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Original Research

Migraine-related white matter lesions: A common cause of misdiagnosis in the multiple sclerosis differential diagnosis

A cross-sectional study

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Abstract

Aim: In this study, we aimed to reveal the neuroimaging and cerebrospinal fluid (CSF) characteristics in the differential diagnosis of multiple sclerosis (MS) and migraine.

Material and Methods: We retrospectively analyzed prospectively collected data from our referral center for individuals with an initial diagnosis of demyelinating disease and eventually not diagnosed with MS and who were diagnosed with migraine without aura according to the International Classification of Headache Disorders, 3rd edition criteria. As a control group, consecutive individuals registered in our iMed database who were diagnosed with MS according to the 2017 McDonald criteria without migraine were enrolled.

Results: Fifty-five individuals with migraine-associated white matter lesions (MAWML) and 55 patients with (pw) MS were included in the study as a control group. The mean age and gender distributions were similar between groups (p=0.212 and 0.864, respectively). Oligoclonal bands (OCBs) were detected in 29 (52.7%) pwMS. In eight (14.5%) pwMS, CSF was normal for OCBs (p<0.0001). Paraventricular lesions, capping lesions, lesions smaller than 3 mm, and subcortical lesions were significantly more frequent in the MSWML group (p=0.001, 0.001, 0.001, and 0,01, respectively). Cortical/juxtacortical lesions, periventricular lesions, middle cerebellar peduncle lesions, infratentorial lesions, and callosal lesions were more frequent in pwMS (p=0.004, 0.0001, 0.001, 0.001, and 0.013, respectively).

Discussion: In this study, the contribution of CSF findings and magnetic resonance imaging (MRI) lesion locations has been shown in the differential diagnosis of MS and migraine as a guide for MS-specific neurologists and neuroradiologists.

Keywords

Multiple Sclerosis, Migraine, White Matter Lesions, Magnetic Resonance Imaging, Oligoclonal Bands

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Introduction

Multiple sclerosis (MS) is an autoimmune, acquired, demyelinating disease of the central nervous system. To date, no biomarker with high specificity and sensitivity has been identified for the diagnosis of MS. Early diagnosis of MS and initiation of the treatment have been associated with better long-term outcomes. The 2017 revisions of the McDonald criteria allowed early diagnosis, but the diagnostic criteria were not highly specific for MS [1, 2]. It is crucial to apply diagnostic criteria to individuals presenting with a typical demyelinating event to avoid misdiagnosis [3]. Also, it is critical to exclude the other possible explanations of the clinic and neuroimaging findings [1]. The conditions most often confused with MS are white matter lesions detected on MRI scans for migraine, fibromyalgia, and functional neurological disorders. Other possible sources of misdiagnosis also include non-MS inflammatory demyelinating disorders and infectious, metabolic, and vascular diseases. It is imperative to carefully identify which imaging features are typical MS lesions identified as green flags and which are lesions atypical for MS identified as red flags [4]. Misdiagnosis of MS can have serious outcomes, including the medical and economic consequences of using unnecessary immunomodulatory therapies [5].

A significant number of individuals referred to MS centers with MS diagnosis do not have MS [1]. Migraine is one of the leading causes of misdiagnosis of MS in many studies [5, 6]. Inappropriate application of the diagnostic criteria in individuals with atypical presentations for demyelinating disease and over-reliance on non-specific MRI abnormalities are the leading causes of misdiagnosis [1].

We previously described neuroimaging findings of the individuals referred with an initial diagnosis of demyelinating disease and eventually diagnosed with migraine-related white matter lesions [7]. In the present study, we aimed to investigate the clinical, radiological, and laboratory findings of individuals referred to our MS referral center with a pre-diagnosis of demyelinating disease and who were not indeed diagnosed with MS in another cohort.

Material and Methods

We retrospectively analyzed prospectively collected data from our MS center for individuals who were referred with an initial diagnosis of demyelinating disease and eventually not diagnosed with MS according to the 2017 McDonald criteria. This study was approved by the institutional ethics review board (Decision number: 2022/830). A single MS specialist neurologist examined all patients, and a single neuroradiologist evaluated the cranial MRI of the individuals from different referral centers. The MRI lesion load was classified based on the localization of FLAIR hyperintensities, and T1 W (weighted) hypointense lesions were also recorded. Alternative diagnoses were also listed for the individuals who were not considered MS. Patients diagnosed with migraine without aura according to the International Classification of Headache Disorders, 3rd edition criteria [8], were included in the study for further analysis. As a control group, consecutive individuals registered in the iMed database and diagnosed with MS according to the 2017 McDonald criteria [2] without a migraine history in the database records were included in the study, as we previously defined [9]. Tests for differential diagnosis for both groups were recorded and analyzed. All statistical analyzes were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, NY, USA). The significance level was considered as $p<0.05$.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The study included 55 individuals with migraine and white matter lesions (MWML) and a control group of 55 patients with (pw) MS. The mean age was 34.0±1.0 in the MWML group and 32.3±0.8 in the MS group. The mean age and gender distributions were similar between the study groups (p=0.212 and 0.864). Cerebrospinal fluid (CSF) examination was performed in four (7.3%) individuals in the MWML group, and no oligoclonal bands (OCBs) were observed. CSF examination was not performed in 18 (32.7%) pwMS. Oligoclonal bands were detected in 29 (52.7%) pwMS. In eight (14.5%) pwMS, CSF examination was normal for OCBs ($p<0.0001$). Antinuclear antibodies (ANAs) were detected in 1/1000 titers in three individuals in the MWML group and two in the MS group. Also, they were observed at a titer of 1/100 in seven individuals in the MS group and eight in the MSWL group. Eighteen (32.7%) individuals in the MWML group and 19 patients (34.5%) in the MS group were normal for ANAs (p=0.983). Clinical and laboratory data of MWML and MS groups are summarized in Table 1.

The total count of FLAIR and T1W lesions was greater in the MS group (p=0.001 and 0.012, respectively) (Figure 1).

Paraventricular lesions, capping lesions, lesions smaller than 3 mm, and subcortical lesions were significantly more frequent in the MSWML group (p=0.001, 0.001, 0.001, and 0.01, respectively). Cortical/juxtacortical lesions, periventricular lesions, middle cerebellar peduncle lesions, infratentorial lesions, and callosal lesions were more frequent in the pwMS group (p=0.004, 0.0001, 0.001, 0.001, and 0.013, respectively) (Figure 2).

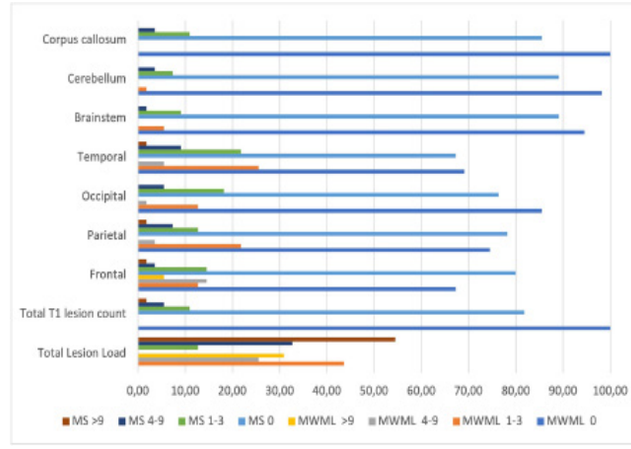

Figure 1. White matter lesion load and anatomical distribution among migraine and MS patient groups.

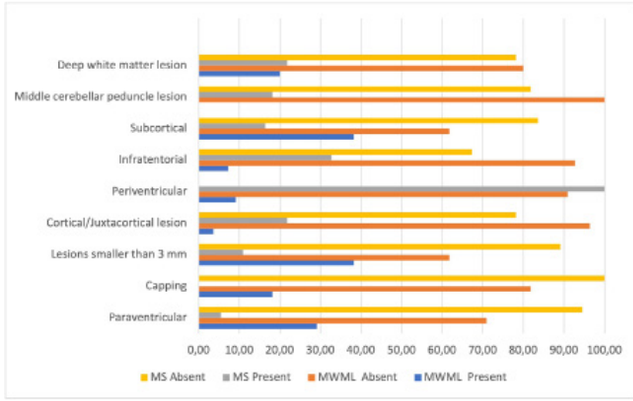

Figure 2. The distribution and characteristics of MRI lesions based on the underlying disease in the study group.

Table 1. Demographics and laboratory data of MWML and MS groups.

	MWML (n=55)	MS (n=55)	p
Age (year)	34.0 (1.0)	32.3(0.8)	0.212*
Gender n, (%)			
Female	33(60)	41(74.5)	0.104#
Male	22(40)	14(25.5)	
CSF			
Not performed	51(92.7)	18(32.7)	
Presence of OCBs	0(0)	29(52.7)	0.0001#
Absence of OCBs	4(7.3)	8(14.5)	
ANA serology			
Not performed	26(47.3)	27(49.1)	
Negative	18(32.7)	19(34.5)	0.983#
1/100 titer positive	8(14.5)	7(12.7)	
1/1000 titer positive	3(5.5)	2(3.6)	

Values are presented as mean± standard deviation, median (IQR, 25th-75th percentile), and n (%). * Mann Whitney U test, #Pearson's chi-square test.

Discussion

Migraine and associated white matter lesions have a prominent place in the differential diagnosis of MS. To avoid misdiagnosis, MS diagnostic criteria should not be applied to individuals whose clinical presentation is not compatible with demyelinating disease, and MRI lesions should be carefully evaluated. In this study, the clinical and imaging characteristics of individuals referred to our tertiary center with a preliminary diagnosis of MS and finally diagnosed with migraine were investigated. Several studies have demonstrated that migraine is one of the leading causes of misdiagnosis [6, 10, 11]. Calabrese et al. [11] reported that the absence of OCBs and dissemination in space, atypical MRI lesions, and normal visual evoked potentials should be considered red flags for the misdiagnosis of MS. Also, OCBs were not detected in 11% of pwMS and 89.6% in individuals without MS in the same study [11]. Likewise, in our study, CSF analysis for OCBs was performed in 37 pwMS, and OCBs were detected in 29 (78.3%) patients in this group. OCB in CSF has been reported to be highly sensitive and specific for MS; this is probably due to the fact that OCB is rarely detected in non-inflammatory diseases of the CNS [12]. Thus, as demonstrated in this present study, the lack of OCBs in CSF should be considered a red flag for misdiagnosis.

Previous MRI studies have reported structural and functional abnormalities in individuals with migraine and suggested that brain dysfunction may be associated with the pathophysiology of migraine [13]. A number of studies have shown that MWMLs are smaller than 3 mm and particularly affect subcortical areas [7, 14, 15]. Also, in a study including female patients with migraine, hyperintense white matter lesions have been located only in the supratentorial region [16]. Controversially Kruit et al. [17] reported that migraineurs had more frequent hyperintense lesions located brainstem than healthy controls. In our study, paraventricular, subcortical, and deep white matter lesions were more frequent in MWML. However, cortical/juxtacortical, periventricular, infratentorial, middle cerebellar peduncle, callosal, and brainstem lesions were more frequent in the MS group. Also, we showed that the total FLAIR lesion load was greater in the MS group, and there was no T1W lesion in the MWML group, unlike the MS group. Hypointense white matter lesions on T1W images, so-called black holes, correspond to the axonal loss in the course of MS and is an unusual imaging finding of patients with migraine [18].

Earlier studies have reported that ANA positivity is more frequent in pwMS [19]. Mejdoub et al. [20] reported a relationship between MS disease activity and ANA seropositivity, reflecting an ongoing immune dysregulation. However, in our study, ANA seropositivity was similar between groups. We think that further studies are needed to clarify this relationship between ANA serostatus and MS.

There are several limitations of our study. First, although a single experienced neuroradiologist interpreted all cranial MRI examinations, MRI images of individuals in the MWML group were obtained from different medical centers. Therefore, MRI examinations might have different imaging parameters. In addition, the fact that a number of MRI scans were performed without contrast administration may also have affected the evaluation owing to not considering active MS plaques. Second, the cross-sectional nature of our study did not allow for follow-up temporal lesions in the MWML group. Finally, visual evoked potentials are prominent in the diagnosis and differential diagnosis of MS, although not included in the MS diagnostic criteria. Calabrese et al. [11] showed that the absence of OCBs and dissemination in time, the presence of atypical MRI lesions, and the presence of normal VEP are red flags for MS, and an alternative diagnosis should be considered. The fact that visual evoked potentials were not evaluated between the two groups in this study can be considered a limitation.

Conclusion

In conclusion, valuable information was presented in the differentiation of MS and MWML based on the localization of the lesions in this study. We revealed that paraventricular, subcortical, and deep white matter lesions were more frequent in MWML, while cortical/juxtacortical, periventricular, infratentorial, middle cerebellar peduncle, callosal, and brainstem lesions were more frequent in the MS group.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References
1. Solomon AJ, Naismith RT, Cross AH. Misdiagnosis of multiple sclerosis: Impact of the 2017 McDonald criteria on clinical practice. Neurology. 2019;92(1):26-33.
2. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-73.
3. Brownlee WJ, Solomon AJ. Misdiagnosis of multiple sclerosis: Time for action. Mult Scler. 2021;27(6):805-6.
4. Filippi M, Preziosa P, Banwell BL, Barkhof F, Ciccarelli O, De Stefano N, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. Brain. 2019;142(7):1858-75.
5. Brownlee WJ. Misdiagnosis of multiple sclerosis: If you have a hammer, everything looks like a nail? Neurology. 2019;92(1):15-6.
6. Kaisey M, Solomon AJ, Luu M, Giesser BS, Sicotte NL. Incidence of multiple sclerosis misdiagnosis in referrals to two academic centers. Mult Scler Relat Disord. 2019;30:51-6.
7. Fatih Yetkin M. Migraine related white matter lesions in the differential diagnosis of multiple sclerosis: Magnetic resonance imaging features. Annals of Medical Research. 2021;27(10):2645-8.
8. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
9. Yetkin MF, Mirza M. Neutrophil to-lymphocyte ratio as a possible predictor of prognosis in recently diagnosed multiple sclerosis patients. J Neuroimmunol. 2020;346:577307.
10. Solomon AJ, Bourdette DN, Cross AH, Applebee A, Skidd PM, Howard DB, et al. The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study. Neurology. 2016;87(13):1393-9.
11. Calabrese M, Gasperini C, Tortorella C, Schiavi G, Frisullo G, Ragonese P, et al. "Better explanations" in multiple sclerosis diagnostic workup: A 3-year longitudinal study. Neurology. 2019;92(22):e2527-e37.
12. Deisenhammer F, Zetterberg H, Fitzner B, Zettl UK. The Cerebrospinal Fluid in Multiple Sclerosis. Front Immunol. 2019;10:726.
13. Maleki N, Gollub RL. What Have We Learned From Brain Functional Connectivity Studies in Migraine Headache? Headache. 2016;56(3):453-61.
14. Dobrynina LA, Suslina AD, Gubanova MV, Belopasova AV, Sergeeva AN, Evers S, et al. White matter hyperintensity in different migraine subtypes. Sci Rep. 2021;11(1):10881.
15. Al-Hashel JY, Alroughani R, Gad K, Al-Sarraf L, Ahmed SF. Risk factors of white matter hyperintensities in migraine patients. BMC Neurol. 2022;22(1):159.
16. Rościszewska-Żukowska I, Zając-Mnich M, Janik P. Characteristics and clinical correlates of white matter changes in brain magnetic resonance of migraine females. Neurol Neurochir Pol. 2018;52(6):695-703.
17. Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: the population-based MRI CAMERA study. Cephalalgia. 2010;30(2):129-36.
18. Kocsis K, Szabó N, Tóth E, Király A, Faragó P, Kincses B, et al. Two Classes of T1 Hypointense Lesions in Multiple Sclerosis With Different Clinical Relevance. Front Neurol. 2021;12:619135.
19. Szmyrka-Kaczmarek M, Pokryszko-Dragan A, Pawlik B, Gruszka E, Korman L, Podemski R, et al. Antinuclear and antiphospholipid antibodies in patients with multiple sclerosis. Lupus. 2012;21(4):412-20.
20. Mejdoub S, Feki S, Farhat N, Dammak M, Hachicha H, Sakka S, et al. Antinuclear antibodies positivity is not rare during multiple sclerosis and is associated with relapsing status and IgG oligoclonal bands positivity. Rev Neurol (Paris). 2022;178(8):812-6.

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