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Presymptomatic MS or radiologically isolated syndrome (RIS) should be actively monitored and treated – NO

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'Presymptomatic multiple sclerosis (MS)' is time-wise a hybrid observation. On the one hand, the terminology refers to the increased healthcare use seen retrospectively in people with MS (pwMS) in the years before diagnosis. After excluding accounts of missed MS, this MS prodrome mainly consists of vague symptoms lacking specificity for use in clinical practice.[1] On the other hand, presymptomatic MS is prospectively suspected in people undergoing brain scans for unrelated conditions (e.g. headache, trauma) or screening purposes (e.g. flight attendants) who have radiological features of MS. In practice, it is only the latter that puts physicians for a treatment dilemma.

A radiologically isolated syndrome (RIS) can be diagnosed based on the 2009 Okuda criteria, incorporating the more stringent Barkhof–Tintoré MS criteria for radiological dissemination in space in combination with thoroughly excluding better (mostly vascular) explanations.[2] Based on these criteria, people with RIS (pwRIS) have about a one in two chance of developing symptoms indicative of an MS flare in 10 years' time.[3] Moreover, the results of the long-awaited Assessment of tecfidera in radiologically isolated syndrome (ARISE) trial showing shorter times to clinical conversion in pwRIS treated with dimethyl fumarate compared to placebo illustrated that at least a subset of pwRIS is responsive to immunosuppressive treatment.[4] Along this line, magnetic resonance imaging (MRI) features indicative of chronic active demyelination (i.e. slowly expanding lesions, perivenular inflammation) and the extent of cognitive deficits are indistinguishable between people with early clinical or mere radiological evidence of MS.[5] Although pathological confirmation is lacking, this circumstantial evidence indicates that RIS and clinically symptomatic MS phenotypes unmistakably have the same underlying biology, albeit with so far different unknown compensatory mechanisms at play in pwRIS increasing the threshold for clinical onset. However, the shared biology between pwRIS and MS does not answer whether we should offer pwRIS regular MRI monitoring or disease-modifying treatments (DMTs) and, if we decide to do so, for how long we should continue with this practice.

First and foremost, it is most likely true that to have a pivotal impact on the disease course of MS (and other neurological diseases) the diagnosis and treatment in the presymptomatic stage should be beneficial in terms of maximizing brain health. However, the practical implications at individual level and for successful medical management as well as the societal and ethical ramifications of such recommendation are enormous. At an individual level, treating RIS converts otherwise healthy individuals into patients, the emotional burden of which should not be taken lightly. Most certainly, this contributes to the omnipresence of depression and anxiety among recently diagnosed individuals.[1] From a medical point of view, as only half of pwRIS will convert to MS over the course of a decade with large uncertainties regarding prognosis both with and without treatment,[3] it remains good practice for clinicians to offer the opportunity of not knowing before discussing monitoring or treating RIS. Importantly, DMTs are especially apt at preventing new relapses, but the effects on less tangible outcomes such as processing

speed or slowly expanding lesions are small or at least difficult to quantify during short- to medium-term follow-up.[6,7] Moreover, real-world cohorts still need to demonstrate how durable perceived benefit of treatment will be in pwRIS choosing to be treated and how it will be weighed against the reality of DMT side effects and DMT-imposed restrictions on family planning or international travel. At the societal level, national healthcare budgets are under pressure with DMT costs being the largest driver in increasing healthcare expenditures among pwMS.[8] The cost of treating pwRIS will thus be significant already years before any clinical manifestations, whereas a similar budget could have a much higher impact on the outcome and quality of life of other diseases. Although reimbursement criteria will be ultimately decided upon by regulating bodies, it does not exempt MS neurologists from their responsibility towards sustainable MS care. On a wider ethical note, it is important to realize that once we start treating RIS as a quintessential MS prodrome, presymptomatic MS will become an ever-broadening notion. Especially given the relatively high prevalence of MS in the Western world, treating pwRIS leaves the door open to using brain MRI as a screening tool for presymptomatic MS in first- or second-degree relatives of pwMS, and subsequently in female individuals or even at population level. Apart from the concerns about privacy and discrimination, there will be many incidental findings and individuals will be burdened with the knowledge of being at risk of a disease with no cure and uncertain prognosis years or decades before the actual onset.

Irrespective of these wide implications, studies have shown that some pwRIS are more presymptomatic than others. Even in truly asymptomatic individuals, it is difficult to ignore contrast-enhancing lesions or new lesions appearing over time as they are clear indicators of active and ongoing inflammation. Observational RIS cohorts have indeed demonstrated that younger people with spinal cord lesions or contrast-enhancing lesions have a much shorter time to a first clinical event.[9] In addition, factors pointing to a shared biology such as the presence of unique intrathecal oligoclonal bands and increased neurofilament light levels have been shown to predict conversion from RIS to MS.[10] However, the interplay between clinical and biological makers when it comes to risk prediction is not clear, and only a small number of pwRIS carry multiple clinical risk factors, leaving clinicians without consensus on how we should value them in practice.

Overall, the current label for RIS encompasses both people who have truly presymptomatic MS and people who are eternally, at least in a clinically meaningful way, asymptomatic. Hence, treating RIS based on the 2009 Okuda criteria is not desirable given the wide implications of this practice. Nonetheless, some of the pwRIS seem to be at higher risk for a first clinical event than others and respond to immunosuppressive treatment. A better compromise between specificity and sensitivity of what we currently label as 'presymptomatic MS' is therefore needed, thereby taking into account practical, societal and ethical perspectives.

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Presymptomatic MS or radiologically isolated syndrome should be actively monitored and treated: Commentary

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The evidence that the biological onset of multiple sclerosis (MS) can anticipate the clinical onset by several years has led to an ever-growing number of studies aimed at characterizing and monitoring the preclinical phase of MS.[1] Individuals with incidental brain or spinal cord lesions highly suggestive of central nervous system (CNS) demyelination without related symptoms and signs are classified as having a radiologically isolated syndrome (RIS).[2] These individuals have a 34% risk of conversion to MS over 5 years[3] and a 51% risk over 10 years[4] especially if they are young, with infratentorial or spinal cord lesions, with cerebrospinal fluid (CSF)-restricted oligoclonal bands, and development of new gadolinium-enhancing lesions on follow-up magnetic resonance imaging (MRI) scans.

Christine Lebrun-Frenay and Ide Smets' opposing views raise important considerations about the practical management (diagnosis, monitoring and treatment) of people with RIS.

In the 2017 diagnostic criteria for MS, a first clinical attack is still required to make the diagnosis of MS. Although considerations for the diagnosis of RIS were not included in the criteria, it was acknowledged that individuals with RIS present a high likelihood of having MS.[5] Importantly, the criteria already consider the presence of new lesions on MRI as equivalent to a relapse in providing evidence for dissemination in time. Moreover, MRI is the most sensitive tool for monitoring disease activity since new lesions occur more frequently than clinical relapses.[6] Therefore, as stated by Lebrun-Frenay and Okuda, RIS patients should undergo clinical and radiological monitoring to decrease time to diagnosis and to receive disease-modifying treatment especially important given the first evidence of a treatment effect provided by the Assessment of Tecfidera® in Radiologically Isolated Syndrome (ARISE) trial.[7]

However, as stated by Smets, whether all individuals with RIS require early treatment with disease-modifying therapies (DMTs) remains a matter of debate. Since approximately 50% of individuals with RIS do not convert to MS over a 10-year follow-up period, treating RIS will turn otherwise healthy individuals into patients with the related emotional burden and with unnecessary exposure to side effects and restrictions to family planning. Finally, we need to consider potential barriers related to sustainability in different health care systems given that DMT cost is the largest component of healthcare expenditures for MS.[8]

RIS diagnosis, monitoring and treatment give us the unique opportunity to implement early preventive interventions in MS. To achieve this goal, we need biomarkers with high diagnostic accuracy which will allow us to stratify 'higher risk' RIS individuals[9] who may benefit most from disease-modifying treatment and from targeting of modifiable risk factors such as smoking, obesity, low vitamin D levels and physical activity, as well as environmental exposures.[1] This, however, may not be so straightforward; therefore, it is advisable that individuals with RIS should be managed by neurologists in tertiary centres with long-standing

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