Role of MR in Evaluating Multiple Sclerosis

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Abstract

Introduction: Multiple sclerosis is an inflammatory disease that attacks the central nervous system CNS (brain and spinal cord). Specifically, it attacks the myeline sheath of the neuron cells (1-3). Up to now there is no known pathophysiological cause of the MS disease but it is believed to be autoimmune. Autoimmune means the immunity system attacks normal tissues without obvious cause. It results in progressive neurological deficits leading to accumulating disabilities. The wide distribution of plaques (name of MS lesion) produces a variety of clinical symptoms.

Key words: Multiple sclerosis, evaluation, MRI

Clinical features

Visual disturbance, loss of sensation, muscle weakness, uncontrolled bladder and bowel motion, incoordination and cognitive impairment are some of the clinical features of MS (1,4).

Causes

The aetiology of MS could be genetic or/and environmental. The genetic aspect of the disease is manifested through gender; MS is seen in women more than men by the ratio of 2:1. However, the presence of environmental cause is seen through the deficiency of vitamin D, smoking and obesity during childhood. Surprisingly Vitamin D deficiency has been found in a large number of MS disease patients. The main source of vitamin D is the sun's rays. Therefore, MS is dominantly seen in areas where exposure to the sun rays is short. On the other hand, Multiple sclerosis attacks young people. Usually, it is found between the age of 20 years to the 40s (5,6). In fact, it is considered as the most non-traumatic disabling disease among young people (1,7).

Types

Clinically, multiple sclerosis is divided to four types according to the course of symptoms of the disease; relapse remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), Primary progressive multiple sclerosis (PPMS) and progressive relapsing multiple sclerosis (PRMS). These types are defined according to disease appearance, disappearance and reappearance (relapse) or speed of worsening (1,8,9).

Multiple sclerosis is clinically diagnosed however, confirmation of the diagnosis or exclusion of conditions that mimic MS requires participation of paraclinical tools such as magnetic Resonance imaging MRI. MRI is known for its sensitivity in diagnosing MS disease. MRI provides several techniques to diagnose MS including but not limited to conventional MR imaging, including Diffusion weighted imaging (DWI), Diffusion tensor imaging DTI, 3D or volume imaging and magnetization transfer imaging MTC. Therefore, MRI is considered to be the best radiology modality in demonstrating neural tissues injury, lesion activity and disease progression. In this literature review we will explore the MRI techniques used to diagnose and demonstrate multiple sclerosis including physics and applications of those techniques (10,11

The Role of MRI in Multiple Sclerosis

First of all, magnet strength plays a role in Multiple sclerosis imaging. It has been agreed by radiologists that 3 tesla MRI is more sensitive than 1.5 tesla in demonstrating MS plaques. The high signal to noise ratio SNR, could be utilized to decrease scan time and/or increase the resolution for more detailed image (12,13).

Diagnosis

Diagnosis of multiple sclerosis is not an easy task for the neurologists. It requires experts who can recognize the central nervous system lesions as MS plaques according to dissemination of lesions in space and time as well as excluding other possibilities which have similar symptoms. There are two pathways to diagnose MS; clinical and paraclinical. There are six clinical criteria set to increase certainty of diagnosis; 1) onset age ranges between 10-50 years 2) objective neurological symptoms 3) symptoms are related to CNS white matter deficits 4) dissemination in space 5) dissemination in time and 6) no better explanation for the symptoms by competent neurologists. Therefore, according to how many points scored from the criteria list, the disease can be classified as definite, probably or possible MS. Value of paraclinical tests is not significant for definite diagnosis as it is for the probable and possible evaluation. In case of definite MS diagnosis, value of paraclinical is to increase the confidence while for probable and possible diagnosis, paraclinical will lead to either positive or negative result. There are two paraclinical tests for diagnosing multiple sclerosis; magnetic resonance imaging (MRI) and laboratory test. MRI is the most sensitive non-invasive investigation. However, laboratory test of cerebrospinal fluid CSF is highly sensitive but rarely done due to being invasive and in fact, other diagnosing tools can lead to true positive or true negative diagnosis. On the other hand, neurologists may encounter difficulties in diagnosing multiple sclerosis for patients presenting with mono symptoms or mono plaque. Optic neuritis, for example, could be focal lesion related to pathology in optic nerve or it could be dissemination in space by MS plaque. Performing MRI scan within 3 months may obscure new tiny plaques disseminated in space. Six months are required to document new MS plaque in space by MRI (1,14,15).

As aforementioned, MS is diagnosed clinically but other related information can be provided by other tools such as Magnetic Resonance Imaging (MRI). When a neurologist suspects the disease as multiple sclerosis, MRI role comes as the next step.

There is no standardized protocol for MR imaging of multiple sclerosis although neurologists and radiologists frequently meet in conventions and discuss this issue. However, all protocols may contain the following sequences ;

Figure 1:

Image weighting	Orientation	Contrast	
T2 FLAIR	Sagittal	Pre-contrast	3D or 2D
T2 FSE	axial	Pre-contrast	3r or 2D
T2 FLAIR	axial	Pre-contrast	
T1 FSE	Axial	Pre-contrast	+/- MTC 3D
DWI	Axial	Pre-contrast	2D
SWI	axial	Pre-contrast	3D
DTI	Axial		3D
A delay period after gadolinium injection			
T1 FSE	Sagittal, axial and coronal	Post contrast	+/- MTC 3D and 2D

Alteration in protocols between MRI centres is expected. These sequences will be explained to clarify the role of these sequences in evaluating MS plaques, how to apply them and a brief physics overview behind these sequences as well as some technical points (16).

-Techniques and applications, physics
-T2 Flair

T2 FLAIR (FLuid Attenuated Inversion Recovery) in sagittal plane is usually the first sequence to be run when MRI is performed for MS patient either diagnosing or follow up. The purpose of applying T2 FLAIR is to increase the conspicuousness of MS plaques. How? The majority of lesions including MS plaques within the brain and spinal cord contain oedema or fluid which appears bright on T2 weighted images. Presence of cerebrospinal fluid CSF around brain and spinal cord decreases the conspicuity of MS plaques. Therefore, FLAIR technique is added to the T2 weighted sequence to suppress the CSF. By suppressing the bright background of the anatomy (CSF), MS plaques appear more prominent on the image and become more feasible for radiological evaluation (17- 19). On the other hand, applying T2 FLAIR in sagittal view would better show if corpus callosum is attacked by the disease or not. Also, sagittal plane demonstrates the orientation of MS plaques to ventricles. MS plaques are generally known as white matter disease which surrounds the ventricles and corpus callosum in the brain. Orientation of MS plaques is perpendicular to ventricles and the best plane to show this feature is sagittal plane (16,12,20).

The T2 FLAIR sagittal should be 3D imaging with isotropic voxel and less than 1.2 mm size. The small isotropic voxel enables reformation of the data to transverse and coronal planes as well as detecting any small plaque (12,21).

IR technique

The suppression of CSF can be achieved by inversion recovery IR technique which is added to the imaging sequence either fast spin echo FSE (as in Figure 2 A and B) or Gradient technique GRE (17,22).

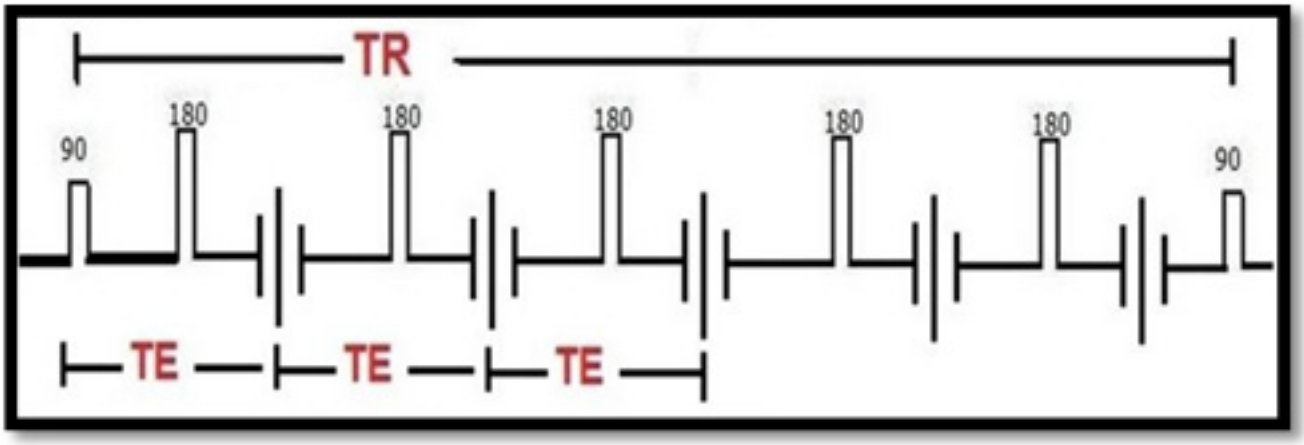

Figure 2A: Fast spin echo technique consists of the 90-excitation pulse followed by multiple 180 refocusing pulses.

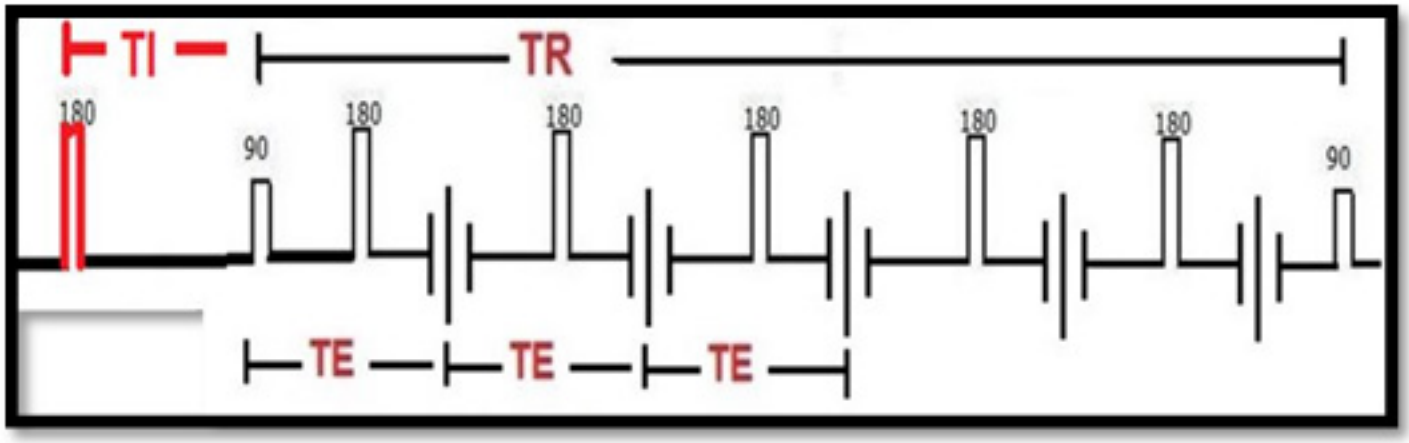

Figure2B: the T2 FLAIR sequence contains two more components than the regular T2 sequence; 1) 180 inversion pulse and 2) time interval between 180 inversion pulse and the 90-excitation pulse.

In fact, all inversion techniques begin with 180 inversion pulse but the difference is usually in time of inversion TI. The time between 180 inversion pulse and 90 excitation is called time of inversion TI and it could be set to target certain tissue. To suppress CSF, the TI should be on the range of 1800-2500ms for 3T MRI system (17,23). T2 FLAIR is applied again but in axial plane because it is more sensitive to plaques on the juxtacortical areas (12,24).

Generally, T2 weighted image is known for its value for pathology evaluation specially in the central nervous system CNS. The T2 weighted images in axial plane is performed for MS evaluation because it is more sensitive for infratentorial MS plaques than the T2 FLAIR (12,25). The T2 contrast is created by setting time of repetition TR and time of echo TE long (17).

T1 weighted

On the other hand, T1 weighted image is known with its anatomical value. However, it is used for pathological purposes when applying post gadolinium injection. Therefore, T1 weighted images must be applied pre contrast to create comparison with the post contrast ones. For MS, T1 imaging is recommended to be 3D for volume measurement which is usually needed for future comparison when atrophy needs to be evaluated (12,26,27). However, T1 2D is more sanative to demonstrate black holes (severe neural axons damage) than the 3D imaging. The majority of T1 2D used in routine MR imaging is carried out with TSE technique but in 3T MR system it is preferable to use T1 GRE which provides better contrast between brain tissues (17,28). In T1 post contrast, only active MS plaques get enhancement while non-active plaque does not (12).

DWI technique

Diffusion weighted imaging (DWI) is a functional sequence depicting motions of the water molecules between intra and extra cellular spaces. DWI is performed with echo planar imaging EPI technique which speed up the sequence (17,29). It is preferable to be less than 5 mm slice thickness and with b values 0 and 1000 for the brain scan. The DWI

is performed for any pathology within the CNS including MS plaques; active MS plaques appear hyperintense in DWI images while non-active appear isointense (16).

SWI technique

Susceptibility weighted imaging (SWI) is sensitive for haemorrhage and calcifications. It is a T2 GRE sequence and depends on long TE, short band width BW and being 3D imaging (17,30). The role of SWI in MS disease evaluation is to provide relationship between the lesion and central vein which is required to draw the picture for nature and progress of the plaque (12,30). Also, it shows the iron deposition around the plaques which give hint with progress of the disease (31,32).

DIR technique

Additionally, there is a new sequence recently introduced to the field of MR imaging called double inversion recovery (DIR) which is applied to improve evaluation of many imaging needs including multiple sclerosis. This sequence uses two inversion radiofrequency RF pulses to suppress CSF and white matter. By doing so, MS plaque within white matter would be further enhanced as well as differentiate between indetermined plaques at juxtacortical; either white or grey matter plaque (33).

DTI technique

Finally, Diffusion Tensor imaging (DTI) is a subdivision of diffusion weighted imaging DWI. However, DTI requires at least six directions to produce accurate images while DWI requires only three directions. The DTI is quite a long sequence but it provides quantification and direction of water diffusion on tissues under imaging. And because MS affects the magnitude and direction of water within white matter for example, DTI could depict these changes on different images. Microscopic changes could not be evaluated with conventional MR imaging like in T1 and T2 images, but DTI fills this gap and provides better sensitivity and specificity for MS plaques diagnosis. Knowing the microscopic profile of MS plaques gives radiologists and neurologists a better management plan for the disease (34,35,36).

Contrast

Decision of Gadolinium injection for MS patients is different from one centre to another but the majority of radiologists are giving it. The five minutes delay after injecting gadolinium is necessary for evaluating MS plaques because the MS plaques get enhanced late. During this period sequences other than T1 can be run because their images will not be affected by the presence of gadolinium. Before giving contrast injection, renal function must be normal otherwise the radiologist has to alter the decision for gadolinium injection (16,37). It is preferable to use macrocyclic contrast agent due to its minor effect to induce nephrogenic systemic fibrosis NSF (12,38).

The post contrast T1 sequences can be improved with magnetization transfer contrast MTC technique. This technique works by transferring magnetization from macromolecule to free water which results in partial saturating of the background and increasead signal of water areas. This technique increases enhancement of small MS plaque which might not be seen without MTC (39,40).

Assessment of the treatment efficacy

Most clinical trials assessment treatment response use MRI results as a secondary measure of outcome and focus on changes in the number and size of hyperintense lesions on T2 and hypointense lesions on T1. A recent meta-analysis of several studies assessed the effect of treatment on injury exposure in treatment studies; that the effects of treatment on MRI lesions for short periods of time (6 to 9 months) may also predict the effects on relapses during longer periods of follow-up (12 to 24 months)(41). Hyperintense lesions on T1 with contrast agent were associated with the number of relapses and the use of MRI, has been suggested as the primary endpoint for treatment studies. Magnetic resonance imaging has been used in several observational studies to identify patients at high risk of treatment failure as measured by clinical disease progression (42-49). In these studies, overall disease activity was lower in interferon-treated patients, but patients who suffer from T2 hyperintense lesions at 1 year follow-up had a much higher risk of poor interferon response disability(44). More specifically, three or more new hyperintense lesions on T2 or one new improved lesion within the first 2 years predicted worse disease progression and the 15 year follow-up confirmed these results (50). With the availability of more effective therapeutic options, emphasis has been placed on achieving multimetric disease stability or “no evidence of disease activity” (NEDA). The definition of NEDA is based on the lack of new activity in magnetic resonance imaging, as well as in the absence of relapse and disability, and was used to assess positive response to treatment in patients with RRMS after 2 years (51). The original criteria are now referred to as NEDA3, as the recently proposed extension to NEDA4, which includes brain atrophy and has been proposed as an improved metric for disease stability (52). It should be noted that NEDA is still under development and there are conflicting studies on the prognostic potential of NEDA3 for long-term stability of the disease (53,54). However, the availability of new treatment modalities offers a more aggressive “treatment to goal” approach and could provide an opportunity to achieve NEDA. The presence of new activity in the MRI is an important marker for the clinical setting, which can be interpreted as suboptimal. Treatment response and treatment changes should be considered on a case-by-case basis. There are no current guidelines as to when imaging should be done for better objective assessment and the following recommendations are based on the literature and protocols used at the MS center. Before starting DMT, an initial MRI (with and without gadolinium) of the entire CNS axis (brain, cervical and thoracic spine) should be performed. Follow-up scans, including imaging of the brain and possibly the spine, are recommended when patients have early active spine disease, 3-6 months after starting treatment to ensure an

early response. Then more MRIs should be done in 6-12 months. Thereafter, if the disease is stable, an annual MRI is required to monitor disease activity and optimal response to contrast agent-free treatment each year, and an MRI of the cervical spine should be considered at least every two years (42,55-59). For patients with diseases of the spine, we recommend doing annual MRIs of the brain and cervical spine. If a patient exhibits new clinical symptoms, an MRI should be done to determine the level of disease activity and based on the imaging result, a change in DMT may be considered. Alternatively, if a patient is clinically stable and new lesions are seen on routine MRI, a more detailed follow-up examination with repeat images, usually taken after 3-6 months, is recommended to ensure disease stability. Routine MRI (or follow-up MRI), a change in DMT can be discussed with the patient. In both of the above cases, MRIs would be done after 6-12 months to ensure treatment response and then returned to annual exams. In RRMS patients receiving DMT with clinically and radiologically stable long-term rest, or in patients with long-term progressive MS, additional images should be adjusted to the individual circumstances. A new MRI may be indicated every 2 to 5 years and more imaging is recommended, especially in younger patients with disease progression. New lesions may appear in patients with progressive MS and treatment adjustments may be considered.

Scan the patients where treatment of CIS is not done every 1 to 3 months for the first 6 months and when recommended stable repeat MRIs every 6 to 12 months unless new clinical symptoms appear. In general, these imaging recommendations allow for close follow-up to assess disease activity and response to treatment to achieve NEDA (60).

Detection of side effects

The role of MRI in drug monitoring in MS is becoming increasingly important as the new generation of immunomodulatory and immunosuppressive drugs become more widespread. In general, MRI has three main tasks in this context: detection of persistent disease activity, comorbidities (neoplastic diseases), and side effects (including opportunistic infections) (61,62). The crucial role of MRI for pharmacovigilance is shown in the case of natalizumab, a recombinant humanized monoclonal antibody against α4integrin (63). Leukencephalopathy (PML), is a life-threatening side effect. The imaging findings of Natalizuma-associated PML are heterogeneous and can therefore be difficult to interpret. However, experienced readers who are informed about the patient's history can reliably detect Natalizuma-associated PML by MRI (64,65,66), even before appear earlier symptoms in the patients (67). Overt Symptoms Detection of progressive multifocal leukoencephalopathy lesions in this symptomatic or presymptomatic stage is associated with better survival and functional outcome (68). To date, there are no strict guidelines as to how and when to perform MRIs for safety monitoring in MS patients treated with natalizumab. Immunosuppressive drugs and the presence (and levels) of antibodies to the JC virus (JCV) have been linked to an increased risk of PML in these patients (69-72). Therefore, the frequency of the MRI examination should be adjusted to the individual risk of PMLv(73). There is substantial evidence that T2FLAIR (Liquid Attenuated Inversion Recovery) is the most sensitive sequence for detecting PML. Diffusion-weighted images are very sensitive in depicting acute demyelination and can also help distinguish acute PML lesions from the chronic and subacute demyelinating lesions of MS (73). Frequent MRI examination with T2FLAIR and diffusion-weighted sequences in combination with conventional T2-weighted images is

therefore recommended for the screening of patients at high risk of PML. Other opportunistic infections that lead to encephalitis may develop in MS patients (e.g., serious paradoxical reactions such as swelling demyelination or overwhelming inflammatory demyelination may occur during treatment with fingolimod). With the growing number of immunosuppressive and immunomodulatory treatments in MS, MRI- based safety monitoring is becoming more complex and valuable. An example of this complexity is when patients treated with natalizumab switch to other drugs such as fingolimod or alemtuzumab. There is increasing evidence that drug-related side effects can occur as soon as an MS treatment is stopped or even several months after the start of a new treatment (so-called "transmitted opportunistic infections") (74- 76). Therefore, patients switching therapy should undergo rigorous pharmacovigilance, including frequent MRI scans, to detect resurgence in MS disease activity and side effects such as opportunistic infections (77).

Benefits

MRI provides a wide spectrum of information about the disease including but not limited to confirmation of the diagnosis, how severe the disease is and monitors the progression over time (1,78). Although MRI provides all of this diagnostic information, it is considered weak in prognostic aspect because the relapse of MS cannot be predicted (10,79).

Needs and recommendations for the future:
-Future research should identify new MRI markers for neuroinflammation and neuroprotection, particularly those related to gray matter pathology (deep gray matter and cortical structures), remyelination, and neuronal repair (77).

- These new markers may require next-generation MRI technology, including newer ones advanced pulse sequences, and improved hardware such as new coils, multi-streaming techniques, and ultra-high- field strengths(77).
- Greater efforts are required to implement and harmonize various advanced MRI techniques and to standardize MRI acquisition and interpretation in MS patients (77).

- Systematic research is required to evaluate the added value of alternative pulse sequences compared to standard pulse sequences, MRI subtraction techniques, and MRI serial scans for disease monitoring and safety (including the most cost-effective monitoring frequency) (77).

Conclusion

Magnetic resonance imaging plays a significant role in detecting and monitoring multiple sclerosis. There are several techniques used to depict the disease and evaluate the progression. These images assist the neurologist to set the treatment plan according to the radiological findings. It is the role of MR technologists not to run only the conventional sequences but to know the new techniques too and apply them in the right way.

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