Chapter

Advances in Magnetic Resonance Imaging in Multiple Sclerosis

Rasha Abdel-Fahim

Abstract

Multiple sclerosis is the second most common cause of disability in young adults. Conventional imaging so far failed to explain the extent of clinical disability even by careful examination of white matter lesion volume and their topographical distribution. The increasing availability of ultra-high field imaging allowed the improvement in understanding the dynamic lesional and extralesional pathology in different stages of the disease and their potential contribution to clinical and cognitive disability. The contribution of cortical lesions of different subtypes, the degree of microstructural damage in those lesions has been examined. This is in addition to the influence of white matter lesions and spinal cord pathology on the degree of disability in multiple sclerosis. Prognostic factors influencing long-term disability in patients with multiple sclerosis have also been a subject of interest for many years, particularly their significance in early decision-making with regard to disease-modifying treatment choice and early initiation. The frequency of iron rims in white matter lesions has been linked to increased disease severity in multiple sclerosis. Iron rim lesions' potential evolution to slowly expanding lesions as well as the long-term prognostic impact of such lesions on the degree of clinical disability has also been examined in this chapter.

Keywords: cortical lesions, multiple sclerosis, iron rims, slowly expanding lesions, magnetization transfer imaging

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the nervous system, and it is the second commonest cause of disability in young adults. It presents with different phenotypes, the commonest being relapsing remitting which presents with relapses, and it constitutes around 80% of patients. Most patients in the relapsing–remitting phase convert to the secondary progressive phase between 10 and 15 years from onset. During the secondary progressive phase of the disease, the clinical decline is usually gradual with some patients experiencing superimposed relapses. A cohort of patients, of around 15%, presents in a progressive phase from onset and labeled as primary progressive MS (PPMS).

Magnetic resonance imaging (MRI) is very significant not only in diagnosis but also in providing prognostic views. Utilization of MRI in diagnosis has depended mainly on white matter (WM) lesion load as well as spatial distribution and temporal accumulation to establish dissemination in space and time.

Despite advances in imaging, extensive examination of WM lesions over the years has not explained the variability in clinical course and the variable degree of physical and cognitive disability posing an obvious struggle to address the clinico-radiological paradox.

The evolution of MRI techniques over the years and more recent advances in high and ultra-high-field imaging has contributed significantly to bridging the gap between radiological, clinical, and even pathological views in MS. This has provided a paramount insight into lesions pathology and in turn MS pathology.

Recent evolution of imaging in MS has focused on exploring imaging techniques that could explain clinical disability given that WM lesions solely cannot account fully for the clinical decline. In turn, such understanding of mechanisms of MS pathology could facilitate prognostic tools which would be a useful biomarker in decision-making with regards to disease-modifying treatment (DMT) initiation.

2. Cortical gray matter pathology in MS

Cortical lesion pathology is an emerging imaging biomarker that has been receiving an increasing attention due to its increasingly perceived contribution to clinical disability.

Cortical lesions are prevalent at the early stages of MS disease course and their abundance has been illustrated in early MRI and histology studies on post-mortem MS brains [1]. It is suggested that they develop in the early stages of the disease even before (WM) lesions [2].

Despite their significant contribution to MS pathology and physical and cognitive disability, their consideration during decision-making is non-existent. This is due to the current challenge in detecting cortical lesions using clinical scanners and the need for higher magnetic field strength to facilitate their depiction.

3. Cortical lesions pathology in MS

Cortical lesions are classified based on their location within the cortex into type 1 (Leukocortical) which extend between the cortex and white matter, type 2 (intra-cortical) which are usually confined to the cortex, and type 3 (subpial) which usually extend from the pia surface to cortical layer 3 or 4 and usually appear as ribbon-like lesions extending through large surface of the cortex [3]. Leukocortical lesions are usually the most prevalent type of cortical lesions, accounting for over 60% of the total cortical lesions count (**Figures 1** and **2**) [4].

Pathology of either cortical lesions or WM lesions development is complex, has been hypothesized over the years, and is likely to involve multiple mechanisms. Spinal lesion load correlated to subpial lesion subtypes despite small WM lesion load, suggesting a similar mechanism of lesion development with their proximity to the meninges [6, 7]. A difference in the intensity of lesions in the cortex from WM lesions in 7Tesla T2* was noted, which could reflect pathology finding of less inflammation in cortical lesions in comparison with WM lesions and supports the notion that they have different mechanisms, degree of tissue damage, and probably contribute to disability in different ways [3, 6].

The small size of cortical lesions and the scarcity of myelin in the cortex posed challenges to their detection via conventional clinical magnetic resonance imaging tools. However, advancement in the magnetic imaging field, especially different sequences, as well as ultra-high field strength, facilitated further

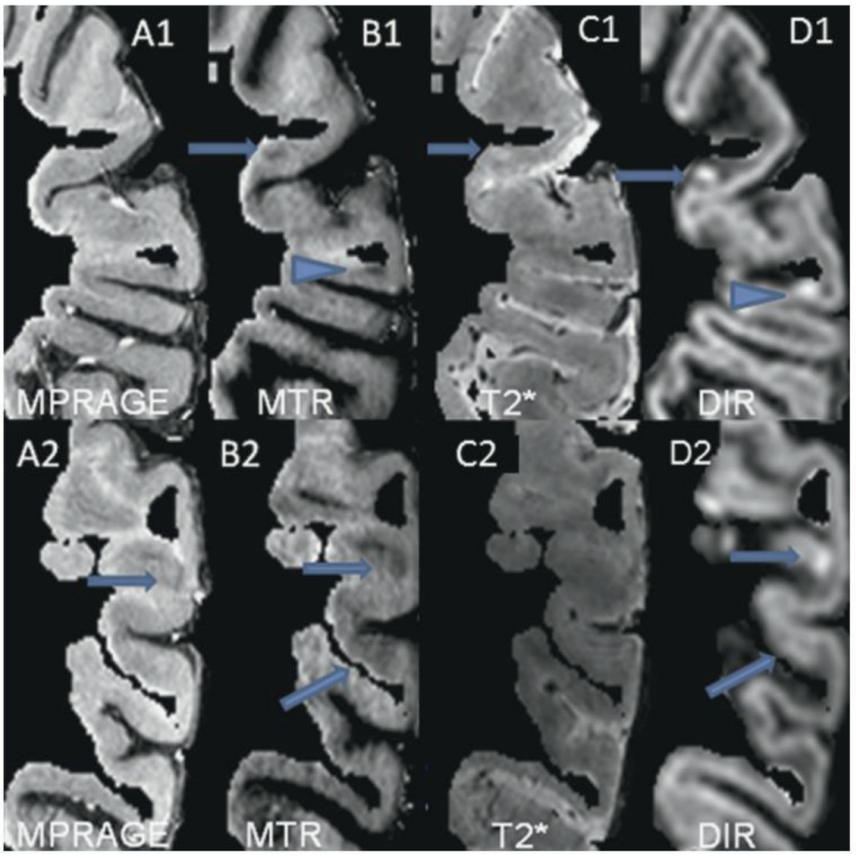

Figure 1.
Cortical lesions as seen in different sequences. To ensure blinding, the white matter was erased and lesion detection was undertaken using the segmented cortical ribbon. MTR offers advantages in providing increased sensitivity in GM lesion detection and more clear classification of lesion location. Intracortical lesions (arrows) and mixed leukocortical lesions (arrow heads) were detected on MTR (B1, B2)and DIR (D1, D2) but were undetectable on MPRAGE (A1, A2) or T2 (C1, C2). DIR (arrows D1) frequently misclassified lesions as leukocortical when MTR maps (arrows B1) clearly show intracortical lesion with normal appearing adjacent WM [5].*

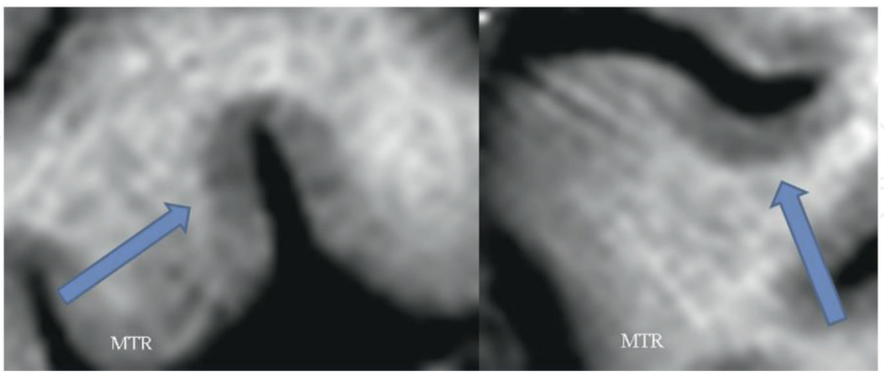

Figure 2.
Examples of subpial cortical lesions (arrows) on MTR [5].

studying of cortical lesions and their contribution to understanding MS clinical course.

Ultra-high-field imaging at 7 Tesla has improved our understanding of cortical pathology via its increased sensitivity to depicting cortical lesions in comparison with 3 T MRI sequences. Magnetization transfer imaging (MTI), magnetization prepared two rapid acquisition gradient echo (MP2RAGE), T2*, and Double inversion

recovery (DIR) sequences at 7 Tesla proved sensitive to depicting cortical lesions *in vivo*, particularly leukocortical lesions, however, with less sensitivity to intracortical and subpial lesions [5, 8–10]. DIR, phase-sensitive inversion recovery (PSIR), and MP2RAGE have proven less sensitive to cortical lesions depiction in comparison with 7 T PSIR, MP2RAGE, T2*, and MTR especially of subpial subtype (**Figure 3**) [5, 8, 11].

Cortical lesion load, especially leukocortical lesions, is generally higher in patients with SPMS in comparison with those in RRMS. However, no significant difference was observed in intracortical or subpial lesion load among different MS phenotypes [6]. Higher cortical lesion load was the main difference between progressive and relapsing cohort even on comparing WM and spinal cord lesion load, favoring the correlation between focal cortical lesion pathology and progressive phase of the disease [6]. Cortical lesion load was higher in those with higher WM lesion loads; leukocortical lesion load in particular correlated with WM lesions load with less correlation indicated with other cortical lesions subtypes [6].

To determine factors influencing the degree of disability in MS patients, the main emphasis should not only be on cortical lesion load but also the topographical

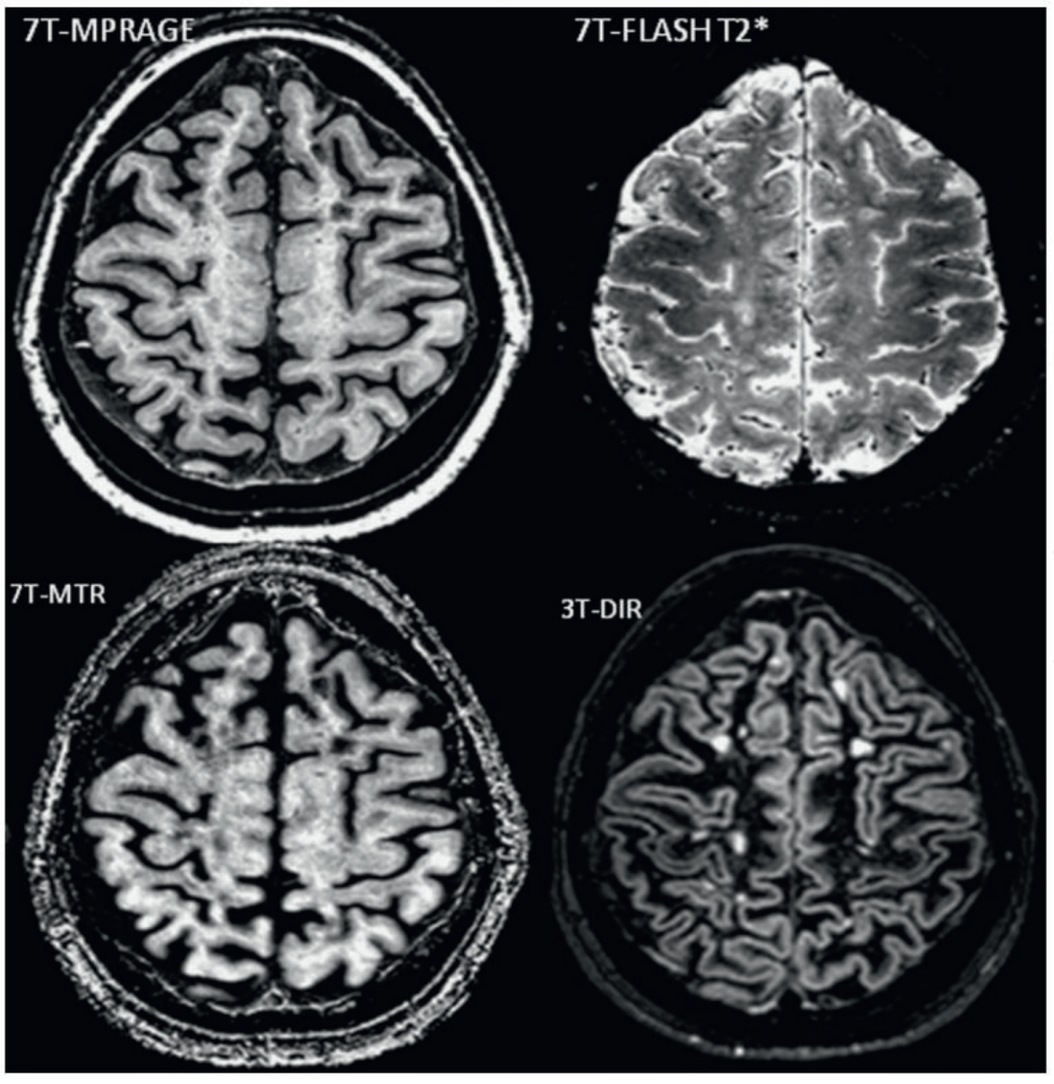

Figure 3.
Axial view of the sequences used in a relapsing–remitting MS patient [5].

distribution of those lesions. Utilizing ultra-high field strength allowed not only improved sensitivity in detecting cortical lesions but also better characterization of their topographical distribution. Cortical lesions tend to have a predilection to motor areas such as premotor cortex, precentral gyrus, and mesial temporal regions [10, 12]. However, it is important to appreciate technical challenges when using ultra-high field imaging to assess cortical lesions as it often underestimates lesion load in temporal and occipital lobes due to associated inhomogeneity observed in those areas at higher magnetic field strength.

4. Cortical lesions and clinical disability in MS

The impact of cortical lesions on physical and cognitive disability has been a subject of interest and extensively examined. Studies revealed a higher number of cortical lesions in patients with progressive MS in comparison with those with relapsing–remitting MS (RRMS), as well as association between worsening physical disability indicated by EDSS and cortical lesion load especially subpial lesions [13]. On the other hand, cognitive performance showed a higher association with leukocortical lesion load, subpial lesion load, and cortical thickness, but the association with leukocortical lesion and subpial lesion load was stronger than with cortical thickness at 7 Tesla imaging [13]. Another study observed that cortical lesions T1 values were not different in RRMS patients in comparison with progressive MS patients, but they were higher in leukocortical lesions in comparison with other cortical lesions subtypes [6].

Using DIR at 1.5 T, analysis of cortical lesion load at baseline correlated with the degree of physical disability, indicated by EDSS, 5 years later, with no significant contribution to the rate of new lesions development. Furthermore, there was no difference in the rate of development of cortical lesions in different disease phenotypes. This could well be due to the lower sensitivity of DIR at 1.5 T to cortical lesions detection [14]. Taking into consideration WM lesion load as well as degree of gray matter atrophy, the association of cortical lesions with cognitive and physical disability in all MS disease phenotypes was more consistent than any other parameters [14].

Improved and early detection of cortical lesions would contribute significantly to earlier consideration of diagnosis, potentially providing a step closer to being considered in diagnostic criteria, and potential implications on prognosis especially on physical and cognitive outcomes. Most importantly, improved imaging detection of cortical lesions would offer a promising biomarker for DMTs evolution and treatment targets.

5. Role of automated lesion detection

Manual segmentation of lesions is time-consuming and subject to inter as well as intra-rater variability. Automated detection of cortical lesions on MRI has been evolving in recent years. However, implementation of deep learning methods in cortical lesions segmentation has been challenging due to the difficulty in detecting some lesion subtypes, especially subpial and intracortical lesions, in addition to the relatively small size of cortical lesions and the lower contrast in comparison with surrounding normal-appearing gray matter tissue. High magnetic field strengths such as 3 T and 7 T are often needed to facilitate cortical lesion detection. Despite higher

field strength providing better resolution and signal-to-noise ratio, it has higher field inhomogeneity across the images in comparison with conventional imaging, which poses a challenge to implementing automated segmentation techniques.

Multiple sclerosis lesion analysis at seven tesla (MSLAST) is a new automated method to detect lesions based on estimation of partial volume and topographical constraints using a single MP2RAGE, which provides good tissue contrast for detection of WM as well as cortical lesions and less affected by B0 and B1 inhomogeneities. Automated segmentation using a single image MP2RAGE showed better performance with WM lesion detection than cortical lesions detection, with sensitivity at 74% and 58%, respectively, and false positive rate at 40%. When the radiological MS lesions definition (volume approximately ≥15 ul) was implemented, its detection rate improved to 80% of WM lesions and 63% of cortical lesions [15].

Automated segmentation was reproducible than manual segmentation, however, with significant challenges, in particular using MSLAST technique, such as the lack of sensitivity to detect periventricular lesions as they have similar contrast to CSF, hence were included in the CSF mask. The same hurdle is noted with cortical lesion segmentation due to the lack of strong contrast between gray matter and cortical lesions, as well as the small size of cortical lesions. MSLAST also underestimated lesions volume, probably due to the partial volume effect and its lack of efficiency in delineating lesions borders [15].

Working on the range of sequences available at 7 T and improving the tissue contrast will help achieve better brain segmentation, partial volume estimation, and lesion segmentation, which in turn will improve the quality of MSLAST technique and its accuracy.

The second method of automated lesion detection at 7 Tesla using MP2RAGE and T2* sequences showed cortical lesion detection rate was 67%, false positive rate was relatively high at 42%, however, with retrospect analysis by a second reviewer false positives were deemed to be potential lesions [16]. This supports the notion of how challenging cortical lesion segmentation could prove.

A relatively new deep learning-based method is Cortical Lesions AI-based Assessment in Multiple Sclerosis (CLAIMS) which compared cortical lesion detection rates using ultra-high field 7 T MP2RAGE and T2*w contrasts (T2* EPI and T2* GRE) fed into their U-net based deep learning method. It showed that T2*w sequences did not add any value to the sensitivity of cortical lesion detection. Furthermore, they showed that models utilized T2*w sequences either T2* EPI or T2* GRE performed very poorly in comparison with models that used only MP2RAGE. Intracortical lesion subtype detection, as expected, was the most challenging with a detection rate of 53%, while performance was better for subpial and leukocortical lesions with a detection rate of 70% and 80%, respectively. CLAIMS also compared models with MP2RAGE of different voxel size at 0.5 mm or 0.7 mm or both 0.5 mm and 0.7 mm. They found that lesion detection rate dropped by 20% on moving from 0.5 mm acquisitions to 0.7 mm acquisitions which confers the importance of higher resolution images for lesion detection rate, even using automated methods of image analysis [17].

On comparing CLAIMS and MSLAST, CLAIMS showed higher performance with a good degree of classification of cortical lesions to intracortical and leukocortical [17].

Despite intense efforts and increasingly sophisticated techniques in automated lesion detection methods, intracortical lesion detection remains poor, as well as overall false positive rates. The lesser contrast between cortical lesions and their surrounding normal-appearing tissue in comparison with WM lesions and their surrounding

tissue constitutes a challenge to a highly accurate deep-based learning method to be utilized reliably in cortical lesion detection.

6. Progression independent of relapses (PIRA)

Progression independent of relapses (PIRA) is an increasingly recognized phenomenon in MS, particularly in the progressive phase of the disease but also in RRMS patients [18]. Studies on the correlation between MS relapses and associated new T2 lesions with disability progression are controversial. Some suggest that the frequency of relapses in early disease course influences long-term disability progression [19], while recent studies did not identify such a correlation [18].

Ocrelizumab appeared to be superior to Betaferon in reducing PIRA as well as reducing the frequency of relapses, explaining why Ocrelizumab is effective in primary progressive MS patients [20]. In the same study, PIRA was observed to account for 80–90% of disability progression [20].

The frequency of new lesions was found to be higher in patients who had progression related to relapses (90%) than in those with PIRA (11%), however, lesion accrual in the PIRA group was identified a few years before disability progression refuting the theory that progression is due to new lesion accrual [21]. Despite the evolution in DMTs, reducing the risk of relapses associated with disability, it did not significantly influence the risk of PIRA which increased with the age of onset of disease and with spinal cord lesions [21].

7. No evidence of disease activity (NEDA)

The use of relapse rate as an outcome measure in MS trials is becoming increasingly irrelevant as it provides a very limited insight into the natural history of the disease and in turn DMTs efficacy.

The use of composite outcome measures that incorporate imaging with clinical data has proven to be more promising in monitoring disease evolution and treatment response in clinical trials. NEDA is a concept that developed over time, states no evidence of disease activity in terms of relapse, disability progression (defined as an increase in EDSS score of 1.5 points from a baseline score of 0, of 1.0 points from a baseline score of 1.0 to 5, or of 0.5 points from a baseline score of greater than 5.0), or MRI activity (NEDA-3) is an increasingly used composite outcome measure to assess disease evolution in clinical trials. With further incorporation of imaging into this composite, NEDA-4 was introduced. NEDA-4 adds whole brain volume loss (mean annualized rate of brain volume loss in healthy brains should be less than 0.4%) to NEDA-3 measures [22].

Even though achieving NEDA-3 in the first 2 years of disease onset was not found to influence long-term progression [21], achieving NEDA-4 was correlated with reduced risk of long-term progression [23] which is compatible with the long-acknowledged view of the role of brain atrophy in long-term disease progression [18].

Despite the advantages around using a composite scale incorporating different measures, there is some skepticism regards some of these scales especially EDSS. The non-linear progression of this scale, the non-uniform progression between different stages, and the inter and intra-assessor variability when implementing at

different clinical visits. It is also not easy to implement and imprecise at the lower end of the scale, too driven by mobility distances at the middle and higher end of the scale and fails to take into account upper limb function which means a patient can score very highly for having one severe cord relapse ending the patient wheelchair dependent [24–26].

It is also important to note that despite the NEDA being a vital tool in monitoring disease outcomes, it mainly evaluates the active aspect of the disease without much emphasis on the neurodegenerative aspect [27]. Given that cognitive decline constitutes a significant aspect of MS disease, and it usually represents one of the earliest signs of disease progression and the degenerative component of MS, it will be crucial that it is taken into account in such composite scales [27].

8. Iron rim and slowly expanding lesions

Prognostic scores have been an area of interest for decades. Prognostic factors employ a mix of clinical features or MRI metrics. However, current radiological prognostic metrics depend on the presence of a higher degree of tissue damage to predict long-term severe disability. Hence targeting those patients with high-efficacy treatments at that stage of the disease, when a lot of the damage is already established, is probably not the most effective way of preventing future disability. It is also important to note that application of various prognostic indicators is challenging at the individual level and more acceptable at the group level.

With the continuous advancement in MS imaging field and the increase availability of ultra-high field imaging, it is important to be able to risk stratify MS patients early in the disease course, to assist DMT choice. In order to do this, we need an early radiological prognostic indicator to salvage brain tissue from future damage and improve brain reserve, which will be crucial when patients are entering the progressive stage of the disease.

Iron is the most abundant trace metal in healthy individuals' brains. Dysregulation of brain iron levels correlates to development of various neurodegenerative diseases, including the worsening of MS [28]. Iron is present in macrophages; however, its concentration varies depending on the stage of the disease. Histopathology showed that iron is present at high levels in slowly expanding lesions, but most importantly not present in remyelinating plaques [28].

Despite the controversies around brain iron accumulation and if it is contributing to neurodegeneration or if it is simply an epiphenomenon reflecting brain tissue degeneration, it is clear the association between its presence and worsening clinical parameters. It is even becoming more apparent as a prognostic factor.

Magnetic resonance imaging is sensitive to iron detection. T2 and T2* relaxation contrasts are shown to be sensitive to iron detection in comparison with T1 relaxation. In particular, T2* and susceptibility-weighted imaging (SWI) are more sensitive to iron detection than T2w. Iron enhancement increases with higher magnetic field strength. Despite how sensitive those parameters are to iron deposition, they do not reflect iron concentration, so they constitute a qualitative measure of iron presence. Magnetic field correlation imaging (MFC), phase imaging, and R2* mapping are semi-quantitative techniques that offer some rough quantification to iron content, but their estimates depend on iron content in a given voxel as well as iron content in voxels surrounding. Quantitative susceptibility mapping (QSM) uses GRE

phase images and eliminates blooming artifacts to quantify the local tissue magnetic properties (**Figure 4**).

Iron rim WM lesions are reported to constitute between 10 and 15% of all WM lesions [29, 30]. Iron rims around WM lesions appearing as rim of elevated R2* using 7 T was found in a small cohort of patients of different disease phenotypes either RRMS or progressive MS and in patients with different degree of disability, which reflects the degree of heterogeneity in iron distribution in MS patients. Other studies showed that the core of white matter lesions had low R2* relaxation reflecting low myelin and iron, while R2* was high around the demyelinated core reflecting high myelin and iron deposition [31]. This pattern of iron deposition is also present in slowly expanding lesions [32].

A study using QSM at 7 T followed patients for 2.4 years showed no significant change in size or signal intensity pattern of WM lesions [33]. However, there was a change in characteristics of some of those lesions, mainly in terms of iron contents and distribution within those lesions [33]. This change in characteristics was explained by the interaction of different macrophages phenotypes, classically iron-rich activated macrophages with M1-polarization which secretes proinflammatory toxic cytokines and are known to be neurotoxic, and M2-polarized macrophages which have the phagocytic capacity and are significant for tissue repair [34]. The change in iron distribution in some iron lesions or the switch from non-iron to iron at times is hypothesized to be due to the alteration in macrophages phenotypes [33].

On the other hand, iron rims in cortical lesions were investigated using 7 T T2* GRE and inversion recovery turbo field echo (TFE) sequences in post-mortem brains of MS patients. They found that iron rims lesions (IRLs) are associated with activated

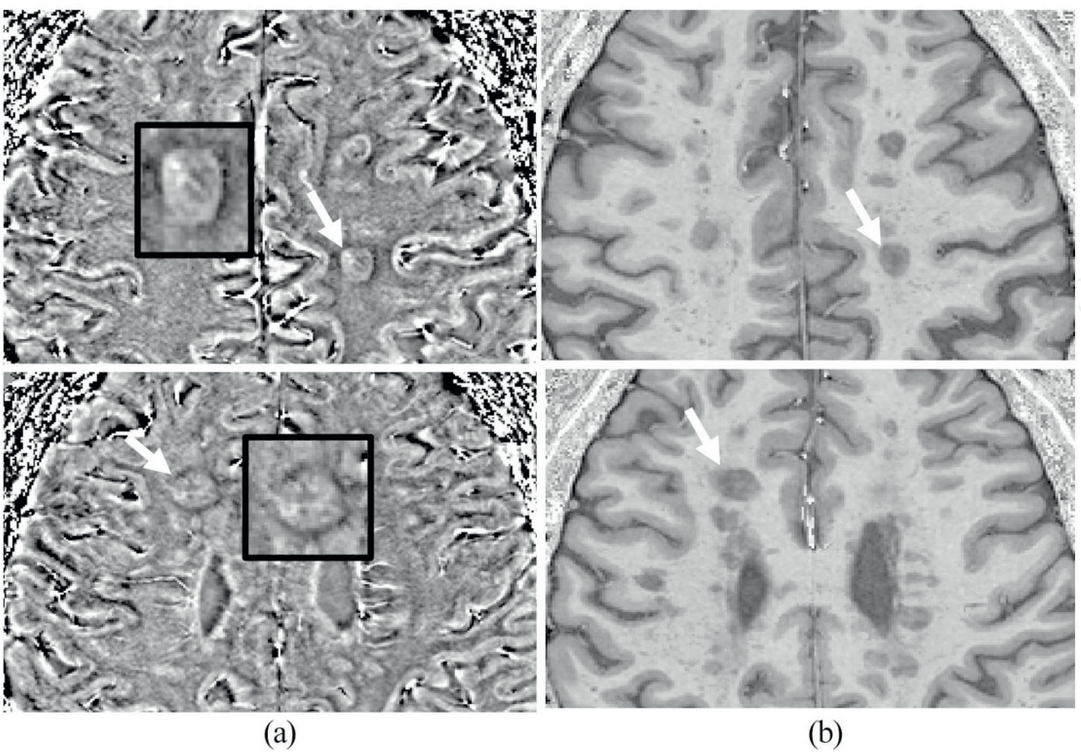

Figure 4.
Typical appearance of two lesions with rims on (a) SWI-filtered phase image corresponding with (b) T1-weighted (MPRAGE). Enlarged images of the lesions indicated using the white arrows from different patients are shown in the black box with the characteristic hypo-intense rim surrounding most of the lesion [5].

microglia at the border of chronic active cortical lesions and show high iron contents [10]. Another post-mortem imaging study that employed T2* maps at 7 T showed large areas of demyelination detected in histopathology, extending from the subpial surface across all layers of the cortex and involving full gyri in some sections, but often went undetected in imaging. Re-examining the images yielded 67% of the undetected lesions detected retrospectively. This disparity between imaging and histopathology was not solely due to the small size of lesions being difficult to detect, but also due to the variability of cortical ribbons contrast according to their function, which affects the contrast between lesions and surrounding normal cortical tissue [35]. However, in that study, no iron-positive lesion edges were detected in cortical lesions, but the study sample was very small to draw any decisive conclusions [35]. A larger post-mortem study observed that cortical lesions with rims of activated microglia were more prevalent in patients with early active disease, died at a younger age and were associated with a higher frequency of chronic active WM lesions [36].

9. Slowly expanding lesions (SELs)

White matter chronic active lesions are prevalent in MS patients and pathologically they are surrounded by iron-laden activated microglia/macrophages that expand in size over time due to continuous demyelination and axonal loss [37]. While MS is composed of relapses and disease progression, it is suggested that active lesions, which are more prevalent in early disease course, contribute to relapses, whereas smoldering slowly expanding lesions (SELs), which are more prevalent in progressive MS, are more associated with disease progression [37]. The frequency of smoldering plaques increased with a longer disease duration [37]. Chronic active lesions have a paramagnetic iron rim, and it showed an increase in size gradually over time with serial T1 and T2w images over years [38]. However, other short-term longitudinal studies over 2.5 years using 7 T T2* did not show expansion of iron rim lesions over time [39].

Another attempt to understand and assess the evolution of WM lesions with and without iron rim is by categorizing lesions into two groups according to the way they take up contrast; centrifugally enhancing lesions (inside-out dynamic contrast leakage) and centripetally enhancing lesions (outside in dynamic contrast leakage) [40]. At follow-up, 18 months later, none of the centrifugally enhancing lesions had a phase rim [40]. The larger the size of lesions at baseline the higher chance phase rims will persist at follow-up regardless of the contrast pattern at baseline [40]. Rim persistence was also associated with the least recovery of T1 intensity in those lesions over time, suggesting that it is likely that phase rim does not only reflect associated inflammation but also a degree of tissue damage [40].

The brain's response to the acute inflammatory process in active lesions is to contain it via immune-mediated process or astroglial reaction, and failure of these processes can break down blood–brain barrier manifesting as centripetal enhancing lesions, and infiltration of macrophages and activated microglia, reflected in early phase rim [40].

Monitoring the change in the size of lesions over time using the Jacobian determinant of the deformation between reference and follow-up scans, showed that patients with PPMS had a higher number of SELs in comparison with RRMS patients [41]. SELs had lower T1 intensity at baseline and a greater drop in T1 intensity over time in comparison with T2 lesions that did not show an increase in size [41].

10. Examining the destructive nature of iron rim lesions and SELs

Rim lesions are noted to be larger in size than non-rim lesions [29] which could be due to the destructive microstructural nature of those lesions with larger centre and more extensive area of axonal loss, or due to the expanding nature of those lesions which could account for their larger size and more destructive nature. Some studies suggest that lesions which are larger at baseline are more likely to expand at follow-up [40] and adopt a slowly expanding lesion pattern. However, we also need to consider that it could be that those rim lesions are simply less likely to shrink in comparison with non-rim lesions [29].

In a post-mortem study using 7 T sequences, it was observed that neither shadow plaques (fully remyelinated lesions) nor active lesions showed edge-related iron accumulation in microglia or macrophages [29]. Most MS lesions had a very low concentration of iron in the centre of lesions in comparison with surrounding white matter [29]. In that study, iron rim lesions were more likely to expand, whereas non-rim lesions were more likely to shrink [29]. Most shadow plaques did not show iron in their lesion edges [29, 40]. The lack of iron at the edges of active lesions was explained by the likelihood that myelin at the edge of active lesions is mainly taken by macrophages, which are mobile and eventually accumulate in perivascular spaces, while in SELs tissue debris are taken by microglia which are far less mobile and remain at lesion edges for prolonged periods of time constituting iron rims [29].

In histopathology studies, remyelinated lesions were often more vulnerable to recurrent demyelination than normal-appearing white matter. Recurrent slowly expanding demyelination, in previously demyelination affecting remyelinated areas, correlated with incomplete remyelination in progressive MS patients [42].

MP2RAGE is composed of a modified MPRAGE sequence to create two different images at different inversion times aiming to alleviate the inhomogeneity at a high magnetic field, which affects spatial resolution [43]. While T1 prolongation manifesting in black holes is accepted as a marker of severe axonal loss, changes in T1 relaxation are suggested to be a good quantitative marker of the degree of demyelination and remyelination *in vivo*, as myelin strongly determines T1 relaxation time in MS lesions [43, 44]. On acquiring quantitative T1 maps with MP2RAGE sequence at 7 T, long T1 relaxation lesions appeared as black holes on T1 images, while short T1 relaxation lesions appeared as iso-intense or hypo-intense to cortex, and lesions with long T1 relaxation and short T1 relaxation areas were categorized as mixed lesions [44]. Correlating imaging to histopathology, T1 time was longer in demyelinated than remyelinated lesions and correlated with severe axonal loss. 7 T MP2RAGE was a good marker to differentiate demyelinated from remyelinated lesions as well as mild from severe axonal loss with a good degree of sensitivity and specificity [44]. Visual inspection of 7 T MP2RAGE T1 maps was a good measure to qualitatively classify fully demyelinated, partially demyelinated, or remyelinated lesions [44]. In the same study, 48% of PRL were long T1 and a similar percentage of mixed T1 while only 4% short T1 relaxation; moreover, PRL status explained 78% of the variance in T1 relaxation time [29, 44].

In keeping with previous studies suggesting that remyelination capacity can be variable depending on the topographical distribution of lesions, long T1 relaxation lesions were mostly noted in the periventricular and juxtacortical white matter with subcortical lesions showing more capacity to evolve into short T1

relaxation, while juxtacortical and periventricular lesions more likely to evolve into long T1 relaxation [44, 45]. In terms of remyelination capacity, small lesions with shorter T1 time showed more repair than large lesions with similarly short T1 relaxation time [44, 46]. As expected, with higher age at the time of lesion formation, there was an associated increase in mean T1 lesion relaxation at 7 T follow-up, even on taking into account disease duration and disease-modifying treatment [44].

Supporting the view of the destructive nature of SEL, a 9-year follow-up study showed EDSS score worsening over the follow-up period in patients with ≥4 SELs and lower baseline MTR in SELs [47]. Another study showed worse EDSS and ARMSS (age-related multiple sclerosis severity) at 10 years follow-up in patients with ≥4 IRL [48] (**Figure 5**). Conversion to SPMS and higher EDSS at 9 years follow-up was associated with lower baseline MTR of SELs and higher T1 signal intensity decline in SELs at 2 years follow-up when compared with baseline, reflecting the contribution of the degree of microstructural tissue damage to the degree of future disability [47]. As the aforementioned factors can overlap in influencing EDSS worsening, and similarly conversion to SPMS is usually associated with higher and worsening EDSS, multivariate analysis that took into account the contribution of baseline SELs MTR, the proportion of SELs among white matter lesions to EDSS worsening at 9 years follow-up, and SPMS conversion found that while both factors contributed to EDSS worsening, the model only retained baseline SELs MTR as an independent predictor to SPMS conversion [47].

Evaluation of the effect of disease DMT on the evolution of SELs is crucial yet limited. It was observed that patients on Fingolimod and Natalizumab had higher volume and number of SELs over 24 months period, however, rate was lower in Natalizumab patients suggesting higher efficacy [49]. Moreover, SELs showed lower MTR values and T1 intensity in comparison with non-SEL, while non-SELs exhibited more improvement in MTR values than SELs [49]. This supports the view of the destructive nature of SELs and the notion that the lesser the degree of damage in lesions the higher the chance of recovering with disease-modifying treatment.

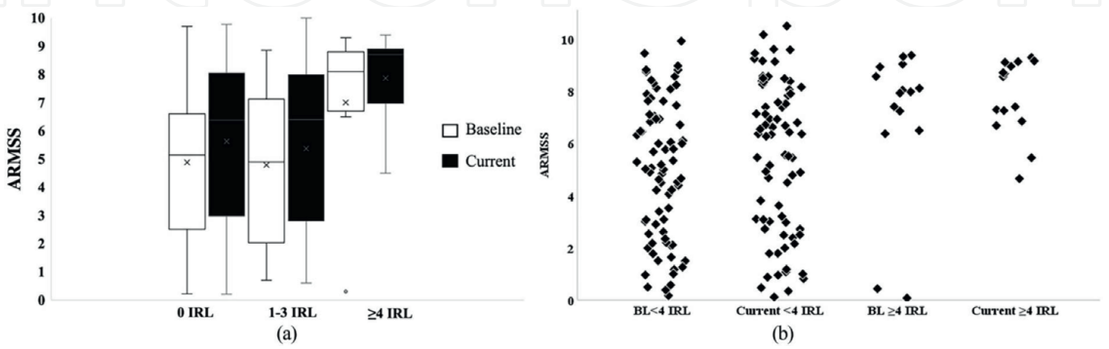

Figure 5.
ARMSS at baseline and current clinical follow-up in IRL patients. The number of IRLs were grouped to (a; 0 IRLs, 1–3 IRLs and ≥ 4 IRLs), (b; less than 4 IRLs and 4 or more rims) [5].

11. SELs and disability

Black holes have been a marker of neurodegeneration and axonal loss. The higher percentage of persistent black holes coincided with SELs; such an association suggests an evolution from an initial stage of chronic active lesions, or SELs to more chronic lesions, or black holes where severe axonal loss is the more prominent feature [50].

Chronic active lesions provide a reasonable explanation for clinical disability worsening in MS patients beyond mere total lesion load [50]. In a retrospective observational study with up to 12 years follow-up, employing a mixed-effects regression model observed that the increase in SELs predicted EDSS worsening not baseline total lesion volume or disease duration which were also included covariates in the model [50]. Moreover, for every unit increase in SELs, a fivefold higher risk for worsening EDSS; when paired with total baseline lesion volume in the same regression, the increase in SELs volume still performed better [50]. SELs log volumes negatively correlated with normalized brain volume and with normalized cortical gray matter [50].

It is thought that the neurodegenerative process in SELs is the main driver of physical disability in MS patients of different phenotypes. In PPMS patients on Ocrelizumab, the increase in T1 lesion volume between baseline and follow-up was less than that in PPMS patients not administering the drug [51]. Moreover, those on treatment had 5.1% of pre-existing T2 lesion volume identified as SELs, while those not on treatment had 7.1% [51]. Despite SELs accounting only for a small portion of T2 lesions, they accounted for a high proportion of T1 lesions developing in both groups of patients [51]. This indicates that the increase in T1 lesion burden in PPMS patients is due to chronic active disease activity and axonal tissue damage and it is predictive of clinical disease progression [51] There was also a greater reduction in normalized T1 signal intensity in SELs regions in comparison with non-SEL regions in both groups [51]. Interestingly, neither whole brain volume loss nor new WM lesion formation predicted clinical disability progression in PPMS patients [51]. This suggests that chronic active lesions accumulation has a more predictive role in disability progression in PPMS patients than brain atrophy [51].

SPMS patients had greater, yet not significant, numbers of SELs in comparison with RRMS patients and had twofold greater T2 volume of SELs [52]. MTR values of SELs at baseline were lower than non-SELs in RRMS and SPMS patients and showed more decrease in their MTR values in comparison with non-SELs by the end of 72 weeks of study follow-up [52]. This suggests the severe tissue damage in SELs in comparison with non-SELs at baseline and their poor prognostic value earlier in the disease course, which would be of a significant value to guide treatment decisions early on in disease course.

MS lesions show a dynamic change in their microstructure mainly in the degree of active inflammation, demyelination, remyelination, or axonal loss. MS lesions detected on T2 sequences can evolve over time either increase in size or shrink. Various factors have been examined over the years to elucidate what contributes to the change in lesions size. This is significant as expanding lesions are thought to have an active edge contributing to their increase in size. Studying this further is relevant and significant as current DMTs in MS are mainly directed at targeting the active element of the disease, not disease progression. And as slowly expanding lesions are more prevalent in progressive MS and are thought to contribute to the progressive course of the disease, understanding its pathology further is crucial to evolve treatments for the progressive stage of the disease.

Taking available literature into consideration, we may need to look at DMTs from a different angle. All available treatments aim at new lesions development which is important for preventing relapses, however, gradual progression prevention seems far from achievable. In order to pave the way for progression prevention, further understanding of SELs as well as inactive lesions pathology is crucial as they are unlikely to remyelinate, and they correlate with worsening disability.

12. Brain volume

The average rate of yearly brain atrophy in a healthy individual is 0.1–0.4%, while it was estimated at 0.5–1.3% in MS patients[53]. There is a technical challenge in assessing brain volume in individual patients longitudinally, this is in addition to the presence of confounding factors such as the resolution of acute inflammation giving a false impression of volumetric brain atrophy, hence usually conclusions are more reliable when drawn on groups of patients rather than individuals. With higher magnetic field strength, it is less challenging examining volumetric brain measures in MS patients.

The correlation between cortical lesion load and cortical volume/thickness is controversial with some studies using DIR illustrating reduction in cortical thickness in patients who had cortical lesions in comparison with those with no visible cortical lesions [54], however, other studies using 7 T did not detect such a correlation either in individual cortical regions or in the cortex as a whole [6, 12].

Several studies showed the correlation of not only WM but also cortical gray matter atrophy with a physical disability at the early stages of the disease [55]. There is a consistent association found between the progressive stage of the disease and the reduction in cortical thickness, as well as a similar association observed between worsening disability and reduction in cortical thickness using 3 Tesla [13].

Gray matter fraction using DIR at 1.5 T showed lower gray matter volume at baseline in patients with progressive MS in comparison with those with relapsing–remitting MS, and the degree of volume loss over 5 years was higher in progressive patients in comparison with RRMS and benign MS patients. Furthermore, patients with higher cortical lesion load at baseline showed lower gray matter fraction in comparison with those with smaller cortical lesion load, and those who cumulated more cortical lesions had associated higher progression of their gray matter atrophy over the same number of years [14].

13. Spinal cord imaging

In pathology and radiology, the emphasis has mostly been on the cerebral involvement in MS with limited analysis of spinal cord involvement. The cervical spine has a predilection for involvement in MS. Spinal cord atrophy is more prevalent in progressive than relapsing MS patients and is considered as a reliable marker of progression in MS patients. Cord atrophy is more prominent in cervical than thoracic cord and shows a higher correlation to clinical disability parameters which supports the view that disease progression starts early in the disease course in RRMS patients and is not limited to the secondary progressive stage of the disease [56]. There was no correlation between the spinal cord lesion load and cord atrophy in all disease phenotypes which suggests that both factors contribute independently to the degree of disability [57].

PPMS patients usually have rapidly cumulating disability in comparison with RRMS patients and were not explained with lesion load which is usually higher in RRMS patients. Post-mortem studies showed an extensive axonal loss in spinal cord MS patients which reflects irreversible damage. Radiologically, cervical cord atrophy is a prominent consistent finding in patients with PPMS in comparison with RRMS patients and was even suggested as a tool to differentiate both phenotypes [58].

Due to technical challenges of cord imaging, image resolution, population variability, registration, and segmentation errors at the edge of the cord resulting in partial volume effect, it has been difficult to implement atrophy measures in clinical trials or indeed in clinical practice. Spinal cord atrophy assessments are mainly done via T1-weighted and T2*-weighted gradient-echo sequences, while methods for segmentation and atrophy calculation can be categorized into image based, intensity based, and surface based. Generalized boundary shift integral (GBSI) is a promising registration-based technique, which is based on BSI (boundary shift integral) but overcomes partial volume effects via measuring the percentage change in cord volume values directly from small intensity changes between images at the cord boundaries accounting for partial volume effects in these regions. As it quantifies spinal cord atrophy using direct estimates via registration-based measurement of cord atrophy, it improves sensitivity to variation in longitudinal volume changes. However, GBSI is very dependent on voxel size as it requires isotropic small voxels, and it also requires consistency between different time points to allow precision [59].

Various studies found the influence of spinal cord lesions on the degree of clinical disability extends beyond lesion load to topographical distribution. Furthermore, spinal cord lesions involving the central areas and the lateral funiculi of cervical spine were associated with a higher degree of disability indicated by EDSS [60]. Via implementing automated methods of assessing lesion distribution in different MS phenotypes and its correlation to disability suggested that RRMS patients show high lesion probability in the posterior column, while PPMS patients in the lateral and central cord and SPMS patients more in the posterior and lateral cord [60].

Limited spinal cord data are partially related to the challenging nature of spinal cord imaging with regards to the small mobile field of view contributing to increased likelihood of artefacts. The evolution of ultra-high-field imaging with the increase in signal-to-noise ratio and improved spatial resolution facilitated further examination of cervical cord pathology and potentially closer analysis of its potential pathogenesis. With histopathological studies suggesting outside-in pathological gradient mechanism of demyelination, describing the penetrating lymphocytes inducing inflammation via activating microglia and macrophages inducing focal demyelination [61]. In support of this theory, the use of 7 Tesla MRI imaging helped the accurate delineation of lesions in such a narrow eloquent space. It showed that spinal cord lesions are more frequent around the central canal as well as the CSF subpial interface, with higher frequency around the outer subpial portion of the cord early in the disease course in RRMS patients and move towards the centre around the central canal in SPMS patients [62]. This reflects the difference in dynamics of MS lesions and CSF inflammatory mediators in different disease phenotypes, which potentially plays an important role in determining future targeting treatments.

Attempting to reduce the gap between macroscopic and microscopic tissue and lesional structure, diffusion imaging where MRI signal is sensitive to random motion of water can be a helpful tool. Diffusion tensor imaging (DTI) is the most conventional diffusion imaging technique, and it represents the movement of water in a single three-dimensional tensor, however, it does not take into account the

heterogeneity in tissue characteristics which in turn influences the reliability of the derived indices. This in turn paved the way for newer multicompartmental diffusion techniques which consider the heterogeneity of tissue compartments. Neurite orientation dispersion and density imaging (NODDI) is a novel diffusion imaging technique that models the CSF space as isotropic volume fraction V_{iso}, while the dendrites and axons are represented as apparent intra-axonal volume fraction V_{in}, and the orientation dispersion ODI, which is a measure of how nonparallel axons disperse about a central orientation providing a cylindrically symmetric Watson distribution [63]. NODDI offered higher sensitivity over other diffusion imaging methods in particular DTI, and especially V_{in} and ODI provide more contrast than other indices which offers helpful insight into MS pathology in the spinal cord as well as microstructural damage in normal-appearing white matter tissue, which does not show any particular abnormality in anatomical scans. It can also provide a valuable monitoring technique to observe tissue evolution even before lesions appearance [63]. However, registration of those sequences to anatomical sequences can pose difficulty.

Magnetic resonance spectroscopy (^{1}H-MRS) of the brain offered insight into the microstructural lesional and extralesional component beyond the macroscopic tissue damage via quantifying different metabolites. However, such application in the spinal cord has been technically challenging until recent years. ^{1}H-MRS is shown to be a good marker of early neuronal loss indicated by lower concentrations of total N-acetyl-aspartate (tNAA), which reflects neuroaxonal integrity, and glutamate-glutamine (Glx), which is a marker of neuronal integrity, in the upper cervical cord of patients with early PPMS even before the development of atrophy. Furthermore, tNAA concentration was lowest in lesional tissue and still affected, but to far less degree, in the normal-appearing tissue when compared with controls. Similarly, Glx concentration was also reduced in spinal cord lesions, likely reflecting axonal degeneration; but levels did not correlate to tNAA which suggests they reflect different pathological processes. On the other hand, both markers showed a good correlation with disability progression in PPMS patients [64].

Magnetization transfer ratio (MTR) is a semi-quantitative technique that provides an indirect estimate of the degree of demyelination and axonal loss, by measuring the magnetization exchange between freely mobile water protons and immobile macromolecular protons. MTR values were found to be significantly lower in cervical spinal cord of early MS patients in comparison with controls even in the absence of spinal cord atrophy; and the same was found in normal-appearing cord tissue which reflects the microstructural demyelination and axonal loss in normal-appearing tissue which should be taken into account in trials developing targeted disease-modifying treatment [65].

A novel approach that showed higher sensitivity to tissue myelin content than conventional MTI is inhomogeneous magnetization transfer imaging. It was proven to be more sensitive to microstructural spinal cord damage in comparison with DTI especially in normal-appearing cord tissue [66]. However, this technique was not compared directly to other myelin-specific imaging techniques such as quantitative MT imaging or myelin water fraction.

Despite the significant contribution of spinal cord imaging to the diagnosis and prognosis of MS, it still faces major technical challenges with a higher likelihood of artifacts due to the cord being a narrow mobile structure, low signal-to-noise ratio, pulse and respiratory-related artifacts, and the lack of normative data. Gray matter disease in the spinal cord as a separate significant entity and its contribution to the disease course has been under-covered due to challenges in imaging acquisition. With

continuous advances in imaging techniques and with the increasing incorporation of higher magnetic field imaging into clinical practice, examining spinal cord gray matter will be feasible. This is in addition to further advances in diffusion and magnetization transfer imaging to help bridge the gap between imaging and pathology and provide a promising biomarker for clinical trials.

14. Conclusion

Understanding disability accumulation is the corner stone of effective management in MS patients. The greatest proportion of disability accumulation is not accounted for by new lesions or relapses hence the term PIRA. The availability of ultra-high-field imaging allowed further exploration of factors associated with PIRA to facilitate the development of targeted disease-modifying treatments in MS. Cortical lesion load contributes to the degree of disability and they need to be taken into consideration during treatment decision-making. Similarly, white matter iron rim lesions frequency is a significant prognostic factor in MS patients, with studies showing that patients who had more than four lesions were more likely to experience future worsening disability. However, this worsening degree of disability was rendered to the higher degree of tissue loss in some iron rim lesions and their evolution into slowly expanding lesions. Further elucidation of the extent of association between those factors and future disability is crucial for the potential evolution of biomarkers to facilitate the development of targeted disease-modifying treatments in MS clinical trials.

Author details

Rasha Abdel-Fahim
Nottingham University Hospitals, Nottingham, UK

*Address all correspondence to: rasha.fahim@doctors.org.uk

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