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Neurological Bulletin

Volume 5 | Issue 1 Article 5

February 2014

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Recommended Citation

Leahy H, Garg N. Radiologically Isolated Syndrome: An Overview. *Neurological Bulletin* 2013;5:22-26, http://dx.doi.org/10.7191/neurol_bull.2013.1044

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Neurol. Bull. 5: 22-26, 2013
doi:10.7191/neurol_bull.2013.1044

NEUROLOGICAL BULLETIN
FEATURING ARTICLES BY TRAINEES IN NEUROLOGY & NEUROSCIENCE

Radiologically Isolated Syndrome: An Overview

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Abstract

The use of brain magnetic resonance imaging (MRI) for evaluation of neurological disorders has increased in the past two decades. This has led to an increased detection of incidental findings on brain MRI. The most common of these asymptomatic abnormalities are white matter lesions that are interpreted as demyelinating based on radiological criteria. However, in the absence of associated clinical symptoms suggestive of multiple sclerosis (MS), a definite diagnosis of MS cannot be made in patients with these incidental white matter lesions. These patients are now diagnosed as radiologically isolated syndrome (RIS). The natural history and clinical approach to patients with RIS are reviewed in this article.

The easy and wide availability of brain magnetic resonance imaging (MRI) in the past two decades has led to its increasing use in evaluation of a variety of neurological symptoms. Given its widespread use, it is common to detect some incidental findings in patients undergoing brain MRI for unrelated medical indications, such as head trauma or headache. The most common of these incidental abnormalities are white matter lesions that based on their appearance, location, and distribution are consistent with demyelination or multiple sclerosis (MS) but are not associated with any clinical symptoms suggestive of MS. The term radiologically isolated syndrome (RIS) has been proposed to describe this entity.

Coined only recently, RIS was first used by Okuda et al[1] to describe subjects with no obvious present or past neurological symptoms suggestive of MS, normal neurological examination, and white matter lesions on brain MRI fulfilling the radiological criteria of MS.[2] The proposed criteria for RIS are listed in Table 1. The Barkhof criteria for radiological evidence of dissemination are depicted in Table 2.

Before the advent and wider availability of MRI, postmortem studies showed a low prevalence (0.1%) of clinically silent demye-

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Keywords: radiologically isolated syndrome, multiple sclerosis, Barkhof criteria, incidental, white matter lesions

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doi:10.7191/neurol_bull.2013.1044

Table 1: Proposed diagnostic criteria for radiologically isolated syndrome[1]

A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:
1. Ovoid, well-circumscribed, and homogeneous foci observed with or without involvement of the corpus callosum
2. T2 hyperintensities measuring ≥3 mm and fulfilling Barkhof criteria (at least three out of four) for dissemination in space
3. Anomalies not following a clear vascular pattern
4. Structural neuroimaging abnormalities identified not explained by another disease process
B. No historical accounts of remitting clinical symptoms consistent with neurological dysfunction
C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized area of functioning
D. The MRI anomalies are not due to the direct physiological effects of substances (recreational drug use, toxic exposure) or a medical condition
E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter changes lacking clear involvement of the corpus callosum
F. The CNS MRI anomalies are not better accounted for by another disease process

Table 2: Barkhof's proposed MRI criteria for MS [2]

T2 lesions	≥9 T2 hyperintense or ≥1 gadolinium enhancing
Infratentorial lesions	≥1
Juxtacortical lesions	≥1
Periventricular lesions	≥4

linating disease.[3, 4] The recent studies including MR imaging have shown somewhat higher prevalence of white matter lesions suggestive of demyelination in asymptomatic individuals, especially among asymptomatic family members of patients with MS. In a recent study using 3 T MR imaging, about 3% of healthy relatives of MS patients and 2.4% of non-familial healthy control subjects showed white matter lesions suggestive of demyelination according to Barkhof criteria.[5] In another study, the prevalence of white matter lesions was 7% in asymptomatic first degree relatives of MS patients using Barkhof and other MRI diagnostic criteria for MS.[6]

The clinical significance and prognostic implication of subclinical lesions in patients with RIS remains controversial. There is some evidence to suggest that the patients with RIS are at increased risk of developing MS over time with approximately two thirds showing radiological progression and one

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third developing clinical symptoms in five years.[7] In a study of 44 patients diagnosed with RIS and followed longitudinally, more than half (24 of 41) showed radiological progression within an average of 2.7 years and 30% (10 of 30) went on to develop clinical symptoms leading to the diagnosis of clinically isolated syndrome (CIS) or clinically definite MS (CDMS).[1] The average time between RIS diagnosis and progression to CIS was 5.4 years, ranging from 1.1 – 9.8 years. The predictors of clinical or radiological progression included higher T2 lesion load, presence of infratentorial or spinal cord lesions, and positive cerebrospinal fluid (CSF) oligoclonal bands.[8] Lebrun et al. found a similar rate of conversion to CIS in their study of 70 patients with RIS; 33% developed clinical symptoms within an average of 2.3 years.[9] In this study, visual evoked potential abnormalities, young age, and gadolinium enhancement were more frequently found in patients who progressed to clinically definite MS whereas gadolinium enhancement and infratentorial lesions were associated with increased likelihood of MRI conversion. Presence of CSF oligoclonal bands or increased IgG index with a high T2-hyperintense lesion load at presentation was predictive of conversion to CIS. These findings are similar to the published data in CIS, where presence of oligoclonal IgG bands plus two T2-hyperintense lesions predicts CIS conversion to MS[10]. In another study, the strongest predictor of clinical progression was the presence of cervical cord lesions; 21 of 25 (84%) RIS patients with cervical cord lesions on MRI went on to develop clinical symptoms over a median period of 1.6 years.[8]

Thus, factors including the presence of cervical cord lesions, CSF abnormalities, and higher baseline T2 lesion load may help recognize patients who may be at relatively higher risk of MS and may benefit from a closer surveillance. It has been proposed that the patients with RIS be stratified into low or high risk groups for future development of MS based on these clinical or radiological predictors. It must be taken into consideration that most of these studies of RIS have included relatively small numbers of patients with variable periods of follow-up, and larger longitudinal studies need to be done to further validate these proposed risk factors.

What are the clinical implications of currently available data? These data suggest that RIS may be a precursor to MS; however, RIS probably represents a somewhat heterogeneous group. Some of these patients probably have a relatively mild and benign form of MS with symptoms so minor that they are not detectable clinically and may never progress; whereas other patients who present in the preclinical or presymptomatic phase of MS will later develop symptoms and/or new MRI lesions. Of the latter, there may be a subgroup of individuals who may be at a relatively higher risk of developing MS if they possess one or more risk factors such as family history of MS, higher baseline T2 lesion load, presence of cervical cord lesion, and CSF oligoclonal bands. The other issue relates to the treatment recommendations for patients with RIS. Although some might support use of disease modifying therapy (DMT) in these patients to delay the clinical or radiological progression similar to CIS patients, there are no studies to suggest this might be beneficial even for RIS patients at higher risk of MS. Moreover, the risk factors are not always clear, and the other caveat may be misdiagnosis of RIS in some cases where other conditions may mimic MS radiologically.[11,12] Given the uncertainty about the diagnosis and management of these patients, only a small proportion of RIS patients get treated with disease modifying therapy.[7]

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There is currently no set protocol for managing patients with RIS. These patients are usually followed with surveillance MRIs every six months to a year or on as needed basis depending on the patient's wishes and the treating neurologist's preference.[13] If clinical symptoms develop over time (conversion to CIS), most of these patients would be initiated on DMT. There is, however, a lack of evidence to support the use of DMT in RIS patients who show radiological progression on follow up imaging in absence of clinical progression.

As apparent from the discussion above, there are many questions that remain to be answered. Are there any biological or other markers that can help identify RIS patients who do or do not progress? For those who do convert to CIS or CDMS, would early treatment with DMT in the RIS stage have prevented the conversion? Future randomized prospective clinical trials may not only help answer the question whether early initiation of DMT in RIS patients would prevent conversion to CIS or radiological progression but may also further validate the risk factors for conversion. With such limited knowledge of the pathologic significance behind RIS, its relationship to MS, and how treatment or lack thereof affects the long term prognosis, the clinical management of incidental white matter lesions remains obscure.

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Disclosure: the authors report no conflicts of interest.

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(ISSN 1942-4043)