Frequency of New or Enlarging Lesions on MRI Outside of Clinical Attacks in Patients With MOG-Antibody–Associated Disease

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

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Contributions:
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Eoin P. Flanagan: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
1

Table Count:
2

Search Terms:

Acknowledgment:
We would like to acknowledge the Mayo Clinic Center for multiple sclerosis and autoimmune neurology.

Study Funding:
This study was funded by an RO1 from the National Institute of Neurological Disorders and Stroke (R01NS113828).

Disclosures:
S.B. Syc-Mazurek reports no disclosures relevant to the manuscript; J. J. Chen is a consultant to UCB and Roche; P. P. Morris reports no disclosures relevant to the manuscript; E. Sechi reports no disclosures relevant to the manuscript; J. Mandrekar reports no disclosures relevant to the manuscript; J. Tillema reports no disclosures relevant to the manuscript; A. S. Lopez-Chiriboga has served on advisory boards for Genentech and Horizon Therapeutics; C. F. Lucchinetti has patents and has received royalties/payments related to aquaporin-4 associated antibodies for diagnosis of neuromyelitis optica. Dr. Lucchinetti has received travel reimbursement as a consultant for Biogen Idec. Dr. Lucchinetti has research support from Amendment 3: A Synchrotron X-ray Fluorescence Based Approach to Examine the Role of Metals in Multiple Sclerosis Tissues. Biogen Idec. (2) BRIGHT-MS study: Utility of ADC maps in patients with acute demyelinating lesions. Mallinckrodt Medical (3) Tissue
ABSTRACT

Objective: To determine the frequency of new or enlarging T2-hyperintense or enhancing lesions outside of clinical attacks in myelin-oligodendrocyte-glycoprotein-antibody-associated-disease (MOGAD) versus multiple sclerosis (MS) and aquaporin-4 antibody-positive-neuromyelitis-optica-spectrum-disorder (AQP4+NMOSD).

Design/Methods: We retrospectively included Mayo Clinic MOGAD patients with: 1) MOG-IgG positivity by live-cell-based-assay; 2) Fulfilling proposed MOGAD diagnostic criteria; 3) Baseline and follow-up paired MRIs without interval attacks. A neurologist and neuroradiologist reviewed MRIs (T2-FLAIR brain, T2 spine, and T1-post-gadolinium brain and spine) to identify new or enlarging lesions. A MOGAD subset was then compared to MS and AQP4+NMOSD patients, based on broadly similar inter-scan intervals.
Results: We included 105 MOGAD patients (median age, 31 years[range, 2-80]; 60% female) with 373 paired MRIs. In total, 10/105 (9.5%) patients and 13/373 (3%) scans had one or more new T2-lesions (brain, 12/213[6%]; spine, 1/160[0.6%]) and 8/367 (2%) had enhancing lesions. New brain lesions were less in MOGAD (1/25[4%]) than MS (14/26[54%], p<0.0001) but did not differ from AQP4+NMOSD (1/13[8%], p=1.0) in subgroup analysis. New spinal lesions were rare across groups (0-4%).

Conclusions: New or enlarging MRI lesions rarely develop outside of clinical attacks in MOGAD differing from MS. Surveillance MRIs in MOGAD have limited utility with implications for clinical practice and trial design.

Introduction
Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a demyelinating disease distinct from multiple sclerosis (MS) and aquaporin-4-IgG-seropositive-neuromyelitis-optica-spectrum-disorder (AQP4+NMOSD). In MS, MRI surveillance is standard of care and new asymptomatic lesions often developed prior to high-efficacy therapy availability but in AQP4+NMOSD such lesions are rare. Details on new lesion frequency outside of attacks in MOGAD is limited. Herein, we determined new lesion frequency in MOGAD and compared it to MS and AQP4+NMOSD.
Methods

Patients were retrospectively identified from the Mayo Clinic MOGAD database (1/1/2000-10/30/2020) and inclusion criteria were: 1) Serum MOG-IgG positive by live-cell-based-assay at any time during disease course; 2) Fulfilling current proposed MOGAD diagnostic criteria; \(^6\) 3) A baseline and follow-up MRI without interval attacks. Paired MRIs (baseline and follow-up) were categorized as attack-to-remission or remission-to-remission scans. A neurologist and neuroradiologist compared follow-up T2-FLAIR (brain), T2 (spine), and T1-post-gadolinium (brain, spine) images to a reference MRI to identify new or enlarging T2-hyperintense lesions or enhancing lesions with consensus reached in discordant cases. We compared the frequency of such lesions in a MOGAD subset (selected based on broadly similar inter-scan-intervals to the other subgroups) to an MS and AQP4+NMOSD subgroup of patients negative for MOG-IgG from a prior study. \(^7\) Continuous variables were evaluated using paired t-test or Mann-Whitney U test, categorical variables with Fisher’s exact test, and Kaplan Meier curve for time to next relapse. All tests were two-sided, and \(p \leq 0.05\) was considered statistically significant (SAS Inc., Cary NC, Version 9.4).

Standard protocol approvals, registrations, and patient consents

Mayo Clinic’s institutional review board approved the study. All participants consented to use of their medical records for research.

Data availability

Anonymized data from this study will be made available on request.
Results

We included 105 patients with 373 paired MRIs (brain, 213; spine, 160). New or enlarging MRI T2-lesions outside of clinical attacks occurred in 10/105 (9.5%; new, 9; enlarged, 1) MOGAD patients representing 13/373 (3.5%) scans (brain, 12/213[5.6%]; spine, 1/160[0.6%]). Table 1 compares those with and without new or enlarging lesions and Figure 1 shows MRI examples. New or enlarging T2-lesions occurred in attack-remission scans (8/171[4.7%]) and remission-remission scans (5/202[2.4%]) but future relapse risk did not differ based on this parameter (data not shown). New lesions were single (6/13[46%]) or multiple concurrent (7/13[54%]). New or enlarged gadolinium enhancing lesions occurred in 8/367 scans (2%; new, 7; enlarged, 1). New or enlarging T2-lesions did not predict future relapse (eFigure1). In the MOGAD subset with broadly similar inter-scan-interval to the comparison groups, new or enlarging brain T2-lesions were less frequent than in MS but similar to AQP4+NMOSD (Table 2). Spinal lesions were similarly rare in the MOGAD subset (0/21[0%]) as MS (1/23[4.4%]; p=1.0) and AQP4+NMOSD (0/13[0%]; p=1.0) with similar inter-scan intervals in months (MS, median 17[range, 12-43]; MS, median 20[range,6-201]; AQP4+NMOSD, median 30.5[range, 6-138]).

Discussion

We found new or enlarging lesions outside of attacks rarely developed on surveillance brain MRI in MOGAD differing from MS. The frequency in MOGAD patients (12/213[5.6%]) was similar to a Canadian pediatric study (16/483[3.3%]) and UK report that included all ages (5/137[3.4%]).4, 5 As noted previously, new or enlarging lesions were more frequent at first follow-up MRI after an attack (attack-to-remission scan) than with remission-to-remission scans.4, 5 This may reflect lesions accumulated during the prior clinical attack but after the attack
MRI was undertaken. New or enlarging MOGAD spinal lesions were rare (<1%) consistent with a prior study.\textsuperscript{4} New or enlarging lesions did not predict subsequent relapse although prior data is conflicting and further studies are needed.\textsuperscript{4, 5} Our inclusion of USA data, an adult MS comparison group, and pediatric spine MRI details are novel and add to knowledge on this topic.

The rarity of new or enlarging lesions suggests MRI surveillance outside of attacks should not be recommended routinely in MOGAD differing from current MS practice with potential cost savings.\textsuperscript{2} Moreover, surveillance MRI as a surrogate biomarker of disease activity in clinical trials will have much lower utility in MOGAD than MS.

The lower frequency of new or enlarging lesions in MOGAD than MS emphasizes its separate pathogenesis and may reflect less subclinical disease, greater T2-lesion resolution, monophasic course in 50%, greater potential for disease restricted to the optic nerve and most MS patients receiving lower-efficacy medications.\textsuperscript{1, 6, 7} Our limitations include the retrospective nature, potential bias of patients with asymptomatic lesions receiving more scans, lack of standardized imaging protocols and intervals, and inability to control for treatment effects for which larger studies are needed. However, this closely mirrors clinical practice, and the results remain generalizable.

**Search terms:** (1) MOG; (2) MOGAD (3) neuromyelitis optica spectrum disorder; (4) multiple sclerosis; (5) neuroimaging
Table 1. Comparison of MOGAD patients without or with new lesions.

<table>
<thead>
<tr>
<th></th>
<th>MOGAD Total</th>
<th>MOGAD without Asymptomatic Lesions</th>
<th>MOGAD with Asymptomatic Lesions</th>
<th>Asymptomatic Lesions vs No Asymptomatic Lesions</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at attack onset, years (range)</td>
<td>31 (2-80)</td>
<td>31 (2-80)</td>
<td>34 (9-66)</td>
<td>0.4677</td>
<td></td>
</tr>
<tr>
<td>Children, &lt;18 y (%)</td>
<td>36 (34.3)</td>
<td>33 (34.7)</td>
<td>3 (30.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>63 (60.0)</td>
<td>58 (61.1)</td>
<td>5 (50.0)</td>
<td>0.8162</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, Caucasian (%)</td>
<td>83 (79.1)</td>
<td>75 (79.0)</td>
<td>8 (80.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Monophasic Disease (%)</td>
<td>52 (49.5)</td>
<td>48 (50.5)</td>
<td>4 (40.0)</td>
<td>0.7415</td>
<td></td>
</tr>
<tr>
<td>High Titer MOG-IgG (%)</td>
<td>58 (59.2)^a</td>
<td>52 (59.1)^a</td>
<td>6 (60.0)^a</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Persistent MOG IgG (%)</td>
<td>52 (74.3)^b</td>
<td>46 (73.0)^b</td>
<td>6 (85.7)^b</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Treatment with DMT (%)</td>
<td>44 (41.9)^c</td>
<td>41 (43.2)^c</td>
<td>3 (30.0)^c</td>
<td>0.5148</td>
<td></td>
</tr>
<tr>
<td>Treatment with acute therapy during previous clinical attack (%)</td>
<td>95 (91.3)^d</td>
<td>86 (91.5)^d</td>
<td>9 (90.0)^d</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Median # of paired MRIs (range)</td>
<td>3 (1-16)</td>
<td>3 (1-13)</td>
<td>5.5 (1-16)</td>
<td>0.0032</td>
<td></td>
</tr>
<tr>
<td>Median interval from disease onset to reference MRI in months (range)</td>
<td>16 (1.5-314)^f</td>
<td>16 (1.5-314)^f</td>
<td>17 (1.5-111)^f</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Median interval between scans in months (range)</td>
<td>7 (0.5-133)^i</td>
<td>7 (0.5-133)^i</td>
<td>4 (1-31)^i</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Median length of follow-up in months (range)</td>
<td>27 (1-168)</td>
<td>27 (1-168)</td>
<td>32 (3-97)</td>
<td>0.8914</td>
<td></td>
</tr>
<tr>
<td>Multiple attacks (%)</td>
<td>15 (14.3)</td>
<td>12 (12.6)</td>
<td>3 (30.0)</td>
<td>0.1523</td>
<td></td>
</tr>
<tr>
<td>Additional attacks (%)</td>
<td>39 (37.1)</td>
<td>34 (35.8)</td>
<td>5 (50.0)</td>
<td>0.4942</td>
<td></td>
</tr>
</tbody>
</table>

^a High titer ≥1:100; Titers available for 98 total MOGAD patients, 88 MOGAD patients with no asymptomatic lesions, all 10 MOGAD patients with asymptomatic lesions

^b Persistent seropositivity was defined as positive MOG IgG titers separated by at least 6 months. Repeat titers were available for 70 total MOGAD patients, 63 with no asymptomatic lesions, and 7 with asymptomatic lesions.
Including one or more of: azathioprine, 14; mycophenolate mofetil, 10; prednisone, 10; rituximab, 9; IVIG, 7; glatiramer acetate, 3, interferon beta, 2.

Including one or more of: azathioprine, 12; mycophenolate mofetil, 10; prednisone, 9; rituximab, 9; IVIG, 7; glatiramer acetate, 3, interferon beta, 2.

Including one or more of: azathioprine, 2; prednisone, 1.

Acute therapy information was available for 104/105 patients, treatment included one or more of: steroids, 90; PLEX, 11; IVIG, 7.

Acute therapy information was available for 94/95 patients, treatment included one or more of: steroids, 81; PLEX, 10; IVIG, 7.

Including one or more of: steroids, 9; PLEX, 1.

These data were calculated by scan pair rather than by patient, total MOGAD patients n=373, MOGAD patients with no asymptomatic lesions n = 360, MOGAD patients with asymptomatic lesions n = 13

Abbreviations: DMT, disease modifying treatment; IVIG, intravenous immune globulin; MOG-IgG, myelin oligodendrocyte glycoprotein antibody; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease, PLEX, plasma exchange.

Table 2. Comparison of new brain T2-lesions in subset of MOGAD to MS and AQP4+NMOSD with broadly similar inter-scan intervals.

<table>
<thead>
<tr>
<th></th>
<th>MOGAD (n=25)</th>
<th>MS (n=26)</th>
<th>MOGAD vs MS P-value</th>
<th>AQP4+NMOSD (n=13)</th>
<th>MOGAD vs AQP4+NMOSD P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Asymptomatic Brain T2-Lesions (%)</td>
<td>1 (4)</td>
<td>14 (53.9)</td>
<td>&lt;0.0001</td>
<td>1 (7.7)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Median age at attack onset, years (range)</td>
<td>31 (11-64)</td>
<td>41.5 (19-64)</td>
<td>0.1199</td>
<td>55 (22-73)</td>
<td>0.0048</td>
</tr>
<tr>
<td>Sex, female (%)</td>
<td>16 (64)</td>
<td>19 (73.1)</td>
<td>0.5551</td>
<td>11 (84.6)</td>
<td>0.2679</td>
</tr>
<tr>
<td>Treatment with DMT (%)</td>
<td>13 (52)(a)</td>
<td>22 (84.6)(b)</td>
<td>0.0167</td>
<td>13 (100)(c)</td>
<td>0.0026</td>
</tr>
<tr>
<td>Median interval between scans in months (range)</td>
<td>21 (16-133)</td>
<td>22.5 (7-138)</td>
<td>0.8801</td>
<td>44 (6-137)</td>
<td>0.4322</td>
</tr>
</tbody>
</table>

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a Including one or more of: Azathioprine, 4; mycophenolate mofetil, 3; prednisone, 3; rituximab, 3; interferon beta, 2; glatiramer acetate, 1; IVIG, 1.

b Including one or more of: Interferon-beta, 14; fingolimod, 5; dimethyl fumarate, 4; glatiramer acetate, 2; natalizumab, 2; teriflunomide, 2; ocrelizumab, 1.

c Including one or more of: Prednisone, 9; azathioprine, 6; rituximab, 6; mycophenolate mofetil, 5; cyclophosphamide, 1; methotrexate, 1.

Abbreviations: AQP4+NMOSD, aquaporin-4-IgG positive neuromyelitis optica; DMT, disease modifying treatment; IVIG, intravenous immune globulin; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MS, multiple sclerosis.

References


Figure 1. Examples of new or enlarging lesions occurring between attacks in myelin oligodendrocyte glycoprotein antibody-associated disease.

A) The reference coronal MRI T2 fluid attenuated inversion recovery (T2-FLAIR) image reveals bilateral internal capsule and a left hemispheric T2-hyperintense lesion (A1, arrowheads) that on follow-up showed enlargement of the right internal capsule and left subcortical white matter T2-hyperintense lesions (A.b, arrows) in the absence of a new attack. B) The reference axial MRI T2-FLAIR image (B.a) reveals normal brainstem and cerebellum signal while the follow-up image shows a new T2-hyperintensity in the left middle cerebellar peduncle (B.b, arrow) in the absence of a new clinical attack. The T2-lesion resolved completely and was no longer visible on a subsequent MRI FLAIR image (B.c) highly consistent with the expected evolution of a MOGAD lesion. C) The reference axial MRI T2-FLAIR image (C.a) and axial T1 post-gadolinium image (C.b) of the supratentorial region reveals no abnormalities but on follow-up show a new T2-hyperintensity had developed in the right frontal region (C.c, arrow) that enhanced after gadolinium (C.d, arrow) in the absence of a new attack. The lesion had resolved.
completely and was no longer visible on FLAIR (C.e) and T1-post gadolinium (C.f) images on a subsequent MRI highly consistent with the expected evolution of a MOGAD lesion. D) The reference sagittal MRI cervical spine T1-weighted images post gadolinium revealed some subtle gadolinium enhancement (D.a, arrowhead) that increased in size in the follow-up (D.b, arrows) in the absence of a new attack despite no change in the T2-hyperintense cord lesion (not shown). The enhancement had resolved completely and was no longer visible on T1-post gadolinium image (D.c) highly consistent with the expected evolution of a MOGAD lesion.
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Neurology published online September 29, 2022
DOI 10.1212/WNL.0000000000201263

This information is current as of September 29, 2022

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