Structural brain changes in migraine and cluster headache

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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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