Title: Brain structural and functional alterations in MOG antibody disease

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Abstract

Background

The impact of myelin oligodendrocyte glycoprotein antibody disease (MOGAD) on brain structure and function are unknown.

Objectives

To study multimodal brain MRI alterations in MOGAD and investigate their clinical significance.

Methods

Seventeen MOGAD, 20 aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders (AQP4+ NMOSD) and 28 healthy controls (HC) were prospectively recruited. Voxel-wise gray matter (GM) volume, fractional anisotropy (FA), mean diffusivity (MD) and degree centrality (DC) were compared between groups. Clinical associations and differential diagnosis were determined using partial correlation and stepwise logistic regression.

Results

In comparison to HC, MOGAD had GM atrophy in frontal and temporal lobe, insula, thalamus, and hippocampus, and WM fiber disruption in optic radiation and anterior/posterior corona radiata; DC decreased in cerebellum and increased in temporal lobe. Compared to AQP4+ NMOSD, MOGAD presented lower GM volume in postcentral gyrus and decreased DC in cerebellum. Hippocampus/parahippocampus atrophy associated with Expanded Disability Status Scale (R=-0.55, p=0.04) and California Verbal Learning Test (R=0.62, p=0.031). The differentiation of MOGAD from AQP4+ NMOSD achieved an accuracy of 95% using FA in splenium of corpus callosum and DC in occipital gyrus.

Conclusion

Distinct structural and functional alterations were identified in MOGAD. Hippocampus/parahippocampus atrophy associated with clinical disability and cognitive impairment.

Introduction

Myelin oligodendrocyte glycoprotein (MOG) antibody is a pathogenic autoantibody which can result in autoimmune demyelination in the central nervous system.[1, 2] The immune attack in MOG antibody disease (MOGAD) are associated with myelin and oligodendrocytes damage,[3, 4] leading to heterogeneous clinical manifestations including optic neuritis, myelitis, brainstem syndromes, encephalomyelitis, acute disseminated encephalomyelitis, encephalitis and seizures.[5, 6] The limited evidence so far suggests that clinical presentation in MOGAD differs from multiple sclerosis but overlaps with aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders (AQP4+ NMOSD).[7] Given the different clinical outcome and treatment strategy compared to AQP4+ NMOSD, accurate diagnosis and evaluation of brain alterations in MOGAD would facilitate optimal treatment decisions and prognosis prediction.[5]

MRI studies have mostly focused on focal lesion distribution to characterize MOGAD.[8, 9] MOGAD tends to present with cortical and subcortical deep gray matter (GM), white mater (WM), brain stem, cerebellum and spinal cord lesions,[4, 8] similar to AQP4+ NMOSD, but rarely area postrema lesions.[8, 10, 11] However, lesion distribution fails to accurately discriminate MOGAD from AQP4+ NMOSD, and only weakly to moderately contributes to the clinical outcome.[1, 12] Additionally, about half of the MOGAD patients showed no obvious brain lesions on clinical routine MRI.[8, 9, 13] The structural and functional characteristics in addition to lesions could contribute to a better understanding of MOGAD especially for those cases without brain lesions and provide new imaging markers for prognosis and disease monitoring.

In this work, we aimed to (1) characterize the structural (gray matter [GM] volume and white matter [WM] fiber integrity) and functional (connectivity strength) alterations in MOGAD using multimodal MRI and (2) investigate their clinical significance for disability assessment and their specificity by comparison with AQP4+ NMOSD.

Materials and Methods

Subjects

This study was approved by the institutional review board of the Beijing Tiantan Hospital, Capital Medical University, Beijing, China and all subjects provided written informed consent.

Seventeen MOGAD patients were recruited from Beijing Tiantan Hospital, Capital Medical University. The inclusion and exclusion criteria were provided in **Supplemental Material**. For comparison, 30 healthy controls (HC) without visible brain lesion on conventional MRI and no history of neurological or neuropsychological diseases and 21 AQP4+ NMOSD patients tested seropositive by cell-based assay and diagnosed based on the 2015 International Panel on NMOSD Diagnosis[14] were recruited, matched for gender and age.

Clinical variables included gender, age, education level, disease duration, disease course, Expanded Disability Status Scale (EDSS), cognitive tests (including Montreal Cognitive Assessment [MoCA], Symbol Digit Modalities Test [SDMT] and California Verbal Learning Test [CVLT]), Hamilton depression and anxiety test, and treatment information.

MRI acquisition

MRI scans were performed on a 3.0T MR scanner (Philips CX, Best, The Netherlands) including fluid-attenuated inversion recovery imaging (FLAIR), 3D T1, diffusion tensor imaging (DTI) and resting-state functional MRI (rs-fMRI) (details see **Supplemental Material**).

Image processing

WM lesions were reported and outlined on FLAIR images by an experienced neuroradiologist (Y.D. with 12 years' experience).[9] Then, 3DT1 images were lesion-filled and segmented for gray matter. Tract-Based Spatial Statistics (TBSS) were conducted on fractional anisotropy (FA) and mean diffusivity (MD) using DTI images. Degree centrality (DC) was calculated using rs-fMRI images (details see **Supplemental Material**).

Statistical analyses

Statistical analyses were performed by SPSS software (Version 22; SPSS, Chicago, Ill), Matlab Statistics Toolbox (Matlab 2019a) and Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/) software. Categorical data were presented as percentage and analyzed by chi-square test. Continuous and ranked data was presented as median and interquartile range (IQR) and analyzed by one-way ANOVA or Kruskal-Wallis H tests followed by post-hoc multi-comparison with Bonferroni correction or Mann-Whitney U tests with statistical significance of $p<0.05$ (two-sided).

Voxel-wise analyses were performed by general linear model in SPM12 with gender, age and total intracranial volume (TIV, only for GM volume) as covariates. In order to explore the potential underlying alterations in MOGAD, statistical significance was considered with an uncorrected $p\leq0.005$ at voxel-level. A cluster restriction of ≥675 mm^3 for GM volume and DC, and ≥100 mm^3 for FA and MD was adopted.[15, 16] Gaussian random filed (GRF) correction with $p\leq0.005$ at both voxel- and cluster-level and false discovery rate (FDR) correction with $p\leq0.05$

at voxel-level were also performed as sensitivity analyses.[17]

Before correlation analyses, log-transformation was carried out for clinical and MRI measures due to their non-normality. Then, partial correlation analyses were used to investigate their associations with adjustment for gender and age. Additionally, disease duration and education were considered as covariates for validation. A p-value <0.05 (two-sided) was deemed statistically significant.

Univariate and multivariate stepwise logistic regression was conducted to separate MOGAD from AQP4+ NMOSD using MRI and clinical measurements. The classification accuracy, sensitivity, specificity, area under the curve (AUC) and Youden index were calculated. A p-value <0.05 (two-sided) was deemed statistically significant.

Results

Demographics and clinical characteristics

One AQP4+ NMOSD patient was excluded due to a history of another neurological disease. Two HC were excluded due to poor image quality. The final sample therefore consisted of 17 MOGAD (13 female [76%]; median [IQR] age, 37 [29-49] years), 20 AQP4+ NMOSD (15 female [75%]; 39 [32-50] years) and 28 HC (19 female [68%]; 36 [27-53] years) with similar gender/age across groups (**Table 1**). The majority of MOGAD patients (15/17, 88%) presented optic neuritis, similar to AQP4+ NMOSD (16/20, 80%; p=0.50). Only a minority of MOGAD patients (6/17, 35%) presented with myelitis, while this was a predominant finding in AQP4+ NMOSD (17/20, 85%; p=0.002). Both MOGAD and AQP4+ NMOSD had lower cognitive scores (including MoCA, SDMT and CVLT) than HC. No significant differences were identified for other variables between MOGAD and AQP4+ NMOSD (Table 1).

Brain lesions

Eight (47%) MOGAD and 11 (55%) AQP4+ NMOSD presented with brain lesions (**Table 1**). In MOGAD with lesions (**Figure 1**), the most frequent locations were deep (75%) and periventricular WM (63%) and brain stem (63%), similar to those in AQP4+ NMOSD (64%, 73% and 55% respectively). Other brain lesions in MOGAD involved juxtacortical WM (50%), basal ganglia (25%) and corpus callosum (25%). No difference on brain lesion volume (2.8 [0.7-6.4] vs. 1.4 [0.5-1.8) ml; p=0.32) between MOGAD and AQP4+ NMOSD were identified (**Table 1**).

Gray matter volume measures

As shown in **Figure 2A**, both MOGAD and AQP4+ NMOSD showed decreased GM volumes in frontal (e.g., orbito-frontal cortex and rectal gyrus) (p≤0.005 GRF-corrected) and temporal lobes (e.g., middle/inferior temporal gyrus) (p≤0.005 uncorrected), insula (p≤0.005 GRF-corrected) and thalamus (p≤0.005 GRF-corrected) compared to HC. Additionally, MOGAD showed GM volume loss in bilateral hippocampus (p≤0.005 GRF-corrected), while in contrast, we found normal volumes in AQP4+ NMOSD. Compared to AQP4+ NMOSD, MOGAD showed milder GM atrophy in right cerebellum (anterior/posterior lobe) (p≤0.005 GRF-corrected) and right lingual gyrus (p≤0.005 uncorrected), but lower GM volume in left postcentral gyrus (p≤0.005 uncorrected).

White matter integrity measures

For diffusion measures (**Figure 2A**), both MOGAD and AQP4+ NMOSD showed lower FA in the optic radiation (p≤0.005 uncorrected for MOGAD; p≤0.005 GRF-corrected for AQP4+ NMOSD) and higher MD in anterior (p≤0.005 uncorrected for both diseases) and posterior corona radiata (p≤0.005 GRF-corrected for both diseases) than HC. Compared to AQP4+ NMOSD, patients with MOGAD had higher FA values in right middle cerebellar peduncle (0.52 [0.50-0.55] vs. 0.49 [0.47-0.51]; p≤0.005 uncorrected), right optic radiation (0.55 [0.54, 58] vs. 0.49 [0.47-0.54]; p≤0.005 uncorrected) and bilateral splenium of corpus callosum (bilateral averaged, 0.61 [0.60-0.63] vs. 0.56 [0.54-0.59]; p≤0.005 uncorrected) and lower MD in left optic radiation (0.79 [0.75-0.80] vs. 0.81 [0.79-0.84] $10^{-3}mm^2/s$; p≤0.005 GRF-corrected) and bilateral splenium of corpus callosum (bilateral averaged, 0.77 [0.75-0.79] vs. 0.80 [0.78-0.85] $10^{-3}mm^2/s$; p≤0.005 GRF-corrected).

Functional MRI measures

Compared to HC, MOGAD showed lower DC in right cerebellum posterior lobe (p≤0.005 uncorrected), but presented with higher DC in right superior temporal gyrus (p≤0.005 uncorrected) (**Figure 2A**). AQP4+ NMOSD showed lower DC in bilateral occipital gyrus (p≤0.005 GRF-corrected) while presented with higher DC in right cerebellum posterior lobe (p≤0.005 uncorrected). Relative to AQP4+ NMOSD, MOGAD showed higher DC in right superior temporal gyrus (p≤0.005 uncorrected) and left middle/inferior occipital gyrus (p≤0.005 FDR-corrected), but lower DC in right cerebellum posterior lobe (p≤0.005 uncorrected).

Cross-modality association

As shown in **Figure 2C**, significant intra-modality (especially GM volume) correlations were observed in MOGAD with few inter-modality correlations. In AQP4+ NMOSD, both intra- and inter-modality correlations were presented (especially between GM volume and diffusion measures).

Clinical correlations

In the MOGAD patients, GM volume in left hippocampus/parahippocampal gyrus (R=-0.55, 95%CI [-0.70, -0.40]; p=0.04) negatively correlated with EDSS. GM volume in right superior temporal gyrus/insula positively correlated with MoCA (R=0.65, 95%CI [0.34, 0.84]; p=0.03) and SDMT (R=0.61, 95%CI, [0.40, 0.86]; p=0.046). GM volume in left hippocampus/parahippocampal gyrus (R=0.62, 95%CI [0.40, 0.78]; p=0.031) positively

correlated with CVLT (**Figure 3**).

For NMOSD, FA in left fornix/stria terminalis (R=-0.52, 95%CI [-0.61, -0.40]; p=0.028) and DC in right middle/inferior occipital gyrus (R=0.47, 95%CI [0.37, 0.56]; p=0.049) correlated with EDSS. GM volume in left rectus gyrus (R=0.59, 95%CI [0.36, 0.72]; p=0.026), FA in right medial lemniscus (R=0.60, 95%CI [0.44, 0.69]; p=0.023) and MD in right optic radiation (R=-0.71, 95%CI [-0.80, -0.51]; p=0.004) correlated with MoCA. GM volume in right superior temporal gyrus (R=0.65, 95%CI [0.56, 0.76]; p=0.041), and DC in left middle/inferior occipital gyrus (R=0.72, 95%CI [0.59, 0.83]; p=0.018) and left middle occipital gyrus (R=0.74, 95%CI [0.57, 0.96]; p=0.014) correlated with SDMT.

Results of additional partial correlations with disease duration and education as covariates were largely consistent with the above findings (**Supplemental Table 1**).

Classification of MOGAD versus AQP4+NMOSD

The univariate logistic regression showed the ability of quantitative structural and functional MRI measures - but not lesion distribution/volume or clinical variables - to differentiate MOGAD and AQP4+ NMOSD (**Supplemental Table 2**). Stepwise logistic regression achieved a classification accuracy of 95%, sensitivity of 94%, specificity of 95%, with an AUC of 0.96 and a Youden index of 0.89 using a combination of DC in occipital gyrus and FA in splenium of corpus callosum (**Table 2** and **Figure 4**). For the patient subgroups with and without brain lesions, the classification achieved accuracies of 89% and 83% using DC in occipital gyrus and

DC in cerebellum respectively.

Discussion

Examining the impact of MOGAD beyond visible lesions, this paper for the first time determines brain structural and functional MRI abnormalities in MOGAD compared to healthy controls and the specificity of these MRI biomarkers compared to patients with AQP4+ NMOSD using voxel-wise analyses. The primary findings were as follows: (1) MOGAD patients presented with GM atrophy in frontal, temporal lobes, insula, thalamus and hippocampus, diffusion abnormities of the optic radiation and anterior/posterior corona radiata, while functional connectivity was impaired in cerebellum but increased in temporal lobe. (2) In MOGAD, GM atrophy (particularly hippocampal atrophy) was associated with clinical disability and cognitive impairment. (3) The classification of MOGAD from AQP4+ NMOSD achieved an accuracy of 95% using a combination of FA in splenium of corpus callosum and DC in occipital gyrus.

Consistent with previous reports,[5, 6] predominant clinical involvement of optic nerve and spinal cord was observed in both MOGAD and AQP4+ NMOSD. About half of MOGAD patients presented with focal brain lesions, which was comparable to previous studies demonstrating lesions in 24% to 83% of patients.[8, 9, 13, 18-20] The brain lesion in MOGAD were mainly located in deep (75%) and periventricular WM (63%), and the brainstem (63%) similar to those in AQP4+ NMOSD, indicating that brain lesion distribution might not be useful for distinguishing MOGAD from NMOSD even though some brain lesion distributions (e.g., presence of juxtacortical lesion) tended to be different;[10, 12] larger sample sizes may be required to demonstrate their potential relevance.

Cortical atrophy in frontal (especially orbito-frontal cortex) and temporal gyrus, and deep grey matter including thalamus and hippocampus, were observed in MOGAD patients. The possible underlying pathological basis includes GM demyelination, meningeal inflammation due to destructed blood brain barrier, Wallerian degeneration secondary to juxtacortical WM demyelination, MOG-specific T cell-mediated cytotoxicity and reactive gliosis.[2, 4, 8, 13, 21-24] Bilateral hippocampus atrophy was found in MOGAD, but not in AQP4+ NMOSD, implying deep grey matter particularly hippocampal atrophy may be a feature specific for MOGAD. The negative hippocampus finding in AQP4+ NMOSD seems contrary to a previous work that demonstrated hippocampus atrophy in those with cognitive impairment, [25] which may be explained by the fact that a part of our patients had preserved cognition function. Additionally, MOGAD patients had milder brain atrophy in the visual cortex (e.g., lingual gyrus) and cerebellum (e.g., anterior/posterior cerebellum lobe) compared to AQP4+ NMOSD, implying the relative structural preservation of the visual and cerebellar systems in MOGAD.[26, 27]

WM disruption in optic radiation and anterior/posterior corona radiata were identified in MOGAD and AQP4+ NMOSD, suggesting a common WM damage target in both diseases, which may due to anterograde degeneration secondary to optic nerve damage, a dominant mode of clinical presentation in adult MOGAD and NMOSD.[5, 28] Other explanations included axonal demyelination by complement or antibody dependent cellular cytotoxicity phagocytosis.[4, 23] The degree of optic radiation and splenium of corpus callosum damage in MOGAD was milder than AQP4+ NMOSD, which supports the clinically favorable visual prognosis in MOGAD compared to the poor visual outcome in AQP4+ NMOSD.[27]

Both functional impairment and adaption were observed in MOGAD. Functional impairment (decreased DC) predominantly occurred in the posterior cerebellar lobe, which may due to disrupted afferent signals from the damaged spinal cord or brainstem or direct damage due to MOG-antibody mediated inflammation.[29] Increased functional connectivity (increased DC) was observed in temporal gyrus, indicating a functional plasticity to compensate for the structural damage in early phase, which was similar to previous findings on MS and NMOSD.[30, 31] The functional alterations in MOGAD differed from AQP4+ NMOSD, with severe functional impairment in visual areas (e.g., occipital cortex) and evidence for functional adaption in the cerebellum as indicated in previous works demonstrating severe visual connectivity damage in visual cortex, and potential functional preservation in damage-free cerebellum.[26, 32]

Cross-modality association in MOGAD indicated an independent pathological process in GM, consistent with cortical involvement associated with meningeal inflammation, which might be different from WM damages caused by complement- and antibody-medicated activities.[4, 33] The close association between GM atrophy and WM disruption in AQP4+ NMOSD might support an mechanism of Wallerian degeneration secondary to WM damage.[32]

Even though MOGAD and AQP4+ NMOSD presented with similar clinical outcomes (e.g., clinical disability and cognitive scores), distinct clinical associations were observed in MOGAD and AQP4+ NMOSD, which might reflect different pathological mechanisms and underlying structural and functional alterations. GM atrophy in hippocampus/parahippocampal gyrus was

associated with more clinical disability, implying the potential driving force of underlying GM involvement for the clinical disability and highlighting the role of the hippocampus in prognosis in MOGAD. Additionally, GM atrophy in temporal gyrus/insula and hippocampus/parahippocampal gyrus was associated with cognitive decline in MOGAD, which was consistent with previous findings of cortical and subcortical GM atrophy driving cognitive impairment in neuroimmune and neuroinflammatory diseases, as potential markers for evaluating cognitive impairment in both diseases.[34, 35] These findings were different from those in AQP4+ NMOSD, where clinical associations were mostly identified with structural and functional characteristics of the visual areas, fornix/stria terminalis and medial lemniscus, some of which are small structures needing further validation. The differential correlation pattern observed suggests that different imaging markers could be used for evaluating clinical disability and cognitive impairment in MOGAD and AQP4+ NMOSD.

The accurate diagnosis of MOGAD is crucial to plan appropriate management,[1] however the identification of MOGAD patients may be difficult in clinical practice if serum MOG antibody testing (e.g., cell-based assays) are not available.[10] Previous work trying to distinguish MOGAD from AQP4+ NMOSD using MRI the lesion distributions and characteristics failed to achieve satisfactory results (classification accuracy<65%).[10] In this work, we achieved a classification accuracy of 95% using a combination DC in occipital gyrus and FA in splenium of corpus callosum. Additionally, the classification accuracies for the two subgroups of patients with MRI-visible and MRI-nonvisible lesions were 89% and 83% using DC in occipital gyrus and cerebellum respectively, highlighting the value of functional measures, which could be furtherly

investigated in clinical practice. Additionally, our findings may also prompt serological testing for MOG antibodies particularly for patients without brain lesions.

This work has several limitations. First, this is a preliminary single center cross-sectional study with small sample size and without strict multiple comparison correction for voxel-based analyses. Larger sample size and longitudinal multicenter studies with strict statistical strategies (e.g., family-wise error correction to control the false positive rate) are warranted to confirm our results. Second, this study focused on quantitative brain MRI measurements, while spinal cord and optic nerve damage were not evaluated; further studies with a more comprehensive assessment of the whole central nervous system in MOGAD are needed. Third, the clinical relevance of the MRI measures were mainly investigated in relation to clinical disability/cognition, and classification between MOGAD and AQP4+ NMOSD; further study is warranted to investigate its value in treatment response and clinical trial design. Lastly, MRI scanning of a few of the recruited patients were conducted after just more than four weeks after the last attack, which might not have allowed complete recovery of the effect of acute presentation.

Conclusion

Going beyond focal lesions, we demonstrated brain structural and functional abnormalities in MOGAD patients including GM atrophy in frontal, temporal lobes, and deep grey matter, diffusion abnormities of optic radiation and anterior/posterior corona radiata, and co-existing functional impairment and adaptation. GM particularly hippocampal atrophy was associated

with clinical disability and cognitive decline in MOGAD, implying GM volume as potential imaging marker for monitoring disease progression. Finally, our classification model based on structural and functional MRI measurements could help differentiate MOGAD from AQP4+ NMOSD even in the absence of focal lesions on MRI.

Author contributions

1 guarantor of integrity of the entire study: Yaou Liu

2 study concepts: Yaou Liu

3 study design: Zhizheng Zhuo, Yaou Liu

4 definition of intellectual content: Yaou Liu; Yunyun Duan

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7 experimental studies: Decai Tian; Chenyang Gao; Xinli Wang

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Data sharing statements

The data can be made available upon reasonable request by a qualified researcher.

Conflicts of interest

Zhizheng Zhuo, Yunyun Duan, Decai Tian, Xinli Wang, Chenyang Gao, Jinli Ding, Fenglian Zheng, Tian Zhang, Xinghu Zhang, Fu-Dong Shi and Yaou Liu declare that there is no conflict of interest.

Professor Frederik Barkhof acts as a consultant for Bayer-Schering, Biogen-Idec, GeNeuro, Ixico, Merck-Serono, Novartis and Roche. He has received grants, or grants are pending, from the Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) initiative, the Biomedical Research Centre at University College London Hospitals, the Dutch MS Society, ECTRIMS–MAGNIMS, EU-H2020, the Dutch Research Council (NWO), the UK MS Society, and the National Institute for Health Research, University College London. He has received payments for the development of educational presentations from Ixico and to his institution from Biogen-Idec and Merck. He is on the editorial board of Radiology, Brain, European Radiology, Multiple Sclerosis Journal and Neurology.

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