J R Coll Physicians Edinb 2017; 47: 271–5 | doi: 10.4997/JRCPE.2017.313 **PAPER**

MRI brain white matter change: spectrum of change – how can we grade?

K Forbes[1]

Abstract

Magnetic resonance imaging has become a widely used clinical tool for the assessment of neurologic symptoms, as well as being increasingly used in neuroscience research. White matter hyperintensities are common findings on brain imaging and their discovery leads to questions about best management, especially when findings are incidental or not considered relevant to the patient's presentation. This review will discuss the varied causes of white matter hyperintensities, consider how best to distinguish between them radiologically, and when they might have potential clinical relevance.

Keywords: brain, MRI, white matter

Declaration of interests: No conflict of interests declared

Correspondence to:
K Forbes
Institute of Neurological Sciences
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow G51 4TF
UK

Email:
kirsten.forbes@ggc.scot.nhs.uk

Based on a lecture given at the Neurology symposium, Royal College of Physicians of Edinburgh, October 2016

Interpretation of magnetic resonance imaging (MRI) of the brain relies on knowledge of MRI techniques as well as both the anatomy and pathophysiology of the brain and appearances on different MR sequences. There are a number of normal white matter appearances that can be confused for white matter hyperintensities (WMH). Focal T2 hyperintensities that suppress on fluid-attenuated inversion recovery (FLAIR) sequences and follow cerebrospinal fluid on all sequences are suggestive of perivascular (Virchow Robin) spaces, a common finding (Figure 1 a,b). Ependymitis granularis, a T2 hyperintense rim surrounding the lateral ventricular margin on FLAIR imaging is often seen and is due to breakdown of the ependymal lining and gliosis, but is of no clinical significance (Figure 2). In children and younger adults, terminal zones of myelination, seen as areas of mild T2 hyperintensity in peri-atrial regions, can still be visible until myelination completes and can be easily confused with pathology (Figure 3).

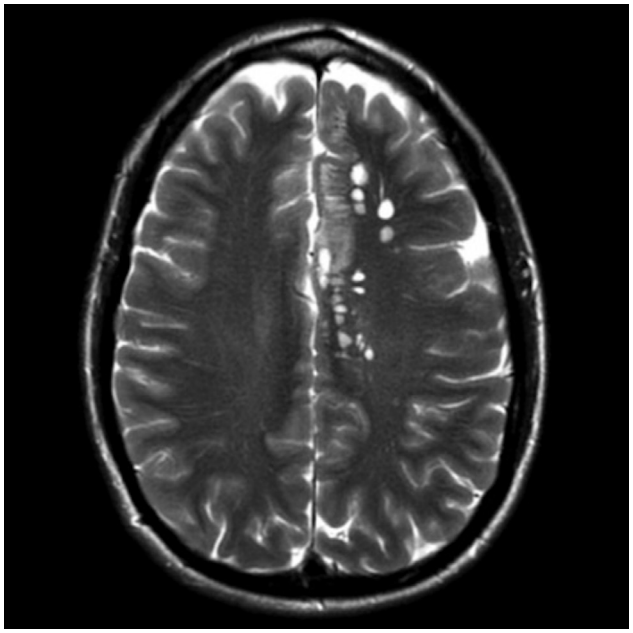
White matter appearances change with age and it is important to distinguish normal appearances from pathologic findings, to avoid patient anxiety and unnecessary investigations. Occasional WMH are commonplace, most often within deep white matter.[1] These increase with age: in asymptomatic individuals, lesions are found in up to 11% by the fourth decade and 83% in the seventh decade. Variation is seen between individuals, likely reflecting past medical history and vascular risk factors. When these WMH are examined microscopically, appearances are of myelin pallor, loss of myelin and axons, tissue rarefaction and mild gliosis.[2,3]

The differential diagnosis of WMH is wide and depends on location, appearance and changes over time (Table 1). There are many potential causes including ischaemic, inflammatory, demyelinating, metabolic, toxic and malignant. Neuroimaging protocols can be targeted to assess the white matter and assist in narrowing the differential diagnosis. White matter changes are best seen on both T2-weighted and FLAIR sequences. The latter are particularly helpful when assessing WMH that lie close to the ventricular margin or the cortex, as nulling of signal from cerebrospinal fluid increases lesion conspicuity. Sagittal or 3D acquired FLAIR sequences can be helpful in detection of multiple sclerosis, improving detection of subtle foci, for example in the corpus callosum. Diffusion-weighted imaging, including both a trace image and an apparent diffusion coefficient map, is important for identifying recent infarcts, while T2* susceptibility-weighted imaging (or T2*-weighted gradient-recalled echo if susceptibility-weighted imaging is not available) allow detection of microbleeds, findings that point to a vascular aetiology.

Patterns of white matter disease that may give a clue to underlying aetiology should be considered, alongside the age and presenting symptoms. Periventricular WMH are common in both multiple sclerosis and small vessel ischaemia. With multiple sclerosis, WMH show a characteristic ovoid

[1]Consultant Neuroradiologist, NHS Greater Glasgow and Clyde and Honorary Senior Lecturer, University of Glasgow, Glasgow, UK

Figure 1 a) Axial T2-weighted sequence depicts multiple WMH in left medial frontal lobe, b) Sagittal FLAIR sequence shows that signal suppresses within these lesions, in keeping with simple fluid and perivascular spaces



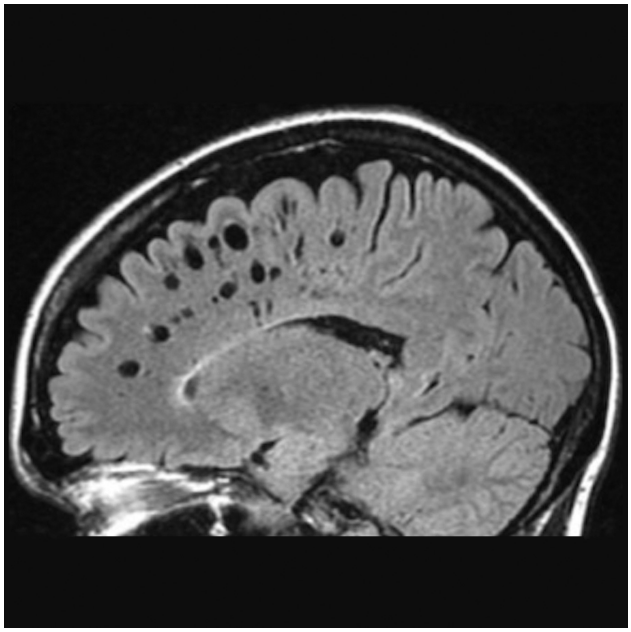


Figure 2 Axial FLAIR sequence. High signal caps both frontal horns, in keeping with ependymitis granularis. This is a normal finding

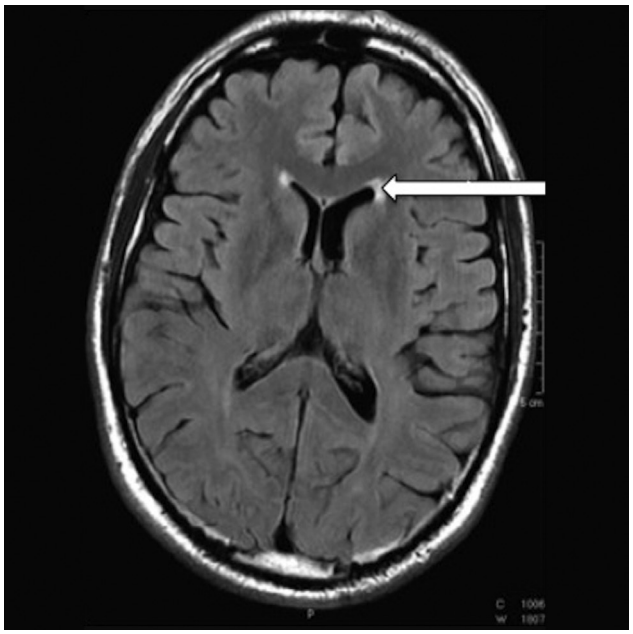
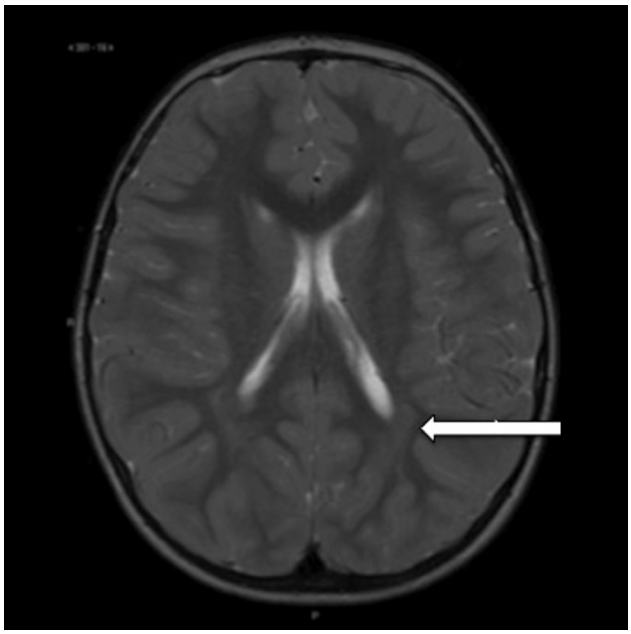


Figure 3 Axial T2-weighted sequence. Subtle T2 hyperintense signal in periatrial white matter, separate from ventricular margin in keeping with terminal zones of myelination, a normal finding



appearance reflecting demyelination occurring alongside a venule (Figure 4), with foci adjacent to the temporal horn, almost pathognomic of demyelination. By contrast, ischaemic WMH tend to show a broad base along the ventricular margin (Figure 5). In both conditions, periventricular lesions increase and become more confluent over time. Demyelinating foci have a predilection for the corpus callosum, especially inferiorly, at the callosal-septal interface, while ischaemic lesions are rarer. Granulomatous or inflammatory conditions such as sarcoid also quite commonly show corpus callosal lesions. Foci in the juxtacortical white matter are most common with demyelination (Figure 6), although are also common in vasculitis with changes occurring at the grey-white matter junction.

While occasional WMH are a normal observation with increasing age, multifocal WMH in an older adult are most suggestive of microvascular ischaemia. These changes are thought to arise from chronic hypoperfusion of the white matter and disruption of the blood-brain barrier, with chronic leakage of plasma into the white matter.[4] Often seen in association with silent brain infarcts and microbleeds, the number and extent of WMH increases with age, hypertension, hypercholesterolemia, diabetes and genetic risk factors,

Table 1

Category	Cause
Hypoxic/ ischaemic	Atherosclerosis, hypertension, diabetes mellitus, migraine, amyloid angiopathy, CADASIL
Inflammation	Multiple sclerosis, vasculopathy eg systemic lupus erythematosus, sarcoid, Behcet, Sjogren
Infectious	HIV, Lyme disease, progressive multifocal leukoencephalopathy, post-infectious: acute demyelinating encephalomyelitis
Toxic/metabolic	B12 deficiency, CO intoxication, central pontine myelinolysis.
Traumatic	Radiotherapy, post contusion.
Hereditary	metabolic
Normal	Virchow Robin-spaces, Fazekas 1

CADASIL, Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; Fazekas 1, Minimal white matter foci.

in particular the APOE*E4 genotype.[5] There has been a wide variation in radiologic terms to describe these white matter changes and in an attempt to unify, the term 'WMH of presumed vascular origin' has been suggested (STRIVE: Standards for Reporting Vascular Changes on Neuroimaging).[6]

Grading scales can be useful to assess both disease extent and prognosis of WMH of presumed vascular origin. The Fazekas grading scale (grade 1–4) is widely used,[7] ranging from no or minimal white matter foci (grade 1) to confluent deep white matter changes (grade 4). Intermediate grades are pathologic, but may be seen in normally functioning individuals. As WMH progress, patients become symptomatic, with prospective longitudinal studies showing that WMH predicts an increased risk of stroke, dementia, and death. The Leukoaraiosis And DISability study group (LADIS) looked at the impact of age-related brain white matter changes on the transition to disability in the elderly and found that severe white matter changes predict rapid global functional decline at 3 years.[8] The link between imaging appearances and function suggests that screening for risk factors of stroke and dementia may be useful in this patient group.[9]

Multiple sclerosis should be considered as a possible cause for WMH, particularly in younger patients who have relevant symptoms and lesions in classic locations, disseminated in space and time. The MAGNIMS consensus guidelines[3] have recently updated the 2010 McDonald diagnostic criteria[10] (Table 2). The optic nerve has been added as an additional site to the previous four defined locations classical for multiple sclerosis: periventricular (Figure 4), juxtacortical (Figure 6), infratentorial (Figure 7) and spinal cord (Figure 8), reflecting that 25% of patients with a clinically isolated syndrome present with acute optic neuritis. The juxtacortical location now also includes the cortex as, with imaging advances, more foci are being identified in this location.

Figure 4 Sagittal FLAIR sequence. Multiple ovoid T2 hyperintense lesions extend into periventricular white matter, characteristic of MS

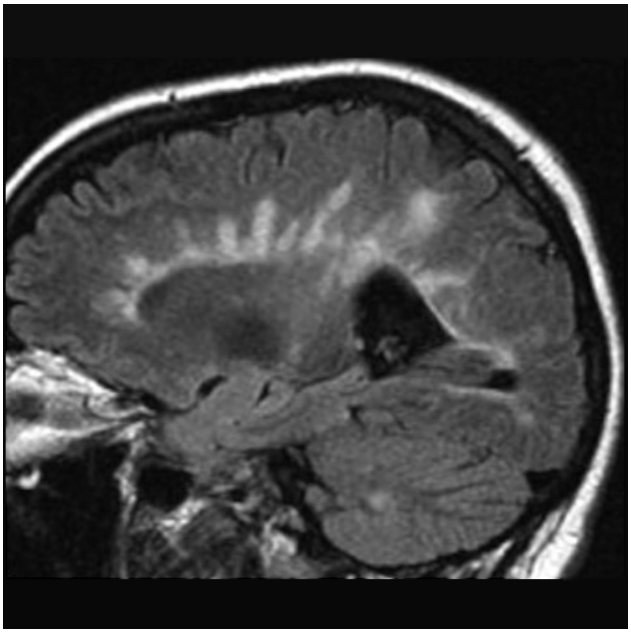
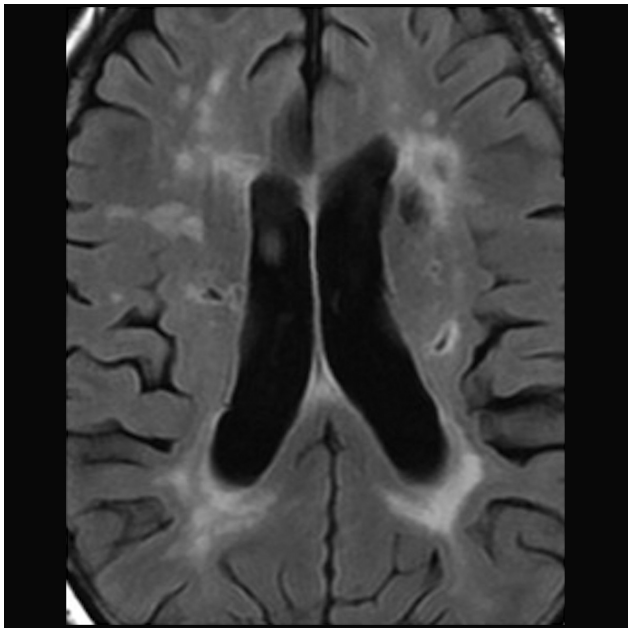


Figure 5 Axial FLAIR sequence. Periventricular white matter changes with a broad ventricular base, which together with small subcortical infarcts, suggest ischaemia



Specificity has improved with an increased requirement of three lesions in a periventricular location to meet criteria. The requirement of being able to identify which lesion is symptomatic has been removed. In addition to obtaining high quality brain imaging, contrast administration may be diagnostically useful, to separate acute enhancing from chronic non-enhancing lesions, allowing the dissemination in time criterion to be met in a single MRI. Further, spine MRI can provide a useful adjunct in patients who do not otherwise meet the dissemination in space criterion (Figure 8).

Table 2

Dissemination in space	
Revised McDonald criteria (10)	MAGNIMS (3)
Involvement of at least 2 of the following areas: Periventricular: ≥ 1 lesion Juxtacortical: ≥ 1 lesion Infratentorial: ≥ 1 lesion Spinal cord: ≥ 1 lesion	Involvement of at least 2 of the following areas: Periventricular: ≥ 3 lesions Cortical-juxtacortical: ≥ 1 lesion Infratentorial: ≥ 1 lesion Spinal cord: ≥ 1 lesion Optic nerve: ≥ 1 lesion
Dissemination in time	
Either new T2 or Gd-enhancing lesion(s) on follow up MR *Or* simultaneous presence of: • Asymptomatic Gd-enhancing *and* • Non-enhancing lesions at any time	

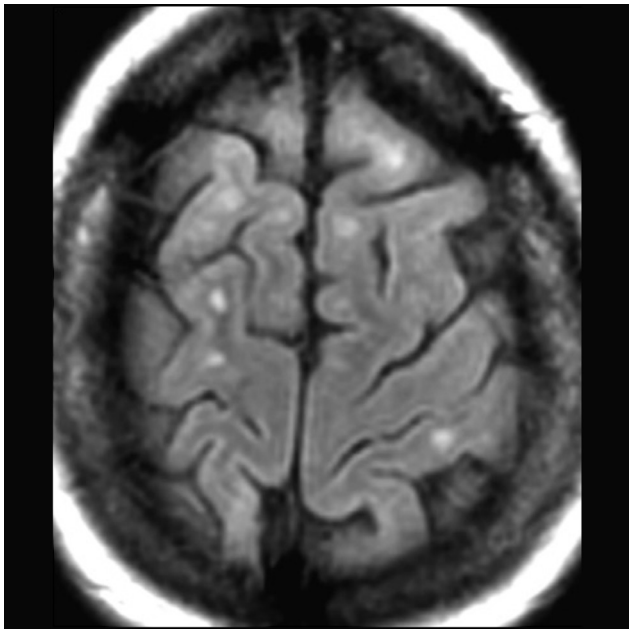


Figure 6 Axial FLAIR sequence. Juxtacortical WMH are highly suggestive of MS

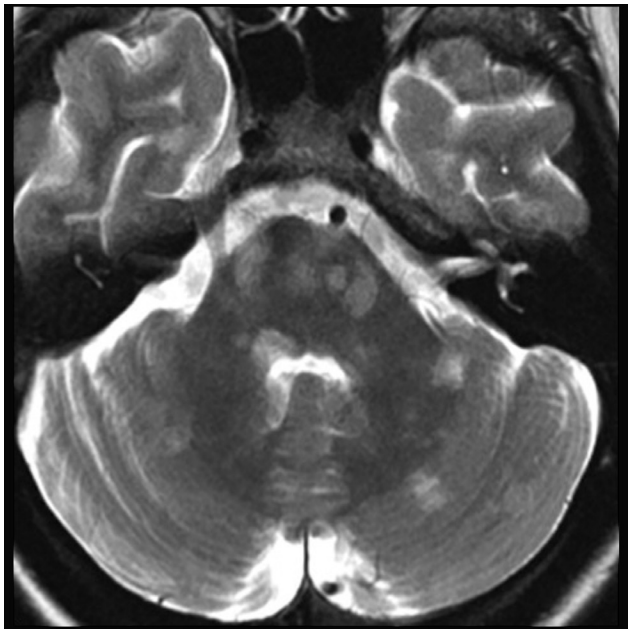


Figure 7 Axial T2-weighted sequence. Multifocal WMH in brainstem, middle cerebellar peduncles and cerebellar hemispheres, in a patient with MS

Uncertainty may arise if WMH suggestive of multiple sclerosis are incidentally identified on MRI brain performed for another clinical indication or as part of a research study. In this 'radiologically isolated syndrome', imaging abnormalities that suggest multiple sclerosis are found in a patient's brain and/or spinal cord, but the patient has not experienced any symptoms, meaning that a diagnosis of multiple sclerosis cannot be made. Okuda and colleagues performed a multinational retrospective review, showing that over a 5-year period up to 34% of such patients go on to have their first clinical symptoms and receive a diagnosis of multiple sclerosis.[11] This suggests that clinical follow up is warranted in this group.

The differential diagnosis of WMH extends beyond multiple sclerosis, age-related changes and small vessel disease (Table 1). In young patients with white matter foci, consider a history of migraine, given that there is an increase in deep white matter foci in migraineurs, especially those with aura. The exact cause of these white matter foci is unclear, but may reflect changes in blood flow.[12]

Other causes are more unusual but should be considered in the appropriate clinical setting. Non-atheromatous vasculopathy may arise secondary to underlying systemic conditions such as systemic lupus erythematous, or as a primary entity, CNS angiitis (isolated vasculitis of the central nervous system). Imaging appearances are those of WMH, often with cortical or juxtacortical involvement, and occasionally with haemorrhage. Vascular imaging techniques may be helpful to look for multifocal vascular narrowing due to vessel wall thickening.

Imaging of WMH is likely to further improve with advances in MR technology. Sensitivity to WMH is increased by the use of higher magnetic field strengths, such as 3 Tesla, now

in routine clinical use, but in time likely also ultra-high field strengths such as 7 Tesla, which may also offer improvements in specificity. These magnets provide a stronger MR signal and improved resolution, allowing better detection of both white and grey matter foci[13,14] offering earlier diagnosis and resultant treatment. MR sequences are constantly evolving and imaging protocols are likely to significantly change over time. Sensitivity to WMH is improved both by magnetisation transfer imaging,[15] and diffusion tensor imaging, which can detect lesions that would otherwise go undetected by conventional techniques.[16]

MRI is an invaluable technique for diagnosis of white matter disease, with detection of both symptomatic and asymptomatic disease. While this creates challenges in managing patients with unsuspected WMH, it also offers an opportunity of early diagnosis and potential early intervention.

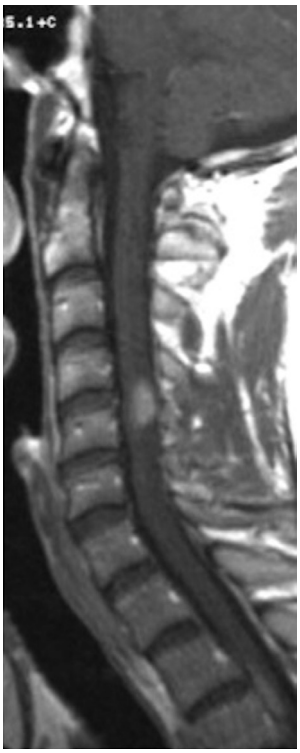


Figure 8 Sagittal T1-weighted post contrast imaging of cervical spine. Enhancing, active demyelinating plaque within the dorsal cord at C5

References

1 Fazekas F. Magnetic resonance signal abnormalities in asymptomatic individuals: Their incidence and functional correlates. *Eur Neurol* 1989; 29: 164–8.
2 Fazekas F, Kleinert R, Offenbacher H et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology* 1993; 43: 1683–9.
3 Filippi M, Rocca MA, Ciccarelli O et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *Lancet Neurol* 2016; 15: 292–303.
4 O'Sullivan M, Lythgoe DJ, Pereira AC et al. Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. *Neurology* 2002; 59: 321–6.
5 LADIS Study Group. Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort. *BMJ* 2009; Jul 6: 339.
6 Wardlaw JM, Smith EE, Biessels GJ et al. STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1). Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 2013; 12: 822–38.
7 Fazekas G, Fazekas F, Schmidt R et al. Brain MRI findings and cognitive impairment in patients undergoing chronic hemodialysis treatment. J *Neurol Sci* 1995; 134: 83–8.
8 Pantoni L, Basile AM, Pracucci G et al. Impact of age-related cerebral white matter changes on the transition to disability – the LADIS study: rationale, design and methodology. *Neuroepidemiology* 2005; 24: 51–62.
9 Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2010; 26: 341: c3666.
10 Polman CH, Reingold SC, Banwell B et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.
11 Okuda DT, Siva A, Kantarci O et al. Radiologically isolated syndrome: 5-year risk for an initial clinical event. *PLoS One* 2014; 9:3
12 Kruit MC, van Buchem MA, Hofman PAM et al. Migraine as a risk factor for subclinical brain lesions. *JAMA* 2004; 291: 427–34.
13 Stankiewicz JM, Glanz BI, Healy BC et al. Brain MRI lesion load at 1.5T and 3T versus clinical status in multiple sclerosis. *J Neuroimaging* 2011; 21: e50–6.
14 Nielsen AS, Kinkel RP, Tinelli E et al. Focal cortical lesion detection in multiple sclerosis: 3 Tesla DIR versus 7 Tesla FLASH-T2. *J Magn Reson Imaging* 2012; 35: 537–42.
15 Pike GB, De Stefano N, Narayanan S et al. Multiple sclerosis: magnetization transfer MR imaging of white matter before lesion appearance on T2-weighted images. *Radiology* 2000.215: 824–30.
16 Rueda F, Hygino LC Jr, Domingues RC et al. Diffusion tensor MR imaging evaluation of the corpus callosum of patients with multiple sclerosis. *Arq Neuropsiquiatr* 2008; 66: 449–53.