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Structural brain changes in migraine and cluster headache

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1

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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