


Oligoclonal bands increase the specificity of MRI criteria to predict multiple sclerosis in children with radiologically isolated syndrome

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Multiple Sclerosis Journal—
Experimental, Translational
and Clinical

January–March 2019, 1–9

DOI: 10.1177/
2055217319836664

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Abstract

Background: Steps towards the development of diagnostic criteria are needed for children with the radiologically isolated syndrome to identify children at risk of clinical demyelination.

Objectives: To evaluate the 2005 and 2016 MAGNIMS magnetic resonance imaging criteria for dissemination in space for multiple sclerosis, both alone and with oligoclonal bands in cerebrospinal fluid added, as predictors of a first clinical event consistent with central nervous system demyelination in children with radiologically isolated syndrome.

Methods: We analysed an international historical cohort of 61 children with radiologically isolated syndrome (≤ 18 years), defined using the 2010 magnetic resonance imaging dissemination in space criteria (Ped-RIS) who were followed longitudinally (mean 4.2 ± 4.7 years). All index scans also met the 2017 magnetic resonance imaging dissemination in space criteria.

Results: Diagnostic indices (95% confidence intervals) for the 2005 dissemination in space criteria, with and without oligoclonal bands, were: sensitivity 66.7% (38.4–88.2%) versus 72.7% (49.8–89.3%); specificity 83.3% (58.6–96.4%) versus 53.9% (37.2–69.9%). For the 2016 MAGNIMS dissemination in space criteria diagnostic indices were: sensitivity 76.5% (50.1–93.2%) versus 100% (84.6–100%); specificity 72.7% (49.8–89.3%) versus 25.6% (13.0–42.1%).

Conclusions: Oligoclonal bands increased the specificity of magnetic resonance imaging criteria in children with Ped-RIS. Clinicians should consider testing cerebrospinal fluid to improve diagnostic certainty. There is rationale to include cerebrospinal fluid analysis for biomarkers including oligoclonal bands in planned prospective studies to develop optimal diagnostic criteria for radiologically isolated syndrome in children.

Keywords: Radiologically isolated syndrome, multiple sclerosis, children

Date received: 1 September 2018; accepted: 15 January 2019

Introduction

Abnormalities suggestive of multiple sclerosis (MS) are being detected with increasing frequency as unexpected or incidental findings in individuals without symptoms of MS who undergo magnetic

resonance imaging (MRI) scans for other reasons (e.g. head trauma). This clinical scenario, termed the radiologically isolated syndrome (RIS), has been reported in adults and recently in children.^{1–6} Criteria for RIS in adults were proposed in 2009 and

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include the incidental detection of MRI abnormalities that meet MRI criteria for dissemination in space as outlined in the 2005 McDonald diagnostic criteria for MS.⁷ In one study, approximately 34% of adults who met this definition developed a first clinical event consistent with MS within 5 years.² There is uncertainty as to whether the criteria for RIS in adults should also be used for children.

We reported preliminary outcomes of the first longitudinal cohort study of children with RIS defined using the 2010 McDonald criteria for dissemination in space on MRI. All children also met the 2017 dissemination in space criteria on MRI at baseline (Ped-RIS). A first clinical event consistent with central nervous system demyelination (hereafter referred to as a first clinical event) occurred in 42% of children (16/38) in a median of 2.0 years.³

We do not know which of the MRI criteria for dissemination in space, developed for a clinical diagnosis of MS, should be used to define RIS in children or whether different criteria that might also include laboratory tests such as oligoclonal bands in cerebrospinal fluid (CSF) are needed. The ideal diagnostic criteria for RIS would be sufficiently sensitive to capture almost all children who later develop a first clinical event while being sufficiently specific to minimise the misclassification of children who are actually at low risk (i.e. a 'false positive' result). Such criteria are critical to minimise misdiagnosis, but still identify high-risk children who might benefit from interventions.

In the time since RIS was defined in adults, other MRI criteria for dissemination in space have either been adopted or proposed for the clinical diagnosis of MS in symptomatic individuals. The 2010 and 2017 McDonald criteria have the least stringent MRI criteria for dissemination in space and require as few as two lesions if they are either located in typical locations for MS in the brain (i.e. periventricular, juxtacortical/cortical or infratentorial) or are in the spinal cord.^{8,9} In 2016, the Magnetic Resonance Imaging in MS (MAGNIMS) group proposed criteria for dissemination in space on MRI.¹⁰ The major differences between the MAGNIMS criteria and the 2010/2017 McDonald criteria include the requirement that three or more periventricular lesions, rather than one, be present and that lesions detected in the optic nerve be counted. Both the MAGNIMS and the 2017 McDonald criteria group cortical lesions and juxtacortical lesions, with the acknowledgement that the assessment of cortical

lesions may require specialised MRI sequences such as double inversion recovery.

The 2017 McDonald criteria for MS allow the presence of unique oligoclonal bands in CSF to substitute for either clinical or radiological dissemination in time (but not space) in individuals with clinically isolated syndrome.⁹ This change was based on studies in adults with clinically isolated syndrome.^{11–16} We reported that oligoclonal bands in CSF were associated with the subsequent development of a first clinical event in children with Ped-RIS.³

The objective of this study, conducted in our cohort of children with Ped-RIS, was to evaluate the diagnostic performance of the 2005 and the MAGNIMS 2016 criteria for dissemination in space, both with and without the addition of oligoclonal bands in CSF, and their associations with the subsequent development of a first clinical event.^{7,8,10}

Methods

Participants and definitions

We identified a historical cohort of 61 children aged 18 years or less without any symptoms suggestive of MS who had abnormalities on MRI found incidentally that met the 2010 and 2017 MRI criteria for dissemination in space for MS. Children were identified between 1 December 1995 and 5 December 2017 at 22 collaborating MS centres (Supplemental Table 1). A detailed clinical history and neurological examination was performed for all children. Tests to exclude other infectious, inflammatory, rheumatological or metabolic diseases were performed based on local practice. Oligoclonal bands were tested at the discretion of the treating physician prior to a first clinical event, if one occurred, using standard isoelectric focusing methods and were defined as present if there were two or more bands present in the CSF, but not corresponding serum.

First clinical events were diagnosed using International Pediatric MS Study Group consensus definitions.¹⁷ Institutional ethical approvals were obtained at all sites. Written informed consent was obtained from parents/guardians and children provided assent.

Neuroimaging

All children underwent MRI scans on either 1.5 T or 3 T MRI scanners. All brain/spinal cord MRI studies included T1 and T2-weighted spin echo sequences in

multiple planes of view (axial and sagittal, with coronal images for brain studies), with and/or without gadolinium.

MRI abnormalities were first identified by a board-certified neuro-radiologist and then confirmed by one or more MS specialist at each site who evaluated the number of MRI lesions, the presence of MRI lesions in specific locations (e.g. periventricular, juxtacortical, infratentorial or spinal cord lesions), and the presence of gadolinium-enhancing lesions using standardised definitions.¹⁸ As sequences highly sensitive to cortical lesions were not obtained, such lesions could not be evaluated. In cases of disagreement or uncertainty, two experienced MRI raters (NM and DP), blinded to all clinical data, made the final adjudication by consensus. We used two methods to classify whether MRI scans met the 2005 and/or the MAGNIMS 2016 dissemination in space criteria: (a) an experienced paediatric neurologist (NM) classified all scans and (b) a software program that took individual subcriteria as inputs and produced an output of whether patients met each set of criteria. Both classification methods were in 100% agreement.

Statistical analysis

We report means (\pm standard deviations), and/or medians with interquartile ranges (IQRs) for continuous variables and frequencies (percentages) for categorical variables. We used Mann–Whitney U tests (continuous variables) and Fisher’s exact tests (categorical variables) to determine the statistical significance of differences in baseline covariates (e.g. age, sex or follow-up time) between children who either did or did not develop a first clinical event.

The following statistical analyses were conducted both using the complete case analysis of all observed cases and, to handle missing data, using 30 multiply imputed datasets by the fully conditional specification method (aka chained equations).^{19–21} We used standard methods to calculate predictive ability (with 95% CIs) as measured by sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy as well as the overall discriminant ability of individual and combinations of predictors using receiver operator characteristic (ROC) curves and area under the ROC curves (AUC). As all index MRI scans met 2010 and 2017 dissemination in space criteria (i.e. there were no true or false negative results), only PPV was determined for these MRI criteria. In order to assess the effect of follow-up time, we graphically

inspected time-dependent AUCs estimated using inverse probability of censoring weighting.^{22,23} ROC curves based on models containing either the 2005 or the MAGNIMS 2016 criteria as individual predictors were compared to the ROCs from models with the addition of oligoclonal bands in CSF using the non-parametric test of DeLong *et al.*²⁴ To adjust for the variable follow-up times in our cohort, we used standard time-to-event survival analysis methods. We used unadjusted Cox proportional hazards models to determine the associations between individual components of the MRI dissemination in space criteria (e.g. the presence of spinal cord lesions) and the time to a first clinical event. Multivariable models included predictors that were statistically significant in unadjusted analyses, as well as age (continuous in years), sex and any exposure to disease-modifying agents for MS, which we felt were clinically relevant variables. The proportional hazards assumption was assessed using graphical methods. We report hazard ratios (HRs) with 95% CIs. We considered two-sided *P* values less than 0.05 as statistically significant. We used SAS v. 9.4 (Cary, NC, USA) for all analyses.

Results

We screened 62 children, of whom one was excluded due to baseline MRI not being available to review (neuro-radiologist report only). We therefore included 61 children with Ped-RIS (Tables 1 and 2). As expected, children who developed a first clinical event had a longer time from index MRI to the most recent clinic visit than those who did not (mean 6.8 ± 5.6 vs. 2.8 ± 3.3 years, $P=0.001$) but were otherwise similar. The most common reason for obtaining initial neuroimaging was headache (50.8%). Eight children were treated with a disease-modifying agent for MS (five with interferon beta-1a and three with glatiramer acetate) to try to prevent a first clinical event. Two of the eight treated children (25%) had spinal lesions detected on MRI as compared to five out of 40 (12.5%) untreated children who had spinal imaging (no significant difference, $P=0.33$). Five of the eight treated children had spinal fluid tested and four out of five (80%) had oligoclonal bands detected in the CSF as compared to 15/29 (52%) of treated children in whom CSF was analysed (no significant difference, $P=0.43$).

The number of children with Ped-RIS whose index MRI scans also fulfilled the 2005 and 2016 MAGNIMS MRI criteria for dissemination in space were 34 (55.7%) and 51 (83.6%),

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Table 1. Characteristics of children in the study.

	Overall N = 61	Children without a clinical neurological event N = 39	Children with a clinical neurological event* N = 22	P value
Age at first scan with RIS (years)				
Mean (SD)	14.7 (2.4)	14.4 (2.3)	15.1 (2.5)	
Median (IQR)	15.0 (13.1–16.4)	14.9 (13.1–16.3)	15.6 (13.1–17.1)	0.21 [†]
Gender				
Girls (%)	42 (68.9%)	24 (61.5%)	18 (81.8%)	
Boys (%)	19 (31.2%)	15 (38.5%)	4 (18.2%)	0.10 [‡]
Follow-up time (years)				
Mean (SD)	4.2 (4.7)	2.8 (3.3)	6.8 (5.6)	
Median (IQR)	2.4 (1.2–5.3)	1.6 (1.0–3.2)	5.1 (1.9–10.8)	0.001 [†]
*Characteristics of a first clinical event included monofocal brainstem deficits (5), optic neuritis (4), transverse myelitis (4), other monofocal deficits (6) and polyfocal deficits without encephalopathy (3). No child developed acute disseminated encephalomyelitis.				
[†] Wilcoxon sum rank test.				
[‡] Fisher's exact test.				
RIS: radiologically isolated syndrome.				

Table 2. Characteristics of children with cerebrospinal fluid tested.

	Overall N = 34	Children without oligoclonal bands N = 15	Children with oligoclonal bands N = 19	P value
Age at first scan with RIS (years)				
Mean (SD)	14.7 (2.4)	14.9 (1.9)	14.6 (2.8)	
Median (IQR)	15.0 (13.1–16.6)	15.0 (13.8–16.4)	15.0 (12.9–17.3)	1.00*
Gender				
Girls (%)	27 (79.4%)	11 (73.3%)	16 (84.2%)	
Boys (%)	7 (20.6%)	4 (26.7%)	3 (15.8%)	0.67 [†]
Follow-up time (years)				
Mean (SD)	5.3 (5.3)	4.2 (5.0)	6.2 (5.4)	
Median (IQR)	3.2 (1.7–7.0)	2.6 (0.9–5.3)	5.3 (1.9–7.6)	0.11*
Children who developed a first clinical event (%)	17 (50%)	4 (26.7%)	13 (68.4%)	0.04 [†]
*Wilcoxon sum rank test.				
[†] Fisher's exact test.				
RIS: radiologically isolated syndrome.				

respectively. Gadolinium was administered for brain MRIs in 39 children (63.9%) and spinal cord imaging was obtained in 48 children (78.7%). There was no association between age, sex, race and whether children had either spinal cord imaging obtained or gadolinium administered on index brain MRIs.

CSF was tested for oligoclonal bands in 34 children (55.7%, Tables 1 and 2) with a median of 25 days from the index MRI (IQR 2–453 days), and in all cases prior to a first clinical event if one occurred. CSF was more likely to be obtained in girls than boys (27/42 (64.3%) vs. 7/19 (36.8%), $P=0.05$). Among the 39 children for whom gadolinium was

administered for the index MRI, CSF appeared to be more commonly obtained in children with one or more enhancing lesion (6/21 (28.6%)) versus those without enhancing lesions (1/18, (5.6%)), but this result was not statistically significant ($P=0.11$). Children who either did or did not have CSF obtained did not differ in age or in the proportion of children with index MRIs that met the 2005 MRI criteria for dissemination in space (which requires the most lesions of all the MRI dissemination in space criteria).

A first clinical event occurred in 22 children (36.1%) with a median of 1.7 (range 0.1–17.1) years from index MRI (Tables 1 and 2). Table 3 shows the diagnostic indices of the different MRI criteria for dissemination in space using the complete case analysis of observed cases, both with and without oligoclonal bands in CSF added, for the subsequent development of a first clinical event. The MAGNIMS 2016 criteria for dissemination in space differed from the 2005 criteria in sensitivity (100% (95% CI 84.6–100%) vs. 72.7% (95% CI 49.8–89.3%)), specificity (25.6% (95% CI 13.0–42.1%) vs. 53.9% (95% CI 37.2–69.9%)) and NPV (100% (95% CI 69.2–100% vs. 77.8% (95% CI 57.7–91.3%)). PPV and accuracy were similar (Table 3). The PPV of the 2010 and 2017 MRI criteria for dissemination in space was 36.1% (95% CI 24.0–48.1%), which is the same as the overall proportion of children in the cohort that developed a first clinical event. With the addition of oligoclonal bands in CSF, the specificity of the 2016 MAGNIMS criteria increased to 72.7% (95% CI 49.8–89.3%) and the specificity of the 2005 criteria increased to 83.3% (95% CI 58.6–96.4%). The presence of oligoclonal bands alone had a sensitivity of 76.5% (95% CI 50.1–93.2%) and a specificity of 64.7% (95% CI 38.3–85.8%). The overall ability of the MAGNIMS 2016 criteria to discriminate between children who either did or did not develop a first clinical event, as measured by the AUC, also significantly increased with the addition of oligoclonal bands ($P=0.03$) with a similar statistical trend for the 2005 criteria ($P=0.16$). All results were similar when we removed the eight children who had been exposed to a disease-modifying agent for MS. The results from multiple imputation showed similar findings (Supplemental Table 3).

Children with oligoclonal bands in CSF were more likely to develop a first clinical event (Tables 1 and 2). In a multivariable model that also included age, sex and exposure to a disease-modifying agent,

the presence of oligoclonal bands in the CSF remained a statistically significant predictor (complete case analysis: adjusted HR 4.1, 95% CI 1.1–14.4, $P=0.03$; multiple imputation: adjusted HR 3.0, 95% CI 1.1–8.5, $P=0.04$).

The presence of one or more spinal cord lesions on the index MRI was the only individual component of the different MRI criteria for dissemination in space (Table 3) that was independently associated with an increased risk of a first clinical event after adjusting for age, sex and prior exposure to a disease-modifying agent (complete case analysis: adjusted HR 7.5, 95% CI 2.2–26.1, $P=0.002$; multiple imputation: adjusted HR 4.7, 95% CI 1.4–15.8, $P=0.012$). We could not calculate hazard ratios for one or more periventricular lesions (only three or more), because all 61 children in the cohort (100%) had at least one periventricular lesion. No child had a lesion detected in the optic nerve, but dedicated optic nerve sequences were not routinely obtained.

Discussion

The main findings of our study were that when used alone in children with Ped-RIS, the 2016 MAGNIMS MRI criteria for dissemination in space had greater sensitivity and NPV, but substantially lower specificity than the 2005 MRI criteria for dissemination in space, criteria that have been used to define RIS in adults.¹ When oligoclonal bands in the CSF were added to the 2005 and 2016 MAGNIMS MRI criteria for dissemination in space, the specificity of both increased.

The high sensitivity and NPV of the 2016 MAGNIMS MRI criteria for dissemination in space may make them useful to identify children with Ped-RIS at low risk of subsequently developing a first clinical event (i.e. children who do not also meet the 2016 MAGNIMS criteria may be at very low risk of developing a first clinical event). A high sensitivity also suggests that nearly all children who will subsequently develop a first clinical event could be identified with these criteria. However, the specificity of the 2016 MAGNIMS criteria was low, which translates into a high number of false positive results.

The greatest specificity was observed for the 2005 MRI criteria for dissemination space, with the addition of oligoclonal bands. High specificity reflects a low false positive rate (that is a low rate of falsely predicting that children will subsequently develop a first clinical event). We believe that for RIS,

Table 3. Diagnostic Indices of different MRI dissemination in space criteria applied to children with RIS.

	Ped-RIS plus OCBs At least one T2 lesion in two of the following areas: <ul style="list-style-type: none">• Periventricular• Juxtacortical• Infratentorial• Spinal cord	2005 McDonald At least three of the following: <ul style="list-style-type: none">• ≥9 T2 or ≥1 gadolinium-enhancing lesions• ≥1 Juxtacortical lesion• ≥1 Infratentorial lesion[†]• ≥3 periventricular lesions	2016 MAGNIMS At least two of the following: <ul style="list-style-type: none">• ≥3 Periventricular lesions• ≥1 Infratentorial lesion• ≥1 Spinal cord lesion• ≥1 Optic nerve lesion• ≥1 Cortical or juxtacortical lesion	2005 McDonald plus OCBs	2016 MAGNIMS plus OCBs
Diagnostic indices*					
Number of children analysed (N)	N = 34	N = 61	N = 61	N = 34	N = 34
Sensitivity	76.5% (50.1–93.2%)	72.7% (49.8–89.3%)	66.7% (38.4–88.2%)	100% (84.6–100%)	76.5% (50.1–93.2%)
Specificity	64.7% (38.3–85.8%)	53.9% (37.2–69.9%)	83.3% (58.6–96.4%)	25.6% (13.0–42.1%)	72.7% (49.8–89.3%)
Positive predictive value	68.4% (43.5–87.4%)	47.1% (29.8–64.9%)	76.9% (46.2–95.0%)	43.1% (29.4–57.8%)	72.2% (46.5–90.3%)
Negative predictive value	73.3% (44.9–92.2%)	77.8% (57.7–91.3%)	75.0% (50.9–91.3%)	100% (69.2–100%)	86.7% (59.5–98.3%)
Accuracy	70.6% (52.5–84.9%)	60.7% (47.3–72.9%)	75.5% (57.7–88.9%)	52.5% (39.3–65.4%)	78.8% (61.1–91.0%)
Area under the curve	0.71 (0.55–0.86)	0.63 (0.51–0.76)	0.76 (0.61–0.92)	0.63 (0.56–0.70)	0.76 (0.62–0.91)

*Diagnostic indices are reported with (95% confidence interval).

[†]A spinal cord lesion can be considered equivalent to an infratentorial lesion in the brain.

MRI: magnetic resonance imaging; RIS: radiologically isolated syndrome; MAGNIMS: magnetic resonance imaging in MS; OCB: oligoclonal band.

especially in children, highly specific criteria are desirable to minimise misdiagnosis, parental anxiety, unnecessary testing and interventions that may have side effects in children who actually are at low risk. This is in contrast to symptomatic children with the clinically isolated syndrome in whom highly sensitive criteria may perhaps be preferable, so that a diagnosis of MS may be made early to allow for prompt treatment.

That the addition of oligoclonal bands improved the specificity of MRI criteria for dissemination in space in children with RIS has biological rationale. Oligoclonal bands present in the CSF, but not serum, reflect intrathecal antibody synthesis and are often detected in children with established MS.^{25,26} Even with the addition of oligoclonal bands, the ability of the 2005 and 2016 MAGNIMS criteria to discriminate between children who either did or did not subsequently develop a first clinical event (as measured by the AUC) remained modest, suggesting that additional biomarkers may be needed.

Both the presence of oligoclonal bands in the CSF and the presence of one or more asymptomatic spinal cord lesions on MRI were independently associated with an increased risk of a first clinical event, findings that we reported previously in a subset of this cohort.³ These results are similar to findings in adults with RIS.^{2,27,28}

Our study has some limitations. First, we analysed data from a historical cohort of children with RIS for whom clinical MRI protocols were not standardised. All scans, however, employed standard sequences for patients with MS. A prospective study using a standardised MRI protocol is planned. We recognise that there were variable follow-up times in our cohort and that some children who have not yet displayed symptoms of MS may do so in the future. In our statistical analyses, we used time-to-event survival analysis to account for this. Furthermore, we examined the time-varying discriminating ability of predictors across the follow-up time and did not observe significant time trends. Not all children had spinal cord imaging, optic nerve imaging or analysis of CSF (i.e. there was missing data). In order to overcome this limitation, we conducted statistical analyses both on the complete set of observed cases and, to handle missing data, also followed up with additional analyses based on multiple imputation, which yielded consistent results. Our study is of modest size. However, RIS in children is rarely

diagnosed, and this is the only international longitudinal study. While the analysis of additional CSF biomarkers (e.g. neurofilament light chain) were beyond the scope of this study, such markers could be evaluated in the future.²⁸ Because of our study design, we could not calculate sensitivity and specificity for the 2010 or 2017 MRI criteria for dissemination in space. The assessment of these criteria will require evaluation in other cohorts.

In summary, oligoclonal bands in the CSF improved the specificity of both the 2005 and 2016 MAGNIMS MRI criteria for dissemination in space in children with RIS. Specificity was greatest for the 2005 criteria, used to define RIS in adults, plus oligoclonal bands. We therefore propose that when CSF is obtained in children with RIS, that oligoclonal bands be tested to increase diagnostic certainty. International collaborative prospective studies are planned to develop evidence-based diagnostic criteria for RIS in children. Based on our findings, we suggest that CSF biomarkers including oligoclonal bands be evaluated. Improved diagnostic criteria for RIS in children will enhance the classification of risk for the subsequent development of a first clinical event. Accurately classifying the risk of a first clinical event would help prevent unnecessary interventions in children at low risk and identify children at high risk for whom interventions such as disease-modifying agents could be tested.

Ethical approvals and consents

Institutional ethical approvals were obtained at all sites. Written informed consent was obtained from parents/guardians and children provided assent.

Conflict of Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: N Makhani received research support from Race to Erase MS Foundation and NIH; C Lebrun served on the scientific advisory board for Biogen, Novartis, Merck, Genzyme, Teva, Roche, received travel funding and/or speaker honoraria from Biogen, Merck, Genzyme, Roche, served as an editorial advisory board member for *Revue Neurologique* (Paris) Elsevier, *Neurology and Therapy*, received research support from French MS Society (SFSEP) EDMUS (OFSEP Center) Foundation; A Siva received travel funding from Merck Serono, Biogen Idec/Gen Pharma of Turkey, Novartis, Genzyme, Roche, Teva, served on the editorial board for the *Journal of Neurological Sciences*, *Journal of Headache and Pain*, *Turkish Neurological Journal*, consulted for Biogen Idec, Novartis, Merck-Serono, Bayer, Teva, Genzyme, Roche, served on the speakers' bureau


for Excemed, Genzyme, Merck Serono, Biogen Idec/Gen Pharma of Turkey and Teva, received research support from the Scientific and Technological Research Council of Turkey; D Brassat served on the scientific advisory board for Chugai Pharma, received travel funding and/or speaker honoraria from Biogen, Bayer, Novartis, Sanofi, Almirall, Merck, Teva, received research support from FP7, PHRC; C Carra-Dalliere received travel funding from Genzyme, Biogen, Novartis; J de Seze served on the editorial board for *Revue Neurologique*; F Durand-Dubief served on the scientific advisory board for Merck-Serono, Roche, received travel funding and/or speaker honoraria from Biogen, Merck-Serono, Sanofi-Aventis, Genzyme, Novartis Pharma, Roche, Teva; OH Kantarci received speaker honoraria from Novartis Pharmaceuticals, Biogen, did a grant review for the National Multiple Sclerosis Society, received research support from European Regional Development Fund, National Multiple Sclerosis Society, Biogen, Multiple Sclerosis Society, Mayo Foundation and Hilton Foundation, Mayo Clinic, received compensation for consulting activities from Teva; His spouse serves on the data safety monitoring board of Takeda Global Research and Development Center, Inc. and the data monitoring boards of Pfizer Inc. and Janssen Alzheimer Immunotherapy and is funded by the NIH, Minnesota Partnership for Biotechnology and Medical Genomics; M Inglese has received research grants from NIH, NMSS, Novartis Pharmaceuticals Corp. and she is a consultant for Vaccinex; J Pelletier served on the scientific advisory board for Biogen, Novartis, Genzyme, received research support from Arsep, Novartis; RF Neuteboom participated in trials with Novartis and Sanofi, advisory board member for Novartis and Zogenix; JI Rojas served on the speakers' bureau for Novartis Argentina, Genzyme Argentina, Merck Serono Argentina; ED Shapiro received speaker honoraria from Eastern Maine Medical Center, received research support from NIH/NIAID/NDDK; RT Stone received research support from Novartis Pharmaceuticals; M Tintore served on the scientific advisory board from Biogen, Novartis, Genzyme, Roche, received travel funding and/or speaker honoraria from Bayer, Teva, Biogen-Idec, Merck-Serono, Novartis, Sanofi-Aventis, Genzyme, Roche, Almirall, served on the editorial board for the *Multiple Sclerosis Journal*, *Neurologia*, *Revista de Neurologia*, is editor of *MSJ-ETC*, served on the speakers' bureau from Almirall, Bayer, Teva, Biogen-Idec, Merck-Serono, Novartis, Sanofi-Aventis, Genzyme, Roche, received research support from Bayer, Teva, Biogen-Idec, Merck-Serono, Novartis, Sanofi-Aventis, Genzyme, Roche, Almirall, Spanish Agency for Sanitary Investigations, REEM, Angencia de Gestio d'ajuts Universitaris I de Recerca of the Generalitat de Catalunya in Spain; U Uygunoglu received travel funding from Merck Serono, Biogen Idec, Novartis, served as an associate editor for *Turkish Neurology Journal*, received research support from Turkish Neurological Society; W Vargas received grant support from the NMSS, Biogen Idec, and Teva. She served as a consultant for Alexion

Pharmaceuticals; P Vermersch served on the scientific advisory board for Sanofi, Biogen, Merck, Teva, Novartis, Roche, Servier, received travel funding and/or speaker honoraria from Biogen, Roche, Novartis, Teva, Sanofi-Aventis, Almirall, Merck Serono, Neurosciences et sclerose en plaques, received research support from Biogen, Bayer, Novartis, Merck, Teva, Sanofi-Genzyme, Roche, received travel funding and/or speaker honoraria from BiogenIdec, Teva, Genzyme, Shire, UCB, Merck Serono, received research support from Biogen Idec, Sanofi, Novartis UK MS Society, Action Medical Research, Birmingham Children's Hospital Research Foundation; DT Okuda received travel funding and/or speaker honoraria from Acorda Therapeutics, Genentech, Genzyme, Teva, consulted for Bayer, EMD Serono, Genzyme, Novartis, served on the speakers' bureau for Acorda Therapeutics, Genzyme, Teva Neuroscience, received research support from Biogen; D Pelletier consulted for Biogen, EMD Serono, Sanofi-Genzyme, Novartis, Hoffmann LaRoche, Vertex, and received research support from Biogen and the National Multiple Sclerosis Society.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: N Makhani was supported by a Junior Investigator Award from Race to Erase MS. This publication was made possible, in part, by CTSA grant number UL1 TR000142 from the National Center for Advancing Translational Science (NCATS) and grant number K23NS101099 from the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) and NIH roadmap for Medical Research, as well as the Intramural Research Program of NINDS. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Supplemental material

Supplemental material for this article is available online.

References

1. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology* 2009; 72: 800–805.

2. Okuda DT, Siva A, Kantarci O, et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. *PLoS one* 2014; 9: e90509.
3. Makhani N, Lebrun C, Siva A, et al. Radiologically isolated syndrome in children: clinical and radiologic outcomes. *Neurology(R) Neuroimmunology & Neuroinflammation* 2017; 4: e395.
4. George IC, DeStefano K and Makhani N. Radiologically isolated syndrome in a pediatric patient. *Pediatr Neurol* 2016; 56: 86–87.
5. Lebrun C, Bensa C, Debouverie M, et al. Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile. *J Neurol Neurosurg Psychiatry* 2008; 79: 195–198.
6. Siva A, Saip S, Altintas A, et al. Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. *Mult Scler* 2009; 15: 918–927.
7. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria”. *Ann Neurol* 2005; 58: 840–846.
8. 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.
9. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2017; 17: 162–173.
10. 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.
11. Tintore M, Rovira A, Brieva L, et al. Isolated demyelinating syndromes: comparison of CSF oligoclonal bands and different MR imaging criteria to predict conversion to CDMS. *Mult Scler* 2001; 7: 359–363.
12. Tintore M, Rovira A, Rio J, et al. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? *Neurology* 2008; 70: 1079–1083.
13. Huss AM, Halbgebauer S, Ockl P, et al. Importance of cerebrospinal fluid analysis in the era of McDonald 2010 criteria: a German–Austrian retrospective multicenter study in patients with a clinically isolated syndrome. *J Neurol* 2016; 263: 2499–2504.
14. Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: a large multicentre study. *Mult Scler* 2015; 21: 1013–1024.
15. Martinelli V, Dalla Costa G, Messina MJ, et al. Multiple biomarkers improve the prediction of multiple sclerosis in clinically isolated syndromes. *Acta Neurol Scand* 2017; 136: 454–461.
16. Arrambide G, Tintore M, Espejo C, et al. The value of oligoclonal bands in the multiple sclerosis diagnostic criteria. *Brain* 2018; 141: 1075–1084.
17. Hintzen RQ, Dale RC, Neuteboom RF, et al. Pediatric acquired CNS demyelinating syndromes: features associated with multiple sclerosis. *Neurology* 2016; 87 (9 Suppl 2): S67–S73.
18. Callen DJ, Shroff MM, Branson HM, et al. MRI in the diagnosis of pediatric multiple sclerosis. *Neurology* 2009; 72: 961–967.
19. Carlin JB, Galati JC and Royston P. A new framework for managing and analyzing multiply imputed data in Stata. *Stata J* 2008; 8: 49–67.
20. Raghunathan TE, Lepkowski J, Van Hoewyk J, et al. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Survey Methodol* 2001; 27: 85–95.
21. Van Buuren SaO and Groothuis-Oudshoorn CGM. Flexible multivariate imputation by MICE. *TNO Preventie en Gezondheid* 1999; 99: 54.
22. Guo C, So Y and Jang W. Evaluating predictive accuracy of survival models with PROC PHREG. *SAS Institute Inc Paper*, 2017; SAS462.
23. Uno H, Cai T, Tian L and Wei LJ. Evaluating prediction rules for t-year survivors with censored regression models. *J Am Stat Assoc* 2007; 102: 527–537.
24. DeLong ER, DeLong DM and Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837–845.
25. Bizjak N, Osredkar D, Perkovic Benedik M, et al. Epidemiological and clinical characteristics of multiple sclerosis in paediatric population in Slovenia: a descriptive nation-wide study. *Mult Scler Related Disord* 2017; 18: 56–59.
26. Belman AL, Krupp LB, Olsen CS, et al. Characteristics of children and adolescents with multiple sclerosis. *Pediatrics* 2016; 138(1): :e20160120.
27. Okuda DT, Mowry EM, Cree BA, et al. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. *Neurology* 2011; 76: 686–692.
28. Matute-Blanch C, Villar LM, Alvarez-Cermeno JC, et al. Neurofilament light chain and oligoclonal bands are prognostic biomarkers in radiologically isolated syndrome. *Brain* 2018; 141: 1085–1093.