Differentiating Multiple Sclerosis From AQP4-Neuromyelitis Optica Spectrum Disorder and MOG-Antibody Disease With Imaging

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Study Question
What are the conventional and advanced brain, cord, and optic nerve imaging markers that differentiate adult patients with relapsing remitting multiple sclerosis (RRMS) from aquaporin-4 antibody–positive neuromyelitis optica spectrum disorders (AQP4-NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)?

What Is Known and What This Paper Adds
Multiple sclerosis (MS) has a wide range of clinical and imaging manifestations, which overlap with those of NMOSD and MOGAD. There is an unmet need for imaging markers that differentiate between them when serologic testing is unavailable or ambiguous. Differences in patterns of brain, spinal cord, and optic nerve lesions and microstructural changes between the 3 diseases have been described, but the approach of reaching a diagnosis of one of these 3 diseases on the basis of conventional and advanced MRI features alone (or in combination) is not standardized. This study’s results provide Class II evidence that selected conventional and advanced brain, cord, and optic nerve MRI and optical coherence tomography (OCT) markers distinguish adult patients with RRMS from AQP4-NMOSD and MOGAD. The key findings are as follows: (1) the number of brain cortical and white matter lesions consistently differentiates RRMS from the 2 antibody-mediated diseases, while the central vein sign (CVS) best discriminates between RRMS and AQP4-NMOSD; (2) magnetization transfer ratio (MTR) of the optic nerve increases the accuracy in differentiating RRMS from AQP4-NMOSD, while retinal nerve fiber layer (RNFL) thickness discriminates RRMS from MOGAD; and (3) AQP4-NMOSD and MOGAD share more similarities than differences, and the only imaging marker which distinguished these groups was the presence of at least 1 cervical cord lesion. These findings may be particularly useful in clinical practice to support a clinical diagnosis and exclude an antibody-mediated condition when the antibody testing is unavailable or suboptimal or when there is a suspicion of false negative/positive serologic testing results.

Methods
This cross-sectional study used data from the National Hospital for Neurology and Neurosurgery, London, and the Walton Centre, Liverpool. Patients older than 18 years with a diagnosis of (1) RRMS according to 2017 McDonald criteria, (2) AQP4-NMOSD according to Wingerchuk criteria, or (3) MOGAD (defined as MOG-Ab positivity using CBA in the context of an acute demyelinating event in patients presenting with a MOGAD phenotype previously described) were recruited consecutively. Age-matched and sex-matched healthy controls who volunteered to join the study were also recruited. Participants were excluded if they had major contraindications to MRI, a neurologic comorbidity, any ophthalmic conditions (such as glaucoma, ocular trauma, or degenerative eye disease), or a relapse in the previous 6 months. In total, we included 31 RRMS, 30 AQP4-NMOSD, 30 MOGAD patients, and 34 healthy controls. All participants underwent a 3T MRI, and conventional (white matter lesions, cortical lesions, CVS, atrophy) and advanced (diffusion tensor imaging, MTR, OCT) brain, cervical cord, and optic nerve imaging modalities were analyzed. All patients were assessed at the time of the MRI with conventional and nonconventional scales for MS. We used multiple linear regression models to assess differences between patients and logistic regression models to identify disease-specific predictors alone and in combination.

Results and Study Limitations
The most accurate measures differentiating RRMS from AQP4-NMOSD were the proportion of lesions with the CVS (84% vs 33%, accuracy/specificity/sensitivity: 91%/88%/93%, \(p < 0.001\)), followed by cortical lesions (median: 2 [range: 1–14] vs 1 [0–1], accuracy/specificity/sensitivity: 84%/90%/77%, \(p = 0.002\) and white matter lesions (mean: 39.07 [±25.8] vs 9.5 [±14], accuracy/specificity/sensitivity: 78%/84%/73%, \(p = 0.001\)). The combination of higher proportion of CVS, cortical lesions, and optic nerve MTR reached the highest accuracy in distinguishing RRMS from AQP4-NMOSD (accuracy/specificity/sensitivity: 95%/92%/97%, \(p < 0.001\)).

The most accurate measures favoring RRMS over MOGAD were white matter lesions (39.07 [±25.8] vs 1 [±2.3], accuracy/specificity/sensitivity: 94%/94%/93%, \(p = 0.006\), followed by cortical lesions (2 [1–14] vs 1 [0–1], accuracy/specificity/sensitivity: 84%/97%/71%, \(p = 0.004\) and RNFL (mean:
87.54 [±13.83] vs 75.54 [±20.33], accuracy/specificity/sensitivity: 80%/79%/81%, \( p = 0.009 \). A higher cortical lesion number combined with higher RNFL thickness best differentiated RRMS from MOGAD (accuracy/specificity/sensitivity: 84%/92%/77%, \( p < 0.001 \)).

The Figure shows the examples of cortical lesions and CVS in the 3 diseases.

Limitations of the study include the lack of availability of scans at disease onset and the cross-sectional design which did not allow us to investigate differential MRI changes over time. Further longitudinal analysis may identify differential patterns of inflammation and neurodegeneration that could better separate these diseases from the onset and predict the course of each demyelinating disorder.

**Study Funding and Competing Interests**

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