Improved performance of the 2017 McDonald criteria for diagnosis of multiple sclerosis in children in a real-life cohort

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Abstract

Objective: To compare the performance of the 2017 McDonald criteria with that of the 2010 criteria for the diagnosis of multiple sclerosis (MS) in children in the clinical setting.

Methods: In this retrospective, multi-centre study, we identified children who presented with symptoms suggestive of a clinically isolated syndrome (CIS) and were followed up for at least two years or until their second attack.

Results: Of 156 children with CIS followed up for a median of 4.17years, 94 (60.3%) were diagnosed with MS. 83 (88.3%) of these fulfilled the 2010 dissemination in space (DIS) criteria at onset. Three additional children fulfilled the 2017 DIS criteria because of the inclusion of symptomatic lesions. Of the 59 children with MS who underwent post-gadolinium MRI, 44 (74.6%) fulfilled the 2010 dissemination in time (DIT) criteria at baseline. When the presence of OCBs was used to substitute DIT, an additional 35 children (79/94, 84.0%) were diagnosed with MS according to the 2017 criteria. The 2017 criteria had higher accuracy (87.2% vs 66.7%), higher sensitivity (84.0% vs. 46.8%), but reduced specificity (91.9% vs. 96.8%) when compared to the 2010 criteria.

Conclusion: The improved performance of the 2017 criteria when compared to the 2010 criteria was predominantly due to the inclusion of intrathecal OCBs.

Introduction

The diagnosis of multiple sclerosis (MS) in children, as in adults, requires evidence of dissemination of inflammatory activity in more than one central nervous system (CNS) location, i.e. dissemination in space (DIS); in combination with recurrent disease over time, i.e. dissemination in time (DIT)[1] In contrast to adults presenting with CIS, in whom the majority of patients will eventually be diagnosed with MS[2], only 15-46% of children presenting with an acquired demyelinating syndrome (ADS) will be diagnosed with MS at 5 years[3]. Relapsing diseases other than MS should be considered in children presenting with features typical of acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica spectrum disorder (NMOSD). In particular, exclusion of myelin oligodendrocyte glycoprotein (MOG) antibody (Ab)-associated disease is recommended in children presenting with ADEM and in NMOSD cases with negative aquaporin-4 (AQP4) antibody[4].

The 2010 McDonald criteria enable a diagnosis of MS in children over the age of 11 years presenting with a clinically isolated syndrome (CIS) and evidence of DIS and DIT on MRI[5], providing that the clinical presentation does not resemble acute disseminated encephalomyelitis (ADEM)[6, 7]. Although a small proportion of children can present with MS before the age of 12 years, the lower positive predictive value of the 2010 McDonald criteria[5] in this age group[8] may lead to false diagnosis of MS in children who do not truly have the disease. The 2017 International "McDonald" MS diagnostic panel has recommended the following modifications to improve diagnostic accuracy and simplify application of the criteria[1]: (i) The presence of intrathecal oligoclonal bands (OCBs) allows for a diagnosis of MS in patients with MRI evidence of DIS but not DIT; (ii) No distinction needs to be made between symptomatic and asymptomatic MRI lesions in DIS and DIT criteria; and (iii) Cortical lesions are used to demonstrate DIS. As with previous iterations of diagnostic criteria for MS, other diagnoses need to be excluded, and the criteria should be applied only to patients with typical CIS presentations. As before, the criteria highlight that alternative diagnoses, including MOG and AQP4 antibodies, need to be excluded in all children with suspected MS, particularly when features overlapping with ADEM and NMOSD are present[1]. The Canadian Paediatric Demyelinating Disease network has shown that the 2017 McDonald criteria for the diagnosis of MS, when applied at the time of onset, performed well in identifying children and young people with MS. The criteria were also checked in children with acute disseminated encephalomyelitis (ADEM) and myelin oligodendrocyte antibody positive[9].

In this study, we aimed to compare the diagnostic performance of the newly proposed 2017 McDonald criteria and that of the 2010 McDonald criteria in children at onset of a CIS, who were clinically assessed and underwent investigations in the clinical setting, as part of routine clinical care. Additionally, we sought to compare the performance of the two sets of McDonald criteria in children presenting before and those presenting after the age of 11yrs.

Methods

Patient selection

This project was a multi-institutional, retrospective study run within the UK-CID network, involving three highly specialised paediatric MS centres: Great Ormond Street Hospital (London), Evelina London Children's Hospital, and Birmingham Children's Hospital. Centres were asked to identify patients with ADS seen in the period September 2014-September 2017. A systematic review of the UK-CID network's dataset was conducted by YH, and the following inclusion and exclusion criteria were applied in order to select from this large, retrospective pool, only those patients presenting with symptoms suggestive of a clinically isolated syndrome (CIS).

The inclusion criteria were: (i) Diagnosis of ADS, (ii) Baseline visit and MRI scan performed within 3 months of symptom onset, (iii) Follow up of ≥2 years and/or ≥2 recorded clinical attacks. All patients with ADS were evaluated for the study. Patients with a diagnosis of ADEM and/or positive MOG-Ab and AQP4 antibody (Ab) were secondarily excluded. It is important to note that all patients of the UK-CID network were tested for MOG-Ab and AQP4-Ab as part of routine clinical care, using a cell-based assay[10], but not always at the time of first presentation.

Cerebro-spinal fluid (CSF) examination for the detection of oligoclonal bands (OCBs) was carried out as part of clinical care when considered to be necessary and was not an inclusion criterion. Similarly, spinal cord MRI at onset was not considered to be an inclusion criterion. MRI was performed using clinical protocols with 1.5 or 3T scanners.

Development of clinically definite MS (CDMS)[11] was defined as the occurrence of a second clinical event attributable to demyelination lasting more than 24 hrs and after an interval of at least 1 month from the first attack, with evidence of two separate lesions[11].

Analysis of MRI scans

On all baseline and follow-up brain MRI scans of the children with CIS a neuroradiologist (FB), blinded to the diagnosis, scored the inflammatory, demyelinating lesions, which were defined as areas of hyperintensity involving at least three voxels, present on at least two slices and visible on two different sequences (e.g., FLAIR and T2-weighted images). MRI scan at presentation were evaluated separately to subsequent scans (even if done within 3month). We evaluated the presence of periventricular lesions (in direct contact with the ventricular system), juxtacortical lesions, and posterior fossa lesions (located in the brainstem and cerebellum). Cortical lesions were also identified on T2 and FLAIR sequences and were combined with juxtacortical lesions into the dissemination in space criterion, when assessing the 2017 McDonald criteria[1]. Spinal cord lesions were areas of hyperintensity seen on short-tau inversion recovery and T2-weighted scans. Gadolinium-enhancing lesions in the brain and spinal cord were identified. Patients were scanned according to clinical protocols, every 6months, and at time of clinical relapse.

This study was approved by Great Ormond Street Hospital Research and Development Department (reference: 16NC10).

Statistical analysis

To compare the demographic, clinical, radiological and serological characteristics between children who were diagnosed with MS during the follow-up and those who did not develop MS, and to compare the performance of the McDonald criteria between children presenting before and those presenting after the age of 11yrs, parametric or non-parametric statistical tests (Mann–Whitney U and Kruskal Wallis tests) were used for continuous distributions, as appropriate given normality, and $\chi 2$ or Fisher's exact tests for nominal data. All results associated with a p-value <0.05 were considered significant. Data were analyzed using GraphPad Prism 7.

The performance of the 2010 and 2017 McDonald criteria for dissemination in space (DIS) in time (DIT) were evaluated by calculating their sensitivity, specificity, accuracy and positive and negative predictive values with 95% confidence intervals (CI), as previously described[12]. The clinical status (both CDMS and the development of MS on the basis of DIS and DIT criteria over time vs. non-MS acquired demyelinating disorder) was used as the outcome. We calculated time to CDMS as the interval between the onset of CIS and second events.

Results

From 274 consecutive patients who met all the inclusion criteria, we excluded children who presented with ADEM (N=73) and children who were MOG-Ab (N=79) and AQP4-Ab (N=14) positive (48 patients with ADEM were also MOG-Ab positive). Therefore, the remaining 156 (56.9%) patients met all the inclusion and exclusion criteria and were considered to present with symptoms suggestive of a CIS (**Figure 1**).

The median follow up of the 156 patients included was 4.17 years (50.4 months [IQR 31.75–66.25]). 132/156 (84.6%) patients had a CSF examination for the detection of OCBs within 3month from presentation. 121/156 (77.6%) had spinal cord MRI at onset in addition to brain MRI. 96/156 (61.5%) patients underwent a post-gadolinium MRI scan at onset. A total of 855 MRI scans were performed (median of 8 for each patient, range 3-19) over the entire follow-up period.

The diagnosis of CDMS was made in 92 children by the end of follow up; two additional patients were diagnosed with MS on the basis of MRI evidence of DIS and DIT during follow up. Patients who were diagnosed with MS by the last visit more often showed abnormal brain MRI and positive OCBs at baseline, and new brain MRI lesions over time, when compared with patients who did not develop MS by the end of follow up. 100% of patients with MS showed the occurrence of new brain lesions over time vs. 6.5% of patients with a non-MS acquired demyelinating syndrome. Radiological phenotyping of the spinal cord lesions (short vs. long) was highly specific

for the clinical diagnosis, with 100% of MS patients having involvement of a short segment of the spinal cord in contrast to the 88.9% of the non-MS patients presenting with involvement of a long (extends over three or more vertebrae) segment of the spinal cord.

Baseline demographic, clinical, and MRI findings in patients who developed MS (N=94) and patients with a non-MS acquired demyelinating syndrome (N=62) are shown in **Table 1**. When considering only patients with CDMS, median time to the second relapse was 6 months (IQR 4-12). During the follow-up period, 78/92 (84.7%) patients with CDMS started disease-modifying drugs (DMDs). None of the patienst were commenced on DMDs at the CIS onset.

When looking only at patients who were diagnosed with MS by the end of the follow up, 26/94 (27.7%) were 11 years or under, and 68 (72.3%) were older than 11. There were no differences in demographic, baseline clinical and radiological characteristics between younger and older children, with the exception of a female predominance, which was only seen in children who were older than 11yrs, and CIS presentations other than optic neuritis and transverse myelitis (involvement of brainstem or cerebellum; cerebral hemisphere), which were more frequent in younger children than older children. There was no difference in the time to CDMS (**Figure 2**) nor in the percentage of OCBs positivity between the two groups. The percentage of patients who met the 2010 and 2017 McDonald criteria at baseline was similar between the two groups. Baseline demographic, clinical, and MRI findings in patients with MS who were 11yrs or younger vs. those who were older than 11yrs are shown in **Table 2**.

Application of McDonald diagnostic criteria

At baseline, 83 out of 94 (88.3%) children with MS fulfilled the 2010 McDonald DIS criteria. Three additional patients (86/94, 91.5%) fulfilled the 2017 DIS criteria; this modest increase in sensitivity was due to the inclusion of lesions within the symptomatic region. Inclusion of spinal cord lesion did not increase the sensitivity of the DIS criteria.

Of the 59 children who underwent post-gadolinium MRI, 44 (74.6%) fulfil radiological DIT according to 2010 McDonald criteria. When the presence of OCBs was used to substitute for the requirement of fulfilling DIT, an additional 35 children showed positive intrathecal OCBs and therefore were diagnosed with MS, with a total of 79/94 (84.0%) fulfilling the 2017 McDonald criteria at onset. When we looked more closely at these 35 children, four (11.4%) of them did not show gadolinium enhancement on MRI (none received steroids prior to MRI), three (8.6%) had a symptomatic enhancing lesion and the remaining 28 (80.0%) patients did not undergo a post-contrast MRI.

The performance of the 2010 and 2017 McDonald criteria for the development of CDMS and MS on the basis of MRI DIS and DIT (mean and 95% confidence interval) is summarised in **Table 3**. The 2017 McDonald criteria

had higher accuracy [87.2% vs 66.7%), higher sensitivity [84.0% vs. 46.8%], and a slightly lower specificity [91.9% vs. 96.8%] when compared with the 2010 McDonald criteria.

No differences in the sensitivity and specificity of the two sets of McDonald criteria were detected between children who presented ≤11years of age and older children. In particular, in children ≤11years the 2017 McDonald criteria had higher sensitivity (84.6% vs 46.2%) and a slightly lower specificity (91.2% vs 94.1%) when compared with 2010 McDonald criteria. Similarly, for children over the age of 11 years at onset, the sensitivity of the 2017 diagnostic criteria was higher (83.8% vs 47.1%) and specificity slightly lower (89.3% vs 92.9%) than the 2010 diagnostic criteria.

Discussion

We evaluated the performance of the McDonald criteria in a large cohort of children with CIS (N=156) who were clinically assessed and underwent investigations in the paediatric centres of the UK-CID network. The majority of patients underwent post-contrast MRI (61.5%), spinal cord MRI (77.6%) and CSF examination for the detection of OCBs (84.6%), but these investigations were requested by the neurologists on an ad-hoc basis, when considered to be necessary. In this real-life clinical cohort, we found that the new 2017 McDonald criteria allow for an additional 35/94 (37.2%) children to be diagnosed with MS at presentation when compared with the 2010 criteria. This increase in sensitivity was predominantly due to the inclusion of OCBs to substitute for MRI evidence of DIT, although not all patients who underwent a CSF examination also performed a gadolinium-enhanced MRI.

The inclusion of symptomatic lesions makes the 2017 criteria easier to score and improved the sensitivity of the DIS criteria, since three additional children fulfilled the 2017 DIS criteria on this basis. Interestingly, we found that the inclusion of symptomatic lesions resulted in a slightly reduced specificity of the 2017 McDonald criteria, since three patients with a diagnosis of non-MS acquired demyelinating syndrome at their last follow-up visit fulfilled the 2017 criteria, but not the 2010 criteria. Similar findings were also reported in a large Canadian cohort of 324 children with acquired demyelinating syndromes (of which 71 had MS)[9] and a study from the Netherlands of 229 adults with CIS[13].

OCBs (clonally expanded IgGs) in CSF, which are not in the serum, are detected in over 90% of adult patients with MS[14] and increase the risk of progression from CIS to MS independent of the baseline MRI findings[15]. CSF analysis at first presentation is often performed in children to exclude other aetiologies; unlike in adult populations, the majority of paediatric patients who present with an ADS have a monophasic disease and even of those who relapse, approximately 40% have a non-MS course[4]. We detected intrathecal OCBs in 94% of children with MS, compared to only 10.8% of the non-MS acquired demyelinating syndromes. A reason for the higher OCBs positivity, which more closely resembles the prevalence reported in adult MS than previous paediatric cohorts[3], may be that we excluded MOG Ab-associated disease[16, 17].

The high prevalence (93.7%) of periventricular lesions on the baseline scan of patients who went on to receive a diagnosis of MS may suggest that an alternative diagnosis should be sought in children who do not have periventricular lesions at onset of CIS. This is in keeping with the findings of a previous study in which the presence of one or more periventricular lesions at onset was associated with an increased likelihood of MS diagnosis (sensitivity 84%, specificity 93%, positive predictive value 76%, negative predictive value 96%) in a large cohort of children with acquired demyelinating syndromes[18]. We did not assess the added specificity of requiring three periventricular lesions for the DIS criteria, as previously suggested by the MAGNIMS group[7]. Spinal lesions were commonly detected in participants for whom spinal imaging was performed (58.8% of the MS group and 58.1% of children in the non-MS, non-ADEM group). As has been reported by other paediatric studies[19], addition of spinal cord lesion data did not meaningfully change the performance of any of the criteria.

The main limitation of our study is its retrospective nature, in which investigations were requested by the clinicians and not as part of a standardised research protocol, thereby introducing possible selection biases. However, this study design has allowed us to compare the performance of the two sets of criteria in a large, real-life clinical cohort, studied in the clinical setting, with over four years follow up; in a large Canadian cohort, the median time to a second clinical event or change on brain MRI in children with MS was 127 days (interquartile range 91–222)[20]. With regard to the MRI protocol, double inversion recovery or phase sensitive inversion recovery sequences were not acquired in the clinical setting, so the number of intracortical grey matter lesions cannot be provided.

As previously suggested[3], children with MS already have the pathobiological disease at the first clinical event (if not before) and hence the diagnosis can be given at the first clinical attack. This was also observed here with 93/94 (98.9%) having abnormal MRI at onset. We did not identify any clinical, radiological or immunological differences when comparing children presenting ≤11years of age and older children; additionally, the performance of the McDonald criteria was similar between the two groups. Although the group younger than 12yrs, had a rather limited age range (median 10.1yrs), our findings suggest that the diagnostic criteria used in adults can be applied to children at any age, thereby further developing the International Paediatric Multiple Sclerosis Study Group (IPMSSG) criteria, which state that caution should be used when apply the diagnostic criteria to young children because of reduced sensitivity[6]. The short time to first relapse observed in the patients with MS (median 6 months) compared to adult CIS cohorts[21], may support the recommendation of waiting for a second relapse prior to giving the diagnosis of MS or commencing treatment in patients with atypical presentations, and in children who at CIS onset do not have evidence of OCBs.

In summary, the 2017 McDonald diagnostic criteria, when applied to a real-life clinical cohort, have higher accuracy and sensitivity, and slightly lower specificity, than the 2010 McDonald criteria, mainly due to the

inclusion of OCBs. Since there are not differences between children older and younger than 11 years, the diagnostic criteria can be routinely applied to children irrespective of age of onset.

	Patients diagnosed with MS during the follow-up (N=94)	**Patients diagnosed with a non-MS acquired demyelinating syndromes at the last visit (N=62)**	**P value**
Age at presentation, Median yrs (IQR)	13.7 (11.35-14.74)	11 (7-13.9)	<0.0001
Sex (M : F)	1 : 2.48	1 : 1.138	0.026
Ethnicity (white : other)	1 : 1.18	1 : 0.82	0.3265
CIS phenotype at onset			
Optic Neuritis	23 (24.5%)*	24 (38.7%)*	0.1540
Transverse Myelitis	3 (3.2%)*	34 (54.8%)*	<0.0001
Involvement of brainstem or cerebellum; cerebral hemisphere	68 (72.3%)	4 (6.5%)	<0.0001
≥2 clinical events	92 (97.8%)	14 (22.6%)	<0.0001
Positive intrathecal oligoclonal bands	81/86** (94.1%)	5/46** (10.8%)	<0.0001
Abnormal brain MRI at onset	93 (98.9%)	11 (17.7%)	<0.0001
Location of lesions at onset			
Periventricular	88 (93.6%)	4 (6.4%)	<0.0001
Infratentorial	70 (74.4%)	8 (12.9%)	<0.0001
Spinal cord	50/85 (58.8%)	36 (58.1%)	1.0
Cortical/Juxtacortical	69 (73.4%)	4 (6.4%)	<0.0001
New brain MRI lesions over time	94 (100%)	4 (6.5%)	<0.0001
Location of new lesions			
Periventricular	94 (100%)	6 (9.7%)	<0.0001
Infratentorial	92 (97.8%)	11 (17.7%)	<0.0001
Spinal cord	72 (76.6%)	36 (58.1%)	0.021
Cortical/Juxtacortical	88 (93.6%)	6 (9.7%)	<0.001

Table 1. Baseline characteristics of patients who were diagnosed with MS and those with a non-MS acquired demyelinating syndrome during the follow-up.

CIS= clinically isolated syndrome; *Only one patient with optic neuritis in the MS group had a normal brain MRI at onset vs 2/24 and 4/34 of non-MS patients presenting with optic neuritis and transverse myelitis respectively. ** 86 + 46= 132 patients underwent a lumbar puncture for detection of intrathecal oligoclonal bands; N.S.= non-significant (>0.05).

Table 2: Baseline demographics, clinical and radiological features of children who were diagnosed with MS over time, presenting before and after the age of 11yrs.

	≤11years at onset (n=26)	**> 11years at onset** (n=68)	**P value**
Age at presentation Median yrs (IQR)	10.1 (8.723-11.23)	14.23(13.42-15.0)	<0.001
Sex (M : F)	1 : 1.17	1 : 3.53	0.040
Ethnicity (white : other)	1 : 1.17	1 : 1.94	1.0
CIS phenotype at onset			
Optic Neuritis	3 (11.5%)	20 (29.4%)	0.5581
Transverse Myelitis	0 (0%)	3 (4.4%)	0.5625
Involvement of brainstem or cerebellum; cerebral hemisphere	23 (88.5%)	45 (66.2%)	0.039
Time to second clinical event (CDMS) Median months (IQR)	6 (4-15)	5 (3-12)	0.3554
Positive intrathecal oligoclonal bands	23/25 (92%)	58/61 (95.1%)	1.0
Abnormal brain MRI at onset	25 (96.2%)	68 (100%)	0.2276
2017 DIS on first scan	23 (88.4%)	63 (92.6%)	0.6804
2017 DIT on first scan if contrast given	12/17 (70.6%)	32/42 (76.2%)	0.7446
2010 McDonald criteria at onset	12 (46.2%)	32 (47.1%)	1.0
2017 McDonald criteria at onset	22 (84.6%)	57 (83.8%)	1.0
MRI lesion location at onset			
Periventricular	23 (88.5%)	65 (95.6%)	0.342
Infratentorial	22 (84.6%)	48 (70.6%)	0.1915
Spinal cord	11/25 (44%)	39/60 (65%)	0.2491
Cortical/Juxtacortical	16 (61.5%)	53 (77.9%)	0.1233
New MRI lesions over time	26 (100%)	68 (100%)	1.0
Lesion location over time			
Periventricular	26 (100%)	68 (100%)	1.0
Infratentorial	26(100%)	66 (97.1%)	1.0
Spinal cord	19 (73.1%)	53 (76.8%)	1.0
Cortical/Juxtacortical	25 (96.2%)	63(92.6%)	1.0

DIS= dissemination in space; DIT= dissemination in time. N.S.= non-significant (>0.05).

Table 3: The performance of the 2010 and 2017 McDonald criteria for the development of CDMS and MS on the basis of MRI DIS and DIT

	2010 McDonald criteria	2017 McDonald criteria
Accuracy	66.7%	87.2%
Specificity	96.8% (95% CI 88.8% to 99.6%)	91.9% (95% CI 75.1% to 90.8%)
Sensitivity	46.8% (95% CI 36.4% to 57.4%)	84.0% (95% CI 82.2% to 97.3%)
Positive predictive value	0.96 (95% CI 0.85-0.99)	0.94 (95% CI 0.87-0.98)
Negative predictive value	0.54 (95% CI 0.44 to 0.64)	0.79 (95% CI 0.68 to 0.88)
Likelihood ratio	14.51	10.42

95% CI= Confidence intervals.

Figure 1: Participant characteristics

274 children with a diagnosis of acquired demyelinated syndrome, studied within 3 months from symptom onset with a baseline MRI and clinical assessment, and with either a follow-up of ≥2 years or/and ≥2 recorded clinical attacks were studied. Of all ADS, 73 (26.6%) presented with acute disseminating encephalomyelitis (ADEM), 76 (27.7%) with optic neuritis (ON), 48 (17.5%) with transverse myelitis (TM) and 77 (28.1%) with non-TM, non-ON clinically isolated syndrome (CIS-other). We excluded children who presented with ADEM (N=73) and children who were MOG (N=79) or AQP4 (N=14) antibody positive (48 patients with ADEM were also MOG antibody positive). The remaining 156 patients were included into this study. At final follow-up, 34.3% were diagnosed with MS.

Figure 2: Time to first relapse in patients with multiple sclerosis

Kaplan-Meier survival curve showing time to first relapse in children with multiple sclerosis. Stratified to children under and over 12years at presentation of CIS.

References

1. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162-173.
2. Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. Lancet Neurol 2012;11:157-169.
3. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. Lancet Neurol2014: 936-948.
4. Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology 2017;89:269-278.
5. 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.
6. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 2013;19:1261-1267.
7. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 2016;15:292-303.
8. Sadaka Y, Verhey LH, Shroff MM, et al. 2010 McDonald criteria for diagnosing pediatric multiple sclerosis. Ann Neurol 2012;72:211-223.
9. Fadda G, Brown RA, Longoni G, et al. MRI and laboratory features and the performance of international criteria in the diagnosis of multiple sclerosis in children and adolescents: a prospective cohort study. Lancet Child Adolesc 2018;2:191-203.
10. Waters P, Woodhall M, O'Connor KC, et al. MOG cell-based assay detects non-MS patients with inflammatory neurologic disease. Neurol Neuroimmunol Neuroinflamm 2015;2:e89.
11. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227-231.
12. Dalton CM, Brex PA, Miszkiel KA, et al. Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. Ann Neurol 2002;52:47-53.
13. van der Vuurst de Vries RM, Mescheriakova JY, Wong YYM, et al. Application of the 2017 Revised McDonald Criteria for Multiple Sclerosis to Patients With a Typical Clinically Isolated Syndrome. JAMA Neurol 2018;75:1392-1398.
14. Dobson R, Ramagopalan S, Davis A, Giovannoni G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. J Neurol Neurosurg Psychiatry 2013;84:909-914.
15. Tintore M, Rovira A, Rio J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 2015;138:1863-1874.
16. Cobo-Calvo A, Ruiz A, Maillart E, et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: The MOGADOR study. Neurology 2018;90:e1858-e1869.
17. Hacohen Y, Wong YY, Lechner C, et al. Disease Course and Treatment Responses in Children With Relapsing Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease. JAMA Neurol 2018;75:478-487.
18. Verhey LH, Branson HM, Shroff MM, et al. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: a prospective national cohort study. Lancet Neurol 2011;10:1065-1073.

19. Hummel HM, Bruck W, Dreha-Kulaczewski S, Gartner J, Wuerfel J. Pediatric onset multiple sclerosis: McDonald criteria 2010 and the contribution of spinal cord MRI. Mult Scler 2013;19:1330-1335.
20. Banwell B, Bar-Or A, Arnold DL, et al. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: a prospective national cohort study. Lancet Neurol 2011;10:436-445.
21. Brownlee WJ, Miller DH. Clinically isolated syndromes and the relationship to multiple sclerosis. J Clin Neurosci 2014;21:2065-2071.

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