

# Clinical and MRI measures to identify non-acute MOG-antibody disease in adults

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## Abstract

MRI and clinical features of myelin oligodendrocyte glycoprotein (MOG)-antibody disease may overlap with those of other inflammatory demyelinating conditions posing diagnostic challenges, especially in non-acute phases and when serologic testing for MOG-antibodies is unavailable or shows uncertain results.

1 We aimed to identify MRI and clinical markers that differentiate non-acute MOG-antibody  
2 disease from aquaporin4 (AQP4)-antibody neuromyelitis optica spectrum disorder and relapsing  
3 remitting multiple sclerosis, guiding in the identification of MOG-antibody disease patients in  
4 clinical practice.

5 In this cross-sectional retrospective study, data from 16 MAGNIMS centres were included. Data  
6 collection and analyses were conducted from 2019 to 2021. Inclusion criteria were: diagnosis of  
7 MOG-antibody disease, AQP4-neuromyelitis optica spectrum disorder and multiple sclerosis,  
8 brain and cord MRI at least 6 months from relapse, EDSS on the day of MRI. Brain white matter  
9 T2 lesions, T1-hypointense lesions, cortical and cord lesions were identified. Random-forest  
10 models were constructed to classify patients as MOG-antibody disease/AQP4-neuromyelitis  
11 optica spectrum disorder/multiple sclerosis; a leave one out cross-validation procedure assessed  
12 the performance of the models. Based on the best discriminators between diseases, we proposed  
13 a guide to target investigations for MOG-antibody disease.

14 One hundred sixty-two patients with MOG-antibody disease (99F, mean age: 41 [ $\pm$ 14] years,  
15 median EDSS: 2 [0-7.5]), 162 with AQP4-neuromyelitis optica spectrum disorder (132F, mean  
16 age: 51 [ $\pm$ 14] years, median EDSS: 3.5 [0-8]), 189 with multiple sclerosis (132F, mean age: 40  
17 [ $\pm$ 10] years, median EDSS: 2 [0-8]) and 152 healthy controls (91F) were studied. In young  
18 patients (<34 years), with low disability (EDSS<3), the absence of Dawson's fingers, temporal  
19 lobe lesions and longitudinally extensive lesions in the cervical cord pointed towards a diagnosis  
20 of MOG-antibody disease instead of the other two diseases (accuracy: 76%, sensitivity: 81%,  
21 specificity: 84%,  $p$ <0.001). In these non-acute patients, a number of brain lesions<6 predicted  
22 MOG-antibody disease versus multiple sclerosis (accuracy: 83%, sensitivity: 82%, specificity:  
23 83%,  $p$ <0.001). An EDSS<3 and the absence of longitudinally extensive lesions in the cervical

1 cord predicted MOG-antibody disease versus AQP4-neuromyelitis optica spectrum disorder  
2 (accuracy: 76%, sensitivity: 89%, specificity: 62%,  $p < 0.001$ ). A workflow with sequential tests  
3 and supporting features has been proposed to guide a better identification of MOG-antibody  
4 disease patients.

5 Adult non-acute MOG-antibody disease patients showed distinctive clinical and MRI features  
6 when compared to AQP4-neuromyelitis optica spectrum disorder and multiple sclerosis. A  
7 careful inspection of the morphology of brain and cord lesions together with clinical information,  
8 can guide for further analyses towards diagnosis of MOG-antibody disease in clinical practice.

9

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14 **Running title:** MRI and clinical markers of MOGAD

15

16 **Keywords:** myelin oligodendrocyte glycoprotein antibody-associated disease; aquaporin 4-  
17 antibody positive neuromyelitis optica spectrum disorder; multiple sclerosis; imaging;  
18 differential diagnosis

19 **Abbreviations:** Acute disseminated encephalomyelitis (ADEM); aquaporin 4-antibody positive  
20 neuromyelitis optica spectrum disorder (AQP4-NMOSD); antibodies (Ab); area under the curve  
21 (AUC); cell-based assays (CBA); expanded disability status scale (EDSS); fluffy infratentorial

1 lesions (FIT); leave one out internal-validation procedure (LOOCV); magnetic resonance  
2 imaging in multiple sclerosis (MAGNIMS); myelin oligodendrocyte glycoprotein antibody-  
3 associated disease (MOGAD); optic neuritis (ON); receiving operated characteristic curve  
4 (ROC); relapsing remitting multiple sclerosis (RRMS)

5

## 6 **Introduction**

7 Myelin oligodendrocyte glycoprotein (MOG) antibody- (Ab) associated disease (MOGAD) is a  
8 recently recognised demyelinating disease of the central nervous system (CNS), with a highly  
9 variable disease course and poorly understood pathogenetic mechanisms.<sup>1</sup> The differentiation  
10 between MOGAD and other inflammatory demyelinating diseases, such as relapsing-remitting  
11 MS (RRMS) and aquaporin-4-antibody-positive neuromyelitis optica spectrum disorder (AQP4-  
12 NMOSD) may be challenging, as they share a number of clinical and radiological features.<sup>2</sup> An  
13 accurate differentiation between these diseases is crucial, however, to recommend an effective  
14 treatment and predict prognosis.<sup>3,4</sup>

15

16 MOGAD can be diagnosed with high specificity by the detection of serum antibodies using anti-  
17 MOG antibody cell-based assays (CBA).<sup>5</sup> However, up to a quarter of positive results may be  
18 false-positives when the test is performed indiscriminately in a real-life clinical setting  
19 (particularly when the titre is low or results are borderline), with MS being the most represented  
20 alternative diagnosis.<sup>6</sup> On the other hand, MOG-Ab titres may fluctuate, with some patients  
21 turning negative in the non-acute phases of the disease.<sup>7,8</sup> Differences in assay methods may  
22 impact on the results of CBA, and discrepancies in low positive or borderline tests may require

1 further investigation.<sup>9</sup> Finally, intrathecal production of MOG-Ab was found in up to 28.9% of  
2 seronegative cases, thus suggesting that performing only the blood test might underestimate the  
3 real prevalence of MOGAD.<sup>10-13</sup> It is therefore important to identify more stringent measures  
4 accompanying MOG-Ab testing to better interpret test results, especially among patients with  
5 low antibody titers and atypical phenotypes.

6  
7 Cerebrospinal fluid restricted oligoclonal bands can help the identification of MOGAD. In  
8 contrast to MS, oligoclonal bands are typically found in a minority of MOGAD patients (about  
9 15%) tested acutely, while they can turn negative on subsequent testing in the non-acute phase.<sup>14</sup>  
10 The fluctuation of cerebrospinal fluid findings may help to gauge the likelihood of false positive  
11 MS patients being included in MOGAD and to guide treatment strategies. However, a second  
12 lumbar puncture is rarely performed in clinical practice.

13  
14 Distinctive MRI lesional features in MOGAD, AQP4-NMOSD and RRMS have been reported,  
15 particularly in acute patients.<sup>7,15</sup> Brain and spinal cord lesions may resolve completely in  
16 MOGAD patients, more often than AQP4-NMOSD and MS, and some acute T2 lesions can  
17 leave small foci of T2 hyperintensity, thus making the identification of typical signatures more  
18 challenging in the chronic phases.<sup>16</sup> Additionally, MOGAD can be clinically heterogeneous, and  
19 in the long term, the course of the disease does not generally reflect the severity of the attacks,  
20 which can lead to misdiagnosis.<sup>17</sup>

21



1 Given the rarity of MOGAD, most of the previous imaging works included a relatively small  
2 number of patients or were conducted in a single-centre setting, limiting the generalizability of  
3 the results. Moreover, only few and relatively small studies have assessed MOGAD patients in  
4 the non-acute phases.<sup>16,18–20</sup>

5 Against this background, we carried out a study aiming at identifying key features able to  
6 distinguish non-acute adult MOGAD from AQP4-NMOSD and RRMS. Our ultimate goal was to  
7 provide advice on how to identify MOGAD patients in clinical practice, by suggesting sequential  
8 tests and supporting features beyond or in addition to serological testing.

## 10 **Materials and methods**

### 11 **Study design and population**

12 This is a multicenter, retrospective cross-sectional study, conducted on previously collected data  
13 from 16 international centres (13 Magnetic Resonance Imaging in Multiple Sclerosis  
14 [MAGNIMS] collaboration [www.magnims.eu] centres and 3 additional centres, respectively  
15 from Europe, Asia and Latin America). The collection and analysis of the MRI scans was  
16 centralised in a single centre (Siena, Italy) from 2019 to 2021.

17  
18 Inclusion criteria were (1) diagnosis of MOGAD (which was made, in each centre, only when  
19 MOGAD was suspected on the basis of patient's history and clinical presentation, and was  
20 confirmed by MOG antibody positivity according to local laboratory guidelines), AQP4-Ab  
21 NMOSD<sup>21</sup> or RRMS<sup>22</sup>, (2) serum antibodies detected using CBA (either live or fixed) (3) age at

1 MRI  $\geq$  18 years, (4) being at least 6 months after an acute event, (5) Expanded Disability Status  
2 Scale (EDSS) score at the time of MRI, (6) information on type of clinical onset (classified as:  
3 isolated optic neuritis [unilateral or bilateral], transverse myelitis, concurrent optic neuritis and  
4 transverse myelitis, acute disseminated encephalomyelitis [ADEM], others), age, sex, and  
5 disease duration (time from disease onset to MRI). Healthy controls (HC) were also recruited.  
6 Exclusion criteria were a history of other known medical conditions that could have affected the  
7 brain and MRI-related contraindications.

8  
9 Each participant provided written consent for research within each centre. The final protocol for  
10 the analysis of fully anonymized scans, acquired independently at each centre, was approved by  
11 the European MAGNIMS collaboration and by the local ethics committees.

## 13 **MRI Acquisition and Processing**

14 Brain and cervical cord images were acquired at 16 sites on 1.5T and 3T scanners, from different  
15 manufacturers and with different scanning parameters based on local protocols, following the  
16 MAGNIMS guidelines<sup>23</sup> (**Supplementary Table 1**). All images were visually checked and  
17 analyzed centrally. Brain white matter lesions were segmented with a semiautomated process  
18 using lesion prediction algorithm<sup>24</sup> as implemented in the LST toolbox version for SPM on 3D  
19 FLAIR and PD-T2-weighted MRI sequences. The quality of all the obtained lesions was  
20 manually checked and corrected by two experienced readers (R.C. and M.B.). Lesion volumes  
21 were subsequently obtained. Brain MRI scans were examined for Dawson's fingers, juxtacortical  
22 lesions in the U-fiber (with a curved/s-shaped morphology), lesions located in the temporal

1 lobes, and fluffy infratentorial lesions (FIT), which were found to be able to discriminate  
2 between MOGAD, AQP4-NMOSD and RRMS.<sup>7</sup> Hypointense lesions on T1 were automatically  
3 identified based on a voxel-by-voxel analysis of the local T1 ratio value within each lesion mask,  
4 using a definition of hypointense lesion, adopting a previous definition of a region with a signal  
5 intensity lower ( $<1sd$ ) similar to or reduced to than the signal intensity of the grey matter of the  
6 slice of the lesion and corresponding to a lesion mask drawn on T2- weighted MRI. Cortical  
7 lesions were assessed on the DIR, PSIR or MPRAGE images, when available, and the presence  
8 of cervical cord lesions was recorded, and they were classified as either short lesions or  
9 longitudinally extensive cord lesion. We included only cervical cord MRI, as this is the part of  
10 the spinal cord which is most frequently scanned in clinical practice; other segments (i.e.,  
11 thoracic, lumbar and sacral cord) were available only for a minority of subjects (10% of the  
12 whole cohort). The analyses were based on the consensus between two raters (R.C. and L.H.),  
13 who had an excellent inter-rater agreement (96% Cohen kappa coefficient).

14 All readers worked independently and were blinded to clinical data.

15

## 16 **Statistical Analyses**

17 The analysis of this study was divided in two parts:

### 18 **Differences between groups**

19 Means, medians, and proportions of demographics, clinical features, and MRI measures were  
20 calculated for patients and healthy controls. Differences were evaluated using Kruskal-Wallis,  
21 ANOVA or  $\chi^2$ , as appropriate.

1

## 2 **Best MRI and clinical discriminators between diseases**

3 The data collection was retrospectively performed using scans already acquired with different  
4 MRI protocols and only images with adequate quality were retained. Therefore, not all patients  
5 had all sequences and relative measures available. To make efficient use of the available data, we  
6 used multiple imputation of missing values for missing data. Imputation was performed using  
7 chained equations,<sup>25</sup> where each incomplete variable is imputed by a separate model and  
8 implemented through the "mice" R package. Continuous variables (age, disease duration, EDSS,  
9 white matter lesion number and volume, T1 hypointense lesions and cortical lesion number)  
10 were parameterized as numeric data and imputed with the predictive mean matching method,  
11 whereas polytomous logistic regression was used for the unordered categorical variables (such as  
12 phenotype at onset), and binomial logistic regression for the binary variables (presence/absence  
13 of temporal lobe lesions, Dawson's finger type lesions, FIT, cortical lesions, cord lesions).  
14 Clinical and available lesion data were used to impute missing lesion data.

15

16 To assess the best set of variables for prediction purpose, we ran a random forest selected  
17 predictor, with 3-step procedure,<sup>26</sup> considering first the three diseases together and then one  
18 disease vs the other. Eight separate models were constructed using MRI data (i.e. lesion number,  
19 volume and morphological characteristics) alone first and then MRI and clinical data (i.e. age,  
20 disease duration, phenotype at onset, EDSS) together. To assess the performance of the selected  
21 best predictors in discriminating the diseases, a leave one out internal cross-validation procedure  
22 using LOOCV of Random Forest and binomial logistic regression model was performed using

1 the set of MRI and MRI and clinical together variables. LOOCV is a cross-validation that  
2 considers each observation as the validation set and the rest (N-1) observations as the training  
3 set; the process is repeated for all observations such that N models are estimated, and  
4 performance averaged. From all models, we obtained the logarithm odds ratio (logOR) of having  
5 one disease vs the other, the model average accuracy and Kappa coefficient, and the area under  
6 the curve (AUC) Receiving Operated Characteristic curve (ROC). The analyses were further  
7 repeated considering only patients with at least one brain or cervical cord lesion.

8  
9 Finally, for the selected variables, a Youden index optimization criterion was used to identify the  
10 best cut-off (i.e., the value associated with the highest sensibility and sensitivity) that predicted  
11 the outcome (e.g. a diagnosis of MOGAD rather than the other two diseases).

12  
13 Sensitivity analyses were run by repeating all the analyses in a model including only patients  
14 with complete data with no imputation and using a leave one-center-out procedure rerunning the  
15 analysis on data from all but one centre and then validating on the centre not included in train  
16 dataset. This was repeated for each centre and reported as average accuracy.

## 18 **Data availability**

19 Fully anonymized data are available from each participating centre on request.

## 21 **Results**

## 1 **Study population**

2 Overall, we included in the study 665 subjects: 162 MOGAD, 162 AQP4-NMOSD, 189 RRMS  
3 and 152 healthy controls. Demographic and clinical details of subjects are summarised in **Table**  
4 **1**. Details about Ab-testing and diagnosis timing are provided in **Supplementary Table 2**.

## 6 **Differences in brain and cervical cord MRI measures between** 7 **groups**

8 Brain T2 white matter lesions were detected in 68% MOGAD, 82% AQP4-NMOSD, 100%  
9 RRMS patients, and 23% of healthy controls. The number of T2 white matter lesions and  
10 corresponding T1 hypointense lesions on T1 was lower in the two Ab-mediated diseases than  
11 RRMS ( $P < 0.001$ ). Temporal lobe lesions and Dawson's finger-type lesions were detected in a  
12 lower % in the MOGAD and AQP4-NMOSD cohorts than RRMS (all  $P < 0.001$ ). At least 1  
13 cortical lesion was seen in 9% of patients with MOGAD, 8% patients with AQP4-NMOSD, in  
14 64% patients with RRMS. At least 1 cervical cord lesion was found in a minority of patients with  
15 MOGAD (8.6% with short lesions and 1.2% longitudinally extensive lesions), while in a high  
16 percentage of patients with AQP4-NMOSD (14.2% with short lesions and 23.5% longitudinally  
17 extensive lesions) and with RRMS (33.9% with short lesions and 1.1% longitudinally extensive  
18 lesions) (all  $P < 0.001$ ). None of the HC showed temporal lobe and Dawson's finger-type lesions,  
19 cortical and cord lesions, therefore they were excluded from the discriminant analysis (**Table 2**).

## 21 **MRI and clinical discriminators between diseases**

1 After imputation, 456 (88.9%) patients were included in the analysis. **Supplementary Table 3**  
2 reports the proportion of missing values for each clinical and MRI measure, which were  
3 homogeneously distributed in the three diseases.

## 5 **MOGAD vs AQP4-NMOSD vs RRMS**

6 When considering the three diseases together, the MRI measures that predicted MOGAD instead  
7 of the other two diseases were the absence of Dawson's fingers, temporal lobe lesions and  
8 longitudinally extensive lesions in the cord (average accuracy: 68%, sensitivity: 82%, specificity:  
9 66 %, *AUC*: 0.75, 95%*CI*: 72 to 80, *P* <0.001). Adding disability level and age at MRI increased  
10 the sensitivity of the model (average accuracy: 76%, sensitivity: 81%, specificity: 84%, *AUC*:  
11 0.85, 95%*CI*: 0.82 to 0.88, *P* <0.001) (**Figure 1, Table 3**).

12 When considering only patients with at least one brain or cervical cord lesion, the model selected  
13 the same best set of MRI measures, which reached the highest accuracy in predicting MOGAD  
14 rather than AQP4-NMOSD and RRMS (average accuracy: 70%, sensitivity: 68%, specificity:  
15 72%, *AUC*: 0.75 95%*CI*: 0.71 to 0.78, *P* <0.001). Adding disability increased the sensitivity of  
16 the model (average accuracy: 79%, sensitivity: 67%, specificity: 83%, *AUC*: 0.84, 95%*CI*: 0.80  
17 to 0.87, *P* <0.001).

18 The best cut-off value in respect to EDSS that predicted the diagnosis of MOGAD was 3, in  
19 respect to age was 34 years.

## 21 **MOGAD vs RRMS**

1 The lower number of brain lesions was the best MRI measure that distinguished non-acute  
2 MOGAD from RRMS (average accuracy: 76%, sensitivity: 80%, specificity: 73%, *AUC*: 0.87,  
3 95% *CI*: 0.83 to 0.91, *P* <0.001). This means that for each unit decrease of lesion there is a 9%  
4 reduced risk of having MOGAD instead of RRMS.

5 When considering only patients with at least one lesion, the combination of lower number of  
6 brain lesions and the absence of Dawson's fingers reached the highest accuracy in predicting  
7 MOGAD instead of RRMS (average accuracy: 79%, sensitivity: 78%, specificity: 80%, *AUC*:  
8 0.85, 95% *CI*: 0.80 to 0.90, *P* <0.001). The best cut-off value in respect to the number of lesions  
9 that predicted the diagnosis of MOGAD was 6.

10 If the phenotype at onset was either bilateral optic neuritis, or concurrent optic neuritis and  
11 transverse myelitis, or ADEM the sensitivity of the model to distinguish the two diseases  
12 increased either when using the whole sample (average accuracy: 83%, sensitivity: 82%,  
13 specificity: 83%, *AUC*: 0.89, 95%*CI*: 0.85 to 0.93, *P* <0.001), or when selecting patients with at  
14 least one lesion (average accuracy: 81%, sensitivity: 58%, specificity: 91%, *AUC*: 0.86, 95%*CI*:  
15 0.81 to 0.91, *P* <0.001).

## 17 **MOGAD vs AQP4-NMOSD**

18 The absence of longitudinally extensive lesions in the cord was the best MRI measure that  
19 distinguished MOGAD from AQP4-NMOSD either when considering all patients (average  
20 accuracy: 67%, sensitivity: 97%, specificity: 37%, *AUC*: 0.67, 95%*CI*: 0.63 to 0.71, *P* <0.001),  
21 or when only patients with at least one lesion were selected (average accuracy: 65%, sensitivity:  
22 94%, specificity: 47%, *AUC*: 0.32, 95%*CI*: 0.27 to 0.38, *P* <0.001).



1 When considering MRI and clinical measures together, the sensitivity of the model to predict  
2 MOGAD increased if low EDSS was considered (average accuracy: 76%, sensitivity: 89%,  
3 specificity: 62%, *AUC*: 0.83, 95%*CI*: 0.78 to 0.88, *P* <0.001), reaching the highest accuracy  
4 when only patients with at least one lesion were considered (average accuracy: 84%, sensitivity:  
5 84%, specificity: 68%, *AUC*: 0.80, 95%*CI*: 0.74 to 0.86, *P* <0.001).

6 The best cut-off value in respect to the EDSS that predicted the diagnosis of MOGAD was 3.

7

### 8 **AQP4-NMOSD vs RRMS**

9 The absence of Dawson's fingers and temporal lobe lesions were the best discriminators between  
10 AQP4-NMOSD and RRMS either when using MRI measures only or MRI and clinical measures  
11 together (average accuracy: 87%, sensitivity: 89%, specificity: 62%, *AUC*: 0.89, 95%*CI*: 0.86 to  
12 0.93, *P* <0.001). This was confirmed when considering only patients with at least one lesion,  
13 reaching the highest accuracy (average accuracy: 88%, sensitivity: 89%, specificity: 85%, *AUC*:  
14 0.89, 95%*CI*: 0.85 to 0.92, *P* <0.001). **Supplementary Table 4** summarises the performances of  
15 the best MRI and clinical measures to discriminate between the diseases. **Supplementary**  
16 **Tables 5 and 6** report details on the analyses performed when considering only patients with at  
17 least one lesion.

18

19 All sensitivity analyses confirmed these findings; the same sets of best discriminators between  
20 diseases were selected when using only complete baseline data with no imputation, with a high  
21 average accuracy between centre validation performance (**Supplementary Tables 7 and 8**).

22

1 Finally, in **Figure 2**, we propose a workflow that can be applied to non-acute adult patients with  
2 suspected CNS inflammatory disease to help in the identification of MOGAD in clinical practice.  
3 **Figure 3** shows representative MRIs of MOGAD patients with different clinical and MRI  
4 characteristics.

## 6 **Discussion**

7 In this large, multicenter study, we identified MRI and clinical features to differentiate non-acute  
8 MOGAD from RRMS and AQP4-NMOSD and proposed a workflow that may serve as a guide  
9 towards a better discrimination of MOGAD.

10  
11 Results of the study showed that brain lesion number and morphology are important to  
12 distinguish patients with non-acute MOGAD from those with RRMS, while clinical features and  
13 cervical cord involvement can differentiate the two antibody-mediated diseases. Absence of  
14 Dawson's fingers and temporal lobe lesions might lead to question the diagnosis of RRMS,  
15 especially in patients with low disability outside an acute event. Previous studies showed that in  
16 MOGAD lesions may disappear after the acute phase and often resolve completely over 6-  
17 months potentially reflecting a greater propensity for remyelination.<sup>16,27</sup> Therefore, it is not  
18 surprising that in our cohort, lesion characteristics which were considered to be specific for acute  
19 MOGAD (i.e. FIT lesions),<sup>28</sup> were found only in a minority of patients and they did not  
20 contribute to the discriminant analysis. This is also in agreement with the previous report of a  
21 reduced visibility of infratentorial lesions in MOGAD patients, when evaluated in the remission  
22 phase.<sup>19</sup> We found white matter lesions in 68% MOGAD, which is higher than expected as

1 disease phenotypes at onset were optic neuritis and/or transverse myelitis for the majority of  
2 patients.<sup>20</sup> Imaging characteristics are age-dependent in MOGAD, with the highest frequency of  
3 brain involvement in children, ranging from poorly demarcated and widespread lesions in the  
4 childhood to small nonspecific cerebral lesions in older children and adults.<sup>29</sup> This discordance  
5 may be due to the inclusion of only adult patients in our study with potential incidental white  
6 matter hyperintensities. In support of this, white matter lesions were found in 23% of healthy  
7 controls, suggesting that discriminating demyelinating white matter lesions from those of  
8 presumably vascular origin, may be challenging in adults in the non-acute phase. Indeed, future  
9 plans are to expand our cohorts with a paediatric subgroup with the same demyelinating  
10 conditions to assess the effect of age.

11  
12 Data presented here showed that the differentiation between non-attack MOGAD and AQP4-  
13 NMOSD scans might be more challenging but can be achieved when clinical information is  
14 available. In patients with low disability levels, the absence of a cervical longitudinally extensive  
15 cord lesions on a spinal cord MRI supports the diagnosis of MOGAD. By contrast, in our cohort  
16 the presence of longitudinally extensive lesions in the cord did not favour MOGAD over MS  
17 patients. This can be explained by two main reasons: i) longitudinally extensive lesions occurs in  
18 MOGAD more often in the caudal spinal cord than in in the cervical cord, which was the  
19 segment evaluated in this study; ii) cord lesions tend to disappear and a complete resolution of  
20 these lesions on conventional MRI in the non-acute phase has been reported.<sup>16</sup>

21 Our data emphasises the importance of cord lesions length in differentiating the three diseases,  
22 which may be even higher when considering patients in the acute phases, as about 85% of  
23 cervical acute lesions span more than 3 vertebral segments in AQP4-NMOSD, while they are

1 typically rare in MOGAD and MS.<sup>15</sup> While longitudinally extensive hazy T2 hyperintensities  
2 may be detected outside attacks in chronic MS, chronic lesions can be short in AQP4-NMOSD  
3 and MOGAD, therefore making the differentiation between the three diseases more  
4 challenging.<sup>15,30</sup> Further studies looking at different cord segments, including  
5 thoracolumbar/conus regions that are preferentially involved in MOGAD, and different disease  
6 phases are needed to accurately quantify the overall extent of cord damage in the three diseases.  
7 Nonetheless, our results suggest that cord MRI findings have significant value in differentiating  
8 patients with CNS demyelinating diseases from controls and may be useful in identifying those  
9 with non-specific brain white matter lesions. This is supported by the absence of cord lesions in  
10 healthy controls versus the disease groups when compared to the frequency of brain lesions in  
11 healthy subjects.

12  
13 By contrast, in patients with high disability levels, the MOG-Ab testing should be limited to  
14 patients who are young at the time of MRI. Previous studies have reported that compared to  
15 NMOSD, accumulated disability in MOGAD as calculated on the EDSS over time is less severe,  
16 but in the majority of these studies, AQP4-NMOSD patients were older at the time of the  
17 observation.<sup>17</sup> In cases of patients with CNS inflammation negative to both Ab and with no  
18 features typical of MS, it is important to consider mimics of CNS demyelination and monitor the  
19 patient over time.

20  
21 A recent study showed that serial MRIs have limited utility in MOGAD, as silent new lesions are  
22 rare outside a clinical attack, in contrast to MS, where new brain lesions can be found  
23 independently of relapses.<sup>31</sup> Importantly, our findings may help to select those patients in whom

1 a surveillance MRI is necessary. In MOGAD, where lesions often resolve over time rather than  
2 enlarge, and new lesions rarely develop, a single follow-up remission brain and cervical cord  
3 MRI may have added value in establishing the diagnosis and provide valuable information to  
4 overcome false positive results or delayed MOG-Ab testing.

5  
6 As we used brain and cord images acquired with different MRI protocols from different centres,  
7 we performed an internal cross-validation using LOOCV, which improves the generalizability of  
8 the predictions. We found a high concordance between centres in the selection of best  
9 discriminators between diseases, suggesting that one can reliably use brain and cervical cord  
10 MRI along with clinical information to separate the three diseases, independently of scanner  
11 characteristics, and results could be generalized to other centres. Cross-validation methods are  
12 useful when the dataset is not very large: an advantage of using cross-validation is that there is  
13 no waste of data. When we have an external validation set, the data that is being used for  
14 validation is being wasted and never used for training, but in cross-validation we use the  
15 validation set also for the training due to the resampling approach. However, limitations of  
16 LOOCV include that the validation error for a given model is highly variable and that this is a  
17 computationally intensive method. A further, external validation would be warranted to  
18 consolidate our results. However, to account for the possible confounding by the imputation of  
19 missing values, we also repeated the analysis on a subset of subjects with complete, non-imputed  
20 data, and confirmed the predictors of diseases, suggesting the robustness of our results.

21

22 In addition to the limitations related to validation, there are limitations related to the dataset and  
23 the study design. First, although this is to our knowledge the largest study combining MRI and

1 clinical features to discriminate MOGAD from AQP4-NMOSD and RRMS, only patients with a  
2 confirmed diagnosis were included in the study. Therefore, the results are not easily  
3 generalizable to patients at the time of the first presentation of the disease and to patients with  
4 seronegative NMOSD. Secondly, the time interval between MRI and the previous relapse and  
5 the scan frequency differed between patient groups, with the potential bias of having more scans  
6 in patients with more severe or atypical disease. Third, the retrospective design did not allow to  
7 assess the role of cerebrospinal fluid findings (i.e., presence/absence of oligoclonal bands), as  
8 this information was only available for a subgroup of patients, and optic nerve lesions, which are  
9 common in MOGAD, in discriminating the diseases, as dedicated sequences were not acquired  
10 by the majority of centres. Finally, we could not consider lesions disappearing over time which  
11 might occur in MOGAD, due to the cross-sectional design of this study. Future prospective,  
12 longitudinal study will test whether the absence of oligoclonal bands (or if present at all, their  
13 persistence after the non-acute phase), the involvement of the optic nerve and lesions evolution  
14 over time can increase the accuracy of our approach to identify MOGAD.

15  
16 In line with previous studies, cortical lesions were seen in a minority of patients with MOGAD  
17 and AQP4-NMOSD.<sup>19,20</sup> Reversible cortical involvement in MOGAD has been described in  
18 patients presenting with encephalopathy and/or seizures, while cortex is typically spared in  
19 NMOSD.<sup>32,33</sup> When detected, cortical lesions in AQP4-NMOSD may have vascular rather than  
20 demyelinating origin, as patients may be more hypercoagulable (e.g. antiphospholipid antibodies  
21 commonly coexist in AQP4-Ab positive patients) and they are typically older, thus small  
22 asymptomatic cortical infarcts may occur.<sup>34</sup> Similarly, the number of T1 hypointense lesions in  
23 the two Ab-mediated diseases was lower than in RRMS, as expected due to the different brain

1 involvement in the three disorders. Surprisingly, both measures were not included as best  
2 discriminating measures by the model. This is in contrast with recent findings suggesting a role  
3 of cortical lesions in differentiating between NMOSD and RRMS.<sup>35</sup> A possible explanation for  
4 this may be the lower number of patients as well as the reduced availability of sequences to  
5 perform the cortical lesions analysis when compared to T2 lesions assessment. Similarly, as T2  
6 and T1 lesions are correlated, only T2 lesions were selected by the statistical model, which was  
7 built to detect only the best set of variables for prediction using stringent criteria.

8  
9 Currently, there are no evidence-based guidelines for the non-acute treatment and management  
10 of MOGAD patients.<sup>1</sup> From a clinical perspective, we hypothesize that our guide will allow  
11 targeted investigation and timely change of treatment strategies, as the decision to initiate  
12 chronic immunosuppression in MOGAD is more controversial than in AQP4-NMOSD and MS  
13 treatments were shown to be ineffective in the two Ab-mediated diseases.<sup>36,37</sup>

14 Future studies are needed to confirm whether our suggested approach can be used to differentiate  
15 the three diseases at an early stage (i.e., after the first attack), or in other challenging clinical  
16 scenarios (i.e., including seronegative NMOSD and controls with focal white matter lesions  
17 presumably of vascular origin).

18  
19 In conclusion, in this large and multicentre study, we found that brain and cord lesion  
20 characteristics as detected by conventional MRI, together with routine demographic and clinical  
21 information, may facilitate an accurate differentiation between MOGAD, AQP4-NMOSD and  
22 RRMS in the non-acute phases. On this basis, we provided here a guide for clinicians that could

1 complement Ab-testing when results are controversial or when CBA testing is not readily  
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3

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9

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3 F. Paul serves on scientific advisory boards for Novartis, Viela Bio, Alexion and has received  
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## 8 9 **Supplementary material**

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## 11 12 **Appendix 1**

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20

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ACCEPTED MANUSCRIPT

## 1 **Figure legends**

2 **Figure 1 Visual representation of the best set of discriminators between myelin**  
3 **oligodendrocyte glycoprotein antibody associated disease (MOGAD), aquaporin-4-**  
4 **antibody-positive neuromyelitis optica spectrum disorder (AQP4-NMOSD) and relapsing-**  
5 **remitting MS (RRMS).** Example of a random tree from a leave one out internal-validation  
6 procedure of Random Forest model, showing the MRI and clinical measures that predicted  
7 MOGAD instead of AQP4-NMOSD and RRMS. The order of measures in the tree represents the  
8 most (Dawson's fingers) to the less (longitudinally extensive lesions in the cervical cord)  
9 accurate discriminator. EDSS=Expanded Disability Status Scale.

10  
11 **Figure 2 Workflow that can be applied to non-acute adult patients with suspected central**  
12 **nervous system inflammatory disease to help in the identification of MOGAD.** The first  
13 recommended approach is to assess disease history and MRI findings. If MRI features resemble  
14 MS (i.e. high number of white matter lesions [ $>6$ ], presence of Dawson's fingers and temporal  
15 lesions), the McDonald criteria should be applied<sup>18</sup>, which may allow a diagnosis of MS.  
16 Alternatively, in patients who have clinical and MRI characteristics suggestive of NMOSD,  
17 AQP4-Ab testing may permit a diagnosis of AQP4-NMOSD if Wingerchuk criteria are met<sup>17</sup>,  
18 particularly in patients having a cervical longitudinally extensive cord lesion, high disability  
19 (EDSS $>3$ ) at the time of MRI, and older than 34 years. In AQP4-Ab negative patients, if disease  
20 presentation is considered to be typical or suggestive of MOGAD (i.e. ADEM, bilateral optic  
21 neuritis, concomitant optic neuritis and transverse myelitis), then MOG-Ab should be checked.  
22 In MOG-Ab positive cases, this helps to reach the diagnosis of MOGAD. In patients with

1 ADEM, bilateral optic neuritis, concomitant optic neuritis and transverse myelitis, concurrently  
2 without longitudinally extensive lesions in the cervical cord or high disability who resulted  
3 MOG-Ab negative, AQP4-Ab should be checked. Consideration of alternative diagnoses, and  
4 then monitoring are recommended in the remaining Ab-negative patients. Ab=antibody;  
5 ADEM=acute disseminated encephalomyelitis; AQP4=aquaporin-4; MS=multiple sclerosis;  
6 NMOSD=neuromyelitis optica spectrum disorder, MOG=myelin oligodendrocyte glycoprotein;  
7 MOGAD=myelin oligodendrocyte glycoprotein associated disease; ON=optic neuritis,  
8 TM=transverse myelitis, WML=white matter lesion; +ve=positive; -ve=negative.

9  
10 **Figure 3 Representative examples of magnetic resonance imaging (MRI) findings in non-**  
11 **acute myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) patients**  
12 **and different clinical and MRI characteristics.** Patients with disease presentation typical of  
13 MOGAD: (A) patient 1 showing poorly marginated brain lesions; (B-C) patient 2 with more than  
14 6 brain white matter lesions and one short cervical cord lesion. Patients with isolated unilateral  
15 optic neuritis at onset: (D-F) patient 3 showing less than six brain white matter lesions, with no  
16 involvement of temporal lobes and no Dawson's fingers; (G-I) patient 4: one periventricular  
17 lesion, brainstem involvement and two short cord lesions.

18

1 **Table 1 Clinical features of MOGAD, AQP4-NMOSD, RRMS and healthy controls**

Features	MOGAD	AQP4-NMOSD	RRMS	Healthy controls	p-value*
Number	162	162	189	152	
Sex (M/F) <sup>a</sup>	63/99	30/132	57/132	61/91	0.004
Age at MRI, years, mean (SD)	40.59 (14.09)	50.65 (14.14)	39.66 (10.44)	37.38 (11.43)	<0.001
Age at onset, years, mean (SD)	34.43 (14.33)	42.87 (15.69)	32.27 (8.57)	NA	0.005
Disease duration, years, mean (SD)	5.8 (7.5)	8.5 (8.2)	7.8 (6.8)	NA	<0.001
Time from last attack to MRI, months <sup>b</sup> median (range)	14 (3–404)	24 (3–263)	17 (3–225)	NA	0.01
EDSS at MRI, median (range)	2 (0–7.5)	3.5 (0–8)	2 (0–8)	NA	<0.001
Race/Ethnicity, n (%) patients					<0.001
Caucasian	116 (72)	108 (67)	144 (76)	93 (61)	
Asian	9 (6)	11 (7)	7 (4)	10 (7)	
Afro-Caribbean	19 (12)	28 (17)	11 (6)	5 (3)	
Mixed	3 (2)	9 (6)	6 (3)	3 (2)	
Unknown	15 (8)	6 (3)	21 (11)	41 (27)	
Patients on treatment, n (%)	78 (48)	144 (88)	189 (100)	NA	<0.001
Type of treatment <sup>c</sup> , n (%) patients					<0.001
MS disease modifying agents	2 (2)	0	181 (96)	NA	
Classical immunosuppressants	73 (94)	134 (93)	7 (3)	NA	
Other immunosuppressants	3 (4)	10 (7)	1 (1)	NA	
Phenotype at onset, n (%) patients					<0.001
Unilateral ON	44 (27)	44 (27)	38 (20)	NA	
Bilateral ON	36 (22)	11 (7)	3 (2)	NA	
TM	38 (24)	55 (34)	38 (20)	NA	
ON+TM	17 (11)	16 (10)	1 (1)	NA	
ADEM	9 (6)	0	1 (1)	NA	
Others	8 (5) <sup>d</sup>	16 (10)	77 (41)	NA	
Disease course, n (%) patients					<0.001
Monophasic	48 (32)	23 (16)	0	NA	
Relapsing	100 (68)	118 (84)	189 (100)	NA	
Number of patients (%) with CSF oligoclonal bands					<0.001
Absence	102 (84%)	86 (75%)	10 (10%)	NA	
Presence	19 (16%)	22 (25%)	93 (90%)	NA	

2 ADEM = acute disseminated encephalomyelitis; EDSS = Expanded Disability Status Scale; ON = optic neuritis TM = transverse myelitis.

3 \*Using Kruskal-Wallis, ANOVA or  $\chi^2$ , as appropriate, depending on the nature of the variable.

4 <sup>a</sup>Refers to biological factors. This information was self-reported by participants

5 <sup>b</sup>A minority of patients presented with a relapse within 3 and 6 months prior to study entry, respectively 40/162 (25%) of MOGAD, 27/162 (17%) of AQP4-NMOSD and 50/189 (26%) of RRMS.

6 <sup>c</sup>MS disease modifying agents included medications approved for MS: interferon, glatiramer acetate, teriflunomide, dimethylfumarate, cladribine, fingolimod, natalizumab, alemtuzumab, ocrelizumab; classical immunosuppressants included: azathioprine, mycophenolate mofetil, rituximab; other immunosuppressants included: cyclophosphamide, methotrexate, mitoxantrone.

7 <sup>d</sup>Seven patients with brainstem involvement, one patient with unilateral tumefactive hemispheric lesion.

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2**Table 2 MRI features of MOGAD, AQP4-NMOSD, RRMS and healthy controls**

Features	MOGAD	AQP4-NMOSD	RRMS	Healthy controls	p-value*
Brain lesion volume, mm <sup>3</sup> Median (range)	82.60 [0.00–851.25]	416.76 [0.00–2739.75]	4231.10 [1392.08–11736.75]	0.002 (0.00–1.80)	<0.001
Total number of brain WML; mean (SD)	1047; 6.80 (12.11)	1604; 10.69 (14.13)	4925; 26.62 (21.16)	144; 2.21 (5.27)	<0.001
Total Number of T <sub>1</sub> hypointense lesions; mean (SD)	647; 7.7 (9.7)	976; 8.4 (10.6)	3749; 13.8 (16.4)	92; 1.4 (4.7)	<0.001
Presence of temporal lobe lesion, number of patients (%) <sup>a</sup>					<0.001
Absence	138 (85)	143 (88.3)	74 (39.2)	152 (100)	
Presence	14 (8.6)	9 (5.6)	111 (58.7)	0	
Presence of U-fibre lesion, number of patients (%) <sup>a</sup>					<0.001
Absence	147 (90.7)	148 (91.4)	161 (85.2)	152 (100)	
Presence	5 (3.1)	4 (2.5)	24 (12.7)	0	
Presence of Dawson's finger lesion, number of patients (%) <sup>a</sup>					<0.001
Absence	135 (83.3)	145 (89.5)	50 (26.5)	152 (100)	
Presence	17 (10.5)	7 (4.3)	135 (71.4)	0	
Presence of FIT lesion, number of patients (%) <sup>a</sup>					<0.001
Absence	149 (92.0)	151 (93.2)	183 (96.8)	152 (100)	
Presence	3 (1.9)	1 (0.6)	2 (1.1)	0	
Presence of cortical lesions, number of patients (%) <sup>a</sup>					<0.001
Absence	88 (91)	87 (92)	40 (36)	152 (100)	
Presence	9 (9)	8 (8)	70 (64)	0	
Total number of cortical lesions	19 6 intracortical 13 leukocortical	8 0 intracortical 8 leukocortical	172 51 intracortical 121 leukocortical	0	<0.001
Median (range) <sup>a</sup>	1 (1–9)	1 (1–1)	2 (1–14)		
Presence of short cord lesion, number of patients (%) <sup>a</sup>					<0.001
Absence	93 (57.4)	77 (47.5)	51 (27.0)	152 (100)	
Presence	14 (8.6)	23 (14.2)	64 (33.9)	0	
Presence of longitudinally extensive cord lesion, number of patients (%) <sup>a</sup>					<0.001
Absence	105 (64.8)	62 (38.3)	113 (59.8)	152 (100)	
Presence	2 (1.2)	38 (23.5)	2 (1.1)	0	

FIT= fluffy infratentorial lesions; MRI=magnetic resonance imaging; WML= white matter lesions.

\*Using Kruskal-Wallis, ANOVA or  $\chi^2$ , as appropriate, depending on the nature of the variable.<sup>a</sup>Assessed on available sequences.3  
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1 **Table 3 Results from the leave one out internal-validation procedure (LOOCV) of Random Forest model using the best sets**  
 2 **of discriminators and the imputed set of data**  
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	Variable importance <sup>a</sup>			Mean decrease in impurity <sup>b</sup>	Mean decrease in accuracy <sup>c</sup>	Accuracy (LOOCV) <sup>d</sup>	Kappa (LOOCV) <sup>d</sup>	AUC (95%CI) <sup>e</sup>
	MOGAD	AQP4-NMOSD	RRMS					
<b>MRI</b>								
Dawson's fingers lesion	77.4	5.3	58.6	72.9	88.4	0.68	0.52	0.75 (0.72–0.78)
Temporal lobe lesion	71.7	12.4	31	16.3	72			
Longitudinally extensive cord lesion	42.6	76.1	26	23.4	73			
<b>Clinical and MRI</b>								
Dawson's fingers lesion	48.1	34.9	38.5	55.6	65.2	0.76	0.64	0.85 (0.82–0.88)
Temporal lobe lesion	39.9	20.2	15.3	30.9	42.7			
Longitudinally extensive cord lesion	36.4	30.0	12.9	19.5	41.4			
Age at MRI	-0.4	15.2	10.9	43.0	14.8			
EDSS	23.1	33.8	9.4	40.4	36.8			

4 EDSS=Expanded Disability Status Scale, MRI=magnetic resonance imaging.

5 <sup>a</sup>Variable importance represents the difference between the prediction errors (on the out-of-bag portion of the data) and the prediction error  
 6 after performing random predictor permutations. Showing the class-specific (MOGAD, AQP4-NMOSD, RRMS) error we attempt to give extra  
 7 information about which predictors are important for which class.

8 <sup>b</sup>Mean decrease in impurity uses the Gini index, which is a measure of impure classification ranging from 0 (totally clear) to 1 (totally random).  
 9 When removing a variable from a model (such as in random variable permutation procedures) the corresponding Gini drop of a variable is a  
 10 measure of the usefulness of such variable to improve the classification performance (the higher the better).

11 <sup>c</sup>Mean decrease in accuracy: also known as permutation importance, is a measure of the usefulness of a variable within a random permutation  
 12 procedure using the proportion of correctly classified cases (i.e., accuracy) as internal metrics instead of impurity. It is more computationally  
 13 expensive than mean decrease in impurity but may offer more reliable estimates when predictors are of mixed data type (categorical and  
 14 continuous).

15 <sup>d</sup>Leave one out validation accuracy and Kappa represent the internal model stability and gives us insight on the generalizability of our  
 16 conclusions in the attempt to mitigate the natural overfit tendency of our model-based predictions. Accuracy is the proportion of correctly  
 17 classified subjects among all the cross-validation cycle. For example, an accuracy of 0.7 means that 7 times out of 10 the model should correctly  
 18 classify a subject not previously seen during model training. This can overestimate performances if once class is overrepresented. Kappa is a  
 19 similar metric but account for the marginal probabilities of the classes and therefore adjust the accuracy for the simplicity of correctly classify  
 20 the most prevalent class only by chance.

21 <sup>e</sup>AUC represents the area under the receiver operating characteristic curve. It is used here as a simple metric for summarizing the performance  
 22 of different classification models (based on a different set of predictors i.e., MRI only or MRI and clinic variables).  
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Sensitivity: 81%  
Specificity: 84%  
Accuracy: 76%  
P < 0.001

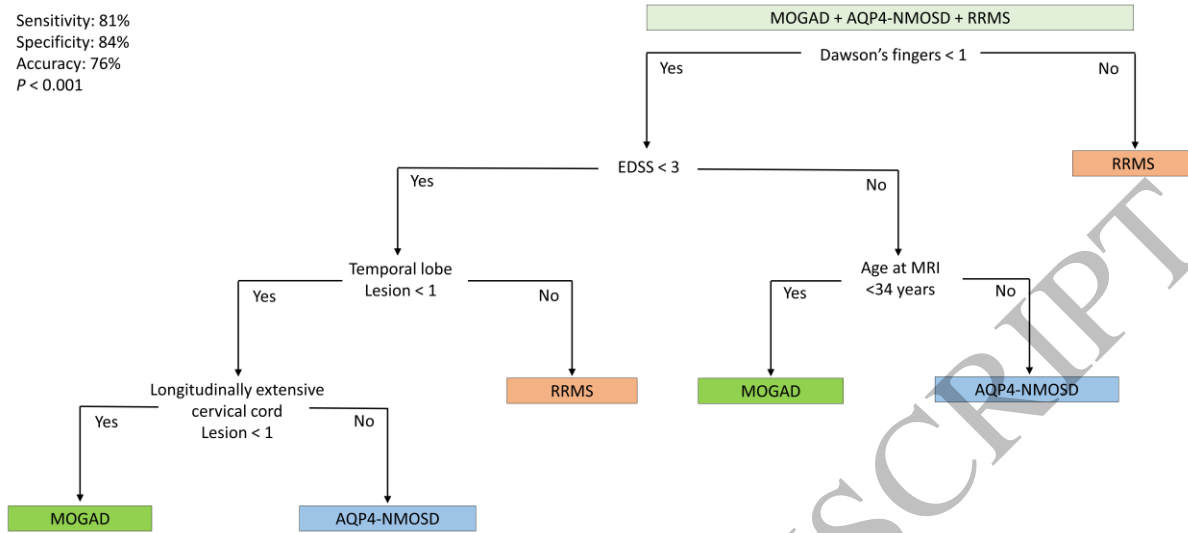


Figure 1  
159x73 mm (5.8 x DPI)

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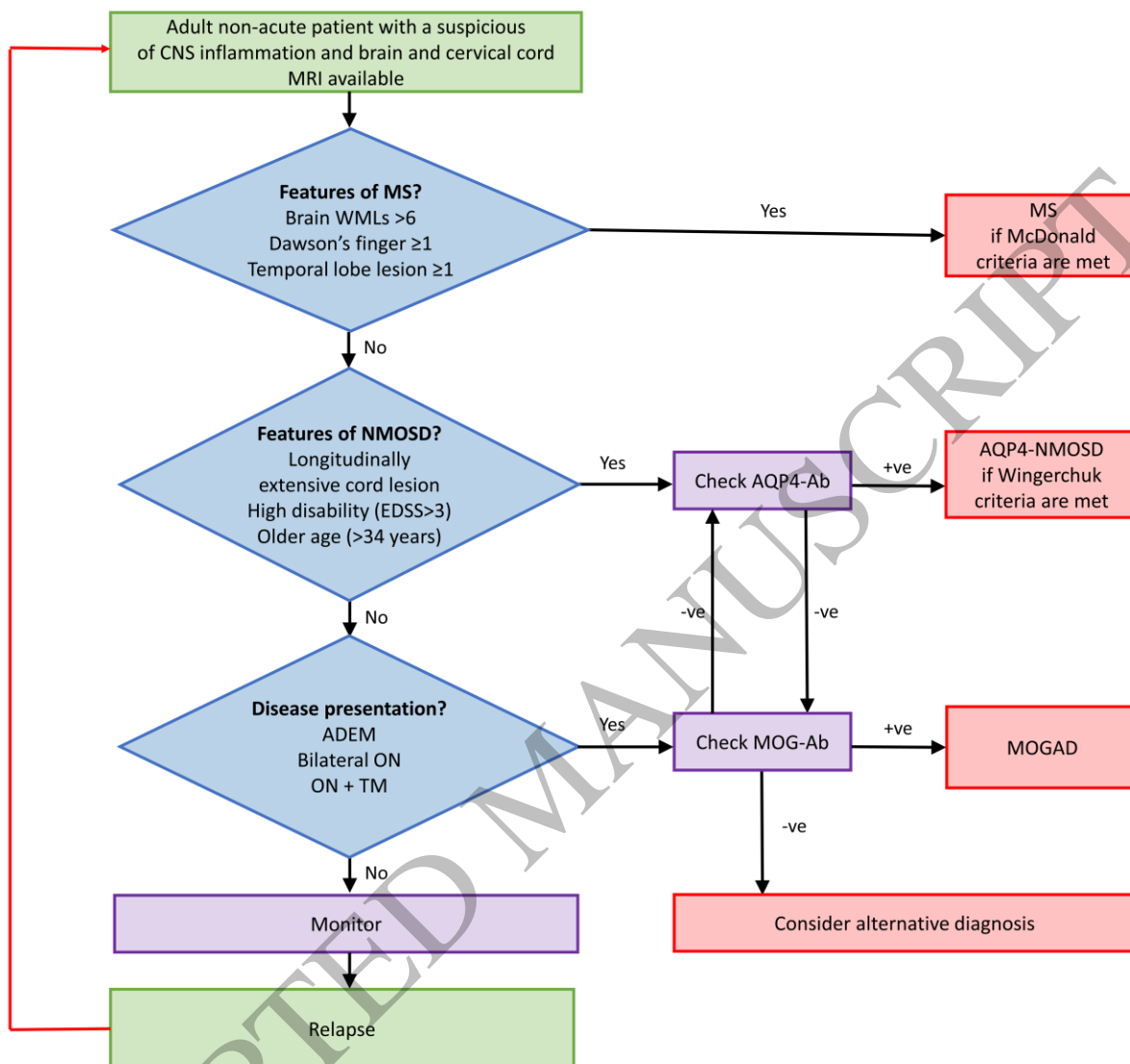
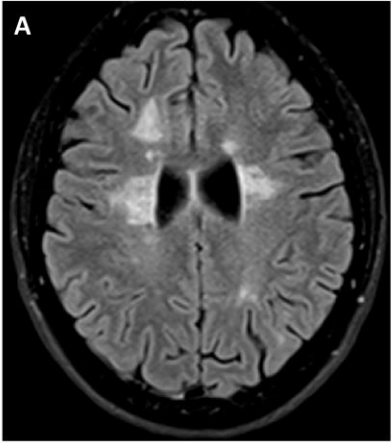


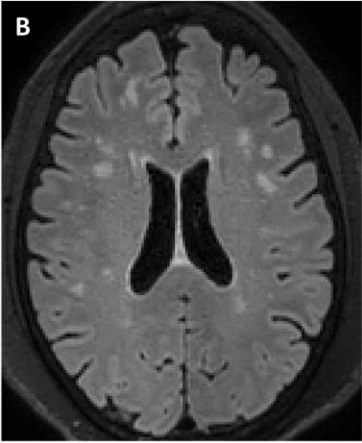
Figure 2  
159x150 mm (5.8 x DPI)

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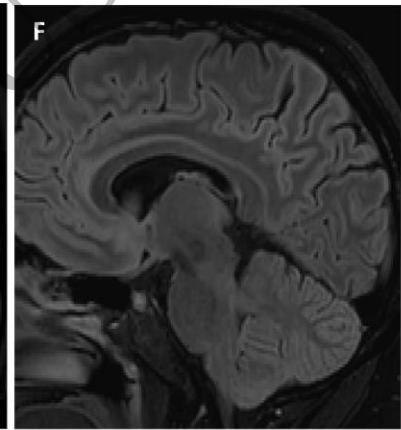
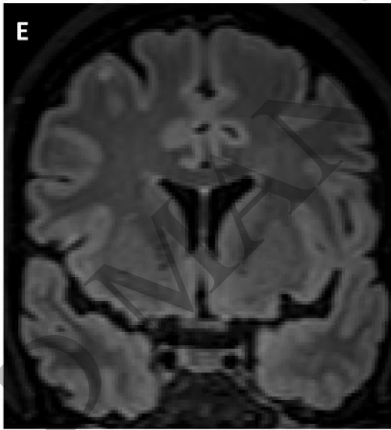
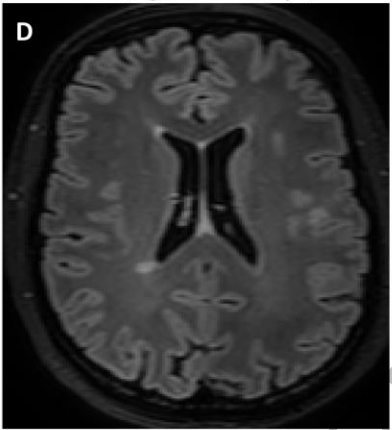
**Patient 1:** F, age at MRI: 33 yo, EDSS at MRI: 1.0, onset: ADEM



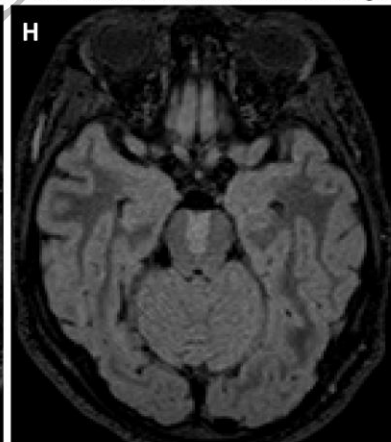
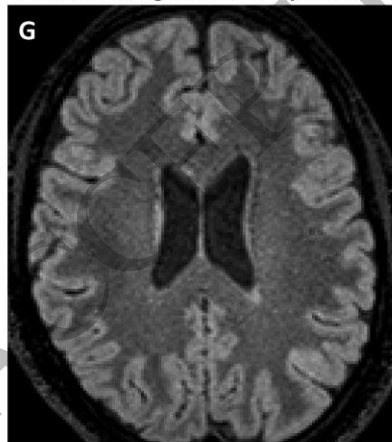
**Patient 2:** M, age at MRI: 59 yo, EDSS at MRI: 5.0, onset: concomitant optic neuritis and transverse myelitis



**Patient 3:** F, age at MRI: 32 yo, EDSS at MRI: 1.5, onset: isolated unilateral optic neuritis



**Patient 4:** F, age at MRI: 28 yo, EDSS at MRI: 2.5, onset: isolated unilateral optic neuritis



**Figure 3**  
159x199 mm (5.8 x DPI)

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