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Magnetic Resonance Imaging Abnormalities in Multiple Sclerosis: A Review

During the last two decades, magnetic resonance imaging has been widely used in the diagnosis and treatment monitoring of multiple sclerosis. MRI, both conventional and non conventional methods, has transformed all aspects of MS research and clinical practice in recent years. Although advanced imaging methods have added much more to our knowledge about pathogenesis and natural history of the disease but their cost, availability, complexity and lack of validation have limited their use in routine clinical practice. Conventional MR techniques including proton density, T1/T2-Weighted images and fluid- attenuated inversion recovery sequences are now accepted in standard protocols for diagnosis and treatment outcome measures in clinical trials of multiple sclerosis. This review will focus on the type, morphology and evolution of MS lesions regarding conventional MRI and their use for treatment monitoring in daily clinical practice.

Keywords: multiple sclerosis, magnetic resonance imaging, MS diagnosis

Introduction

Magnetic resonance imaging (MRI) has become the most sensitive paraclinical test in diagnosis, assessment of disease evolution and treatment effects in multiple sclerosis (MS). Conventional T2-weighted and contrast enhanced T1-weighted images are currently the standard assessment methods for early diagnosis and to show clinically silent lesions in MS.[1-3] MRI is used as a prognostic tool at the first presentation of symptoms, suspicious of central nervous system (CNS) demyelination[4,5] and also in providing primary outcome measures in phase I/II trials or secondary outcomes in phase III trials on MS. These are the main reasons why MRI findings have a major role in recently-developed international diagnostic criteria for MS. In this article, we review individual MRI changes detected by conventional imaging approach and discuss the role of MRI in estimating disability and treatment monitoring in multiple sclerosis.

MS lesions in T2-weighted images

Multiple hyperintense lesions on T2-weighted sequences are the characteristic MR appearance of MS. The majority are small, although, lesions can occasionally measure several centimeters in diameter.

They may occur in most parts of the CNS, but periventricular or callosal lesions are typical. Other common sites of involvements are juxtacortical and infratentorial regions (Fig.1). Although MS is a white matter disease, 5%–10% of the lesions may involve the gray matter including cerebral cortex and basal ganglia.[6] In gray matter, MS lesions are usually small with intermediate high signal intensity with less severe degree of inflammation, which may cause the obscure appearance of gray matter lesions on MR imaging compared with that of white matter lesions.[7] MS lesions tend to have an ovoid configuration with the major axis perpendicular to the ventricular borders (Dawson's fingers).

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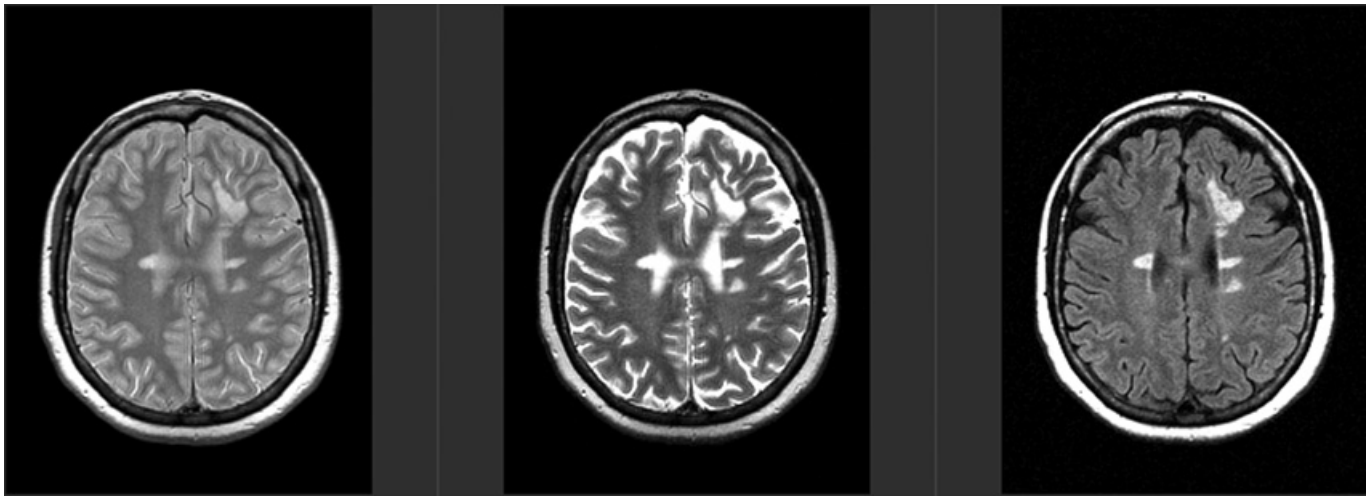


Fig. 1. A-C. Axial proton density (PD), T2-weighted and FLAIR images of a patient with remitting-relapsing multiple sclerosis (RRMS) demonstrate multiple hyperintense lesions with periventricular predominance. The lesions are usually ovoid or round and their major axes are perpendicular to the ventricular surface.

Most lesions, especially in the early stages of the disease, are discrete on conventional MRI but diffuse irregular hyperintensities have also been demonstrated in the later stages of the disease. These areas with poorly defined borders, are usually seen around the ventricles and called dirty appearing white matter (DAWM). Such abnormalities have been reported in 17% of patients with remitting-relapsing MS.[8]

T2-weighted lesions do not have any pathologic value since almost any alteration in the brain tissue composition can change the signal intensity. Inflammation, demyelination, gliosis, edema and axonal loss will increase the signal without any specific pattern.[9] New T2 lesions represent new inflammation; they may increase in size during acute phase to contract later while the intensity is reduced as edema resolves and tissue repair occurs. However, most lesions, once evident on T2-weighted images, rarely disappear unless they are located in brainstem or spinal cord.[10-12] Acute lesions may have more complex appearances on T2-weighted images and show a central spherical hyperintensity with an iso- to hypo-intense ring around the central hyperintensity corresponding to the area of Gd ring enhancement in T1-weighted with contrast. This hypointensity may result from paramagnetic free radicals that are produced by macrophages.[13]

MS lesions in T1-weighted images with contrast

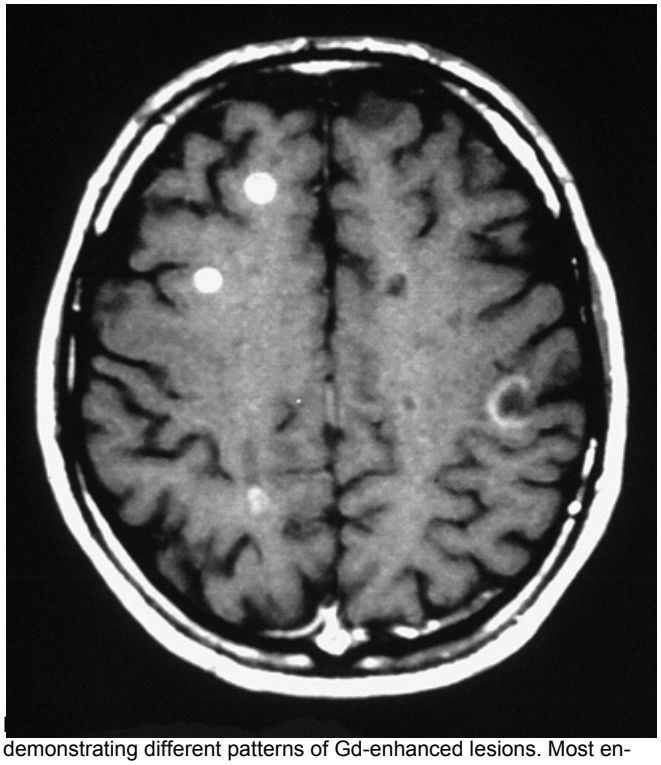
Gadolinium (Gd) enhancement is a marker for blood-brain barrier breakdown; histologically, it correlates with the development of inflammatory phase of lesion.

In MS, most new lesions go through a phase of enhancement, usually persisting for 2–6 weeks. Only a small number of lesions demonstrate enhancement for 3–4 months.[14] The natural history of contrast-enhancing lesions is highly variable and unpredictable. Among the possible evolutions, axonal loss and axonal degeneration are thought to be correlated with clinical worsening and disability.[15]

Approximately, 65%–80% of contrast-enhancing lesions appear hypointense on the correlating unenhanced T1-weighted images.[14,16] However, once contrast enhancement ends, the hypointense lesions may become isointense and less than 40% of them develop into persistent black holes.[17,18] This return to the T1 isointense state or mild T1 hypointensity may indicate partial remyelination.

Enhancing lesions may differ in size, shape or pattern. Most of them demonstrate a nodular pattern (68%) whereas 23% show ring-like enhancement and 9% have other enhancement patterns (Fig.2).[19]

Ring-like enhancement probably arises from recent inflammation at the periphery of a chronic active lesion, where the blood-brain barrier defect has been partially or completely repaired in the center.[20] Occasionally it is also noted, that the ongoing activity affects one margin of the plaque and while remainder is quiescent and may be a cause of the formation of arc pattern.[19] None of these patterns is specific for MS. The only exception might be the“open-ring” sign for



demonstrating different patterns of Gd-enhanced lesions. Most enhanced lesions demonstrate nodular pattern.

differentiating large tumor-like demyelinating lesions from actual tumors and infections. These lesions create an incomplete ring and typically the open section is oriented towards the gray matter or is adjacent to it (Fig 3).[13]

Most Gd-enhancing lesions are clinically silent.[21] Thus, MRI has become an important tool for supporting an early and accurate diagnosis of MS in many patients.

Steroid treatment may strongly suppress appearance of enhancing lesions whereas higher (double or triple) doses of Gd, longer delays between injection and acquiring the images, thinner slices and incorporating a magnetization transfer sequence have been shown to increase the number of enhancing lesions. This could result in reduced pathological specificity because even old and inactive lesions can show enhancement.[13,22,23]

T1- weighted hypointense lesions in multiple sclerosis

A subset of T2-weighted lesions are also identifiable as T1 hypointense area. These hypointense lesions are commonly referred to as black holes. T1 hypointense lesions were first described by Ulhenbrock, et al, who noted that such lesions were more common in MS than in subcortical arteriosclerotic encephalopathy.[24]

A black hole is defined as any hypointense region visible on T1-weighted sequences concordant with a region of high signal intensity on T2-weighted images. Black holes are considered to be acute when they coincide with a contrast-enhanced lesion (CEL) and to be chronic or persistent when no corresponding CEL exists. It is advised that true chronic black holes be defined as T1-hypointense lesions that persist for a minimum of six months after their first appearance.[25]

T1 black holes typically begin as contrast-enhanced lesions and evolve differently from patient to patient and also within the same patient. The longevity of persistent black holes may vary after contrast enhancement. Some lesions may be visible for a relatively short period of time, some enlarge or shrink and some others may eventually become permanent.[26]

Contrast enhancing lesions persisting for more than one month and leisions with ring enhancement have a greater chance to evolve into chronic black holes.[17,26]

T1 hypointensity is in principle caused by an expansion of the extracellular space either by an increase in water content or the loss of structural components. Pathologically, this may be a consequence of tissue destruction or often increase water influx via a disrupted blood barrier. In fact, the pathological correlates of T1 hypointense lesions depend, in part, on the lesion age. Newly-formed hypointense lesions likely reflect variable combination of inflammation, edema, demyelination, early remyelination, axonal transection and glial activation. Lesions that show most profound hypointensity on T1-weighted images correlate pathologically with the most profound demyelination and axonal loss.[13,27-29]

MS lesions in Fluid Attenuated Inversion Recovery images

Fluid attenuated inversion recovery (FLAIR) MR imaging produces a heavily T2-weighted images with nulling the signal from cerebrospinal fluid (CSF) using an inversion time that usually ranges from 1800 to 2500 ms.[30] By suppressing the signal intensity of bulk water, FLAIR images increase the conspicuity of lesions located in the periventricular area. Tissue wa-

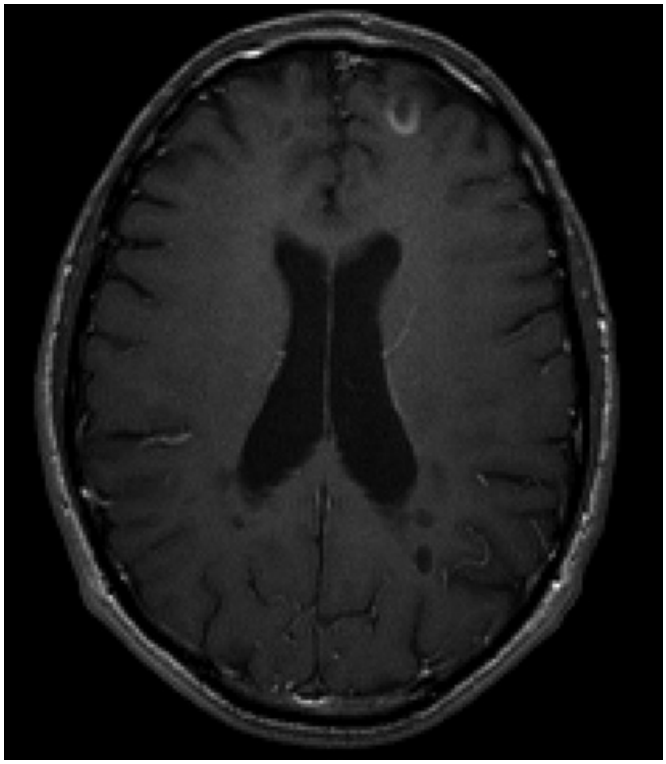


Fig. 3. Axial T1-weighted with contrast image of a patient with MS demonstrate open ring sign in the left frontal lobe.

Note: A complete ring enhanced lesion poses a common diagnostic challenge and is not valuable in differentiating demyelinating from other similar lesions, which may show complete ring enhancement. On the other hand, an open ring pattern of enhancement is more likely to be associated with demyelinating lesions than other pathologies.

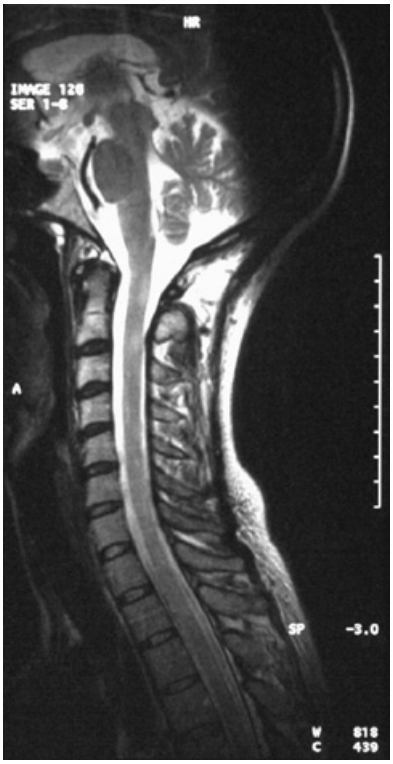


Fig. 4. Sagital T2-weighted image of a patient with RRMS demonstrate typical MS lesions in the cervical spinal cord.

ter is also affected and FLAIR images provide better lesion contrast than PD or T2-weighted images, particularly in gray matter. This technique was first reported by Hajnal, *et al,* and on account of its unique characteristics in identifying lesions close to the ventricles, juxtacortical and cortical regions, it has attracted strong attention of radiologists with respect to its clinical utility.[31] Unfortunately, FLAIR images are less sensitive in depicting plaques involving brainstem and cerebellum, therefore the lesion load may be underestimated in posterior fossa.[32] Two other disadvantages of FLAIR MR sequences are CSF flow artifacts and the long acquisition time required for imaging a limited number of slices. Pulsatile CSF flow generates inflow effects in the selected slice during the inversion time interval, which causes incomplete nulling of CSF signal intensity and production of hyperintense artifacts appearing in areas of prominent CSF pulsation, such as foramen of Monro, the third and fourth ventricles.[33] The limitation of long acquisition times has been overcome by applying fast spin echo images.[34] The quality of spinal FLAIR imaging is variable and often degraded by motion artifacts arising from CSF pulsation. Although FLAIR can produce visually pleasing images of the spinal cord, it is less sensitive to the detection of lesions than T2-weighted images.[35] Regarding available data, it is concluded that FLAIR can be added to the examination of a patient suspected for MS or in established MS, but it should not substitute other sequences such as PD.

Multiple Sclerosis and brain atrophy

Atrophy of the brain and spinal cord has been recognized as part of MS pathology for a long period of time. Several studies have demonstrated annual decrease in brain volume of MS patients ranging from 0.6% –1% compared to 0.1%–0.3% in the general population during the normal aging process.[36-39]

The exact mechanism has not been determined yet and the etiology seems to be multifactorial. It may largely result from myelin and axonal loss.[38] Wallerian degeneration particularly in the neuronal path-

ways, may also contribute to tissue loss. Atrophy is a progressive phenomenon and seems to be independent of disease subtypes.[40] Patients with RRMS tend to lose 17.3 mL/year of brain parenchymal volume.[38]

The changes that occur over time are relatively small and very sensitive measures are required to detect atrophy especially on an individual basis.[41,42]

Application of semi- and fully-automated image analysis results in more precise measurement of atrophy for longitudinal studies. Different studies suggest that any correlation between T2 lesion volume, black holes, Gd-enhanced lesions and atrophy is partial at best.[43]

The correlation between brain atrophy and clinical disability seems to be stronger than T2-lesion load.[44]

Fisher, *et al,* showed that whole brain atrophy changes in the first two years were the best MRI predictor of the eight-year disability score.[45] A number of studies have also established an association between brain atrophy and cognitive impairment in MS patients. Furthermore, whole brain atrophy predicts cognitive impairment in both cross-sectional and longitudinal studies.[46,47] Atrophy has been considered as a surrogate marker in some clinical trials of MS.[48] Although this issue is of growing interest in the therapeutic monitoring of MS, the limitations and challenges like effects of non-disease factors on tissue volume loss, need to be better evaluated. In fact, brain volume changes are complex and may be affected by inflammation, edema, hormonal levels and medication.

Role of MRI in diagnosis of MS

MS is a clinical diagnosis depending on a detailed history, careful neurologic examination and supportive paraclinical investigations. In fact, the diagnosis is based on the principle of dissemination in time and space of a disease compatible with MS in the absence of a better explanation. According to McDonald criteria, the diagnosis of MS requires objective evidence of lesions disseminated in time and space and MRI findings may contribute to the determination of dissemination in time and space. Other supportive investigations include CSF and visually evoked potential (VEP). For dissemination in space, Barkhof's MRI criteria requiring three out of the following four elements have been included in the McDonald criteria:

(1) At least one Gd-enhanced lesion or nine T2 hyperintense lesions

(2) At least one infratentorial lesion

(3) At least one juxtacortical lesion

(4) At least three periventricular lesions

In the light of subsequent studies and criticism, the original McDonald's criteria were revised for a more rapid diagnosis, to clarifying the presence of spinal cord lesions and to simplify the diagnosis of primary progressive MS.

A constant feature in both original and revised criteria is the use of Barkhof-Tintore criteria for demonstrating dissemination in space. The first modification attempted to simplify the criteria for dissemination in time. In this revised form dissemination in time can be demonstrated by detection of a Gd-enhanced lesion at least three months after the onset of the initial clinical presentation, if not at the site corresponding to the initial event or detection of a new T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event. The reason for selecting the 30-day time period was to exclude new T2 lesions occurring in the first few weeks after the onset of the first clinical episode which would not be considered a new separate event. New revised criteria also differ in the extent to which a spinal cord lesion can assist with fulfillment of dissemination in space; in recent revised criteria any number of cord lesions can substitute for brain lesions. In addition, a cord lesion is also assigned the same status of an infratentorial lesion. Finally, another change to the original McDonald criteria was proposed for diagnosis of primary progressive MS (Table 1). In primary progressive MS, the presence of CSF oligoclonal band is no longer required, though in their absence it is necessary to have at least two spinal cord lesions and either nine brain lesions or 4–8 brain lesions plus abnormal VEP.[49] It should be noted that even with wide utility of MRI in MS, diagnosis should remain on clinical setting and exclusion of other possible etiologies that can mimic MS in clinical presentation or MRI findings. Another important point is that these criteria have been mainly validated in young adults and middle age patients. Several reports have shown that MS may begin even in childhood and these diagnostic criteria need to be validated in this group of patients.[50,51]

Table 1. The 2005 Revisions to the McDonald Diagnostic Criteria for Multiple Sclerosis

Clinical presentation	Additional data needed for diagnosing MS
Two or more attacks[a]; objective clinical evidence of two or more lesions	None[b]
Two or more attacks[a]; objective clinical evidence of one lesion	Dissemination in space demonstrated by: MRI[c] *or* Two or more MRI-detected lesions consistent with MS plus positive CSF[d] *or* await further clinical attack[a] implicating a different site
One attack[a]; objective clinical evidence of two or more lesions	Dissemination in time demonstrated by: MRI[e] *or* second clinical attack[a]
One attack[a]; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space demonstrated by: MRI[c] *or* two or more MRI-detected lesions consistent with MS plus positive CSF[d] *and* dissemination in time demonstrated by: MRI[e] *or* second clinical attack[a]
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) *and* two of the following: positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP)[f] Positive spinal cord MRI (two focal T2 lesions) Positive CSF[d]

If criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if suspicious, but criteria are not completely met, the diagnosis is "possible MS;" if another diagnosis arises during the evaluation that better explains the entire clinical presentation, then the diagnosis is not MS.
a. An attack is defined as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature. There should be subjective report (back up by objective findings) or objective observation that the event lasts for at least 24 hours.
b. No additional tests are required; however, if tests (MRI, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnosis must be considered. There must be no better explanation for clinical picture and some objective evidence to support a diagnosis of MS.
c. MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof and colleagues and Tintore and coworkers as presented in the text.
d. Positive CSF determined by oligoclonal bands detected by established methods (isoelectric focusing) different from any such bands in serum, or by an increased IgG index.
e. MRI demonstration of time dissemination must fulfill the criteria explained in the text.
f. Abormal VEP of type seen in MS.[47]

Clinical Correlation and Prognosis

MRI lesions are often clinically silent and MRI changes do not necessarily correlate well with the extent of clinical disability. Several reasons have been advanced to explain this clinicoradilogical paradox in MS. These reasons include poor sensitivity of traditionally used Kurtzke expanded disability scale (EDSS), appearance of lesions in silent areas of the brain and poor specificity of lesions found on conventional imaging.[52] As we mentioned before, chronic black holes are associated with greater tissue destruction and show higher correlation with disability as compared to T2 burden of disease.[53]

MRI measurs are rarely used for predicting prognosis and clinical outcome in MS. The only exception is the patients presenting with clinically isolated syndrome (CIS) who are at higher risk for developing MS. The presence and the number of MRI lesions in these patients are strong predictors of developing definite MS.[54]

Spinal cord imaging in MS

The spinal cord is known to be frequently involved in MS; 50%–90% of clinically-definite patients have lesions on spinal cord MR imaging. These lesions are more common in the cervical than the thoracic cord. On T2-weighted images, MS plaques are peripherally located (commonly dorsolateral) and are less than two vertebral body segments in length (Fig. 4).

Spinal cord atrophy is another MR finding in these patients and may reflect axonal loss.

Spinal imaging is recommended if the main presenting symptoms are at the level of spinal cord and have not been resolved. It is also justified if the results of brain images are equivocal and diagnosis of MS is still being entertained.

As T2 hyperintense lesions do not develop in the spinal cord from normal aging or are very uncommon from small vessel disease such as that attributed to hypertension, spinal imaging is valuable in doubtful cases.[49,55]

General recommendations in patients with established MS and CIS

1. MRI scans (dual-echo and post-contrast T1-weighted images) should be obtained using standardized protocols and accurate procedures for patients' repositioning in order to facilitate the interpretation of follow-up studies. Post-contrast T1-weighted scans should be acquired after an interval of 5–7 min from the injection of contrast material. The use of surveillance MRI for the purpose of making treatment decisions can not be generally recommended. Serial MRI scans should be considered when diagnostic issues arise.[56]

2. Repetition of MRI of the spinal cord is advisable only if suspicion arises concerning the evolution of an alternate process (e.g., mechanical compression) or atypical symptoms develop.

3. Although preliminary work based on clinical trial data has suggested that presence and amount of MRI-detected disease activity may identify INF-β response status in terms of relapse rate and accumulated disability in MS patients at a group level, there are no validated methods for monitoring disease-modifying therapy in individual patients.

4. The application of non-conventional MRI techniques in monitoring patients with established MS in clinical practice is, at the moment, not advisable. All these techniques still need to be evaluated for sensitivity and specificity in detecting tissue damage in MS and its changes over time.

5. In the case of steroids treatment, which is known to dramatically suppress Gd enhancement, MRI should be performed before treatment or, at least, one month after treatment termination.

6. MRI of the spinal cord is useful in those circumstances when brain MRI is normal or equivocal, and in patients with non-specific brain T2-abnormalities (especially when the age is more than 50 years), because, contrary to what happens in the brain, cord lesions rarely develop with ageing *per se*. In patients presenting with a spinal cord syndrome, spinal cord MRI is highly recommended to rule out other conditions that may mimic MS, such as compressive lesions.

7. In patients with acute optic neuritis, MRI of the optic nerve can be useful in ruling out alternative diagnoses. In this case, STIR sequences should be used.

8. Repeated scanning beyond the two initial studies need to be considered by individual neurologists considering the clinical circumstances that are appropriate for each patient and is not routinely recommended as the disease becomes more likely to manifest clinically in the longer term.[57]

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