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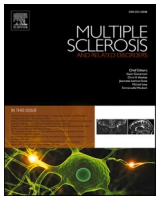

Original article

A multicenter study of radiologically isolated syndrome in children and adolescents: Can we predict the course?

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ABSTRACT

Objectives: To evaluate clinical characteristics, imaging features and etiological profile of Radiologically Isolated Syndrome (RIS) along with clinical and radiological follow-up.
Methods: Demographic, clinical and radiological data of patients younger than 18 years fulfilling the criteria for RIS were retrospectively analyzed. RIS was defined by the detection of lesions meeting the revised 2010 McDonald Criteria for dissemination in space on magnetic resonance imaging (MRI) in the absence of any symptoms of demyelinating disease or an alternative cause for the MRI findings.
Results: There were total 69 patients (38 girls, 31 boys). The median age at index MRI was 15.7 years, and median follow-up time was 28 months. The most common reason for neuroimaging was headache (60.9%). A first clinical event occurred with median 11 months in 14/69 (20%) of cases. Those with oligoclonal bands (OCB) in cerebrospinal fluid (CSF) and follow-up longer than 3 years were more likely to experience a clinical event ($p<0.05$): 25% of those with OCB manifested clinical symptoms within the first year and 33.3% within the first two years compared to 6.3% and 9.4%, respectively in those without OCB. Radiological evolution was not associated with any variables: age, sex, reason for neuroimaging, serum 25-hydroxyvitamin D level, elevated IgG index, OCB positivity, total number and localization of lesions, presence of gadolinium enhancement, achievement of 2005 criteria for DIS and duration of follow-up.
Conclusion: Children and adolescents with RIS and CSF OCB should be followed-up for at least 3 years in order to detect any clinical symptoms suggestive of a demyelinating event. Because disease-modifying treatments are not approved in RIS and no consensus report justifies their use especially in pediatric RIS, close follow-up of OCB-positive patients is needed for early recognition of any clinical event and timely initiation of specific treatment.

1. Introduction

The presence of demyelinating lesions highly suggestive of multiple sclerosis (MS) in individuals with no symptoms compatible with MS is defined as radiologically isolated syndrome (RIS) (Makhani et al., 2019, Lebrun, 2015). This term was first suggested by Okuda et al. (2009).

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Prevalence rates are reported as 0.1–0.7% in adults and 0.02–0.12% in children, and incidence rates as 0.1% in 0–91year-old individuals (de Mol et al., 2021, Forslin et al., 2016). These figures match those of autopsy-based studies in the general population, reported as 0.08–0.2% (Engell, 1989).

The initial description of RIS required the presence of 2005 criteria for dissemination in space (DIS) in adults without symptoms of demyelinating or other disorders that might explain imaging findings (Okuda et al., 2009). No separate diagnostic criteria have been defined for pediatric RIS: studies in this age group apply either the 2010 McDonald DIS criteria, or the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) 2016 criteria consisting of at least two of the following: ≥3 periventricular lesions, ≥ 1 infratentorial lesion, ≥ 1 spinal lesion, ≥ 1 optic nerve lesion and ≥1 cortical or juxtacortical lesion (Makhani et al., 2019, Makhani et al., 2017, Polman et al., 2011, Wattjes et al., 2015).

The outcome of pediatric RIS is also uncertain. About 35% of adults with RIS will develop a clinical attack and receive the diagnosis of MS within 5 years. The few studies in the pediatric age group reported less than half of children with RIS will develop a clinical event in 1-2 years (Makhani et al., 2017, Lebrun et al., 2016, Wilbur and Yeh, 2018).

The objectives of this study were to evaluate demographic, clinical and radiological characteristics of RIS in children and adolescents for any features associated with subsequent clinical events or MRI activity.

2. Materials and methods

Clinical data from patients aged <18 years who met the McDonald 2010 criteria for DIS by the presence of ≥ 1 ovoid, well-circumscribed, homogenously hyperintense lesions larger than 3 mm diameter on at least 2 of the following 4 locations: periventricular white matter, juxtacortical region, spinal cord, infratentorial region on T2 weighted MR images, with or without corpus callosum involvement were collected from 10 pediatric neurology centers in Turkiye (Polman et al., 2011). Patients were excluded if they had a history of neurological symptoms compatible with inflammatory demyelinating disorders lasting >24 hours, other central nervous system (CNS) diseases, or if their medical or radiological data were incomplete. Approval was obtained from the Ethics Committee -2 of the Ankara City Hospital, Turkish Ministry of Health (E2–22–2042).

Detailed clinical history and neurological examination at initial presentation were reviewed for the following factors: sex, age at onset of symptoms and index MRI, family history, interval between index MRI and first clinical attack or radiological evolution, brain and spinal cord MRI studies, cerebrospinal fluid (CSF) analysis for IgG index, oligoclonal bands (OCB) and serum 25-hydroxyvitamin D levels. Laboratory studies including infectious, inflammatory, rheumatologic and metabolic tests performed at the referring clinic to exclude alternative diagnoses were reviewed, but not included in the analysis.

Results of the index and follow-up MRI examinations of the brain and, if performed, spinal cord, including T1- and T2-weighted sequences in multiple planes (axial, coronal, sagittal) with or without administration of contrast material were recorded as reported by the radiologists in each center. The results were analyzed with respect to Mc Donald 2010 and 2005 criteria (Okuda et al., 2009, Polman et al., 2011). The outcome was evaluated according to the occurrence and time to the first clinical or new radiological event. A new radiological event is a new T2 or an enhancing lesion in the brain or spinal cord.

Data from the medical records sent by the treating pediatric neurologists were entered into the SPSS data editor by two of the researchers (DY, PG).

2.1. Statistical analysis

Statistical analyses were performed using the SPSS software version 20 IBM. The variables were tested using Shapiro-Wilk test for normal distribution. Categorical data were described as percentage and continuous data as mean ± standard deviation (SD) and median (min-max). Statistical comparisons were made using the chi-square test for categorical variables, and parametric (Independent's Samples T Test or Mann-Whitney U Test) and non-parametric (One Way ANOVA or Kruskall-Wallis Test) tests for continuous variables according to the distribution of the variable. Univariate analyses to evaluate the risk factors for clinical and radiologic evolution were performed calculating the odds ratios (OR) with 95% confidence intervals (CI). Variables that resulted significant at the univariate logistic regression analyses were subjected to multivariate logistic regression analysis. The outcome based on the time to the first clinical and radiological event was tested with the Kaplan-Meier method. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics (Table 1)

Total 69 patients (38 female, 31 male) were included. Age at onset of symptoms was median 13.8 years (min-max: 7–17) and 17 (24.6%) were younger than 12 years; age RIS was diagnosed was median 15.7 years (min-max: 9–17). The most common reason for neuroimaging was headache (42/69, 60.9%). The median duration of follow-up was 28 months (min-max: 8–103 months). Twenty-five (36.2%) patients had follow-up ≥3 years.

The family history was positive for MS in first- (one patient) and second- (three patients) degree relatives of 4 patients two of whom developed new radiologic findings. Neurological examination in 61 patients (88%) was normal at presentation while intentional tremor (n=5), and mental retardation, grade 1 papilledema, and unilateral abducens palsy (n=1 each) were noted in others. Abnormalities in neurological examination did not correlate with the MRI findings.

3.2. Laboratory studies (Table 2)

Laboratory data of the entire cohort is shown in Table 2. Lumbar puncture (LP) was performed in 57 (82.6%) patients. CSF OCB and elevated CSF/serum IgG index were detected in 24/56 (42.9%) and 21/45 (46.7%) pediatric and adolescent patients, respectively. Of the 14

Table 1
Characteristics of the cases.

Variables	
Total number	69
Sex, n (%)	31 (45)
Male	38 (55)
Female	
Age at onset of symptoms that led to the first MRI, median (min-max), years	13.8 (7–17)
<12 years, n (%)	17 (24.6)
≥12 years, n (%)	52 (75.4)
Age at presentation, median (min-max), years	15.7 (9–17)
<12 years n (%)	3 (4.35)
≥12 years n (%)	66 (95.65)
Follow-up, median (min-max), months	28 (8–103)
in the clinical event group, median (min-max)	43 (15–67)
in the MRI event group, median (min-max)	31 (11–103)
Reasons for neuroimaging n (%)	42 (60.9)
Headache	5 (7.25)
Seizure/epilepsy	5 (7.25)
Syncope	3 (4.35)
Trauma	3 (4.35)
Hormonal screening	3 (4.35)
Attention deficit disorder	3 (4.35)
Tremor	2 (2.89)
Myopia	1 (2.89)
Cochlear implant	1 (2.89)
Neck mass	

Table 2
Laboratory and imaging data of the entire cohort.

CSF analyzed, n (%)	57 (82.6)
Presence of OCB, (%)	42.9
Elevated IgG index, (%)	46.7
Vitamin D level determined, n (%)	48 (69.6)
Number of lesions on indexMRI	29 (42.02)
≤5, n (%)	25 (36.23)
6–10, n (%)	7 (10.1)
11–15, n (%)	8 (11.6)
≥15, n (%)	
Administration of gadolinium, n (%)	54 (78.3)
Gadolinium enhancement, (%)	18.5
Spinal cord imaging obtained, n (%)	31 (44.9)
Meeting 2005 DIS criteria, n (%)	28 (40.6)

patients who developed a first clinical event, 11 (78.6%) had CSF OCB and 8/13 (61.5%) had an elevated IgG index (p=0.005 and 0.121, respectively compared to those who did not develop a clinical event). Of the patients with radiologic evolution, OCB and elevated IgG index were present in 18/31 (58.1%) and 13/28 (46.4%) (p=0.010 and 0.967, respectively compared to those who did not show radiologic evolution).

Serum 25-hydroxyvitamin D levels were determined in 48 patients (69.6%), among whom 32 (66.7%) had deficiency (levels <20 ng/ml) and 11 (22.9%) had insufficiency (21–30 ng/ml). The rates of vitamin D deficiency and insufficiency were 9 (75%) and 3 (25%) in the 12 patients who developed a clinical event and 17/26 (65.6%) and 8/26 (30.8%) in those whose radiologic findings expanded or progressed.

3.3. Imaging characteristics (Table 2)

The majority of index MRI studies displayed 5 or fewer lesions (29/69, 42.0%), most commonly in the periventricular area, where 67/69 (97%) had at least one lesion. Contrast enhancing lesions were observed in 10/54 (18.5%). Spinal MRI was obtained in 31/69 patients (44.9%): 9 (29%) had lesions in the cervical spine, one of them enhancing, and one also had multiple lesions at thoracic level. The number of patients whose index MRI scans also fulfilled 2005 DIS criteria (Okuda et al., 2009) was 28/69 (40.6%).

3.4. Clinical and radiologic outcomes (Tables 3–5)

A first clinical event developed in 14/69 (20%) patients within median 11 (min-max: 5–36) months. Radiologic progression occurred in 37/69 (53.6%), of whom 14 were also in the clinical event group within median 7 (min-max: 1–24) months. Of those meeting 2005 DIS criteria (n=28) a first clinical event occurred in 6/28 (21.4%) within median 16.5 (min-max: 5–36) months. The clinical event-free survival time was median 29 months (95% CI:21.3–36.7 months) (Fig. 1 a,b). The clinical events consisted of monofocal signs (6 cases), optic neuritis (4 cases) and polyfocal signs (4 cases) in cases meeting the McDonald and monofocal signs (3 cases) optic neuritis (2 cases) and polyfocal signs (1 case)in those meeting the 2005 criteria.

All patients had at least one follow-up MRI study of the brain. The intervals and protocols varied. The median interval between index and follow-up MRI was 5.5 months (min-max: 1–18) in those with a clinical event and 6 months (min-max: 2–24) in those without. Radiologic progression occurred in 37 (53.9%) patients (26 new and 11 enhancing lesions) within median 7 months (min-max: 1–24) and radiologic event-free survival was median 12 months (95% CI: 9.1–14.9 months) (Fig. 1 c, d). Of the 28 patients who met 2005 DIS criteria, 14 (50%) had radiologic progression at median 9 (min-max:1–18) months. Among patients experiencing a first clinical event, 11 had follow-up spinal MRI scans and 4 (36%) had new lesions. The risk factors for clinical conversion and radiologic evolution are shown in Tables 3 and 4, respectively and Table 5 summarizes the clinical and radiologic outcomes of the patients.

Analyses of potential predictors of clinical events are shown in Table 6. Univariate logistic regression analysis identified two significant risk factors: follow-up ≥3 years and OCB positivity (Fig. 2). Statistical significance persisted in multivariate analysis with odds ratios of 10.353 and 16.828, respectively. Potential predictors of radiologic evolution are shown in Table 7. Univariate logistic regression analyzes identified two risk factors: OCB positivity and presence of MRI enhancement. However,

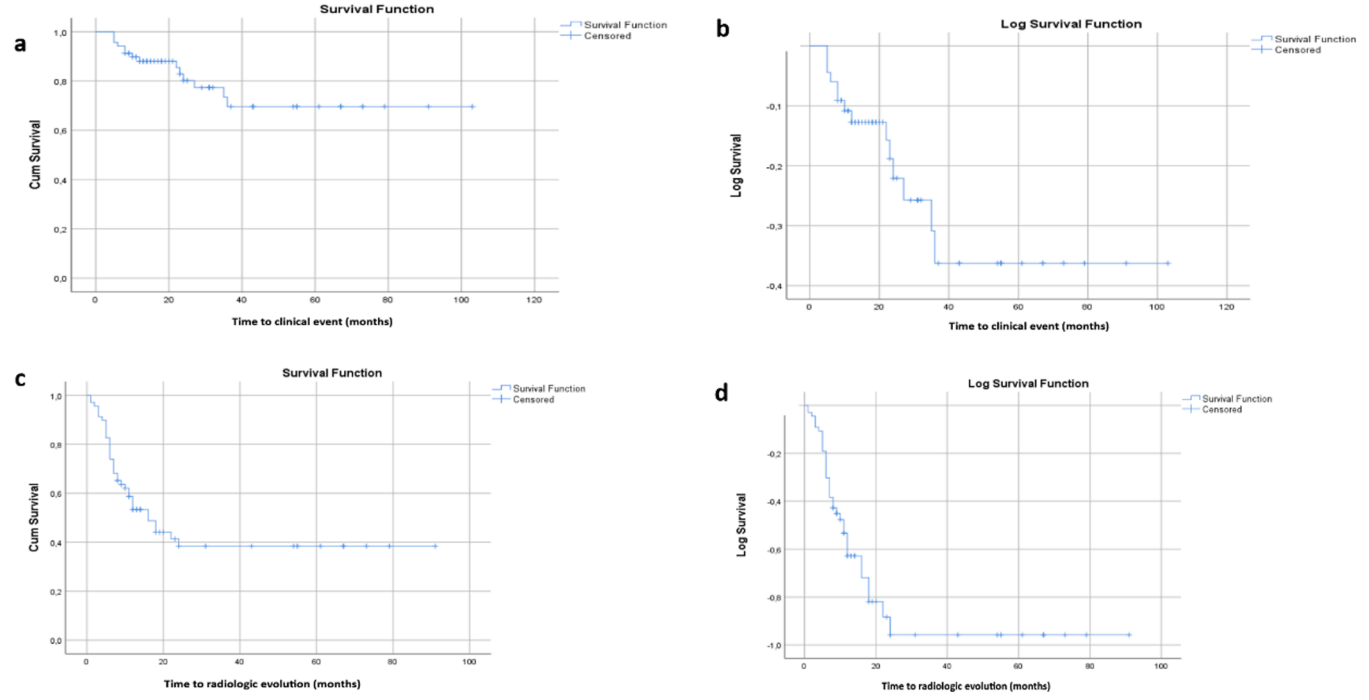

Fig. 1. (a,b). Kaplan-Meier survival curve analyses for time from the diagnosis of RIS to a first clinical event and (c,d) Kaplan-Meier survival curve analyses for time from the diagnosis of RIS to a radiological evolution. Censored patients (no radiological evolution at the last follow-up) are indicated on the curves. Time to clinical event is reported in months.

Table 3
Risk factors for developing a clinical event.

	RIS+Clinical (n=14)	RIS only (n=55)	p
Sex (female/total, %)	57.1	42.9	0.712
Median age at onset of symptoms, months (range)	198,5(162–216)	188 (128–216)	0.230
Median age at index MRI, months (range)	198(162–216)	186 (128–214)	0.26
Reason for neuroimaging (%)	57.1	55.8	0.931
Median follow-up time, months (range)	43(15–67)	31(8–103)	0.220
Follow-up time≥3 years	9	18	**0.033**
Vitamin D deficiency (%)	75	25	0.470
Presence of OCB (%)	78.6	33.3	**0.005**
Elevated IgG index	61.5	34.8	0.121
Number of lesions on index MRI (range)	5(2–23)	6(2–29)	0.791
Spinal lesion on index MRI (%)	36.4	37.5	0.960
Gadolinium enhancement on index MRI(%)	30.8	12.9	0.164
2005 DIS criteria	26.1	28.6	0.843

RIS+Clinical: RIS patients with a clinical event; RIS only: RIS patients without a clinical event

Table 4
Risk factors for radiological evolution.

	RIS+ New (n=37)	RIS only (n=32)	p
Sex (female/total, %)	56.8	43.2	0.762
Median age at onset of symptoms, months (range)	189 (108–216)	187.5 (128–214)	0.968
Median age at index MRI, months (range)	192 (142–216)	186 (128–214)	0.72
Reason for neuroimaging (%)	61.8	42.1	0.168
Median follow-up time, months (range)	31(11–103)	18.5(8–91)	0.076
Follow-up time≥3 years	16	11	0.307
Vitamin D level (%)	65.4	34.6	0.214
Presence of OCB (%)	58.1	24	**0.010**
Elevated IgG index (%)	46.4	47.1	0.967
Number of lesions on index MRI (range)	6 (2–20)	7 (2–20)	0.717
Spinal lesion (%)	31.6	25	0.511
Gadolinium enhancement (%)	30	4.2	**0.016**
2005 DIS criteria (%)	50	56.1	0.618

RIS+New: RIS patients with radiological evolution; RIS only: RIS patients without radiological evolution

neither showed statistical significance in multivariate logistic regression analysis.

The following variables had no significant effect on clinical or radiologic evolution: age at onset of symptoms, age at index MRI, sex, reason for neuroimaging, serum 25-hydroxyvitamin D level, elevated IgG index, total number of lesions, location of lesions (juxtacortical, periventricular, infratentorial, spinal) and initial MRI meeting 2005 criteria for DIS.

3.5. Treatment and course

Twenty-one patients received first-line disease modifying therapy (DMT) for MS, 14 after a clinical event and 7 after radiologic evolution. All patients with a clinical event and 6 patients with radiologic evolution were clinically stable at 12–43 months' follow-up under DMT. One child treated with interferon beta 1a after radiologic evolution developed a first clinical event 12 months after index MRI and 6 months after treatment was started, and DMT was changed.

Table 5
Clinical and radiologic outcome of the patients.

Variables	
Clinical event	14 (20)
McDonald 2010 criteria n (%)	11 (5–36)
Time to a first clinical event median (min-max), months	29
Clinical event free survival time median (min-max), months	(21.3–36.7)
Clinical event	6 (21.4)
2005 DIS criteria n (%)	16.5 (5–36)
Time to a first clinical event median (min-max), months	
Radiological evolution	37 (53.6)
McDonald 2010 criteria n (%)	7 (1–24)
Time to radiological evolution median (min-max), months	12 (9.1–14.9)
Radiologic event free survival time median (min-max), months	
Radiological evolution	14 (50)
2005 DIS criteria n (%)	9 (1–18)
Time to radiological evolution median (min-max), months	
Interval between index MRI and the first follow-up scan median (min-max), months (Clinical event group)	5.5 (1–18)
Interval between index MRI and the first follow-up scan median (min-max), months (Radiologic evolution group)	6 (1–18)
Interval between index MRI and the first follow-up scan median (min-max), months (cases with no clinical / radiological event)	6 (2–24)

Table 6
Logistic regression of potential predictors of clinical event in children with RIS.

Predictors	Univariate regression model		Multivariate regression model	
	OR (95% CI lower-upper)	*p* value	OR (95% CI lower-upper)	*p* value
Gender (female)	1.111 (0.340–3.631)	0.862		
Age at onset of symptoms (≥15 years)	1.354 (0.392–4.672)	0.631		
Age at index MRI (≥15 years)	1.319 (0.365–4.773)	0.673		
Reason for imaging (headache & others)	1.214 (0.369–3.992)	0.749		
Follow-up time (≥3 years)	3.700 (1.082–12.656)	**0.037**	10.353 (1.809–59.262)	**0.009**
Vitamin D deficiency	2.143 (0.495–9.274)	0.308		
OCB positivity	8.179 (1.949–34.332)	**0.004**	16.828 (2.726–103.903)	**0.002**
Elevated IgG index	2.338 (0.624–8.766)	0.208		
Number of lesions on index MRI (≥6 lesions)	0.463 (0.141–1.523)	0.205		
Presence of spinal lesion	1.714 (0.349–8.421)	0.507		
Presence of Gadolinium enhancement	2.593 (0.601–11.185)	0.202		
Fulfilled 2005 DIS criteria	1.125 (0.343–3.691)	0.846		

Abbreviations: CI: confidence intervals, IgG: immunoglobulin G, MRI: magnetic resonance imaging, OCB: oligoclonal band, OR: odds ratio

4. Discussion

The main finding in this series of pediatric and adolescent RIS was the risk of a clinical event: 20% (14/69) in median 11 months; 8 in the first and 3 in the second year. This rate was 42% in median 2 years in Makhani et al's study of 38 children (Makhani et al., 2017). Less than half of adults with RIS develop a clinical event within 5 years (Wilbur and Yeh, 2018): follow-up of our RIS cases for at least 5 years would allow comparison with adult series. In MS, relapses are more frequent in

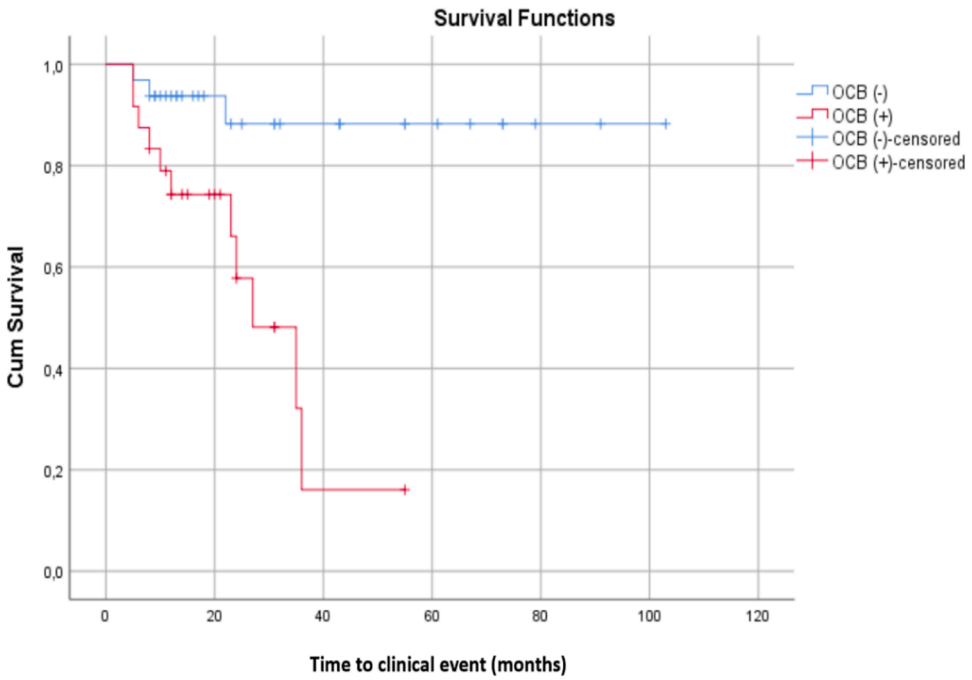

Fig. 2. Kaplan-Meier survival curve analyses for time from the diagnosis of RIS to a first clinical event consistent with CNS demyelination stratified by the presence of OCBs in CSF, with an ultimate Kaplan-Meier estimate of 54% clinical event-free patient with OCB and an ultimate Kaplan-Meier estimate of 91% clinical event-free patient without OCB. Censored patients (no clinical event at the latest follow-up) are indicated on the curves.

Table 7
Logistic regression of potential predictors of radiological evolution in children with RIS.

Predictors	Univariate regression model		Multivariate regression model	
	OR (95% CI lower-upper)	*p* value	OR (95% CI lower-upper)	*p* value
Gender (female)	1.158 (0.447–2.999)	0.762		
Age at onset of symptoms (≥15 years)	0.931 (0.333–2.601)	0.891		
Age at index MRI (≥15 years)	1.418 (0.519–3.873)	0.495		
Reason for neuroimaging (headache & others)	0.423 (0.157–1.137)	0.088		
Follow-up time (≥3 years)	1.455 (0.547–3.865)	0.452		
Vitamin D deficiency	0.914 (0.283–2.958)	0.881		
OCB positivity	4.385 (1.371–14.021)	**0.013**	2.806 (0.736–10.700)	0.131
Elevated IgG index	0.975 (0.291–3.262)	0.967		
Number of lesions on index MRI (≥6 lesions)	0.553 (0.209–1.464)	0.233		
Presence of spinal lesion	1.385 (0.272–7.037)	0.695		
Presence of Gadolinium enhancement	9.857 (1.149–84.538)	**0.037**	5.600 (0.578–54.230)	0.137
Fulfilled 2005 DIS criteria	0.783 (0.289–2.052)	0.618		

Abbreviations: CI: confidence intervals, IgG: immunoglobulin G, MRI: magnetic resonance imaging, OCB: oligoclonal band, OR: odds ratio

pediatric-onset compared with adult-onset groups: this suggests higher inflammatory activity in young patients (Gorman et al., 2009). Therefore, pediatric and adolescent RIS may be expected to manifest earlier or more frequent clinical events, and the course of MS developing in such cases might be worth comparison with other pediatric-onset MS as well as adult-onset patients.

The predictive value of age for conversion to MS is controversial. Young adults tend to show a higher rate of conversion to MS in most studies except one where older age was associated with conversion to primary progressive MS (PPMS). Pediatric series including ours do not support age as a risk factor (Makhani et al., 2017, Matute-Blanch et al., 2018, Lebrun et al., 2009, Lebrun-Frenay et al., 2020, Bisulca et al., 2019, Kantarci et al., 2016). The limited number of preadolescent patients in pediatric RIS series, the frequency of postinfectious and metabolic disorders mimicking demyelinating CNS disorders may underlie this difference from adult series.

Female sex usually predominates in MS and clinically isolated syndrome (Bisulca et al., 2019). However, two large studies reported male sex associated with clinical conversion to MS (Kantarci et al., 2016, Okuda et al., 2014) whereas others reported sex as non-predictive (Makhani et al., 2017, Matute-Blanch et al., 2018, Lebrun et al., 2009, Thouvenot et al., 2019). Since only 35% of RIS patients convert to MS, the predominance of male sex in RIS may not be reflected to MS cases. We did not find a difference between males and females in the young age group.

The symptom that prompted the initial MRI study, mostly headache in this series, was not predictive of clinical or radiological evolution. The main predictive biomarker in the current study was CSF OCB, associated with clinical (78.6%) and radiological (58.1%) evolution. The presence of OCB has also been reported to predict shorter time to a clinical event (Matute-Blanch et al., 2018). Our rate of OCB positivity, 43% of those analyzed, was lower than in Makhani et al's study (57%) although the time to a first clinical event was shorter in ours (median 11 months vs. 2 years) (Makhani et al., 2017). Our lower rate of OCB even in the group with DIT is unlikely to be a matter of technique, as isoelectric focusing is applied in all centers. OCB synthesis in RIS is not expected to be as common as in MS, the two conditions not being equivalent. The

synthesis of OCB is associated with time; the timing of LP is bound to differ between RIS cases because the beginning of RIS cannot be defined. Also, clinical approach is variable: some patients may have undergone LP at the time of index MRI whereas others at the onset of symptoms. In fact, it might be possible to study the time to conversion to MS by re-sampling CSF at standard intervals, or, more feasibly, comparing large series of patients tested for OCB at various time points after the diagnosis of RIS.

A new MRI activity was observed in 54% in maximum 24 months which suggests follow-up with MRI after 2 years from baseline may not be cost-effective in pediatric and adolescent patients. Makhani et al. reported 61% within median 1.1 years, a rate similar to the 60%, but interval shorter than the 2.7 years in adult RIS. Median 7 months found in our study might be related to earlier MRI follow-up, median 5.5 months after the index MRI compared to approximately 12 months in others (Okuda et al., 2009, Makhani et al., 2017). The Mexican Committee for Treatment and Research in Multiple Sclerosis (MEXCTRIMS) surveyed the diagnostic approach and treatment criteria for RIS among Mexican neurologists: one of the points of consensus was follow-up brain and spinal cord MRI obtained within 3 months if 2005 DIS criteria were met (Skromne-Eisenberg et al., 2021). Also, 66 Argentinean neurologists agreed to perform brain (100%) and spinal (80%) MRI during follow-up in a web-based survey (Carnero Contentti et al., 2019). Neurologists treating MS in Europe generally agreed (94%) that they would perform a follow-up MRI in RIS and 73% suggested that the MRI should be performed within 6 months (Fernández et al., 2017). MAGNIMS guidelines also recommend 3–6 months after the initial MRI in adults with RIS (Wattjes et al., 2015). The shorter interval between first and follow-up MRIs in our study is in line with these recommendations and with the tendency of pediatric demyelinating diseases to relapse early (Duignan et al., 2019).

The role of gadolinium enhancement in predicting clinical or radiological outcome is controversial. The presence of an enhancing lesion was associated with an increased risk of radiological but not of a clinical event in Okuda et al.'s study (Okuda et al., 2009). Enhancement is observed in new lesions during a few weeks of acute inflammation and blood brain barrier (BBB) disruption before cells and mediators which cross the impaired BBB induce and maintain repair (Kappos et al., 1999, Cotton et al., 2003). This may explain the lack of correlation between contrast enhancement and the clinical or radiological course in this study.

A recent review identified imaging features that were associated with early conversion from RIS to MS within 5 years. The presence of T2 hyperintense lesions in the cervical and thoracic spinal cord were suggested as strong predictors (Bisulca et al., 2019). Our results do not support the role of localization in clinical event or radiologic progression. However, less than half of the patients in our series had a spinal MRI, and we can recommend spinal cord imaging for the management of RIS to acquire more data.

Serum 25-hydroxyvitamin D levels showed deficiency in 75%, insufficiency in 25% of patients in the clinical event group and 65.6% and 30.8% in the radiologic evolution group. Yilmaz et al. found similar rates in pediatric MS (73% and 68.5%), which were higher than reported for vitamin D deficiency (<20 ng/mL) and insufficiency (20–29 ng/mL) in Turkish children and adolescents (8% and 25.5%) (Yılmaz et al., 2022, Yeşiltepe-Mutlu et al., 2020). Low vitamin D level during childhood is linked to the development of MS (Gombash et al., 2022), and our results suggest its possible role in conversion of isolated lesions to MS.

None of the patients diagnosed with RIS were prescribed DMTs for MS, while 30% were treated after clinical or radiological evolution. Currently no data demonstrate the efficacy of DMT in preventing or delaying clinically definite disease. However, George et al. recently reported that early use of a DMT in RIS may reduce the likelihood of conversion to clinically definite CNS demyelinating disease in high-risk adults (George et al., 2021). Because the majority of patients did not develop clinical event during follow-up in our and other published studies (Engell, 1989, Makhani et al., 2017) the risk does not justify exposing children and adolescents to possible side effects of DMTs. However, further studies might help to identify a set of biomarkers defining a high-risk group among pediatric and adolescent RIS, thereby justifying a revision of the indications for DMT in RIS.

None of the MS cases in our study showed a progressive course. Primary progressive forms of MS are extremely rare in children (less than 1%) and the secondary progressive forms take longer time (10 years or more) to develop in MS with onset <18 years old (Deiva, 2020). Although median duration of follow-up was 5.8 (min-max: 1.1–18.0) years in adult series of RIS, 15/453 (3%) evolved to PPMS, a rate apparently unrelated to duration follow-up after RIS was diagnosed (Kantarci et al., 2016). Only 9 patients had a follow-up ≥ 5 years in our study and longer follow-up is needed to reveal the long term course of pediatric RIS.

Radiological evolution according to 2010 and 2005 MRI criteria for DIS did not differ in groups meeting the two sets of criteria (53.6% and 50%), and the risk of clinical event was also similar (20% and 21.4%). This suggests patients who meet 2005 DIS criteria should also have follow-up MRI scans.

The strengths of our study include: the detailed and standardized clinical data, the large sample size despite the rarity of RIS before 18 years old and the need for sufficient follow-up for clinical conversion. We could not use the 2017 McDonald criteria including ≥1 cortical lesion since most cortical lesions go undetected on conventional MRI. The availability of advanced techniques in only few centers is a limitation in many other studies. In our study, it would have been preferable to re-examine MR images by a dedicated neuroradiologist. However, the well-defined characteristics and criteria of RIS, and the experience of radiologists of participating centers, all tertiary level research institutions, support the accuracy of MRI reports. Our results are applicable in the majority of pediatric neurology clinics. We suggest spinal cord imaging be included in prospective studies with standardized MRI protocols. Also, longer observation can determine the optimal duration and frequency of follow-up, as well the significance of RIS in childhood and adolescence and also the subgroups at higher risk for MS. Monitoring serum vitamin D levels in children and adolescents with RIS can be recommended. The diagnosis of RIS might also provide the opportunity to study the "MS prodrome" in objective and standardized fashion.

In summary, this large national study contributes to knowledge on a rare condition like RIS in pediatric and adolescent patients. Analysis of CSF in combination with brain and spinal cord MRI, at least 3 years' follow-up are advisable according to our results.

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CRediT authorship contribution statement

Deniz Yılmaz: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Serap Teber:** Conceptualization, Methodology, Writing – original draft. **Pembe Gültutan:** Formal analysis, Data curation, Visualization, Methodology. **Miraç Yıldırım:** Formal analysis, Data curation, Formal analysis, Visualization. **Ömer Bektaş:** Resources, Formal analysis. **Defne Alikılıç:** Resources, Formal analysis. **Mesut Güngör:** Resources, Formal analysis. **Bülent Kara:** Resources, Formal analysis. **İbrahim Öncel:** Resources, Formal analysis. **Tuğçe Damla Dilek:** Resources, Formal analysis. **Sema Saltık:** Resources, Formal analysis. **Seda Kanmaz:** Resources, Formal analysis. **Sanem Yılmaz:** Resources, Formal analysis. **Hasan Tekgül:** Resources, Formal analysis. **Dilek Çavuşoğlu:** Resources, Formal analysis. **Pakize Karaoğlu:** Resources, Formal analysis. **Ünsal Yılmaz:** Resources, Formal analysis. **Sibğatullah Ali Orak:** Resources, Formal analysis. **Olcay Güngör:** Resources, Formal analysis.

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Declaration of Competing Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.104948.

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