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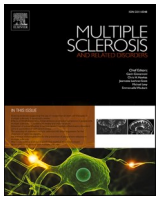

Silent findings: Examination of asymptomatic demyelination in a pediatric US cohort

Vikram Bhise [a,*], Michael Waltz [b], T. Charles Casper [b], Gregory Aaen [c], Leslie Benson [d], Tanuja Chitnis [e], Mark Gorman [f], Manu S. Goyal [g], Yolanda Wheeler [h], Timothy Lotze [i], Soe Mar [j], Mary Rensel [k], Aaron Abrams [l], Moses Rodriguez [m], John Rose [n], Teri Schreiner [o], Nikita Shukla [p], Emmanuelle Waubant [q], Bianca Weinstock-Guttman [r], Jayne Ness [s], Lauren Krupp [t], Jan Mendelt-Tillema [m], on behalf of the U.S. Network of Pediatric Multiple Sclerosis Centers

[a] *Robert Wood Johnson Medical - Rutgers, Pediatrics & Neurology, 89 French Street, Suite 2300, New Brunswick, NJ 08901, USA*
[b] *University of Utah, Pediatrics, USA*
[c] *Loma Linda University, Neurology, USA*
[d] *Massachusetts General Hospital, Partners Pediatric Multiple Sclerosis Center, Neurology, USA*
[e] *Brigham and Women's Hospital, Neurology, USA*
[f] *Massachusetts General Hospital, Partners Pediatric Multiple Sclerosis Center, USA*
[g] *Washington University in Saint Louis, Neurology, USA*
[h] *The University of Alabama at Birmingham School of Medicine Tuscaloosa, Neurology, USA*
[i] *Texas Childrens Hospital, Child Neurology, USA*
[j] *Washington University St. Louis, Neurology, USA*
[k] *Cleveland Clinic, Neurology, USA*
[l] *Cleveland Clinic Neurological Institute, Pediatric Neurology, USA*
[m] *Mayo Clinic, Neurology, USA*
[n] *University of Utah, Neurology, USA*
[o] *University of Colorado School of Medicine, Neurology, USA*
[p] *Texas Children's Hospital, Child Neurology, USA*
[q] *University of California San Francisco, Regional Pediatric Multiple Sclerosis Center, USA*
[r] *University at Buffalo - The State University of New York, Pharmaceutical Sciences, USA*
[s] *University of Alabama at Birmingham, Pediatrics, USA*
[t] *New York University Medical Center, Neurology, USA*

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ABSTRACT

Background and objectives: Limited data is available on children with evidence of silent central nervous system demyelination on MRI. We sought to characterize the population in a US cohort and identify predictors of clinical and radiologic outcomes.

Methods: We identified 56 patients such patients who presented with incidental MRI findings suspect for demyelination, enrolled through our US Network of Pediatric Multiple Sclerosis Centers, and conducted a retrospective review of 38 patients with MR images, and examined risk factors for development of first clinical event or new MRI activity. MRI were rated based on published MS and radiologically isolated syndrome (RIS) imaging diagnostic criteria.

Results: One-third had a clinical attack and ¾ developed new MRI activity over a mean follow-up time of 3.7 years. Individuals in our cohort shared similar demographics to those with clinically definite pediatric-onset MS. We show that sex, presence of infratentorial lesions, T1 hypointense lesions, juxtacortical lesion count, and callosal lesions were predictors of disease progression. Interestingly, the presence of T1 hypointense and infratentorial lesions typically associated with worse outcomes were instead predictive of delayed disease progression on imaging in subgroup analysis. Additionally, currently utilized diagnostic criteria (both McDonald 2017 and RIS criteria) did not provide statistically significant benefit in risk stratification.

* Corresponding author.
E-mail address: bhisevi@rwjms.rutgers.edu (V. Bhise).

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Conclusion: Our findings underscore the need for further study to determine if criteria currently used for pediatric patients with purely radiographic evidence of demyelination are sufficient.

1. Introduction

The incidental finding of MRI lesions indicative of CNS demyelination in asymptomatic individuals is the phenomenon now labelled as radiologically isolated syndrome (RIS), but only when meeting specific criteria (Lebrun et al., 2009). These have been shown to significantly increase the risk of developing multiple sclerosis (MS), and may in fact be the earliest visible manifestation of MS (Azevedo et al., 2015). These radiologic findings pose a challenging clinical dilemma in the pediatric population given that an early diagnosis of MS can have lifelong implications. If caught early, some cases likely have lesions even prior to meeting RIS criteria (Callier et al., 2019). The utility of these criteria for RIS diagnosis, subsequent diagnosis of MS, and potential treatment for these individuals have had limited studies in pediatrics (Kim et al., 2002; Makhani et al., 2017). We performed this study where the suspicion for demyelination on MRI was high by neurologists with expertise in pediatric MS.

In general for pediatric MS, studies have shown that at least 3% of MS cases begin before 16 years of age, which is likely an underestimate (Boiko et al., 2002; Duquette et al., 1987), as increasing numbers of pediatric onset cases are recognized globally (Walton et al., 2020), likely in part related to increase utilization of MRI. Recent studies in the adult RIS population suggest that 30% of patients will have a clinical demyelinating event within 5 years of lesion identification, and have suggested several risk factors that may increase the risk of conversion to clinically isolated syndrome (CIS) or MS. These include asymptomatic spinal cord lesions, male sex, and younger age (Okuda et al., 2014). One recent study found that the positive finding of oligoclonal bands unique to CSF was associated with the future development of a first clinical event and increased the specificity of the 2016 MAGNIMS criteria for dissemination in space in children with RIS (Makhani et al., 2019).

Diagnosis of RIS in adults currently relies on more stringent imaging 2009 Barkhof criteria, but these criteria are less accurate in the pediatric population with CIS (Sadaka et al., 2012). Thus, improved criteria may be needed to conduct predictive modeling for disease conversion in pediatric patients with RIS.

We performed this study where the suspicion for demyelination on MRI was high by neurologists with expertise in pediatric MS. Patients presenting with any quantity of incidental brain lesions suspicious for demyelination were included to maximize inclusion and shed more light on potential risk factors involved in conversion to CIS or MS. We sought a broad inquiry not limited by current diagnostic criteria to look at a cohort of children throughout the US with demyelination identified incidentally and examined their baseline features, and radiologic and clinical outcomes.

2. Methods

We conducted a retrospective clinical and imaging review of multisite data from the United States Network of Pediatric MS Centers (USNPMSC) cohort and Rutgers – Robert Wood Johnson Medical School (RWJMS).

Patients were identified from 12 pediatric MS centers and RWJMS with evidence of suspected demyelination on initial MRI studies between 2005 and 2018. The initial query into our database was inclusive to capture any subject with abnormal lesions suspected to be demyelinating in nature. This included the search terms “RIS,” “demyelinating disease not otherwise specified,” and “abnormal MRI.” At time of onset and follow up, demographic characteristics, serum studies, CSF studies, family history, time to clinical attack, time to new MRI lesion, and neurological examination results were extracted from RWJMS and the network database, housed at the DCAC database at the University of Utah.

All MRIs were obtained in the clinical setting and thus performed with non-standardized imaging protocols. DICOM images were uploaded to a centralized imaging repository, and independently reviewed by two pediatric neuroimmunologists with experience in MS imaging (JMT, VB). Lesions were classified based on location (juxtacortical/cortical, deep white matter, callosal, periventricular, infratentorial and spinal cord (when available)), recording number of lesions for each specific location. If present, gadolinium enhancing lesions were counted. All scans reviewed were interpretable and had comparable quality of T2 sequence, which were utilized for the location attribution. Expansive lesions extending from ventricle to cortex were coded as periventricular, as were lesions in the corpus callosum. As protocols varied, the T1-hypointense lesions were only scored when not enhancing and when visually lower intensity than the gray matter.

Clinical attacks were defined by MS-trained physicians at respective enrolling sites. Patients were assigned if and when they had a new clinical attack, new enhancing lesion, new or enlarging T2 lesion, and/or new MRI activity (new enhancing and/or new/enlarging T2 lesion). Clinical variables included age, gender, race, ethnicity, presence of unique CSF oligoclonal bands, CSF IgG index, and family history of MS. MOG and AQP4 antibodies were not uniformly tested in all patients. Time to clinical attack was censored at last clinical update, and time to next MRI activity was censored at most recent MRI date. MRI studies were further classified as meeting either 2017 McDonald dissemination in space MRI criteria [defined as 1 or more lesions in at least 2 of 4 specified locations (periventricular, cortical/juxtacortical, infratentorial, spinal cord)] or Barkhof criteria [defined as meeting 3 of 4 criteria (having 1 or more gadolinium enhancing lesions or 9 or more T2 lesions, 3 or more periventricular lesions, 1 or more juxtacortical lesions, and/or 1 or more infratentorial lesions)]. CSF studies were considered baseline if occurring within 6 months of initial brain MRI.

2.1. Statistical analysis

Continuous variables were summarized with mean and standard deviations; categorical variables were summarized with frequency and percentages. The RIS cohort was compared to our known MS cohort using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. P-values less than 0.05 were considered significant. Univariate cox regression survival models were generated for time-to-next clinical attack and time-to-new MRI lesion, with hazard ratios and 95% confidence intervals. Predictors for conversion to CIS/MS were also analyzed in this manner using a Cox regression model, with hazard ratios of occurrence at 95% confidence intervals. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Multivariate analysis and adjustment for multiple comparisons was not performed due to the limited subject number.

2.2. Standard protocol approvals, registrations, and patient consents

This study was approved by the following regulatory ethics committees: Rutgers – Robert Wood Johnson Medical School, the Data Coordinating Analysis Center (DCAC) IRB, and the IRBs at each of the participating network centers. Study data was de-identified, and consent was obtained where required by local site IRBs.

2.3. Data availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of additional insight and replicating results.

3. Results

A total of 38 patients with abnormal MRI concerning for demyelination without clinical symptoms suggestive of demyelination were identified, stemming from an initial query of 56 patients. Eighteen patients were excluded by reviewers due to MRI white matter abnormalities inconsistent with typical demyelinating lesions, or being incorrectly coded in the database as abnormal imaging prior to clinical symptoms. Baseline MR spinal cord and lumbar puncture studies were not available in all subjects. The majority of patients were white (78%), 8 self-identified as Hispanic (Table 1). The cohort was predominantly female (61%). Twenty patients had baseline CSF data, and 5 patients had spinal MRI studies. No patients were on medication prior to first new event or lesion. Neurological examinations of all subjects were normal at time of study inclusion. Reason for referral was not recorded, but headache was the most common impetus for imaging based on our overall experience. Only 12 patients were tested for aquaporin-4 antibodies and 4 for MOG antibodies; and all were negative.

Patients (ages 7.6 to 17.8 years) were followed for a mean duration of 3.7 years (range 5 months to 10 years, SD 2.5 years) after initial MRI. Fourteen of these 35 patients (40%) experienced a new clinical attack and 27 of 37 (73%) exhibited new MRI lesions. Mean time to first attack was 2.2 years, and to new MRI activity was 1.2 years. Ultimately, nearly three-quarters (74%) presented with new activity either with new MRI activity and/or a first clinical attack. These and other characteristics are presented overall, and for patients meeting Barkhof and McDonald imaging criteria on initial available scans, in Table 1.

Table 1
Subject demographics.

	Overall subjects ($N = 38$)	Barkhof/RIS imaging criteria met* ($N = 14/38$)	2017 McDonald criteria met* ($N = 25/38$)
Age at baseline: Mean (SD)	13.8 (2.8)	13.8 (2.7)	14.0 (2.7)
Follow-up years: Mean (SD)	3.7 (2.5)	4.4 (2.5)	3.8 (2.6)
Sex: Female	23/38 (61%)	9/14 (64%)	15/25 (60%)
Race			
White	29/37 (78%)	10/14 (71%)	19/24 (79%)
Black	5/37 (14%)	3/14 (21%)	3/24 (13%)
Asian	1/37 (3%)	1/14 (7%)	1/24 (4%)
Other	2/37 (5%)	0	1/24 (4%)
Ethnicity: Hispanic or Latino	8/38 (21%)	3/14 (21%)	5/25 (20%)
MS family history	5/27 (19%)	1/11 (9%)	2/17 (12%)
Earliest recorded BMI: Mean (SD)	24.4 (6.6)	25.4 (7.7)	25.6 (6.9)
MR Imaging			
Juxtacortical lesion	27/38 (71%)	13/14 (93%)	23/25 (92%)
Periventricular lesion	32/38 (84%)	14/14 (100%)	25/25 (100%)
Infratentorial lesion	14/38 (37%)	11/14 (79%)	13/25 (52%)
Deep white lesion	29/38 (76%)	13/14 (93%)	22/25 (88%)
Deep gray lesion	2/38 (5%)	2/14 (14%)	2/25 (8%)
Callosal lesion	13/38 (34%)	7/14 (50%)	11/25 (44%)
Gadolinium enhancing lesion	9/24 (38%)	6/12 (50%)	7/18 (39%)
T1 hypointense lesion	20/33 (61%)	9/12 (75%)	17/20 (85%)
CSF			
CSF WBC/mL: Mean (SD)	16.6 (26.5)	22.7 (37.0)	18.0 (31.2)
CSF protein mg/dL: Mean (SD)	29.1 (9.0)	32.6 (7.5)	29.3 (7.5)
Presence of CSF oligoclonal bands	14/19 (74%)	5/7 (71%)	11/14 (79%)
Elevated CSF IgG index	8/17 (47%)	3/7 (43%)	6/13 (46%)
Elevated CSF IgG index and/or presence of oligoclonal bands	17/19 (89%)	6/7 (86%)	13/14 (93%)
New activity			
New T2 lesion	26/37 (70%)	11/14 (79%)	18/25 (72%)
New Gd lesion	17/37 (46%)	7/14 (50%)	12/25 (48%)
New T2 and/or Gd lesion	27/37 (73%)	11/14 (79%)	18/25 (72%)
Clinical event	14/35 (40%)	4/13 (31%)	9/23 (39%)

* McDonald criteria defined as 1 or more lesions in at least 2 of the following locations: a). periventricular, b) cortical/juxtacortical, c) infratentorial, d) spinal cord, acknowledging that spinal cord data were not available on all, thus excluded. Barkhof criteria defined as having met at least 3 of 4 criteria: a) 1 or more gadolinium enhancing (Gd) lesions or 9 or more T2 lesions, b) 3 or more periventricular lesions, c) 1 or more juxtacortical lesions, d) 1 or more infratentorial lesions. Criteria applied at baseline.

3.1. Comparison to clinically definite MS cohort

When compared to our larger pediatric MS cohort ($n = 1152$) over the same period, we found no significant differences between age, sex, race, ethnicity, or family history of autoimmune disease (Table 2). RIS subjects were more likely to have a family history of MS in first-degree relatives (19% vs 5%, $p = 0.002$) and extended family members (i.e. including grandparents, 26% vs 8%, $p = 0.003$). No differences were evident in demographic characteristics when looking separately at the subset meeting McDonald criteria or meeting the Barkhof criteria compared to the larger cohort.

3.2. Risk analysis

In the survival analysis, gender, race, ethnicity, presence of unique CSF oligoclonal bands, elevated CSF IgG index and other CSF markers did not predict either new clinical or MRI activity (Table 3). The presence of deep gray matter lesions was the only feature identified as predictive of time to new attack ($p = 0.046$), but for only 2 subjects. The presence of callosal lesions at baseline was predictive of developing new T2 lesions ($p = 0.049$), while the total number of baseline juxtacortical lesions was predictive of time to new gadolinium enhancing lesion(s). Conversely, the presence of T1 hypointense lesions was predictive of a lower likelihood of developing a new T2 lesions ($p = 0.033$).

3.3. Examination of current RIS MRI criteria

We further analyzed subgroups meeting only current RIS MRI criteria: 25 patients (66%) met McDonald MRI criteria, while 14 patients (37%) met Barkhof criteria, as we included patients with any number of demyelinating appearing lesions. Patient age at baseline for both groups ranged from 8.4 to 17.6 years. Approximately one third of patients in both groups had a clinical event and three-quarters developed new MRI activity (Table 1) within the mean follow up time of 3.7 years (standard deviation 2.5 years). Among patients meeting McDonald criteria, no specific variables predicted time to attack, but female sex ($p = 0.041$) (Fig. 1) and juxtacortical lesion count ($p = 0.009$) predicted time to new gadolinium- enhancing lesion(s). In addition, the presence of callosal lesions remained predictive of time to new T2 lesion in this subgroup (p

Table 2
Cohort vs. Clinically Definite Pediatric MS subjects.

	Diagnosis RIS ($N = 38$)	MS ($N = 1152$)	P-value
Age at baseline: Mean (SD)	13.8 (2.8)	13.9 (3.5)	0.429[1]
Sex			0.359[2]
Male	15/38 (39%)	373/1152 (32%)	
Female	23/38 (61%)	779/1152 (68%)	
Race			0.353[2]
White	29/37 (78%)	716/1066 (67%)	
Black	5/37 (14%)	232/1066 (22%)	
Other	3/37 (8%)	118/1066 (11%)	
Ethnicity			0.180[2]
Hispanic or Latino	8/38 (21%)	339/1084 (31%)	
Not Hispanic or Latino	30/38 (79%)	745/1084 (69%)	
BMI	24.4 (6.6)	25.7 (7.0)	0.117[1]
MS family history	5/27 (19%)	40/807 (5%)	0.002[2]
MS extended family history	6/23 (26%)	68/807 (8%)	0.003[2]
Autoimmune disease family history	11/23 (48%)	302/807 (37%)	0.310[2]
Autoimmune disease extended family history	13/23 (57%)	468/807 (58%)	0.888[2]
Follow-up years: Mean (SD)	3.7 (2.5)	4.2 (3.4)	0.719[1]

[1] Kruskal-Wallis test.
[2] Chi-squared test.

= 0.019). T1 hypointense lesions were again associated with a lower chance of developing new T2 lesions ($p = 0.033$). While female sex did not appear as a predictive factor among those meeting Barkhof criteria, callosal lesion count still predicted time to new T2 lesion ($p = 0.029$), and the number of juxtacortical lesions still predicted time to new gadolinium enhancing lesion(s). Infratentorial lesions were seen uniquely in this subgroup to be predictive of longer time to new T2 lesion ($p = 0.05$) and any new MRI lesion ($p = 0.01$) (Fig. 2).

Development of new lesions and new clinical attacks was not limited to patient's meeting only Barkhof or McDonald MRI criteria. For patients not meeting Barkhof criteria ($n = 24$), 10 of 22 had a first clinical attack, while 16 of 23 had new MRI activity. Similarly, for patients not meeting McDonald criteria ($n = 13$), 5 of 12 had a first clinical attack and 9 of 12 had new MRI activity. In the 12 patients who did not meet McDonald criteria, we again analyzed survival outcomes. Periventricular lesion count and total lesion count were predictive of time to new T2 lesion ($p = 0.042$ and $p = 0.026$ respectively). Notably, identification as Hispanic or Latino ethnicity was predictive of a combined measure of time to any new lesion and/or attack ($p = 0.04$, HR 6.8 [1.09–42.7]).

We also compared the subgroup of individuals meeting the specific criteria to those who did not meet the same criteria. Patients were not significantly different in terms of time to first attack or new MRI activity for the subset meeting McDonald ($p = 0.8$ and 0.4 respectively) or Barkhof criteria ($p = 0.5$ and 0.5 respectively) compared to those not meeting the same criteria. No other risk factor variables differed between criteria. However, although not reaching significance, we noted that, for all patients meeting Barkhof criteria who had their first clinical attack (diagnosed with MS), the attack occurred within the first two years from baseline MRI.

Lastly, we examined a subset of 28 patients who completed data collection for a minimum of 12 months with outcomes assessed at 1 year. No significant differences in sex, ethnicity, lesion distribution, CSF findings, or criteria-met were identified as predictive on univariate logistic regression models.

Table 3
Univariable Cox regression hazard ratios (95% CI) in pediatric RIS patients.

	Time to T2 lesion	Time to GdE lesion	Time to Clinical Attack
Demographic			
Age at baseline	1.08 (0.93, 1.26)	1.09 (0.90, 1.32)	1.18 (0.95, 1.47)
Sex: Female	1.68 (0.72, 3.94)	3.24 (0.91, 11.57)	0.71 (0.25, 2.06)
Race			
Black	1.28 (0.43, 3.82)	0.36 (0.05, 2.75)	0.71 (0.16, 3.21)
Other	0.63 (0.08, 4.82)	0.00 (0.00, .)	0.00 (0.00, .)
Ethnicity: Hispanic or Latino	1.41 (0.51, 3.90)	2.08 (0.72, 6.03)	1.33 (0.41, 4.29)
MR Imaging			
Juxtacortical lesion count	1.06 (0.90, 1.24)	**1.24 (1.04, 1.47)**	1.05 (0.87, 1.26)
Periventricular lesion count	1.14 (0.94, 1.39)	0.97 (0.75, 1.27)	0.84 (0.61, 1.16)
Infratentorial lesion count	0.85 (0.55, 1.31)	1.07 (0.69, 1.65)	1.17 (0.71, 1.94)
Deep white lesion count	1.02 (0.96, 1.09)	1.01 (0.91, 1.12)	0.98 (0.89, 1.09)
Deep gray lesion count	1.34 (0.31, 5.79)	2.66 (0.58, 12.17)	**5.13 (1.03, 25.56)**
Callosal lesion count	**1.67 (1.16, 2.41)**	1.10 (0.73, 1.65)	1.19 (0.79, 1.80)
Gadolinium enhancing lesion count*	1.00 (0.72, 1.39)	1.08 (0.79, 1.48)	0.70 (0.32, 1.53)
T1 hypointense lesion count*	0.93 (0.78, 1.11)	1.06 (0.90, 1.24)	1.09 (0.91, 1.31)
Total lesions	1.02 (0.97, 1.07)	1.03 (0.96, 1.10)	0.99 (0.93, 1.06)
Juxtacortical lesion	0.49 (0.19, 1.27)	1.73 (0.39, 7.68)	2.01 (0.56, 7.25)
Periventricular lesion	1.94 (0.57, 6.57)	1.22 (0.34, 4.32)	0.80 (0.22, 2.93)
Infratentorial lesion	0.60 (0.26, 1.42)	0.81 (0.28, 2.33)	0.64 (0.20, 2.03)
Deep white lesion	1.79 (0.66, 4.85)	1.30 (0.41, 4.14)	3.97 (0.51, 30.69)
Deep gray lesion	1.34 (0.31, 5.79)	2.66 (0.58, 12.17)	**5.13 (1.03, 25.56)**
Callosal lesion	**2.45 (1.00, 5.97)**	1.31 (0.45, 3.79)	1.79 (0.58, 5.58)
Gadolinium enhancing lesion *	1.75 (0.60, 5.06)	2.39 (0.75, 7.59)	0.67 (0.16, 2.81)
T1 hypointense lesion*	**0.38 (0.15, 0.92)**	1.29 (0.43, 3.86)	1.04 (0.31, 3.43)
Other			
Positive oligoclonal bands*	1.55 (0.40, 5.95)	2.01 (0.39, 10.31)	1.47 (0.30, 7.30)
CSF IgG Index $\geq$ 0.85*	0.40 (0.12, 1.37)	0.27 (0.07, 1.08)	0.92 (0.20, 4.13)
McDonald criteria met	0.72 (0.30, 1.69)	1.11 (0.38, 3.21)	1.17 (0.39, 3.53)
Barkhof criteria met	1.29 (0.57, 2.91)	1.26 (0.47, 3.42)	0.64 (0.20, 2.06)
Neither criteria met	1.40 (0.59, 3.30)	0.90 (0.31, 2.62)	0.85 (0.28, 2.56)

Results are based on univariable models. Bold hazard ratios are significant at 0.05 level.
* Greater than 10% missingness for the associated variable.

4. Discussion

Diagnostic criteria have continuously evolved to identify MS earlier, and now extend to asymptomatic or pre-symptomatic individuals with MRI findings characteristic of demyelination (Nakamura et al., 2014). The 2009 RIS criteria, initially applied to adults, employed revisions to the 2001 Barkhof criteria. However, these criteria have not been thoroughly assessed for the pediatric population for predictive value. Overall, 40% of our asymptomatic pediatric cohort with an abnormal

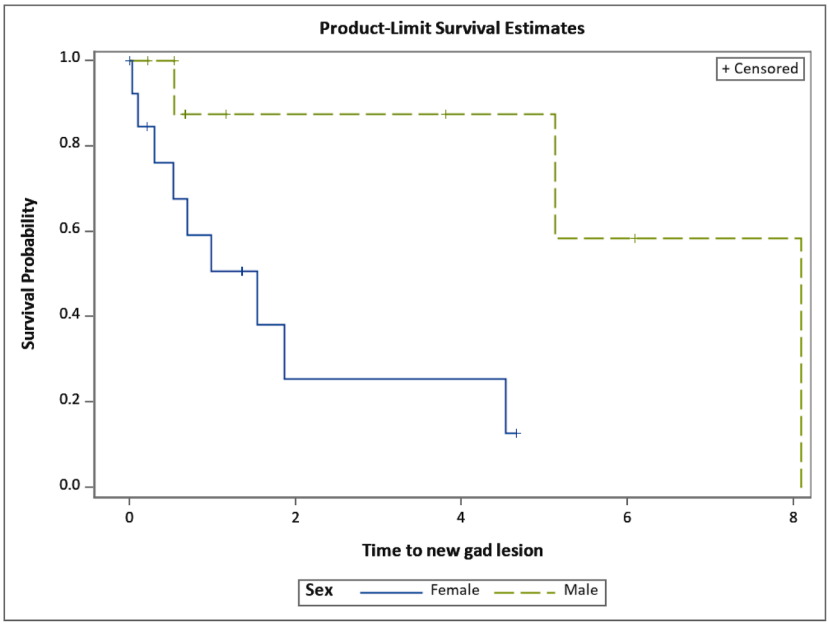

Fig. 1. McDonald MRI criteria met: time to new gadolinium enhancing lesion by sex.

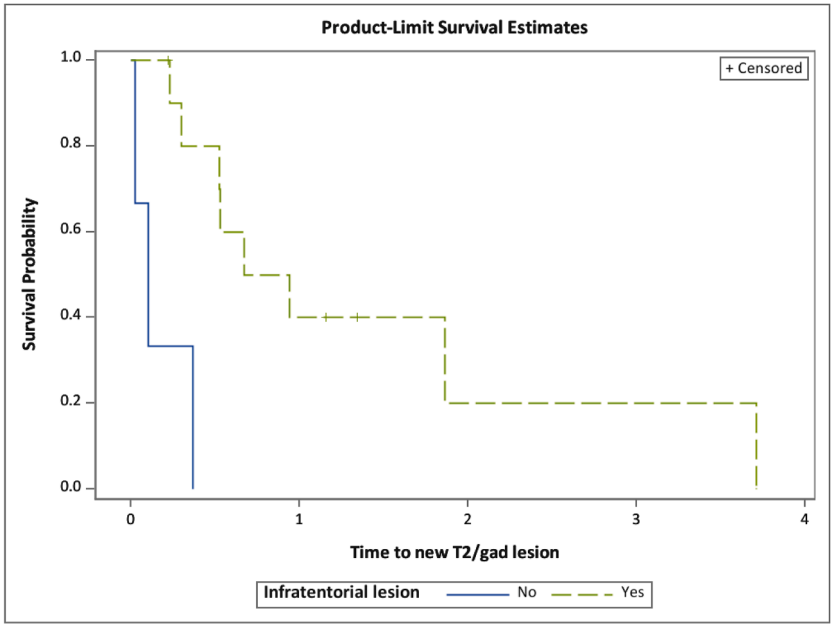

Fig. 2. Barkhof MRI criteria met: time to any new MRI lesion by infratentorial lesion.

MRI with any number of lesions suggestive of demyelination, experienced a first clinical attack, on average within 2 years of initial MRI. This finding confirms that a substantial fraction of asymptomatic pediatric cases of cerebral demyelination represent a preclinical phase of CIS or MS, or even RIS. Higher than in the adult cohort (Okuda et al., 2014), this value may be expected given that pediatric MS patients tend to be in the earliest stage possible of the disease, and in general experience higher relapse rates (Koch-Henriksen and Sørensen, 2010; Gorman et al., 2009). Alternatively, this proportion may be explained by the use of tertiary care centers in the Network, where pediatric MS specialists monitor these patients closely. Additionally, nearly three-quarters of our cohort developed new MRI activity over a mean of 3.7 years, again concerning for development of demyelinating relapsing disease. Others report conversion rates to MS in asymptomatic adults with abnormal brain MRI as high as 47% to 88% over mean follow-up times of 5.3 to 14.1 years (Nakamura et al., 2014; Okuda et al., 2009). These values are in line with the global cohort reporting outcomes for RIS in children of 42% over a median of 2 years in a single study, similar to our 40% conversion rate. Our study found a slightly higher rate of new lesion development (73% vs 61%) (Makhani et al., 2017).

Surprisingly, our study showed that unique CSF oligoclonal bands, IgG CSF index and other CSF markers were not significantly predictive of clinical attacks. A recent study examining a cohort of 34 children meeting Barkhof criteria found that unique CSF oligoclonal bands were more likely to develop a first clinical event (Makhani et al., 2019). In adults with RIS, these findings were not substantiated when looking at 41 and 70 patients respectively (Lebrun et al., 2009; Okuda et al., 2009). Given our smaller sample size having completed CSF studies, differences

may not have been detected (yet), or risk factors in the US may differ from patients globally.

Callosal and juxtacortical lesion count were predictive of MRI outcomes, similar to adult studies (Pareto et al., 2015; Jafari et al., 2009). As these findings did not overlap with clinical predictors, it remains unclear if serial scanning of asymptomatic patients offers utility in relapse risk assessment. Nonetheless, more subtle measures of change, such as with cognition, requires further analysis for potential correlates to MRI activity. Counterintuitively, the presence of T1 hypointense lesions was seen to have a lower likelihood of new MRI activity. Other studies have shown strong correlations with T1 hypointense lesions and MS disability (Simon et al., 2000; Akaishi et al., 2020; Thaler et al., 2015; Tam et al., 2011). Our findings are confounded though as imaging protocols for the T1 sequences varied largely and not all series had associated gadolinium scans, therefore uncertainty existed whether these lesions represented newer or older lesions. Given this limitation, larger studies are needed with a stringent protocolized T1 sequence.

We further explored the utility of applying current RIS MRI criteria to this cohort. We elected to include all patients with lesions suggestive of demyelination, since a lower lesion burden may imply a process closest to true disease onset. Clinically, such incidental findings are important as we lack both specific guidelines and predictive data. A striking finding in our study was the similar rates of new clinical and MRI activity between groups who either did or did not meet McDonald or Barkhof criteria, respectively. The term pre-RIS has been suggested for cases not meeting Barkhof criteria (Callier et al., 2019). Given the specificity of the Barkhof criteria, it has been debated whether to limit analyses only to these criteria (Sastre-Garriga et al., 2004), in pediatrics in particular. If these findings hold true in prospective studies, it would strongly argue that these criteria are neither relevant nor sufficient in risk assessment for asymptomatic demyelination, at least in the pediatric age group. Critically, in cases of incidentally found lesions with the particular appearance of demyelination, patients require careful follow up and ongoing evaluation for new disease activity. Future prospective studies including e.g. volumetric MRI assessments and biochemical studies could provide further insight into predictive measures.

Uniquely, we noted that in our cohort female sex had predictive value for development of new gadolinium enhancing lesions in those meeting 2017 McDonald MRI criteria. The absence of infratentorial lesions had greater predictive value for earlier time to new T2 lesion in those patients meeting Barkhof MRI criteria, though not statistically significant in the overall cohort. Classically, infratentorial lesions correlate with greater disability (Minneboo et al., 2004) and remain a valuable element of the McDonald criteria for dissemination in space, but may also have predictive utility (Zhang and Hou, 2013). Conflicting outcomes are present in adult RIS studies regarding their predictive value (Okuda et al., 2014; Maia et al., 2012). In pediatric MS patients, in one study, the presence of cerebellar lesions at baseline has been associated with a better prognosis at 9 years, though brainstem lesions were not (De Meo et al., 2021). The presence of cerebellar lesions in the absence of disability may indicate a milder course for this pediatric asymptomatic cohort or suggest another underlying pathology. Moreover, we noted that all patients meeting Barkhof criteria who subsequently experienced their first clinical event did so within two years of abnormal MRI identification, and thus may be the minimum needed observation period in US populations meeting those criteria.

We noted that patients with asymptomatic imaging findings of demyelination more often had a family history of MS in immediate and extended family members. The implication of this finding is unclear. Selection bias may have occurred with more MRI screening obtained in patients with family members of demyelinating disease. Otherwise, a higher genetic susceptibility in patients with incidental findings of demyelination may be present. This is in line with historical reports of 7–52% of first-degree relatives of individuals who had MS showing evidence of probable asymptomatic demyelination (De Stefano et al., 2006; Tienari et al., 1992; Fulton et al., 1999), and could explain individuals who never manifest clinically.

Lastly, patients with asymptomatic demyelination presented at the same mean age as the larger MS cohort (13.8 years versus 13.9 years), including those meeting Barkhof (13.8 years) or McDonald (14.0 years) criteria. We had anticipated that these patients represented a preclinical phase of MS, and would have presented at an earlier age. Alternatively, they may be a milder disease phenotype whose clinical expression is relatively delayed.

Limitations of this study included the non-standardized use of baseline MRIs. In particular, this makes the finding of the T1 lesions less robust and limited. The overall T2 sequences had low variability in quality and appearance, and thus lesion burden and localization of the lesions are without this limitation. While the USNPMSC has implemented a rigorous standardized protocol in recent years, many patients were referred from nearby institutions after having had their first imaging study. While several factors predicted the development of new enhancing lesions, their true occurrence may be underestimated for activity occurring between imaging time points. Due to the low number of subjects in this rare population, more subtle differences may not have been identified. In addition, only half of the studied cohort had CSF data, which could explain our inability to corroborate our findings with other studies. Data on presenting complaints (i.e. prodrome) for the initial brain MRI were not collected, but could inform understanding of early RIS/CIS/MS. Follow-up times varied on patients but our analyses accounted for differences. We examined a subgroup of patients completing one year, but longer-term analysis is needed to examine later fixed time points (e.g. 5 years). A selection or survivorship bias may explain certain findings, as this cohort was mainly limited to individuals with access to a USNPMSC center. The nature of the Network, with predominantly tertiary care centers, can increase this selection bias. The lack of spinal cord imaging and postcontrast sequences in all subjects prevented us from more thoroughly exploring the performance of the 2017 revision of the McDonald criteria and the Barkhof criteria. Also, 4 of 20 scans demonstrating T1 hypointense lesions did not have a corresponding a postcontrast sequence. Nevertheless, this study demonstrates that development of both new lesions and clinical disease may be seen in children despite the presence of a low number of lesions, in patients who may not meet standard MS or RIS criteria.

Overall, our study showed that children with lesions highly suspicious for asymptomatic demyelination on initial MRI can have significant rates of new activity on MRI or conversion to MS/CIS, and that location of the lesions (T1 hypointense, juxtacortical, infratentorial, and callosal) possess potential predictive value. We also provided evidence that the current RIS diagnostic criteria may not be suitable for the pediatric population and should be re-evaluated especially for pediatric cases where the overall lesion burden is low. Further prospective studies will be required to corroborate our findings.

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CRediT authorship contribution statement

Vikram Bhise: Conceptualization, Methodology, Validation, Resources, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition. **Michael Waltz:** Writing – review & editing, Software, Formal analysis, Data curation, Visualization. **T. Charles Casper:** Writing – review & editing, Formal analysis, Data curation, Resources. **Gregory Aaen:** Writing – review & editing, Resources. **Leslie Benson:** Writing – review & editing, Resources. **Tanuja Chitnis:** Writing – review & editing, Resources. **Mark Gorman:** Writing – review & editing, Resources. **Manu S. Goyal:** Writing – review & editing, Resources. **Yolanda Wheeler:** Resources, Investigation. **Timothy Lotze:** Writing – review & editing, Resources. **Soe Mar:** Writing – review & editing, Resources. **Mary Rensel:** Writing – review & editing, Resources. **Aaron Abrams:** Writing – review & editing, Resources. **Moses Rodriguez:** Writing – review & editing, Resources. **John Rose:** Writing – review & editing, Resources. **Teri Schreiner:** Writing – review & editing, Resources. **Nikita Shukla:** Writing – review & editing, Resources. **Emmanuelle Waubant:** Writing – review & editing, Resources. **Bianca Weinstock-Guttman:** Writing – review & editing, Resources. **Jayne Ness:** Writing – review & editing, Resources. **Lauren Krupp:** Writing – review & editing, Resources, Conceptualization. **Jan Mendelt-Tillema:** Writing – review & editing, Resources, Conceptualization.

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