CNS Spectrums (2021), **26**, 307–309.
doi:10.1017/S1092852919001202

EDITORIAL

Radiologically isolated syndrome is antiquated amidst evolving McDonald criteria for multiple sclerosis

*Jagannadha Avasarala,** *and Fawad Yousuf*

Department of Neurology, University of Kentucky Medical Center & Kentucky Neuroscience Institute, Lexington, KY, USA

The diagnosis of radiologically isolated syndrome (RIS) is untenable in the modern era as new diagnostic criteria for multiple sclerosis (MS) continue to evolve. Even without optic nerve involvement, the shift in the diagnostic criteria for MS forces clinicians to make a diagnosis at the earliest possible time and appropriate treatment initiated. In this analysis, we revisit the original RIS criteria as published and conclude that RIS as a diagnostic entity is obsolete.

Received 14 May 2019; Accepted 15 May 2019

Based on a retrospective analysis of 44 patients, Okuda et al.[1] coined the term radiologically isolated syndrome (RIS) to denote a cohort of patients who had incidental MRI of brain changes suggestive of multiple sclerosis (MS). Contrast enhancement, a hallmark of new lesion development in MS, was present in 21 brain and 7 cord lesions. Of the 44 patients studied, 24% had one or more gadolinium-enhancing lesions fulfilling the dissemination-of-time (DIT) diagnostic criteria for MS proposed in 2010;[2] additionally, cerebrospinal fluid (CSF) profiles were highly characteristic of MS in 27/44 (61.3%) fulfilling DIT criteria for MS based on the 2017 McDonald criteria.[3] The original study[1] findings also included headaches, spells of uncertain etiology, lacunar syndrome, and hypersomnolence; such symptoms cannot be disregarded as atypical or ignored particularly in an era of evolving diagnostic criteria for MS.

In a follow-up study in 2011, Okuda et al.[4] noted that 25 of 71 patients (35.2%) had asymptomatic lesions in the cervical cord and 6/71 (8.4%) were gadolinium-enhancing. Eventually, 21/25 (84%) subsequently progressed to clinically isolated syndrome or primary progressive MS. It is noteworthy that none of the patients with asymptomatic cord lesions underwent a lumbar puncture to screen for MS, a procedure recommended by the 2017 McDonald criteria[3] in such instances. What would the classification be for patients with abnormal CSF findings and asymptomatic gadolinium-enhancing cord lesions? Is it possible to conclude a diagnosis of RIS without CSF studies in an era of new McDonald criteria?[3] Although Okuda et al.[1] suggested that additional studies would define the risk of conversion to clinically definitive MS, the newer guidelines speed up[3] MS diagnosis and make RIS criteria obsolete by adding CSF analyses as a biomarker of DIT. Most importantly, RIS patients have axonal loss, brain atrophy, and cognitive defects similar to changes that occur in MS,[3,5] and while such patients have been described as asymptomatic, they are not clinically or pathologically silent. Taken together, RIS, first described as a diagnostic curiosity in 2009 and extended to include asymptomatic cord lesions in 2011, cannot continue in the current MS diagnostic developments. It is a diagnostic anachronism amidst continually evolving McDonald diagnostic criteria (Table 1).[6] The new 2017 McDonald criteria[3] specify that symptomatic lesions seen on MRI of the brain fulfill the criteria of either DIT or dissemination in space (DIS) when lesions are noted in the supratentorial, infratentorial, or cord; the presence of cortical lesions alone can denote DIS, and CSF abnormalities are now linked to DIT criteria fulfilment.

In a 2009 study by Okuda, patients who presented with migraine-type headaches, spells of uncertain etiology, or underwent imaging studies for "curiosity," but were otherwise asymptomatic, were considered having RIS if their MRIs showed lesions suggestive of MS. However, evidence shows that patients who complain of headache as the first symptom no longer have

*Address correspondence to: Jagannadha Avasarala, MD, PhD, Department of Neurology, University of Kentucky Medical Center, Kentucky Neuroscience Institute, 740 S Limestone, Lexington, KY 40536, USA. (Email: javasarala@uky.edu)

TABLE 1. Differences between MS, RIS, and CIS

Disease	Symptoms	MRI changes	CSF changes	Drug therapy	Histopathology changes
RIS**	–	++	++	No	Yes
CIS*	+	+/–	+/–	Yes	?
MS	+	++	++	Yes	Yes

RIS = radiologically isolated syndrome; CIS = clinically isolated syndrome; MS = multiple sclerosis.
*First demyelinating event suggestive of MS.
**Can present with headaches, unexplained spells, or lacunar syndromes.

inconsequential neurological symptoms;[7] headache presentation might imply an inflammatory process that is even influenced by ethnicity.[8,9] A recent longitudinal study noted 78% of patients had headache as the first neurological symptom in MS.[7] Incidentally, headache was the most common symptom presentation in the RIS study.[1] Additionally, clinicians cannot dismiss "brain fog" or "episodic memory impairment" as not being consistent with MS presentation. Published data show that cognitive function in a cohort of 26 RIS patients, matched against healthy controls for age, gender, and level of education, was significantly lower in the RIS cohort,[10] indicating possible cortical involvement. Newer and higher-strength (4.7 T, 7 T, and 11 T) MRIs currently being studied threaten to confine RIS to a diagnostic curiosity as these have the potential to detect cortical lesions.

Lastly, MS does not have to present initially as a clinical attack – sometimes historical events and symptom evolution characteristic of MS provide reasonable evidence of a prior demyelinating event.[2]

The struggle to diagnose patients with MS is real and challenging even to experts in the field. Adding to the myriad diagnostic issues, in more recent times, the exclusion of antibody-specific autoimmune diseases, specifically neuromyelitis optica spectrum disorders and anti-MOG-Ab disease (MOG-Ab-related optic neuritis, encephalitis, and myelitis – MONEM), is key to establishing a diagnosis of MS, among exclusion of other mimics. The McDonald criteria, originally developed in 2001,[6] facilitate the diagnosis of MS in a variety of clinical presentations – without clear attacks and remissions and an insidious onset/presentation. Since disease onset can be insidious,[2] the application of newer *clinical, radiological, and CSF criteria* [2,3] to patients studied in the original studies[1,4] would probably re-classify patients as having MS. Although diagnostic criteria mention clinical attacks as a prerequisite[2] for applying the radiological criteria and CSF analyses, not all patients present with a clinical attack.[6]

Incidental findings of white matter lesions that suggest MS appear in about 0.1–0.7% of the population as evidenced by autopsy and MRI studies,[5] but it remains unknown if any of them fit the RIS criteria. It has been well documented that, even at the earliest stage of MS, loss of brain volume occurs as cortical and white matter atrophy accrue over time.[11] Since axonal transection occurs early,[12] treatment offers the best chance for function preservation. Failure to recognize RIS as MS could potentially lead to poor outcomes.

To cite a parallel example, patients with inflammatory bowel disease (IBD) can present with extra-intestinal signs that include the occurrence of white matter lesions in the brain that are asymptomatic or cause vague symptomatology.[13] The importance of finding brain lesions in IBD represents the recognition of extra-intestinal disease, leading to unearthing other systemic manifestations. Such novel findings and conclusions are likely only if we approach RIS from a similar perspective derived from an ever-evolving MS diagnosis. In a 2018 editorial,[14] the statement suggesting the "need for further research into radiologically isolated syndrome and solitary sclerosis before they could be included in the criteria as MS" is questionable given that 24% of patients had gadolinium-enhanced lesions and 61.3% had CSF-positive data in the original RIS study.[1] How does one include these in the RIS category using 2017 McDonald criteria?

To summarize, symptoms and examination findings coupled with brain/cord MRI data with typical lesions that are old and new (T1-gadolinium lesions) suggest MS while additional CSF studies when required can also aid in the diagnosis. Secondly, patients presenting with vague symptoms such as dizziness, vertigo, sensory symptoms, or "brain fog" should be investigated for MS as a possible diagnosis.

Disclosures

The authors do not have anything to disclose.

Competing interests

The authors report no competing interests.

Patient and public involvement

None.

https://doi.org/10.1017/S1092852919001202 Published online by Cambridge University Press

REFERENCES:

1. Okuda DT, Mowry EM, Beheshtian A *et al*. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology*. 2009; **72**(9): 800–805.
2. Polman CH, Reingold SC, Banwell B *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011; **69**(2): 292–302.
3. Thompson AJ, Banwell BL, Barkhof F *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018; **17**(2): 162–173.
4. Okuda DT, Mowry EM, Cree BA *et al*. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. *Neurology*. 2011; **76**(8): 686–692.
5. Yamout B, Al Khawajah M. Radiologically isolated syndrome and multiple sclerosis. *Mult Scler Relat Disord*. 2017; **17**: 234–237.
6. McDonald WI, Compston A, Edan G *et al*. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001; **50**(1): 121–127.
7. Gebhardt M, Kropp P, Hoffmann F *et al*. Headache at the time of first symptom manifestation of multiple sclerosis: a prospective, longitudinal study. *Eur Neurol*. 2018; **80**(3–4): 115–120.
8. Mohrke J, Kropp P, Zettl UK. Headaches in multiple sclerosis patients might imply an inflammatorial process. *PLoS One*. 2013; **8**(8): e69570.
9. Sahai-Srivastava S, Wang SL, Ugurlu C *et al*. Headaches in multiple sclerosis: cross-sectional study of a multiethnic population. *Clin Neurol Neurosurg*. 2016; **143**: 71–75.
10. Lebrun C, Blanc F, Brassat D *et al*. Cognitive function in radiologically isolated syndrome. *Mult Scler*. 2010; **16**(8): 919–925.
11. Bermel RA, Bakshi R. The measurement and clinical relevance of brain atrophy in multiple sclerosis. *Lancet Neurol*. 2006; **5**(2): 158–170.
12. Trapp BD, Peterson J, Ransohoff RM *et al*. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med*. 1998; **338**(5): 278–285.
13. Dolapcioglu C, Guleryuzlu Y, Uygur-Bayramicli O *et al*. Asymptomatic brain lesions on cranial magnetic resonance imaging in inflammatory bowel disease. *Gut and liver*. 2013; **7**(2): 169–174.
14. Carroll WM. 2017 McDonald MS diagnostic criteria: evidence-based revisions. *Mult Scler*. 2018; **24**(2): 92–95.

https://doi.org/10.1017/S1092852919001202 Published online by Cambridge University Press