Radiologically Isolated Syndrome: the First Visible Manifestation of Multiple Sclerosis

The Radiologically Isolated Syndrome is the description given to cases where MRI examinations show a risk of future demyelinating events in the CNS in subjects who however have no clinical symptoms suggestive of CNS demyelination.

In the field of neuroscience, magnetic resonance imaging (MRI) has been invaluable to healthcare providers in nearly all cases, data derived from imaging studies provide guidance to the underlying biology of the disease process present. These data are based on signal characteristics and the spatial distribution of abnormalities. Observations from neurological examination are helpful for localization. However, the information provided by the patient is still essential to uncover the underlying diagnosis.

Multiple sclerosis (MS) is a common cause of severe neurological disability in young adults, and results from autoimmune interruption of both myelin and axonal integrity within the central nervous system (CNS). The advent of MRI and its application to the field of neuroimmunology has improved diagnostic capabilities, enhanced clinical surveillance of disease and assessment of therapeutic response, and also increased our understanding of the complexities of immune-related injury in this heterogeneous demyelinating process.

A diagnosis of MS is made by fulfilling both spatial criteria, i.e. by having a requisite number of lesions with specific topography within the brain, with or without involvement of the spinal cord, and temporal criteria, e.g. through demonstration of a history of at least a second clinical attack or the development of a new MS lesion as detected by MRI after the seminal neurological event. In many other chronic conditions, signs of impending disease may be observed in diagnostic testing in the months to years prior to the first clinical symptom and formal diagnosis.

Sometimes, healthy individuals without any clinical signs related to CNS demyelination undergo brain MRI examinations, carried out for reasons other than for an evaluation of suspected MS. Occasionally, such MRI examinations reveal unexpected anomalies which, given their size, location, and morphology are highly suggestive of demyelinating plaques [see Figure 1] [2-4].

The Radiologically Isolated Syndrome descriptor does not imply that the subject is at risk for future demyelinating events. The Radiologically Isolated Syndrome descriptor does not just involve subjects with abnormal imaging findings but also includes clinical parameters so as to exclude the presence of prior neurological symptomatology that could be related to MS, as well as the exclusion of other conditions that could better explain the observed structural abnormalities.

The concept of using imaging to identify structural abnormalities within the CNS prior to first symptom manifestation can also be found in other medical disciplines than neuroimmunology. Individuals with a slow growing space-occupying tumor or with a vascular anomaly such as an arteriovenous malformation or cerebral aneurysm may be identified before any actual symptom development. In the case of MS such symptom development is a first seizure event or neurological deficit.

The precise management of such disorders varies but can sometimes be perceived to be aggressive, given the clinical-radiological paradox of the presentation of an apparently healthy subject who happens to have generated images that may be visually concerning.

In MS, the notion of disease beginning prior to the onset of first symptoms is supported by the fact that clear signs of disease within the brain and, at times, spinal cord are commonly observed, supported by the existence of T2-hyperintensities highly suggestive of MS within the brain, along with identified brain volume changes that appear beyond the stated chronological age.

In addition, prospective imaging studies involving asymptomatic relatives of sporadic and familial MS cases have revealed a lesion distribution pattern indistinguishable from MS and supportive of a pre-symptomatic phase. The scientific literature also describes the observation of post-mortem incidental demyelinating disease. Lebrun and colleagues [2] were the first to report on a group of individuals with MRI features typical of MS. This important finding was followed by work from a group of researchers at the University of California, San Francisco who introduced the criteria and the formal description of the Radiologically Isolated Syndrome (RIS).

Despite these data, there are still concerns regarding the possibility of over-diagnosis in such cases given the fact that non-specific white matter changes are relatively common...
place within the brain. It has been pointed out that the criteria for spatial dissemination in MS were principally designed to be applied to individuals who have experienced a first demyelinating event and were not intended for screening of the general population.

The establishment of a diagnosis of RIS extends beyond just having an abnormal MRI study but also involves rigorous clinical investigation as well. The specificity of the previously described criteria for dissemination in space does, however, offer a general guide regarding the classification of MRI lesions when found. Are radiologists more likely to attribute white matter anomalies to in situ demyelination if in the first place it is known that the reason for imaging is to assess for MS following a first neurological attack? One would hope that, regardless of the basic reason for the study, only objective parameters would be utilized to arrive at a given conclusion regarding the potential etiologies of any white matter changes. Future efforts involving the use of susceptibility weight imaging and quantitative susceptibility mapping may assist in improving lesion characterization. Data from these emerging radiological metrics may likely be incorporated into future criteria for the diagnosis of MS.

After an accurate classification of a patient as having RIS, a critically important scientific question involves the understanding of the risk factors for evolution to a first clinical event attributable to CNS demyelination (e.g. weakness in a leg or arm, a spinal cord syndrome, optic neuritis, etc.). In 2014, the Radiologically Isolated Syndrome Consortium (RISC) published data from a multinational effort involving 5 countries that included the largest cohort of individuals with asymptomatic MRI anomalies typical of MS [7]. The goal of the study was to report on the 5-year risk and to identify risk factors for a first neurological event resulting from aberrant immune behavior within the CNS.

A total of 451 individuals were included using data from 22 clinical databases. The study cohort was principally composed of young white women. The time to a first clinical event resulting from an acute attack or the first symptom suggestive of a progressive course was recorded.

The top three reasons for performing an initial scan were 1) evaluation of a complaint of headache; 2) a traumatic event, and 3) evaluation for anxiety.

Clinical events were identified in 34% of individuals within a 5-year period from the first brain MRI study. Interestingly, 9.6% of those who developed clinical symptoms possessed a clinical phenotype highly suggestive of MS. The factors that appeared to place an individual at risk for a first clinical event included sex (male), age less than 37 years, and the presence of lesions either within the cervical or thoracic spinal cord. In addition, if there was more than one risk factor there was a greater risk for first symptom onset. Overall, this scientific effort supported the existence of an asymptomatic form of MS and highlighted that those with RIS are at risk of an initial clinical event.

**TO TREAT OR NOT TO TREAT?**

A significant question now presents itself. Should these individuals be treated to prevent a first clinical attack? Or should routine MRI surveillance simply be used to follow individuals until a clinically meaningful event occurs? With every demyelinating episode, there is a risk of incomplete recovery and residual neurological deficits. Recommending a preventative treatment approach appears inherently sensible and represents a management strategy similar to therapeutic approaches for other chronic disease such as hypertension, diabetes, and hypercholesterolemia. To address this vital question, RISC has formed a strategic research alliance with Biogen Idec (Cambridge, Massachusetts, U.S.A.) to assess the impact of dimethyl fumarate (Tecfidera) in extending the time to a first demyelinating attack. This multi-center, double blind, randomized novel trial will take place in the United States and should provide the first evidence for any impact of early treatment in an asymptomatic group.

With advancing technology and the increase in the use of non-invasive techniques it will be increasingly possible to not only verify expected anomalies that correspond to clinical events but also to discover unanticipated findings that may result in more dynamic approaches to clinical surveillance and treatment for the subjects imaged. The mindful application of the existing RIS diagnostic criteria is key in preventing the over-recognition of white matter anomalies that may be cryptogenic in origin. Although substantial advances in imaging techniques enable better classification of disease, we should always remember that, as in the case of RIS, in general the patient’s clinical history ultimately provides us with the diagnosis.

**REFERENCES**