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MINI-REVIEW

White Matter Lesions in Migraine

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Migraine, the third most common disease worldwide, is a well-known independent risk factor for subclinical focal deep white matter lesions (WMLs), even in young and otherwise healthy individuals with no cardiovascular risk factors. These WMLs are more commonly seen in migraine patients with transient neurologic symptoms preceding their headaches, the so-called aura, and those with a high attack frequency. The pathophysiology of migraine-related deep white matter hyperintensities remains poorly understood despite their prevalence. Characteristic differences in their distribution compared with those of common periventricular WMLs in the elderly suggest a different underlying mechanism. Both ischemic and inflammatory mechanisms have been proposed, as there is increased cerebral vulnerability to ischemia in migraineurs, whereas there is also evidence of blood–brain barrier disruption with associated release of proinflammatory substances during migraine attacks. An enhanced susceptibility to spreading depolarization, the electrophysiological event underlying migraine, may be the mechanism that causes repetitive episodes of cerebral hypoperfusion and neuroinflammation during migraine attacks. WMLs can negatively affect both physical and cognitive function, underscoring the public health importance of migraine, and suggesting that migraine is an important contributor to neurologic deficits in the general population. *(Am J Pathol 2021, 191: 1955–1962; https://doi.org/10.1016/j.ajpath.2021.02.007)*

Migraine is one of the most common neurologic disorders and is the third most common disease worldwide. It is characterized by throbbing/pulsatile unilateral headaches that last for 4 to 72 hours. Thirty percent of patients with migraine develop transient neurologic symptoms in the setting of an attack, the so-called migraine aura. Aura symptoms characteristically precede or overlap with the headache phase. The most common types of migraine aura involve visual impairment, followed by sensory, language, or motor symptoms.[1]

Neuroimaging studies have identified a twofold to fourfold increased incidence of white matter hyperintensities suggestive of white matter lesions (WMLs) in migraineurs compared with control subjects.[2–7] WMLs are focal lesions without associated mass effect within the deep, subcortical, periventricular, or infratentorial white matter.[3,8–11] WMLs are typically seen on T2 and fluid-attenuated inversion recovery sequences, and are believed to occur due to gliosis, demyelination, and/or loss of axons, possibly resulting from microvascular damage.[12] WMLs exhibit a negative effect on both physical and cognitive function in older adults.[13–15] If this association also holds true for lesions that develop as a consequence of migraine, migraine may be a major contributor to neurologic deficits in the general population. Therefore, better characterization and understanding of the etiology of WMLs in migraineurs are important, with possible implications for the management and treatment of migraine.

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WMLs in Migraineurs and Their Implications

Age and hypertension are well-known risk factors for common *periventricular* WMLs in the elderly that are presumably caused by increased interstitial fluid and altered periventricular fluid dynamics.[16–18] In contrast, migraine is mostly associated with *deep* WMLs[9,10] that present as early as in childhood migraineurs. In fact, WMLs are found in 10% of pediatric patients with migraine.[19] However, in pediatric patients with migraine with or without aura,WMLs are not more prevalent than in control subjects and that no silent infarct-like lesions are identified.[20] Interestingly, associations between migraine and WMLs are stable over time, suggesting that they occur earlier in life.[7] In the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) population-based study sample of 30- to 60-year–old Dutch adults, female patients with migraine, were at increased risk of high deep WML-load (top 20th percentile), independent of migraine subtype and risk factors (odds ratio, 2.0; 95% CI, 1.0-4.2). This risk was higher in those with high attack frequency (odds ratio, 2.6; 95% CI, 1.2-6.0), suggestive of a causal relationship. Concurrent smoking, hypertension, and long-term oral contraceptive use further increased the risk.[10] A follow-up investigation using the same study population showed that hyperintense lesions are predominantly located in the brainstem and cerebellar vascular border zone. WMLs are more commonly seen in patients with migraine with aura than those without aura and in those with a high attack frequency. Again, cardiovascular risk factors are not more prevalent in migraineurs with WMLs. Notably, progression of WMLs in individuals with migraine is not associated with migraine attack frequency, duration, severity, or antimigraine treatments.[21]

Another longitudinal magnetic resonance spectroscopy study showed evidence of progression of migraine-related WMLs over time, with signs of more severe axonal loss and glial hypocellularity, as well as decreased intracellular energy production within a 3-year period.[22] The number of newly developed T2 hyperintensities exceeded the number of disappeared ones, further suggesting a progression of disease.

In contrast, the Epidemiology of Vascular Aging (EVA) study, a population-based, cross-sectional study in 780 elderly participants (mean age, 69 years), showed that migraine with aura is strongly associated with the cumulative volume of hyperintense lesions predominantly outside the cerebellum and brainstem.[9] Another study found that the number of WMLs also increased with the intensity of nausea and disability during attacks.[23] In contrast, a population-based sample of female twins aged 30 to 60 years identified through the Danish Twin Registry showed no association between silent brain infarcts, WMLs, and migraine with aura.[6] The discrepancies between these studies might be related to different study designs (population versus hospital-based; prospective versus retrospective), characteristics of the participants (age, sex, headache or aura frequency, and conventional vascular risk factors), ascertainment of diagnosis (diagnosed by physician interview versus self-report), and neuroimaging methods (in particular lack of standardization, such as high versus low magnetic field, scanner type, and selection of sequences or slice thickness). It is important to also note that the sensitivity to detect WMLs using 1.5- or 3-T magnetic resonance imaging (MRI) may be higher than the sensitivity to detect cortical lesions.[24]

The common periventricular WMLs in elderly nonmigraineurs are known to be associated with an increased risk of stroke, dementia, and cognitive decline. With respect to migraine patients, it is still not entirely clear whether deep WMLs have negative long-term functional consequences. In migraineurs, cerebral WMLs, but not subclinical infarcts or infratentorial lesions, are independently associated with syncope and orthostatic intolerance.[25] There is no association between autonomic nervous system symptoms and the severity of migraine or migraine subtype. Cardiovascular measurements do not differ significantly between migraineurs and control subjects.[21] The CAMERA-2 study found no association between deep WML load and change in cognitive scores. In addition, longitudinal studies show no evidence of an association between a history of migraine and an increased risk of dementia.[8] This is in agreement with a prospective study by Rist et al,[26] which found no link between cognitive changes and WMLs in migraineurs. In fact, in some studies, better cognition was noted in migraineurs.[27–29] The effect of WMLs on the clinical course of migraine is also not entirely clear. One study showed more frequent baseline WMLs in patients who did not report an improvement in migraine frequency after 3 years.[30]

Advanced MRI of White Matter in Migraineurs

A variety of advanced MRI techniques have been applied to characterize the microstructural substrate of WMLs in migraineurs. Magnetization transfer imaging is a myelin-sensitive imaging technique that indirectly quantifies the myelin content of white matter through the exchange of free water protons with bound water protons attached to macromolecules such as proteins or lipids.[31] The magnetization transfer ratio (MTR) measures the amount of magnetization exchanged between the free and macromolecular-bound water protons, such that a ratio can be estimated from the signal intensities. MTR is lower in the presence of demyelination, and it may also be influenced by the elevated water content in tissues as a result of inflammation or edema as well as changes in axonal density.[32] Several studies using magnetization transfer imaging in patients with migraine have suggested the presence of migraine-related focal microstructural damage.[33,34] However, other studies found

no significant differences in MTR in the whole brain and normal-appearing white matter in migraineurs compared with control subjects.[35,36] A recent study of participants from the CAMERA-1 and CAMERA-2 studies examined whether visible WMLs exhibited alterations in MTR values compared with baseline MTR measurements in the normal-appearing white matter on prior imaging, before the appearance of these lesions.[36] The normal-appearing white matter that later progressed to WMLs at 9-year follow-up had a lower mean MTR at baseline compared with the contralateral white matter, suggesting that occult changes in microstructural tissue integrity may precede the development of frank WMLs on conventional T2-weighted MRI.

Diffusion-weighted imaging uses the Brownian motion of water molecules as a probe of brain tissue microstructure and has been applied to study white matter integrity in migraine. Diffusion tensor imaging models the diffusive motion of water as a tensor and offers several quantitative metrics for characterizing tissue microstructure: fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity. Diffusion tensor imaging studies have revealed decreased fractional anisotropy and increased mean diffusivity, indicating altered white matter integrity in the corpus callosum,[37,38] optic radiations,[39] and corticospinal tracts.[40] A recent study reported a bilateral volume decrease in the occipital white matter adjacent to visual processing cortical areas not co-localizing with WMLs.[41] Previous diffusion tensor imaging studies showed decreased fractional anisotropy in white matter tracts in the visual processing pathway, including the middle temporal region[42] and optic radiations of participants with migraine,[39] possibly due to increased axonal diameter as a manifestation of experience-dependent structural plasticity. However, decreased white matter volume makes less myelination due to abnormal maturation or axonal loss a more likely explanation.[41]

Ischemia as a Possible Mechanism Underlying WMLs in Migraineurs

The pathophysiological mechanisms leading to the development of WMLs in migraine and the histopathologic correlates of migraine-related WMLs are not fully understood. The proposed etiologic mechanism underlying WMLs includes ischemic microvascular disturbances with subsequent focal hypoperfusion of the cerebral parenchyma.[43] In fact, reduced cerebrovascular reactivity to carbon dioxide precedes the development of WMLs in normal individuals without migraine.[44] Decreased cerebral perfusion pressure/sluggish cerebral blood flow has been observed during and after migraine attacks.[45–47] A decrease in cerebral perfusion pressure during migraine attacks impairs the clearance of embolic particles, and occlusive thrombi further reduce blood flow.[48] In fact, there is support for impaired cerebrovascular reactivity/autoregulation in migraine patients with WMLs, with evidence of increased levels of the vasoconstrictive nitric oxide synthase inhibitor asymmetric dimethylarginine in migraine patients with WMLs compared with those without WMLs and healthy control subjects.[49] Because deep cerebellar territories, which are areas of predilection for migraine-related hyperintensities, have a pattern of progressively tapering arteries with only few anastomotic networks, these anatomic locations seem particularly vulnerable to hypoperfusion-related border zone ischemic lesion formation.[50]

Multiple factors support the assumption of episodic ischemia underlying or contributing to WMLs in migraineurs. First, migraineurs seem to be prone to cerebrovascular clot formation, with reported evidence of endothelial dysfunction,[51,52] an increased incidence of hypercoagulability,[53] and atrial fibrillation.[54] Evidence for an important role of endothelial dysfunction in the generation of spreading depolarization (SD) and migraine comes from the observation that the potent vasoconstrictor endothelin-1, the strongest SD trigger in rodents *in vivo*, cannot cross the blood–brain barrier and only acts when secreted by endothelial cells abluminally via binding to receptors located on vascular smooth muscle and pericytes.[55] Accordingly, intravascular endothelin-1 administration does not induce aura symptoms.[56,57] Reactive narrowing of the arterial lumen and endothelial abnormalities stimulates thrombus formation. As a potential path for cerebral microembolism, an increased incidence of persistent foramen ovale has been reported in migraineurs.[58] Second, the extent of WMLs in migraineurs correlates with reduced cerebrovascular reactivity in response to carbon dioxide.[59] Hypoperfusion during migraine attacks may lead to delayed vascular restoration and predispose patients to subclinical or clinical ischemia, as well as the development of WMLs, in the setting of a reduced cerebrovascular response. Interestingly, the use of vasoactive medications is positively correlated with better cerebrovascular response, suggesting that vasoactive medications and the effective acute control of headaches might protect vascular function. In contrast, no association between cerebral vasodilatory dysfunction and WML load is observed in control subjects.

There is also evidence for migraineurs being prone to increased vasoconstriction in the interictal phase.[60] At resting state, there is evidence for mild vasoconstriction of cerebral arterioles in migraineurs, as suggested by a prolonged time delay between the R-wave of an ECG and the arterial pulse wave of cerebral microcirculation when measured by transcranial near-infrared spectroscopy.[61] In addition, migraineurs exhibit diminished reactive arterial vasodilation, as evidenced by a decreased cyclic guanosine monophosphate and hemodynamic response to nitric oxide.[62] Another study describes systemic arterial stiffness, lower carotid pulsatility index, and systolic blood pressure as being associated with WML load in migraineurs.[63] During a migraine attack, vasospasm and hypoperfusion homolateral to the side of pain have been shown with MRI.[64] One study reports that the dominant side of WMLs

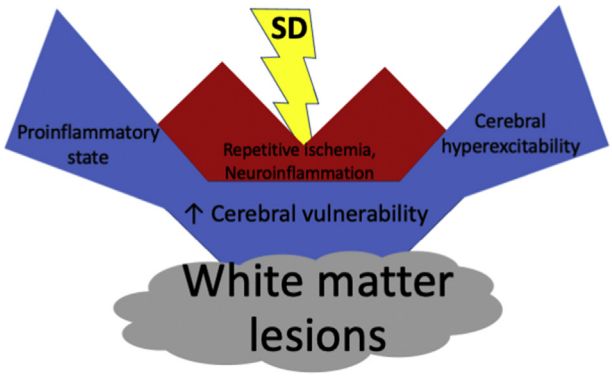

Figure 1 In migraineurs, there is evidence for cerebral hyperexcitability and a proinflammatory state at baseline, both of which may increase cerebral vulnerability (blue). SD during migraine attacks causes episodic ischemia and neuroinflammation, which may lead to cumulative damage over time in the vulnerable brain, contributing to the development of white matter lesions.

matched with the dominant side of headache.[65] These findings suggest cerebral and systemic vascular dysfunction possibly causing relative cerebral ischemia in the setting of an impaired vasodilatory response, in case of an increase in cerebral metabolic demand. Third, the brains of migraineurs seem particularly vulnerable to ischemia. Cerebral blood flow required for tissue survival seems higher in migraine-susceptible brains, leading to infarction with milder ischemia.

Mutant mouse models of migraine develop larger and more rapidly expanding cerebral infarcts compared with their wild-type littermates,[66] while acute stroke patients with a migraine history show accelerated infarct growth with less potentially salvageable brain tissue/penumbra.[67,68] As the proposed underlying mechanism, there is evidence for an increased susceptibility to SD in migraine-susceptible brains in response to ischemia, which is known to exacerbate the metabolic mismatch and worsen stroke outcomes.[66] Therefore, microembolic small vessel occlusions that remain completely unnoticed in the brains of non-migraineurs might cause SD in migraine-susceptible brains which leads to ischemic complications, including the development of WMLs.

Neuroinflammation as a Possible Contributor to WMLs in Migraineurs

The etiology of WMLs might not be identical to that of migraine-related strokes or WMLs in the elderly, and stroke typically does not develop as a continuum from WMLs. This is supported by the 9-year follow-up analysis of the CAMERA study, which shows that women with migraine have interval progression of their deep WMLs but do not exhibit increased territory infarct-like lesions/infarcts.[8] Therefore, different mechanisms, at least in part, may underlie the development of WMLs versus infarcts in migraineurs. These factors might include local excessive neuronal activation, as well as neurogenic inflammation with neuropeptide and cytokine release.

Neurogenic inflammation has been well studied in migraine models and involves the release of vasoactive neuropeptides such as calcitonin gene–related peptide, pituitary adenylyl cyclase activating peptide, and substance P from trigeminovascular axons, protons (acid-sensing ion channels), cyclooxygenase-2–generating prostaglandins and other cyclooxygenase products, serine proteases, and nitric oxide (inducible nitric oxide synthase), as well as macrophages, dendritic cells, and mast cells.[69] In fact, there is evidence for a proinflammatory baseline state in migraineurs, with increased peripheral levels of the proinflammatory cytokines IL-1β, IL-6, and tumor necrosis factor-α. Moreover, during a migraine attack, serum concentrations of C-reactive protein, von Willebrand factor, IL-1β, IL-6, IL-8, and tumor necrosis factor-α increase further.[70] There is evidence for intracranial plasma extravasation ipsilateral to the side of headache, with the demonstration of technetium-99m human serum albumin tracer extravasation in the area of reported pain,[71] and gadolinium enhancement in close vicinity to the middle meningeal artery following a series of migraine attacks has been reported.[72]

Neuroinflammation has been studied more extensively in multiple sclerosis. Glial activation in the white matter with increased glial uptake of the positron emission tomography ligand [11C]PBR28, a proxy for neuroinflammation, has been shown in patients with multiple sclerosis, in both normal-appearing white matter and WMLs. Higher levels of microglial activation are reportedly associated with a greater volume of subsequently enlarging lesions,[73] suggesting that innate immune activation contributes to inflammatory neurodegeneration, confirmed by histopathologic analysis of WMLs in multiple sclerosis.[74] Recent neuroimaging studies in migraineurs confirmed the importance of prolonged neuroinflammation during and after migraine attacks. Migraineurs exhibit an increased glial uptake of the same positron emission tomography TSPO-ligand [11C]PBR28, for at least 14 days after an attack.[75] Interestingly, a strong, persistent extra-axial inflammatory signal was found in the meninges and calvarial bone overlying the occipital lobe in migraineurs during and after visual auras, implicating newly discovered bridging vessels that provide bidirectional crosstalk between the brain and skull marrow.[76] A sustained signal in the calvarium may serve as a local repository of inflammatory cells and as a potential candidate to trigger subsequent attacks or possibly to promote migraine chronification.

SD as a Possible Mechanism to Contribute to WMLs via both Neuroinflammation and Ischemia

Neuroimaging studies suggest an important role for SD as the electrophysiological event underlying migraine attacks. The strongest evidence for a key role of SD in migraine aura

comes from functional MRIs, with the demonstration of retinotopic congruence between the visual aura perception and SD-typical blood oxygen level–dependent signal changes traversing the occipital cortex.[77] In addition, a typical sequence of speech and motor deficits characteristic of migraine aura have been observed in a patient with subarachnoid hemorrhage and electrocorticographic evidence for the occurrence of SD and SD-induced spreading depression of activity.[78] Similarly, migraine aura symptoms have been described in patients with reversible cerebral vasoconstriction syndrome. SD is a self-propagating neuronal and glial depolarization wave that spreads at a speed of 2 to 9 mm per minute.[79] In fact, transgenic mice carrying human familial hemiplegic migraine mutations are highly susceptible to developing SD upon weak stimuli and express migraine aura–like symptoms after SD, akin to patients with the respective mutations.[80]

These severe aura symptoms are associated with a facilitated spread of SD,[81] which seems related to stronger synaptic connections.[82] SD can be triggered by neural disruption (Leão's hypothesis)[55] or by vascular events (Wolff's hypothesis). For example, SD can be induced by embolic events,[83] and even occlusion of a single cortical arteriole is sufficient to trigger SD,[84] providing a candidate mechanism for SD induction in migraineurs, who seem prone to cerebrovascular clot formation and have an increased susceptibility to develop SD.[85]

SD, induced by acute neuronal hyperexcitation, results in a cascade of events producing sterile inflammation in rodent models[86,87] by triggering the release of proinflammatory prostaglandins and nitric oxide, while promoting mast cell degranulation, meningeal edema, and dilation of the middle meningeal artery as well as macrophage and dendritic cell activation.[88] Cortical spreading depolarization leads to the opening and activation of pannexin 1 channels that release proinflammatory mediators and in turn induce cyclooxygenase-2 and inducible nitric oxide synthase expression in astrocytes with microglial activation. Astrocytic release of cytokines, prostanoids, and nitric oxide into the subarachnoid space promotes sustained activation of trigeminal nerve fibers surrounding pial vessels and trigeminal nerve collaterals innervating the middle meningeal artery, thereby initiating neurogenic inflammation.

At the same time, in the healthy brain, SD stimulates the neurovascular unit to respond with marked vasodilatation and spreading hyperemia in the setting of normal neurovascular coupling to match increased neuronal energy demand. More specifically, single-photon emission computed tomography studies show a pattern of gradually spreading cortical hyperperfusion followed by gradual spreading hypoperfusion reminiscent of SD during a migraine aura. In contrast, during a migraine without an aura attack, there is no consistent evidence for a pattern of uniform vascular changes, although local changes have been shown, possibly due to neuronal activation.[89] In fact, reversible MRI abnormalities that can be caused by SD have been observed during migraine aura, and they include regional cerebral vasogenic edema[90] with evidence of vasogenic blood–brain barrier leakage in prolonged aura and an enhanced permeability of meningeal microvessels.[54]It has been proposed that hyperperfusion and vasogenic leakage impair cortical function, leading to a delay in spontaneous recovery of neuronal suppression. It should be emphasized that, although SD typically propagates in gray matter, the hemodynamic consequences of SD also involve white matter, as previously confirmed with a near-infrared spectroscopy probe placed in the white matter of a patient with an aneurysmal subarachnoid hemorrhage.[91] The correlation and complete resolution of both clinical and neuroimaging abnormalities suggest reversible changes/neuroinflammation in migraine with typical aura. Under pathologic conditions, the neurovascular unit may respond to SD with marked and prolonged vasoconstriction/spreading ischemia in the setting of inverse neurovascular coupling.[55,92,93] These events may contribute to secondary neuronal injury in the migraineur's brain, with repetitive attacks causing cumulative injury, thereby contributing to the formation of WMLs (Figure 1).

In summary, migraine is a well-known independent risk factor for the development of subclinical, focal, deep WMLs early in the disease process, even in young and otherwise healthy individuals with no cardiovascular risk factors. Both ischemic and inflammatory mechanisms are proposed as underlying factors, as there is increased cerebral vulnerability to ischemia in migraineurs, as well as evidence for neuroinflammation during migraine attacks. SD, the electrophysiological event underlying migraine, may be the mechanism that causes repetitive episodes of cerebral hypoperfusion and neuroinflammation during migraine attacks, possibly producing cumulative neuronal damage over time. In migraine-susceptible brains, both an increased susceptibility to SD and the enhanced consequences of SD may promote the development of WMLs.

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