Review Article

Systematic imaging review: Multiple Sclerosis

Aparna Katdare, Meher Ursekar

Department of Neuroradiology, Sir HN Reliance Foundation Hospital, Mumbai, Maharashtra, India

Abstract

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system characterised by immune-mediated demyelination, and is a leading cause of neurological disability worldwide. It has a wide spectrum of clinical presentations which overlap with other neurological conditions many times. Further, the radiological array of findings in MS can also be confused for multiple other conditions, leading to the need to look for the more typical findings, and interpret these in close conjunction with the clinical picture including temporal evolution. This review aims to revisit the MRI findings in MS, including recent innovations in imaging, and to help distinguish MS from its mimics.

Key Words

MRI, MS, mimics

For correspondence:
Dr. Meher Ursekar, Department of Neuroradiology, Sir HN Reliance Foundation Hospital, Mumbai, Maharashtra India.
E-mail: meherursekar@gmail.com

Ann Indian Acad Neurol 2015;18 (Supplement 1):S24-S29

Introduction

Multiple sclerosis (MS) is a chronic, inflammatory disease of the central nervous system characterised by immune-mediated demyelination. It has for long been recognised among the leading causes of neurological disability in the West. Its diagnosis in India has also been reported to be on the rise, with the Multiple Sclerosis International Federation estimating a prevalence of 3/100000 for India.[1]

Clinical Profile

Typically a disease of young adults (although onset in childhood and late adulthood is well-recognised), MS has a myriad clinical course in different individuals, leading to terminologies which can be slightly confusing. In about 85% of cases, there is a "relapsing-remitting (RR)" course, with presence of a clinically isolated syndrome (CIS) of the optic nerve, brain stem or spinal cord.[2] When the deficits become progressive without remissions, the term "secondary progressive (SP)"MS is used.[3] If MS is progressive right from the onset, the term used is "Primary Progressive (PP)"MS.[4] A fourth rare variety is the "progressive relapsing (PR)"MS, which is characterised by progressive course with acute relapses.[3] In "Benign" MS (BMS), there is no or minimal disability for a long period after the initial episode,[5] while "malignant" MS is rapidly progressive into disability or death.[3] Additionally, there is an imaging entity of "radiologically isolated syndrome" where T2 hyperintense brain lesions are incidentally diagnosed on MRI in asymptomatic individuals.[6]

MRI Findings as Criteria to Diagnose MS

Over years, many criteria have been developed and revised for diagnosis of MS, with the radiologically pertinent landmark revision coming in 2001, when McDonald *et al*. formally included MR imaging features in the diagnostic criteria.[7] Demonstration of lesion dissemination in time and space

Access this article online

Quick Response Code:

Website: www.annalsofian.org

DOI: 10.4103/0972-2327.164821

How to cite this article: Katdare A, Ursekar M. Systematic imaging review: Multiple Sclerosis. Ann Indian Acad Neurol 2015;18:24-9.

Received: 07-07-15, **Revised:** 06-08-15, **Accepted:** 05-08-15

with exclusion of other conditions is the basis of these criteria, which have been periodically revised, the latest criteria being proposed by the European Multicenter Collaborative Research Network for Magnetic Imaging in MS in 2010.[8] As per this revision, the criteria for dissemination in space are "one or more lesion in each of two or more characteristic locations: periventricular, juxtacortical, posterior fossa, spinal cord; all lesions in symptomatic regions, excluded in brain stem and spinal cord syndromes"; and the criteria for dissemination in time are "simultaneous presence of asymptomatic gadolinium-enhanced and non-enhanced lesions at any time, or a new T2 and/or gadolinium-enhanced lesion on follow-up MR images irrespective of timing of baseline study". Aided with technological advances, MRI is now the most crucial paraclinical tool for evaluating MS, helping establish diagnosis and disease burden, mapping temporal changes and monitoring treatment response in clinical trials.[9]

MRI Findings

Conventional MRI

The classical findings in MS include high T2 signal lesions of varied sizes and shapes, ovoid lesions historically considered more specific, correlating to the pathological findings of perivenular inflammation (Dawson's fingers)[10] [Figure 1]. Lesions in Periventricular location [Figure 2] along the 4th ventricle and temporal horns and in midbrain and Cerebellar peduncle [Figure 3], although less prevalent, are more specific for MS.[11] Apart from periventricular region, the corpus callosum, subcortical region, brain stem subcortical U-fibres, optic nerves and visual pathway are also commonly involved.[9] The location of these lesions at the calloso-septal interface on sagittal sequences has been reported to have a very high sensitivity and specificity for differentiating MS from vascular disease.[12] Some lesions are tumefactive and may be confused for tumours. The lesion burden is reported to be higher in SPMS as compared to BMS, RRMS and PPMS.[13] However, there is very poor correlation between T2 hyperintense lesion load and disability,[14] and therein lies its limitation.

Gray matter (GM) involvement is also well-established for long.[15] Double inversion recovery MR sequences, which suppress signal from white matter and cerebrospinal fluid (CSF) are used to detect these lesions which appear hyperintense; further, these are reportedly more common in SPMS than in CIS or RRMS.[16] The lesion load is associated with disability progression and cognitive impairment.[17,18]

Magnetisation transfer imaging

Magnetisation transfer imaging involves arriving at the magnetisation transfer (MT) ratio, which is calculated by using gradient-echo or spin-echo imaging with and without an off-resonance saturation pulse. The MT ratio has been proved to depict extent of tissue structure disruption.[19] Many of the T2 hyperintense lesions are seen to have low T1 signal — "black holes", which were speculated to be the most demyelinated regions, thus reflecting the grade of the lesion, when correlated with MT ratio.[20] A decrease in MT ratio is also observed in normal-appearing white matter (NAWM), and in fact is seen weeks before new lesions are appreciated; this is more severe in progressive phenotypes.[19] Conversely, an increase in this ratio was found in remyelination in a study by Chen *et al*., where different temporal patterns were found in demyelination and remyelination after enhancement.[21]

Brain volume morphometry

Average brain volume reduction in MS is 0.7-1% per year[22] and is best seen on T1-weighted sequences. Atrophy quantification

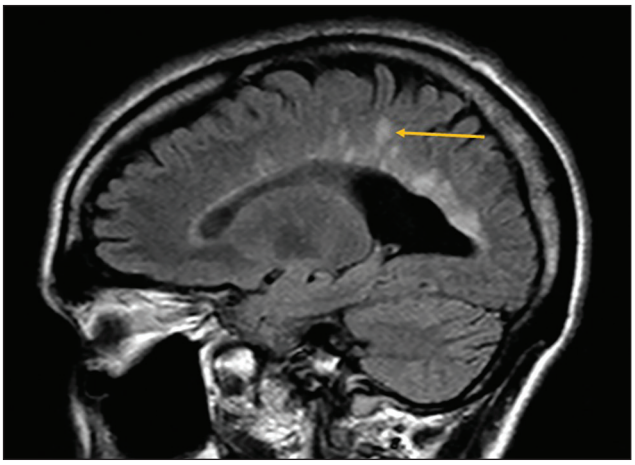

Figure 1: Sagittal T2 FLAIR image reveals 'Dawson's fingers' (arrow), which are demyelinating plaques at callososeptal location, running at right angles along medullary veins, due to perivenular inflammation

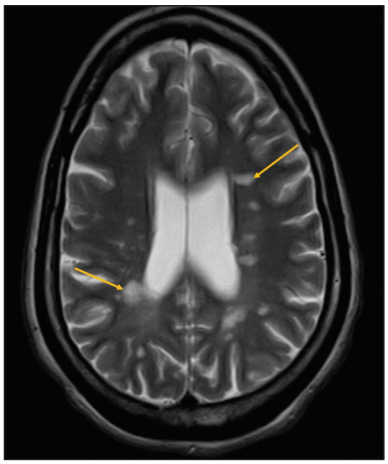

Figure 2: Axial T2 image shows hyperintense lesions (arrows) in the periventricular location along bilateral lateral ventricles

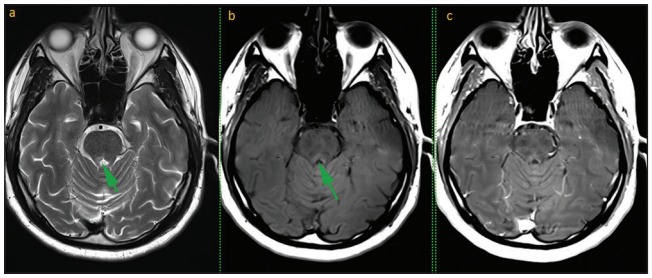

Figure 3: Axial T2 (a), MT suppressed (b) and post-contrast (c) Axial images show lesion in the right superior cerebellar peduncle (arrows)

and distribution have been analysed by various studies, and it has been found that GM atrophy occurs early,[23] correlates with disability[24] and cognitive dysfunction[25] and progresses over a period of time,[26] and demonstrates regional variability according to the disease phenotype.[27]

Contrast enhancement

Enhancement of lesions on gadolinium contrast administration has been a traditional indicator of disease activity. Normal enhancement window in MS plaques is 2 to 8 weeks, but they can enhance even upto 6 months.[28] A combination of MT and 20-60 minute delayed scans with multiple doses has been found to detect more lesions.[29] A new exciting recent development has been the use of ultrasmall particles of iron oxide (USPIOs) as a contrast agent. These target the monocyte-macrophage system, and hence are indicators of cellular inflammatory reaction, in contrast to gadolinium enhancement of lesions, which is due to leaky blood-brain barriers. Also, enhancement by USPIOs may precede and may persist after gadolinium enhancement of lesions.[30] Thus, USPIOs can complement gadolinium contrast for MS imaging.

Iron deposition

Multifactorial non-heme iron deposition is seen in MS, seen as T2 hypointensities in basal ganglia, thalami, dentate nucleus and cortex, correlating with disability, cognitive impairment and progression.[31,32]

Optic neuritis

Imaging the optic nerve is an inherent part of any MRI study for MS. T2-weighted and STIR coronal sequences through the optic nerve, along with post contrast sequences are performed. Dilatation of the optic sheath along with sheath enhancement on T1-weighted contrast studies [Figure 4] is commonly found in acute optic neuritis.[33] The mean diffusivity in the diseased nerve was found to be higher than the contralateral eye in one study.[34]

Spinal cord affection

Spinal cord involvement is uncommon in the usual MS mimics such as inflammatory and hypoxic-ischemic disorders, and hence helps in distinguishing MS from these entities.[35] Spinal cord imaging is performed to rule out other conditions, and in established MS if there is suspicion of mechanical compression or atypical symptoms.[36] Cervical cord is the most common site of involvement, with peripheral WM affection, typically with less than 2 segment involvement [Figure 5] with cross-sectional area involvement of less than 50% and with no low T1 signal.[37] Use of T1-weighted IR imaging has been found to have increased lesion-to-normal appearing cord than STIR and fast spin echo images.[38]

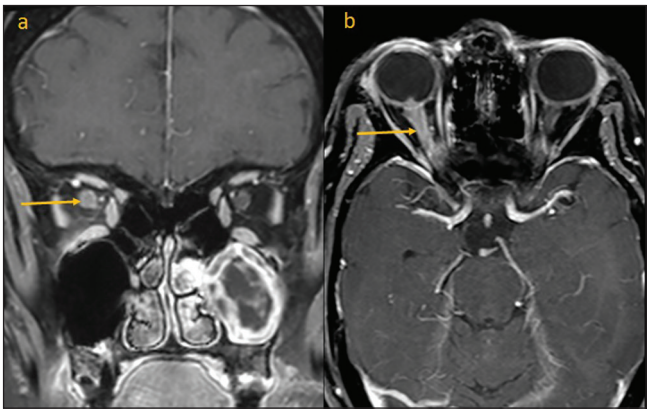

Figure 4: Coronal (a) and axial (b) post contrast T1 weighted images show thickening and asymmetric excessive enhancement of the right optic nerve (arrows)

MR spectroscopy

Proton MR Spectroscopy (MRS) is valuable in MS as the biochemical changes, which precede anatomical changes, are visible even in NAWM before lesion formation and the metabolite changes can be monitored in MS lesions over a period of time.[39] MRS can be single-voxel or multivoxel and the acquisition time can be reduced using echoplanar imaging (EPI) with parallel MR imaging [sensitivity encoding (SENSE)/ generalised autocalibrating partially parallel acquisitions (GRAPPA)] with radiofrequency (RF) coil arrays.[39] The hallmark of acute MS lesions is reduced NAA levels due to neuronal injury along with increased choline levels due to increased cell membrane turnover and lactate peaks due to metabolism of inflammatory cells.[39] Reduced NAA and choline and increased myoinositol levels have also been found in some studies in NAWM, cortex and subcortical GM.[40,41] The quantitative nature of MRS is useful for monitoring disease and response to therapy in MS. Although NAA/Cr ratio is commonly used for quantification,[42] absolute quantification is considered more desirable, with software packages available for the same.[39] MRS metabolite values, particularly decreased NAA,[43] and also decreased cortical glutamate-glutamine[44] and increased myoinositol[45] levels, have correlated with various disabilities in some studies. Whole brain NAA level measurements have been found to reduce faster than atrophy progression, and could be used as marker for disease progression.[46]

Diffusion tensor imaging

Diffusion Tensor Imaging (DTI) uses multidirectional diffusion-weighted magnetic field gradients to measure diffusion of water molecules. Abnormalities in mean diffusivity and fractional anisotropy (FA) values are seen in NAWM, cortex and deep GM nuclei very early in the disease, with worsened GM involvement over time, which in turn correlates with cognition impairment and hence is a disability predictor.[47,48] The CIS involvement is depicted as DTI abnormalities in respective regions, such as in optic radiations in optic neuritis and in the corticospinal tract in motor impairment.[49] Further, reduced FA values have been observed in NAWM which have only

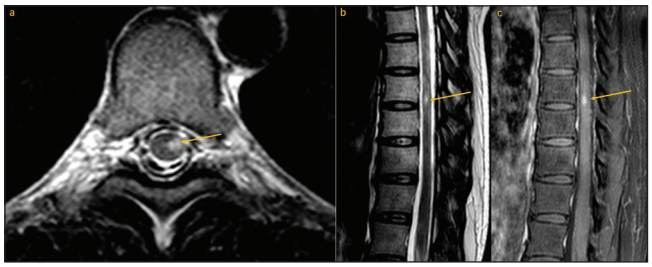

Figure 5: Axial (a) and Sagittal (b) T2 weighted images show hyperintense dorsal cord lesion (arrows) which enhances as seen on the T1 weighted sagittal image (c)

partially coincided with T2 hyperintense lesions, underlining the role of NAWM in cognitive disturbances.[50]

Perfusion weighted imaging

Perfusion weighted MRI reflects the vascular changes in MS, of vascular occlusion and fibrin deposits,[51] and these studies are performed either by administering gadolinium contrast with dynamic imaging or by arterial spin labelling which obviates need of an exogenous contrast. Apart from the increased perfusion in enhancing lesions, the real value of MR perfusion is in the decreased perfusion in NAWM, cortex and deep GM that has been observed in some studies to correlate with disability and neuropsychologic impairment.[52,53]

Functional MRI

Functional MRI (fMRI) in MS is based on the premise of brain plasticity, in which the brain adapts to axonal injury by several mechanisms to limit the functional loss.[54] The net result of axonal loss in MS is in the form of increased recruitment of parallel or latent pathways. The fMRI signal changes are blood oxygen level-dependent (BOLD), which in turn is related to the neuronal activity. Hence, in optic neuritis after recovery, in addition to the primary visual cortex, extensive visual network activation is seen, which includes claustrum, lateral temporal and posterior parietal cortices, and thalamus.[55] Similarly, at late stage motor involvement, in addition to the primary sensorimotor cortex, recruitment of higher order areas is seen even for simple tasks, as against their recruitment only for complex tasks in unaffected individuals.[56] In the spinal cord, the "signal enhancement by extravascular protons" (SEEP) effect is found more suitable than BOLD effect.[57] Combined fMRI and DTI measures have been studied to measure structural damage to WM.[58]

High field strength MRI

High field strength MRI studies at 7.0 Tesla have been found to better depict WM and GM lesions, to be more sensitive to iron induced local magnetic field shifts and improve quantitative, metabolic and fMRI studies.[59,60]

MS Mimics

MS mimics have to be ruled out by clinical, laboratory and paraclinical investigations, of which MRI is an important investigation.

Most of the hypoxic-ischemic vasculopathies show similar white matter T2 hyperintensities as in MS. In small vessel disease, sparing of the U-fibres, relative sparing of the corpus callosum, temporal lobe and cerebellum, more central involvement of brain stem, presence of lacunar infarcts and microbleeds and sparing of spinal cord are handy findings to distinguish it from MS.[61] In Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencepahalopathy (CADASIL), although there are subcortical and periventricular T2 hyperintensities like in MS, the presence of microbleeds and distended perivascular spaces, lack of lesion enhancement and sparing of the corpus callosum, cortex and extrapontine infratentorial brain parenchyma are useful distinguishing features.[61] Microhemorrhages are also seen in amyloid angiopathy.[62]

Among the inflammatory disorders, acute disseminated encephalomyelitis (ADEM) is particularly difficult to distinguish from first attack of MS in children. Its monophasic nature, affecting mostly children, following viral syndrome or vaccination, presence of encephalopathy, bilateral optic neuritis, relative sparing of periventricular regions and involvement of the thoracic cord[37,61] are some features which may help distinguishing it from MS. Neuromyelitis Optica (NMO) spectrum includes classic NMO, Asian opticospinal MS, longitudinally extensive myelitis, and ON or myelitis with brain lesions typical of NMO,[63] many of these entities overlapping with MS. In NMO, the cord affection is more profound on cross-section and extends over longer segments, while the brain lesions are more in the periventricular region along third ventricle and aqueduct, following the ependymal surface, and cortical lesions are rare.[61] Serum NMO IgG is diagnostic.[61]

A few other handy tips to rule out other MS mimics have been suggested by Aliaga *et al*. in a recent review.[61] Hereditary, metabolic and toxic disorders have a more symmetric involvement. Apart from Progressive Multifocal Leukoencephalopathy, U-fibres and juxtacortical lesions, very typical in MS, are not seen in infectious disorders or in adult onset leukoencephalopathies. Vasculitis and mitochondrial lesions tend to involve basal ganglia, which is uncommon in MS. Leptomeningeal enhancement is another feature of vasculitis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gupta S, Tewari AK, Nair V. Multiple Sclerosis: Indian Perspective. In: API India Medicine Update 2013. pp. 547-551. [Last accessed on August 17, 2015 from http://www.apiindia.org/medicine_update_2013/chap120.pdf].
2. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938-52.
3. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: Results of an international survey. National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Neurology 1996;46:907-11.
4. McAlpine D, Compston N. Some aspects of the natural history of disseminated sclerosis. Q J Med 1952;82:135-67.
5. Hawkins SA, McDonnell GV. Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors. J Neurol Neurosurg Psychiatry 1999;7:148-52.
6. Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, *et al*. Incidental MRI anomalies suggestive of multiple sclerosis: The radiologically isolated syndrome. Neurology 2009;72:800-5.
7. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, *et al*. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121-7.
8. Montalban X, Tintore M, Swanton J, Barkhof F, Fazekas F, Filippi M, *et al*. MRI criteria for MS in patients with clinically isolated syndromes. Neurology 2010;74:427-34.

9. Ge Y. Multiple sclerosis: The role of MR imaging. AJNR Am J Neuroradiol 2006;27:1165-76.
10. Horowitz AL, Kaplan RD, Grewe G, White RT, Salberg LM. The ovoid lesion: A new MR observation in patients with multiple sclerosis. AJNR Am J Neuroradiol 1989;10:303-5.
11. Grossman RI, McGowan JC. Perspectives on multiple sclerosis. AJNR Am J Neuroradiol 1998;19:1251-65.
12. Gean-Marton AD, Vezina LG, Marton KI, Stimac GK, Peyster RG, Taveras JM, *et al*. Abnormal corpus callosum: A sensitive and specific indicator of multiple sclerosis. Radiology 1991;180:215-21.
13. Thompson AJ, Miller DH, MacManus DG, McDonald WI. Patterns of disease activity in multiple sclerosis. BMJ 1990;301:44-5.
14. Filippi M, Rocca MA. Conventional MRI in multiple sclerosis. J Neuroimaging 2007;17(Suppl 1):3-9S.
15. Brownell B, Hughes JT. The distribution of plaques in the cerebrum in multiple sclerosis. J Neurol Neurosurg Psychiatry 1962;25:315-20.
16. Calabrese M, De Stefano N, Atzori M, Bernardi V, Mattisi I, Barachino L *et al*. Detection of cortical inflammatory lesions by double inversion recovery magnetic resonance imaging in patients with multiple sclerosis. Arch Neurol 2007;64:1416-22.
17. Calabrese M, Rocca MA, Atzori M, Mattisi I, Favaretto A, Perini P, *et al*. A 3-year magnetic resonance imaging study of cortical lesions in relapse-onset multiple sclerosis. Ann Neurol 2010;67:376-83.
18. Calabrese M, Agosta F, Rinaldi F, Mattisi I, Grossi P, Favaretto A, *et al*. Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. Arch Neurol 2009;66:1144-50.
19. Filippi M, Agosta F. Magnetisation transfer MRI in multiple sclerosis. J Neuroimaging 2007;17(Suppl 1):22-6S.
20. Hiehle JF Jr, Grossman RI, Ramer KN, Gonzalez-Scarano F, Cohen JA. Magnetisation transfer effects in MR-detected multiple sclerosis lesions: Comparison with gadolinium enhanced spin-echo images and non-enhanced T1-weighted images. AJNR Am J Neuroradiol 1995;16:69-77.
21. Chen JT, Collins JL, Atkins HL, Freedman MS, Arnold DL; Canadian MS/BMT Study Group. Magnetisation transfer ratio evolution with demyelination and remyelination in multiple sclerosis lesions. Ann Neurol 2008;63:254-62.
22. Miller DH, Barkhof F, Frank JA, Parker GJ, Thompson AJ. Measurement of atrophy in multiple sclerosis: Pathological basis, methodological aspects and clinical relevance. Brain 2002;125:1676-95.
23. De Stefano N, Matthews PM, Filippi M, Agosta F, De Luca M, Bartolozzi ML, *et al*. Evidence of early cortical atrophy in MS: Relevance to white matter changes and disability. Neurology 2003;60:1157-62.
24. Prinster A, Quarantelli M, Lanzillo R, Orefice G, Vacca G, Carotenuto B, *et al*. A voxel-based morphometry study of disease severity correlates in relapsing — Remitting multiple sclerosis. Mult Scler 2010;16:45-54.
25. Amato MP, Portaccio E, Goretti B, Zipoli V, Battaglini M, Bartolozzi ML, *et al*. Association of neocortical volume changes with cognitive deterioration in relapsing-remitting multiple sclerosis. Arch Neurol 2007;64:1157-61.
26. Valsasina P, Benedetti B, Rovaris M, Sormani MP, Comi G, Filippi M. Evidence for progressive gray matter loss in patients with relapsing-remitting MS. Neurology 2005;65:1126-8.
27. Riccitelli G, Rocca MA, Pagani E, Rodegher ME, Rossi P, Falini A, *et al*. Cognitive impairment in multiple sclerosis is associated to different patterns of gray matter atrophy according to clinical phenotype. Hum Brain Mapp 2011;32:1535-43.
28. Harris JO, Frank JA, Patronas N, McFarlin DE, McFarland HF. Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: Implications for clinical trials and natural history. Ann Neurol 1991;29:548-55.
29. Silver NC, Good CD, Barker GJ, MacManus DG, Thompson AJ, Moseley IF, *et al*. Sensitivity of contrast enhanced MRI in multiple sclerosis: Effects of gadolinium dose, magnetisation transfer contrast and delayed imaging. Brain 1997;120:1149-61.
30. Vellinga MM, Oude Engberink RD, Seewann A, Pouwels PJ, Wattjes MP, van der Pol SM, *et al*. Pluriformity of inflammation in multiple sclerosis shown by ultra-small iron oside particle enhancement. Brain 2208;131:800-7.
31. Neema M, Stankiewicz J, Arora A, Dandamudi VS, Batt CE, Guss ZD, *et al*. T1- and T2-based MRI measures of diffuse gray matter and white matter damage in patients with multiple sclerosis. J Neuroimaging 2007;17(Suppl 1):16-21S.
32. Neema M, Arora A, Healy BC, Guss ZD, Brass SD, Duan Y, *et al*. Deep gray matter involvement on brain MRI scans is associated with clinical progression in multiple sclerosis. J Neuroimaging 2009;19:3-8.
33. Glisson CC, Galetta SL. Nonconventional optic nerve imaging in multiple sclerosis. Neuroimaging Clin N Am 2009;19:71-9.
34. Hickman SJ, Wheeler-Kingshott CA, Jones SJ, Miszkiel KA, Barker GJ, Plant GT, *et al*. Optic nerve diffusion measurement from diffusion-weighted imaging in optic neuritis. AJNR Am J Neuroradiol 2005;26:951-6.
35. Bot JC, Barkhof F, Lycklama à Nijeholt GJ, van Schaardenburg D, Voskuyl AE, Ader HJ, *et al*. Differentiation of multiple sclerosis from other inflammatory disorders and cerebrovascular disease: Value of spinal MR imaging. Radiology 2002;223:46-56.
36. Filippi M, Rocca MA. MR imaging of multiple sclerosis. Radiology 2011;259:659-81.
37. Lycklama G, Thompson A, Filippi M, Miller D, Polman C, Fazekas F, *et al*. Spinal-cord MRI in multiple sclerosis. Lancet Neurol 2003;2:555-62.
38. Poonawalla AH, Hou P, Nelson FA, Wolinsky JS, Narayana PA. Cervical spinal cord lesions in multiple sclerosis: T1-weighted inversion-recovery MR imaging with phase-sensitive reconstruction. Radiology 2008;246:258-64.
39. Sajja BR, Wolinsky JS, Narayana PA. Proton magnetic resonanace spectroscopy in multiple sclerosis. Neuroimaging Clin N Am 2009;19:45-58.
40. Sarchielli P, Presciutti O, Tarducci R, Gobbi G, Alberti A, Pelliccioli GP, *et al*. Localised (1)H magnetic resonance spectroscopy in mainly cortical gray matter of patients with multiple sclerosis. J Neurol 2002;249:902-10.
41. Geurts JJ, Reuling IE, Vrenken H, Uitdehaag BM, Polman CH, Castelijns JA, *et al*. MR spectroscopic evidence for thalamic and hippocampal, but not cortical, damage in multiple sclerosis. Magn Reson Med 2006;55:478-83.
42. Narayana PA, Wolinsky JS, Rao SB, He R, Mehta M; PROMiSe Trial MRSI Group. Multicentre proton magnetic resonance spectroscopy imaging od primary progressive multiple sclerosis. Mult Scler 2004;10(Suppl 1):S73-8.
43. Staffen W, Zauner H, Mair A, Kutzelnigg A, Kapeller P, Stangl H, *et al*. Magnetic resonance spectroscopy of memory and frontal brain region in early multiple sclerosis. J Neuropsychiatry Clin Neurosci 2005;17:357-63.
44. Sastre-Garriga J, Ingle GT, Chard DT, Ramió-Torrentà L, McLean MA, Miller DH, *et al*. Metabolite changes in normal-appearing gray and white matter are linked with disability in early primary progressive multiple sclerosis. Arch Neurol 2005;62:569-73.
45. Summers M, Swanton J, Fernando K, Dalton C, Miller DH, Cipolotti L, *et al*. Cognitive impairment in multiple sclerosis can be predicted by imaging early in the disease. J Neurol Neurosurg Psychiatry 2008;79:955-8.
46. Ge Y, Gonen O, Inglese M, Babb JS, Markowitz CE, Grossman RI. Neuronal cell injury preceded brain atrophy in multiple sclerosis. Neurology 2004;62:624-7.
47. Rovaris M, Agosta F, Pagani E, Filippi M. Diffusion tensor MR imaging. Neuroimaging Clin N Am 2009;19:37-43.
48. Rovaris M, Judica E, Gallo A, Benedetti B, Sormani MP, Caputo D, *et al*. Grey matter damage predicts the evolution of primary progressive multiple sclerosis at 5 years. Brain 2006;129:2628-34.
49. Pagani E, Filippi M, Rocca MA, Horsfield MA. A method for obtaining tract-specific diffusion tensor MRI measurements in

the presence of disease: Application to patients with clinically isolated syndromes suggestive of multiple sclerosis. Neuroimage 2005;26:258-65.
50. Dineen RA, Vilisaar J, Hlinka J, Bradshaw CM, Morgan PS, Constantinescu CS, *et al*. Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. Brain 2009;132:239-49.
51. Wakefield AJ, More LJ, Difford J, McLaughlin JE. Immunohistochemical study of vascular injury in acute multiple sclerosis. J Clin Pathol 1994;47:129-33.
52. Adhya S, Johnson G, Herbert J, Jaggi H, Babb JS, Grossman RI, *et al*. Pattern of hemodynamic impairment in multiple sclerosis: Dynamic susceptibility contrast perfusion MR imaging at 3.0 T. Neuroimage 2006;33:1029-35.
53. Inglese M, Adhya S, Johnson G, Babb JS, Miles L, Jaggi H, *et al*. Perfusion magnetic resonance imaging correlates of neuropsychological impairment in multiple sclerosis. J Cereb Blood Flow Metab 2008;28:164-71.
54. Filippi M, Rocca MA. Functional MR imaging in multiple sclerosis. Neuroimag Clin N Am 2009;19:59-70.
55. Werring DJ, Bullmore ET, Toosy AT, Miller DH, Barker GJ, MacManus DG, *et al*. Recovery from optic neuritis is associated with a change in the distribution of cerebral response to visual stimulation: A functional magnetic resonance imaging study. J Neurol Neurosurg Psychiatr 2000:68;441-9.
56. Rocca MA, Colombo B, Falini A, Ghezzi A, Martinelli V, Scotti G, *et al*. Cortical adaptation in patients with MS: A cross-sectional functional MRI study of disease phenotypes. Lancet Neurol 2005;4:618-26.
57. Stroman PW. Magnetic resonance imaging of neuronal function in the spinal cord: Spinal fMRI. Clin Med Res 2005;3:146-56.
58. Rocca MA, Valsasina P, Ceccarelli A, Absinta M, Ghezzi A, Riccitelli G, *et al*. Structural and functional MRI correlates of Stroop control in benign MS. Hum Brain Mapp 2009;30:276-90.
59. Hammond KE, Metcalf M, Carvajal L, Okuda DT, Srinivasan R, Vigneron D, *et al*. Quantitative *in vivo* magnetic resonance imaging of multiple sclerosis at 7 Tesla with sensitivity to iron. Ann Neurol 2008;64:707-13.
60. Srinivasan R, Ratiney H, Hammond-Rosenbluth KE, Pelletier D, Nelson SJ. MR spectroscopic imaging of glutathione in the white and gray matter at 7 T with an application to multiple sclerosis. Magn Reson Imaging 2010;28:163-70.
61. Aliaga ES, Barkhof F. MRI mimics of multiple sclerosis. Handb Clin Neurol 2014;122:291-316.
62. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, *et al*. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: Evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol 1999;20:637-42.
63. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-15.