Multiple Sclerosis and Related Disorders 36 (2019) 101381

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

MRI features associated with high likelihood of conversion of radiologically isolated syndrome to multiple sclerosis

Joseph Bisulca[1], Amy De Lury[1], Patricia K Coyle, Olga Syritsyna, Robert Peyster, Lev Bangiyev, Tim Q Duong[*]

Departments of Radiology and Neurology, Stony Brook Medicine, 101 Nicolls Rd, Stony Brook, NY 11794, USA

ARTICLE INFO

Keywords:
Brain T2 lesions
Spinal cord lesions
Contrast-enhancement
Brain atrophy
Relapsing-remitting MS
Clinically isolated syndrome

ABSTRACT

Radiologically isolated syndrome (RIS) is the asymptomatic precursor to clinically isolated syndrome, relapsing-remitting multiple sclerosis (MS) or primary progressive MS. RIS is frequently diagnosed when an individual gets an MRI for an unrelated medical issue, such as headache or trauma. Treating RIS patients is controversial, but physicians may be inclined to offer prophylactic treatment for high-risk RIS patients. Identifying imaging and clinical features associated with high likelihood of early clinical conversion may prove helpful to identify a high-risk subset for potential MS therapy. The goal of this paper is to review current literatures to identify imaging and clinical features that predict early (*within* 5 years) conversion from RIS to MS.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating and neurodegenerative disease of the central nervous system (CNS) (Kantarci et al., 2016; Rojas et al., 2015). Patients with MS experience a wide range of neurological problems, including motor and cognitive dysfunction (Yamout and Al Khawajah, 2017). MS has four recognized phenotypes: clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), primary progressive multiple sclerosis (PPMS), and secondary progressive multiple sclerosis (SPMS) (Thompson et al., 2018). Radiologically isolated syndrome (RIS) is the asymptomatic precursor to both RRMS and PPMS, but not all patients with RIS will clinically convert. RIS is often found when the individual gets an MRI for an unrelated issue, such as migraines, other headaches, or trauma. RIS is a rare, but clinically significant, condition occurring at a rate of 0.8 cases per 100,000 person-years (Forslin et al., 2016). RIS was first defined in 2009 by Okuda and colleagues (see Table 1a). The established RIS diagnostic criteria uses the Barkhof criteria (Barkhof et al., 1997) for MRI dissemination in space (DIS); however, some studies (Rojas et al., 2015) use the revised McDonald diagnostic criteria (Thompson et al., 2018) for DIS. Differences between the Barkhof (Table 1b) and McDonald (Table 1c) criteria may categorize certain patients as RIS in one study, but not others. The definition of RIS has evolved over time due to better imaging methods and improved understanding of the RIS concept.

Within 5 years, one third of RIS patients convert clinically to CIS, RRMS, or PPMS, one third will have radiological activity but no clinical symptoms, and one third will remain radiologically and clinically stable (Okuda et al., 2014). Treating RIS patients is controversial because RIS is not a recognized MS phenotype, and disease modifying therapies can have negative side effects. However, continuing observation may delay treatment which could result in irreversible damage to the CNS (Akbar et al., 2016; Labiano-Fontcuberta and Benito-Leon, 2017; Lebrun, 2017; Okuda, 2017). Predictors of high likelihood of early clinical conversion could identify high-risk RIS patients for potential MS therapy. Although a few studies have previously reported predictors of RIS conversion to CIS and MS, the key predictors are unclear.

A typical brain MRI protocol for MS patients and monitoring of RIS patients includes proton density or T2-weighted sequence, T2-weighted fluid attenuated inversion recovery (FLAIR) sequence, and pre and post-contrast T1-weighted spin echo sequence (Wattjes et al., 2007). Double-inversion recovery is sometimes used to enhance lesion conspicuity where the first inversion pulse suppresses cerebrospinal fluid (CSF) signal and the second inversion pulse suppresses white-matter signal

Abbreviations: CHI3L1, Chitinase-3-Like Protein 1; CIS, Clinically Isolated Syndrome; CSF, Cerebrospinal Fluid; DIS, Dissemination in Space; DIT, Dissemination in Time; DTI, Diffusion Tensor Imaging; IgG, Immunoglobulin G; MS, Multiple Sclerosis; PPMS, Primary Progressive Multiple Sclerosis; RIS, Radiologically Isolated Syndrome; RRMS, Relapsing-Remitting Multiple Sclerosis; SC, Spinal Cord; SPMS, Secondary Progressive Multiple Sclerosis

[*] Corresponding author.
E-mail address: tim.duong@stonybrookmedicine.edu (T.Q. Duong).

[1] JB and ADL contributed equally.

https://doi.org/10.1016/j.msard.2019.101381
Received 27 February 2019; Received in revised form 30 August 2019; Accepted 31 August 2019

Table 1a
Definition/Proposed Diagnosis Criteria of RIS according to Okuda and colleagues (Okuda et al., 2009).

A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:
i. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum
ii. T2 hyperintensities measuring >3 mm and fulfilling Barkhof criteria (at least three out of four) for DIS
iii. CNS white matter anomalies not consistent with a vascular pattern
B. No historical accounts of remitting clinical symptoms consistent with neurologic dysfunction
C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized areas of functioning
D. The MRI anomalies are not due to the direct physiologic effects of substances (recreational drug abuse, toxic exposure) or a medical condition
E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter pathology lacking involvement of the corpus callosum
F. The CNS MRI anomalies are not better accounted for by another disease process

CNS = Central Nervous System, DIS = Dissemination in space.

Table 1b
Diagnosis Criteria of DIS according to Barkhof and colleagues (Barkhof et al., 1997). Three or more of these criteria must be fulfilled for DIS.

A. At least 1 gadolinium-enhancing lesion or at least 9 lesions on T2-weighted images
B. At least 3 periventricular lesions
C. At least 1 juxtacortical lesion
D. At least 1 infratentorial lesion

Table 1c
Diagnosis Criteria of DIS according to McDonald and colleagues (Thompson et al., 2018).

A. One or more T2-hyperintense lesions characteristic of MS in two or more of four CNS areas:
i. Periventricular
i. For some patients—e.g., individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions
ii. Cortical or juxtacortical
iii. Infratentorial
iv. Spinal cord

(Wattjes et al., 2007). Diffusion-weighted MRI and diffusion-tensor imaging (DTI), which can detect microstructural and white-matter changes, are used in research settings but not widely used in clinical settings. Similarly, a typical spinal cord MRI protocol includes proton density, short T1 inversion recovery (STIR), multi-echo recombined gradient echo (MERGE), and post-contrast T1-weighted spin echo (Simon et al., 2006). MRI of the spinal cord is more challenging compared to MRI of the brain, given its small structure, location, and length of the spinal cord, amongst others which could limit lesion detection. From these images, the number, volume and location of lesions, lesion characteristics, whether lesions are contrast-enhanced (indicative of active lesions with permeable blood-brain barrier), and fractional anisotropy in the brain and spinal cord can be obtained. Changes in these MRI features in time and space (dissemination in time and space [4]) are also used in the MS diagnosis (Thompson et al., 2018).

Some of the non-imaging features include CSF markers (e.g. oligoclonal bands, immunoglobulin levels, antibodies, proteins etc.), demographic information (e.g. age, sex, ethnicity etc.), initial symptom leading to the first MRI, and cognitive impairment index score.

The goal of this paper was to review the literature to date, to identify imaging and clinical features that predict or are associated with high likelihood of early conversion (ca. 5 years) from RIS to MS.

2. Methods

This retrospective literature review was conducted by searching PubMed. Search keywords included: radiologically isolated syndrome, RIS, multiple sclerosis, MS, magnetic resonance imaging, and MRI. Although no publication date restriction was applied as a search filter, essentially all journal articles found were published from 2009 to May 2019 because the term RIS was explicitly defined only in 2009 by Okuda et al. (2009). Any paper published before 2009 did not discuss or recognize a condition with the term RIS; however, journal articles analyzing a condition that describes what is now known as RIS were also considered.

The inclusion criteria for our review consist of studies published during and after 2009, original research papers, and peer-reviewed journals printed or translated into English. Reviews, small series, and individual case studies were excluded. There were six reviews excluded. The process is detailed in the Fig. 1.

A total of 19 articles with 1546 RIS patients were identified for this study. We carefully reviewed individual papers to avoid double counting. A table of predictive and non-predictive factors were created. Similar factors were grouped together into broad categories, with the text describing the factors that made up those categories.

During our review, we paid attention to the statistics within each paper, the authors' opinions, and other factors that contributed to the strengths of predictors and non-predictors of early RIS conversion. The review summarizes our interpretation of the key predictors, current controversial factors, and clear non-predictors of early (*within* 5 years) RIS conversion. The conclusions of our review paper are qualitative, derived from original authors' conclusions, weighted by number of study subjects, quality of the experimental design, confounding variables being considered, where available. We note where the conclusion was weighted by few papers with large number of participants. There was no statistical analysis of data from original analysis.

3. Results

3.1. Spinal cord MRI features

Macroscopic (T2) lesions: Spinal cord lesions detected by T2-weighted MRI was the strongest predictive factor for RIS conversion, based on 9 studies and 671 patients (Kantarci et al., 2016; Rojas et al., 2015; De Stefano et al., 2018; De Stefano et al., 2011; Gabelic et al., 2014; Lebrun et al., 2012; Maia et al., 2012; Makhani et al., 2017; Thouvenot et al., 2018). 56% of patients with spinal cord lesions converted to MS (Thouvenot et al., 2018). A number of other potential predictors (chitinase-3-like protein 1 (CHI3L1), oligoclonal bands, contrast-enhanced lesions, sex, age, and IgG index) were only predictive if paired with macroscopic spinal cord lesions (Thouvenot et al., 2018). One pediatric study also reported macroscopic spinal cord lesions as a clinical conversion predictive factor (Makhani et al., 2017). In a study of RIS patients, 69% of all 128 clinical converters to RRMS or PPMS had spinal cord lesions (Kantarci et al., 2016). That is more than double the general clinical conversion rate of 33.3% for RIS (Okuda et al., 2014). Additionally, all of the patients who converted to PPMS and who had early spinal cord MRI (n = 12) had spinal cord lesions, and 64% of converters to CIS or RRMS had spinal cord lesions (Kantarci et al., 2016). De Stefano et al. also found spinal cord lesions to increase the likelihood for clinical conversion (De Stefano et al., 2011). Asymptomatic spinal cord lesions were noted as a predictive factor, although only the cervical region was monitored (Maia et al., 2012); nevertheless, all patients who had spinal cord lesions in this study developed clinically defined MS. In a Brazilian cohort of 12 patients, most (83.3%) patients clinically converted or had new activity on an MRI in the initial years of follow-up, although some individuals did not convert over a 4-year follow-up (Maia et al., 2012). In addition, macroscopic spinal cord lesions were found to predict future disability as well as clinical

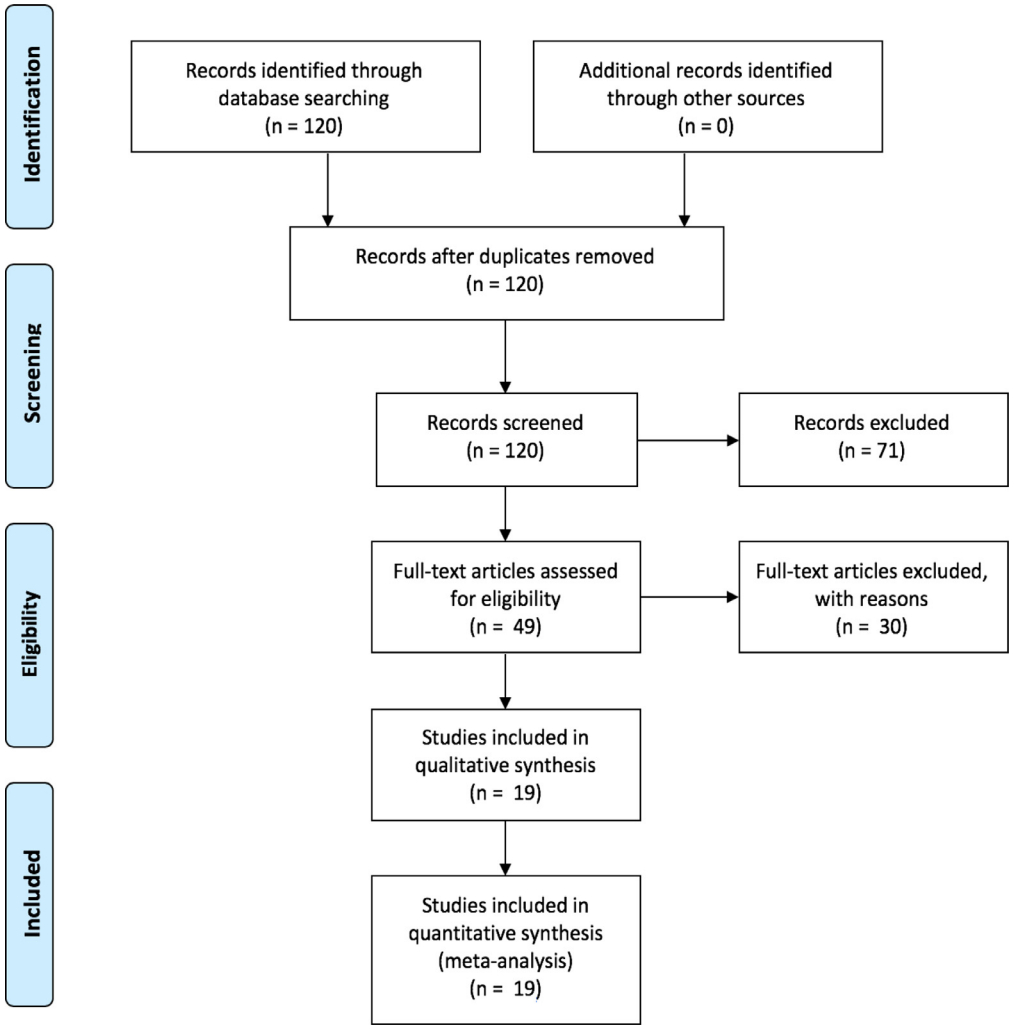

Fig. 1. The flow chart used to sort through the articles.

conversion (Kantarci et al., 2016). There was one study that found spinal cord lesions to be non-predictive of clinical conversion (Rossi et al., 2015), but it had a small sample size (n = 18) and short follow-up time of 2 years (instead of the 5 years reported in many studies).

DTI characteristics: Changes in DTI parameters, such as fractional anisotropy, mean diffusivity, axial diffusivity, and radial diffusivity, are indicative of damage to myelin and axons. DTI changes in spinal cord were found to be non-predictive in a study with 24 patients (Maia et al., 2012; Alcaide-Leon et al., 2018; Zeydan et al., 2018). Between the RIS and control groups, there were no significant differences in fractional anisotropy (p = 0.20) and mean diffusivity (p = 0.84) (Alcaide-Leon et al., 2018). Small sample size could be a limitation.

Spinal-cord atrophy: Spinal cord atrophy was evaluated in 2 studies involving 58 patients (Alcaide-Leon et al., 2018; Zeydan et al., 2018) and included segmental white matter, gray matter, and spinal cord cross-sectional area at C2 and C7. There was no significant difference in the spinal cord white matter or gray matter area between controls and RIS patients (n = 24) (Alcaide-Leon et al., 2018), but there was a trend toward a difference (p = 0.06) in the spinal cord cross-sectional area between controls and RIS patients (Alcaide-Leon et al., 2018). In another study comparing sex- and age-matched RIS (n = 58) and MS patients, there was no significant difference in the average cervical cross-sectional area (Zeydan et al., 2018). Furthermore, there was no difference between the C2 and C7 areas of sex- and age-matched RIS (n = 34) and MS patients (Zeydan et al., 2018).

Spinal-cord lesion location: Many studies have investigated whether different lesion locations in the spinal cord are associated with likelihood of MS presentation. Cervical spinal cord lesions are the strongest predictive factor for RIS conversion within the category of macroscopic spinal cord MRI lesions. Cervical spinal cord lesions alone had 3 studies involving 534 patients (Okuda et al., 2014; Maia et al., 2012; Okuda et al., 2011). In one study, 84% of RIS patients with cervical spinal cord lesions converted clinically, while only 6.5% of RIS patients without cervical lesions converted (Okuda et al., 2011). Maia et al. reported that spinal cord abnormalities (scored by number, location, size, MRI appearance regarding focal lesion or diffuse abnormality, and gadolinium enhancement) predicted MS even if no clinical symptoms from the spinal cord were present (n = 12) (Maia et al., 2012). Cervical spinal cord volume (n = 34) was found to be a predictive factor for clinical conversion compared to sex and age-group matched controls with RIS and MS (Zeydan et al., 2018). There was one study that found cervical spinal cord lesions to be non-predictive; however, this is likely limited due to a small sample size (n = 25 patients) and a short follow-up time (0.67–2.42 years) (Etemadifar et al., 2014). We thus conclude that cervical lesions are strong predictors of clinical conversion. Thoracic spinal cord lesions are comparatively less frequently mentioned than cervical spinal cord lesions as a predictive factor, with only one article with 451 patients (Okuda et al., 2014). Nevertheless, asymptomatic thoracic spinal cord lesions are considered a significant risk factor for clinical conversion and equal to asymptomatic cervical spinal cord lesions (Okuda et al., 2014). A review paper noted the predictive value

of thoracic spinal cord lesions (Yamout and Al Khawajah, 2017). As a result, thoracic spinal cord lesions can be considered a strong predictor of clinical conversion.

Contrast-enhanced spinal-cord lesions: There are limited studies of contrast-enhanced spinal cord lesions in RIS patients. We found only one study ($n = 453$) showing contrast-enhanced spinal cord lesions to be not predictive of RIS conversion (Kantarci et al., 2016). The presence of contrast-enhanced spinal-cord lesions is not predictive of RIS conversion to MS.

In summary, macroscopic T2 hyperintense lesions in the cervical and thoracic spinal cord appeared to be strong predictors of early clinical conversion. It is unclear whether DTI changes in the spinal cord are predictive of RIS conversion because of small sample sizes. Although RIS already shows spinal cord volumes similar to established early MS, spinal cord atrophy does not appear to predict early RIS conversion. The presence of contrast-enhanced spinal cord lesions does not appear to predict early RIS conversion.

3.2. Brain MRI features

T2 brain lesions: In five studies and 191 patients, the number of T2 lesions was found to be non-predictive of RIS conversion (Maia et al., 2012; Rossi et al., 2015; Okuda et al., 2011; Giorgio et al., 2011; Matute-Blanch et al., 2018). The number of T2 hyperintense lesions did not matter for RIS prognosis prediction (Giorgio et al., 2011) or did not predict RIS conversion (Maia et al., 2012; Giorgio et al., 2011). Patients with nine or more lesions on MRI (Rossi et al., 2015), or 5–10 lesions and greater than 10 lesions (Okuda et al., 2011), were found to be non-predictive for RIS clinical conversion. Only one study found the number of T2 lesions to be a significant predictor (Gabelic et al., 2014).

Brain atrophy: Brain volume normalized for head size were found to be non-predictive in four studies involving 65 patients (Rojas et al., 2015; De Stefano et al., 2011; Giorgio et al., 2011; Azevedo et al., 2015). In one study, normalized brain volume did not differ between patients with and without cortical lesions, despite a larger white-matter lesion volume in subjects with cortical lesions (Giorgio et al., 2011). In another study, there were no differences between the normalized brain volumes of CIS and RIS patient groups (Rojas et al., 2015). Brain volumes were similar in demographically matched RIS and RRMS patients (De Stefano et al., 2011). Normalized gray matter, white matter, and total brain volume did not differ significantly between RIS patients ($n = 44$) and controls (Azevedo et al., 2015).

Location of brain lesions: We separated location of brain lesions into: (i) periventricular lesions, (ii) juxtacortical lesions, (iii) infratentorial lesions, and iv) corpus callosal lesions. The lesion location category had 5 predictive studies involving 166 patients, in addition to 5 non-predictive studies involving 1037 patients.

Infratentorial lesions: Although 4 earlier studies involving 151 patients suggested infratentorial lesions were significant predictors of clinical conversion, and were a potential factor for subclinical MS diagnosis (De Stefano et al., 2018; Gabelic et al., 2014; Maia et al., 2012; Okuda et al., 2011), 5 studies and 1037 patients found infratentorial lesions non-predictive for RIS clinical conversion (Kantarci et al., 2016; Okuda et al., 2014; Makhani et al., 2017; Etemadifar et al., 2014; Lebrun et al., 2009). For example, according to a 5-year follow-up study ($n = 451$), infratentorial lesions were not found to be significant predictors based on a univariate analysis test despite its importance for CIS conversion (Okuda et al., 2014). In another article, the presence of infratentorial lesions was found to be in significant in predicting conversion to CIS, MS, or PPMS (Kantarci et al., 2016). According to the pediatric study, no statistically significant difference was found between converters and non-converters in regard to infratentorial lesions (Makhani et al., 2017). Despite four studies claiming that infratentorial lesions are predictive, these studies ($n = 151$) are comparatively small. One study with a small sample ($n = 25$) and a short follow-up time (0.67–2.42 years) found brainstem lesions to be non-predictive (Etemadifar et al., 2014), whereas another paper, which had a larger sample size ($n = 71$) and a longer follow-up time (1.3–4.8 years), found brainstem lesions to be predictive (Okuda et al., 2011). Since the studies arguing that infratentorial lesions are non-predictive have a considerably larger sample size, it is concluded that infratentorial lesions are likely not predictive for RIS clinical conversion.

Periventricular lesions: Although included in the modified criteria for RIS and considered a more likely location for demyelinating lesions (De Stefano et al., 2018), periventricular lesions were found to be non-predictive in three studies and 514 patients (Okuda et al., 2014; Makhani et al., 2017; Etemadifar et al., 2014). According to a short-term follow-up study, periventricular lesions were not found to be significant predictors for clinical conversion to MS (Etemadifar et al., 2014). Based on a 2014 study, periventricular lesions did not significantly contribute to clinical conversion within 5 years (Okuda et al., 2014). In the pediatric RIS study, periventricular lesions were not significantly different between converters and non-converters (Makhani et al., 2017). Periventricular lesions can be considered non-predictive factors for clinical conversion in RIS.

Juxtacortical: Although juxtacortical lesions were included in a diagnostic for subclinical MS (De Stefano et al., 2018), juxtacortical lesions were found to be non-predictive factors in two studies and 489 patients (Okuda et al., 2014; Makhani et al., 2017). In an article about the 5-year conversion rate, juxtacortical lesions were not found to be significant predictors with univariate analysis (Okuda et al., 2014). In a 2017 article and its associated reviews, there was no statistically significant difference in juxtacortical lesions between converters and non-converters (Makhani et al., 2017). Juxtacortical lesions appear to be a non-predictive factor.

Corpus Callosal lesions: One study found corpus callosal lesions to be a non-predictive factor (Etemadifar et al., 2014). In this paper, corpus callosal lesions were found to have no impact on the conversion of RIS to MS (Etemadifar et al., 2014). However, the study has limited weight because of its small sample ($n = 25$). Further study is needed.

Cortical lesions: Cortical lesions were found to be predictive factors for RIS clinical conversion in one article (Giorgio et al., 2011). However, their predictive value must be considered weak because of the small sample size.

Contrast-enhanced lesions: Contrast-enhanced brain lesions were found to be non-predictive in 5 studies and 648 patients (Okuda et al., 2014; Maia et al., 2012; Makhani et al., 2017; Thouvenot et al., 2018; Okuda et al., 2011). In a 5-year study by Okuda and colleagues ($n = 451$), contrast-enhanced lesions failed as a predictive factor in the univariate analysis (Okuda et al., 2014). According to another study ($n = 12$), other factors such as infratentorial and spinal cord lesions, as well as the total number of lesions, were found to be more predictive than contrast-enhanced lesions (Maia et al., 2012). In a pediatric study there were no statistically significant differences in contrast-enhanced lesions between converters and non-converters (Makhani et al., 2017). In one additional study, contrast-enhanced lesions failed the univariate Cox regression test for predictors (Okuda et al., 2011). Although three studies and 548 patients found contrast-enhanced lesions to be predictive (Kantarci et al., 2016; Etemadifar et al., 2014; Lebrun et al., 2009), one of those studies ($n = 25$) found them to be only marginally significant predictors (Etemadifar et al., 2014). In a study on RIS conversion to PPMS, contrast-enhanced lesions were found to increase disability independent of its predictive value (Kantarci et al., 2016). According to a follow-up study ($n = 70$), contrast-enhanced lesions were found to be predictive, but this study's findings were only found one other time in a smaller sample size (Lebrun et al., 2009). Despite the Barkhof criteria (see Table 1b), a consensus of neurologists (Granberg et al., 2013), and a 2013 review declaring contrast-enhanced lesions predictive for RIS (Tornatore et al., 2016), contrast-enhanced lesions as a predictor of RIS conversion remains controversial due in part to low prevalence of contrast-enhanced lesions. The published literature, however, does not support the presence of contrast-enhanced lesions as a predictor of rapid RIS clinical conversion, but further study

is required.

It is also important to note that, although sample sizes are small, thalamic atrophy (1 study with 21 patients) (Azevedo et al., 2015), DIS (1 study with 68 patients) (De Stefano et al., 2011), and dissemination in time (DIT) (2 studies with 87 patients) (De Stefano et al., 2011; Lebrun et al., 2009) were also found to be predictive of early clinical conversion. In a 2011 study, DIT was classified as at least one new T2 white matter lesion, which was found in 10 out of 19 patients while DIS was mentioned as being suggestive of MS (De Stefano et al., 2011). In a 2009 study, DIT based on the McDonald Criteria (see Table 1c) was used as diagnostic criteria for MS on the MRI, and 91% of the cohort fulfilled it (Lebrun et al., 2009). A separate study concluded that thalamic atrophy was a novel predictor of conversion since it was consistent with previous reports of early stage MS. Further studies are however needed since only one study confirmed each of these factors.

In summary, the data does not support that the number of T2/FLAIR lesions in the brain is predictive of early RIS conversion. Although RIS already shows brain volumes similar to established early MS, brain atrophy is not suggested to be predictive of RIS conversion. Lesion locations (periventricular, juxtacortical, infratentorial, and corpus callosal lesions) are suggested to be poor predictors of early RIS conversion. Cortical lesions have weak predictive value. The presence of contrast-enhanced brain lesions does not appear to predict early RIS conversion.

3.3. CSF biomarkers

The studied CSF biomarkers consisted of (i) oligoclonal bands, (ii) CSF neurofilament light chain protein, (iii) CSF Interleukin-8 and Sorcin Antibodies, (iv) Chitinase-3-Like Protein 1 (CHI3L1), and (v) IgG Index.

Oligoclonal Bands: In the 2017 revised McDonald diagnostic criteria, CSF-specific oligoclonal bands can replace DIT for a diagnosis of MS (Thompson et al., 2018). This revision came based on 5 studies and 705 patients supporting oligoclonal bands as a predictive factor (Kantarci et al., 2016; Okuda et al., 2014; Makhani et al., 2017; Thouvenot et al., 2018; Matute-Blanch et al., 2018). Oligoclonal bands were found to be a dependent predictive factor for RIS clinical conversion when paired with spinal cord lesions (Thouvenot et al., 2018). Although two studies reported that oligoclonal bands were not a significant predictive factor (Rossi et al., 2015; Lebrun et al., 2009), one article conceded that oligoclonal bands were a predictive factor when combined with two or more hyperintense T2 lesions (similar to the results in another paper) (Thouvenot et al., 2018; Lebrun et al., 2009). Meanwhile, the other study stating that oligoclonal bands were not a significant predictive factor had only 18 RIS patients (Rossi et al., 2015). When abnormal CSF is counted, only one study ($n = 451$) found abnormal CSF to be non-predictive, but it includes oligoclonal bands and the IgG Index (Okuda et al., 2014). In this study more than 2 unique oligoclonal bands, or an IgG Index higher than 0.7 was classified as abnormal CSF. In the multivariate Cox regression model, CSF profiles were found to be a non-predictive factor for the first clinical event (Okuda et al., 2014). Although one paper ($n = 19$) suggested that abnormal CSF had predictive value (De Stefano et al., 2011), oligoclonal bands are still strongly predictive. Although it appears that oligoclonal bands represent a small section of the predictive factors for RIS clinical conversion, this is misleading. In a meta-analysis, oligoclonal bands were reaffirmed as strong predictors for MS (Gastaldi et al., 2017). Indeed, oligoclonal bands are emphasized in the most recent 2017 revised McDonald criteria (Thompson et al., 2018; De Stefano et al., 2018). In addition, oligoclonal bands were also found to predict disability for MS as well (Gastaldi et al., 2017). Thus, oligoclonal bands should be considered strong predictors of RIS conversion.

Neurofilament Light Protein: Only one study with 75 patients examined CSF neurofilament light protein levels and found them to be predictive (Matute-Blanch et al., 2018). According to this study, high levels of CSF neurofilament light protein were found to have an even higher value than oligoclonal bands in both univariate and multivariate analysis, and shortened the time for conversion to CIS or MS (Matute-Blanch et al., 2018). Neurofilament light protein has been examined more closely because of a new SIMOA (Single Molecule Array) assay that can detect ultra-low levels in serum (Disanto et al., 2017). They are often higher in progressive MS as markers for axonal damage. This method of measuring blood neurofilament light protein is more practical; however, the SIMOA assay is not widely available clinically. A potential confounding variable is that neurofilament light protein in serum and CSF could also increase as a result of acute injury or other neurodegenerative disorders, rendering it less specific (Disanto et al., 2017). It should also be noted that neurofilament light protein increases with age. As neurofilament light protein is relatively recent, further studies are warranted.

A single study found CSF Interleukin-8 levels to be predictive for RIS clinical conversion (Rossi et al., 2015). However the small sample ($n = 18$) limits its applications. Sorcin antibodies, which attack a protein that binds to calcium, were found to be predictive in a single study with 13 patients (Sehitoglu et al., 2014). It was found that 75% of RIS patients who converted to MS had these antibodies (Sehitoglu et al., 2014). However, the total sample for these factors was small ($n = 125$). Interleukin-8 and Sorcin are new CSF markers and further studies are needed.

Chitinase-3-like protein 1 (CHI3L1): Although other studies have implicated this protein in CSF with predicting CIS conversion to MS (Canto et al., 2015; Comabella et al., 2010; Comabella and Montalban, 2014; Hinsinger et al., 2015), there were only two studies with 146 patients that reported on its predictive value for RIS clinical conversion (Makhani et al., 2017; Thouvenot et al., 2018; Matute-Blanch et al., 2018). One study claimed that this protein had a dependent predictive value based on spinal cord lesions (Thouvenot et al., 2018). The other claimed that the protein was not predictive (Matute-Blanch et al., 2018). The predictive value of this protein is unclear because it was only examined in two studies, so it requires further investigation.

IgG index: As part of the abnormal CSF category, the IgG index has one additional study involving 70 patients linking it as a non-predictive factor with no value for RIS conversion (Lebrun et al., 2009). Although one article claimed the IgG Index was predictive if paired with spinal cord lesions, the study had a significantly shorter (< 5 years) follow-up time (Thouvenot et al., 2018). In addition, a meta-analysis on the predictive value of the IgG Index found it to be unhelpful for prediction because of false positives, so IgG Index should not be used to predict conversion (Gastaldi et al., 2017).

In summary, CSF-specific oligoclonal bands appears to be a good predictor of RIS conversion. CSF neurofilament light protein, Interleukin-8, and Sorcin antibodies require further studies. CHI3L1 and IgG index appear not to be predictors of RIS conversion according to the data.

3.4. Demographics

The studied demographics categories included: i) age, ii) biological sex, and iii) pregnancy. The demographic category had 5 studies and 1056 patients.

Although age was not found to be a predictor in 6 studies with a total of 276 patients (Makhani et al., 2017; Thouvenot et al., 2018; Rossi et al., 2015; Etemadifar et al., 2014; Giorgio et al., 2011; Matute-Blanch et al., 2018), four studies and one review found that a younger age (less than 37) at diagnosis of RIS predicts its clinical conversion with a total number of 607 patients (Yamout and Al Khawajah, 2017; Okuda et al., 2014; Maia et al., 2012; Okuda et al., 2011; Lebrun et al., 2009). Younger age predicted clinical conversion, along with male sex and spinal cord lesions (Okuda et al., 2014; Okuda et al., 2011). Young age also predicted a worse prognosis for RIS (Lebrun et al., 2009). In another article, younger age was once again associated with clinical conversion (Maia et al., 2012). Only one study found older age (1 study

Table 2
Summary of RIS patient and study MRI features (Y = Yes).

Author; Year	Journal, Impact Factor	Number of RIS/ Female	Number of Controls/ Female	% Clinical Conversion	Mean (Median) Years to Conversion	Range Years to Conversion	Predictive Factors	Non-predictive Factors	Comments	Inclusionary Criteria Fulfilled
Giorgio et al.; 2011	Neurology, 7.592	15/10F	None	—	—	—	Cortical Lesions[a]	Age; Biological Sex; Cognitive Impairment Index Score; Normalized Brain Volume; Number of T2 Hyperintense White Lesions	No FLAIR	Y
Okuda et al.; 2011	Neurology, 7.592	71/56F	None	36.6%[b]	(1.6)	—	Asymptomatic Cervical Lesions; Younger Age; Brain Stem Lesions	Number of T2 Lesions; Contrast-Enhanced Lesions	median follow-up time 3.3 years	Y
Okuda et al.; 2014	PLOS One, 2.806	456/354F	None	34%[c]	Follow-up at 5 years	—	Asymptomatic Cervical Lesions; Asymptomatic Thoracic Lesions; Male Sex; Age < 37 at Diagnosis	Ethnicity, Abnormal CSF, Periventricular, Infratentorial, Juxtacortical, and Contrast-Enhanced Lesions	One third showed radiological progression	Y
Lebrunet al.; 2009	JAMA Neurology, 10.029	68/53F	None	33.80%	2.3	—	Both DIS and DIT; Contrast-Enhanced Lesions on the MRI; Young Age	Oligoclonal bands; Increased IgG index; Sex; Initial Symptom; Infratentorial Lesions	Oligoclonal bands and IgG Index are predictors when combined with 9 or more T2 lesions; 5-year follow-up time; Used DIT as a diagnosis of MS; no FLAIR	Y
Maia et al.; 2012	Arquivos De Neuro-Psiquiatria, 0.902	12/10F	None	33.30%	2.9	0.58–5.92	Infratentorial Lesions; Spinal Cord Involvement; Number of Baseline Lesions; Asymptomatic Brain and Spinal Cord Lesions; Male Sex; Younger Age	Contrast-Enhanced Lesions; Number of T2 Lesions	Cervical Region monitored only; median 4.1 years follow-up time; uses clinical attack for MS diagnosis; uses FLAIR	Y
Kantarci et al.; 2016	Annals of Neurology, 9.89	453/322F	None	56.50%	2.4[d]	2.0–2.8	Spinal Cord Lesions[e]; 1 or more Contrast-Enhanced Lesions; Older Age (PPMS); Male Sex (PPMS); Younger Age at diagnosis;	Contrast-Enhanced Spinal Cord Lesions	5-year follow-up time	Y
Etemadifar et al.; 2014	Internat Journal Preventative Medicine, 0.98	25/17F	None	24%	1.1	—	Contrast-Enhanced Lesions (marginal)	Age at first MRI; Biological Sex; Periventricular, Corpus Callosal, Brain Stem and Cervical Lesions	Small n; mean follow-up time 1.45 years; uses both Barkhof Criteria and McDonald Criteria for conversion	Y
Makhani et al.; 2017	Neurology, 7.592	38/27F	None	68.40%	(5.0)	2–7	2 or more Oligoclonal Bands; Spinal Cord Lesions	Age; Biological Sex; Race; Reason for first MRI; Contrast-Enhancing Lesions; Infratentorial Lesions; Periventricular Lesions; Juxtacortical Lesions	mean follow-up time 4.8 years; uses Barkhof and 2005 DIS criteria for DIS; uses FLAIR	Y
Alcaide-Leon et al.; 2018	Neurology, 7.592	24/19F	14/8F	—	—	—	Spinal Cord Involvement	Spinal Cord Cross-Sectional Area; Spinal-Cord DTI metrics; Spinal Cord Gray Matter Area; Spinal Cord White Matter Area	—	Y
Zeydan et al.; 2018	Neurology, 7.592	34/25F	None	—	—	—	Cervical Spinal Cord Atrophy (progressive disease)	C2 Area; C7 Area; Cervical Spinal Cord Average Cross Sectional Area; Sex; Age	Uses 2010 McDonald Criteria for diagnosis	Y
Azevedo, et al.; 2015	Neurology, 7.592	21/13F	42/29F	—	—	—	Thalamic Atrophy	Normalized Gray, White Matter, and Parenchymal Volumes	—	Y

(*continued on next page*)

Table 2 (*continued*)

Author; Year	Journal, Impact Factor	Number of RIS/ Female	Number of Controls/ Female	% Clinical Conversion	Mean (Median) Years to Conversion	Range Years to Conversion	Predictive Factors	Non-predictive Factors	Comments	Inclusionary Criteria Fulfilled
Lebrun et al.; 2012	Multiple Sclerosis Journal, 5.280	60 (7 pregnant)/ 60F	None	57.1% (pregnant); 41.5% (non-pregnant)	Pregnant: 1.3; Non-pregnant: 2.97	Pregnant: 0.83–1.5; Non-Pregnant: 0.67–6.33	Pregnancy	—	Small n that became pregnant; uses FLAIR	Y
Rojas, et al.; 2015	Journal of Neuroimag, 1.664	10/5F	None	—	—	—	Spinal cord lesions	Brain Volumes	Small n; 5-year follow-up time; uses McDonald and Barkhof criteria for DIS; uses FLAIR	Y
Rossi et al.; 2015	Multiple Sclerosis J, 5.280	18/9F	76/47F	56%	(0.92)	—	Interleukin 8 levels	Age; Biological Sex; >9 MRI Lesions; Spinal Cord Lesions; Oligoclonal Bands	2-year follow-up time; uses FLAIR	Y
Thouvenot et al.; 2018	Multiple Sclerosis Journal, 5.280	71/47F	None	28.2%[f]	—	—	Spinal Cord Lesions; CHI3L1; Oligoclonal Bands; IgG Index	Contrast-Enhanced Lesions; Sex; Age	Only Spinal Cord Lesions were an independent predictive factor; median follow-up time 1.33 years; uses FLAIR	Y
Gabelic, et al.; 2014	Amer J of Neurorad, 3.55	68/48F	82/57F	—	—	—	Number of T2 Lesions; Infratentorial Lesions; Oligoclonal Bands; Spinal Cord Lesions	—	5-year follow-up is planned; uses both McDonald and Barkhof Criteria for DIS; uses FLAIR and T2WI	Y
De Stefano et al.; 2011	PLoS One, 2.806	19/14F	20/13F	—[g]	—	—	Abnormal CSF; Spinal Cord Lesions; DIT	Normalized Brain Volumes;	Tractography; Small n	Y
Matute-Blanch et al.; 2018	Brain, 10.292	75/55F	None	30.7%[h]	1.8	—	Oligoclonal Bands; Neurofilament Light Chains[i]	CHI3L1; Age; Sex; # of T2 Lesions	Spinal cord lesions not analyzed due to missing info in 66% RIS patients; mean follow-up time 2.8 years	Y
Sehitoğlu et al.; 2014	Inflammation Research, 2.659	13/10F	50	31%[j]	—	1–3	Sorcin antibody; Signal ratios	—	Small n; 5-year follow-up time; uses 2005 McDonald criteria	Y

[a] Only when associated with other risk factors,
[b] 84% with cervical lesions; 6.5% without cervical lesions,
[c] 9.8% developed PPMS,
[d] (3.5) for PPMS;
[e] 100% of PPMS patients and 64% of CIS/MS patients had them,
[f] RIS with spinal cord lesions will convert 56% of the time,
[g] 68.4% expected to convert,
[h] Converted to CIS,
[i] Restricted to patients 37 and older,
[j] 75% of converted patients had Sorcin antibodies; no converters had Sorcin antibodies.

Table 3
A summary of predictive and non-predictive factors for 5-year clinical conversion along with number of studies and number of patients. It is divided into categories of spinal cord MRI, brain MRI, and non-imaging characteristics.

Category		Predictive		Non-predictive	
		# of studies	# of patients	# of studies	# of patients
Spinal cord MRI	Number of T2 lesions	9	1193	1	18
	Volume	1	34	2	58
	Location	2	522	1	25
	Contrast enhancement	0	0	1	453
Brain MRI	Number of T2 lesions	2	138	4	173
	Volume	1	21	4	65
	Location	4	151	5	1037
	Contrast enhancement	3	548	5	648
Non-imaging characteristics	CSF markers	6	289	4	614
	Demographics	5	1057	10	346
	Ethnicity	0	0	4	489
	Initial symptoms	0	0	4	108

with 453 patients) to be predictive of RIS clinical conversion and it was only for conversion to PPMS (Kantarci et al., 2016). Younger age appears to be associated with a higher rate of conversion to MS.

Although biological sex was found to be non-predictive in six studies and 346 patients (Makhani et al., 2017; Thouvenot et al., 2018; Rossi et al., 2015; Etemadifar et al., 2014; Giorgio et al., 2011; Matute-Blanch et al., 2018; Lebrun et al., 2009), males had a higher rate of conversion to CIS, RRMS, and PPMS in three studies and 921 patients (Kantarci et al., 2016; Okuda et al., 2014; Okuda et al., 2011). In two articles, male sex predicted clinical conversion in univariate and multivariate analyses (Okuda et al., 2014; Okuda et al., 2011). In another paper, male sex was associated with clinical conversion to PPMS (Kantarci et al., 2016). Because of a larger sample and similarity in follow-up times in the three predictive studies, male sex is associated with higher likelihood to convert to CIS or MS compared to the female sex. This is in contrast to MS and CIS, which have a higher prevalence in female sex (Lebrun et al., 2012).

Only one study found pregnancy to be a risk factor for clinical conversion in RIS (Lebrun et al., 2012). This study reported that pregnant RIS subjects had a higher rate of conversion (57.1%) and a shorter mean conversion time despite pregnancy's protective status in CIS and RRMS (Okuda et al., 2011). Although pregnancy is a novel trait for RIS conversion, the study was limited in its sample size ($n = 7$) for its pregnant group. Further studies are needed.

In summary, we conclude that young age (less than 37 years old) and male sex are associated as risk factors for early RIS conversion to MS.

3.5. Ethnicity

Ethnicity was found to be non-predictive in two studies with 489 patients total (Okuda et al., 2014; Makhani et al., 2017). In a 5-year follow-up, white, African American, Hispanic, Middle Eastern, and Asian or Pacific Islander ethnicities failed as a predictive factor in the univariate Cox regression test (Okuda et al., 2014). According to a pediatric study and its reviews, there were no significant differences in white, African-American, Asian, American Indian or Alaska Native, Hispanic, and non-Hispanic races or ethnicities between converters and non-converters (Makhani et al., 2017). Ethnicity has only been explored in relation to contracting MS but not the conversion of RIS into clinical syndromes.

3.6. Initial symptom

There were a few miscellaneous factors that have been reported as non-predictive for conversion. In a pediatric study ($n = 38$), the reason for MRI based on headache vs. non-headache did not differ between converters and non-converters (Makhani et al., 2017) In another study, it found the cognitive impairment index (a grading system applied to each subject's score on every cognitive test of the Rao Brief Repeatable Battery, dependent on the number of standard deviations from the mean normative values where two or more failed tests mean cognitive impairment) to be non-predictive ($n = 15$) (Giorgio et al., 2011).

4. Limitations and future studies

This study used the total number of patients as an index of strength. We also accounted for the number of articles since conclusions based on a single study with a large number of subjects are limited. Our analysis could not statistically weigh the strength of statistics within each study because most studies did not have the information to perform such analysis. That said, we paid attention to the statistics, such as univariate and multivariate analyses, and experimental designs within each paper, the authors' opinions, and other factors that contributed to the strengths of predictors and non-predictors of RIS conversion. The total number of participants including controls could alternatively be used in our table, but doing so did not alter the overall conclusions of this study. It is not possible to determine which predictors are stronger than others because there are no head-to-head comparisons of various predictors in the literature. The majority of studies to date reported RIS conversion in 2–5 years; however, it may take longer (i.e., 20 plus years) to convert. In addition, certain studies with large sample sizes may have skewed the conclusions (Tables 2 and 3).

A few non-conventional MRI techniques such as DTI, resting-state functional MRI (Conrad et al., 2018; Droby et al., 2016), susceptibility-weighted imaging (Londono and Mora, 2014; Siemonsen et al., 2016), and quantitative susceptibility mapping (Deh et al., 2018; Langkammer et al., 2013) have been shown to provide valuable information for MS patients with respect to improving early detection and understanding of MS pathophysiology, amongst others. These imaging techniques, although not currently used on RIS, may prove useful for monitoring RIS patients.

5. Conclusions

This review paper identified imaging, laboratory, and clinical features that predict or are associated with high likelihood of conversion from RIS to CIS and MS. By far, spinal cord MRI features, especially macroscopic T2 lesions in the cervical and thoracic regions, are the most predictive of *early* clinical conversion of RIS to MS rate. Contrast-enhanced lesions and atrophy are controversial predictors and warrant further study. Location-specific lesions, IgG Index, and CHI3L1 were non-predictive factors. Although a consensus of neurologists in the United States support using contrast-enhanced lesions as a predictive factor (Tornatore et al., 2016) of RIS conversion, our review of the current literature does not support such a conclusion. Thus, this practice would be misleading.

Although some conclusions about the predictive value of macroscopic spinal cord lesions and oligoclonal bands were shared between our paper and a 2013 review (Granberg et al., 2013), the 2013 review concluded that contrast-enhanced lesions along with the number of T2 lesions seemed to be predictive for radiological and clinical conversion. Our paper disagrees since more papers have been published about RIS disputing the reliability of both contrast-enhanced lesions and the number of T2 lesions as radiological and clinical prognostic factors. In addition, the 2013 review stated that infratentorial lesions and the IgG Index predicted clinical conversion. We do not believe this is supported. These differences occurred because the 2013 review was published only

four years after RIS was officially defined and relied on the earliest papers about the topic that came to these conclusions. As a result, some of the 2013 review's conclusions may be inaccurate.

Currently, there are a few clinical trials on RIS, evaluating MS treatments dimethyl fumarate [NCT02739542] and teriflunomide [NCT03122652] for RIS patients, and another [NCT03357887] examining the prognostic value of CSF Tumor Necrosis Factor, CSF Protein X, CSF Protein Y, and CSF Secreted Glycoprotein on conversion time.

Identifying imaging and clinical features associated with the high likelihood of clinical conversion could have important clinical applications. These findings may help guide future research studies and clinical trials to explore specific imaging, laboratory, and clinical features. Such knowledge may enable healthcare providers to monitor specific features more diligently, thereby providing patients with a more informative or definitive prognosis of their disease condition. Our findings argue that spinal cord MRI and CSF biomarker analysis should be performed in all RIS patients because they are associated with high likelihood of early conversion from RIS to MS. As treating RIS patients remains controversial to date, physicians may be inclined to offer prophylactic treatment to high-risk RIS patients with a more definitive prognosis to prevent disease conversion.

Funding

Stony Brook School of Medicine (FUSION) pilot grant. We would like to acknowledge the use of the resources of the Biomedical Imaging Research Center (Radiology, Stony Brook Medicine).

Declaration of Competing Interest

None of the authors declare any conflicts of interest.

References

Akbar, N., et al., 2016. Alterations in functional and structural connectivity in pediatric-onset multiple sclerosis. PLoS One 11 (1), e0145906.
Alcaide-Leon, P., et al., 2018. Quantitative spinal cord MRI in radiologically isolated syndrome. Neurol. Neuroimmunol. Neuroinflamm. 5 (2), e436.
Azevedo, C.J., et al., 2015. Early CNS neurodegeneration in radiologically isolated syndrome. Neurol. Neuroimmunol. Neuroinflamm. 2 (3), e102.
Barkhof, F., et al., 1997. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 120 (Pt 11), 2059–2069.
Canto, E., et al., 2015. Chitinase 3-like 1: prognostic biomarker in clinically isolated syndromes. Brain 138 (Pt 4), 918–931.
Comabella, M., Montalban, X., 2014. Body fluid biomarkers in multiple sclerosis. Lancet Neurol. 13 (1), 113–126.
Comabella, M., et al., 2010. Cerebrospinal fluid chitinase 3-like 1 levels are associated with conversion to multiple sclerosis. Brain 133 (Pt 4), 1082–1093.
Conrad, B.N., et al., 2018. Multiple sclerosis lesions affect intrinsic functional connectivity of the spinal cord. Brain 141 (6), 1650–1664.
De Stefano, N., et al., 2011. Improving the characterization of radiologically isolated syndrome suggestive of multiple sclerosis. PLoS One 6 (4), e19452.
De Stefano, N., et al., 2018. Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. Mult. Scler. 24 (2), 214–221.
Deh, K., et al., 2018. Magnetic susceptibility increases as diamagnetic molecules breakdown: myelin digestion during multiple sclerosis lesion formation contributes to increase on QSM. J. Magn. Reson. Imaging.
Disanto, G., et al., 2017. Serum neurofilament light: a biomarker of neuronal damage in multiple sclerosis. Ann. Neurol. 81 (6), 857–870.
Droby, A., et al., 2016. Changes in brain functional connectivity patterns are driven by an individual lesion in MS: a resting-state fMRI study. Brain Imaging Behav. 10 (4), 1117–1126.
Etemadifar, M., et al., 2014. Conversion from radiologically isolated syndrome to multiple sclerosis. Int. J. Prev. Med. 5 (11), 1379–1386.
Forslin, Y., et al., 2016. Incidence of radiologically isolated syndrome: a population-based study. AJNR Am. J. Neuroradiol. 37 (6), 1017–1022.
Gabelic, T., et al., 2014. Prevalence of radiologically isolated syndrome and white matter signal abnormalities in healthy relatives of patients with multiple sclerosis. AJNR Am. J. Neuroradiol. 35 (1), 106–112.
Gastaldi, M., Zardini, E., Franciotta, D., 2017. An update on the use of cerebrospinal fluid analysis as a diagnostic tool in multiple sclerosis. Expert. Rev. Mol. Diagn 17 (1), 31–46.
Giorgio, A., et al., 2011. Cortical lesions in radiologically isolated syndrome. Neurology 77 (21), 1896–1899.
Granberg, T., et al., 2013. Radiologically isolated syndrome–incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review. Mult. Scler. 19 (3), 271–280.
Hinsinger, G., et al., 2015. Chitinase 3-like proteins as diagnostic and prognostic biomarkers of multiple sclerosis. Mult. Scler. 21 (10), 1251–1261.
Kantarci, O.H., et al., 2016. Primary progressive multiple sclerosis evolving from radiologically isolated syndrome. Ann. Neurol. 79 (2), 288–294.
Labiano-Fontcuberta, A., Benito-Leon, J., 2017. Radiologically isolated syndrome should be treated with disease-modifying therapy - No. Mult. Scler. 23 (14), 1820–1821.
Langkammer, C., et al., 2013. Quantitative susceptibility mapping in multiple sclerosis. Radiology 267 (2), 551–559.
Lebrun, C., Bensa, C., Debouverie, M., Wiertlevski, S., Brassat, D., de Seze, J., ..., Tourbah, A., 2009. Association between clinical conversion to multiple sclerosis in radiologically isolated syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential follow-up of 70 patients. Arch. Neurol. 66 (7), 841–846.
Lebrun, C., et al., 2012. Impact of pregnancy on conversion to clinically isolated syndrome in a radiologically isolated syndrome cohort. Mult. Scler. 18 (9), 1297–1302.
Lebrun, C., 2017. Radiologically isolated syndrome should be treated with disease-modifying therapy - Commentary. Mult. Scler. 23 (14), 1821–1823.
Londono, A.C., Mora, C.A., 2014. Nonconventional MRI biomarkers for in vivo monitoring of pathogenesis in multiple sclerosis. Neurol. Neuroimmunol. Neuroinflamm. 1 (4), e45.
Maia Jr, A.C.M., Rocha, A.J.D., Barros, B.R., Tilbery, C.P., 2012. Incidental demyelinating inflammatory lesions in asymptomatic patients: a Brazilian cohort with radiologically isolated syndrome and a critical review of current literature. Arq. Neuropsiquiatr. 70 (1), 5–11.
Makhani, N., et al., 2017. Radiologically isolated syndrome in children: clinical and radiologic outcomes. Neurol. Neuroimmunol. Neuroinflamm. 4 (6), e395.
Matute-Blanch, C., et al., 2018. Neurofilament light chain and oligoclonal bands are prognostic biomarkers in radiologically isolated syndrome. Brain 141 (4), 1085–1093.
Okuda, D.T., et al., 2009. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology 72 (9), 800–805.
Okuda, D.T., et al., 2011. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. Neurology 76 (8), 686–692.
Okuda, D.T., et al., 2014. Radiologically isolated syndrome: 5-year risk for an initial clinical event. PLoS One 9 (3), e90509.
Okuda, D.T., 2017. Radiologically isolated syndrome should be treated with disease-modifying therapy - Yes. Mult. Scler. 23 (14), 1818–1819.
Rojas, J.I., et al., 2015. Brain atrophy in radiologically isolated syndromes. J. Neuroimaging 25 (1), 68–71.
Rossi, S., et al., 2015. Subclinical central inflammation is risk for RIS and CIS conversion to MS. Mult. Scler. J. 21 (11), 1443–1452.
Sehitoglu, E., et al., 2014. Sorcin antibody as a possible predictive factor in conversion from radiologically isolated syndrome to multiple sclerosis: a preliminary study. Inflamm. Res. 63 (10), 799–801.
Siemonsen, S., et al., 2016. Chronic T2 lesions in multiple sclerosis are heterogeneous regarding phase mr imaging. Clin. Neuroradiol. 26 (4), 457–464.
Simon, J.H., et al., 2006. Standardized MR imaging protocol for multiple sclerosis: consortium of MS centers consensus guidelines. AJNR Am. J. Neuroradiol. 27 (2), 455–461.
Thompson, A.J., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17 (2), 162–173.
Thouvenot, E., Hinsinger, G., Demattei, C., Uygunoglu, U., Castelnovo, G., Pittion-Vouyovitch, S., Okuda, D., Kantarci, O., Pelletier, D., Lehmann, S., Marin, P., Siva, A., Lebrun, C., 2018. Cerebrospinal fluid chitinase-3-like protein 1 level is not an independent predictive factor for the risk of clinical conversion in radiologically isolated syndrome. Mult. Scler. 25 (5), 669–677.
Tornatore, C., et al., 2016. Consensus opinion of us neurologists on practice patterns in RIS, CIS, and RRMS: evolution of treatment practices. Neurol. Clin. Pract. 6 (4), 329–338.
Wattjes, M.P., et al., 2007. Double inversion recovery brain imaging at 3T: diagnostic value in the detection of multiple sclerosis lesions. AJNR Am. J. Neuroradiol. 28 (1), 54–59.
Yamout, B., Al Khawajah, M., 2017. Radiologically isolated syndrome and multiple sclerosis. Mult. Scler. Relat. Disord. 17, 234–237.
Zeydan, B., et al., 2018. Cervical spinal cord atrophy: an early marker of progressive MS onset. Neurol. Neuroimmunol. Neuroinflamm. 5 (2), e435.