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REVIEW

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Advanced brain MRI may help understand the link between migraine and multiple sclerosis

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Abstract

Background There is a clinical association between migraine and multiple sclerosis.

Main body Migraine and MS patients share similar demographics, with the highest incidence among young, female and otherwise healthy patients. The same hormonal constellations/changes trigger disease exacerbation in both entities. Migraine prevalence is increased in MS patients, which is further enhanced by disease-modifying treatment. Clinical data show that onset of migraine typically starts years before the clinical diagnosis of MS, suggesting that there is either a unidirectional relationship with migraine predisposing to MS, and/or a "shared factor" underlying both conditions. Brain imaging studies show white matter lesions in both MS and migraine patients. Neuroinflammatory mechanisms likely play a key role, at least as a shared downstream pathway. In this review article, we provide an overview of the literature about 1) the clinical association between migraine and MS as well as 2) brain MRI studies that help us better understand the mechanistic relationship between both diseases with implications on their underlying pathophysiology.

Conclusion Studies suggest a migraine history predisposes patients to develop MS. Advanced brain MR imaging may shed light on shared and distinct features, while helping us better understand mechanisms underlying both disease entities.

Background

Migraine is one of the most common neurological disorders, characterized by throbbing/pulsatile unilateral headaches that last for 4–72 h. Thirty percent of migraineurs develop transient neurological 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].

Multiple sclerosis (MS) is the leading non-traumatic cause of neurological disability in young adults, affecting more than 2.2 million individuals globally [2]. MS is characterized by episodes of neurological disability of varying severity and duration, typically on the order of days to weeks in length. Common symptoms include visual

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loss or double vision and loss of motor function and/or sensation. Progressive disability usually develops over the course of decades and may result in profoundly impaired mobility, cognitive dysfunction and loss of bowel/bladder function. Inflammatory demyelination is considered the hallmark of MS pathology, with axonal degeneration and loss thought to be the substrate of progressive disability [3–7].

Migraine and MS share similar features, see Table 1, as well as comorbidities [8, 9]. Both entities predominantly affect the same demographic group, young and otherwise healthy females. The same environmental factors, for example hormonal constellations during the pre/perimenstrual phase, trigger MS flares and migraine attacks [10]. Neuroinflammation seems to play a key role in both disease entities, at least as a shared downstream pathway. Episodic and chronic courses are possible, and both diseases can cause significant disability. Migraine is the second leading cause of disability in the United States of America, accounting for more than 5% of all disability. About forty percent of patients with MS rely on disability insurance for their income.

There is a clinical association between migraine and MS. In this review article, we summarize evidence for this clinical association, compare shared and disease-specific brain imaging findings as pertinent to better understand the migraine – MS connection, and discuss possible underlying mechanisms.

Main text

Evidence for a clinical association between migraine and MS

A clinical association between migraine and MS has been proposed for more than half a century. Already in 1952, Compston described a possible link between migraine and MS, reporting that 2% of MS patients develop migraine within 3 months of MS onset [11]. In 1969, Watkins [12] et al. interviewed 100 consecutive MS clinic patients and 100 random hospital visitors matched for age and sex. The authors found that the incidence of migraine in the MS group was increased with 27% of MS patients reporting migraine compared to 12% in the control group. A later study with blinded design described an increased migraine prevalence in MS patients of 21%, which was higher when compared to the migraine prevalence of 10% in the control group [13]. The strongest evidence to date for an association between migraine and MS comes from a cohort study within the Nurses Health Study II [14]. Migraine status in this study was based on the nurses' report of a physician-diagnosis of migraine. Women who had migraine at enrollment had a 39% increased risk of an incident MS diagnosis over the 15.5 year follow-up period ($p=0.008$). Another study showed that one third of patients with headaches preceding MS onset had migraine with aura, and that two thirds of those MS patients without a history of headache report the presence of auras [15]. Interestingly, in turn, a diagnosis of MS at baseline was not a risk factor for developing migraine over the follow-up period. A systematic review and meta-analysis by Mirmosayyeb et al. revealed an increased pooled prevalence of migraine in MS patients of 31% [16]. Another systematic review confirmed a significant association between migraine and MS (OR = 2.60) [17]. It should be mentioned that the more recent studies investigating migraine incidence in MS patients may be confounded by disease-modifying treatments, which have been associated with new-onset migraine and worsening of pre-existing migraine [18]. For example, a survey revealed a 46% migraine prevalence in MS patients on interferon treatment [19]. Similarly, a recent online survey revealed a 54% incidence of migraine in MS patients [20]. In summary, most studies report an increased migraine prevalence of 20–45% in MS patients (see Lipton et al. for a review) [19], particularly in patients with relapsing–remitting type MS [21].

The effect of migraine on the clinical course of MS and vice versa has not been well studied yet. However, the NYU MS cohort study showed that MS patients with a history of migraine show more symptoms, pain-related and non-pain related, when compared to those MS patients without migraine [22]. In contrast, presence or absence of migraine in MS patients does not seem to influence the age at MS onset, disease duration or disability [23]. MS patients at first clinical manifestation of their disease showed the highest prevalence of headache, with 78% of MS patients suffering from migraine attacks. Headache prevalence was similarly high in patients with clinically isolated syndrome [24]. MS exacerbation caused a worsening of headaches in two third of MS patients with a history of migraine [15]. In summary, MS patients with headache seem to be younger, have shorter disease duration and are less physically affected than those MS patients without headache. Therefore, headache can be seen as an early MS symptom. In turn, in migraine patients, a history of MS does not seem to affect migraine characteristics such as demographics, clinical presentation and response to therapy. These parameters do not seem to differ between migraine patients with MS and those without [25].

Neuroimaging in MS and migraine patients

Both a history of migraine and MS predispose to the development of white matter hyperintensities (WMHs). WMHs are non-expansile focal lesions in the deep, subcortical, periventricular or infratentorial white matter [26–30], and thought to be due to gliosis, demyelination

Table 1 Main findings of selected papers investigating the relationship between migraine and MS

			Migraine	Multiple sclerosis
Demographics	Age at onset		late teens/20 s	30 s
	Gender		F > M (Ratio 2:1)	F > M (Ratio 3:1)
Incidence			Lifetime prevalence: 12% of males and 24% of females	Lifetime prevalence: 0.15% of males and 0.45% of females
Comorbidities			Multiple Sclerosis, Depression	Migraine, Depression
Environmental factors			EBV and other types of infection, stress	EBV and other types of infection, stress
Clinical symptoms			Throbbing unilateral headache for 4–72 h, transient neurological impairment	Episodes of neurological disability of varying severity and duration
Clinical course			Mostly episodic. Chronic courses can cause significant disability (2nd leading cause of disability in the USA)	Mostly episodic. Chronic courses can cause significant disability (40% of MS patients rely on disability in the USA)
Brain MRI findings	Conventional Imaging:		Deep and subcorticalWMHs, increased # with worsening symptoms, dominant side matches HA laterality	Perivenular WMHs (McDonald criteria)
	Advanced Imaging:	Magnetization transfer imaging	Decreased MTR in WMHs	Decreased MTR in WMHs, subsequent increase reflects partial remyelination
		Diffusion tensor imaging	Decreased FA/altered intergrity in optic WM tracts	Increased FA in acute demyelinating lesions; correlates with myelin content and axonal count

and/or loss of axons secondary to inflammatory mechanisms and/or microvascular damage [31]. WMHs are best visualized on T2 and fluid-attenuated inversion recovery (FLAIR) MRI sequences. WMHs might represent a shared end stage of white matter change in patients with migraine and MS, visible with conventional MRI techniques. Advanced MRI techniques investigating subtle changes in WM that appears normal with conventional MRI techniques ("non-affected WM") may help us better understand the process leading to WMHs in migraine patients, shedding light on differences and similarities between pathophysiology of both disease entities. The process of white matter change has not been fully characterized particularly in migraine patients, and inflammatory mechanisms similar to those seen in MS-related WMHs might be involved.

In patients with migraine, there is a two- to four-fold increased prevalence of WMHs, when compared to controls [26, 32–36]. In contrast to the common age-related WMHs in the general population, migraine is mostly associated with *deep or subcortical* rather than *periventricular* WMHs [29, 37], and cardiovascular risk factors are *not* more prevalent in those migraineurs with WMHs. Interestingly, WMHs in migraineurs seem to occur earlier in life [36], affecting 10% of pediatric migraine patients [38]. WMHs are more commonly seen in patients with migraine with aura than those without aura, and those with a high attack frequency. Another study showed that the number of WMHs increases with intensity of nausea and disability during attacks [39]. Interestingly, progression of WMHs in individuals with migraine was not associated with migraine attack frequency, duration, severity, or anti-migraine treatments [40]. One study reports that the dominant side of WMHs matches the dominant side of headache [41]. Interestingly, some WMHs are only transient, related to migraine attacks. These reversible findings represent regional cerebral vasogenic edema on MRI [42] likely related to vasogenic blood–brain barrier leakage and enhanced permeability of meningeal microvasculature [43].

In MS patients, the dissemination of WMH in space and time has been a key feature of the MS diagnostic criteria, the McDonald criteria [44–47]. Demonstration of WMH in at least two of four locations in the spinal cord and brain (periventricular, juxtacortical, or infratentorial white matter) satisfies the criterion of dissemination in space. Dissemination in time may be satisfied by showing new WMHs in comparison to a baseline reference MRI or simultaneous presence of gadolinium-enhancing and non-enhancing WMHs. WMHs are typically round or ovoid in configuration and tend to follow a perivenular distribution. On FLAIR sequence, MS-typical perivenular T2 hyperintensities are located in the periventricular region and juxtacortical white matter, where blood–brain barrier breakdown takes place. Demyelination along straight medullary venules likely causes the characteristic orientation of MS lesions, perpendicular to the ventricular walls ("Dawson's fingers"). Interestingly, no difference was found in number or distribution of T2 or enhancing lesion between MS patients with migraine and those without [25]. A recent study showed that a history of migraine in MS patients was associated with a lower hazard ratio of new lesions on MRI [48].

Advanced MR imaging may help us better understand the migraine—MS association

Advanced MR imaging in patients with MS and migraine helps to further characterize the microstructural substrate of brain changes in both disease entities.

Magnetization transfer imaging is a myelin-sensitive imaging technique, indirectly quantifying the myelin content of white matter [49]. The magnetization transfer ratio (MTR) measures the amount of magnetization exchange between free and macromolecular bound water protons. MTR is affected by demyelination, elevated water content in tissues as a result of inflammation or edema, and/or changes in axonal density [50]. Several studies have suggested the presence of migraine-related focal microstructural damage [51, 52]. The CAMERA-1 and -2 studies showed that normal-appearing white matter that later progressed to WMHs at 9-year follow-up had lower mean MTR at baseline compared to the contralateral white matter. This finding suggests that occult changes in microstructural tissue integrity may precede the development of frank WMHs on conventional T2-weighted MRI [53]. In MS patients, MTR appears decreased in demyelinating lesions, reflecting compromised myelin integrity, although its measurement can be affected by edema, inflammation, and axonal density, reducing its specificity. Dynamic changes in MTR have been measured over time in acute gadolinium-enhancing lesions, with an initial decrease in average lesional MTR followed by an increase that is thought to reflect partial remyelination [54]. In individual lesions, MTR changes correlate with the degree of remyelination and clinical recovery following treatment [43, 55].

Diffusion-weighted imaging uses the Brownian motion of water molecules to characterize tissue microstructure. Diffusion tensor imaging (DTI) models the diffusive motion of water as a tensor and has revealed altered white matter integrity in the corpus callosum [56, 57], optic radiations [58] and corticospinal tracts [59] in patients with migraine. A recent study showed bilateral volume decrease in the occipital white matter adjacent to visual processing cortical areas, not colocalizing with WMHs [60]. Previous DTI studies showed decreased

fractional anisotropy (FA) in white matter tracts in the visual processing pathway including the middle temporal region [61] and optic radiations of participants with migraine [58]. Decreased white matter volume makes less myelination due to abnormal maturation or axonal loss a likely explanation [60]. In MS patients, DTI measures have shown some degree of sensitivity and specificity to demyelination and axonal loss. Increased mean diffusivity (MD) and FA appear to reflect demyelination to a greater degree than axonal loss [62, 63]. Radial diffusivity (RD) is also sensitive to myelin content, with increased RD identified in acute demyelinating lesions [64]. RD can differentiate between mild, moderate and severe demyelination but also reflects axonal loss [63]. It has been shown that patients with chronic migraine exhibit widespread increase in RD and MD values in comparison to healthy controls, and decreased FA with increased MD compared to patients with episodic migraine [65]. Advanced diffusion MRI measures incorporating stronger diffusion weighting and multi-compartment models may be more specific to the microstructural changes associated with axonal damage [66, 67] and may benefit from ultra-high field and high-performance gradient systems that are becoming more widely available [68].

Possible mechanisms underlying the association of migraine and MS

The nature of the association between migraine and MS is unclear. One of the following two hypotheses to explain the migraine – MS association, or a combination thereof, may be proposed.

First, a unidirectional relationship suggests that migraine predisposes to MS, supported by the clinical observation that migraine typically precedes MS onset by about 7 years [13] and implying that migraine could be a treatable risk factor for MS [15]. Mechanistically, spreading depolarization (SD), the electrophysiologic event underlying migraine and an attack trigger [69], may be a crucial factor for promoting MS onset by facilitating contact between peripheral immune cells and the usually privileged CNS structures. SD increases blood–brain barrier permeability via activating matrix metalloproteinases, thereby initiating neuroinflammation [70]. Elevated levels of MMP-9 and ICAM-1 as well as endothelial cell-specific molecule-1 (ESM-1) and claudin-5 have been observed in migraine patients supporting the involvement of BBB disruption during attacks [71–73]. Therefore, during a migraine attack, circulating immune cells pass the leaky blood brain barrier and may get exposed to myelin antigen in the privileged CNS compartment, causing sensitization. Environmental factors may further trigger the development of autoimmune clones. For example, it has been shown that Ebstein-Barr virus exposure increases the risk of MS [74]. Interestingly, those MS patients with a history of migraine more frequently report exposure to Epstein-Barr virus than do MS patients without a history of migraine [75]. Furthermore, during a migraine attack, SD activates neuronal Pannexin 1 channels that release pro-inflammatory mediators and induce cyclooxygenase-2 / inducible Nitric Oxide synthase expression in astrocytes with microglial activation [76]. 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 [77]. In certain cases, a unidirectional relationship between migraine and MS might function in the opposite direction, with an MS lesion in a migraine-relevant pathway initiating migraine. Migraines have been associated with lesions in the brainstem and C2 dorsal horn [78], with the preferential brainstem location of migraine-related lesions being unclear. In particular, migraine onset has been observed with lesion formation in the trigeminocervical complex and periaqueductal gray matter [79, 80]. The trigeminocervical complex is composed of major relay neurons for nociceptive afferent input from the meninges and cervical structures that are important for headache [81] and the periaqueductal gray is an important structure for pain modulation. MS patients with lesions in the periaqueductal gray matter have been shown to display a four-fold increase in migraine-like headaches [82].

Second, increased inflammatory mechanisms might underlie the migraine-MS association [83]. Recent studies suggest that inflammatory mechanisms might also promote the development of WMHs in migraineurs [84], acknowledging that ischemia may be another important underlying mechanism given evidence for increased neuronal vulnerability to ischemia in migraineurs' brains [85]. There is evidence for a pro-inflammatory baseline state in migraineurs. For example, regulatory T cells that have been shown to suppress mediators of autoimmune responses, the effector T cells, are decreased in migraineurs [86], while peripheral levels of pro-inflammatory cytokines such as IL-1β and TNF-α are increased [87]. Increased peripheral pro-inflammatory cytokines may then activate pain-related CNS structures, as has been shown in animal models. For example, the pro-inflammatory cytokine IL-17A readily crosses the blood–brain-barrier (BBB) and triggers activation of the trigeminovascular complex through microglia-mediated neuroinflammation in a nitroglycerin model of chronic migraine [88]. Furthermore, certain microglial inflammasome, NLRP3, mediate the release of IL-1β and thereby contribute to central sensitization [89]. SD as the electrophysiologic event underlying migraine

attacks has been demonstrated to further temporarily upregulate pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α during migraine attacks [90]. A transient increase in the proinflammatory cytokine ICAM-1 and chemokine levels has been confirmed in the jugular blood of migraine patients during attacks [91] and intracranial inflammatory plasma extravasation ipsilateral to the side of headache has been demonstrated with Tc-99 m human serum albumin tracer extravasation in the area of pain [92] as well as gadolinium enhancement close to the middle meningeal artery [93]. Prolonged neuroinflammation during and following migraine attacks has been demonstrated for at least 14 days following a migraine attack by increased glial uptake of the PET TSPO-ligand [11C]PBR28 [94]. Strong persistent extra-axial inflammatory signal was found in the occipital meninges and calvarial bone in migraineurs during and after visual auras, implicating bidirectional crosstalk between brain and skull marrow [95]. In MS pathogenesis and the development of MS-related WMHs, inflammatory mechanisms play a key role, as shown by increased glial uptake of the PET ligand [11C]PBR28, a proxy for neuroinflammation, in both normal appearing white matter and WMHs. Higher levels of microglial activation have been shown to be associated with a greater volume of subsequently enlarging lesions [96], suggesting that innate immune activation contributes to inflammatory neurodegeneration.

Conclusion

In summary, there is clinical evidence for an association of migraine and MS. Both clinical studies as well as animal experiments suggest the following scenario to possibly underly the migraine-MS link. Patients with migraine and MS share a pro-inflammatory predisposition. Viral infections or other environmental circumstances trigger the development of T or B autoreactive clones in the peripheral blood. Migraine attacks cause transient opening of the BBB, allowing autoreactive immune cells to enter the CNS. These infiltrated immune cells may get exposed and sensitized to myelin proteins. Previously sensitized autoreactive immune cells may re-enter the CNS from the peripheral circulation during migraine attack-triggered BBB breakdown. These clones may get re-exposed to their respective antigen and

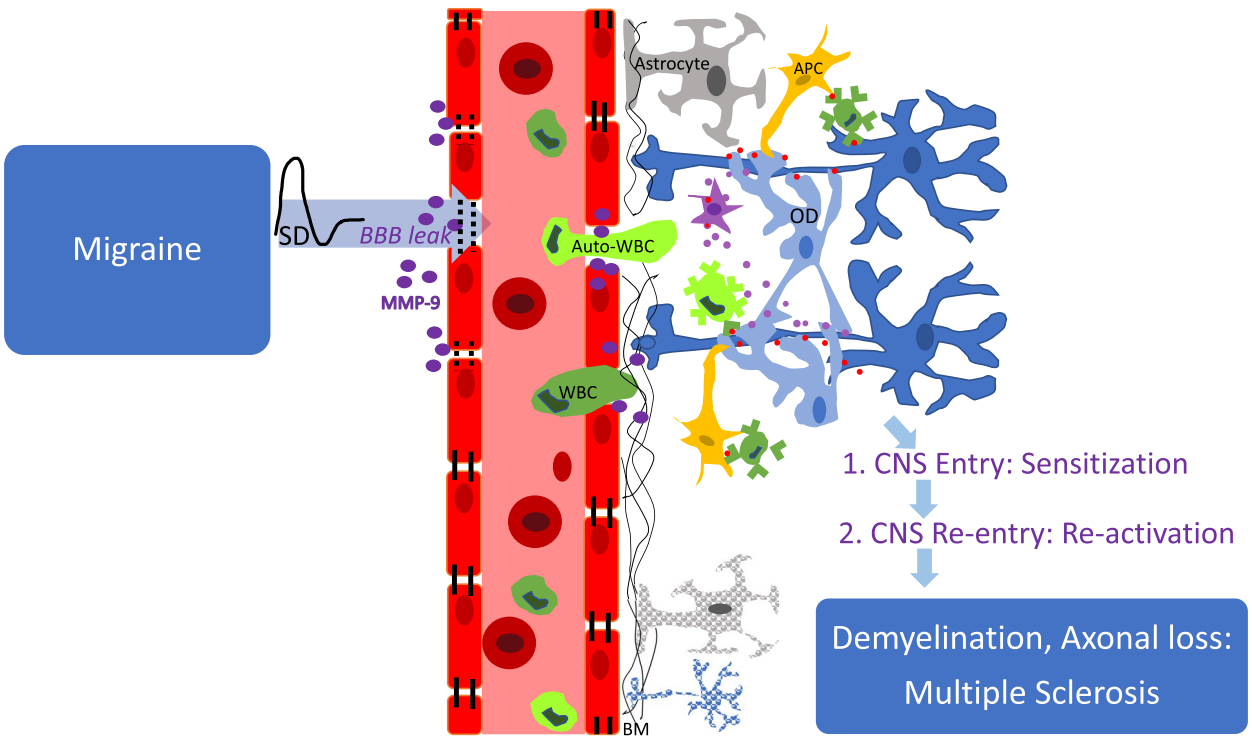

Fig. 1 Proposed mechanism on how migraine might facilitate the onset of MS. During a migraine attack, SD causes leakage of the blood–brain-barrier (BBB) (indicated by black dotted lines between endothelial cells) through release of matrix metalloproteinases (MMP-9; purple dots). Peripheral white blood cells (WBC; green) traffic across the permeable BBB. Infiltrated immune cells may get exposed and sensitized to myelin proteins (red dots), via antigen-presenting cells (APC) or through direct exposure from oligodendrocytes (OD). Previously sensitized autoreactive WBC (auto-WBC; light green) may re-enter the CNS from the peripheral circulation during migraine attack-triggered BBB breakdown and release inflammatory mediators (purple dots) with the help of microglia (purple cell), resulting in demyelination and axonal loss.

release inflammatory mediators with the help of microglia, resulting in demyelination and axonal loss (Fig. 1). Advanced brain MR imaging might shed light on shared and distinct features of migraine and MS, as well as underlying disease mechanisms.

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KEH and SH wrote the manuscript text and KEH prepared figure 1. MS prepared table 1. All authors reviewed and revised the manuscript and response letter.

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