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

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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

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 2005 and...
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. In one study, approximately 34% of adults who met this definition developed a first clinical event consistent with MS within 5 years. 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. All children also met the 2017 dissemination in space criteria on MRI at baseline. 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. We reported that oligoclonal bands in CSF were associated with the subsequent development of a first clinical event in children with Ped-RIS.

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.

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. 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...
MR images. 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 standardized 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 (±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%), respectively.
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.

**Table 1.** Characteristics of children in the study.

|                     | Overall     | Children without a clinical neurological event | Children with a clinical neurological event* |
|---------------------|-------------|----------------------------------------------|----------------------------------------------|
|                     | N = 61      | N = 39                                       | 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)                                  | 0.21*            |
| Median (IQR)        | 15.0 (13.1–16.4) | 14.9 (13.1–16.3) | 15.6 (13.1–17.1) |                 |
| Gender              |             |                                              |                                              |                 |
| Girls (%)           | 42 (68.9\%) | 24 (61.5\%)                                  | 18 (81.8\%)                                 |                 |
| Boys (%)            | 19 (31.2\%) | 15 (38.5\%)                                  | 4 (18.2\%)                                  |                 |
| 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     | Children without oligoclonal bands | Children with oligoclonal bands | P value          |
|---------------------|-------------|------------------------------------|---------------------------------|                 |
|                     | N = 34      | N = 15                             | N = 19                          |                 |
| Age at first scan with RIS (years) |             |                                    |                                 |                 |
| Mean (SD)           | 14.7 (2.4)  | 14.9 (1.9)                         | 14.6 (2.8)                      | 1.00*           |
| Median (IQR)        | 15.0 (13.1–16.6) | 15.0 (13.8–16.4) | 15.0 (12.9–17.3) |                 |
| 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 (%) |             |                                    |                                 | 0.04†           |

*Wilcoxon sum rank test.

†Fisher’s exact test.

RIS: radiologically isolated syndrome.

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. 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.

| Diagnostic indices* | Ped-RIS plus OCBs | 2005 McDonald At least three of the following: | 2016 MAGNIMS At least two of the following: |
|---------------------|-------------------|------------------------------------------------|---------------------------------------------|
|                     | At least one T2 lesion in two of the following areas: | • ≥9 T2 or ≥1 gadolinium-enhancing lesions | • ≥3 Periventricular lesions |
|                     | • Periventricular | • ≥1 Juxtacortical lesion | • ≥1 Infratentorial lesion |
|                     | • Juxtacortical | • ≥1 Infratentorial lesion† | • ≥1 Spinal cord lesion |
|                     | • Infratentorial | • ≥3 periventricular lesions | • ≥1 Optic nerve lesion |
|                     | • Spinal cord | | • ≥1 Cortical or juxtacortical lesion |

|                     | Number of children analysed (N) | 2005 McDonald plus OCBs | 2016 MAGNIMS plus OCBs |
|---------------------|---------------------------------|-------------------------|------------------------|
| Number of children analysed (N) | 34 | 61 | 34 | 61 | 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 | 70.7% (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. 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. These results are similar to findings in adults with RIS.

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. 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.

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Supplemental material
Supplemental material for this article is available online.

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