ARTICLE CLASS OF EVIDENCE

How much do periventricular lesions assist in distinguishing migraine with aura from CIS?

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Abstract

Objective
To evaluate in clinically isolated syndrome (CIS) and migraine with aura (MA) how the number of periventricular lesions (PVLs) detected at MRI influences diagnostic performance when the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) or the 2017 revised criteria are applied.

Methods
In this retrospective study, white matter hyperintensities (WMH) of 84 patients with MA and 79 patients with CIS were assessed using manual segmentation technique. Lesion probability maps (LPMs) and voxel-wise analysis of lesion distribution by diagnosis were obtained. Furthermore, we performed a logistic regression analysis based on lesion locations and volumes.

Results
Compared to patients with MA, patients with CIS showed a significant overall higher T2 WMH mean number and volume (17.9 ± 16.9 vs 6.2 ± 11.9 and 3.1 ± 4.2 vs 0.3 ± 0.6 mL; $p < 0.0001$) and a significantly higher T2 WMH mean number in infratentorial, periventricular, and juxtacortical areas ($p < 0.0001$). LPMs identified the periventricular regions as the sites with the highest probability of detecting T2 WMH in patients with CIS. Voxel-wise analysis of lesion distribution by diagnosis revealed a statistically significant association exclusively between the diagnosis of CIS and the PVLs. MAGNIMS criteria demonstrated the highest specificity in differentiating patients with CIS from patients with MA (100% vs 87%) against a predictable lower sensitivity (63% vs 72%).

Conclusions
PVLs play a key role in the differential diagnosis between MA and CIS, particularly when there are more than 3. Future studies on multiple sclerosis criteria might reconsider the 3 PVLs to minimize the risk of misdiagnosis.

Classification of evidence
This study provides Class IV evidence that the presence at least 3 PVLs increases the specificity in distinguishing MA from CIS.

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Glossary

CIS = clinically isolated syndrome; **DIS** = dissemination in space; **FLAIR** = fluid-attenuated inversion recovery; **LPM** = lesion probability map; **MA** = migraine with aura; **MAGNIMS** = Magnetic Resonance Imaging in Multiple Sclerosis; **MS** = multiple sclerosis; **PVL** = periventricular lesion; **WMH** = white matter hyperintensities.

The diagnosis of multiple sclerosis (MS) is based on the correct interpretation of radiologic features in patients with a clinical examination suggestive of demyelination. Migraine is the most common misdiagnosis[1] and may be associated with small white matter hyperintensities (WMH), including the periventricular areas.[2] The number of periventricular lesions (PVLs) to fulfil dissemination in space (DIS) criteria is a debated issue and varies among the different MS criteria. Particularly, 3 PVLs are suggested by the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) group[3] while the 2017 criteria[4] maintained the requirement for 1 PVL.

Methods

Aims

To analyze the differences in T2 WMH volume and location (level of evidence IV) in 2 large migraine with aura (MA) and clinically isolated syndrome (CIS) cohorts and to evaluate how PVL number influences diagnostic performance when the MAGNIMS or the 2017 criteria are applied (level of evidence IV).

Standard protocol approvals, registrations, and patient consents

The study received approval from local ethics committees. A written informed consent was obtained from all patients.

Patients

In this retrospective study, we collected data of 84 patients with MA and 79 age- and sex-matched patients with CIS. Patients with MA were diagnosed applying the International Classification of Headache Disorders criteria, 2nd edition. Patients with CIS, identified using clinical criteria,[4] were studied at 3 MS centers (Genoa, Siena, and Rome). Part of the MA cohort has been analyzed previously in a study not focused on PVLs.[5]

MRI acquisition and analysis

All data were collected on 1.5T MRI. For each patient, axial T2 fluid-attenuated inversion recovery (FLAIR) and T2-weighted images, all 3 mm slice thickness, were used for the analysis. Images were anonymized and analyzed in a random order, during multiple sessions by consensus of 2 experienced observers (1 neurologist, 1 neuroradiologist), blinded to subjects' identity. WMH was defined as a T2 hyperintensity at least 3-mm-long axis. WMH were visually counted on T2/FLAIR images, performing a further inspection of the posterior fossa on turbo spin-echo T2 sequences. Four WMH subgroups were defined: infratentorial, subcortical/deep, juxtacortical (involving U-fibers), and periventricular (abutting the third and lateral ventricles without WM in between, including corpus callosum). Symmetrical "caps" adjacent to the tips of lateral ventricles frontal horns were excluded. The fulfilment of the 2017 revised[4] and the 2016 MAGNIMS criteria[3] for DIS was assessed. Lesion probability maps (LPMs) were generated by registering the lesion masks, obtained using a manual segmentation technique on FLAIR images (Jim version 7.0, Xinapse) to the Montreal Neurological Institute 152 template (nonlinear registration, NiftyReg). Normalized FLAIR WMH masks were entered into a voxel-wise analysis of lesion distribution by diagnosis using nonparametric permutation-based toolbox from MRICron software package (4,000 permutations, correction for multiple comparisons, p family-wise error <0.05; voxels affected in at least 8 patients). T2 WMH numbers and volumes were compared between patients with CIS and patients with MA by a Student t test. Furthermore, a logistic regression analysis considering T2 WMH locations and volumes was performed.

Data availability

Raw data are available upon appropriate request.

Results

The table summarizes demographic and MRI features in patients with MA and patients with CIS.

A total of 68 of the 84 patients with MA and 46 of the 79 patients with CIS were women (mean age ± SD 37.8 ± 11.5 years, range 18–66; and 35.2 ± 9, range 21–68, respectively). The mean disease duration was 16.1 ± 11.9 years (MA) and 0.39 ± 0.19 years (CIS). Visual aura was reported in 84 (100%) with additional episodes of sensory in 34 (40.5%), motor in 12 (14.3%), and aphasic aura in 20 patients (23.8%). CIS onset was indicative of optic nerve in 21 (26.6%), brainstem in 19 (24%), sovratentorial in 12 (15.2%), and spinal cord involvement in 24 patients (30.4%). Three patients (3.4%) presented multifocal onset. Compared to patients with MA, patients with CIS showed a statistically significant overall higher T2 WMH mean number (17.9 ± 16.9 vs 6.2 ± 11.9; $p < 0.0001$) and volume (3.1 ± 4.2 vs 0.3 ± 0.6 mL; $p < 0.0001$) and a statistically significantly higher T2 WMH mean number in infratentorial (1.4 ± 1.9 vs 0.1 ± 0.5; $p < 0.0001$), periventricular (6.5 ± 5.7 vs 0.2 ± 0.4; $p < 0.0001$), and juxtacortical (3.4 ± 6.5 vs 0.6 ± 1.6; $p < 0.0001$) areas. Conversely, there was no significant difference in the subcortical/deep WMH mean number between the cohorts ($p = 0.348$).

LPMs identified the frontal subcortical/deep WM in MA and the periventricular regions in CIS as areas with highest probability of detecting T2 WMH (figure 1). Voxel-wise

Table Demographic data and MRI features in migraine with aura (MA) and clinically isolated syndrome (CIS)

	Patients with MA (n = 84)	Patients with CIS (n = 79)	*p* Value
Sex, F/M	68/16	46/33	
Age, y, mean (SD)	37.8 (11.5)	35.2 (9)	
Number of WMH, mean (SD)	6.2 (11.9)	17.9 (16.9)	<0.0001
WMH volume, mL, mean (SD)	0.3 (0.6)	3.1 (4.2)	<0.0001
≥1 Infratentorial WMH, n (%)	9 (10.7)	46 (58.2)	<0.0001
≥1 Periventricular WMH, n (%)	15 (17.9)	70 (88.6)	<0.0001
≥1 Juxtacortical WMH, n (%)	24 (28.6)	49 (62)	<0.0001
≥1 Subcortical/deep WMH, n (%)	58 (69)	66 (83.5)	0.348
Infratentorial WMH, n (%)			
1	7 (8.3)	21 (26.6)	
2	1 (1.2)	9 (11.4)	
3	1 (1.2)	7 (8.9)	
>3	0 (0)	8 (10.1)	
Periventricular WMH, n (%)			
1	14 (16.7)	6 (7.6)	
2	1 (1.2)	8 (10.1)	
3	0 (0)	10 (12.7)	
>3	0 (0)	40 (50.6)	
Juxtacortical WMH, n (%)			
1	11 (13.1)	12 (15.2)	
2	10 (11.9)	9 (11.4)	
3	2 (2.4)	5 (6.3)	
>3	1 (1.2)	22 (24.7)	
Subcortical/deep WMH, n (%)			
1	15 (17.9)	10 (12.7)	
2	11 (13.1)	7 (8.9)	
3	5 (5.6)	6 (7.6)	
>3	25 (29.8)	41 (51.9)	
No. (%) of patients with DIS MRI requirements according to the 2017 revised McDonald criteria	11 (13.1)	57 (72.1)	
No. (%) of patients with DIS MRI requirements according to the 2016 MAGNIMS criteria	0 (0)	50 (63.3)	

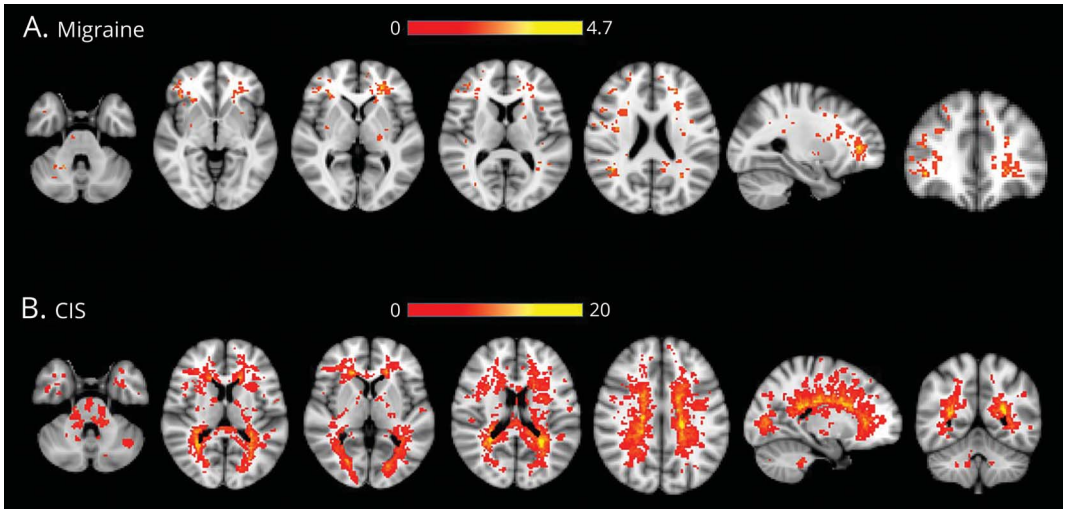
Abbreviations: DIS = dissemination in space; WMH = white matter hyperintensities.

analysis of lesion distribution by diagnosis revealed a statistically significant association exclusively between the diagnosis of CIS and periventricular location of T2 WMH (figure 2).

Logistic regression analysis confirmed that PVLs were the best factor separating CIS from MA, with an 85% decrease in the probability to be a migraineur for each additional PVL over the first one (odds ratio 0.156, 95% confidence interval 0.076, 0.319; $p < 0.001$).

DIS requirements according to the 2017 revision were satisfied by 11 (13.1%) patients with MA and by 57 (72.1%) patients with CIS, while 0 (0%) patients with MA and 50 (63.3%) patients with CIS fulfilled the 2016 MAGNIMS

Figure 1 Lesion probability maps (LPMs) in patients with migraine with aura (MA) and patients with clinically isolated syndrome (CIS)



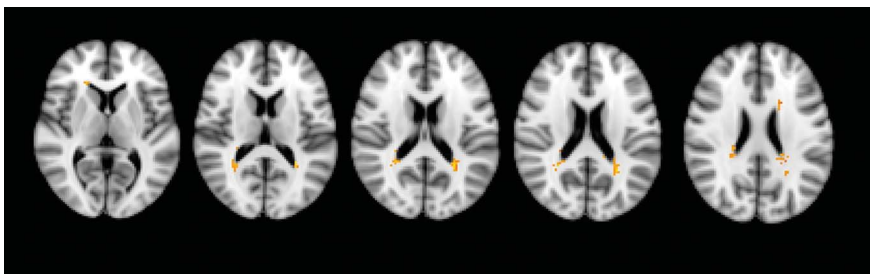
Fluid-attenuated inversion recovery LPMs in MA (A, n = 84) and CIS (B, n = 79). The color overlay created on top of the Montreal Neurological Institute standard brain shows probability range. Brain sites characterized by the highest probability of detecting white matter hyperintensities on T2-weighetd sequences were frontal subcortical/deep white matter in patients with MA and periventricular regions in patients with CIS (4.7% peak probability in frontal deep white matter for patients with MA and 20% peak probability in the white matter in contact with the posterior horns of the lateral ventricles for patients with CIS). Images are shown in radiologic convention.

criteria. Thus, MAGNIMS criteria demonstrated the highest specificity in differentiating CIS from MA (100% vs 87%) against a predictable lower sensitivity (63% vs 72%) (table).

Discussion

In most cases, clinical features enable a correct differential diagnosis between CIS and MA and misleading clinical presentations are uncommon. Nevertheless, migraine was the most common misdiagnosis in a recent study.[1] One of the potential contributing factors could be the inappropriate use of DIS criteria as a guide for neuroradiologic differential diagnosis. Indeed, on brain MRI, MA may be associated with T2 WMH, including the periventricular region,[2] traditionally considered a hallmark of MS. Absinta et al.[6] demonstrated that at least 1 PVL may be detected in up to 30% of migraine patients. Two studies involving patients with CIS[7,8] showed that the presence of at least 3 PVLs had a strong prognostic value for conversion to MS. One study found that although MRI is of limited value in the differential diagnosis of inflammatory diseases involving the CNS, the proportion of patients with 3 or more PVLs was significantly higher in MS, thus suggesting that the number of PVLs may be a neuroradiologic feature useful in favoring MS over systemic lupus erythematosus or Sjögren syndrome.[9] Therefore, the 2016 MAGNIMS criteria[3] proposed to consider 3 PVLs. Conversely, 2 studies demonstrated that, combining DIT and DIS, the sensitivity and accuracy of 1 PVL was higher than 3 PVLs but specificity was the same.[10,11] Finally, the 2017 criteria maintained the requirement for 1 PVL but finally stated that "it might be prudent for the clinician to seek a higher number of periventricular lesions for some patients, including those with vascular risk factors as migraine."[4]

Figure 2 Colored voxel-wise analysis of lesion distribution by diagnosis obtained by nonparametric permutation-based analysis



Only statistically significant voxels surviving the *p* family-wise error <0.05 threshold were displayed and overlaid onto the Montreal Neurological Institute template. Voxel-wise analysis of lesions distribution by diagnosis revealed a statistically significant association exclusively between the diagnosis of clinically isolated syndrome and the periventricular location of the T2 white matter hyperintensities.

Comparing 2 large MA and CIS cohorts, we showed that patients with CIS have a higher overall T2 WMH load with a statistically significantly higher number of T2 WMH in periventricular, juxtacortical, and infratentorial areas. LPMs identified periventricular regions in patients with CIS as the site with the highest probability of detecting T2 WMH. Voxel-wise analysis of lesion distribution by diagnosis revealed a statistically significant association exclusively between CIS diagnosis and PVLs. Furthermore, the logistic regression analysis confirmed that PVLs represent the best factor separating CIS from MA, playing a key role in the differential diagnosis particularly when there are more than 3, with an 85% decrease in the probability to be migraineur for each additional PVL over the first one. MAGNIMS criteria demonstrated the highest specificity in differentiating CIS from MA (100% vs 87%) against a predictable lower sensitivity (63% vs 72%). The appropriateness of increasing the number of PVLs from 1 to 3 could be reconsidered in future revisions of diagnostic criteria to reduce the risk of misdiagnosis.

The lack of evaluation of optic nerves, cortex, and spinal cord and the absence of post-gadolinium administration and follow-up MRI study are limitations of our study.

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Disclosure

C. Lapucci received honoraria for travel expenses for attending meetings from Genzyme and Roche. L. Saitta and G. Bommarito report no disclosures relevant to the manuscript. M. Sormani received consulting fees from Biogen Idec, Merck Serono, Teva, Genzyme, Roche, Novartis, GeNeuro, and Medday. M. Pardini received research support from Novartis and personal fees from Teva and Merck. L. Bonzano reports no disclosures relevant to the manuscript. G. Mancardi received honoraria for lecturing, travel expenses for attending meetings, and financial support for research from Bayer Schering, Biogen Idec, Sanofi-Aventis, Merck Serono Pharmaceuticals, Novartis, Genzyme, and Teva. C. Gasperini received compensation for consulting services and/or speaking activities from Teva, Merck, Genzyme, Biogen, Bayer, and Roche. A. Giorgio reports no disclosures relevant to the manuscript. M. Inglese received research grants from NIH, DOD, NMSS, FISM, and Teva Neuroscience. N. De Stefano is a consultant for Schering, Biogen-Idec, Teva, Novartis, Sanofi-Genzyme, Roche, and Merck-Serono; has grants or grants pending from FISM and Novartis; is on the speakers bureaus of Biogen-Idec, Teva, Novartis, Sanofi-Genzyme, Roche, and Merck-Serono; and has received travel funds from Teva, Novartis, Sanofi-Genzyme, Roche, and Merck Serono. L. Roccatagliata reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Appendix Authors

Name	Location	Role	Contribution
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References

1. Solomon AJ, Bourdette DN, Cross AH, et al. The contemporary spectrum of multiple sclerosis misdiagnosis: a multicentre study. Neurology 2016;87:1393–1399.
2. Kruit MC, van Buchem MA, Hofman PA, et al. Migraine as a risk factor for subclinical brain lesions. JAMA 2004;291:427–434.
3. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 2016;15:292–303.
4. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162–173.
5. Del Sette M, Dinia L, Bonzano L, et al. White matter lesions in migraine and right-to-left shunt: a conventional and diffusion MRI study. Cephalalgia 2008;28:376–382.
6. Absinta M, Rocca MA, Colombo B, et al. Patients with migraine do not have MRI-visible cortical lesions. J Neurol 2012;259:2695–2698.

7. Ruet A, Arrambide G, Brochet B, et al. Early predictors of multiple sclerosis after a typical clinically isolated syndrome. Mult Scler 2014;20:1721–1726.
8. Moraal B, Pohl C, Uitdehaag BM, et al. Magnetic resonance imaging predictors of conversion to multiple sclerosis in the BENEFIT study. Arch Neurol 2009;66: 1345–1352.
9. Kim SS, Richman DP, Johnson WO, Hald JK, Agius MA. Limited utility of current MRI criteria for distinguishing multiple sclerosis from common mimickers: primary and secondary CNS vasculitis, lupus and Sjogren's syndrome. Mult Scler 2014;20: 57–63.
10. Brownlee WJ, Miszkiel KA, Altmann DR, Ciccarelli O, Miller DH. Periventricular lesions and MS diagnostic criteria in young adults with typical clinically isolated syndromes. Mult Scler 2017;23:1031–1034.
11. Arrambide G, Tintore M, Auger C, et al. Lesion topographies in multiple sclerosis diagnosis: a reappraisal. Neurology 2017;89:2351–2356.