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The diagnostic workup of children with the radiologically isolated syndrome differs by age and by sex

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Abstract

Background—Cerebrospinal fluid (CSF) and spinal MRIs are often obtained in children with the radiologically isolated syndrome (RIS) for diagnosis and prognosis. Factors affecting the frequency and timing of these tests are unknown.

Objective—To determine whether age or sex were associated with (1) having CSF or spinal MRI obtained or (2) the timing of these tests.

Methods—We analyzed children (≤ 18 y) with RIS enrolled in an international longitudinal study. Index scans met 2010/2017 multiple sclerosis (MS) MRI criteria for dissemination in space (DIS). We used Fisher's exact test and multivariable logistic regression (covariates = age, sex, MRI date, MRI indication, 2005 MRI DIS criteria met, and race).

Results—We included 103 children with RIS (67% girls, median age = 14.9 y). Children ≥ 12 y were more likely than children < 12 y to have CSF obtained (58% vs. 21%, adjusted odds ratio [AOR] = 4.9, $p = 0.03$). Pre-2017, girls were more likely than boys to have CSF obtained ($n = 70$, 79% vs. 52%, AOR = 4.6, $p = 0.01$), but not more recently ($n = 30$, 75% vs. 80%, AOR = 0.2, $p = 0.1$; $p = 0.004$ for interaction). Spinal MRIs were obtained sooner in children ≥ 12 y (median 11d vs. 159d, $p = 0.03$).

Conclusions—Younger children with RIS may be at continued risk for misdiagnosis and misclassification of MS risk. Consensus guidelines are needed.

Keywords

Children; Multiple sclerosis; Radiologically isolated syndrome; Pediatric; MRI

Introduction

Multiple sclerosis (MS) in children is typically a chronic, relapsing–remitting condition diagnosed by a combination of clinical symptoms, magnetic resonance imaging (MRI), and laboratory features [1]. Compared with adults, children with multiple sclerosis have more frequent relapses in the first few years after diagnosis and reach similar levels of disability at a much younger age [2–4]. Immunomodulatory treatments for multiple sclerosis in children reduce relapse rates and delay disability highlighting the importance of early identification and intervention [5].

Children with radiologically isolated syndrome (RIS) are at increased risk for clinical MS [6]. These children had neuroimaging for reasons other than suspected MS (e.g., headaches), but nonetheless lesions typical for MS were detected incidentally [7]. Approximately 42% of children with RIS subsequently developed clinical multiple sclerosis in one study, highlighting the importance of identifying those children at greatest risk for subsequent MS [6].

The presence of asymptomatic lesions on MRIs of the spinal cord and oligoclonal bands unique to cerebrospinal fluid (CSF) and not present in serum have been associated with an increased risk of subsequent MS in children with RIS (hazard ratios of 7.8 and 10.9, respectively, in a prior international study), similar to findings in adults [6, 8–10]. MRI scans of the spinal cord and CSF are, therefore, often, but not always, obtained for diagnostic and prognostic purposes. Such investigations help exclude other diagnoses (minimizing the

chance of a misdiagnosis of RIS) and to identify those children with RIS at the highest risk of developing clinical multiple sclerosis. Children at highest risk may benefit from closer monitoring for the development of neurological symptoms conferring a diagnosis of MS so that treatments may be started early.

Studies in adults have reported differences based on demographic features in evaluating several autoimmune conditions, including rheumatoid arthritis and ankylosing spondylitis (AS) [11–13]. For instance, in patients with AS, a longer time to diagnosis was reported for females and younger individuals [12]. In adults with MS, one study reported that a longer time to diagnosis was associated with several factors, including age > 40 years [14]. In contrast, a Canadian study reported that younger patients, especially those aged 18–29 years, had particularly long delays in referrals to a specialist and in time to diagnosis [15]. No studies have examined whether age and sex affect the diagnostic workup of children at risk for MS.

In this study, we aimed to determine whether age and sex affected the frequency with which diagnostic tests were performed in children with RIS. Our secondary objective was to determine whether age and/or sex affected the timing of investigations when performed. Significant differences in the use and/or timing of these tests would offer an opportunity to address these health disparities by alerting clinicians to our findings and would support the need for standardizing care for these children and ultimately improve clinical outcomes.

Methods

Participants and definitions

We identified 103 children with RIS from within an ongoing longitudinal study. All children had abnormalities on magnetic resonance imaging (MRI) studies of the brain that met both the 2010 and 2017 MRI dissemination in space criteria for MS in the absence of any neurological symptoms suggestive of demyelinating disease [1, 16]. Children were identified between December 1, 1995, and May 1, 2021, from collaborating academic centers that are members of the international Pediatric and Adolescent RIS (PARIS) Consortium (Supplementary Table 1). A detailed clinical history was obtained, and a neurological examination was performed on all children by a licensed neurologist with a subspecialty neuroimmunology practice. Laboratory tests to exclude other infectious, inflammatory, and metabolic conditions were conducted based on local practice. The first clinical demyelinating event was defined using criteria developed by the International Pediatric Multiple Sclerosis Study Group [17].

Standard protocol approvals and patient consents

Institutional ethical approvals were obtained at all sites. All children provided assent, and adolescents/parents consented per local regulatory guidelines.

Neuroimaging

All children with RIS underwent MRI brain scans using clinical protocols on 1.5 or 3 T MRI scanners. Additional MR imaging of the spinal cord (cervical and/or thoracic) was obtained

at the discretion of the treating neurologist. 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 licensed neuro-radiologist and then confirmed by one or more MS specialists at each site who used standardized definitions to evaluate 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. In cases of disagreement or uncertainty, two experienced MRI raters (NM and DP), blinded to all clinical data, made the final adjudication by consensus. The study's principal investigator (NM) reviewed all MRI data collection forms to ensure that the 2010/2017 criteria for dissemination in space on MRI were met for all index scans.

CSF analyses

CSF was obtained for analysis at the discretion of the treating neurologist using standard local methods.

Statistical analyses

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 examine the unadjusted associations between the outcomes of either having either CSF or a spinal MRI obtained and demographic variables (e.g., age, sex, and race). CSF and spinal MRIs were considered as having been obtained as part of the initial workup if they were procured within one year of the index MRI scan on which the diagnosis of RIS was based and before any clinical or radiological progression. We then created unadjusted and adjusted logistic regression models for the outcomes of having either CSF or a spinal MRI obtained. Multivariable models included age (dichotomized as ≥ 12 or < 12 years), sex, indication for index MRI (dichotomized as headache vs. not headache), whether index MRIs met MS 2005 MRI criteria for dissemination in space (a surrogate marker for the number of lesions), date of procurement (dichotomized by epoch as < 2017 or ≥ 2017), and race. We considered gadolinium-enhancing lesions as an additional variable of interest. There were notable missing data for this variable (20.4%). Among children with available data there were comparable percentages of children with either spinal imaging (73.7% vs. 66.7%, $p = 0.56$) or CSF obtained (50.0% vs. 53.3%, $p = 0.80$) among those with gadolinium enhancement versus without in unadjusted analyses. For these reasons, this variable was not included in the adjusted model. We considered center as a cluster in our statistical models. The effect of clustering by center on our outcomes of interest was examined through the variance of a random intercept reflecting center. We did not include center in the final adjusted model due to its effect being negligible and not different from zero. We also examined whether the date of RIS detection had a moderating effect on the associations between being a girl or ≥ 12 years of age and the odds of having either CSF or a spinal MRI obtained, by including an interaction term between epoch and sex or epoch and age group, followed by adjusted logistic regressions stratified by epoch. Results were summarized using

unadjusted and adjusted odds ratios (ORs), with surrounding 95% Confidence Intervals (CIs). Statistical hypotheses were tested at the two-sided alpha level of 0.05. We used SAS v9.4 (Carey, NC) for all statistical analyses.

Results

Characteristics of children with RIS

We screened 128 children for participation in the current analysis. Of these, 25 children were excluded due to incomplete clinical data or because a diagnosis other than RIS was ultimately identified in follow-up. We, therefore, included 103 children in the current study whose demographic and clinical characteristics are shown in Table 1. Most children (69/103, 67%) were girls. The median age at the index MRI scan first demonstrating RIS was 14.9 years (interquartile range [IQR] = 13.6–16.6 years); 87% of children (90/103) were ≥ 12 years of age. The majority of children (55/103, 53%) also met the 2005 MRI criteria for dissemination in space, which requires more lesions than either the 2010 or the 2017 MRI dissemination in space criteria on their index scans. The median time from the index MRI to the most recent follow-up visit was 3.2 years (IQR = 1.6–5.7 years). The most common reason for obtaining the index MRI was to evaluate headaches (58/103, 56%). Other common reasons included generalized seizures (10), concussion or head trauma (6), syncope or loss of consciousness (4), and fatigue or malaise (4).

Of the children, 50% underwent CSF analysis (52/103), and 68% had an MRI of the spinal cord (70/103) obtained as part of the initial diagnostic workup. One-third of children with RIS (34/103) subsequently developed a first clinical neurological event and a diagnosis of MS within the follow-up period. The proportion of children who developed a first clinical neurological event was comparable in those in whom either CSF or spinal imaging were obtained vs. not obtained (38% vs. 23%, $p = 0.14$ and 31% vs. 26%, $p = 0.66$, respectively).

Factors associated with the acquisition of spinal imaging

An MRI of the spinal cord (cervical MRI with or without thoracic) was performed in (70/103, 68%) of children as part of their initial diagnostic workup. A similar percentage of children aged ≥ 12 years had spinal imaging obtained compared to those aged < 12 years (69% vs. 62%, adjusted OR = 1.3, $p = 0.7$). In addition, a similar percentage of girls and boys had spinal imaging (67% vs. 71%, adjusted OR = 0.8, $p = 0.6$). There were no meaningful differences in whether spinal imaging was obtained based on indication for the index brain MRI scan, race, country, date of the index MRI acquisition (2017 or later vs. before 2017), or whether the index brain MRI also met MS 2005 MRI criteria for dissemination in space (Table 2).

Factors associated with the acquisition of CSF

CSF was obtained after a first clinical event for three children who were therefore excluded from this portion of the analysis. Fifty-three percent of children (53/100) had CSF obtained during their initial workup, prior to any symptoms. Children aged ≥ 12 years were more likely than those aged < 12 years to have CSF obtained (58% vs. 21%, adjusted OR = 4.9, $p = 0.03$, Table 2). The date of the index MRI moderated the effect of sex on the odds

of obtaining CSF ($p = 0.004$ for the interaction term). Specifically, in analyses stratified by CSF acquisition date, CSF was more likely to be obtained in girls than boys amongst 70 children in whom RIS was detected before 2017 (79% of girls vs. 52% of boys tested, adjusted OR = 4.6, $p = 0.01$) but not amongst the 30 children in whom RIS was detected in 2017 or more recently 75% of girls vs. 80% of boys tested, adjusted OR = 0.2, $p = 0.1$). There were no differences in whether CSF was obtained based on indication for obtaining the index MRI scan, race, country, or whether the index brain MRI also met 2005 MRI criteria for dissemination in space (Table 2).

Sequencing and timing of investigations

After excluding the three children in whom CSF was obtained after a first clinical event, 63% (42/67) of children with spinal cord imaging also had CSF obtained. In contrast, only 33% (11/33) of children without spinal cord imaging had CSF obtained ($p = 0.01$). MRIs of the spinal cord were typically obtained before CSF (median of 21 days vs. 24 days from the index brain MRI demonstrating RIS, $p = 0.015$). CSF was more likely to be obtained in children with a spinal lesion detected on MRI (71.4% of children with a spinal lesion had CSF obtained vs. 53% who did not have a spinal lesion, adjusted OR = 5.9, $p = 0.05$). The timing of CSF acquisition was similar in the 50 children aged ≥ 12 years compared to the three children aged < 12 years (median 23 days vs. 45 days, $p = 0.82$). It was also similar for 14 boys and 39 girls (median 22 days vs. 25 days, $p = 0.89$). There was also no statistically significant difference in the timing of spinal MRIs by sex (median 23 days in 46 girls vs.15 days in 24 boys, $p = 0.43$). However, there was a significant difference by age with a longer time to spinal imaging in younger children (median 11 days in 62 children ≥ 12 years vs. 159 days in 8 children < 12 years, $p = 0.03$).

Discussion

In this international study of children with RIS, both age and sex were associated with the likelihood of a comprehensive diagnostic workup (Box 1). Our main finding is that younger children with RIS (those < 12 years of age) were less likely to have CSF obtained as part of the diagnostic workup than older children, even after adjustment for potential confounders, including brain MRI findings and geographic location. In addition, boys (amongst those with index MRI scans obtained before 2017) were less likely to have CSF obtained than girls. While we do not know precisely what the underlying cause of these findings is, our findings may be related to the increased prevalence of MS in girls than boys and in older children as compared to younger children, resulting in practitioners having a higher degree of suspicion or concern for the condition, leading to an increase in the number of tests performed [18]. A contributing factor may also be that practitioners felt CSF could be more easily obtained in older children (for instance, because younger children may need to be sedated), parental acceptance of the procedure, or other factors. The precise factors contributing to practitioners' practice patterns in evaluating children with RIS is an area for further study.

Our finding that girls were more likely than boys to have CSF obtained was moderated by time (i.e., the date of the index MRI), with a similar percentage of boys and girls having this

test after 2017 in contrast to pre-2017. We first described RIS occurring in an adolescent in 2016, first described outcomes amongst children with RIS in in 2017, and there is a recent report of RIS in children from the U.S. [6, 19, 20]. We suspect that an increased awareness of RIS in children may, therefore, have contributed to this finding.

In contrast to CSF, MRIs of the spinal cord were obtained with a similar frequency in girls and boys and older versus younger children with RIS. This may reflect the relative ease of combining an MRI examination of the spinal cord with a planned brain MRI. It is also possible that practitioners or parents considered an additional MRI a less invasive test than obtaining CSF and, therefore, these MRIs were deemed acceptable even in young children.

We found that younger children underwent MRIs of the spinal cord, on average, several months later than older children. We did not find a difference in the median time to obtain CSF or an MRI of the spinal cord between girls and boys. We could not determine whether this delay in the timing of spinal MRIs in younger children was associated with any future delay in a clinical diagnosis of MS. This may have occurred, for instance, if younger children were followed less frequently based on initially incomplete prognostic information. This is another area for further study with important clinical implications for young children.

We found that, on average, spinal MRIs were obtained sooner than CSF. We also found that children who had spinal lesions detected were much more likely to have CSF obtained. This may have reflected a heightened concern for demyelinating disease in the presence of spinal lesions or the desire to exclude other alternative diagnoses [21]. There may also have been greater parental acceptance for additional diagnostic investigations in the setting of an abnormal spinal MRI.

While our study did not assess the treatment of children with RIS, the presence of oligoclonal bands in spinal fluid and the presence of asymptomatic spinal cord lesions on MRI are known prognostic factors associated with increased risk of clinical MS [6]. The presence of these factors may identify a subset of children with RIS who could be considered for enrollment in future clinical trials to try to prevent/delay clinical multiple MS. Two such trials have been completed in adults with RIS [22, 23]. Accurate risk stratification in children will be needed to determine those children for whom the potential benefits of enrollment in an intervention trial would outweigh the risk of possible adverse effects from exposure to immunomodulatory/immunosuppressive treatments (e.g., infection).

Our study has some limitations. We analyzed a historical group of children with RIS in whom diagnostic investigations were ordered at the discretion of the treating physician. This limited our ability to assess certain variables of interest including the presence of gadolinium-enhancing lesions (since not all children had gadolinium administered on their index scans) and to exclude diagnoses such as anti-MOG antibody disease for which testing may not have been available at the time of assessment. While some of our findings were likely influenced by such local practices and the availability of tests, we adjusted for site in our statistical models. We were also unable to ascertain the reasons for the decisions to perform (or not to perform) certain diagnostic investigations. This is an area

for future study. All children in this study were followed at academic medical centers where a neuroimmunologist was part of the care team. This may impact our study's generalizability as we do not know if children with RIS would have been investigated differently at non-academic centers. We suspect, however, that given the implications of the imaging findings and the heightened risk of MS, that many such children would be referred to academic neuroimmunology clinics. Finally, we did not assess the age, gender, race, ethnicity, or training background of the treating physicians which may have also influenced the likelihood of performing evaluations. Assessing these factors is a planned next step.

In summary, we found multiple differences by age and sex in the diagnostic workup of children with RIS. These affected the frequency and timing of investigations, particularly for younger children. These differences in the workup of children with RIS may alter how some children, especially younger children, are subsequently monitored for the signs and clinical symptoms of MS. Future research goals are to evaluate the reasons for these differences and to identify any barriers in the diagnostic evaluation of children with RIS, including those that may affect the time to a subsequent diagnosis of clinical MS. In addition, there are currently no formal guidelines for investigating and managing children with RIS. Consensus guidelines would greatly aid standardization of care for all children with RIS allowing these children to be quickly and accurately diagnosed, subsequently monitored, and potentially treated earlier for MS, if clinical symptoms occur. Ongoing international collaborations will greatly aid these future initiatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Box 1

Key factors affecting the diagnostic workup of children with the radiologically isolated syndrome

1. Age
   - Younger children* were less likely than older children to have cerebrospinal fluid obtained
   - Younger children* had spinal imaging obtained months later than older children
2. Sex
   - Boys were less likely than girls to have cerebrospinal fluid obtained prior to 2017

* < 12 years versus ≥ 12 years

Table 1

Clinical, demographic, laboratory, and MRI characteristics of the entire cohort ($n = 103$)

Age at first MRI demonstrating RIS in years, median (IQR)	14.9 (13.6–16.6)
Sex, n (%)	Girls: 69 (67) Boys: 34 (33)
Race, n (%)	White: 86 (84) Non-white: 17 (17)
Indication for Index MRI, n (%)	Headache: 58 (56) Not headache: 45 (44)
Index MRI also met 2005 MRI criteria for dissemination in space, n (%)	55 (53)
Index MRI demonstrated enhancement with gadolinium *	19 (23)
Follow-up time in years, median (IQR)	3.2 (1.6–5.7)
CSF obtained, n (%) **	53 (53)
Spinal cord MRI obtained, n (%)	70 (68)
Subsequently developed a first clinical neurological event, n (%)	34 (33)

* Data available for $n = 82$

** Data available for $n = 100$

Table 2

Unadjusted and adjusted associations

Variable	Unadjusted odds ratio (95% confidence interval, *p* value)	Adjusted odds ratio*** (95% confidence interval, *p* value)
A. CSF obtained		
Sex *	1.9 (0.8–4.4, $p = 0.1$)	1.8 (0.7–4.3, $p = 0.2$)
Sex pre-2017	4.6 (1.5–13.7, $p = 0.007$)	
Sex 2017 or later	0.3 (.04–1.5, $p = 0.1$)	
Age **	5.1 (5.3–19.6, $p = 0.02$)	4.9 (1.2–20.2, $p = 0.03$)
Age pre-2017	10.0 (1.2–85.6, $p = 0.03$)	
Age 2017 or later	2.7 (0.4–19.1, $p = 0.3$)	
B. MRI of the spine obtained		
Sex *	0.8 (0.3–2.0, $p = 0.7$)	0.8 (0.3–2.0, $p = 0.6$)
Sex pre-2017	0.9 (0.3–2.8, $p = 0.9$)	
Sex 2017 or later	0.7 (0.2–3.4, $p = 0.7$)	
Age **	1.4 (0.4–4.6, $p = 0.6$)	1.3 (0.4–4.5, $p = 0.7$)
Age pre-2017	0.9 (0.2–5.0, $p = 0.9$)	
Age 2017 or later	2.0 (0.3–14.4, $p = 0.5$)	

* Girls compared to boys

** ≥ 12 years versus < 12 years

*** Models included age, sex, date of index MRI acquisition, indication for index MRI, whether MRI met 2005 criteria for dissemination in space and race