The radiologically isolated syndrome dilemma: just an incidental radiological finding or presymptomatic multiple sclerosis?

With the increasing use of brain magnetic resonance imaging (MRI) by clinicians, researchers and even companies that carry out health check-ups, the finding of asymptomatic intracranial abnormalities of potential clinical significance has risen tremendously. In a recent meta-analysis, the prevalence of neoplastic and non-neoplastic incidental findings on brain MRI was 2.7%, a percentage that, as would be expected, increases with age. Although the incidental findings that could be interpreted as inflammatory/demyelinating lesions seem to be relatively rare (<0.1% if white matter hyperintensities of suspected cerebrovascular origin are excluded), this has increased the awareness of MRI findings suggestive of multiple sclerosis (MS) overall. Thus, the presence of MRI findings which meet the Barkhof criteria for the diagnosis of MS in subjects without any symptom suggestive of MS and normal neurological findings has been recently characterized as the radiologically isolated syndrome (RIS), a complex entity that still needs to be better defined.

In this issue of the Multiple Sclerosis Journal, Granberg and colleagues provide an extensive systematic review of the most recent RIS studies, shedding light on some of the paramount questions associated with this new entity. They emphasize, for example, that approximately two-thirds of persons with RIS show radiological progression and one-third of persons with RIS develop neurological symptoms during mean follow-up times of up to five years. They also point out that, as shown by recent studies, clinical conversion is more likely if cervical cord lesions are found but that this risk can also increase with other markers such as the presence of oligoclonal bands in the cerebro-spinal fluid (CSF) and/or a high number of MRI lesions. Finally, it is stressed how some of these subjects with RIS may show cognitive disturbances which are found in a high proportion of MS patients, raising the question as to whether subjects with these hidden symptoms should really be considered asymptomatic. Taken together, these findings are very informative and can certainly help to improve the characterization of this new entity. There are, however, a number of unresolved issues regarding the management of RIS subjects that need our attention and urgently require solutions.

The first issue relates to what still needs to be done to provide a more specific characterization of RIS subjects. Assuming a carefully collected clinical history and a meticulous clinical examination, both mandatory to proposing a diagnosis of RIS, the first step of the management of these up-to-now asymptomatic subjects is to consider an appropriate differential diagnosis. Often the investigations vary with factors that are difficult to control including the resource availability of a given center. This can create discrepancies in diagnostic procedures and must be avoided. That having been said, the main issue remains the extent to which MRI lesions fulfilling the RIS criteria in asymptomatic subjects may be related to disorders other than MS or even to a real pathological process. In this context, the international consensus reports provided by the Magnetic Imaging in MS (MAGNIMS) European network can be helpful in identifying/excluding differential diagnoses and in defining a series of MRI red flags that should alert clinicians to reconsider the differential diagnosis more extensively.

It is only when RIS subjects are expertly diagnosed that the stratification of risk can be accurate. Indeed, this is a crucial issue since we require sufficient information to be able to differentiate RIS subjects into those with a low or high risk of developing MS. At present, since the follow-up periods of the available RIS studies are relatively short, we need longer prospective studies to estimate the long-term risk of RIS subjects for MS conversion. However, as mentioned above, given the number of prognostic factors which may increase the risk of clinical progression, we can make a reasonable attempt to differentiate amongst RIS subjects. For example, do we not now have sufficient information to consider at high risk of MS those young females meeting the Okuda criteria and showing MRI features such as spinal lesion(s), enhancement after gadolinium injection, significant brain atrophy, T1 hypointensities and new lesion formation over time as well as signs of cognitive dysfunction and/or CSF abnormalities? Should we not consider at low risk for MS, those subjects who incidentally show a white matter lesion pattern similar to that of patients with MS on brain MRI but do not demonstrate any other paraclinical marker of MS? And should we not take particular care of RIS subjects with a family history of MS? We do have factors which we can use to stratify RIS patients with a high and low risk of developing MS, although there remains some degree of uncertainty and recognition that we need more (longitudinal) studies to confirm those factors.

The possibility of differentiating between subjects with just an incidental radiological finding and those who likely...
have presymptomatic MS raises the question as to whether the potentially high-risk group of subjects should be started on disease-modifying therapies as if they were MS patients. This is highly controversial. Indeed, although in RIS subjects the treatment with disease-modifying therapies is generally not recommended, the review of recent studies testifies that about 10% of the reported RIS population is treated.3 This is not good practice and must be avoided. In fact, while we do not agree with the simplistic view that ‘we treat the patient, not the MRI scan’ (should not an asymptomatic malignant brain tumor discovered incidentally by MRI be treated?), it is also true that current evidence does not support treatment in subjects with presymptomatic MS. It is conceivable that RIS subjects have an exceptional capacity to repair, and/or a particularly pronounced functional connectivity which could explain, at least in part, the lack of symptoms despite the evidence of macroscopic tissue damage.5 Thus, in principle, RIS subjects may develop clinical symptoms very late (or never) which raises the real risk of over treating these subjects. Randomized controlled trials that have proved the efficacy of early initiation of disease-modifying therapies in relapsing MS, and have been shown to delay the conversion to MS in clinically isolated syndromes, will aid in defining the role of disease-modifying therapies in RIS and need to be considered in the near future, particularly in high-risk RIS populations.

References

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