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Radiologically Isolated Syndrome – a not so rare prelude to Multiple Sclerosis

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ABSTRACT

Radiologically isolated syndrome (RIS) was defined for the first time in 2009 with an attempt to establish objective criteria of diagnosis for the patients, who underwent brain MRI scanning for a reason other than multiple sclerosis (MS), but were found to have white matter lesions in their central nervous systems (CNS) similar to those present in patients with diagnosed MS. RIS has been defined as separate entity with the presence of MRI findings strongly suggestive of MS in a patient with no neurological manifestations or other clear-cut explanation. Healthy patients may have an initial MRI procedure performed due to different reasons other than suspicion of MS, mainly because of headaches. However, a clinical examination does not reveal any signs of focal neurological deficits and there are no evidence for the focal damage in the CNS in these patients as well. Although RIS is not the first stage of multiple sclerosis in every patient, 30 up to even 45% of individuals diagnosed with this condition will present clinical symptoms in the future, within median time from 2.3 to 5.4 years depending on various researches. Most authors agree, that about 1/3 of patients with RIS will convert to clinically definite MS within 5 years of follow-up. There are some significant predictors of

conversion, among others - presence of lesions in cervical and thoracic spinal cord. Moreover, patients with RIS, although asymptomatic in the meaning of classic clinical presentation of MS, are proved to experience early axonal loss, brain atrophy, increased anxiety and depression and subclinical inflammatory disease, as well as some signs of cognitive impairment. In this article we aim to make a review of the newest papers published in 2017 and 2018 concerning Radiologically Isolated Syndrome.

Keywords: radiologically isolated syndrome, multiple sclerosis, magnetic resonance imaging, biomarkers, cerebro-spinal fluid, headache, cognitive impairment, neurological disorders, disability, demyelinating diseases

1. INTRODUCTION

Radiologically isolated syndrome (RIS) was defined for the first time in 2009 with an attempt to establish objective criteria of diagnosis for the patients, who underwent brain MRI scanning for a reason other than multiple sclerosis (MS), but were found to have white matter lesions in their central nervous systems (CNS) similar to those present in patients with diagnosed MS. RIS has been defined as separate entity with the presence of MRI findings strongly suggestive of MS in a patient with no neurological manifestations or other clear-cut explanation. Healthy patients may have an initial MRI procedure performed due to different reasons other than suspicion of MS, mainly (up to 60%) because of headaches. However, a clinical examination does not reveal any signs of focal neurological deficits and there are no evidence for the focal damage in the CNS in these patients as well. Although RIS is not the first stage of multiple sclerosis in every patient, 30 up to even 45% of individuals diagnosed with this condition will present clinical symptoms in the future, within median time from 2.3 to 5.4 years depending on various researches. Most authors agree, that about 1/3 of patients with RIS will convert to clinically definite MS within 5 years of follow-up. There are some significant predictors of conversion, among others – age (less than 35-37, when diagnosed), sex (males), oligoclonal bands (OBs) found in cerebro-spinal fluid and the strongest predictor, which is a presence of lesions in cervical and, optionally, thoracic spinal cord. Moreover, patients with RIS, although asymptomatic in the meaning of classic clinical presentation of MS, are proved to experience early axonal loss, brain atrophy, increased anxiety and depression and subclinical inflammatory disease, as well as some signs of cognitive impairment. Due to a quick development and improvement of diagnostic imaging techniques, white matter lesions are suspected to be found more often, thus the emerging problem of increasing number of patients diagnosed with radiologically isolated syndrome should be a matter of a serious concern for neurologists dealing with multiple sclerosis diagnosing and treating [1-6].

2. FIRST DIAGNOSTIC CRITERIA

2. 1. 2009 Okuda's criteria

To properly understand the concept of Radiologically Isolated Syndrome, one has to take note, that not every white matter abnormality found in MRI is typical for this entity. The distinctive features of radiologically isolated syndrome are depicted in Table 1.

Table 1. 2009 Okuda's diagnostic criteria for Radiologically Isolated Syndrome [7].

2009 Diagnostic criteria for Radiologically Isolated Syndrome
<p>A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:</p> <ol style="list-style-type: none">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.
<p>B. No historical accounts of remitting clinical symptoms consistent with neurological dysfunction.</p>
<p>C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized area of functioning.</p>
<p>D. The MRI anomalies are not due to the direct physiological effects of substances (recreational drug use, toxic exposure) or a medical condition.</p>
<p>E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter changes lacking clear involvement of the corpus callosum.</p>
<p>F. The CNS MRI anomalies are not better accounted for by another disease process.</p>

2. 2. 1997 Barkhof's diagnostic imaging criteria for Multiple Sclerosis

Okuda's criteria focus on the lack of clinical manifestation and excluding of different states that may affect the diagnosis of Radiologically Isolated Syndrome, including other disease processes, toxic exposure, neurological dysfunctions etc. The morphology of lesions are also strictly defined. However, in case of defining the amount and localization of white matter abnormalities, Okuda refers to much earlier Barkhof's diagnostic imaging criteria for MS, that are depicted in Table 2.

Table 2. 1997 Barkhof's diagnostic imaging criteria for Multiple Sclerosis [8].

1997 Radiological criteria for Multiple Sclerosis
<p>At least 9 T2 hyperintense lesions including:</p> <ol style="list-style-type: none">1. At least 1 infratentorial lesion;2. At least 1 juxtacortical lesion;3. At least 4 periventricular lesions; <p>or</p> <p>At least 1 gadolinium enhancing lesion.</p>

3. MODIFIED DIAGNOSTIC CRITERIA

Table 3. 2017 MAGNIMS Modified diagnostic criteria for Radiologically Isolated Syndrome [9].

2017 Modified diagnostic criteria for Radiologically Isolated Syndrome
<p>Inclusion criteria:</p> <ol style="list-style-type: none">1. Demonstration of lesion dissemination in space (by ≥ 1 T2-hyperintense lesions involving at least two of the 2 following topographies):

<ul style="list-style-type: none">a. Periventricular white matter;b. Cortico-juxtacortical;c. Spinal cord;d. Infratentorial;
<p style="text-align: center;">Exclusion criteria:</p> <ul style="list-style-type: none">1. Clinical evidence of neurological dysfunction suggestive of MS based on historical symptoms and/or objective signs;2. MRI abnormalities explained by any other disease process, with particular attention to aging or vascular-related abnormalities, and those due to exposure to toxins or drugs.

Bearing in mind, that Radiologically Isolated Syndrome in part of cases is a preclinical stage of Multiple Sclerosis, to improve the diagnostic process, MAGNIMS (Magnetic Resonance Imaging in MS) has proposed revised diagnostic criteria for Radiologically Isolated Syndrome, which are depicted in Table 3.

4. GENERAL ISSUES

Among patients with incidental findings in brain MRI, only few happen to have white matter abnormalities similar to demyelinating plaque in patients with clinically definite multiple sclerosis, without any history of previous neurological disorders. Non-specific MRI white matter lesions are much more often than those fulfilling Radiologically Isolated Syndrome criteria. Although RIS, as well as CIS (Clinically Isolated Syndrome) are considered potential new phenotypes of multiple sclerosis, there are still limited diagnostic and prognostic tools for the individuals to use in everyday clinical practice. Therefore, the last 2017 McDonald's criteria revision does not recognize RIS as MS phenotype and still requires at least one clinical manifestation (together along with typical MRI abnormalities and presence of oligoclonal bands in cerebro-spinal fluid) to diagnose clinically definite multiple sclerosis [3, 10-14].

5. LACK OF CLINICAL MANIFESTATION – IS RADIOLOGICALLY ISOLATED SYNDROME REALLY ASYMPTOMATIC?

Although Radiologically Isolated Syndrome is considered to be asymptomatic (in terms of neurological deficits typical for demyelination) and lack of clinical manifestation is one of

the diagnostic criteria for the syndrome, a rising number of papers published in last few years indicate, that patients with white matter lesions fulfilling RIS criteria may experience some health issues which may be associated with their radiological state. As it was mentioned before, RIS patients are often suffering from cognitive deficits, increased anxiety and depression [3]. The cognitive-motor interference, which is well described for MS patients has been recently confirmed in a study involving 10 RIS patients and 10 sex- and age-matched healthy controls, who underwent a static posturography with opened eyes and two different cognitive tasks to perform [15]. It seems that the most common disorder affecting RIS patients are headaches. It is worth mentioning, that if it was possible to define a typical headache for MS, patients with RIS suffering from this kind of headache should be diagnosed as CIS or even clinically definite multiple sclerosis. It is already known, that nearly 80% of CIS or early MS patients experience headaches on regular basis [16].

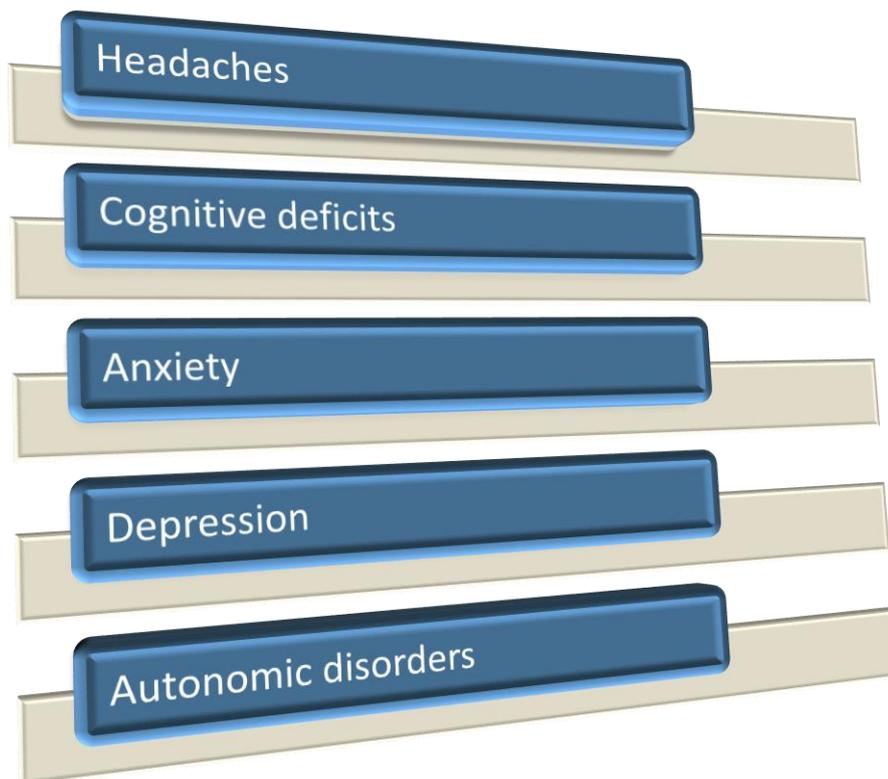


Figure 1. Possible health issues affecting patients diagnosed with Radiologically Isolated Syndrome.

Besides, RIS changes located in spinal cord can probably cause some hard-to-diagnose autonomic disorders. The latest case report of a female patient with postural orthostatic tachycardia syndrome (POTS) turning out to be Radiologically Isolated Syndrome seems to confirm this possibility [17].

Possible health issues affecting patients with Radiologically Isolated Syndrome are depicted on Figure 1.

6. CONVERSION TO MULTIPLE SCLEROSIS – PREDICTIVE FACTORS

A growing number of studies have recently searched for factors which may be helpful in predicting the possible conversion of Radiologically Isolated Syndrome to Multiple Sclerosis. Patients who would be qualified as being at a high risk of conversion, should be put under watchful neurological supervision.

It seems that biomarkers from body fluids (serum and cerebro-spinal fluid) may play a vital role in predicting the risk of conversion not only in CIS, but even in RIS patients in not so distant time [18-20]. Especially, chitinase 3-like 1 in cerebro-spinal fluid is a matter of ongoing researches, as it was already shown to be a good prognostic factor in evolution from CIS to relapsing-remitting Multiple Sclerosis. However, these results does not simply apply to RIS; conclusions of the latest studies show, that chitinase 3-like 1 is not an independent prognostic factor in RIS [21]. There are also many studies concerning the neurofilament light chain (Nfl), a marker of neuro-axonal damage. It is proven that cerebro-spinal levels of Nfl correlate well with inflammatory/demyelinating diseases of the central nervous system, as well as in Alzheimer's disease [22]. Additionally, some interesting conclusions were made after French research involving 12 RIS, 46 CIS, 31 relapsing-remitting MS patients and 36 healthy controls. It turned out, that high IL-6/IL-10 producing B-cell ratio was associated with increased risk of clinical conversion in 6 months [23].

Body fluids' testing is not the only way of stratifying the risk of conversion from RIS to MS. Magnetic resonance imaging, especially high-field, may contribute to better assessment of patients with white matter abnormalities. According to different studies, even more than 70% of patients diagnosed with Radiologically Isolated Syndrome present lesions in cervical spinal cord and many of them are proven to experience brain atrophy [24, 25]. Moreover, nearly 60% of patients develop new lesions detectable in MRI during two-year follow-up [2, 4].

Also other diagnostic procedures may be helpful in determining the risk of clinical conversion from RIS to MS. For example, applying multifocal-visual-evoked-potential (mfVEP) when proper algorithms are used (for example empirical mode decomposition) can be an effective diagnostic tool for identifying patients at high risk of conversion [26]. An interesting direction in further research may be evaluating the level of thinning of the retinal nerve fiber layer (RNFL), using optimal coherence tomography [27].

It is stated, that about $\frac{1}{3}$ of patients with RIS will convert to clinically definite Multiple Sclerosis within 5 years from the beginning of the follow-up. It seems that subclinical activity in RIS evolving to primary progressive MS is similar to relapsing-remitting MS evolving to secondary progressive MS [28]. The topic of conversion risk needs further researches including clinical, radiological and laboratory assessment of patients with RIS.

7. TREATMENT – IS IT NECESSARY?

The possible ways of treating the Radiologically Isolated Syndrome with Disease Modifying Therapy (DMT) used in Multiple Sclerosis stays controversial. Although early treatment in carefully selected patients might improve long term outcome, it is substantial to remember, that DMTs have many side effects and can even affect cognitive functions [6, 29-33]. An interesting survey from 2017 conducted in 11 countries among 233 specialists in the

field of neurology revealed, that there is a general consensus, that Radiologically Isolated Syndrome, although in part of cases – a preclinical stage of MS, should not be treated with Disease Modifying Therapy [34].

8. CONCLUSIONS

There are further studies needed to determine the most important risk factors for conversion from Radiologically Isolated Syndrome to clinically definite Multiple Sclerosis. The risk assessment should involve diagnostic imaging (MRI – even at ultra-high-fields, if available), as well as body fluids’ (serum and cerebro-spinal fluid) laboratory tests (including oligoclonal bands and neurofilament light chain presence, as well as new markers, which are not yet used in clinical practice like chitinases). The clinical assessment including neurological examination, psychological tests and using of different scales (the most important one – Extended Disability Status Scale, EDSS) should be also maintained in patients diagnosed with RIS. A proper defining of risk factors would allow for determining the group of patients at high risk of conversion. In these patients, the DMTs should be at least considered, while watchful neurological supervision is inevitable.

Table 4. Ways of assessment and supervision over patients with Radiologically Isolated Syndrome

Ways of assessment	Diagnostic tools
Clinical assessment	Neurological examination; psychologic examination; cognitive tests; EDSS scale.
Diagnostic imaging	MRI of the brain and the spinal cord (including high-field scanners); MR spectroscopy; MR volumetry; diffusion tensor imaging.
Laboratory tests	Serum and/or cerebrospinal fluid’s tests for oligoclonal bands, neurofilament light chain and other novel biomarkers (chitinases, tubulins, heat shock proteins)
Other diagnostic possibilities	Visual evoked potentials

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