Role of MRI in diagnosis and treatment of multiple sclerosis

Mohammad Ali Sahraian a,*, Arman Eshaghi b

a Department of Neurology, Sina Hospital, Tehran University of Medical Sciences, Iran
b Sina MS Research Center, Sina Hospital, Tehran University of Medical Sciences, Iran

1. Introduction

Magnetic resonance imaging (MRI) has played an expanding and unique role in the diagnosis and management of multiple sclerosis (MS), since the beginning of its application by Young et al. in this field [1,2]. Actually the initial evaluation of a patient suspected of MS starts with MRI due to its exquisite sensitivity to depict focal white matter abnormalities and clinically silent lesions. Despite their limitations to demonstrate diffuse damage to the white matter, neuroaxonal degeneration and irreversible demyelination, conventional T2-weighted and contrast enhanced T1-weighted images are currently the standard assessment methods to confirm or reject the clinical diagnosis [3]. MRI is also used as a prognostic tool at the first presentation in patients with clinically isolated syndrome (CIS) [4,5]. Both conventional and new MR techniques including MR spectroscopy, diffusion tensor, magnetization transfer and functional MRI have changed our understanding about the underlying mechanism and pathophysiology of the disease. As the disease activity is detected 5–10 times more frequently on conventional MRI compared to clinical assessment of relapses, this method is used as the primary outcome measure in phase II and secondary outcome measure in phase III clinical trials [6].

In this article, we review individual MRI changes detected by conventional imaging approach and discuss the role of MRI in diagnosis, estimating disability and treatment monitoring in MS.

2. MS lesions in T2-weighted images

T2-weighted images are highly sensitive for detection of MS lesions. The characteristic MR appearance of MS is multiple hyperintense lesions on this sequence. Typical lesions are usually small, round or oval in shape and may occur in any part of the central nervous system where myelin exists. These lesions are more frequent in periventricular area, but juxtacortical and infratentorial regions are other common sites of involvement (Fig. 1). Although MS is a white matter disease 5–10% of the lesions may involve the gray matter (GM) including cerebral cortex and basal ganglia [5]. GM lesions are usually small with intermediate high signal intensity and a less severe degree of inflammation, which may cause the obscure appearance of GM lesions on MR imaging compared with that of white matter lesions [6].

MS lesions are not always typical. Atypical large, confluent lesions with several centimeters in diameter are occasionally seen on T2-weighted images that may mimic tumors, leukodystrophies and other white matter abnormalities.
Most of lesions especially in the early stages of the disease are discrete on conventional MRI but subtle, abnormal and diffuse signal intensity changes may be depicted on T2-weighted images. These areas which have poorly defined borders are usually seen around the ventricles and are called dirty appearing white matter (DAWM). Such abnormalities have been reported in 17% of the patient with remitting-relapsing (RR) MS [7].

T2-weighted lesions do not have pathological specificity and almost any alteration in the brain tissue composition can change signal intensity. These lesions may be due to inflammation, demyelination, gliosis, edema or axonal loss [8].

New lesions represent new inflammatory activity, they may increase in size during acute phase then contract and their intensity reduces as edema resolves and some tissue repair occurs. However, most lesions, once evident on T2-weighted images rarely disappear unless they are located in brainstem or spinal cord [9–11].

Acute lesions may have more complex appearances on T2-weighted images and show a central spherical hyperintensity with an iso to hypointense ring around the central hyperintensity corresponding to an area of Gd ring enhancement in T1-weighted with contrast. This hypointensity may result from paramagnetic free radicals that are produced by macrophages [12].

Another MRI abnormality in patients with MS is GM T2 hypointensity. The GM areas affected include the red nucleus, thalamus, dentate nucleus, lentiform nucleus, caudate and rolandic cortex. Such hypointensities are thought to represent pathologic iron deposition [13].

Fluid-attenuated inversion recovery (FLAIR) imaging produces heavily T2-weighted images with nulling the signal from cerebrospinal fluid (CSF) using an inversion time that usually ranges from 1800 to 2500 ms [14]. By suppressing the signal intensity of bulk water, FLAIR images increase the conspicuity of lesions located in the periventricular area. Unfortunately, FLAIR images are less sensitive in depiction of plaques involving brainstem and cerebellum, so lesion load may be underestimated in posterior fossa [15].

3. MS lesions in T1-weighted images with contrast

Gadolinium enhancement reflects blood–brain-barrier (BBB) breakdown and histologically correlates with the inflammatory phase of lesion development.

Enhancing MS plaques can precede new T2 lesions by hours or days [16]. Most new lesions go through a phase of enhancement usually persisting for 2–6 weeks. It is extremely unusual for a lesion to have gadolinium enhancement beyond 6 months [17]. The natural history of contrast-enhancing lesions is highly variable and unpredictable. Approximately 65–80% of contrast-enhancing lesions have a corresponding hypointensity on native T1-weighted images [18,19]. These acute hypointense lesions may become isointense or develop into persistent black holes [20,21].

Enhancing lesions may vary in size, shape or pattern of enhancement. This considerable variability may be associated with the different severity of inflammation and extent of BBB breakdown. Most of them are small and demonstrate a homogeneous nodular pattern (68%). 23% show ring-like enhancement and 9% have other enhancement patterns [17] (Fig. 2). Ring enhancing lesions show higher levels of tissue destruction and thus tend to resolve more slowly. None of these patterns is characteristic for MS. The only exception might be the “open-ring” sign for differentiating large tumor-like demyelinating lesions from actual tumors and infections. These lesions create an incomplete ring and typically the open section is orientated towards the gray matter or is adjacent to it [12]. Open-ring pattern can be seen in 66–90% ring enhancement in demyelinating lesions compared with 6–17% in abscess or tumors [22].

Although MRI activity (lesion enhancement) can increase during clinical relapses, most enhancing lesions are clinically silent [23]. Corticosteroid administration significantly reduces the number of enhancing lesions and suppresses their appearance, whereas higher (double or triple) doses of gadolinium, longer delay between injection and acquiring the images, 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 [12,24,25].

New MRI contrast agents composed of iron particles, ultra-small particles of iron oxide (USPIO) or super-paramagnetic iron particles of oxide have been used in patients with MS to track macrophages. MRI studies of patients with MS that used ultra small particles of iron oxide and gadolinium have confirmed a mismatch of enhancement, indicating heterogeneity of the underlying pathology [26]. Actually most of the lesions showed enhancement with both USPIO and gadolinium, while some of them enhanced only with one of these two agents [27].

4. T1-weighted hypointense lesions in multiple sclerosis

A subset of T2-hyperintense MS lesions may appear hypointense on corresponding T1-weighted images. These hypointense lesions are commonly referred to as black holes. Black holes are considered to be acute when they coincide with a contrast-enhancing lesion and to be chronic or persistent when no corresponding enhanced lesion exists. True chronic black holes are usually defined as T1-hypointense lesions that persist for a minimum of 6 months after their first appearance [28]. The age and degree of T1 hypointensity reflect the underlying pathology. These hypointensities are com-
Fig. 2. Axial T1-weighted and proton density images of a patient with RRMS demonstrate multiple hyperintense lesions mainly around the ventricles. Some of the lesions are enhanced in T1-weighted with contrast. Note that all enhancing lesions have a corresponding T2 hyperintensity.

monly seen in the supratentorial brain regions and rarely seen in the posterior fossa or spinal cord [29].

Newly formed hypointense lesions most likely reflect variable combination of inflammation, edema, demyelination, early remyelination, axonal transection and glial activation. Permanent lesions that show most profound hypointensity correlate pathologically with the most profound demyelination and axonal loss [12,30].

T1 black holes typically begin as contrast enhanced lesions and evolve differently from patient to patient and also within the same patient. Each T1-hypointense lesion has about a 50–50 chance of being either transient (i.e., lasting about 6 months) or being permanent.

The longevity of persistent black holes may vary after contrast enhancement. Some lesions may be visible for a relatively short period of time, some shrink or disappear and some others may eventually become permanent [19]. It is generally believed that longer-lasting, ring shaped and larger lesions are more likely to form chronic black holes than a nodular enhancing lesion with a shorter duration [31,32].

5. Multiple sclerosis and brain atrophy

Atrophy of the brain and spinal cord is another common finding in patients with MS which can be seen at all stages of the disease. Progressive brain atrophy has been estimated to occur at a rate of...
0.6–1.35% per year, with the highest rate occurring in patients with active RRMS [33].

The histological basis of CNS atrophy has not been determined and the etiology seems to be multifactorial [34]. A more fundamental question, “what drives cerebral atrophy in MS?” has not been precisely answered yet. There is evidence that focal inflammation can lead to brain atrophy; however, attempts to correlate brain atrophy with lesion measures have produced mixed results. While some studies of CIS and MS showed an association between brain volumes and T1-hypointense lesions, T2-hyperintense lesions [35,36], and gadolinium (Gd)-enhancing lesions [37,38], others did not [39–41].

Wallerian degeneration (XE “Wallerian degeneration”) particularly in the neuronal pathways may also contribute to tissue loss and decreased brain parenchymal volume. Atrophy is a progressive phenomenon and seems to be independent of disease subtypes [42]. Patients with RRMS tend to lose 17.3 ml/year of brain parenchymal volume [40]. Brain atrophy is typically widespread and involves both GM and WM. With various emerging techniques allowing assessment of regional brain atrophy and segmentation of GM versus WM atrophy, it has become apparent that GM is disproportionately affected compared to WM. The deep gray nuclei are particularly affected by atrophy, and the rate of atrophy in the GM is higher than that in the WM in the early stages of MS [29].

With recent advances in more precise volume measurement, atrophy has been considered as a surrogate marker in some clinical trials of MS [43]. 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 medications, for example, steroid treatment decreases the enhancing lesion activity and can induce short-term brain volume changes [44].

6. Role of MRI in diagnosis

The diagnosis of MS is based on the principle of dissemination in time (DIT) and space (DIS) of a disease compatible with central nervous system demyelination in the absence of a better explanation. In fact MS is a clinical diagnosis and MRI findings may contribute to the determination of dissemination in time and space. In 2001, an international panel (IP) headed by Ian McDonald published new guidelines for the diagnosis of MS. These criteria for the first time utilized specific MRI evidence of lesion dissemination in time and space, with the potential to enable an earlier diagnosis, especially in patients presenting with CIS [45]. For dissemination in space, Barkhof–Tintore criteria requiring 3 out of the following 4 elements have been included in the McDonald criteria:

(1) At least 1 Gd-enhancing lesion or 9 T2-hyperintense lesions.
(2) At least 1 infratentorial lesion.
(3) At least 1 juxtacortical lesion.
(4) At least 3 periventricular lesions.

In the light of subsequent studies and criticism, the original McDonald's criteria were revised for a more rapid diagnosis, clarifying the use of spinal cord lesions and simplifying 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-enhancing lesion at least 3 months after the onset of the initial clinical event, 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 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 as that of an infratentorial lesion. Finally another change to original McDonald criteria was proposed for diagnosis of primary progressive MS. In primary progressive MS, the presence of CSF oligoclonal band is no longer mandatory, though in their absence, it is necessary to have at least 2 spinal cord lesions and either 9 brain lesions or 4–8 brain lesions plus abnormal VEP [46].

The revised McDonald criteria have, however, been criticized for their perceived complexity and low (60%) sensitivity. Less complex criteria have been produced, such as the Swanton criteria, which are claimed to offer similar specificity (87%) but increased sensitivity (72%) compared with the McDonald criteria. The MRI criteria proposed by Swanton and colleagues consist of a less stringent definition for DIS (at least 1 or more lesions in at least 2 of the 4 anatomical regions – periventricular, juxtacortical, infratentorial, and spinal cord – considered characteristic for demyelination) and enable a more flexible rule for DIT (a new T2 lesion without the requirement for a gadolinium-enhancing lesion on follow-up MRI, irrespective of the timing of the baseline scan) [47]. Despite apparent advantages for the Swanton criteria, there has been hesitation among most clinicians to adopt them. Another study investigating simplified criteria for diagnosing MS reported that a single MR imaging study performed <3 months after the onset of CIS is highly specific for the development of clinically definite MS in the presence of dissemination in space, providing that both gadolinium-enhancing and nonenhancing lesions are found, indicative of dissemination in time [48,49]. 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. The MRI, like other clinical features or laboratory tests, is simply one piece of evidence that must be placed in context to arrive at a correct diagnosis.

7. MRI red flags in diagnosis of MS

The diagnosis of MS should be questioned when MRI findings are unexpected or atypical. These unusual features or “red flags” should raise suspicion that MS is not present; however, some patients with these red flags do have MS. In such cases all other possible explanations for the clinical presentation should have been excluded. Actually the most common reason for falsely attributing a patient’s symptoms to MS is faulty interpretation of the MRI [50]. Normal MRI is one of the most important red flags in diagnosis of MS, although it can happen in less than 5% of the patients. Symmetrically distributed lesions, T2 hyperintensity of the temporal pole, external capsule involvement, absent MRI activity at follow-up, lesions in the center of corpus callosum (sparing the periphery), simultaneous enhancement of all lesions, meningeal enhancement and extensive spinal cord lesions are some other findings that raise the possibility of diagnosis other than MS. For a more comprehensive review on this issue the reader should refer to the article by Charil et al. who elaborated the concept of “no better explanation” in diagnosis of MS considering MRI atypical findings [51].
8. Clinical correlation and prognosis

MRI lesions are often clinically silent and MRI changes do not necessarily correlate well with clinical disability. A number of explanations have been suggested for why MR imaging assessments are dissociated from clinical status and the development of disability—the so-called “clinicoradiologic paradox”. These reasons include poor sensitivity of traditionally used Kurtzke expanded disability expanded disability scale (EDSS), appearance of lesions in silent areas of the brain and poor specificity of lesions depicted on conventional imaging [52].

The relationship of T2-weighted abnormalities of the brain with the degree of cognitive impairment of MS patients is stronger than that with physical disability [53].

Several studies have investigated the prognostic role of enhancing MRI on corresponding clinical parameters. The number of enhancing lesions increases shortly before and during clinical relapses and predicts subsequent MRI activity. A moderate correlation has been demonstrated between the degree of clinical disability and the mean frequency of enhancing lesions in those with RRMS and SPMS [3].

As we mentioned before chronic black holes are associated with greater tissue destruction and showed higher correlation with disability compared to T2 burden of disease [54].

MRI measures are rarely used for predicting prognosis and clinical outcome in MS. The only exception is the patients presenting with CIS who are at higher risks for developing MS. In these patients, the burden of T2 lesions is a robust predictor of subsequent evolution to clinically definite MS. Nevertheless, even in CIS patients, the increase of lesion load in the few years following the onset of the first clinical symptoms is only moderately correlated with the long-term accumulation of disability.

The presence and the number of MRI lesions in these patients are strong predictors of developing definite MS [55].

9. The role of MRI in monitoring treatment efficacy

In patients with multiple sclerosis (RR and SP types), disease activity is detected 5–10 times more frequently on conventional MRI than with clinical assessment of relapses [56]. This potential to detect subclinical activity encouraged investigators to use MRI as a valuable surrogate marker in clinical trials for MS. Historically, T2 volume was first used as potential supportive outcome in major clinical trials of cyclosporine versus azathioprine in Europe, and versus placebo in North America. Both studies failed to show clinical benefit, and both documented progression of MRI-monitored pathology that was unaffected by treatment. Several years later, the first study used attenuated change in T2 BOD on active treatment with IFNβ-1b compared with placebo to supplement the clinical endpoint and support drug approval by the FDA [11,57]. Nowadays MRI is a key tool in providing primary therapeutic outcome measures for phase I/II trials and secondary outcome measures in phase III trials. Conventional MRI quantities including new or enlarged T2 lesion counts total lesion volume, total enhancing and new enhancing lesion counts, and enhancing lesion volume are commonly evaluated together in recent years. In phase II studies, such outcome variable, as measured on monthly scans for periods of 6–12 months, may serve to explore the impact of a novel substance on the suppression of new lesion formation. In phase III studies with less frequent (e.g., yearly) MRI such data are used to support a drug’s effect on the suppression of relapses [58]. It should be noted that standard data acquisition and exact repositioning of the patient’s head at repeat examinations are mandatory for reliable interpretation. In some trials of MS T1 lesion load has been included as a secondary MRI outcome variable. As stated earlier in this article, only a proportion of new MS lesions progress to permanent black holes, and it could be demonstrated that therapeutic intervention may serve to prevent such an evolution. This has been associated with both an antiinflammatory and/or neuroprotective effect of the drug. Recently a meta-analysis of MS trials reported strong correlations between the effects of therapies on relapses and their influence on MR imaging activity [59].

Although preliminary work based on clinical trial data has suggested that presence and amount of MRI-detected disease activity may identify IFN-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 [59,60]. In routine practice the use of surveillance MRI for the purpose of making treatment decisions cannot be generally recommended. Serial MRI scans should be considered when diagnostic issues arise [60]. A recent consensus suggested waiting for further evidence to support a role for MR imaging in monitoring therapeutic response in routine clinical practice [48].

10. Spinal cord imaging in MS

The spinal cord is known to be frequently involved in MS. In patients with established MS, the prevalence of cord lesions may increase to more than 80% [61,62]. Asymptomatic spinal cord lesions described in 30–40% of patients with CIS [63]. 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 [46] (Fig. 3). Gadolinium-enhancing lesions are less frequently seen in the spinal cord than in the brain [64,65].

T1-hypointense lesions are rarely seen in the spinal cord, whereas, spinal cord atrophy is a common MR finding in MS patients and may reflect axonal loss [66,67]. MRI of the spinal cord can contribute to confirm the diagnosis of MS and exclude other possible conditions. In patients presenting with a spinal cord syndrome, spinal MRI is highly recommended to rule out other conditions that may mimic MS, such as compressive lesions.

Some patients may present with clinical signs and symptoms of acute partial or complete transverse myelitis and longitudinal extensive lesions of the spinal cord with more than 3 vertebral segments in length. The differential diagnoses of such patients are quite complex, but neuromyelitis optica (NMO) spectrum is one of the most important diagnostic considerations.
The typical NMO consists of myelitis with extensive cord lesions (>2 vertebral segments) and optic neuritis. Brain MRI is usually normal but brain stem involvement may be seen in some cases. The resemblance of the symptoms with MS makes a debate in diagnosis. Detection of a highly specific autoantibody against aquaporin-4, also known as the “NMO-IgG,” makes it possible to differentiate NMO from MS [68–70].

Spinal cord imaging can be helpful in patients more than 50 years old. As T2-hypointense lesions do not develop in the spinal cord from normal aging or are very uncommon from small vessel disease such as that related to hypertension, spinal imaging is valuable in doubtful cases [71,72].

References


