Introduction

The widespread use of brain magnetic resonance imaging (MRI) has greatly

increased findings of unanticipated asymptomatic intracranial abnormalities of

uncertain clinical significance. These incidental findings on brain MRI are of

various nature and origin and only rarely include abnormalities that could be

interpreted as inflammatory or demyelinating lesions(1). However, the

increase of unexpected MRI alterations has overall augmented the awareness

for findings that have the morphology, size, location and distribution highly

suggestive of a demyelinating disease. This has led to the definition of

"radiologically isolated syndrome" (RIS), which was recently introduced to

describe those asymptomatic subjects with brain MRI abnormalities

suggestive of multiple sclerosis (MS) and lacking historical accounts of prior

demyelinating events or an identifiable better reason for the observed

changes(2).

Since its first description, RIS has been widely debated and the risk of RIS

evolving into MS has been investigated. According to existing data, a number

of RIS subjects evolve to MS over time, demonstrating that RIS, at least in

some cases, represents a preclinical stage of MS. RIS, however, is an entity

that still needs to be better defined, with a number of issues needing to be

addressed. These include the lack of expert guidelines on the management of

RIS subjects and criteria that can establish the extent to which MRI lesions

fulfilling the RIS criteria in asymptomatic subjects may represent subclinical

MS or may be related to abnormalities that are not related to MS.

We provide here expert recommendations that can help distinguish between subjects with low risk of developing MS and those that can be diagnosed with subclinical MS. Suggestions for the management of subjects stratified by risk for a future demyelinating event will also be provided. A summary of the main proposed recommendations is given in Table 1.

Radiologically Isolated Syndrome

Different terminology has been used in the recent past to describe subjects who reveal unanticipated brain spatial dissemination of MRI lesions highly suggestive of MS in the absence of characteristic clinical signs and symptoms attributable to CNS demyelination(3-5). Okuda and colleagues defined this nosological entity as RIS(2), a term that has become widely used in the last few years. They provided easily applicable criteria that focus on structural MRI findings while excluding clinical changes and other disease entities that could account for the observed paraclinical anomalies(2).

In terms of MRI characteristics, the Okuda criteria(2) consider ovoid and well-circumscribed lesions with or without corpus callosum involvement, measuring >3 mm and fulfilling at least three out of four criteria for dissemination in space (DIS)(6, 7). Subsequently, new MRI criteria for the diagnosis of MS were proposed by the MAGNIMS study group(8) based on new evidence, and were incorporated in the 2010 version of the McDonald criteria(9). These new criteria focus on lesion location rather than lesion count for the assessment of DIS, which facilitates MRI interpretation and their use in clinical practice in

typical scenarios suggestive of MS. More recently, these criteria were again modified in a MAGNIMS consensus paper(10), which recommended that modifications to MRI criteria should be applied for the diagnosis of RIS (Table 2). Finally, fulfillment of McDonald criteria for MRI dissemination in time (DIT) (gadolinium [Gd]-enhancing lesions and/or new T2 lesions), as described in the MAGNIMS MRI criteria(8), could further improve the identification of RIS subjects with a high risk of developing neurological symptoms, and will allow a definite diagnosis of MS once the subject shows a seminal neurological event suggestive of CNS demyelination. Validation studies will be required in order to assess the value of these modified RIS diagnostic criteria(10) (Table 2).

RIS and the imperative of differential diagnosis

The Okuda criteria, which were based on expert opinion, imply the exclusion of an alternative diagnosis in addition to the presence of CNS lesions meeting the concept of DIS. However, the Barkhof criteria for DIS, which are the basis of the Okuda criteria(2), were not designed to differentiate MS from other disorders, but to predict conversion of CIS to MS. This might become of particular relevance in the case of headache, which is by far the most common reason why RIS subjects perform a brain MRI scan and where multifocal WM lesions can be identified in a significant proportion of patients(11).

In general, focal WM lesions, presumably of vascular origin, are more prevalent than demyelinating lesions in young adults and particularly in migraineurs(11). These lesions have quite different morphological and

topographic characteristics compared to the typical brain demyelinating lesions seen in MS(12) (Table 3), with the common incidental lesions found in migraine being usually small, punctuate and rarely confluent(12). They are often localized in the anterior, deep WM, subcortical, juxtacortical brain regions, are rarely present in the infratentorial regions, and usually do not progress over time(13). In this context, the demonstration of the perivenular distribution within subclinical MS-like lesions can be particularly helpful(14). This sign is particularly visible with MRI systems that operate at higher magnetic field strengths (≥3.0 Tesla) and using susceptibility-weighted imaging (SWI), a sequence that has shown high sensitivity for detecting small veins because of their paramagnetic properties. A substantial proportion of MS lesions show this central vein, particularly when the T2-FLAIR and SWI are combined(14). This seems to be useful in discriminating MS lesions from vascular or migraine-related WM lesions, or other neurological disorders(14), in particular when evaluating lesions located in the subcortical WM. In addition, using the same or similar MRI techniques, it has been shown that most chronic, and some acute MS focal lesions, can be depicted as rim or focal areas of low signal intensity. These hypointensities probably represent free radicals or iron deposition from several cellular sources that are present in the lesions, although myelin loss might also contribute to the signal abnormality(14). The presence of this intralesional signal loss appears to be a useful finding for differentiating patients with CIS or MS from those with other neurological disorders, including migraine.

The above-mentioned MRI features could improve the specificity of MRI diagnosis of RIS and should be carefully evaluated when a migraine-related lesion pattern is suspected.

Truly asymptomatic?

According to the Okuda criteria, the diagnosis of RIS implies "no historical accounts of remitting clinical symptoms suggestive of neurological dysfunction". This assumes the absence of relevant notes after a carefully collected clinical history and a meticulous clinical examination for proposing the diagnosis of RIS. That having been said, the reason for the initial brain MRI should always be carefully considered as one might object that if these subjects were truly neurologically normal there would have been only little chance to find an abnormality on this scan.

It is known from the literature that while there are some RIS subjects whose brain MRI is performed for reasons which have no relation with the CNS (e.g., research studies, health check-ups, familial cases, etc.) or with MS (e.g., head trauma, endocrinological disorders, etc.), in many occasions MRI is performed due to symptoms that might be somehow related with MS. As mentioned before, headache is by far the most common reason for performing an MRI (about 50% of cases with RIS[15-17]), but other relatively less frequent indications for an MRI are also seizures, paroxysmal symptoms, anxiety, depression and other psychiatric disorders[15, 18]. While it is not possible to establish whether these conditions were related to the MRI findings, it is also true that they might represent unusual clinical symptoms associated with

MS(19). Extreme caution is therefore needed in classifying these subjects as up-to-now asymptomatic subjects with RIS.

In this context, of particular note is the occurrence of cognitive deficits in RIS subjects. They have been shown in several studies in about one third of the published cases(18, 20, 21), with a prevalence similar to that of patients with clinically isolated syndrome(22). It is a matter of discussion whether subtle cognitive impairment found in apparently normal subjects after extensive neuropsychological tests should be considered "asymptomatic". Indeed, with the possible exception of isolated cognitive relapses(23), it is difficult to consider the isolated and mild cognitive deficit as an overt clinical manifestation of the disease. However, the robust documentation through validated neuropsychological batteries of deficits in information processing speed, complex attention, episodic memory and executive functions, which are the cognitive functions most frequently impaired in patients with MS, could help stratify RIS subjects, thus recognizing those who are most likely to have a subclinical form of MS.

Predictors of clinical conversion

A number of recent studies in relatively small RIS cohorts have suggested relevant predictors of conversion to MS. Specifically, some studies(2, 4, 24, 25) identified MRI predictors for clinical conversion to MS such as Gd-enhancing lesions, high T2-lesion load, the presence of infratentorial lesions and spinal cord lesions. The latter, in particular, seem to have the highest impact as predictor for conversion to MS due to their high sensitivity, positive

predictive value and specificity(24). In addition, other paraclinical predictors

for clinical conversion such as the pathological immunoglobulin-G index

and/or presence of oligoclonal bands (OCB) in cerebrospinal fluid (CSF), and

abnormal visual evoked potentials (VEP) have been reported as relevant(25).

Importantly, the combination of these predictors (e.g., high lesion load with

CSF abnormalities) may increase the prognostic value. Similarly, young age

and pregnancy may shorten the time to clinical conversion(26).

Recently, a large, multicenter, retrospective study has been performed by the

RIS Consortium (RISC)(16). On 451 RIS subjects, in a multivariate model

young age, male gender, and spinal cord lesions were identified as the most

significant predictors for a first clinical event. In the study, CSF abnormalities

were reported to be significant, but did not survive in the multivariate model,

possibly because of lower number of samples (CSF was collected in 67% of

RIS) in comparison with other factors. Despite the limitation of a retrospective

design with non-standardized procedures of MRI acquisition and clinical

surveillance, this study has provided, for the first time, convincing results on

independent predictors of symptom onset in RIS subjects, helping in

stratifying subjects at high risk for evolving to MS.

Recommendations for diagnosis of subclinical MS

As stated before, in the recent revision of the MRI criteria for the diagnosis of

MS, the MAGNIMS expert consensus has recommended that the identical

criteria used to establish DIS and DIT in MS patients should be applied for

RIS(10) (Table 2). Furthermore, it has been suggested that when a clinical

attack occurs in RIS subjects with evidence of DIT (who, by definition, have DIS), a diagnosis of MS can be made(10). This provides specific criteria for a prompt diagnosis when the first symptom of CNS involvement occurs. In the context of RIS, however, it is important as well to establish criteria helping stratify these asymptomatic subjects, possibly differentiating those who are unlikely to evolve to MS from those who might have a subclinical form of the disease.

In each RIS subject, it would be of paramount importance to classify the pathological process underlying the observed MRI changes. Since MRI is very sensitive to changes, but provides only indirect information about the underlying pathology, it is essential to show that MRI findings can be closely related to a specific pathological process and are sustained by other findings that can confirm it. The lack of systematically acquired data makes it difficult generating evidence-based risk algorithms. However, RIS subjects who have the classical paraclinical features of MS patients and several MRI risk factors for conversion to MS clearly need to be distinguished from those without these factors, since they are likely to have a subclinical form of MS (see Table 4).

Thus, a person without a history of relapsing neurological symptoms, an unremarkable neurological examination and brain MRI lesions consistent with MS, without red flags suggestive of an alternative diagnosis(12), could be considered as having subclinical MS when showing most of the features summarized in Table 4. These include MRI features such as spinal cord

lesions and Gd-enhancing lesions that can increase the specificity of the MRI pattern and are strong predictors of conversion to MS, and abnormalities that are not specific for MS, but that can be found in the majority of MS patients, such as i) OCB in the CSF, ii) abnormal VEP, and iii) deficits in specific cognitive functions (i.e., information processing speed, complex attention, episodic memory and executive functions) (27). All these paraclinical tests should be part of the standard investigation to allow an appropriate stratification of RIS cases. An assessment of OCB in tears has been proposed to avoid lumbar puncture in asymptomatic subjects(28). Further, younger age of the subject (<35 years), male gender and the detection on MRI of high brain lesion load and cortical lesions (usually not found in patients with alternative MS diagnosis)(29, 30) can further increase specificity in identifying subjects with subclinical MS. It must be stressed here that the term 'subclinical', as opposed to 'pre-clinical', does not imply clinical conversion. The occurrence of incidental brain demyelinating lesions in subjects who did not have symptoms or signs of MS during lifetime is well documented in a number of post-mortem studies(31-34). Overall, these studies demonstrated that brain demyelination might remain clinically silent for the whole lifetime in a proportion of people (about 0.1-0.3% of the autopsies in those studies). The occurrence of silent demyelination should be therefore considered uncommon but possible in clinical practice.

Treatment and Management

Based on the evidence that early disease-modifying treatment (DMT) is favorable for relapsing-remitting MS patients and may delay the conversion to

MS in CIS patients, it would be tempting to believe that these advantages may also apply to these asymptomatic subjects. Indeed, a survey among neurologists reported that 17.8% of RIS subjects received DMT(35) and in the retrospective study of the RISC, 73 out of the 451 RIS subjects (16%) were treated with approved DMTs for MS prior to the development of a first clinical episode(16). The reasons prompting neurologists to initiate DMT in RIS subjects are usually related to MRI findings, such as high lesion load, lesion DIT (i.e., Gd-enhancing lesions or new lesions in a subsequent MRI) or the presence of spinal cord lesions(35). Particularly relevant seems to be the presence of Gd-enhancing lesions as in a recent survey assessing current practice patterns of United States neurologists using case-based surveys there was a large consensus (80%) to initiate treatment in RIS subjects who show more than two Gd-enhancing lesions on MRI(36).

This background and the possibility of discriminating subjects who might be more likely to have subclinical MS raise the question as to whether in high-risk RIS subjects DMTs should be initiated as in MS patients. This is highly controversial. However, current evidence does not support treatment in RIS subjects, even when the findings suggest subclinical MS. These subjects may have an exceptional capacity to repair and/or absence of functional connectivity maladaptive changes, which could explain the lack of symptoms despite the, sometimes even greater, MRI-detectable tissue damage with respect to MS patients(37). The notion coming from neuropathological studies(15, 31, 34) that brain demyelination might remain clinically silent for the whole lifetime in a proportion of people (about 0.1-0.3% of the autopsies in

those studies) is in great concordance with this. Under these circumstances, only randomized controlled trials can define the role of DMTs in RIS subjects and need to be considered, particularly in high-risk populations. Indeed, multi-center, randomized trials are currently underway(38) and will provide an evidence-based answer to this issue in the near future. For the time being, active monitoring of patients with periodical (every 6-12 months) clinical and radiological follow-up can be justified in the subjects with possible subclinical MS. No further follow-up is suggested in RIS individuals without the characteristics of subclinical MS, although the subjects should be instructed to seek healthcare if they develop symptoms.

Finally, in the management of a subject with suspected RIS diagnosis, it is important to ask and consider her/his opinion. Since at present no specific treatment is recommended, the individual with RIS must have the "opportunity of not knowing". It is therefore imperative to let the individual decide whether she/he wants to be investigated further as this may have a major impact on her/his life.

References

1.   Morris Z, Whiteley WN, Longstreth WT, Jr., Weber F, Lee YC, Tsushima Y, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2009;339:b3016.
2.   Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology. 2009 Mar 3;72(9):800-5.
3.   Siva A, Saip S, Altintas A, Jacob A, Keegan BM, Kantarci OH. Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. Multiple sclerosis (Houndmills, Basingstoke, England). 2009 Aug;15(8):918-27.
4.   Lebrun C, Bensa C, Debouverie M, De Seze J, Wiertlievski S, Brochet B, et al. Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile. Journal of neurology, neurosurgery, and psychiatry. 2008 Feb;79(2):195-8.
5.   De Stefano N, Cocco E, Lai M, Battaglini M, Spissu A, Marchi P, et al. Imaging brain damage in first-degree relatives of sporadic and familial multiple sclerosis. Annals of neurology. 2006 Apr;59(4):634-9.
6.   Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain. 1997 Nov;120 (Pt 11):2059-69.
7.   Tintore M, Rovira A, Martinez MJ, Rio J, Diaz-Villoslada P, Brieva L, et al. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. Ajnr. 2000 Apr;21(4):702-6.
8.   Montalban X, Tintore M, Swanton J, Barkhof F, Fazekas F, Filippi M, et al. MRI criteria for MS in patients with clinically isolated syndromes. Neurology. 2010 Feb 2;74(5):427-34.
9.   Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Annals of neurology. 2011 Feb;69(2):292-302.
10.   Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet neurology. 2016 Mar;15(3):292-303.
11.   Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: a systematic review and meta-analysis. Neurology. 2013 Oct 1;81(14):1260-8.
12.   Charil A, Yousry TA, Rovaris M, Barkhof F, De Stefano N, Fazekas F, et al. MRI and the diagnosis of multiple sclerosis: expanding the concept of "no better explanation". Lancet neurology. 2006 Oct;5(10):841-52.
13.   Gupta A, Nair S, Schweitzer AD, Kishore S, Johnson CE, Comunale JP, et al. Neuroimaging of cerebrovascular disease in the aging brain. Aging Dis. 2012 Oct;3(5):414-25.
14.   Sati P, Oh J, Constable RT, Evangelou N, Guttmann CR, Henry RG, et al. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. Nat Rev Neurol. 2016 Dec;12(12):714-22.

15.   Granberg T, Martola J, Kristoffersen-Wiberg M, Aspelin P, Fredrikson S. Radiologically isolated syndrome - incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review. Multiple sclerosis (Houndmills, Basingstoke, England). 2012 Jul 3.

16.   Okuda DT, Siva A, Kantarci O, Inglese M, Katz I, Tutuncu M, et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. PLos One. 2014;9(3):e90509.

17.   Forslin Y, Granberg T, Jumah AA, Shams S, Aspelin P, Kristoffersen-Wiberg M, et al. Incidence of Radiologically Isolated Syndrome: A Population-Based Study. Ajnr. 2016 Feb 4.

18.   Labiano-Fontcuberta A, Benito-Leon J. Radiologically isolated syndrome: An update on a rare entity. Multiple sclerosis (Houndmills, Basingstoke, England). 2016 Jun 10.

19.   Ehling R, Bsteh G, Di Pauli F, Hegen H, Auer M, Obermair K, et al. Rethinking the importance of paroxysmal and unusual symptoms as first clinical manifestation of multiple sclerosis: They do matter. Multiple Sclerosis and Related Disorders. 2016;9:150-4.

20.   Lebrun C, Blanc F, Brassat D, Zephir H, de Seze J. Cognitive function in radiologically isolated syndrome. Multiple sclerosis (Houndmills, Basingstoke, England). 2010 Jul 7.

21.   Amato MP, Hakiki B, Goretti B, Rossi F, Stromillo ML, Giorgio A, et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. Neurology. 2012 Jan 31;78(5):309-14.

22.   Labiano-Fontcuberta A, Martinez-Gines ML, Aladro Y, Ayuso L, Mitchell AJ, Puertas-Martin V, et al. A comparison study of cognitive deficits in radiologically and clinically isolated syndromes. Multiple sclerosis (Houndmills, Basingstoke, England). 2016 Feb;22(2):250-3.

23.   Pardini M, Uccelli A, Grafman J, Yaldizli O, Mancardi G, Roccatagliata L. Isolated cognitive relapses in multiple sclerosis. Journal of neurology, neurosurgery, and psychiatry. 2014 Sep;85(9):1035-7.

24.   Okuda DT, Mowry EM, Cree BA, Crabtree EC, Goodin DS, Waubant E, et al. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. Neurology. 2011 Feb 22;76(8):686-92.

25.   Lebrun C, Bensa C, Debouverie M, Wiertlevski S, Brassat D, de Seze J, et al. 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. Archives of neurology. 2009 Jul;66(7):841-6.

26.   Lebrun C, Le Page E, Kantarci O, Siva A, Pelletier D, Okuda DT. Impact of pregnancy on conversion to clinically isolated syndrome in a radiologically isolated syndrome cohort. Multiple sclerosis (Houndmills, Basingstoke, England). 2012 Sep;18(9):1297-302.

27.   Rocca MA, Amato MP, De Stefano N, Enzinger C, Geurts JJ, Penner IK, et al. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. Lancet neurology. 2015 Mar;14(3):302-17.

28.   Lebrun C, Forzy G, Collongues N, Cohen M, de Seze J, Hautecoeur P. Tear analysis as a tool to detect oligoclonal bands in radiologically isolated syndrome. Rev Neurol (Paris). 2015 Apr;171(4):390-3.

29.   Absinta M, Rocca MA, Colombo B, Copetti M, De Feo D, Falini A, et al. Patients with migraine do not have MRI-visible cortical lesions. Journal of neurology. 2012 Dec;259(12):2695-8.

30.   Calabrese M, Oh MS, Favaretto A, Rinaldi F, Poretto V, Alessio S, et al. No MRI evidence of cortical lesions in neuromyelitis optica. Neurology. 2012 Oct 16;79(16):1671-6.

31.   Georgi W. [Multiple sclerosis. Anatomopathological findings of multiple sclerosis in diseases not clinically diagnosed]. Schweiz Med Wochenschr. 1961 May 20;91:605-7.

32.   Gilbert JJ, Sadler M. Unsuspected multiple sclerosis. Archives of neurology. 1983 Sep;40(9):533-6.

33.   Engell T. A clinical patho-anatomical study of clinically silent multiple sclerosis. Acta Neurol Scand. 1989 May;79(5):428-30.

34.   Johannsen LG, Stenager E, Jensen K. Clinically unexpected multiple sclerosis in patients with mental disorders. A series of 7301 psychiatric autopsies. Acta Neurol Belg. 1996 Mar;96(1):62-5.

35.   Freedman M, Cree B, Lublin F. Medscape Great Debate: Radiologically Isolated Syndrome. American Academy of Neurology (AAN) 62nd Annual Meeting 2010.

36.   Tornatore C, Phillips JT, Khan O, Miller AE, Hughes M. Consensus opinion of US neurologists on practice patterns in RIS, CIS, and RRMS: Evolution of treatment practices. Neurol Clin Pract. 2016 Aug;6(4):329-38.

37.   Giorgio A, Stromillo ML, De Leucio A, Rossi F, Brandes I, Hakiki B, et al. Appraisal of brain connectivity in radiologically isolated syndrome by modeling imaging measures. J Neurosci. 2015 Jan 14;35(2):550-8.

38.   Okuda DT, Lebrun Frenay C, Siva A, Hotermans C, Von Hehn C, Remington G, et al. Multi-center, randomized, double-blinded assessment of dimethyl fumarate in extending the time to a first attack in radiologically isolated syndrome (RIS) (ARISE Trial). Neurology. 2015;84(14 Supplement P7.207).

Table 1: **MAGNIMS recommendations for diagnosis and management of RIS and subclinical MS**

Diagnostic Criteria

- The diagnosis of RIS assumes that findings are unremarkable for remitting clinical symptoms after a carefully collected clinical history and a meticulous clinical examination.
- The description of MRI lesion dissemination in space and time proposed in the most recent MRI criteria for the diagnosis of MS should be applied in subjects with RIS(10)
- The presence of MRI dissemination in time (i.e., gadolinium-enhancing lesions and/or new T2 lesions) in RIS can allow a definite diagnosis of MS once the subject shows a neurological event, confirmed by clinical examination, suggestive of CNS demyelination.
- The diagnosis of RIS is mainly based on the interpretation of MRI findings, but it is necessary to exclude other disease entities that could account for the observed MRI anomalies

Predictors of conversion and subclinical MS
- There are a number of relevant predictors of conversion from RIS to MS. They should be used to identify RIS subjects who might have higher risk of developing MS.
- Individuals with RIS who have the classical paraclinical features of MS patients and several MRI risk factors for conversion to MS are likely to have a subclinical form of MS

Treatment and management
- Current evidence does not support treatment in subjects with RIS, even when the findings suggest subclinical MS.
- Active monitoring of patients with periodical (every 6-12 months) clinical and radiological follow-up is recommended in the subjects with possible subclinical MS.
- Each individual with RIS must have the "opportunity of not knowing". It is therefore imperative, after a first diagnosis of RIS, to let the individual decide whether she/he wants to be investigated further

Table 2: Modified Criteria for the diagnosis of RIS

Exclusion criteria:
- ✓ Clinical evidence of neurological dysfunction suggestive of MS based on historical symptoms and/or objective signs
- ✓ 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

Inclusion criteria:
- ✓ Demonstration of lesion dissemination in space (at least involving two of the following topographies)(10)
  - Periventricular white matter ($\geq$ 3 lesions)
  - Cortico-juxtacortical ($\geq$ 1 lesion)
  - Spinal cord ($\geq$ 1 lesion)
  - Infratentorial ($\geq$ 1 lesion)
  - Optic nerve ($\geq$ 1 lesion)

Table 3: **Characteristics of migraine-related brain white matter lesions versus demyelinating lesions**

	Migraine	**Demyelinating**
Lesion size	punctate (usually < 5 mm)	variable (usually > 5 mm)
Lesion number	low	variable
Lesion confluency	rare	variable
Lesion topography	anterior, subcortical, juxtacortical, deep white matter	posterior, periventricular
Infratentorial lesions	≈10%	frequent
New lesions	rare	frequent
Venocentric pattern*	rare	frequent
Intralesional signal loss*	absent	frequent
Spinal cord lesions	absent	frequent
Gadolinium-enhancing lesions	absent	frequent
Corpus callosum lesions	absent	frequent

* On susceptibility-weighted imaging (SWI)

Table 4: Stratification of RIS and supporting features for a diagnosis of subclinical MS

✓ Extreme caution should be used in considering RIS subjects with
  - Migraine / chronic headache
  - Seizures
  - Paroxysmal symptoms
  - Psychiatric disturbances
  - Overt cognitive impairment

✓ Increased likelihood to be subclinical MS in case of
  - Dissemination in time on MRI (gadolinium-enhancing and/or new T2 lesions
  - Infratentorial and/or spinal cord lesions on MRI
  - High T2-lesion load on MRI
  - Cortical-juxtacortical lesions on MRI
  - Presence of oligoclonal bands in cerebrospinal fluid
  - Abnormal visual evoked potentials
  - Deficits of specific cognitive functions (information processing speed, complex attention, episodic memory and executive functions)