Chapter 6

CURRENT NEUROIMAGING STRATEGIES ON MULTIPLE SCLEROSIS

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INTRODUCTION

Multiple sclerosis (MS) was first described in 1868 by Jean-Martin Charcot a French neurologist. It is the most common autoimmune disorder of the central nervous system. The incidence is about 2.5/100,000 per year (1). Young/middle-age, female gender, Epstein–Barr virus positivity, HLA-DR 15 positivity, obesity, vitamin D deficiency, smoking and geographical factors are described as predisposing factors (2, 3). It is defined as a chronic neurodegenerative disease characterized by disruption of the blood-brain barrier due to autoimmune inflammation around the venules, with involvement of oligodendrocytes, myelin sheath and less frequently axons. In the affected area, focal inflammation, active myelin breakdown, demyelination, axonal loss and gliosis with associated volume loss occur. The first episode of the disease is defining as clinical isolated syndrome (CIS) (4). It occurs either acutely or subacutely, with a duration of at least 24 hours, and in the lack of fever or infection status. It can be monofocal or multifocal. 30-60% of CIS develop into MS. Optic neuritis, pons, bulbus, cerebellar involvement or partial involvement of spinal cord are the most frequently forms of CIS. On the other hand, the presence of lesions that were detected clinically for other reasons and incidentally detecting on Magnetic Resonance Imaging (MRI), and suggestive of MS is named as radiological isolated syndrome (5).

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CLINICAL CLASSIFICATION

- Relapsing-remitting MS is the most common form which accounts for 70-85 % of the patients (F>M). It progresses with periodic symptoms and complete recovery.
- Seconder progressive MS: The 80% of relapsing-remitting patients progress to seconder progressive form.
- Primary progressive MS: It is a rare form of MS and includes 10% of patients (F=M). Remission is not observed in this group, and it shows a progressive course with relapses.
- Atypical presentation such as Marburg, Schilder, Balo, Devic, Tumefactive forms.

Marburg form of multiple sclerosis, also called Acute Malignant Multiple Sclerosis is defined as severe and fulminant acute demyelination, that frequently results in mortality within one year of the onset of clinical symptoms. The MRI findings show extensive confluent areas of tumefactive demyelination characterized by defined rings or incomplete ring enhancement which causes mass effect (6). Schilder disease, is an extremely rare progressive form of MS that occurs in childhood. There have been less than 10 cases reported in the literature. The disease is characterized by 1-2 massive demyelinating plaques with >2 cm diameter which are hyperintense on T2-weighted (T2W) imaging in each cerebral hemisphere (7). Tumefactive MS is a variant which manifests as a relatively large intra-parenchymal lesion. Contrary to expectations, less mass effect is observed on MRI. Unlike gliomas or abscesses, it may show some peripheral enhancement, often with an incomplete ring.

Benign MS is observed in 15-20% of all MS cases. Patients generally remain functionally active for more than 15 years.

The course of the disease is scored with the Expanded Disability Status Scale (EDSS) in current clinical practice. It is a method for evaluating impairment in MS and tracking changes in disability level over time. It has been commonly used in clinical investigations and in the evaluation of patients with MS. It is based on the clinical evaluation of many regions of the central nervous system, including the pyramidal, cerebellar, brainstem, bowel, and bladder functions, ocular functions etc. by the neurologist. According to EDDS, the cases are

scored from the normal neurologic examination to the confined to bed and totally dependent form. However, since the subjective nature of the neurological examination and insufficiently evaluated variables, such as emotion, cognitive function, and quality of life, EDSS scores can differ. Steroids, disease-modifying agents, and autologous hematopoietic stem cell transplantation are all used in the treatment. There are some specific complications such as Progressive multifocal leukoencephalopathy (PML), Jacob-Crutzfield virus encephalopathy, meningitis (8) and primary CNS lymphoma should be considered in screening examinations.

When normal clinical signs are present, diagnose is easy; however, if the findings are nonspecific or atypical, several auxiliary tests are required. MRI is the primary modality to support clinical MS diagnosis, and it can replace some clinical criteria in revealing the CNS abnormalities (9,10). MRI also plays a major role in the differential diagnosis of MS mimicking lesions. In addition, it is indispensable in the follow-up of the diagnosed patients and in the evaluation of the response to treatment.

The radiological diagnostic criteria for MS focus on the shape and localization of the white matter lesions (WML), as well as the dissemination of the lesions in space (DIS) and dissemination of the lesions in time (DIT), although these findings alone are insufficient to distinguish MS from other disorders. However, typical findings such as WML at different ages, Dawson's fingers, cortical lesions (highly specific for disease), eccentric spinal cord lesions can strongly support the diagnosis of MS (10-12). Also the temporal lobe involvement is a specific finding.

MRI findings of brain

- Acute period: The plaques are hyperintense, ovoid-shaped lesions with a long axis less than 3 mm on T2W and Fluid attenuation inversion recovery (FLAIR) series. In the first 4-6 weeks of the active plaque period, contrast enhancement is observed due to perivenular inflammation and disruption of the blood-brain barrier (13).
- In the subacute period, due to perilesional edema, ring or rim-like contrast enhancement can be observed on postcontrast T1-weighted (T1W) series (14). Almost 80% of acute MS plaques are hypointense on unenhanced T1W, and half of the lesions progress into permanent low T1W "Black dotes" indicating axonal damage and scar tissue (13) (Figure 1).

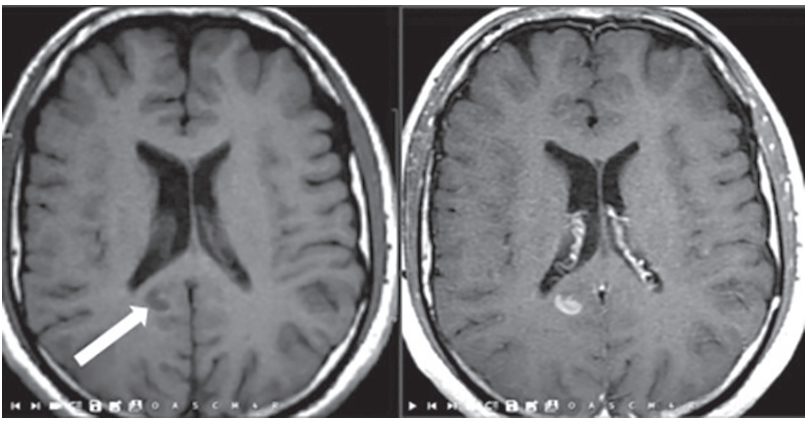

Figure 1. Axial T1W image demonstrates pericallosal "Black dot" lesion (arrow) and same lesion shows incomplete ring-like contrast enhancement on the right.

Chronical period: The lesions are seen as hypointense on T1W and hyperintense (White dot) on T2W, and are not enhanced due to gliosis developing in the chronic period (15). During this period, T2W hyperintense plaques eventually coalesce into confluent areas of signal abnormalities.

The common finding on MR spectroscopy is that the Relapsing-remitting MS switched to Seconder progressive MS during the disease course, N-Acetyl-L-aspartate peaks tend to the shortening (16).

Spinal Findings on MRI

Except for Acute Disseminated Encephalomyelitis (ADEM), Sarcoidosis, and Neuromyelitis Optica Spectrum Disorder (NMOSD), spinal cord lesions are uncommon in most other neurological disorders. Typical spinal cord lesions of MS are small and peripherally localized. The length of the lesions is less than two vertebral segments. The presence of a spinal cord lesion in combination with a cerebellar or brainstem lesion is a reliable predictor of MS. Also the brainstem lesions are small/peripheral and asymmetrically located. The cerebellar peduncle, pons are most affected brainstem regions (17).

Current Findings

The central vein sign is recognized as a key marker for diagnosis. In the presence of this biomarker, which represents the pathophysiology of the disease explained by perivenular inflammation, MS should be considered rather than MS mimics.

Susceptibility Weighted Imaging (SWI) performed with 3T technology could identify central vein signals in 45% of lesions (19, 20) (Figure 2).

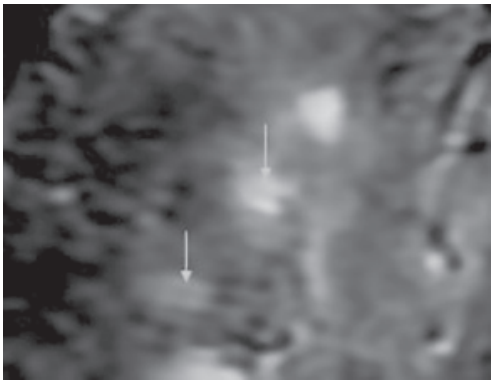

Figure 2. Figure shows the "Central vein sign" on SWI.

Paramagnetic rim, which is observed in SWI with 3 T MRI and represents chronic active lesions, is another powerful biomarker with the potential of distinguishing MS. Although access to 3 T technology including SWI is limited, this finding can also be detected with 1.5 T devices (20, 21) (Figure 3).

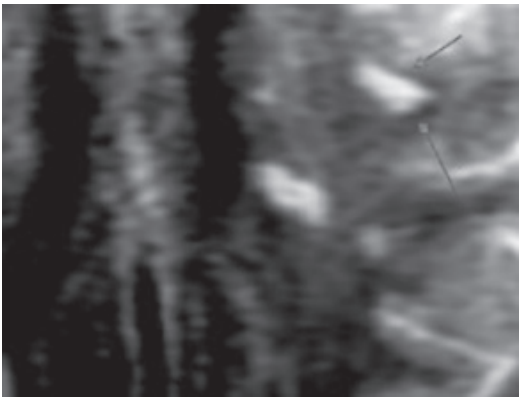

Figure 3. Paramagnetic rim sign on SWI.

Another feature is the Dot-dash sign, which is considered to be an early sign of MS with its typical appearance around the corpus callosum (22).

The presence of cortical plaques, which play a major role in the diagnosis of MS, can be easily demonstrated with sequences such as Double Inversion Recovery (DIR).

The use of volumetric studies, which can show the decrease in brain volume that may occur in the chronic phase of MS, is non-routine and can be done for research purposes.

Differential Diagnosis

Small vessel disease: MS has a broad differential diagnosis that includes nearly all white matter diseases. Small vessel disease (SVD) is the most prevalent in differential diagnosis. If a patient is clinically suspected of having MS and at least three WMLs are discovered in the periventricular white matter, the main issue should be establishing the differentiation between MS and SVD, which is the more common condition in daily practice. While MR diagnostic criteria focus on DIS and DIT with current imaging developments which not enough on its own to distinguish from MS mimics. However, there are too many differential diagnosis findings of SVD as shown Table 1.

Table 1. Differential findings of MS and SVD

MS	SVD
Black dot on T1W	Isointense on T1W
Ovoid form	Round form
Presence of temporal lobe involvement	Temporal lobe involvement is not observed
CC involvement	CC involvement is not observed
Presence of the lesions perpendicular to the CC	Absence/ presence of the lesions to perpendicular to the CC
Presence of juxtacortical lesions	Subcortical lesions
Hyperintensity on DWI	No hyperintensity on DWI
Contrast enhancement (activation sign)	No enhancement

Abbreviations: DWI: Diffusion weighted imaging, CC: Corpus callosum

Acute Disseminated Encephalomyelitis: The disease is defined by monophasic acute inflammation and demyelination which typically occurs after a viral infection or vaccination. There are frequently diffuse and relatively

symmetrical lesions in the supratentorial and infratentorial white matter, which may enhance at the same scan. The basal ganglia and thalami are usually involved (23).

Neuromyelitis Optica Spectrum Disorder: This is a demyelinating disease induced by antibodies against aquaporin 4 and myelin oligodendrocyte glycoprotein (MOG) that usually affects the optic nerves and spinal cord. MOG-related demyelination is usually defined by hazy, large T2 lesions and affects long segments of bilateral optic nerves. including intraorbital segments. Unlike MS, cord lesions are described as longitudinally extensive myelitis (more than 3 vertebral segments) with low T1W-signal intensity and involve the central gray matter of the cord, usually including the conus. As a result, cord and orbital imaging play an important role, particularly in children with visual problems.

The 2017 McDonald criteria can reliably identify pediatric MS in children as young as 11 years old. For the first attack of relapsing-remitting MS, these criteria provide the same sensitivity and specificity as for adult-onset illness (24).

MAGNIMS Studies

The Magnetic Resonance Group in Multiple Sclerosis (MAGNIMS), which was established to solve common problems in the diagnosis and follow-up of MS, has been working for last decades. Main aims of this group are that:

- To revise the imaging markers of common MS mimicking diseases.
- To identify disease-specific findings using SWI, DIR, proton magnetic resonance spectroscopy, magnetization transfer ratio, and diffusion tensor imaging.
- To study the role of current sequences in the identification of unusual MS mimics. McDonald diagnostic criteria were revised in 2017, within the recommendations they presented in 2015 workshop of MAGNIMS in Milano. As a result of these studies;

1. The coexistence of age-related changes and vascular changes in patients with MS poses certain diagnostic challenges.
2. Features are described that distinguishing the MS from NMOSD and ADEM.
3. New markers of the latest MRI techniques have been accepted as disease-specific findings (eg, Central vein sign, Dot-dash sign).

Proposed revisions for the 2010 McDonald criteria for MRI in the diagnosis of MS are: 1. The optic neuritis was added to the diagnostic criteria (because 25% of CIS patients have optic neuritis). 2. The number of white matter T2W hyperintensities on the periventricular area should be at least 3 for the DIS positivity since the most common incidental finding on brain MRI is related to SVD due to myelin loss and gliosis. 3. Intracortical location was also added together the previous juxtacortical location because it is also observed in the recent pathology specimens of patients with MS (10) (Figure 4).

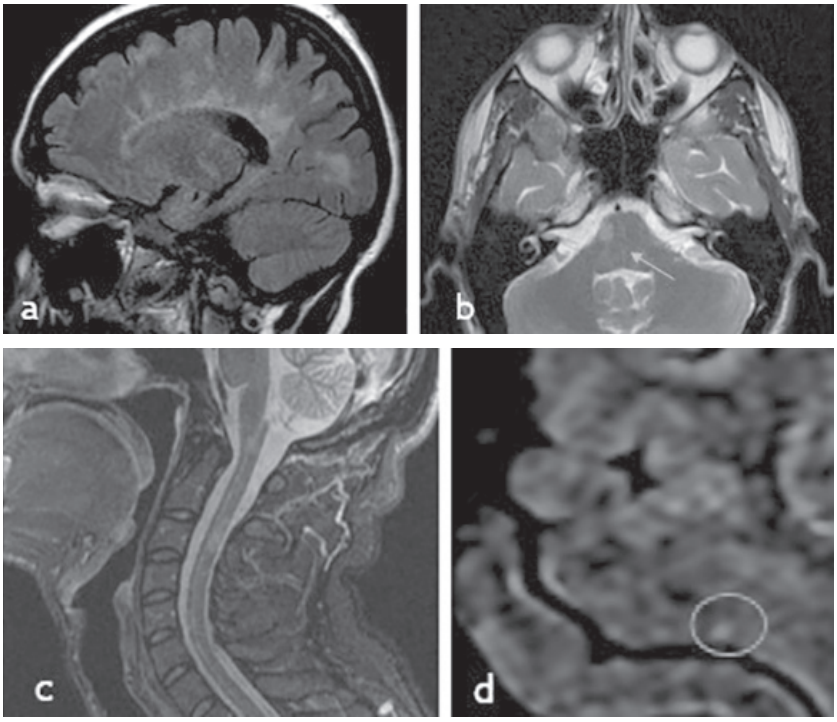

Figure 4. The figures show 4 different localization of plaques as periventricular (a), infratentorial (b), spinal cord (c) and intracortical (d) classified for DIS.

McDonald criteria were updated in 2017 to meet these recommendations. According to these, the presence of DIS should be confirmed by the presence of one or more lesions in at least two of the four regions as periventricular, juxtacortical/intracortical, infratentorial, and spinal cord. Additionally, for the presence of DIT, the new T2W lesion or the presence of contrast-enhancing

lesions; the presence of contrast enhancing and non-enhancing lesions at the same time (Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required), and the presence of oligoclonal band in cerebrospinal fluid should be confirmed (25).

MAGNIMS, Consortium of Multiple Sclerosis Centers and North American Imaging in Multiple Sclerosis Cooperative published their consensus report which was revealed the research findings to improve the use of MRI for diagnosis, prognosis, and monitoring of in patients with MS on June 14, 2021 (26). They worked on recommendations on changes to MRI protocols, the safely use of Gadolinium-based contrast agents, the correct use of MRI in patients with MS in childhood, pregnancy, and lactation, and reporting standardization. They reported that 3T has no added value above 1.5 T for the detection of brain lesions at the time of diagnosis, as long as scans are of high quality with an appropriate signal-to-noise ratio and spatial resolution. Furthermore, three-dimensional (3D) acquisition techniques (FLAIR and T1W sequences) have been suggested as a strong alternative to two-dimensional acquisitions due to their role in improving both lesion detection and accuracy of anatomic detailing for detecting new lesions. However, in cases where this technology is not available, 0.3 mm slice thickness and no gaps between the slices are recommended as a good alternative.

MAGNIMS Recommendations

- **Brain imaging:** Axial T2W, 3D T2 FLAIR (1 mm isotropic) or 3 mm contiguous and axial or 3D post-contrast T1W series should be taken in brain examinations, however precontrast T1W series is not required (Table 2). However using contrast agent are optional for the evaluation of disease activity and monitoring the effectiveness of the disease-modifying treatment and PML screening. Post-contrast images should be taken at least 5 minutes, ideally 10 minutes after contrast administration. The brain scan should be covering the whole brain (including the cervical cord). Spinal scanning should be covering the whole thoracolumbar spinal cord including conus. Suggested slice thickness for the brain on 3D imaging, 1 mm isotropic is suggested but, if over contiguous (through plane and in-plane), not >1,5 mm, with 0·75 mm overlap; for 2D imaging, 3 mm with no gap (except for diffusion-weighted imaging, for which the slice thickness should be ≤ 5 mm with a 10–30% gap) is preferred. Suggested

ın-plane resolution is 1 mm × 1 mm for all three regions. Sequences such as DIR or phase-sensitive inversion recovery, were included in the 2017 revisions of the McDonald criteria to show DIS, as they facilitate the visibility of cortical MS lesions. DIR is a special sequence that contains an inversion pulse that simultaneously suppresses cerebrospinal fluid and WM. In this sequence, a precise anatomical boundary is created on the surface between the cortex and the subcortical WM, making it easier to detect cortical lesion. The central vein sign detecting in the SWI series, is a powerful diagnostic marker, but its use is optional since this technology is not common on worldwide. While diffusion restriction may develop as a result of the destroyed blood-brain barrier in the plaques, it should not be considered as an activation. Diffusion weighted imaging is only recommended in drug-induced PML screening. The use of high-resolution T1W studies for the use of brain volume measurements is mostly for research purposes and its use is optional.

- **Optic nerve imaging** is recommended as "optional" if there are symptoms in the initial scans performed for MS diagnosis. However it is not recommended in follow-up. It could be taken for the differential diagnosis of CIS (Atypical recurrent isolated optic neuritis, etc.), other diseases causing optic neuritis to exclude alternative diagnoses such as NMO spectrum or anti-MOG disease. In the follow-up, it could be performed to exclude comorbidity in newly developing vision problems. Axial and coronal fat-suppressed T2W sequences or Short Tau Inversion Recovery and post-contrast imaging of the optic nerve are suggested. Slice thickness should be 2–3 mm with no gap on axial series.
- **Spinal cord imaging**: Since asymptomatic spinal cord lesions can be seen frequently in CIS, whole spinal MRI including conus medullaris should be performed in the initial examination for diagnosis. Slice thickness should be ≤3 mm with no gap on sagittal slices and should be ≤5 mm with no gap on axial slices. While performing of three different sagittal series including the Short Tau (inversion time) Inversion Recovery sequence is mandatory. Axial series are recommended because small and peripheral lesions may be overlooked in sagittal sections. In spinal examinations, postcontrast sagittal series should be taken after brain scanning (Table 2). Scanning of the spinal cord can be considered optionally in the assessment of disease activity and monitoring of the effectiveness of the disease-modifying treatment. However, it is not required for the screening of drug-induced PML.

Table 2. Recommended MRI protocols					
Brain	3D T1W (O.)	2D TSE T2W*	DWI (O.)	3D T2W FLAIR*	2D or 3D CE T1W (O)
Spinal	2DTSE T2W [Sagittal and axial(S)]	2DTSE PDW or 2D STIR		2D CE T1W (S)	

Abbreviations: FLAIR: Fluid attenuation inversion recovery * Axial 2D FLAIR could be alternative. TSE: Turbo spin echo, PDW: Proton density weighted, STIR: Short tau inversion recovery, DWI: Diffusion weighted imaging, CE: Contrast-enhanced, O: Optional, S: Only in selected case

Contrast use recommendations: For the safely using of Gadolinium, it is recommended to minimize and use a single dose (not double or triple dose) if it is possible. Contrast should be used before starting or switching disease-modifying treatment. It is not recommended for the first control examination after 3-6 months of diagnosis except for the severely active disease at the base scan or occurrence of an unexpected disease activation. Annual follow-up scans should be non-contrast in routinely. If there is a presence a suspect of disease activation, it should not be used before 6 months. Contrast can be used optionally in patients with high lesion burden in follow-up examinations. PML is not recommended for screening. It is strictly contraindicated in pregnancy, it should not be used in lactation unless necessary.

Reporting recommendations: The features contrary to the MS diagnosis should be described in the report. If the number of T2 lesions for the brain is less than 20, the exact number should be specified, if it is more, it should be reported as between 20-50 or 50-100. For the spinal cord, exact number should be given if it is less than 10. Cortical lesions should be identified separately (with juxtacortical lesions). Active (new or increasing size) T2 lesions should be reported. If the lesion load is high, it should be reported using subtraction and fusion techniques.

PML: MS patients with high antibody levels (>0.9) who are Jacob-Crutzfield seropositive and treated with natalizumab for 18 months are in the risk group and should be scanned with FLAIR and diffusion weighted imaging every 3-4 months. Contrast should be used in the case of PML suspicion on follow-up.

Child age, pregnancy and lactation: In pediatric patients, the adult protocol should be used in the diagnosis, the brain and the whole spinal cord are included. If there is clinical suspicion of NMO or Anti-MOG, the optic nerve should also be examined. Contrast agent and MRI over 1.5 T are contraindicated in pregnant women. In case of lactation, if necessary, macrocyclic agents should

be used. The presence of a new or large T2 lesion should be preferred for the diagnosis of active disease.

In recent years, studies have been spread on topics such as automatic MS diagnosis, prediction, quantification, follow-up of the disease, and distinguishing MS from mimicking disorders with the help of developing artificial intelligence technology. In fact, evaluations such as automatic brain volume measurement and automatic MS lesion segmentation can be performed with machine learning and deep learning algorithms such as Icometrix, NeuroQuant, and Quantib with 90% accuracy and advances in artificial intelligence methods of diagnosing and monitoring MS which are expected to change drastically (27).

CONCLUSION

The most important contribution of these valuable reports to MS imaging is the limitation of Gadolinium use in first-control brain MRI and follow-up scans. The other is that the development and dissemination of new sequences such as SWI, DIR and the integration of volumetric evaluation and deep learning algorithms into imaging which are important in determining treatment preferences and follow-up. Reporting standardization plays an essential role in ensuring the effectiveness of treatment by using a common language in clinician-radiologist cooperation. Finally, recommendations regarding the careful and appropriate use of contrast agents in children and pregnant women are very valuable decisions in terms of public health.

REFERENCES

1. World Health Organization (2008). *Atlas: Multiple Sclerosis Resources in the World* 2008. Geneva: World Health Organization. pp. 15–16.
2. Sarbu, N., Shih, R. Y., Jones, R. V., et al. White Matter Diseases with Radiologic-Pathologic Correlation. *Radiographics*: a review publication of the Radiological Society of North America, Inc, 2016; 36(5): 1426–1447. https://doi.org/10.1148/rg.2016160031.
3. Valery N. Kornienko, I.N. Pronin. *Diagnostic Neuroradiology*. (2008) ISBN: 9783540756521.
4. Gaillard F, Yap J, Sharma R, et al. Multiple sclerosis. Reference article, *Radiopaedia.org* (Accessed on 09 Feb 2023) https://doi.org/10.53347/rID-1700.
5. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology*. 2009;72(9):800-805. doi:10.1212/01. wnl.0000335764.14513.1a

6. Sarbu N, Shih RY, Jones RV, et al. White Matter Diseases with Radiologic-Pathologic Correlation. *Radiographics*. 2016;36(5):1426-1447. doi:10.1148/rg.2016160031.
7. Kurul S, Cakmakçi H, Dirik E, et al. Schilder's disease: case study with serial neuroimaging. *J Child Neurol*. 2003;18(1):58-61. doi:10.1177/08830738030180011301
8. McNamara C, Sugrue G, Murray B, et al. Current and Emerging Therapies in Multiple Sclerosis: Implications for the Radiologist, Part 2-Surveillance for Treatment Complications and Disease Progression. *AJNR Am J Neuroradiol*. 2017;38(9):1672-1680. doi:10.3174/ajnr. A5148.
9. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol*. 2011;69(2):292-302. doi:10.1002/ana.22366.
10. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol*. 2016;15(3):292-303. doi:10.1016/S1474-4422(15)00393-2.
11. Toledano M, Weinshenker BG, Solomon AJ. A Clinical Approach to the Differential Diagnosis of Multiple Sclerosis. *Curr Neurol Neurosci Rep*. 2015;15(8):57. doi:10.1007/s11910-015-0576-7.
12. Chen JJ, Carletti F, Young V, et al. MRI differential diagnosis of suspected multiple sclerosis. *Clin Radiol*. 2016;71(9):815-827. doi:10.1016/j.crad.2016.05.010
13. Tillema JM, Pirko I. Neuroradiological evaluation of demyelinating disease. *Ther Adv Neurol Disord*. 2013;6(4):249-268. doi:10.1177/1756285613478870.
14. Ge Y. Multiple sclerosis: the role of MR imaging. *AJNR Am J Neuroradiol*. 2006;27(6):1165-1176.6.
15. Truyen L, van Waesberghe JH, van Walderveen MA, et al. Accumulation of hypointense lesions ("black holes") on T1 spin-echo MRI correlates with disease progression in multiple sclerosis. *Neurology*. 1996;47(6):1469-1476. doi:10.1212/wnl.47.6.1469.
16. Aboul-Enein F. MR spectroscopy in multiple sclerosis - a new piece of the puzzle or just a new puzzle. *Magnetic Resonance Spectroscopy*. InTech 2012; 3:47-72. https://doi.org/10.5772/32340.
17. Brownlee WJ, Hardy TA, Fazekas F, et al. Diagnosis of multiple sclerosis: progress and challenges. *Lancet*. 2017;389(10076):1336-1346. doi:10.1016/S0140-6736(16)30959-X.
18. Maggi P, Absinta M, Grammatico M, et al. Central vein sign differentiates Multiple Sclerosis from central nervous system inflammatory vasculopathies. *Ann Neurol*. 2018;83(2):283-294. doi:10.1002/ana.25146.
19. Kilsdonk ID, Wattjes MP, Lopez-Soriano A, et al. Improved differentiation between MS and vascular brain lesions using FLAIR* at 7 Tesla. *Eur Radiol*. 2014;24(4):841-849. doi:10.1007/s00330-013-3080-y.
20. Clarke MA, Pareto D, Pessini-Ferreira L, et al. Value of 3T Susceptibility-Weighted Imaging in the Diagnosis of Multiple Sclerosis. *AJNR Am J Neuroradiol*. 2020;41(6):1001-1008. doi:10.3174/ajnr. A6547.
21. Maggi P, Sati P, Nair G, et al. Paramagnetic Rim Lesions are Specific to Multiple Sclerosis: An International Multicenter 3T MRI Study. *Ann Neurol.* 2020;88(5):1034-1042. doi:10.1002/ana.25877.

22. Lisanti CJ, Asbach P, Bradley WG Jr. The ependymal "Dot-Dash" sign: an MR imaging finding of early multiple sclerosis. *AJNR Am J Neuroradiol*. 2005;26(8):2033-2036.
23. Tenembaum SN. Acute disseminated encephalomyelitis. *Handb Clin Neurol*. 2013;112:1253-1262. doi:10.1016/B978-0-444-52910-7.00048-9
24. Fadda G, Brown RA, Longoni G, et al. MRI and laboratory features and the performance of international criteria in the diagnosis of multiple sclerosis in children and adolescents: a prospective cohort study. *Lancet Child Adolesc Health.* 2018;2(3):191-204. doi:10.1016/S2352-4642(18)30026-9
25. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi:10.1016/S1474-4422(17)30470-2.
26. Wattjes MP, Ciccarelli O, Reich DS, et al. 2021 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI in patients with multiple sclerosis. *Lancet Neurol*. 2021;20(8):653-670. doi:10.1016/S1474-4422(21)00095-8.
27. Wang C, Beadnall HN, Hatton SN, et al. Automated brain volumetrics in multiple sclerosis: a step closer to clinical application. *J Neurol Neurosurg Psychiatry.* 2016;87(7):754-757. doi:10.1136/jnnp-2015-312304.