in migraine. De hypothalamus bestaat uit een onderverdeling van kernen die verschillende functies hebben en die betrokken zijn in een aanzienlijk aantal autonome, metabole en endocriene regelprocessen en fysiologische gebeurtenissen omtrent honger, dorst, opwinding, slaapwaakritme en circadiaanse ritmen. De hypothalamus is zelfs betrokken in het verwerken van pijnstimuli.[1] Daarom zou de structuur kunnen dienen als een belangrijke mediator of trigger in een deel van de symptomatologie van zowel migraine als clusterhoofdpijn. Helaas zijn huidige beeldvormende onderzoeksmethoden niet in staat een duidelijk onderscheid te maken tussen verschillende hypothalame nuclei, maar met technische vooruitgang die leidt tot betere signaalruisverhouding, spatiële en temporele resolutie wordt het in de nabije toekomst wellicht mogelijk om de betrokkenheid van verscheidene subsets van hypothalame nuclei in de verschillende primaire hoofdpijnsyndromen aan te tonen.

Een betere beeldkwaliteit heeft wellicht ook een positieve invloed op het bestuderen van de hersenstam in migraine. Activiteit van deze structuur wordt geacht specifiek te zijn voor migrainepathofysiologie.[15] Het dorsorostrale gedeelte van de pons wordt traditioneel beschouwd als de generator van migraineaanvallen.[14] Bij een patiënt, gebukt gaande onder zowel clusterhoofdpijn als migraine, werd activatie van de dorsorostrale pons enkel gezien in migraineaanvallen.[16] Deze activatie lijkt ipsilateraal aan de hoofdpijnzijde gelokaliseerd te zijn[17] en is mogelijkerwijs al in de prodromale fase aanwezig.[12] In deze fase van een migraineaanval tonen spinale trigeminale nuclei in het mesencefalon verlaagde activiteit na trigeminale pijnstimulatie.[18] Ook wordt activatie van

de area tegmentalis ventralis aan de onderzijde van de middenhersenen en in de periaqueductale grijze stof waargenomen.[12] Dit toont aan dat er talrijke kleine hersenstamstructuren betrokken zijn bij migraine (en waarschijnlijk ook bij andere primaire hoofdpijnsyndromen). Voor optimale lokalisatie van de betrokken structuren is een betere spatiële resolutie noodzakelijk. Verder is een hoge temporele resolutie nodig in studies met functionele beeldvorming om de rol van hersenstamonderdelen in de verschillende momenten in de aanvalscyclus van migraine (of andere hoofdpijnsyndromen) in kaart te brengen.

Confounding en patiëntselectie

Studies die tot dusverre met neurobeeldvorming primaire hoofdpijnsyndromen hebben onderzocht corrigeren in hun onderzoeksdesign vaak niet voor een belangrijke factor die deze aandoeningen met elkaar delen: hoofdpijn. Door slechts één type primaire hoofdpijn te onderzoeken blijft de specificiteit van bevindingen onduidelijk, omdat structurele en functionele veranderingen het gevolg kunnen zijn van herhaalde nociceptieve stimuli en autonome, endocriene, gedrags- en emotionele reacties op deze onaangename ervaring. Daardoor is het niet duidelijk welke resultaten van eerdere neurobeeldvormingsstudies als uiterst belangrijk moeten worden beschouwd in het ontrafelen van de biologische processen die ten grondslag liggen aan primaire hoofdpijnsyndromen. Door personen die lijden aan andere (primaire) hoofdpijnsyndromen toe te voegen, zoals wij deden in onze VBM-studie in clusterhoofdpijnpatiënten (Hoofdstuk 3), zou deze beperking kunnen worden omzeild.

Patiëntselectie bij neurobeeldvorming in primaire hoofdpijn kost eveneens heel wat hoofdbrekens. Naast de reeds genoemde neuroplasticiteitsveranderingen ten gevolge van terugkerende pijn lijden personen met primaire hoofdpijn vaker aan (psychiatrische) comorbiditeit die hersenstructuur eveneens kan beïnvloeden. Verder is het effect van aanvals- en profylactische medicatie die hoofdpijnpatiënten gebruiken op de plasticiteit van de hersenen onbekend. Dergelijke factoren die van invloed zouden kunnen zijn worden uitgeschakeld door jongere, relatief medicatienaïeve personen zonder comorbiditeit te onderzoeken, korte tijd nadat bij hen de diagnose van een primair hoofdpijnsyndroom is vastgesteld. Over het algemeen hebben zij minder hoofdpijnaanvallen ervaren die de hersenstructuur zouden kunnen hebben beïnvloed en zijn eventueel aangetoond verschillen aannemelijker specifiek voor het hoofdpijnsyndroom zelf.

Multi-gefaseerde en sequentiële beeldvorming

Naast de eerder genoemde beperkende factoren is het misschien nog wel belangrijker om op te merken dat migraine een heterogene, multifactoriële aandoening is, met grote interindividuele verschillen in cyclisch karakter en bijkomende symptomen. Zo wordt migraine gekarakteriseerd door verschillende aanvalsfasen (prodromale, aura-, hoofdpijn-, postdromale en interictale fase) die elkaar ook nog eens overlappen. Het moet helder zijn op welk moment in de migrainecyclus onderzoeksdeelnemers worden onderzocht. Zo varieerden in één studie de functionele bloedzuurstofniveau-afhankelijke ("functional blood oxygen level dependent", BOLD) MRI-signalen in de nucleus spinalis van de nervus trigeminus na het geven van pijnstimulatie met de verschillende fasen van een migraineaanval.[18] Het is goed mogelijk dat vergelijkbare fase-afhankelijke functionele (en derhalve ook structurele) signaalveranderingen elders in de hersenen op vergelijkbare wijze variëren ten gevolge van het cyclische karakter van aanvallen van primaire hoofdpijn. Aangezien veel recente studies met structurele en functionele beeldvorming onvoldoende rekening hebben gehouden met dit schommelende gedrag van signaalveranderingen, is men er mogelijk niet in geslaagd veranderingen te identificeren die de gevoeligheid van de hersenen om ten prooi te vallen aan nieuwe hoofdpijnaanvallen weerspiegelen. Het is daarom van doorslaggevend belang om beeldvorming in primaire hoofdpijnpatiënten op hetzelfde moment gedurende aanvalscycli te laten plaatsvinden. Daarnaast zouden onderzoeken naar primaire hoofdpijn met behulp van beeldvorming baat kunnen hebben bij opeenvolgende beeldvorming; eerder genoemde functionele of structurele signaalveranderingsschommelingen gerelateerd aan primaire hoofdpijnaanvallen zouden daarmee gemakkelijker kunnen worden opgemerkt. Sequentiële beeldvorming zou het ook eenvoudiger maken om de postdromale fase, de fase waarin patiënten herstellen van hun hoofdpijnaanval, in kaart te brengen. Voor deze fase is tot dusverre weinig aandacht geweest in studies die gebruik maakten van neurobeeldvorming.

Echter, zelfs wanneer deelnemers op dezelfde momenten binnen de aanvalscyclus worden onderzocht, moet men zich er ook van bewust zijn dat, naast de effecten van primaire hoofdpijnsyndromen, er bovendien een fysiologische circadiaanse schommeling bestaat in normale biologische processen (waaronder bijvoorbeeld slaap) die ook synaptische plasticiteit kunnen beïnvloeden.[19-22] Om de zaken nog complexer te maken, oefenen primaire hoofdpijnsyndromen op zichzelf ook nog invloed uit op deze biologische circadiaanse ritmes.[1;23] Daar het onmogelijk zal zijn om deze

fysiologische confounders volledig uit te schakelen wordt het belang om patiënten op hetzelfde moment in de aanvalscyclus te onderzoeken nog groter. Dit is wellicht in de eerste plaats relevant voor functionele studies die gebruiken maken van technieken met een beperkte mogelijkheid om herhaalde metingen te verrichten, zoals dynamische susceptibiliteitscontrast MRI.[24] Gezien er sprake is van een hoge inter- en intraindividuele variantie in cerebrale hemodynamica, kunnen nieuwe beeldvormende technieken zoals arteriële spin-labelling MRI ons wellicht de mogelijkheid geven om cerebrale bloedstroomveranderingen niet-invasief met voldoende spatiële en temporele resolutie te vervolgen.[24]

Naast de verschillende aanvalsfasen in migraine bestaat bij migraine een grote variatie in type, ernst en duur van gerelateerde symptomen. Zo treden voorbijgaande focale neurologische verschijnselen (aura) bij slechts een derde van migrainepatiënten op. Grondige kennis van de geassocieerde symptomatologie moet worden verkregen in primaire hoofdpijnpatiënten die aan beeldvormende studies deelnemen. Door goed vooraf gedefinieerde subgroepen van migraine- en clusterhoofdpijnpatiënten te onderzoeken wordt men in staat gesteld om de neuronale mechanismen te ontdekken die personen gevoelig maken voor het ontwikkelen van een hoofdpijnaanval en gerelateerde symptomatologie. Zo is het nu nog onbekend waarom sommige migrainepatiënten hoofdpijn ontwikkelen zonder voorafgaand aura, anderen gedurende of direct na een aura, terwijl sommige migrainepatiënten typische aurasymptomen ervaren die niet worden vergezeld of opgevolgd door wat voor hoofdpijn dan ook. De hiervoor genoemde patiënten met "migraine sans migraine" laten geen activatie en sensibilisatie van hun trigeminovasculaire trajecten in de hersenstam en het diencefalon zien, maar de precieze wijze waarop deze hersenstructuren in migraine met hoofdpijn geactiveerd worden is niet bekend.[25;26] Het vergelijken van verschillende groepen hoofdpijnpatiënten die slechts verschillen voor wat betreft één symptoom zou kunnen helpen in het vaststellen van hersenstructuren die deze symptomen mediëren of triggeren.

Multimodale beeldvorming in primaire hoofdpijn

Bij voorkeur maken toekomstige studies gebruik van multimodale beeldvormende technieken om de fysiologische en metabole processen bloot te leggen die ten grondslag liggen aan veranderingen in grijze en witte stof. Denkend aan multimodale beeldvorming kan men natuurlijk overwegen conventionele MRI-methoden, inclusief T1- en T2-gewogen sequenties, te combineren met func-

tionele MRI-methoden inclusief diffusiegewogen MRI, perfusiegewogen MRI, arteriële spin-labelling, functionele connectiviteitsstudies die de hersenen in ruststand onderzoeken (zogenaamde "resting-state fMRI") en MR-spectroscopie, hetgeen reeds in de afgelopen jaren is gedaan.[1] De daaruit voortvloeiende combinatie van structurele en functionele gegevens zou – door subgroepen te vergelijken, hetzij met op een voxel-bij-voxel gebaseerde benadering dan wel middels een analyse met een gebied van interesse – aanwijzingen kunnen bevatten over de onderliggende neuronale, vasculaire en metabole mechanismen die plaatsvinden in verscheidene hersengebieden gedurende verschillende momenten in de aanvalscyclus van primaire hoofdpijnsyndromen. Nieuwe ontwikkelingen in MRI-technologie leiden tot afbeeldingen met een betere signaal-ruisverhouding en een hogere resolutie, wat afbeeldingen met onovertroffen anatomisch detail oplevert.[27] Deze hoge anatomische resolutie is cruciaal om onderscheid te kunnen maken tussen verschillende kleine hersenkernen en andere verfijnde hersengebieden om zo beter hun functie en hun rol in gerelateerde hersennetwerken in primaire hoofdpijnpatiënten te begrijpen. Recente technische vooruitgang geeft bovendien de mogelijkheid om hoge resolutie MRI te combineren met andere beeldvormingsmodaliteiten, zoals positronemissietomografie (PET).Waar deze laatstgenoemde modaliteit eerder voornamelijk werd gebruikt om het metabolisme en de perfusie in de migrainehersenen te onderzoeken, zijn andere nieuwe technische mogelijkheden, zoals het onderzoeken van de status van receptorbinding op het celmembraan van neuronen in de hersenen, nog nauwelijks toegepast in migraine en andere hoofdpijnsyndromen. Zo werd in een recente studie gebruik gemaakt van PET in combinatie met 11C-flumazenil, een ligand die selectief bindt aan de gamma-aminoboterzuur (GABA)A-receptoren, om zo de functie van deze receptor te onderzoeken in de hersenen van personen met familiaire hemiplegische migraine type 1 (FHM1) en spinocerebellaire ataxie type 6 (SCA6) gerelateerd aan de CACNA1A-genmutatie.[28] De resultaten van deze studie toonden verminderde binding van 11C-flumazenil in de kleine hersenen van zowel patiënten met FHM1 als SCA6 en in de temporale cortex van FHM1-patiënten. Men zou kunnen overwegen soortgelijke PET-liganden te gebruiken bij conventionele migraine. $GABA_A$-receptoren vormen daarbij slechts een subtype van receptoren die betrokken zijn in het complexe moduleringsproces van trigeminovasculaire nociceptieve transmissie bij migraine.[1] Het aantal radioliganden dat voor PET beschikbaar komt, is continu groeiende en momenteel zijn er ook liganden voor glutamaat-,[29] serotonine-[30] en orexinereceptoren[31;32] beschikbaar. Het in kaart brengen van het

hersenmetabolisme zal uitdagend worden vanwege het heterogene, multifactoriële karakter van primaire hoofdpijnsyndromen, vooral in migraine. Soortgelijke problemen openbaarden zich bij het gebruik van moleculaire beeldvorming in depressie,[33] een aandoening met nogal wat overeenkomsten en, niet te vergeten, een hoge comorbiditeit met migraine. Een andere uitdaging in neurobeeldvorming met gebruikmaking van PET in primaire hoofdpijn zal worden gevormd door de spatiële en temporele resolutie van deze techniek. Het eerstgenoemde probleem van spatiële resolutie verhindert precieze anatomische lokalisatie van veranderingen in metabolisme of receptorbinding. Dit probleem kan echter worden opgelost door gebruik te maken van hybride beeldvorming op een PET-MRI-systeem, die de onderzoeker in staat stelt gelijktijdig conventionele MRI-beelden met een hoge resolutie te verkrijgen voor het benodigde anatomische detail. Een dergelijk systeem maakt het ook mogelijk om gelijktijdig metabole beeldvorming met PET en MR-spectrografie te verrichten.[34] Het gebruik van deze verschillende modaliteiten zou een beter inzicht kunnen geven in de processen die verantwoordelijk zijn voor de toe- en afnamen in grijze- en wittestofvolume zoals waargenomen in voxel-gebaseerde (VBM) en op oppervlakte gebaseerde morfometrische ("surface-based morphometry", SBM) methoden.

Migraine en cerebrovasculaire schade

Naast de hierboven bediscussieerde microstructurele veranderingen focuste een ander deel van dit proefschrift zich op visueel detecteerbare structurele veranderingen op MRI bij primaire hoofdpijnsyndromen, met een bijzondere interesse voor cerebrovasculaire schade in het migrainebrein.

Genexpressiedata: de volgende stap voor de associatie tussen migraine en cerebrovasculaire schade?

In de huidige thesis vonden wij bewijs dat migraine is gerelateerd aan verschillende gevolgen van microangiopathie, hoewel de associaties soms alleen werden gevonden bij subgroepen van migrainepatiënten. Mannelijke personen met migraine hadden bijvoorbeeld een verhoogd risico op het hebben van infratentoriële hyperintensiteiten. Eerdere studies vonden een verhoogd risico op supratentoriële wittestoflaesies in vrouwelijke, maar niet in mannelijke migrainepatiënten.[35] Dit suggereert dat de ontwikkeling van cerebrovasculaire schade bij migraine multifactorieel is en wordt beïnvloed door zowel geslacht, genetische factoren en omgevingsfactoren, zoals hormonale veranderingen. Onlangs werden genetische loci, die zijn gerelateerd aan migraine in genoombrede

associatiestudies, gekoppeld aan genexpressiedata van de normale volwassen hersenen van de Allen Human Brain Atlas, om zo mogelijke hersengebieden, celtypes en neuronale routes te ontdekken die in de migrainepathofysiologie zouden kunnen zijn betrokken.[36] De met migraine geassocieerde genen bleken te zijn verrijkt in modules die betrokkenheid toonden bij corticale neurotransmissie, metabolisme, mitochondriële functie en de werking van oligodendrocyten, wat suggereert dat deze een hoofdrol spelen bij de ontwikkeling van migraine. Op dezelfde manier kan het interessant zijn om te onderzoeken welke patronen van cerebrovasculaire schade in grijze en witte stof correleren met genexpressiedata, omdat dit mogelijk kan wijzen op specifieke mono- of oligogene aandoeningen die vasculopathieën veroorzaken die zowel de migrainesymptomatologie als hersenlaesies bij subgroepen van migrainepatiënten kunnen verklaren.

Het aantal zeldzame, erfelijke, cerebrale microangiopathische aandoeningen met migraine als een belangrijk symptoom, die dikwijls ook extracerebrale, systemische manifestaties hebben, is sterk gegroeid in de afgelopen periode. Zo is de aandoening die recentelijk is hernoemd tot "retinale vasculopathie met cerebrale leuko-encefalopathie en systemische manifestaties" of RVCL-S[37;38] in de afgelopen jaren klinisch niet herkend en foutief gediagnosticeerd en heeft zij pas recentelijk erkenning gekregen. Het is waarschijnlijk dat soortgelijke ondergediagnosticeerde ziekten voorkomen in de populatie van personen die nu worden behandeld voor "algemene" migraine. Het associëren van cerebrovasculaire schadepatronen met genexpressiegegevens zou kunnen verklaren waarom sommige migrainepatiënten, of waarom specifieke hersengebieden, zoals de fossa posterior, vatbaarder zijn om bepaalde typen van cerebrovasculaire schade te ontwikkelen. Anderzijds, voor het geval dat met migraine geassocieerde genen ook kunnen worden verbonden met hersenschade, kan hun expressieprofiel wellicht leiden tot de ontdekking van cerebrovasculaire schade die tot dusverre nog niet is gedetecteerd; als genen in specifieke gebieden worden geëxpresseerd, wordt men zich wellicht pas bewust van de cerebrovasculaire schade in deze gebieden.

Migraine: noodzaak voor ultrahoge magnetische veldsterkte?

Vanuit eerdergenoemd oogpunt wordt het ook belangrijk MRI-beelden te verkrijgen met hoge spatiële resolutie op een ultrahoge magnetische veldsterkte van 7T, wat eenvoudigere detectie van cerebrale microinfarcten, die tot dusverre waarschijnlijk te weinig zijn herkend in migrainepatiën-

ten, mogelijk maakt.[37] Corticale microinfarcten zijn pas enkele jaren geleden voor het eerst vastgesteld bij patiënten met cerebrale, autosomaal dominante arteriopathie met subcorticale infarcten en leuko-encefalopathie (CADASIL), een ziekte die migraine met aura als een belangrijk symptoom heeft.[40] Deze microinfarcten zijn kenmerkend voor microangiopathie en zouden dus vaker kunnen voorkomen bij migrainepatiënten.

Vooral de mogelijkheid van cerebellaire microinfarcten moet hierbij worden genoemd, omdat deze infarcten mogelijkerwijs niet het gevolg zijn van lage bloedstroom in arteriële waterscheidingsgebieden, maar meer het eindresultaat van occlusie van kleine eindarteriën in het cerebellum.[41] MRI-beelden met een hoge resolutie van het cerebellum zouden kunnen tonen of deze cerebellaire microinfarcten ook met migraine zijn geassocieerd, evenals andere typen van microangiopathische schade in de fossa posterior die eerder in deze thesis werden beschreven. Naast een verbeterde detectie van corticale en cerebellaire microinfarcten zou beeldvorming op 7T ook de inzichten in andere aspecten van microangiopathie kunnen verbeteren, zoals van de anatomie van kleine arteriën op 3D time-of-flight MR-angiografie en van veneuze anatomie, hemosiderine en ijzerdeposities op T2*-gewogen sequenties.[39] Derhalve zou scannen op een hogere magnetische veldsterkte met dientengevolge beter anatomisch detail de gevolgen van microangiopathie bij migrainepatiënten beter kunnen tonen en zo kunnen helpen bij de identificatie van migrainepatiënten die een verhoogde kans hebben op het krijgen van deze typen van cerebrovasculaire schade.

Migraine en cerebrovasculaire reactiviteit

Microangiopathie tast de structuur van kleine bloedvaten aan, zoals arteriën, arteriolen, capillairen en soms venulen.[42] Verschillende mechanismen kunnen bijdragen aan zowel de hemorragische als de ischemische gevolgen van microangiopathie. Hier kan bijvoorbeeld worden gedacht aan veranderingen in de functie van het endotheel, aan een opeenstapeling van trombocyten en aan inflammatoire reacties. Deze processen kunnen leiden tot verstoorde cerebrovasculaire reactiviteit, dat wil zeggen de reactie van cerebrale bloedvaten om te reageren op vasoactieve stimuli. Specifieke geavanceerde beeldvormingsmethoden kunnen bijdragen aan het begrip van de onderliggende pathofysiologie van microangiopathie bij migraine door deze cerebrovasculaire reactiviteit te meten. In de laatste jaren wordt MRI met BOLD en arteriële spin-labelling in toenemende mate gebruikt om cerebrovasculaire reactiviteit in reactie op een stimulus, zoals koolstofdioxide,

vast te stellen.[43] Het gebruik van dergelijke technieken bij migraine kan onze inzichten in de onderlinge relatie tussen migraine, microangiopathie en cerebrovasculaire schade vergroten.

Conclusie

Samenvattend zijn primaire hoofdpijnsyndromen geassocieerd met zowel macrostructurele als microstructurele hersenveranderingen. Sommige van deze veranderingen kunnen aangeboren zijn, sommige weerspiegelen mogelijk omkeerbare of onomkeerbare neuroplastische veranderingen als aanpassingsreactie van de hersenen op externe stimuli en andere moeten worden beschouwd als hersenschade gerelateerd aan deze primaire hoofdpijnsyndromen. Clusterhoofdpijnpatiënten hebben grotere volumes in het anterieure deel van de hypothalamus en bredere schedels, observaties die in strijd zijn met bevindingen van eerdere neurobeeldvormingsstudies en pathofysiologische theorieën. Migraine is geassocieerd met microstructurele veranderingen, hoofdzakelijk gelokaliseerd in visuele verwerkingsgebieden in zowel corticale als subcorticale grijze stof en in wittestofbanen die deze structuren met elkaar verbinden. Deze veranderingen kunnen ten dele onomkeerbaar zijn of hebben bestaan gedurende het hele leven. Sommige migrainepatiënten hebben ook een verhoogd risico op visueel detecteerbare veranderingen op MRI, zoals infratentoriële microbloedingen en, bij mannelijke migrainepatiënten, infratentoriële hyperintensiteiten. De onderliggende etiologie van deze typen van cerebrovasculaire schade blijft vooralsnog ongrijpbaar en is vermoedelijk het gevolg van een multifactorieel proces.

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Curriculum vitae

Enrico Arkink werd op 6 januari 1983 geboren in Hengelo, Overijssel. In 2001 behaalde hij zijn vwo-gymnasiumdiploma aan het Pius X College te Almelo. Datzelfde jaar begon hij aan de Universiteit van Leiden aan de studie geneeskunde.
In 2007 behaalde hij cum laude zijn doctoraalexamen geneeskunde. Deze doctoraalfase van de studie sloot hij af met een wetenschapsstage op de afdeling Radiologie van het Leids Universitair Medisch Centrum (dr. N. Schmitz), waarbij hij onderzoek deed naar structurele veranderingen bij migraine. In 2008 behaalde Enrico zijn artsexamen en begon hij onder supervisie van dr. Kruit met het onderzoek waarvan het eindresultaat in dit proefschrift is beschreven. In 2011 startte hij in het Leids Universitair Medisch Centrum aan zijn opleiding tot radioloog (prof. dr. J.L. Bloem & dr. A. Šramek), waarbij hij zich sinds 2014 in het Leids Universitair Medisch Centrum en het Medisch Centrum Haaglanden (thans Haaglanden Medisch Centrum) heeft gedifferentieerd in neuro-/hoofd-halsradiologie. In 2017 volgde hij zijn fellowship neuro-/hoofd-halsradiologie, waarbij hij als radioloog in opleiding tot neuro-/hoofd-halsradioloog werkzaam was in het Leids Universitair Medisch Centrum, het Haaglanden Medisch Centrum en het HagaZiekenhuis. Na zijn fellowship begin 2018 te hebben voltooid, was hij tot 1 april 2018 als radioloog verbonden aan het Leids Universitair Medisch Centrum. Sedert 1 juli 2018 is hij als neuroradioloog werkzaam in het Landspítali, het Nationaal Universiteitsziekenhuis van IJsland, te Reykjavík.