Paramagnetic Rim Lesions Frequency in Pediatric and Adult Multiple Sclerosis Patients with Similar Disease Duration

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BACKGROUND AND AIMS

Paediatric Onset Multiple Sclerosis (POMS) is a rare disease displaying different clinical-radiological features compared to adult MS. Specifically, this population exhibits greater recover from relapses and increased remyelination potential. However, most POMS patients exhibit a high burden of acute inflammation, and a substantial proportion of patients can experience progression independent of relapse activity, even from the early phases of the disease.

Quantitative Scusceptibility Mapping (QSM) has emerged as a valuable tool for characterizing white matter lesions (WMLs) in MS. QSM hypo-isointense lesions seem to correspond to remyelinated WMLs, while paramagnetic rim lesions (**PRLs**) correspond to chronic active lesions, associated with iron loaded microglia. QSM homogeneously hyperintense lesions (HILs) represent chronic inactive lesions, although some can manifest chronic activity and demyelination. Although more represented in long disease duration progressive MS, PRLs have been shown in early stages of MS.

We aimed to provide a QSM classification of WMLs in a cohort of low disease-duration, highly treated, POMS patients and to evaluate differences in QSM lesions subtype between POMS patient and a disease duration matched AOMS group

METHODS

Inclusion criteria for POMS: MS diagnosis according to 2017 revised McDonald-s criteria. Disease onset before 18 years of age.
Exclusion criteria for POMS were MOG Ab presence (a cell based assessment was used to exclude MOG antibodies) and MRI intolerance.

MRI protocol included:
3D sagittal T2-FLAIR (TR/TI/TE 5000 ms/1800 ms/393 ms; resolution 0.4x0.4x1 mm^3);
3D sagittal T1 MPRAGE (TR/TI/TE 2300 ms/919ms/2.96 ms; resolution 1x1x1 mm^3);
3D sagittal segmented echo-planar imaging (EPI) (TR/TE 64ms/35 ms; Flip Angle = 10°; resolution 0.65x0.65x0.65 mm^3) providing magnitude (MAG) and phase (PHA).

MRI processing
Through 3D sagittal segmented EPI we obtained **SWI** and **QSM** with an isotropic resolution of 0.65 mm for lesions assessment. WMLs masks were obtained with manual segmentation by using Jim Xinapse version 7.0 and registered to the MAG space using Advanced Normalization Tools (ANTs).
MS lesions were classified as PRLs, HILs or iso/hypointense lesions by two indipendent raters. In case of non-agreement by the two raters, a consensus was reached in a second evaluation. 7 contrast enhancing lesions on MRI assessment were excluded from the analysis. SWI was used to support lesion classification by identifying QSM hyperintensities ascribable to veins (Fig. 1)

Statistical analyses
Descriptive statics were applied in order to describe QSM lesions subtypes in POMS patients.
A multivariate analysis including sex, total lesion burden and total lesion volume as covariates was used in order to compare QSM lesions subtypes between POMS and a disease-duration matched AOMS group.

FIG. 1
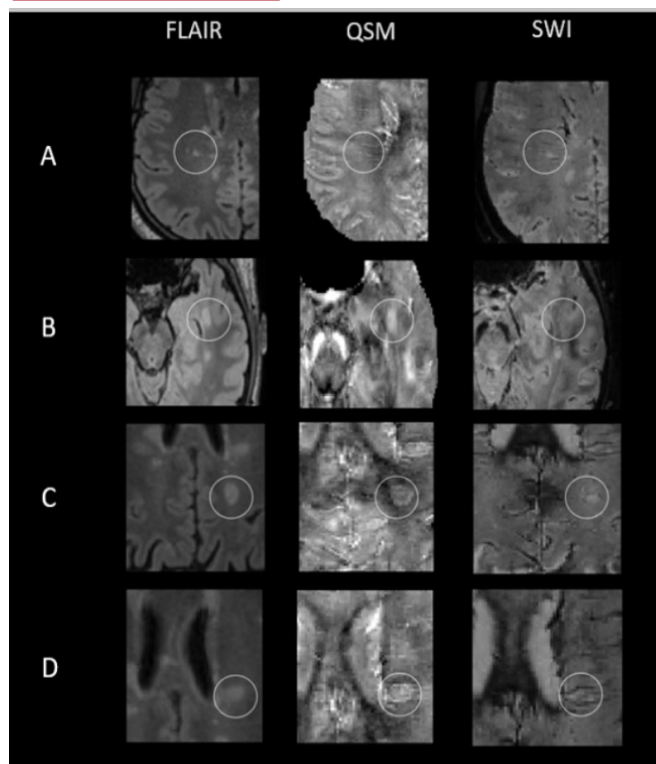
A. QSM Iso-Hypointense white matter lesions (WMLs) in the right parietal white matter of a 15 years-old MS patient. QSM hyperintensities are completely ascribable to veins, highlighted by Susceptiblity Weighted Imaging (SWI).

B. QSM Hyperintense lesion (HIL) in the left temporal white matter of a 14 years-old MS patient. QSM hyperintensity is uniformly distributed in the entire WML.

C. Paramagnetic Rim Lesion (PRL) in the left periventricular white matter of a 13 years-old MS patient. QSM hyperintensities do not correspond to SWI hypointensities ascribable to veins.

D. WML in the same 13 years-old MS patient with QSM hyperintensies corresponding to SWI-hypointensities ascribable to veins. This lesion has not been classified as PRL.

RESULTS

Demographics and clinical data:
Fourteen POMS (seven females, 50%) and fifteen disease-duration matched AOMS (eight females, 53%) patients were included in the analyses, with a mean (SD) age of 16.1 (2.1) and 33.8 (10.6) respectively and overall mean disease duration of 2.2 (1.9) years. 13/14 POMS and 14/15 AOMS were treated with moderate-to-high efficacy therapies. No differences in EDSS scores, annualized relapse rate (ARR) in the last two years, total lesions burden and total brain volume were found between the two groups (Table 1).

Lesions analysis:
123/577 lesions were excluded due to brain-air interface, infratentorial position or confluence (85 in POMS, 38 in AOMS, p= 0.45).
PRLs were found in 6/14 (43%) POMS and 8/15 (53%) AOMS patients (p= 0.42).
PRLs represented 6% of WMLs in POMS (0.86 per subject) and 10% (1.73 per subject) in AOMS (p=0.27), with 1/14 POMS and 2/15 AOMS patients exhibiting ≥4 PRLs.
PRLs number and percentage were not associated with total brain volume, thalamic volume and EDSS scores in the whole population and in the two study groups.
Notably, POMS patients showed higher HILs percentages (p=0.03).
No differences were noted in number and percentage of iso-hypointense lesions (p= 0.45 and p = 0.41 respectively).

TABLE 1

	PEDIATRIC-ONSET MS	ADULT_ONSET MS	P-value
Number	14	15	
Female (%)	7 (50%)	8 (53%)	0.58
Disease Duration, y	2.5 (2.1)	2.0 (1.8)	0.46
EDSS (IQR)	1 (1-2)	1 (0-3.5)	0.49
ARR last two y (SD)	0.39 (0.35)	0.53 (0.35)	0.33
TLV, cm^3 (DS)	2.78 (2.00)	3.2 (4.18)	0.66
TBV, cm^3 (DS)	1.46 (0.14)	1.40 (0.12)	0.7
GMV, cm^3 (DS)	0.72 (0.10)	0.61 (0.07)	0.43
WMV, cm^3 (DS)	0.51 (0.06)	0.49 (0.05)	0.63
Therapy			
ALT	0	1	
CDB	0	2	
DMF	1	1	
FTY	4	0	
NTZ	6	6	
OCR	2	5	
RTX	1	0	
PRL/subj	0.9 (1.2)	1.7 (2.7)	0.27
HIL/subj	3.6 (3.1)	1.6 (2.1)	0.05
Iso-Hypo/Subj	13.1 (11.4)	10.3 (8.9)	0.45
Not val	6.1 (16.6)	2.7 (3.2)	0.45
%PRL	6.6 (11.2)	10.0 (11.2)	0.42
%HIL	20.0 (11.6)	9.9 (12.1)	0.03
%Iso-Hypo	73.5 (20.0)	79.7 (20.1)	0.41

SD=standard deviation; ARR=annualized relapse rate TLV = Total lesion volume; TBV = Total Brain Volume; GMV = Grey Matter Volume; WMV = White matter volume; ALT = alemtuzumab; CDB = cladribine; DMT = dimethylfumarate; FTY = fingolimod; NTZ = natalizumab; OCR = ocrelizumab; RTX = rituximab; PRLs=paramagnetic rim lesions; HILs = hyperintense lesions

KEY POINTS

Chronic compartmentalized inflammation occurs early in MS pathogenesis.

PRLs occurrence exhibit a similar fashion in POMS and AOMS.

Further studies are needed to assess the impact of age and disease duration in PRLs occurrence

Higher HILs number in POMS represent a controversial results; further studies are needed to understand the pathological correlates of HILs

BIBLIOGRAPHY

Rahmanzadeh R, et al. A New Advanced MRI Biomarker for Remyelinated Lesions in Multiple Sclerosis. Ann Neurol. 2022 Sep;92(3):486–502.

Absinta M, et al. Association of Chronic Active Multiple Sclerosis Lesions With Disability In Vivo. JAMA Neurol. 2019 Dec 1;76(12):1474.

Ng Kee Kwong KC, et al. The prevalence of paramagnetic rim lesions in multiple sclerosis: A systematic review and meta-analysis. Jiang Q, editor. 2021 Sep 8;16(9):e0256845.