



The Role of Magnetic Resonance Imaging in Early Diagnosis and Monitoring of Multiple Sclerosis: A Comprehensive Review

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ABSTRACT:

Multiple Sclerosis (MS) is a chronic, immune-mediated, demyelinating disorder of the central nervous system (CNS) that mainly affects young adults. Inflammation in the brain and spinal cord is accompanied by demyelination, axonal loss, and gliosis. The disease course is sometimes very uncertain with the changes from relapse to remission and vice versa, therefore making early and correct diagnosis the cornerstone of an effective treatment(1). Around the world, MS is responsible for approximately 2.8 million cases. The disease is more common in women than men and the prevalence of the disease is higher among people living at a greater distance from the equator, which is suggestive of a role for heredity and the environment in its etiology. The average age of onset has been reported in the range of 20-40 years, which means it is among the main causes of neuro-disability without trauma in young adults(2).

1. Introduction

Multiple Sclerosis (MS) is a chronic, immune-mediated, demyelinating disorder of the central nervous system (CNS) that mainly affects young adults. Inflammation in the brain and spinal cord is accompanied by demyelination, axonal loss, and gliosis. The disease course is sometimes very uncertain with the changes from relapse to remission and vice versa, therefore making early and correct diagnosis the cornerstone of an effective treatment(1). Around the world, MS is responsible for approximately 2.8 million cases. The disease is more common in women than men and the prevalence of the disease is higher among people living at a greater distance from the equator, which is suggestive of a role for heredity and the environment in its etiology. The average age of onset has been reported in the range of 20-40 years, which means it is among the main causes of neuro-disability without trauma in young adults(2).

On a pathophysiological level, MS is an immune-mediated disorder, where over-activated T-cells, B-cells, and macrophages penetrate the blood-brain barrier and attack the sheath (myelin) surrounding nerve cells in the brain. This process causes demyelination, axonal transection, and neural degeneration. The inflammation leads very focal lesions, thus areas affected mainly with

white matter of the brain and spinal cord, which can still expand and turn into chronic plaques accompanied by gliosis(3). These lesions, interrupting the transmission of electrical signals, lead to a range of neurological symptoms among which: visual disturbances, motor weakness, sensory deficits, balance problems, and cognitive impairment(4). The continuous loss of myelin and axons over the years cause neurodegeneration, which is the progressive nature of disability that can be seen in a lot of patients. The main mechanisms here are complicated as they involve the combination of genetic susceptibility, immune system dysregulation, and some triggering factors from the environment like viral infections, lack of vitamin D, and smoking(5).

Multiple sclerosis (MS), can be seen in a variety of different ways in several different subtypes as distinct diseases, each with its own particular activity, and progression. The most widespread is Relapsing-Remitting Multiple Sclerosis (RRMS), which relapses, and remissions, or partial or complete recovery, characterize it(7). The gradual neurological decline may be accompanied or unaccompanied by acute episodes in most cases of RRMS that later convert to Secondary Progressive Multiple Sclerosis. Besides, the group of primary progressive MS (PPMS) patients is separated from other MS clinically groups(8). The total number is



10–15% of patients, and the disease is going through a steady progression from the start without any definite relapses or remissions. The first demonstrable event of neurologic symptomatology compatible with demyelination, with a duration of at least 24 h, and thus not fulfilling the criteria for a definite diagnosis of multiple sclerosis (MS), defines the entity Clinically Isolated Syndrome (CIS). Very important clinically, since a substantial fraction of these patients develop definite MS, the early recognition and follow-up necessary for prognostic and therapeutic decisions(9).

An early diagnosis of multiple sclerosis (MS) is very important, as the beginning of the disease-modifying therapies (DMTs) at an early stage can have a very big impact on the reduction of the relapse rate, the delay of the disability progression, and the avoidance of neuronal damage to which the recovery is not possible. A late diagnosis, conversely, can lead to the situation where the early intervention as well as neuroprotection are missing(9). Yet, early diagnosis is still a difficult task due to the various possible symptoms of the disease and the similarity of the signs with other neurological disorders. In the past, making a diagnosis was very dependent on the clinical findings and ruling out other conditions(10). Nonetheless, the advent of magnetic resonance imaging (MRI) changed the whole process of diagnosis to be more efficient, accurate, and less invasive as it is possible to see the lesions that cause the demyelination even if the signs are not yet apparent.(11)

MRI has become the primary diagnostic tool for MS, as well as for its follow-up, and research. This method has the power to find the characteristic white matter lesions not only in the brain, but also in the optic nerves and the spinal cord, thus allowing the imaging of both newly recruited inflammatory activity and chronic demyelinating changes. Conventional MRI sequences, including T1-weighted, T2-weighted, and FLAIR (Fluid-Attenuated Inversion Recovery) imaging, are capable of depicting lesion load, distribution, and morphology, with very high sensitivity(12). The appearance of lesions that were either new or had become larger over time is a source of radiological evidence of the changes being disseminated in space and time, i.e., both a place and moment, thus an essential feature of the McDonald diagnostic criteria. Besides, gadolinium-enhanced MRI is very helpful in locating the active inflammation sites by showing the areas of blood–brain barrier disruption,

which are those corresponding to acute lesions(13). Conventional MRI has its limitations. Still, it seems like these obstacles can be surpassed with the help of ultramodern methods such as magnetization transfer imaging, diffusion tensor imaging, susceptibility-weighted imaging, and MR spectroscopy that have pioneered deeper insights into microstructural damage, myelin integrity, and neuronal metabolism, thus eventually culminating into the most thorough evaluation of disease activity and progression.(14)

Besides identification, MRI is the main instrument, to disease monitoring and therapeutic assessment, plays. Consequently, serial MRI scans are frequently performed for monitoring new lesion formation, quantifying brain atrophy, and to assessing the effectiveness of DMTs. Quantitative MRI parameters may become the biomarkers of the disease activity to serve as the source of the objective data that can be even before clinical deteriorations(15). In addition, this has also aided in the designing and the assessment of the clinical trials by providing easily quantifiable endpoints for treatment effectiveness. The implementation of artificial intelligence (AI) and automated image analysis has greatly contributed to the lesion segmentation and volumetric quantification, which, in turn, has raised the accuracy of reproducibility and the clinical utility of MRI findings in MS management. Though MRI is central to the only interpretation of MS, it undoubtedly suffers from limitations(16). Among the difficulties that MRI in MS include interpretation variability between the observers, the difference between scanning devices, and non-specific white matter lesions that can look like demyelination. As a result, uniform imaging protocols, standardized reporting systems and integration of imaging with other clinical and laboratory data are the primary measures that could enhance the diagnostic accuracy(18).

This systematic review is aimed at a thorough and comprehensive qualitative and quantitative study of all the pieces of evidence available about the role of MRI for early identification and monitoring of multiple Sclerosis (MS). The review's goal is to assess standard and advanced MRI techniques, their accuracy in diagnosis, and their input in disease tracking and treatment evaluation. Besides, it intends to present the changing imaging biomarkers, the new quantitative techniques, and the research that may lead to further improvements



of MRI in MS for predictive and prognostic purposes(19). By bridging the gap in knowledge, the review will be a major source of new ideas for clinical, radiological, and research professionals working in MS and thus, it will highlight the tremendous role of MRI as both a diagnosis and monitoring tool in this intricate neurological disorder(20).

2. Pathophysiological Basis of MRI Findings in Multiple Sclerosis

Multiple Sclerosis (MS) is essentially an immune system-mediated disease of the central nervous system (CNS) which results in demyelination, axonal injury, and gliosis. These mechanisms have changed from normal brain function to the abnormal which are the reasons behind most of the symptoms that these patients present. MRI's capability to directly detect these very small changes in the body has really changed the way clinicians comprehend, diagnose, and treat MS. Every histological event - demyelination, inflammation, axonal loss, and gliosis - changes the MRI signal intensities in a way that these changes can be detected and differentiated and are the basic concept of radiologic evaluation in MS(21).

2.1 Demyelination is the core of multiple sclerosis (MS) disease process. The myelin sheaths in healthy CNS tissue not only provide electrical insulation but also allow rapid conduction of the nerve impulses along the axons. In MS, the immune-system attacks that target myelin and oligodendrocytes cause the areas of demyelination to become confluent resulting in so-called plaques or lesions. Due to this process, water content in the affected white matter increases, thus changing local magnetic properties that can be seen on MRI. Demyelinated lesions show hyperintensity on T2-weighted and FLAIR images as a result of unbound protons, whereas chronic demyelinated plaques generally appear as low signal on T1-weighted sequences, also known as "T1 black holes." These black holes are indicative of the most severe tissue destruction, which is usually accompanied by axonal loss and, therefore, are considered signs of irreversible damage. The localization of lesions, i.e. around the ventricles, close to the cortex, below the tentorium, and in the spinal cord, corresponds to the immune mechanisms involved and characterizes the stage of disease in the McDonald criteria(22).

2.2. Inflammation is one of the main things that have an effect on the creation and along with the development of

lesions in MS. The inflammatory reaction of the body that first occurs is done by the cells called T-cells as well as B-cells that are autoreactive and thus cross the blood-brain barrier (BBB) and get into the central nervous system (CNS). Due to the infiltration of these immune cells, perivascular cuffing, production of cytokines, and the activation of microglia and macrophages occur. All these together lead to focal demyelination and edema. The acute inflammatory phase of MS lesions can be reached with the enhancing lesions on gadolinium-enhanced T1-weighted MRI(23). The use of gadolinium-based contrast agents is the standard way of identifying the integrity of the BBB. Normally, these contrast agents do not pass through the BBB. However, in the case of inflammation, the rupture in the BBB allows the contrast to leak into the tissue, which results in contrast enhancement on MRI. The period of this enhancement at the site of active inflammation is generally 2-6 weeks. Hence, the contrast-enhancing lesions are the main signs of disease activity and are usually the endpoints in clinical trials and therapy monitoring. The point where both enhancing and non-enhancing lesions appear in one scan illustrates "dissemination in time," which is the main premise for MS diagnosis(24).

2.3. Axonal loss is another essential pathological process that explains MS progression and the occurrence of permanent disability. At the beginning stage, demyelination could be partially restored through remyelination carried out by the remaining oligodendrocytes, however, relapse of inflammation leads to the severing of axons and death of neurons. The loss of axons is the main reason that is most closely associated with the severity of the disease compared to the number of lesions only(25). On the MRI, axonal loss can be seen as brain atrophy, T1 hypointense lesions, and decreased fractional anisotropy on diffusion tensor imaging (DTI). Different MRI methods, like magnetization transfer imaging (MTI) and DTI, are very sensitive to changes in the structure of the brain at a microscopic level and thus, they allow the detection of axonal and myelin damage even in areas that look unchanged on the traditional MRI. Research has proven that axonal degeneration is a source of problems that has been pointed out very early in the disease course, which is the reason for the necessity of an MRI-based assessment at the early stage of the disease to avoid neurological decline(26).



2.4. Gliosis is a non-acute reaction after central nervous system damage, in which the astrocytes around the injured area multiply and increase in size. This glial scarring, being devoid of axons and myelin, is the source of the chronic MS plaques seen by histology in the late stages of the disease. On MRI, gliotic tissue shows T2 hyperintensity and T1 signal intensity of a variable range, depending on the amount of tissue lost and the degree of remyelination. Chronic plaques rarely have leakage on contrast studies and are often well-margined, thus representing stable, non-active lesions. The magnitude of gliosis correlates with the length of disease and with the extent of neurodegeneration thus is an important factor for determining disease load over the long-term(27).

2.5. blood-brain barrier (BBB) disruption is the core inflammatory process in MS and one of the main factors that determine the contrast on MRI. Under normal conditions, the BBB very strictly controls the movement of cells and molecules from the blood and CNS tissue. In MS relapse, immune activation, and cytokine release, the endothelial integrity is compromised, thereby allowing immune cells and plasma proteins to enter the CNS. The leakage of gadolinium contrast from these vessels makes the visualization on T1-weighted images as bright, ring-like, or patchy enhancement, indicating active demyelination. Various enhancement patterns- opening, nodular, or homogeneous- can represent certain stages of lesion evolution. With a decrease in inflammation and BBB being intact, the enhancement disappears, and thus the lesion moves to a chronic demyelinated plaque(28).

2.6. Clinical and MRI research findings have demonstrated a strong correlation between histopathology and MRI in MS, hence the same has been confirmed through various studies both in vivo and post-mortem. Results of histopathological examination show that MRI-identified lesions correspond to areas of myelin loss, inflammation, and gliosis. T2 hyperintense lesions mainly correspond to the areas which have increased water content and demyelination. At the same time, T1 hypointense lesions indicate a severe destruction of the matrix and a loss of axons. The decrease in the magnetization transfer ratio (MTR) reflects the damage both the myelin and the axons, while the abnormalities in DTI show the disorganization of the white matter tracts. Besides, MRI can visualize the so-called “normal-appearing white matter” (NAWM) which is considered

as a source of pathology beyond visible lesions and from where subtle inflammatory and degenerative changes that are not detectable by conventional imaging usually occur. Thus, these correlations highlight MRI's ability as a non-invasive surrogate marker for in-vivo tissue pathology in MS, bridging the gap between the ultra-structural histological changes and clinical manifestations(29).

3. MRI Techniques in Multiple Sclerosis (MS)

Magnetic Resonance Imaging (MRI) is the best method used for the identification and follow-up of multiple sclerosis, as it is highly sensitive in the detection of demyelinating lesions in the brain and spinal cord. The use of both regular and innovative MRI has been instrumental in the performance of many tasks in the field of multiple sclerosis, such as identifying the number of lesions, establishing their activity status, confirming progression, and monitoring treatment efficacy(30).

3.1 Conventional MRI Sequences

3.1.1 T1-weighted imaging gives the excellent detailing of the anatomical structure and is especially indispensable for the evaluation of the damage of the tissue in multiple sclerosis (MS). The first acute lesions on T1-weighted images can be both isointense and slightly hypointense in the case of edema and inflammation. Later, the areas with the most severe tissue destruction change to those with a low signal intensity which are referred to as T1 “black holes” that are the places of the affected axonal loss and matrix damage. Besides that, this sequence plays a vital role in the identification of brain atrophy and volume reduction of the cerebral cortex which are both associated with the extent of the disease(31).

3.1.2 T2-weighted imaging is a really sensitive tool to any changes of liquid inside the body. Hence, it can very well show the inflammatory demyelinating lesions developed. As the plaques of MS become hyperintense on T2-weighted images because of the combination of edema and myelin loss. These scars may happen in quite different places, e.g. areas around the ventricles of the brain, close to the cortex and below the tentorium, and also the spinal cord. So, with this method you actually can track the total lesion burden quite effectively; however, it is still not very specific as it cannot tell apart old and new lesions or give a sign of active inflammation.



Still, this is a very important tool in determining the disease extent and total lesion load in follow-up imaging(32).

3.1.3 The FLAIR (Fluid-Attenuated Inversion Recovery) sequence is definitely a great tool to detect periventricular and cortical lesions as it allows the signal from cerebrospinal fluid (CSF) to be suppressed. Such a suppression makes the detection of lesions close to the ventricles, corpus callosum, and cortical gray matter easier since these are the regions that usually appear with no or very low contrast on normal T2 images. So, FLAIR imaging is very important in meeting the McDonald criteria of **dissemination in space**, while 3D FLAIR methods provide more detailed and more consistent results for follow-up scans(33).

3.1.4 Gadolinium-enhanced MRI remains the most dependable tool in the identification of active inflammatory lesions. Inflammation in the brain or spinal cord, with its consequent disruption of the blood-brain barrier (BBB), allows the gadolinium contrast agents to diffuse to the interstitial space. This causes the area of acute inflammation to be visualized on T1-weighted images as localized enhancement. The enhancing regions that are seen here, which are usually present for 2–6 weeks, are considered to be the areas in which demyelination and immune activation have not yet ceased. The morphology of the enhancement may also be suggestive of the stage of the lesion—different types such as nodular or ring-shaped. Hence, gadolinium enhancement is one of the most valuable and earliest indications of disease activity that forms the basis of assessment of the effectiveness of treatment with disease-modifying agents (DMTs)(34).

3.2 Advanced MRI Techniques

3.2.1 Magnetization Transfer Imaging (MTI) is a sophisticated MRI technique which evaluates the interaction between free water protons and biological macromolecules, such as myelin. The Magnetization Transfer Ratio (MTR) extracted from MTI gives a quantitative indication to the integrity of myelin. Lowered MTR values point to the loss of myelin or the damage of axons, even in normal-appearing white matter (NAWM), hence MTI is an extremely sensitive instrument for locating minimal disease-related alterations and following the process of remyelination over time(35).

3.2.2. Diffusion Tensor Imaging (DTI) maps the movement of water molecules along nerve fibers and this way it becomes possible to assess the microstructure of the brain. Several metrics like Fractional Anisotropy (FA) and Mean Diffusivity (MD) are changed in the areas of demyelination—FA goes down while MD goes up—signifying a disordered and damaged axonal structure. Besides that, this method is very sensitive in the early stages of the disease when the pathological changes are still invisible in conventional MRI, thus offering a big part in providing the clues of the disease course.(35)

3.2.3. Susceptibility-Weighted Imaging (SWI) picks up tiny changes in a magnetic field that indicate iron deposition and micro haemorrhages. Long-term MS plaques gradually gather iron into the activated microglia and macrophages, which can be detected as hypointense rims on SWI. The “central vein sign” that is a small vein going right through the middle of a lesion seen on SWI is regarded as a possible imaging biomarker that helps to differentiate MS lesions from other white matter abnormalities(36).

3.2.4. ProtonMR Spectroscopy (MRS) offers information about the metabolism of the brain by measuring the metabolites of the brain such as N-acetylaspartate (NAA), choline (Cho), and creatine (Cr). Reduced NAA concentration is indicative of the neuronal and dendritic loss, whereas raised choline levels signify that the membrane is turning over as there is actively demyelination. MRS, therefore, an imaging modality which visualizes the structural abnormalities in the brain, but with the help of biochemical assessment, it can now also help in determining the extent of the disease and the response to therapy(37).

3.2.5. Functional MRI (fMRI) tracks blood-oxygen-level-dependent (BOLD) signals that are used to evaluate functional reorganization and neuroplasticity due to demyelination. It illustrates the activated compensatory areas of the brain that are different from the ones that have been damaged, giving an idea of why the patients' neurological functions have not been affected by the structural destruction. fMRI leads to the comprehension of cognitive impairment and rehabilitation in MS.

3.2.6. Quantitative MRI techniques such as voxel-based morphometry (VBM), quantitative susceptibility mapping (QSM), and relaxometry (T1/T2 mapping) aim



at providing objective and reproducible metrics of brain tissue properties. Using these methods, one can accurately measure myelin content, iron accumulation, and tissue microstructure, thus these methods become very attractive for the personalized disease monitoring and for the comparison that is done automatically by different imaging centers(38).

4. MRI-Based Diagnostic Criteria and Differential Diagnosis in Multiple Sclerosis

4.1. McDonald Criteria (2021 Revision)

The McDonald Criteria is a set of standards that were first put forward in 2001 and have gone through a number of changes with the latest being in 2021 which are now the basis for diagnosing Multiple Sclerosis (MS). The criteria input from clinical as well as radiological findings help to identify the diagnosis by showing both dissemination in space (DIS) and dissemination in time (DIT). MRI is the main instrument in meeting these conditions which, most of the time, can give the diagnosis before the appearance of the clinical features. In brief, dissemination in space defines the identification of the present lesions, found in different typical anatomical areas of the central nervous system (CNS), e.g. periventricular, juxtacortical, infratentorial, and spinal cord regions. Time dissemination shows that over time new lesions appear, hence the disease is in an active stage. The 2021 update has made it easier to prove DIT by the existence of both enhancing and non-enhancing lesions in one single MRI scan, regardless of the time of the scan. Besides this, the presence of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) specific for MS can be a substitute for DIT, thus, in effect, making the early diagnosis less complicated. This amendment has not only heightened the diagnosis sensitivity but also has kept specificity thus enabling an earlier treatment with the chance of the disease altering progression(39).

4.2. MRI Criteria for Clinically Isolated Syndrome (CIS)

Clinically Isolated Syndrome (CIS) characterizes the first medical instance with neurological signs that imply demyelination, lasting 24 hours or more but still does not comply with the full criteria for MS. Magnetic resonance imaging (MRI) results play a key role in risk stratification of CIS patients. The existence of typical MS-like lesions on brain MRI considerably boosts the

probability of progression to definite MS in the next years(40). Based on McDonald Criteria, if MRI at the time of CIS shows both DIS and DIT, the diagnosis of MS can be made without any second clinical event wait. Therefore, MRI is instrumental both as a diagnostic and a prognostic tool, facilitating early treatment in high-risk patients that may slow down or stop the relapse further occurrence. Moreover, follow-up MRI scans are employed to detect any new lesions that verify dissemination in time, hence providing additional proof of disease evolution(41).

4.3. Role of Spinal Cord MRI and Optic Nerve Imaging

While brain MRI remains the primary imaging modality, **spinal cord MRI** is equally critical in the evaluation of MS, especially when brain findings are inconclusive or when symptoms indicate spinal involvement such as weakness, sensory disturbances, or sphincter dysfunction. Spinal cord lesions in MS typically appear as short-segment (less than two vertebral body lengths), asymmetric lesions affecting less than half the cross-sectional area of the cord. These features help differentiate MS from other demyelinating diseases like neuromyelitis optica spectrum disorder (NMOSD), where lesions are longer and more centrally located(42).

4.4. Optic nerve imaging

Especially a dedicated orbital MRI with fat suppression and contrast enhancement gives a great insight into the situation in case of optic neuritis, which is one of the most frequent first symptoms of MS. Inflammation of the optic nerve in the acute stage is usually shown by enhancement and T2 hyperintensity of the affected optic nerve, which is regarded as active inflammation. At the chronic stages, the affected optic nerve may demonstrate atrophy that indicates the loss of axons. The latest technological advances like high-resolution 3D MRI and diffusion imaging have resulted in the improvement of the visualization of optic nerve pathology, thus making the diagnosis and disease activity monitoring possible(43).

4.5. Differential Diagnosis Using MRI

MRI not only makes diagnosis easier but also is very important in separating MS from other demyelinating and non-demyelinating disorders. For instance, Neuromyelitis Optica (NMO) is characterized by



horizontally extensive spinal cord lesions exceeding three vertebral segments and central cord involvement that are different from the shorter peripheral lesions of MS. Acute Disseminated Encephalomyelitis (ADEM) tends to have large, ill-defined lesions that involve both white and gray matter, most times with the symmetry of involvement and no chronic lesions, thus these features are used to differentiate it from MS. Blood vessel lesions, e.g., small-vessel ischemic changes, can imitate MS but they usually avoid the corpus callosum and have a periventricular distribution that is different from demyelinating plaques(44).

5. MRI in Disease Monitoring and Progression

Magnetic Resonance Imaging (MRI) has gone beyond the traditional limit of being a mere diagnostic tool in the management of Multiple Sclerosis (MS) and has emerged as a fundamental tool not only for the disease monitoring but also for the disease progression assessment. Since MS is a chronic, unpredictable disease with different phases of inflammation and degeneration of neurons, thus any change in the condition of the patient should be confirmed by an MRI which is able to detect even very small changes. Hence the whole procedure of the MRI is used to evaluate the response to therapy and to prognosticate in the long run. Furthermore, MRI is superior to neurological examination alone in the sensitivity for detection of subclinical disease activity, as new lesions may arise even when no relapses are evident(45).

5.1. MRI for Assessing Disease Activity and Relapse

MRI is an accurate detector of the presence of a disease in MS. Besides clinical relapse, the period of active inflammation is usually mirrored by new or expanding lesions on MRI. Methods of visualization with the use of gadolinium-enhanced T1-weighted images show spots where the blood-brain barrier (BBB) is broken, indicating an ongoing inflammatory reaction. These enhancing lesions are the source of inflammation, and they usually last from 2 to 6 weeks, in which time they can be a marker of acute disease activity(46). T2-weighted and FLAIR sequences allow the visualization of total lesion burden, indicating the areas of demyelination both newly formed and old. It is worth noting that studies indicate that activity of the disease as detected by MRI may occur prior to clinical relapses, thus there is a chance for early treatment initiation before

neurological decline. In everyday clinical practice, MRI surveillance every 6 to 12 months is instrumental in determining the efficacy of disease-modifying therapies (DMTs) and in making decisions about the further escalation of therapy in cases of breakthrough disease(47).

5.2. New Lesion Detection and T1 Black Holes

One of the main areas where MRI is substantially used for monitoring MS is the detection of new or expanding lesions in sequential imaging. Such lesions are signs of the disease spreading and an ongoing demyelination process. New lesions found on T2 or FLAIR sequences between scans are an indication of disease activity at the subclinical level, in which the patient can be clinically stable. On the other hand, chronic hypointense lesions in the T1 weighted image, referred to as T1 black holes, are those spots of complete axonal damage and tissue loss(48). Unlike transient T1 hypointensities which are due to acute inflammation, the chronic black holes continue to exist beyond six months and are accompanied with permanent neurological deficits and MS progression. Therefore, the measurement of T1 black holes becomes a good marker for the neurodegenerative part of MS and furthermore it is helpful in predicting the degree of disability that will be retained in the future(49).

5.3. Brain Atrophy Measurements

Brain atrophy—brain volume reduction—is very much identified as a sign of the neurodegenerative process in MS. It is a reflection on the main events in the disease process like demyelination, axonal loss and neuronal degeneration. Quantitative MRI-based brain measurement is one way to show this atrophy, which may be present even in the early stage of the disease and hence progress independently from the inflammatory activity(50). Both gray matter and white matter atrophy are capable of having a role in cognitive and physical disability of MS patients. The present-day automated software can measure brain atrophy both global and regional very accurately, thus the doctors would have the possibility to assess the progression of the disease over the period of time. The rate of yearly brain volume loss in the case of normal adults is around 0.1–0.3%, while MS patients can suffer at rates higher than 0.6–1.0% a year. Hence, the follow-up of atrophy via serial MRI scans is an indispensable tool in the evaluation of



neuroprotective therapies to help at-risk patients in whom disability accumulation is a potential threat(51).

5.4. Lesion Load and Volume Quantification

Measuring lesion load and volume is another important part of MRI-based monitoring in MS. Lesion load is made up of the total number and the size of demyelinating plaques that can be seen on MRI. Advanced image-processing software can measure lesion volumes on T2-weighted or FLAIR images, thus giving an objective metric for disease burden(52). In clinical trials, the first instance of changes in lesion volume is often selected as surrogate endpoints for treatment efficacy. An increase in lesion load over time indicates that there is still inflammatory activity and may suggest that the therapeutic control is not optimal. On the other hand, a quantitatively or qualitatively stable lesion load as well as a decreased lesion load mean that treatment leads to a good effect. Quantitative MRI parameters also allow the scientists to link lesion volume with clinical disability scores, cognitive deficits, and fatigue intensity thus, making it possible to understand the disease dynamics more fully(53).

5.5. Longitudinal Follow-up Imaging

Longitudinal, or follow-up, MRI is a vital part of the MS management plan. A standardized imaging protocol is recommended in order to achieve uniformity and reliability in the results of the serial scans. Besides, it allows the identification of subclinical disease activity, the confirmation of radiological progression as well as an evaluation of the long-term impact of disease-modifying therapies. Identification of treatment-related complications, such as progressive multifocal leukoencephalopathy (PML) in patients on certain immunosuppressive drugs, is the other aspect of monitoring that is made possible by longitudinal MRI. The timing of follow-up imaging, however, is generally dependent on the activity of the disease, the clinical status, and any changes in the treatment. In the case of newly diagnosed patients or those that are going to have a therapy change, the first MRI is taken at the 6-month mark, and then, as usual, the follow-up scans are done annually to check up on stability. Besides, the longitudinal design of these studies could be more sensitive to subtle microstructural changes by implementation of advanced MRI metrics such as magnetization transfer ratio (MTR), diffusion tensor

imaging (DTI), and susceptibility-weighted imaging (SWI) besides the use of conventional imaging. These procedures open the way for the evaluation of remyelination, axonal integrity, and iron deposition—the sources of pathological processes that lead to disease progression—under the implementation of these techniques(54).

6. Quantitative and AI-Based MRI Approaches

One of the developments that have put MRI in a new position in the diagnosis of Multiple Sclerosis (MS) is neuroimaging. MRI has not yearly its role as a qualitative tool but also as a quantitative and intelligent imaging modality. The combination of machine learning (ML), artificial intelligence (AI), and radiomics in MRI has tremendously improved the ability of the diagnostic accuracy, the characterisation of the lesion and the disease gauges. These new computational methods permit the objective, the reproducible, and the automated quantification of disease burden, thus, providing a more sensitive way of detecting slight pathological changes that might be invisible to the naked eye(55).

6.1. Machine Learning and AI in Lesion Segmentation and Prediction

One of the biggest problems in MS imaging has been the accurate segmentation of lesions—identifying true demyelination plaques that have not only been separated from the rest of the normal structures in the brain but also the artifacts. The process of manual segmentation is time-consuming and the results are inconsistent as different people perform it. Machine learning algorithms have made this process very efficient by automating lesion detection as well as the classification. The goal of supervised ML models is to teach them to separate MS lesions by intensity, shape, and spatial distribution features through the use of large datasets of annotated MRI scans(56). AI algorithms can accurately carry out the segmentation of lesions found in all MRI modalities, such as T1, T2, and FLAIR sequences. The utilization of deep learning architectures, such as convolutional neural networks (CNNs), which has been demonstrated, is very successful in locating lesions even in the most difficult instances where the lesion contrast is low or the lesion is small in size. These devices are not only alleviating the workload of the radiologist but also are giving them the results which are consistent and reproducible in lesion numbers, an essential requirement in tracing disease



monitoring(57). In addition, the creation of predictive AI models aims at the future development of lesions that a patient is at risk to and the treatment response by the study of temporal MRI data and clinical parameters thus relapse is being predicted. Predictive analytics of this sort may have the potential to become a help tool in personalized medicine when it comes to MS management(58).

6.2. Automated Lesion Detection and Volumetric Analysis

AI-powered tools can do all the lesion detection, classification, and volumetric quantification work automatically. These systems evaluate the total lesion load, lesion count, and volume changes over time—these are the main indicators of disease activity and treatment response. Quantitative MRI enables accurate measurement of new or growing lesions between follow-up scans, thus giving the objective metrics that are usually closely related to clinical outcomes. Software volumetric tools, automated ones, can also be used for measuring brain and spinal cord atrophy, the main markers of neurodegeneration in MS, apart from the lesion load. Programs like SIENA, FreeSurfer and SPM use voxel-based morphometry to calculate global and local atrophy(59). The AI algorithms bring further improvements to these studies by providing the correction of movement, noise, and imaging artifacts, thus letting the accuracy be higher. By combining different MRI parameters—lesion volume, black holes, and atrophy indices—AI-based systems might be able to generate detailed, follow-up reports for the doctors, thus facilitating both diagnostic and disease monitoring at a higher level of precision(60).

6.3. Radiomics and Deep Learning Models for MS Diagnosis and Progression Monitoring

Radiomics means one big data type change, where medical images are broken down into a large number of quantitative features showing the same visual MRI as biomarkers. To be more specific in MS, radiomics depict the changes of the lesion, texture, intensity and shape, and these changes can be different pathological processes, e.g. inflammation or axonal loss(Alshanova et al., 2025a). Now, these radiomic features supplemented with machine learning algorithms can separate lesion areas which are newly active from those which have been inactive for a long time, moreover, they

can detect various disease subtypes as well as predict the transition of Clinically Isolated Syndrome (CIS) to multiple sclerosis if so. Deep learning models, notably CNNs and RNNs, have progressively transformed MS imaging by their adeptness in extracting elaborate spatial and temporal pattern features from multi-modal MRI data(62). These models can combine the details from T1, T2, FLAIR, DTI, and MRS sequences to unravel the disorder's complete activity. Besides that, deep learning has been harnessed for longitudinal MRI datasets to foresee the disease progression, the rate of brain atrophy, and the therapy response. Additionally, the hybrid methods fusing radiomics, genomics, and clinical data—known as radiogenomics—are gaining ground, offering deep insight into the biological basis of MS and facilitating exact diagnostics(63).

7. Limitations and Challenges

Some of the limitations and difficulties that can influence the accuracy, reproducibility, and availability of MRI which is the best choice for diagnosis and follow-up of MS are still present. The challenges come from differences in technology, difficulties in interpretation and some practical constraints that obstruct a homogeneous application in clinical practice as well as in research settings. Comprehending these limits is a necessary condition to achieving better diagnostic reliability, coming up with standardized imaging protocols and providing patient care of equal quality(64).

7.1 MRI Variability Across Centers and Scanners

One of the biggest difficulties in MRI-based MS assessment is the variability from different scanners, imaging protocols, and centers. Depending on the field strength (1.5T vs. 3T), scanner manufacturer, coil type, and acquisition parameters, MRI results can vary greatly. Even very small changes in the thickness of the slice, the timing of the sequence, or the dosage of the contrast agent can make lesions more or less visible and can change the quantification. All these inconsistencies represent a problem in longitudinal studies and in multi-center clinical trials where reproducibility is needed to monitor the progression of the disease or to compare the results of the treatment. Besides that, the image post-processing and the software tools for lesion segmentation or volumetric analysis might get different outputs depending on the algorithms they apply. In order to reduce variability, attempts have been made to set up



standard MRI protocols like the Magnetic Resonance Imaging in MS (MAGNIMS) consensus guidelines. But, the compliance with these standards is not total, especially in resource-poor areas, which causes differences in the diagnosis and follow-up. The problem of MRI acquisition and analysis still persists and is a big challenge in the field.(65)

7.2. Limitations in Sensitivity and Specificity for Certain Lesions

Despite MRI being extremely sensitive in detecting multiple sclerosis-related white matter lesions, it cannot always be specific in differentiating the demyelinating plaques from other pathological conditions. A typical example of small cortical lesions is when they remain invisible on traditional MRI sequences because of the limited spatial resolution and partial volume effects. In the same way, lesions in the spinal cord and optic nerves may be hardly visible due to their small size and the possibility of motion artifacts affecting them(66). Besides this, MRI findings are not the only to give a certain diagnosis of MS. Other disorders, which include demyelinating, inflammatory, or vascular ones, such as neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), and small-vessel ischemic disease, are very close to MS in terms of clinical and radiological aspects. Hence, possible false interpretations of positive or negative may be the consequence of such situations, especially in atypical cases or early-stage disease. Notwithstanding imaging modalities' progress, like double inversion recovery (DIR) or susceptibility-weighted imaging (SWI), the imperfections of the sensitivity and specificity still pose a great challenge to the radiologists and neurologists(67).

7.3. Cost and Accessibility Issues

Especially advanced sequences and high-field imaging in MRI remain an expensive and resource-intensive modality. The price of an MRI scan, along with the need for specialized equipment and personnel, limits accessibility, especially in low- and middle-income countries. 3T scanners or advanced imaging capabilities are lacking in many healthcare centers, which limits their ability to find the slight lesion or to do the quantitative analysis(68). The frequent MRI follow-ups that are very important for disease monitoring lead to increased costs for patients and healthcare systems. Moreover, a few patients may suffer from claustrophobia, anxiety or have

contraindications to gadolinium contrast, and thus their MRI usage is further limited. Solving these problems requires policy-level action to make the MRI cheaper and more accessible, thus bringing timely diagnosis and treatment of MS patients, regardless of their location(69).

7.4. Artifacts and Pitfalls in MRI Interpretation

MRI is a various artifacts that may represent or hide the pathology of the patient. Among these artifacts include movement artifacts that arise from patient movements, flow artifacts that are caused by cerebrospinal fluid or blood vessels, susceptibility artifacts, etc. occurring in the vicinity of air-bone interfaces, which can result in either falsely detecting lesions or hiding the ones that are too small, thus, diagnostic accuracy is decreased. In addition, the process of gadolinium enhancement might be impacted by certain technical factors, e.g., timing, dosage, or renal function, whereby the changes of active lesions are not always clearly identified(69). Besides human expertise, when MRI is interpreted, errors due to subjective bias, poor image quality, or similar features of different diseases in imaging might occur. Moreover, although automated tools and AI-based systems are considered a potential solution, they still confront some obstacles, e.g., generalizability and reliability, when they are different datasets or scanner types(70).

8. Future Perspectives

The progression of MRI technology in the case of MS is changing quickly with new technologies being implemented alongside the use of advanced imaging biomarkers, which have profoundly changed the diagnosing, the monitoring and the treatment of the disease by the clinicians. Among the coming technologies, there is ultra-high-field MRI, newly discovered imaging biomarkers, multimodal imaging and personalized MRI-based management strategies that are expected to increase imaging in the right way, making it possible to characterize the disease more exactly as well as to provide patients with tailored care(71).

8.1. Ultra-High-Field MRI (7T) and Its Role in MS Research

Ultra-high-field MRI (7 Tesla) is a great step forward in neuroimaging, just like a super-power that offers better spatial resolution, higher signal-to-noise ratio, and easier lesion contrast than the usual 1.5T or 3T systems. Somebody can see the very small cortical and



juxtacortical lesions with this, which are the ones that were not detected before, so the diagnostic accuracy is increased, in particular, the early or atypical MS. Also, 7T MRI is the best method for detecting most veins in the lesions, the main feature of MS pathology, that differentiates MS from similar conditions such as small-vessel ischemic disease(72). 7T MRI has been used in the research field for the very clear visualization of gray matter pathology, meningeal inflammation, and iron deposition that, in fact, are the aspects of the disease that caused neurodegeneration. At the moment, the use of 7T MRI is strictly limited to the research area because of its cost and safety reasons. However, the 7T MRI is an excellent clinical future that is very close, and it will surely make its way to clinical application very soon.(73)

8.2. Novel Imaging Biomarkers

Future MRI studies in MS have their scope narrowed down to defining the quantitative imaging biomarkers that would be indicative of the biological processes happening with the patient such as inflammation, demyelination, axonal damage, and remyelination. The parameters that arise from magnetization transfer ratio (MTR), diffusion tensor imaging (DTI), and quantitative susceptibility mapping (QSM) can be considered as biomarkers of the integrity of the myelin, the health of the axonal part and the deposition of iron, respectively. Furthermore, correlations of myelin water imaging and neurofilament light chain (NfL) are being investigated for the identification of neurodegeneration and the existence of repair mechanisms. Such biomarkers will facilitate the early recognition of inactive disease, the evaluation of therapeutic effectiveness, and the implementation of personalized treatment strategies(74).

8.3. Integration of Multimodal Imaging (MRI + PET + Optical Coherence Tomography)

The combination of MRI with other imaging modalities, for example, Positron Emission Tomography (PET) and Optical Coherence Tomography (OCT) is the next stage in MS research. MRI-PET hybrid imaging allows simultaneous evaluation of anatomical changes and molecular processes, e.g., inflammation, and the loss of myelin, by employing a clear PET tracer for microglia activation or demyelination. On the other hand, OCT is a thankfully non-invasive look at axon health through measuring the thickness of the retinal nerve fiber layer, a parameter that is correlated with brain atrophy and

neurodegeneration. The integration of these modalities provides a thorough understanding of the disease process from microstructural, functional, and molecular aspects, thus, enabling the development of more complete diagnosis and surveillance(75).

8.4. Personalized MRI-Based Management Approaches

The future of multiple sclerosis treatment is changing to personalized, MRI-guided management. Along with AI-powered lesion analysis, radiomic biomarkers, and follow-up imaging, doctors can customize the treatment for the patient's specific disease pattern and pace of progression. Predictive models will be able to detect high-risk patients for relapses or quick progression, thus, leading to a more urgent and intensive treatment(76).

9. Conclusion

MS has benefited from MRI in many different areas that include early detection, diagnosis, and follow-up, thus, the use of MRI has changed the way MS is understood a lot. As a matter of fact, MRI has evolved substantially from the traditional T1- and T2-weighted imaging to quantitative and artificial intelligence-based techniques, which have tremendously raised the accuracy of the diagnosis and clinical decision-making (77). By being more sensitive to the detection of clinically silent lesions, MRI is very often a diagnosis tool that is able to detect the disease at an earlier stage than what leads to irreversible neurological deficits, thereby, the therapeutic interventions of the time and the prognosis of the disease are improved. MS is an inflammatory demyelinating disease of the central nervous system in which axonal injury remains the morphological hallmark. Conventional MRI techniques, i.e., T2-weighted and FLAIR images, are essential in identifying the white matter lesions, thus providing a simple and rapid way of assessing the disease load (78). This deficit has been fixed by sophisticated imaging methods such as magnetization transfer imaging, diffusion tensor imaging (DTI), and newer volumetric MRI techniques for quantitative assessment of tissue integrity, connectivity, and atrophy patterns. Such techniques may enable very early detection of neurodegenerative processes, put forward candidates as potential markers of disease progression and response to treatment, thus, they can be a bridge between the clinical and the radiological (79). MRI, presently considered as a confirmatory diagnosis,



has turned out to be a very effective monitoring tool for disease activity and treatment success. The identification of lesions that exhibit new activity or enhancement via consecutive MRI examinations allows clinicians to decide on modifying treatment regimens, which results in the least possible irreversible damage of the patient's nervous system. Therefore, MRI is a potent diagnostic and prognostic tool that directs clinical management of an individual throughout the stages of the disease(80).

The entire frontier of MS diagnoses has been changed essentially by the AI application and the quantitative MRI progress. Magnetization Transfer Ratio (MTR), Fractional Anisotropy (FA), and Mean Diffusivity (MD) are quantitative MRI techniques that provide objective and reproducible metrics for evaluating the severity of demyelination, axonal injury, and neurodegeneration, beyond visual evaluation of lesions. Disease evolution can be very well and accurately gauged through longitudinal quantification (81). Radiomics' comprehension, which stands for a novel manner of keeping track of the disease by the complex quantitative features extraction from the MRI data, gives a deep insight into lesion biology and facilitates the predictive modeling of disease conversion and therapeutic response. Besides that, the multimodal amalgamation of MRI, cerebrospinal fluid, serological, and genetic data has started to create pathways towards individualized disease modeling and predictive analytics for MS- the change towards precision medicine (82). However, a number of challenges need to be addressed before universal standardization, inter-scanner reproducibility, and the validation of novel imaging biomarkers for clinical translation will be possible, in spite of the significant advances made. The centers' data consistency can be challenged by the differences in imaging protocols, the field strengths of scanners, and post-processing algorithms. In spite of AI tools demonstrating high diagnostic potentials in research environments, they will still need validation, ethical supervision, and also interpretability in being adjusted to routine clinical workflows (83). While cost and accessibility apart from technical skills present paradigmatic barriers that can limit the democratization of this level, especially in low-resource areas, these barriers need to be overcome. The impressive MRI, both in research and clinical practice of multiple sclerosis, is not only the main diagnostic tool but also the means by which the disease is 'seen' in the

brain. The question is already settled that the invention of MRI and similar technologies has enabled early detection of lesions, disease monitoring, and treatment outcome evaluation, thus MS has become a clinical condition that can be easily handled rather than one that is hard to grasp (84). As the science moves towards harmonization, automation, and personalized analytics, MRI will be still the most powerful and non-invasive method of early detection and thorough monitoring of multiple sclerosis which, in turn, will be instrumental in the development of personalized treatment regimens and improvement in the quality of life of patients anywhere in the world (85).

10. References

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