Slowly Expanding Lesions Differentiate Pediatric Multiple Sclerosis from Myelin Oligodendrocyte Glycoprotein Antibody Disease

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Slowly expanding lesions (SELs) in adults with multiple sclerosis (MS) indicate a progressive pathological process. Whether SELs are present in pediatric-onset MS (POMS) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is unknown. We studied 19 children with POMS and 14 with MOGAD (median age 14.3 and 9.4 years, respectively) recruited to the Canadian Pediatric Demyelinating Disease Study with: (1) ≥3 research scans 12 months apart; and (2) ≥1 T2-lesions on the earliest scan. A total of 70 SELs from 16 POMS participants and 1 SEL in the MOGAD group were detected. SELs are an early feature of POMS and essentially not a feature of MOGAD.

ANN NEUROL 2024;00:1–6

Multiple sclerosis (MS) is characterized by multifocal T2-hyperintense lesions that may enhance after administration of gadolinium, indicative of acute inflammation and focal perturbation of the blood–brain barrier. Some chronic lesions show slow, concentric expansion over time on serial magnetic resonance imaging (MRI), denoted as slowly expanding lesions (SELs).[1] SELs are considered a hallmark of progressive, rather than acute inflammatory, tissue injury, and the presence of SELs correlates with progressive clinical disability.[2-4] SELs are considered an in vivo marker of chronic-active lesions described on pathology, with the latter showing central demyelination with a paucity of infiltrating peripheral immune cells, surrounded by a rim of activated microglia and iron-laden macrophages.[5]

The onset of MS during childhood or adolescence is associated with frequent relapses and by a high T2 lesion burden, indicating a highly inflammatory disease state (reviewed in Fadda et al.[6]). However, failure of age-expected brain growth leading to atrophy of whole brain and thalamic tissue in particular is also a feature of pediatric-onset MS (POMS),[7,8] suggesting that more chronic injury processes (such as compartmentalized inflammation and degeneration) are operative even in POMS, despite the relative rarity of progressive clinical disability in this MS population. Whether POMS is also associated with progressive focal tissue injury, as illustrated by the presence of SELs, is unknown, but if present, would further substantiate the need for early initiation of neuroprotective strategies before the onset of clinical disability.

The specificity of lesional features in POMS is also of interest. There has been recent recognition of pediatric and adult patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD).[9] Both the 2017 McDonald MS criteria[10] and the MOGAD criteria

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Additional supporting information can be found in the online version of this article.

Received Apr 26, 2024, and in revised form Aug 8, 2024. Accepted for publication Aug 9, 2024.

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.27066.

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require exclusion of a "better explanation." As clinical features at onset can overlap between MS and MOGAD, MRI features that accurately discriminate these two conditions are clinically relevant. Notably, pathology studies of MOGAD lesions have not detected a rim of activated microglia, suggesting that chronic-active lesions may be rare in MOGAD.[11,12]

We compared the MRI features of children with POMS and MOGAD to assess whether POMS shares the progressive focal tissue injury characteristic of disease progression seen in adult-onset MS, and whether this process is also present in MOGAD.

Methods

Participants

Participants with an incident (first clinical) central nervous system demyelinating attack were enrolled in the prospective Canadian Pediatric Demyelinating Disease study between 2004 and 2018 at a single site (Hospital for Sick Children, Toronto, ON, Canada), within 30 days of symptom onset. Clinical examination, research MRI scans, and laboratory samples were obtained at baseline, 3, 6, and 12 months, and annually thereafter. MRI scans were acquired using a single 1.5- or 3-T MRI scanner optimized for the study protocol (as detailed previously).[7] The diagnosis of MS was conferred using international criteria dependent on year of enrolment and then re-assessed for the present study using 2017 McDonald criteria.[10] Archived serum samples obtained at baseline were analyzed for the presence of MOG immunoglobulin G in a single laboratory, as previously described.[13] The diagnosis of MOGAD was conferred according to the International MOGAD criteria.[9] In both groups, relapses were defined by new neurological deficits persisting for greater than 24 hours and occurring more than 30 days from the onset of a prior attack.[9,10]

The study was approved by the research ethics boards of all participating institutions. Guardians and participants provided written informed consent. Younger children provided verbal assent.

MRI Analyses

To evaluate lesion change over time, only participants with 3 research brain MRI scans, each 12 months apart, and with at least 1 T2 lesion present on the earliest scan were eligible for inclusion. Considering that the baseline scan obtained in proximity to the first attack might include a large proportion of lesions with acute edema, SEL detection was performed using scans taken at 1, 2, and 3 years after study enrollment to avoid the confounder of excessive resolution of edema in the Jacobian analysis. For 2 participants who did not have a year 3 scan, the baseline, year 1, and year 2 scans were used for SEL detection. Four participants were excluded due to artifact (motion, metal dental hardware).

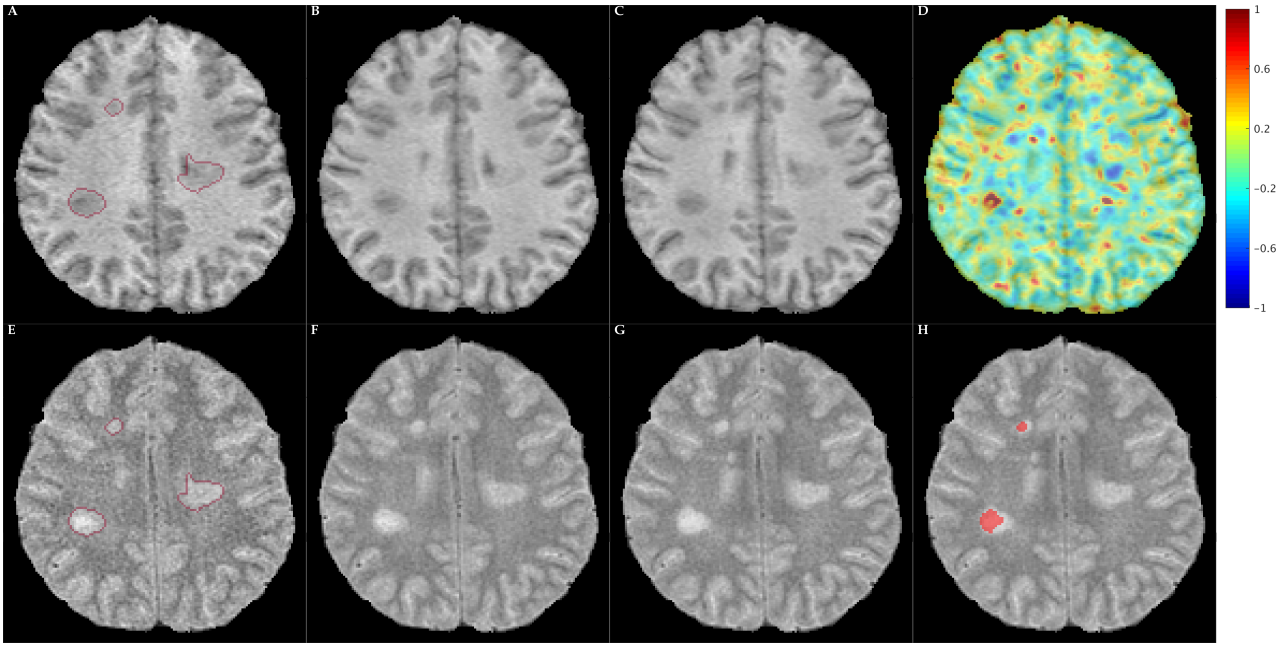

Figure 1: Example slowly expanding lesion (SEL) detection. (A–C): T1-weighted scan at years 1, 2, and 3. (E–G) T2-weighted scan at years 1, 2, and 3. T2 lesions at year 1 are outlined in (A) and (E). (D) Jacobian determinant quantifying local volume change from year 1 to year 3, where positive values denote expansion and negative values denote contraction. (H) Boundaries of detected slowly expanding lesions.

Table. Demographic, Clinical, and Imaging Features for Multiple Sclerosis and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease Populations

	MS (N = 19)	MOGAD (N = 14)	*p* value
Age at onset, yr (median [IQR])	14.3 (12.8–15.2)	9.4 (6.8–11.5)	0.00010
Female (n [%])	13 (68)	7 (50)	0.47
Presenting phenotype (n [%])			
Monofocal ON	6 (32)	5 (36)	>0.99
Polyfocal symptoms including ON	1 (5)	0	>0.99
Monofocal TM	0	2 (14)	0.17
Polyfocal symptoms including TM	1 (5)	2 (14)	0.56
ADEM	0	3 (21)	0.067
Other	11 (58)	2 (14)	0.16
EDSS at onset (median [IQR])	3.0 (2.25–4.5)	4.75 (1.0–6.5)	0.85
OCB positive (n [%])[a]	12/14 (86%)	2/10 (20%)	0.0027
Relapsing course (n [%])[b]	14 (74)	4 (29)	0.015
Single attack (n [%])	5 (26)	10 (71)	0.015
Exposure to DMT (n [%])[c]	14 (74)	1 (7)	<0.00024
Time between initial and last scan assessed (weeks, mean ± SD)	105.2 (4.6)	103.5 (2.8)	0.40
No. participants with ≥1 SEL (%)	16 (89)	1 (7)	<0.00001
T2 lesion volume, mm^3 (median [IQR])	7,203 [2158–10,806]	516 [168–662]	<0.00001
SEL count (median [IQR])	2 [1–6]	0 [0–0]	<0.00001
SEL volume, mm^3 (median [IQR])	300 [77–822]	0 [0–0]	<0.00001
%T2 volume as SEL (median [IQR])	4.6 [2.5–13.1]	0 [0–0]	0.00002
Discrete T2 lesions (median [IQR])[d]	22 [9–25]	4 [2–6]	0.00005
%T2 lesions that overlap SEL (median [IQR])	12.5 [6.9–20.0]	0 [0–0]	0.00007

Note: Detected SELs.

Abbreviations: ADEM = acute disseminated encephalomyelitis; EDSS = Expanded Disability Status Scale score; IQR = interquartile range; MOGAD = myelin oligodendrocyte glycoprotein antibody-associated disease; OCB = oligoclonal bands; ON = optic neuritis; SEL = slowly expanding lesion.

[a]OCB results were available only from a subgroup of patients, as cerebrospinal fluid analysis was performed following clinical indication and not as part of the research protocol. The only MOGAD participant with evidence of SELs was negative for cerebrospinal fluid restricted OCB.

[b]Absence of clinical relapses was reported in 4 of 16 MS participants with SELs (25%, 2 of whom treated with DMT) and 1 of 3 of the MS participants without SELs (33%), whereas monophasic disease course was observed in the only MOGAD participant with SELs and in 9 of 13 without SELs (69%).

[c]The DMTs used in our patient cohort were for the vast majority interferons and glatiramer acetate.

[d]Discrete T2 lesions = count of discrete T2 lesions (determined by connectedness) at least 10 voxels in size. %T2 lesions that overlap SEL = percentage of discrete T2 lesions at least 10 voxels in size that overlap with a SEL. All *p* values based on Wilcoxon sum rank test or Fisher's exact test.

Identification of SELs. T2 lesions were identified at the initial timepoint using a semiautomated approach. Briefly, an automatic segmentation was generated using a convolutional neural network based on the U-net architecture.[14] This initial segmentation was subsequently reviewed by an expert reader (D.F.) and manually corrected as

needed. SELs were automatically identified using a previously developed method[1]. Briefly, a SEL was defined as a region of the initial T2 lesion mask of at least 10 voxels (30 mm^3) in size that demonstrated constant and concentric local expansion on the serial scans acquired over 2 years, where local expansion was assessed based on Jacobian integration (Fig. 1).[1,15] SELs were filtered to ensure that the expansion was gradual (ie, not occurring at a single timepoint) and followed a radial inside-out pattern[1].

Quantitative Analyses. The following measurements were performed for each participant: total volume of T2 lesions at the initial timepoint, total number of SELs, total volume of SELs, percentage of the initial T2 lesion volume identified as SEL, total number of discrete T2-lesions (determined by connectedness) at the initial timepoint that are at least 10 voxels in size, and the percentage of discrete T2-lesions at the initial timepoint overlapping with SELs.

For each measurement, a statistical comparison was made between the POMS and MOGAD populations using the Wilcoxon Rank Sum Test (R version 4.3.1; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Of 210 children with incident central nervous system demyelination recruited at the Hospital for Sick Children, 19 of 32 (59%) POMS and 14 of 50 (28%) MOGAD participants were included in the present study (Table and Data S1). Of the excluded participants, all 13 MS and 29 of 36 MOGAD participants did not have appropriate timing for brain MRI acquisition. Seven additional MOGAD participants were excluded, because brain lesions were absent at baseline (all presenting with optic neuritis or transverse myelitis). The mean (±standard deviation) time between the first and last MRI scans examined was

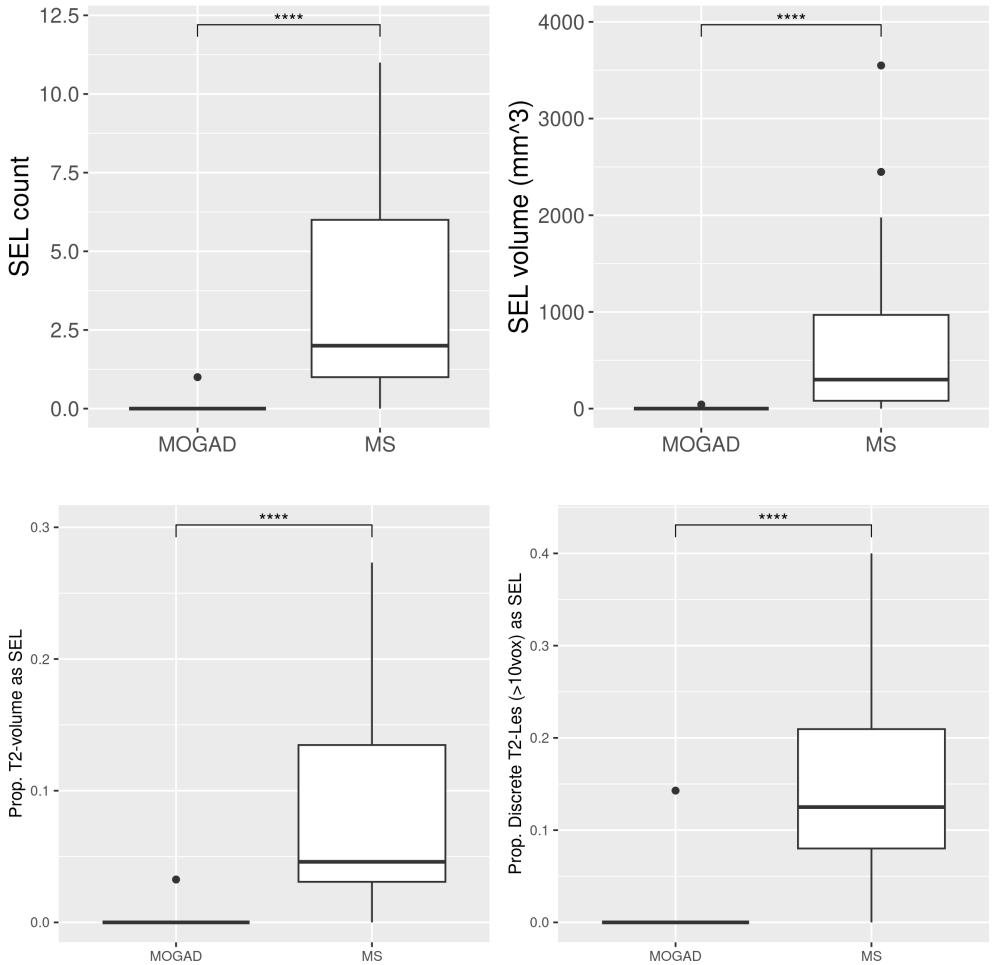

Figure 2: Slowly expanding lesions (SELs) in multiple sclerosis (MS) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) populations. (A) SEL counts, (B) SEL volume, (C) proportion of T2 volume at initial timepoint identified as SEL, and (D) proportion of discrete T2 lesions of at least 10 voxels in size (minimum size for SEL detection) at initial timepoint that overlap with SEL. **** p<0.0001

105.2 weeks (±4.6 weeks) for the MS group, and 103.5 weeks (±2.8 weeks) for the MOGAD group ($p = 0.40$).

POMS patients had approximately 5-fold more lesions compared with the MOGAD group (median [IQR] 22 [9–26], vs 4 [2–6]; Table), and the POMS group had a much higher T2 lesion volume at the initial timepoint (median 7.2 cm^3 vs 0.5 cm^3, $p < 0.00001$).

While 70 SELs were identified in the POMS group and only 1 SEL was identified in the MOGAD group. The proportion of T2 lesion volume detected as SEL (median 4.6% vs 0.0%, $p = 0.00002$) and the proportion of discrete T2 lesions at least 10 voxels in size that were overlapping with SEL (median 12.5% vs 0.0%, $p = 0.00007$) were greater in the POMS group. More precisely, for the MS population, of 613 discrete T2 lesions (determined by spatial connectedness), 366 were ≥10 voxels (30 mm^3) in size, of which 55 overlapped 70 SELs. Because SEL boundaries are determined via the Jacobian determinant, a larger confluent lesion may overlap with >1 area detected as SEL. Thus, SELs represented 9.0% of all discrete T2 lesions and 15.0% of discrete T2 lesions that met the minimum size requirements for SEL detection. For the MOGAD population, of 174 discrete T2 lesions, 63 were ≥10 voxels in size, of which 1 overlapped with a SEL. Complete results are presented in Table and Figure 2.

Discussion

The high prevalence of SELs in POMS and their virtual absence in MOGAD emphasizes the distinct pathobiology of these two conditions. This radiographic distinction also aligns with the strictly relapse-related accrual of disability and the paucity of brain volume changes detected outside of the occurrence of clinical attacks in MOGAD,[16] compared with the association of SELs with progressive MS. Although progression of clinical disability independent of relapse is exceptionally rare in POMS,[6] the presence of SELs early in the disease adds evidence that focal tissue damage related to progressive disease biology develops years before its clinical manifestations become apparent.[7,8,17] When added to evidence of reduced brain volume at presentation and progressive failure to follow expected brain growth in children with MS,[7,8,18] the imperative for prompt initiation of strategies to prevent progressive central nervous system damage in POMS is clear. Studies over longer periods of time would be valuable to establish whether SELs change in frequency over time, including following treatment exposure. We note that only 4 of the 16 MOGAD patients included in this study were of post-pubertal age, in contrast to the vast majority of patients with POMS. Although none of these 4 children demonstrated the presence of SELs, further studies on older MOGAD patients should assess whether immunological changes occurring in the post-pubertal age influence the likelihood of SEL development. Although detection of SELs, which requires serial imaging over a 2-year period, would not be helpful as an early diagnostic determinant, imaging techniques sensitive to iron-laden macrophages at the border of acute lesions might help characterize MS lesions at the time of disease onset, and their absence would argue against MS.

Acknowledgements

This study was funded in part by the Multiple Sclerosis Scientific Research Foundation (A.B.-O., D.L.A., R.A.M., E.A.Y., and B.B), with some aspects supported by the Canadian Institutes of Health Research (SN, PJT153005).

Author Contributions

G.F., B.B., C.E., D.L.A., A. B-O., and S.N. contributed to the conception and design of the study. G.F., B.B., C.E., D.F., D.L.A., P.W. E.A.Y., R.A.M., A. B-O., and S.N. contributed to the acquisition and analysis of data. G.F., B.B., C.E., R.A.M., A. B-O., and S.N. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

C.E. is an employee of NeuroRx, an imaging contract research organization that developed and published the SEL method used in this work. D.L.A. has an equity interest in NeuroRx. D.F. and S.N. are part-time employees of NeuroRx. P.W. is co-Director of the Oxford Autoimmune Neurology Diagnostic Laboratory where MOG immunoglobulin G antibody assays are performed.

Data Availability

Anonymized derived data used for this article will be made available by request from qualified investigators.

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