Periventricular T2-hyperintense lesions: does the number matter in CIS?

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Migraine is the most common misdiagnosis for Multiple Sclerosis (MS)

Table 1 Diagnoses and syndromes mistaken for multiple sclerosis

	No. (%)
Migraine alone or in combination with other diagnoses	24 (22)
Fibromyalgia	16 (15)
Nonspecific or nonlocalizing neurologic symptoms with abnormal MRI	13 (12)
Conversion or psychogenic disorder	12 (11)
Neuromyelitis optica spectrum disorder	7 (6)
Clinically isolated syndrome	3 (3)
Neurodegenerative cerebellar syndrome	2 (2)
MRI changes caused by vascular disease	2 (2)
Parkinsonism with nonspecific white matter abnormalities	2 (2)
"Radiologically isolated syndrome"	2 (2)
Cervical spondylosis with myelopathy	2 (2)
Genetic leukodystrophy	2 (2)
Idiopathic transverse myelitis	2 (2)
Noninflammatory myelopathy	2 (2)
Nonspecific symptoms with positive CSF OCBs	2 (2)
Stroke, nonembolic	2 (2)
Anti-Ma2 paraneoplastic syndrome	1 (1)
Acute disseminated encephalomyelitis	1 (1)
Astrocytoma	1 (1)
Mitochondrial disorder	1 (1)
Neurosarcoidosis	1 (1)
Moyamoya disease	1 (1)
Hypertension and alcohol abuse	1 (1)
Neuropathy	1 (1)
Unclear diagnosis; complaints of paresthesias	1 (1)
Nonspecific or nonlocalizing neurologic symptoms with normal MRI	1 (1)
Viral meningoencephalitis with subsequent abnormal MRI and acute labyrinthitis	1 (1)
White matter lesions due to TNF-α inhibitor use for psoriasis	1 (1)
Behçet syndrome	1 (1)
CADASIL	1 (1)
Degenerative joint disease of lumbar spine	1 (1)

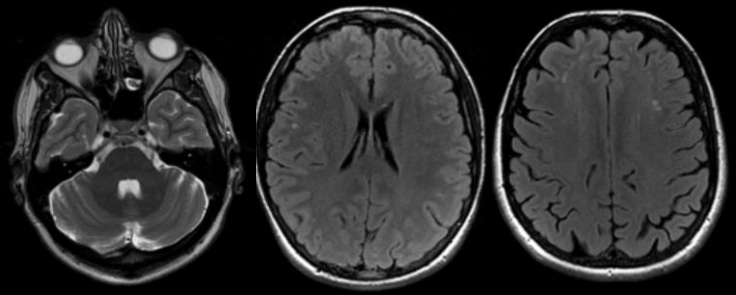
Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; OCB = oligoclonal band; TNF-α = tumor necrosis factor α.

Solomon et al., Neurology 2016

Demographical and clinical mimics

- young age at the onset
- > female sex
- occurence and re-occurence of focal or multifocal neurological signs

Neuroradiological mimics

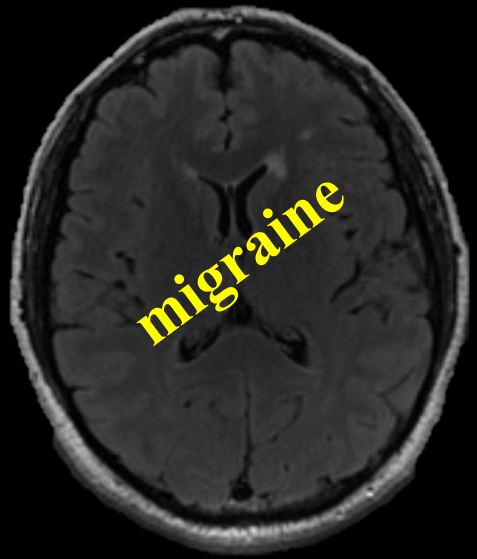


Migraine-related white matter abnormalities are small, ovoid or circular located in both the periventricular and deep brain white matter

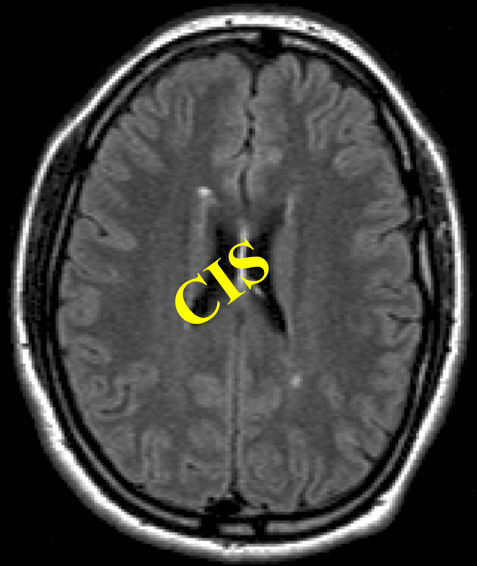
Kruit et al., JAMA 2004

Periventricular lesions has been considered a hallmark of MS

Casini et al., J Neurol Neurophysiol 2013



Migraine or CIS-related periventricular white matter hyperintensities?



The number of periventricular lesion (PVLs) to fulfill dissemination in space (DIS) in MS varies among the different diagnostic criteria

MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines

Massimo Filippi, Maria A Rocca, Olga Ciccarelli, Nicola De St
Mar Tintorè, Jette L Frederiksen, Claudio Gasperini, Jacquelin
on behalf of the MAGNIMS Study Group*

≥ 3PVLs

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Alan J Thompson, Brenda L Banwell, Frederik Bar ... orreale, Franz Fazekas,
Massimo Filippi, Mark S Freedman, Kazuo Fujiha ... Lublin, Ruth Ann Marrie,
Aaron E Miller, David H Miller, Xavier Montalban ... raboulsee, Maria Trojano,
Bernard M J Uitdehaag, Sandra Vukusic, Emman ... Cohen

≥ 1 PVL

Why ≥ 3 PVLs ?

Table 1 Main magnetic resonance imaging findings in migraine and relapsing-remitting multiple sclerosis (RRMS) patients

	Migraine patients (n = 32)	RRMS patients (n = 15)	p values	Bonferroni adjusted p values
Mean number of WM lesions (SD)	23.3 (31.0)	96.0 (72.4)	<0.0001*	<0.0001
Mean WM LV (SD) (ml)	1.52 (2.53)	10.4 (12.0)	<0.0001**	<0.0001
≥1 periventricular lesion n (%)	12 (32)	15 (100)	–	–
≥1 infratentorial lesion n (%)	1 (3)	14 (93)	–	–
≥1 juxtacortical lesion n (%)	17 (53)	15 (100)	–	–
No. of patients with DIS MRI criteria (%)	11 (34)	15 (100)	–	–
No. (%) of DIS patients with at least:				
≥1 periventricular lesion and ≥1 juxtacortical lesion	10 (29)	15 (100)	–	–
≥1 periventricular lesion and >1 infratentorial lesion	1 (3)	14 (93)	–	–
≥1 juxtacortical lesion and ≥1 infratentorial lesion	0 (0)	14 (93)	–	–
Mean number of CLs (SD)	0	1.3 (1.3)	0.0002*	0.001
Mean number of intracortical lesions (SD)	0	0.4 (0.9)	<0.0001*	<0.0001
Mean number of mixed GM/WM lesions (SD)	0	0.9 (1.1)	<0.0001**	<0.0001
Mean CLs volume (SD) (ml)	0	0.083 (0.09)	0.005	0.03

Absinta et al., J Neurol 2012

≥ 1PVL in the 30% of migraine patients

Table 3. Risk assessment and performance of the 2010 McDonald criteria and the predictive factors (PFs) by Ruet et al. for predicting fulfilment of 2010 McDonald multiple sclerosis (MS) (second relapse or magnetic resonance imaging (MRI) criteria for dissemination in space (DIS) and dissemination in time (DIT)) in clinically isolated syndrome (CIS) patients.

2010 McDonald MS	Cox regression models in the entire cohort n=652		Performance in patients followed for at least two years n=401			
	n (%)	aHR (95% CI)	n (%)	Sensitivity (95% CI)	Specificity	Accuracy
2010 DIS and DIT criteria according to baseline MRI						
2010 DIS only	495 (75.9)	5.1 (3.7–7.0)[a]	360 (89.8)	72.3 (65.2–78.6)	75.6 (68.5–81.7)	73.9 (69.0–78.4)
2010 DIT only	459 (70.4)	10.7 (7.9–14.5)[a]	339 (84.5)	47.1 (39.5–54.8)	97.6 (93.9–99.3)	71.7 (66.6–76.4)
Predictive factors in cases not fulfilling DIS						
≥2 PFs	266 (40.8)	3.3 (1.9–5.8)[a]	184 (45.9)	60.8 (46.1–74.2)	74.4 (66.2–81.6)	70.7 (63.5–77.1)
Age≤40 and ≥3 PV	266 (40.8)	4.6 (1.3–16.2)[a]	184 (45.9)	29.4 (17.5–43.8)	88.0 (81.2–93.0)	71.8 (64.6–78.1)
Age≤40 and +OBs	212 (32.5)	2.7 (0.8–9.1)	184 (45.9)	54.9 (40.3–68.9)	79.0 (71.0–85.5)	72.3 (65.2–78.6)
≥3 PV and +OBs	212 (32.5)	2.9 (1.3–6.2)[b]	184 (45.9)	23.5 (12.8–37.5)	89.5 (83.0–94.1)	71.2 (64.1–77.6)

aHR: adjusted hazard ratio; CDMS: clinically definite multiple sclerosis; CI: confidence interval; PV, periventricular; OBs: oligoclonal bands.
The value of n represents the size of the sample for each variable of interest.
[a]p value<0.001; [b]p value<0.01; [c]p value<0.05.

Ruet et al., MSJ 2014

Table 2. Conversion to Clinically Definite Multiple Sclerosis (CDMS) After 3 Years by Baseline Magnetic Resonance (MR) Imaging Characteristic

	Individual Barkhof Criteria				
≥1 Gadolinium-enhancing lesions or ≥9 T2-weighted lesions				1.63 (1.10-2.43)	.02
Yes	69 (53)	86 (41)	**155** (45)		
No	16 (43)	13 (22)	**29** (30)		
≥1 Infratentorial lesions				1.10 (0.81-1.48)	.55
Yes	49 (53)	57 (37)	**106** (43)		
No	36 (48)	42 (35)	**78** (40)		
≥1 Juxtacortical lesions				1.06 (0.78-1.45)	.71
Yes	52 (50)	69 (38)	**121** (42)		
No	33 (52)	30 (34)	**63** (42)		
≥3 Periventricular lesions				1.66 (1.14-2.41)	.009
Yes	67 (55)	84 (41)	**151** (46)		
No	18 (39)	15 (23)	**33** (29)		

Moraal et al., Arch Neurol. 2009

Why ≥ 1 PVL ?

Table 2. Performance of diagnostic criteria for development of clinically definite MS with varying numbers of periventricular lesions.

	2010 McDonald criteria in all patients (n=151)			New MAGNIMS-recommended criteria in the subgroup with symptomatic region MRI (n=27)		
	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)
DIS only						
⩾1 PV lesion	81% (72%–89%)	72% (59%–83%)	77% (70%–84%)	100% (75%–100%)	64% (35%–87%)	78% (62%–94%)
⩾2 PV lesions	74% (63%–82%)	75% (62%–85%)	74% (66%–81)	85% (55%–98%)	64% (35%–87%)	74% (54%–89%)
⩾3 PV lesions	70% (60%–79%)	77% (64%–87%)	73% (65%–80%)	77% (46%–95%)	64% (35%–87%)	70% (50%–86%)
DIS + DIT combined						
⩾1 PV lesion	64% (53%–74%)	78% (66%–88%)	70% (62%–77%)	92% (64%–100%)	71% (42%–92%)	81% (62%–94%)
⩾2 PV lesions	57% (46%–67%)	78% (66%–88%)	66% (57%–73%)	85% (55%–98%)	71% (42%–92%)	78% (58%–91%)
⩾3 PV lesions	55% (44%–65%)	78% (66%–88%)	64% (56%–72%)	77% (46%–95%)	71% (42%–92%)	74% (54%–89%)

MS: multiple sclerosis; MAGNIMS: Magnetic Resonance Imaging in Multiple Sclerosis; MRI: magnetic resonance imaging; CI: confidence interval; DIS: dissemination in space; DIT: dissemination in time; PV: periventricular.

Brownlee et al., MSJ 2017

Table 3 DIS performance in all cases and by age groups, according to the PV lesion cutoffs (≥1 vs ≥ 3) (total n = 326)

	DIS, n (%)	Second attack in patients with DIS, n (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS ≥1 PV							
All	236/326 (72.4)	218/236 (92.4)	77.3 (72.0-82.1)	59.1 (43.3-73.7)	74.8 (69.8-79.5)	92.4 (89.4-94.6)	28.9 (22.7-36.0)
40-49 y	45/57 (78.9)	40/45 (88.9)	88.9 (76.0-96.3)	58.3 (27.7-84.8)	82.5 (70.1-91.3)	88.9 (80.3-94.0)	58.3 (35.0-78.4)
30-39 y	84/122 (68.9)	78/84 (92.9)	73.6 (64.1-81.7)	62.5 (35.4-84.8)	72.1 (63.3-79.9)	92.9 (87.2-96.1)	26.3 (17.9-36.9)
20-29 y	97/130 (74.6)	90/97 (92.8)	78.3 (69.6-85.4)	53.3 (26.6-78.7)	75.4 (67.1-82.5)	92.8 (88.1-95.7)	24.2 (15.1-36.5)
≤19 y	10/17 (58.8)	10/10 (100.0)	62.5 (35.4-84.8)	100.0 (2.5-100.0)	64.7 (38.3-85.8)	100.0 (69.2-100.0)	14.3 (8.1-23.9)
DIS ≥3 PV							
All	221/326 (67.8)	204/221 (92.3)	72.3 (66.7-77.5)	61.4 (45.5-75.6)	70.9 (65.6-75.7)	92.3 (89.1-94.6)	25.7 (20.4-31.9)
40-49 y	41/57 (71.9)	37/41 (90.2)	82.2 (68.0-92.0)	66.7 (34.9-90.1)	78.9 (66.1-88.6)	90.2 (80.4-95.4)	50.0 (32.2-67.8)
30-39 y	77/122 (63.1)	71/77 (92.2)	67.0 (57.2-75.8)	62.5 (35.4-84.8)	66.4 (57.3-74.7)	92.2 (86.1-95.8)	22.2 (15.2-31.3)
20-29 y	93/130 (71.5)	86/93 (92.5)	74.8 (65.8-82.4)	53.3 (26.6-78.7)	72.3 (63.8-79.8)	92.5 (87.6-95.5)	21.6 (13.5-32.8)
≤19 y	10/17 (58.8)	10/10 (100.0)	62.5 (35.4-84.8)	100.0 (2.5-100.0)	64.7 (38.3-85.8)	100.0 (69.2-100.0)	14.3 (8.1-23.9)

Table 4 DIS plus DIT performance in all cases and by age groups, according to the PV lesion cutoffs (≥1 vs ≥3) (total n = 326)

	DIS + DIT, n (%)	Second attack in patients with DIS + DIT, n (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
DIS + DIT ≥1 PV							
All	128/326 (39.3)	123/128 (96.1)	43.6 (37.8-49.6)	88.6 (75.4-96.2)	49.7 (44.1-55.3)	96.1 (91.4-98.3)	19.7 (17.5-22.1)
40-49 y	23/57 (40.4)	21/23 (91.3)	46.7 (31.7-62.1)	83.3 (51.6-97.9)	54.4 (40.7-67.6)	91.3 (74.0-97.5)	29.4 (22.3-37.7)
30-39 y	39/122 (32.0)	37/39 (94.9)	34.9 (25.9-44.8)	87.5 (61.7-98.5)	41.8 (32.9-51.1)	94.9 (83.1-98.6)	16.9 (13.9-20.4)
20-29 y	59/130 (45.4)	58/59 (98.3)	50.4 (41.0-59.9)	93.3 (61.7-98.5)	55.4 (46.4-64.1)	98.3 (89.6-99.7)	19.7 (16.4-23.6)
≤19 y	7/17 (41.2)	7/7 (100.0)	43.8 (19.8-70.1)	100.0 (2.5-100.0)	47.1 (23.0-72.2)	100.0 (59.0-100.0)	10.0 (6.7-14.6)
DIS + DIT ≥3 PV							
All	126/326 (38.7)	121/126 (96.0)	42.9 (37.1-48.9)	88.6 (75.4-96.2)	49.1 (43.5-54.6)	96.0 (91.3-98.2)	19.5 (17.3-21.9)
40-49 y	23/57 (40.4)	21/23 (91.3)	46.7 (31.7-62.1)	83.3 (51.6-97.9)	54.4 (40.7-67.6)	91.3 (74.0-97.5)	29.4 (22.3-37.7)
30-39 y	38/122 (31.1)	36/38 (94.7)	34.0 (25.0-43.8)	87.5 (61.7-98.5)	41.0 (32.2-50.3)	94.7 (82.7-98.5)	16.7 (13.7-20.1)
20-29 y	58/130 (44.6)	57/58 (98.3)	49.6 (40.1-59.0)	93.3 (68.1-99.8)	54.6 (45.7-63.4)	98.3 (89.5-99.7)	19.4 (16.1-23.2)
≤19 y	7/17 (41.2)	7/7 (100.0)	43.8 (19.8-70.1)	100.0 (2.5-100.0)	47.1 (23.0-72.2)	100.0 (59.0-100.0)	10.0 (6.7-14.6)

regarding age, **⩾3 PVLs improved DIS specificity** over ⩾1 PVLs in the **40–49 years of age** bracket (66.7 vs 58.3)

This difference disappeared when adding DIT

Arrambide et al., Neurology 2017

The Panel recently maintained the requirement for 1 PVL

Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria

Alan J Thompson, Brenda L Banwell, Frederik Barkhof, William M Carroll, Timothy Coetzee, Giancarlo Comi, Jorge Correale, Franz Fazekas, Massimo Filippi, Mark S Freedman, Kazuo Fujihara, Steven L Galetta, Hans Peter Hartung, Ludwig Kappos, Fred D Lublin, Ruth Ann Marrie, Aaron E Miller, David H Miller, Xavier Montalban, Ellen M Mowry, Per Soelberg Sorensen, Mar Tintoré, Anthony L Traboulsee, Maria Trojano, Bernard M J Uitdehaag, Sandra Vukusic, Emmanuelle Waubant, Brian G Weinshenker, Stephen C Reingold, Jeffrey A Cohen

Panel 6: 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with a disease course characterised by progression from onset (primary progressive multiple sclerosis)

Primary progressive multiple sclerosis can be diagnosed in patients with:

- 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus two of the following criteria:

- One or more T2-hyperintense lesions* characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions* in the spinal cord
- Presence of CSF-specific oligoclonal bands

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

Thompson et al., Lancet Neurol 2018

The study

Aims

In two large cohorts of migraine with aura (MA) and Clinically Isolated Syndrome (CIS) patients:

- to analyse the differences on T2 white matter hyperintensities (WMH) volumes and locations
- to evaluate the impact of 1 vs 3 PVLs on sensibility and specificity of the DIS requirements according to the MAGNIMS group and the recent 2017 revisions to McDonald criteria

Neurology, under review

The study
Material and Methods

a) Patients

84 migraine with aura patients
Department of Neurology in Genoa

- ✓ 68/16 women/men
- ✓ mean age = 37.8±11.5, range = 18–66 years

79 CIS patients

Department of Neurology in Genoa
Department of Neurological and Behavioral Sciences in Siena
Department of Neurosciences S. Camillo-Forlanini in Rome

- ✓ 46/33 women/men
- ✓ mean age = 35.2±9, range = 21–68 years
- ✓ typical demyelinating event suggestive of CIS

no previous history of neurological symptoms

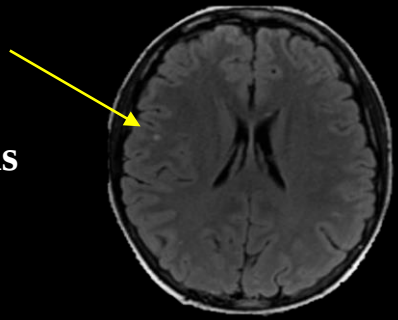
b) MRI acquisition

1.5-T scanner
1) T2-weighted turbo spin-echo (TSE)
2) FLAIR
3-mm-thick-slices

Neurology, under review

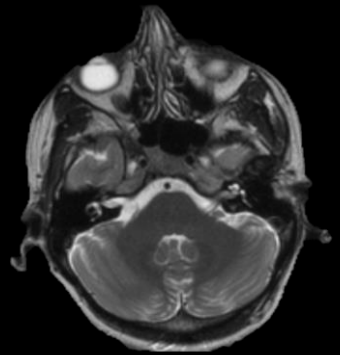
c) MRI analysis

- consensus of **two** experienced **observers** (one neurologist, one neuroradiologist) blinded to subjects' identity



- **WMH**: area of **T2 hyperintensity** that is **at least 3 mm in long axis**

- WMH were visually evaluated and counted on the **FLAIR images**, adding a further inspection on **T2-weighted images for** the analysis of **the posterior fossa**



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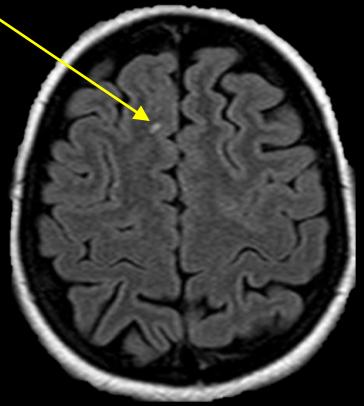
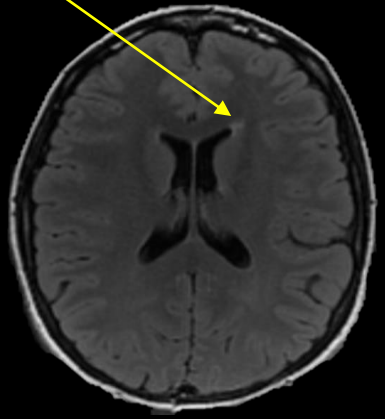
- **4 subgroups**:

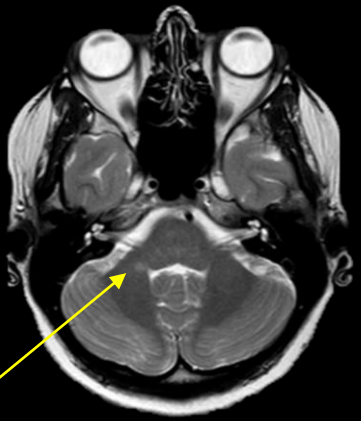
juxtacortical



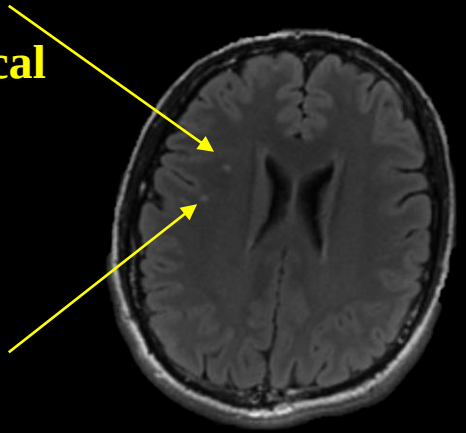
periventricular



infratentorial



deep/subcortical WM



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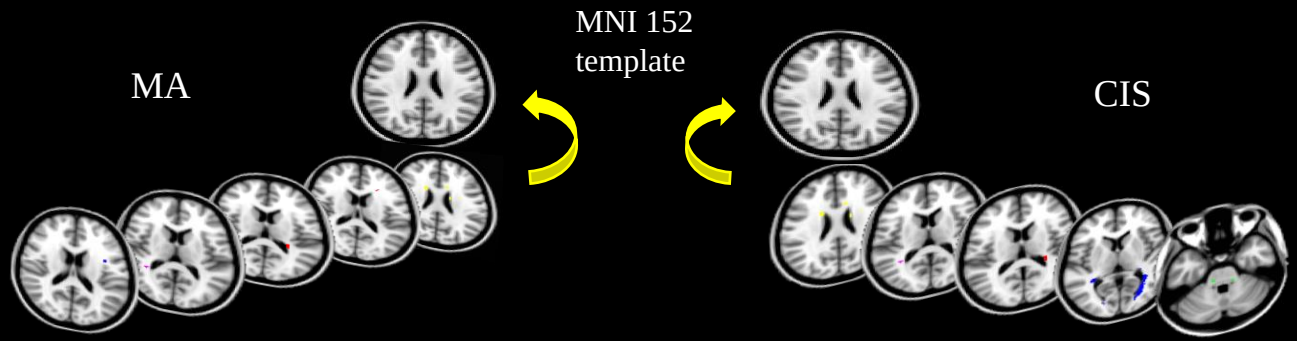
c) MRI analysis

a) Lesion volume of T2 WMH was obtained using a **manual segmentation technique** (Jim version 7.0 Xinapse Systems Ltd., Northants, UK)

b) FLAIR **Lesion Probability Maps (LPMs)** generated by registering the binary lesion masks to MNI152 template using non-linear registration (NiftyReg) and then by summing the FLAIR lesion masks in standard space



c) Correlations between the diagnosis and lesion location: Voxel-based Lesion Symptom Mapping (VLSM) analyses using a non-parametric permutation-based mapping (NPM) software from MRIcron package

Neurology, under review

d) Statistical analysis

Assessment of the fulfilment
of the 2017 revision to McDonald
and
the 2016 MAGNIMS criteria for DIS

Neurology, under review

The study - Results

Compared to migraine with aura, CIS patients have higher T2 WMH number and volume

	Migraine patients (n=84)	CIS patients (n=79)	p values
Mean number of WMH (SD)	6.2 (11.9)	17.9 (16.9)	<0.0001
Mean WMH volume (SD) (ml)	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

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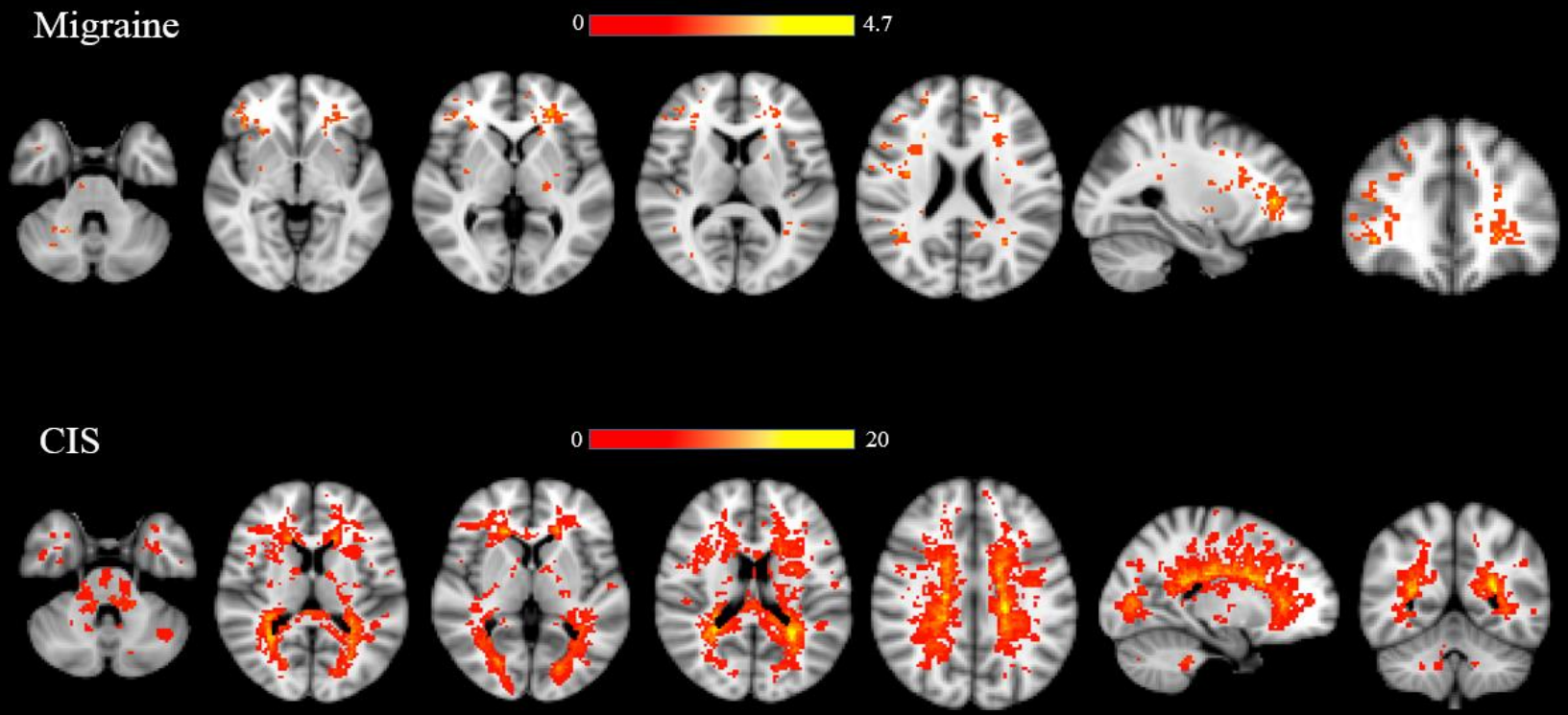
Results - LMPs

frontal subcortical/deep white matter in MA patients
periventricular regions in CIS patients



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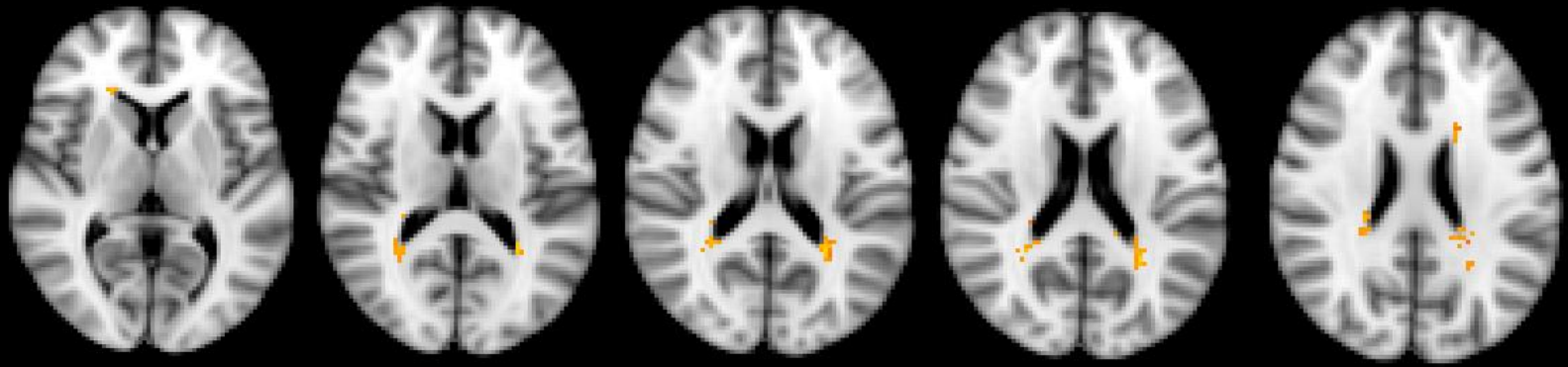
Results - VLSM

statistically significant association exclusively between the diagnosis of CIS and the periventricular location of the T2 WMH



pFWE< 0.05
voxels damaged in at least 8 patients

Neurology, under review

Results – Statistical analysis

Logistic regression analysis **confirmed** that **PVLs were the best factor separating CIS from migraine patients**

and

revealed a **85% decrease** **in the probability to be migraineur** **for each additional PVL over the first one** (OR=0.156, 95%, CI=0.076, 0.319, p<0.001)

Neurology, under review

Results – Statistical analysis

	Migraine patients (n=84)	CIS patients (n=79)	p values
Mean number of WMH (SD)	6.2 (11.9)	17.9 (16.9)	<0.0001
Mean WMH volume (SD) (ml)	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
No. patients with DIS MRI requirements according to the 2017 revised McDonald criteria (%)	11 (13.1)	57 (72.1)	-
No. patients with DIS MRI requirements according to the 2016 MAGNIMS criteria (%)	0 (0)	50 (63.3)	-

CIS= clinically isolated syndrome, WMH= white matter hyperintensities, SD= standard deviation, DIS= dissemination in space

Neurology, under review

MAGNIMS criteria demonstrated the **highest specificity** in differentiating CIS from MA patients (100% vs 87%) against a predictable **lower sensibility** (63% vs 72%)

Neurology, under review

Why more specific DIS criteria?

- WMH may progress over time in migraineurs (*Dinia et al., J Neuroimaging 2013; Terwindt GM, et al. JAMA 2012*)

- more appropriate indications for lumbar puncture procedures (OCBs substitute for the radiological DIT in the last MS criteria)

… For some patients—eg, older individuals or those with vascular risk factors including migraine—it might be prudent for the clinician to seek a higher number of periventricular lesions…

Thompson et al., Lancet Neurol 2018

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