Brain lesion distribution criteria distinguish demyelinating diseases in China

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Abstract
Objective: To verify the utility of brain lesion distribution criteria in distinguishing multiple sclerosis (MS) from aquaporin-4 (AQP4)-immunoglobulin G (IgG)-positive/-negative neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein IgG-associated encephalomyelitis (MOG-EM) in the Chinese population. Methods: A total of 253 patients with MS (80), NMOSD (129 AQP4-IgG positive, 34 AQP4-IgG negative), and MOG-EM (10) were enrolled. Anonymized magnetic resonance imaging results were scored on the previous reported criteria of “at least one lesion adjacent to the body of the lateral ventricle and in the inferior temporal lobe; or the presence of a subcortical U-fiber lesion; or a Dawson’s finger-type lesion.” Chi-squared test (or Fisher’s exact test) was used to analyze the data. Results: The distribution criteria were able to distinguish MS with a same sensitivity of 93.8% from all type of NMOSD and MOG-EM, with a specificity of 89.7% from the whole NMOSD cohort, 89.1% from AQP4-IgG-positive NMOSD 91.2% from AQP4-IgG-negative NMOSD, and 70.0% from MOG-EM. Dawson’s finger-type lesion was the most sensitive and specific feature, whereas the U-fiber lesion was the least. Conclusion: The brain lesion distribution criteria were helpful in distinguishing MS from NMOSD and MOG-EM in the Chinese population. Dawson’s finger-type lesion was highly suggestive of MS.

Introduction
Multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are both common idiopathic inflammatory demyelinating diseases (IIDDs), whereas myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG)-associated encephalomyelitis (MOG-EM) was recognized as an independent IIDD in the latest international recommendation. Initial manifestation of those IIDDs overlap to a great extent, covering a wide range of manifestations like limb weakness, sensory disturbance, and visual loss. Although similar in clinical features, these diseases are yet different in treatment options and prognosis. Thus, early differentiation between those IIDDs was crucial but challenging as well.

Radiological examinations emerged to be a promising tool in this regard, given the false positives and late-coming results associated with antibody testing. Recent studies have revealed preliminary evidence on the utility of neuroimaging in diagnosing and differentiating IIDDs. Matthews et al. first proposed the brain imaging criteria to distinguish MS from NMOSD in 2013, including “at least one lesion adjacent to the body of the lateral ventricle and in the inferior temporal lobe; or the presence of a subcortical U-fiber lesion; or a Dawson’s finger-type lesion.” Subsequent researches tested these criteria in distinguishing MS from aquaporin-4 (AQP4)-IgG-positive NMOSD and MOG-EM in European, Korean, and South American cohorts, respectively, further showing its utility across a wide range of populations.

However, the previous studies mainly focused on areas with a high prevalence of MS. In China, as opposed to western countries, NMOSD was more prevalent than MS. Furthermore, the latest diagnostic criterion of

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MOG-EM has not been validated in previous studies. And studies comparing AQP4-IgG-negative NMOSD are lacking. Therefore, our study aimed to identify the distinguishing radiological features of MS when compared with NMOSD and MOG-EM. We evaluated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the previously reported brain lesion criteria in the three IIDDs in the Chinese population.

Methods

Patients

Our study enrolled 253 consecutive Chinese patients admitted from December 2015 to August 2018 in the Second Affiliated Hospital School of Medicine Zhejiang University (80 met the 2017 McDonald criteria for MS, 163 fulfilled the 2015 NMOSD Wingerchuk criteria by International Panel for NMO (all with negative MOG-IgG), among which 129 were positive for AQP4-IgG and 34 were negative for AQP4-IgG. Ten were positive for MOG-IgG and fulfilled the international consensus of MOG-EM1). All 253 patients were admitted to our hospital and diagnosed with IIDDs at their first attack of neurological symptoms. The antibody test of AQP4-IgG and MOG-IgG was tested by cell-based assay (CBA), the recommended testing method for both antibodies by international consensus.1,10 Our study was approved by the ethics committee of the Second Affiliated Hospital School of Medicine Zhejiang University. All patients were consented for the use of their anonymized MRI examinations and clinical details for research purposes.

MRI scanning

Brain MRI scans were performed with a GE 1.5 Tesla MR scanner (Siemens Healthcare, Erlangen, Germany) within the first onset of disease in our hospital. The scan parameters: T1-weighted images (T1WIs) (400/9 msec, TR/TE), T2-weighted images (T2WIs) (3000–4700/88–110 msec, TR/TE), and fluid-attenuated inversion recovery (FLAIR) images (7800–9602/100–160 msec, TR/TE) for brain MRI. The slice thickness of the axial scans was 5–6 mm.

The brain lesion distribution criteria2 were described as follows (Fig. 1): (a) at least one lesion adjacent to the body of lateral ventricle and in the inferior temporal lobe, or (b) juxtacortical lesions in the U-fiber (with a curved/s-shaped morphology), or (c) Dawson’s finger-type lesion. Radiological images were evaluated on T2WIs or FLAIR sequences. MRI scans were independently rated by two neuroradiologists blinded to each other’s findings. When the nature of the lesions could not be established, a third experienced neuroradiologist would evaluate and a final consensus was reached.

Statistical analysis

Statistical analysis was performed with SPSS version 23.0. All quantitative data in this study were analyzed with the Chi-squared test or Fisher’s exact test. Values with P < 0.05 was considered statistically significant. Results were reported as the mean ± standard deviation (SD) for numerical variables, and as the percentage (%) of the total number of patients for categorical variables. Cohen’s kappa was used to evaluate the interobserver variability, and the kappa values for all criteria were ≥0.84 for all criteria (kappa values ≤ 0 indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement13). True positive (TP, fulfilled the criteria and diagnosed with MS), true negative (TN, inconformity to the criteria but the diagnosis was MS) were calculated. Performance of the imaging criteria were expressed as specificity, PPV, and NPV, odds ratio (OR), positive likelihood ratio (+LR), and negative likelihood ratio (−LR) (with respective 95% confidence intervals, 95% CI).

Results

The basic demographic, and radiologic features of patients with MS, NMOSD, and MOG-EM are summarized in Table 1. Female accounted for a larger proportion of patients with NMOSD, whereas males made up the majority in MOG-EM.

The brain lesion distribution criteria had a high sensitivity and specificity for diagnosing MS. The sensitivity, specificity, PPV, and NPV of the brain lesion distribution criteria in differentiating MS from NMOSD and MOG-EM are summarized in Table S1. When identifying MS from the whole NMOSD cohort, the full brain lesion distribution criteria had a sensitivity of 93.8%, specificity of 89.6%, PPV of 81.5%, and NPV of 95.7%. In detail, the sensitivity, specificity, PPV, and NPV were 93.8%, 89.1%, 84.3%, and 95.8% in the AQP4-IgG positive cohort and 93.8%, 91.2%, 96.2%, and 86.1% in the AQP4-IgG-negative cohort. As for the MOG-EM cohort, values for the previously described features were 93.8%, 70.0%, 96.2%, and 58.3%, respectively. The trends of +LR and −LR were consistent with other four features. Meanwhile, the OR in
all cohorts was >1, and the $P$ values of all criteria among the different cohorts were all less than 0.001 except the “b” ($P = 0.044$) and “c” ($P = 0.49$) features in comparing MS with MOG-EM.

Next we looked into specific items of the brain lesion distribution criteria. The differential characteristics of brain lesion distribution were similar in MS and the other two diseases: the criterion of Dawson’s finger-type lesions had the highest diagnostic value, whereas the U-fiber lesions the lowest. The $+LR$ and OR were obviously several times higher than other indicators. Particularly, when compared with AQP4-IgG-negative NMOSD and MOG-EM, MS had a high specificity and PPV for Dawson’s finger-type lesions (100%), and the $+LR$ and OR were infinite.

Notably, we found several exceptional cases. Some patients without the diagnosis of MS fulfilled one of the

Figure 1. Matthews’s brain lesion criteria. (A) lesions adjacent to the body of lateral ventricle; (B) lesions in the inferior temporal lobe; (C) subcortical U-fiber lesion; (D) Dawson’s finger-type lesion (periventricular demyelinating plaques distributed along the axis of medullary veins, perpendicular to the body of the lateral ventricles and/or callosal junction with a clear margin and an externally perpendicular orientation from the lateral ventricle, a diameter ranging from 3 to 19 mm).4,11
Table 1. Demographic and clinical characteristics of patients with MS, NMOSD, and MOG-EM.

|                | MS (n = 80) | NMOSD (n = 163) | AQP4 + NMOSD (n = 129) | AQP4-NMOSD (n = 34) | MOG-EM (n = 10) |
|----------------|------------|----------------|------------------------|---------------------|-----------------|
| Age at onset, mean ± SD (IQR), years | 33.5 ± 13.4 (9–66) | 43.4 ± 14.9 (12–81) | 43.8 ± 15.4 (12–81) | 41.9 ± 13.1 (12–69) | 43.5 ± 15.5 (25–64) |
| Gender, F:M, n | 49:31 | 144:19 | 121:8 | 23:11 | 4:6 |
| No. of patients meeting the lesion criteria, n (%) | | | | | |
| (a): Lesions adjacent to the body of a lateral ventricle and in the inferior temporal lobe | 45 (56.3%) | 14 (8.6%) | 12 (9.3%) | 2 (5.9%) | 2 (20.0%) |
| (b): U-fiber lesions | 30 (37.5%) | 10 (6.1%) | 8 (6.2%) | 2 (5.9%) | 2 (20.0%) |
| (c): Dawson’s finger-type lesions | 59 (73.8%) | 2 (1.2%) | 2 (1.6%) | 0 (0) | 0 (0) |
| Full criteria (a, b, or c) | 75 (93.8%) | 17 (10.4%) | 14 (10.9%) | 3 (8.9%) | 3 (30%) |

Abbreviations: AQP4, aquaporin protein 4; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; MOG-EM, myelin oligodendrocyte glycoprotein immunoglobulin G-associated encephalomyelitis; IQR, interquartile range; SD, standard deviation.

Discussion

Our study for the first time demonstrated that the brain lesion distribution criteria in MRI were a great tool to distinguish MS from NMOSD and MOG-EM in the Chinese population. We used the latest diagnostic criteria and regarded MOG-EM as an independent entity. Their differences are concluded in Table 2.

Highlights of our study lay in the application of the latest diagnostic criteria, and a large-sized representative sample of the Chinese population. We screened MS patients with the 2017 McDonald criteria instead of previous versions like 2010 McDonald criteria or the Barkhof criteria. NMOSD cohorts were diagnosed with the 2015 Wingerchuk criteria. MOG-EM was diagnosed with the latest international expert consensus. Moreover, our study had the largest sample size with a focus on the Chinese population, where the criteria have not been validated before. The ratio of patients with MS and NMOSD in our study was close to 1:2, in line with the ratio of the two diseases in the general Chinese population. In contrast, previous studies mainly enrolled patients with a ratio consistent with the epidemiological features of the Caucasian population. Therefore, our conclusion can be better extrapolated into the whole Chinese population.

Different conclusions were reached through intragroup comparisons between our study and the Matthews’s study, and intergroup comparisons between MS and other diseases in our cohorts. By intragroup comparisons of MS to AQP4-IgG-positive NMOSD cohort, our study showed a lower specificity (89.1% vs. 96.2%) and PPV (84.3% vs. 97.9%), but a higher sensitivity (93.8% vs. 92.0%) and NPV (95.8% vs. 86.2%). The discrepancy existed in other comparisons as well. In fact, the specificity and PPV were inversely proportional to the prevalence of IIDDs in each population, the PPV in direct proportion to the prevalence, whereas the sensitivity was affected more gently. Therefore, sensitivity and specificity could better reflect the utility of the criteria for each disease, whereas the

Table 2. Discriminatory sensitivity, specificity, PPV, and NPV between MS, NMOSD, and MOG-EM.

|                | MS & NMOSD | MS&AQP4 + NMOSD | MS&AQP4-NMOSD | MS&MOG-EM |
|----------------|------------|----------------|---------------|-----------|
| Sensitivity, % (95%CI) | 93.8 (85.4–97.7) | 93.8 (85.4–97.7) | 92.8 (85.4–97.7) | 93.8 (85.4–97.7) |
| Specificity, % (95%CI) | 89.6 (83.6–93.6) | 89.1 (82.2–93.7) | 91.2 (75.2–97.7) | 70.0 (35.4–91.9) |
| PPV, % (95%CI) | 81.5 (71.8–88.6) | 84.3 (74.7–90.8) | 96.2 (88.4–99.0) | 96.2 (88.4–99.0) |
| NPV, % (95%CI) | 96.7 (92.0–98.8) | 95.8 (52.5–14.21) | 86.1 (69.7–94.8) | 58.3 (28.6–83.5) |

Abbreviations: AQP4, aquaporin protein 4; CI, confidence intervals; MOG-EM, myelin oligodendrocyte glycoprotein immunoglobulin G-associated encephalomyelitis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; NPV, negative predictive value; PPV, positive predictive value; parenthesis denotes 95% confidential interval.
PPV and NPV could better indicate the diagnostic accuracy of the criteria in routine clinical practice.\(^{18}\) For a better accuracy our study included some other indicators when evaluating the criteria. \(+LR\) (the greater the ratio, the greater the probability of being diagnosed with MS when meeting diagnostic criteria) and \(-LR\) (the smaller the ratio, the lower the probability of being diagnosed with MS when not meeting diagnostic criteria) were chosen to avoid the impact of the variable, and OR \((\text{the greater the ratio, the stronger the correlation between the indicator and MS})\) to further clarify the relevance of these diagnostic criteria to MS. With the mutual verification through these indicators, the three main criteria features, especially the Dawson’s finger-type lesions, were definitely great screening tools for MS in the Chinese population.

As for intergroup comparisons, different criteria showed discrepant results. First of all, when applying the criteria to AQP4-IgG-negative NMOSD cohort, our result was analogous to Matthews’s research, showing a higher specificity and PPV but a lower NPV, compared with the AQP4-IgG-positive cohort. It might be explained by the small number of patients diagnosed with AQP4-IgG-negative NMOSD in both studies.\(^{19}\) The differences were clinically important in AQP4-IgG-negative NMOSD since the evidence of treatment and prognosis was lacking in this group of patients. The differential diagnosis between AQP4-IgG-negative NMOSD and MS posed a great challenge, as they both had similar clinical manifestations and negative antibody test results, and the characteristics of brain lesions in AQP4-IgG-negative NMOSD remain understudied.\(^{20}\)

According to the 2015 Wingerchuk criteria,\(^{10}\) NMOSD with negative AQP4-IgG antibody had more strict requirements and could only be diagnosed after excluding other alternative diagnoses. Thus, for recurrent episodes with negative AQP4-IgG, the brain lesion criteria were of great significance to differentiate MS from AQP4-IgG-negative NMOSD. When analyzing the differences between the MOG-EM and AQP4-IgG-positive NMOSD cohorts, the specificity and NPV were lower, whereas the PPV was higher, consistent with previous studies\(^ {3-5}\) employing the previous criterion of MOG-EM.\(^ {10}\) Notably, in the newly proposed criterion of MOG-EM, the MOG-IgG testing was recommended in patients presenting with an abnormal brain MRI but no lesion according to Matthews’s criteria.\(^2\)

The three items of the brain lesion distribution criteria were similar in the overall trends among these comparing cohorts, but different in their respective characteristics. Dawson’s finger-type lesions had the highest diagnostic value, whereas the U-fiber lesion the lowest. When comparing MS with AQP4-IgG-positive NMOSD, the result was consistent with previous researches even with a different proportion of patients with MS and NMOSD.\(^ {2-5,21,22}\) Moreover, the specificity was higher than before, implicating that Dawson’s finger-type lesion is of greater significance in the diagnosis of MS. As for AQP4-IgG-negative NMOSD and MOG-EM, we came to similar conclusions with previous studies, further showing the validity of the diagnostic criteria.

Several limitations existed in our study. First, there were relatively few patients with MOG-EM. It might affect the statistical results as the higher disease prevalence caused a higher PPV, but lower specificity and NPV. Multicenter studies with a larger sample size is required to verify our conclusion. Second, it was a cross-sectional study with newly onset patients. However, the three diseases all had a relapsing-remitting course. Considering the alternating sites of brain lesions in relapses, further follow-up studies are needed. Moreover, the low prevalence of U-fiber lesions could be influenced by the low field-strength (1.5 T) of MR scanner with its relatively low resolution. The higher field-strength (like 3.0 T) of MR scanner are needed to help identify the morphological features of the lesions, and verify the characteristics of the three indicators accurately.

In conclusion, our study validated the brain lesion distribution criteria in the Chinese population for differentiating MS from other IIIDs, including AQP4-IgG positive, AQP4-IgG-negative NMOSD and MOG-EM, all diagnosed with the latest diagnostic criteria. Further radiological studies are needed to extend the follow-up time and detect other lesion criteria like spinal lesions to differentiate MS from other more demyelinating diseases.

**Author Contributions**

M.-T. Cai and Y.-X. Zhang performed statistical analysis and also involved in drafting the manuscript and study concept or design. M.-P. Ding involved in study supervision or coordination. M.-T. Cai, Y.-X. Zhang, and Y. Zheng contributed to analysis or interpretation of the data. Y.-X. Zhang, F. Yang, W. Fang, C.-H. Shen, and M.-P. Ding involved in acquisition of data. All authors contributed to revision of the manuscript and involved in contribution of vital reagents/tools/patients.

**Conflicts of Interest**

The authors have no conflict of interest to report.

**References**

1. Jarius S, Paul F, Aktas O, et al. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. J Neuroinflammation 2018;15:134.
2. Matthews L, Marasco R, Jenkinson M, et al. Distinction of seropositive NMO spectrum disorder and MS brain lesion distribution. Neurology 2013;80:1330–1337.
3. Juryńczyk M, Tackley G, Kong Y, et al. Brain lesion distribution criteria distinguish MS from AQP4-antibody NMO and MOG-antibody disease. J Neurol Neurosurg Psychiatry 2017;88:132–136.
4. Hyun JW, Huh SY, Shin HJ, et al. Evaluation of brain lesion distribution criteria at disease onset in differentiating MS from NMOSD and MOG-IgG-associated encephalomyelitis. Mult Scler 2019;25:585–590.
5. Bensi C, Marrodan M, Gonzalez A, et al. Brain and spinal cord lesion criteria distinguishes AQP4-positive neuromyelitis optica and MOG-positive disease from multiple sclerosis. Mult Scler Relat Disord 2018;25:246–250.
6. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. Curr Opin Neurol 2018;31:752–759.
7. Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. Mayo Clin Proc 2017;92:663–679.
8. Hor JY, Lim TT, Chia YK, et al. Prevalence of neuromyelitis optica spectrum disorder in the multi-ethnic Penang Island, Malaysia, and a review of worldwide prevalence. Mult Scler Relat Disord 2018;19:20–24.
9. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162–173.
10. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177–189.
11. Geraldes R, Ciccarelli O, Barkhof F, et al. The current role of MRI in differentiating multiple sclerosis from its imaging mimics. Nat Rev Neurol 2018;14:199–213.
12. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med 2012;22:276–82.
13. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292–302.
14. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997;120(Pt 11):2059–2069.
15. Eskandarieh S, Heydarpour P, Minagar A, et al. Multiple sclerosis epidemiology in East Asia, South East Asia and South Asia: a systematic review. Neuroepidemiology 2016;46:209–221.
16. Ochi H, Fujihara K. Demyelinating diseases in Asia. Curr Opin Neurol 2016;29:222–228.
17. Grunau G, Linn S. Commentary: sensitivity, specificity, and predictive values: foundations, pliabilities, and pitfalls in research and practice. Front Public Health 2018;6:256.
18. Smith CJ. Diagnostic tests (2) - positive and negative predictive values. Phlebology 2012;27:305–306.
19. Juryńczyk M, Weinshenker B, Akman-Demir G, et al. Status of diagnostic approaches to AQP4-IgG seronegative NMO and NMO/MS overlap syndromes. J Neurol 2016;263:140–149.
20. Matute-Blanch C, Montalban X, Comabella M. Multiple sclerosis, and other demyelinating and autoimmune inflammatory diseases of the central nervous system. Handb Clin Neurol 2017;146:67–84.
21. Juryńczyk M, Geraldes R, Probert F, et al. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 2017;140:617–627.
22. Tackley G, Kuker W, Palace J. Magnetic resonance imaging in neuromyelitis optica. Mult Scler 2014;20:1153–1164.

Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Diagnostic performances of brain lesion distribution criteria for differentiating MS from NMOSD and MOG-EM.