Received:
30 August 2016

Revised:
20 March 2017

Accepted:
28 March 2017

<https://doi.org/10.1259/bjr.20160721>

Cite this article as:

Igra MS, Paling D, Wattjes MP, Connolly DJA, Hoggard N. Multiple sclerosis update: use of MRI for early diagnosis, disease monitoring and assessment of treatment related complications. *Br J Radiol* 2017; **90**: 20160721.

REVIEW ARTICLE

Multiple sclerosis update: use of MRI for early diagnosis, disease monitoring and assessment of treatment related complications

¹MARK S IGRA, FRCP, ²DAVID PALING, MA, MRCP, ³MIKE P WATTJES, MD, ¹DANIEL J A CONNOLLY, MRCP, FRCP and ⁴NIGEL HOGGARD, MRCP, FRCP

¹Department of Neuroradiology, Royal Hallamshire Hospital, Sheffield, UK

²Department of Clinical Neurology, Royal Hallamshire Hospital, Sheffield, UK

³Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, Netherlands

⁴Academic Unit of Radiology, University of Sheffield, Sheffield, UK

Address correspondence to: Dr Mark Igra

E-mail: drmarkigra@gmail.com

ABSTRACT

MRI has long been established as the most sensitive *in vivo* technique for detecting multiple sclerosis (MS) lesions. The 2010 revisions of the McDonald Criteria have simplified imaging criteria, such that a diagnosis of MS can be made on a single contrast-enhanced MRI scan in the appropriate clinical context. New disease-modifying therapies have proven effective in reducing relapse rate and severity. Several of these therapies, most particularly natalizumab, but also dimethyl fumarate and fingolimod, have been associated with progressive multifocal leukoencephalopathy (PML). PML-immune reconstitution inflammatory syndrome (IRIS) has been recognized in patients following cessation of natalizumab owing to PML, and discontinuation for other reasons can lead to the phenomenon of rebound MS. These complications often provide a diagnostic dilemma and have implications for imaging surveillance of patients. We demonstrate how the updated McDonald Criteria aid the diagnosis of MS and describe the imaging characteristics of conditions such as PML and PML-IRIS in the context of MS. Potential imaging surveillance protocols are considered for the diagnosis and assessment of complications. We will explain how changes in MS treatment are leading to new imaging demands in order to monitor patients for disease progression and treatment-related complications.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, inflammatory neurological disease characterized by demyelination, axonal injury and gliosis within the brain and spinal cord. MRI is an important tool in the diagnosis of MS and has been part of the diagnostic criteria since 2001.¹ The latest 2010 revision has simplified the diagnostic process further and can allow a diagnosis of MS to be made following a single attack on a single contrast-enhanced MR study, by the demonstration of the simultaneous presence of asymptomatic enhancing and non-enhancing lesions.^{2,3} MRI also has an integral role in the monitoring of disease and assessing treatment efficacy and prediction of treatment response.⁴

The development of new disease-modifying drugs (DMDs) such as natalizumab, fingolimod and dimethyl fumarate has reduced MS relapse rates as well as short-term disability progression.^{5–8} However, progressive multifocal leukoencephalopathy (PML), an opportunistic lytic infection

of the white and grey matter cells in the central nervous system (CNS) by John Cunningham virus (JCV), is a recognized severe adverse event.⁹ PML can cause death or permanent neurological disability. However, prompt and accurate diagnosis can reduce these risks, and PML can be detected by MRI before the patient develops symptoms.^{10,11} PML-related immune reconstitution inflammatory syndrome (IRIS) is also a recognized complication following natalizumab cessation.¹²

MS may present with atypical imaging and clinical features such as tumefactive MS and Balo concentric sclerosis and pathophysiologically different entities such as neuromyelitis optica, other neuroinflammatory conditions, vasculitis, infections and tumours, and it can mimic the neuroradiological and clinical manifestations of MS.

In this review, we focus on typical MR findings which also constitute the new McDonald Criteria. A thorough review of the imaging findings in classic MS and its variants is

beyond the scope and aims of this study. For a full overview of all imaging findings related to MS and its differential diagnoses, we direct the reader to other comprehensive reviews.^{13–15}

We highlight how the most recent imaging guidelines affect diagnosis of MS and also provide information regarding the imaging characteristics of natalizumab-related complications, such as PML and PML-IRIS. We discuss recent suggested imaging protocols for MS and the potential impact that new imaging surveillance and more frequent monitoring of patients may have on radiology departments.

THE REVISED 2010 MCDONALD CRITERIA

MRI can establish a diagnosis of MS in patients with at least one clinical attack consistent with CNS inflammatory demyelinating disease in two ways. First, MRI can help by outruling alternative differential diagnoses for symptoms and signs.¹⁶ Second, MRI can help make a positive diagnosis of MS using the McDonald Criteria which have most recently been revised in 2010.^{2,3} These criteria allow MRI to aid diagnosis of MS, allowing demonstrating dissemination in time (DIT) and dissemination in space (DIS) of lesions where this cannot be established clinically.

For example, in a patient with a single typical clinical attack, MS can be diagnosed based on a single MRI scan, provided this scan demonstrates both DIS and DIT. DIS can be demonstrated with at least one T2 lesion in at least two of four recognized locations for MS plaques (periventricular, cortical/juxtacortical, infratentorial and spinal cord), although it should be noted that the symptomatic lesion in the case of a brainstem or spinal cord syndrome is excluded. DIT can be demonstrated as the simultaneous presence of asymptomatic contrast-enhancing and non-enhancing lesions on the same study. If this is not seen, DIT can be demonstrated by a further T2 lesion on follow-up MRI or a new clinical attack (Figure 1).

MRI is also able to detect lesions fulfilling DIS and DIT criteria in patients who may have no signs or symptoms of MS in scans performed for other indications (*i.e.* headaches, head injury, research). These patients do not fulfil the McDonald Criteria for

a diagnosis of MS, since they have not had at least one clinical attack. This has led to the concept of radiologically isolated syndrome, which does carry a higher risk for developing MS. Criteria for radiologically isolated syndrome including the number, location and morphology of lesions have been suggested.¹⁷

The 2010 McDonald Criteria allow a more rapid diagnosis of MS without losing sensitivity. They should in theory result in fewer MRI examinations being performed. It should be reiterated that they only apply in those patients who have experienced a typical clinically isolated syndrome.

Suggested imaging protocol

The McDonald Criteria do not suggest specific imaging protocols. Various MRI acquisition parameters have a significant influence on the detection of MS-related pathology. Several expert groups have recently suggested protocols for baseline and follow-up MRI for the brain and spine in MS.^{18,19}

Brain imaging

The recommended minimum sequences required include three-dimensional (3D) T₁ weighted, 3D T₂ fluid-attenuated inversion-recovery (FLAIR), 3D T₂ weighted and pre- and post-single-dose gadolinium T₁ weighted imaging.¹⁹ 3.0-T MRI is preferable to 1.5-T if available owing to the improved signal-to-noise ratio and resolution. While higher field strengths increase sensitivity for lesions, they have not resulted in earlier diagnosis of MS.²⁰ Two-dimensional (2D) sequences should have a maximum slice thickness of no greater than 3 mm and an in-plane spatial resolution of 1 × 1 mm.²¹ While spin-echo or fast spin-echo T₂ weighted and proton density (PD) sequences have been considered the reference standard to detect demyelinating lesions, they are considered optional in this new suggested protocol. 2D FLAIR sequences are more sensitive in detecting periventricular and juxtacortical lesions, although they are less sensitive for posterior fossa lesions. For this reason, the groups suggest that isotropic 3D T₂ weighted FLAIR is preferred owing to improved contrast-to-noise ratio and the ability to create multiplanar reformats. These are usually acquired in the sagittal plane to assess lesions in the

Figure 1. A 29-year-old male presented with a 2-week history of right leg numbness, right hand weakness and brisk reflexes bilaterally with sustained clonus. T₂ weighted and fluid-attenuated inversion recovery imaging show multiple hyperintensities. A posterior left frontal lobe lesion (arrows) shows enhancement following contrast administration. An anterior right frontal lobe lesion does not (dashed arrows). This single study demonstrates both dissemination in space and dissemination in time.

corpus callosum, and this is also the fastest plane for acquisition. We recognize that 3D MR techniques are not available in all institutions. When assessing for MS lesions using a 1.5-T scanner without the option of 3D imaging, we recommend both axial 2D FLAIR and spin-echo axial T_2 weighted sequences in order to improve assessment of the posterior fossa (Tables 1 and 2).

A thin-section 3D inversion recovery-prepared, T_1 weighted, spoiled gradient echo sequence is useful for volumetric analysis, which may become more widespread in the future in assessing brain atrophy.¹⁹ T_1 weighted imaging is essential in detecting “black holes”, a marker of chronic axonal loss. However, this particular sequence renders all hyperintense lesions on T_2 weighted imaging to be hypointense, thus losing the specificity of T_1 black holes.²²

Axial diffusion-weighted imaging (DWI) may detect acute inflammatory lesions as well as non-MS pathology and has a role in detecting early manifestations of PML. Given that it has histopathological specificity over conventional T_2 weighted and

FLAIR imaging, inclusion of DWI sequences in an MS protocol has been advised by some authors.²³

Spinal imaging

Imaging of the spinal cord is more challenging owing to small tissue volume and artefact from vascular and cerebrospinal fluid (CSF) pulsations. At a minimum the cervical cord should be imaged, as MS lesions are more common and better visualized in this region.¹⁹ Thoracic cord imaging should be performed if clinical symptoms localize to this region. There is no published evidence that higher field strengths improve lesion detection in the spinal cord and 1.5-T MRI is recommended.¹⁸ Two sagittal sequences with different contrasts (T_2 and PD and/or short tau inversion recovery) improve lesion detection rate. The diagnostic standard is considered to be sagittal 2D spin echo or fast dual-echo, although short tau inversion-recovery T_2 , PD and T_1 weighted inversion recovery sequences may also be used. As opposed to brain MRI, T_2 FLAIR sequences are no more sensitive than conventional T_2 sequences.²¹ While not included in this recommended spinal imaging protocol, it is our experience that axial imaging greatly improves lesion detection and

Table 1. Standardized brain MRI protocol and standardized spinal cord protocol (adapted from Traboulsee 2016)

Parameters	Description
Standardized brain MRI protocol	
Field strength	Sufficient to allow adequate signal-to-noise ratio with resolution ($\leq 1 \times 1$ mm)
Scan orientation	Axial oblique sequences should be along the subcallosal line
Coverage	Whole brain
Section thickness and gap	≤ 3 mm. No gap for 2D or 3D acquisition
Core sequences	Anatomic 3D inversion recovery T_1 gradient echo
	3D sagittal T_2 weighted imaging FLAIR
	3D T_2 weighted imaging
	2D axial DWI
	3D FLASH post-gadolinium
Optional sequences	Axial PD
	Pre or post gadolinium T1 spin-echo
	SWI for central vein identification
Standardized spinal cord protocol	
Field strength	Sufficient to allow good signal-to-noise ratio and resolution ($\leq 1 \times 1$ mm)
Coverage	Cervical cord, although thoracic cord is recommended if lesions localize to this region
Core sequences	Sagittal T_2
	Sagittal proton attenuation, STIR or PST1-IR
	Axial T_2 through lesions
Section thickness and gap	Sagittal ≤ 3 mm, no gap
	Axial 5 mm, no gap
Optional sequences	Axial T_2 through complete cervical cord
	Post-gadolinium sagittal T_1

2D, two dimensional; 3D, three dimensional; DWI, diffusion-weighted imaging; FLASH, fast low angle shot; PD, proton density; PST1-IR, indicates phase-sensitive T1 inversion recovery; STIR, short tau inversion recovery.

Table 2. Clinical features and imaging characteristics of multiple sclerosis (MS) and progressive multifocal leukoencephalopathy (PML)

Parameters	MS	PML
Clinical features		
Onset	Acute	Subacute
Evolution	Hours to days	Over weeks
	Normally stabilize. May resolve spontaneously even without therapy	Progressive
Clinical presentation	Diplopia	Aphasia
	Paraesthesia	Behavioural and neuropsychiatric alteration
	Paraparesis	Hemiparesis
	Optic neuritis	Hemianopia
	Myelopathy	Seizures
	MS	PML
Imaging characteristics		
Appearance	Well-defined lesions	Ill-defined lesions, white matter, often large (>3 cm), multifocal. Sharp border towards grey matter, ill-defined border towards white matter. Often surrounded by punctate lesion
Location	Periventricular, deep white matter, cerebellum, spinal cord	Subcortical white matter, parietal, occipital, frontal lobes. Can involve corpus callosum. Rarely brainstem and posterior fossa
FLAIR	Hyperintense equal to T_2	Hyperintense, more sensitive for detection of PML in subcortical structures.
T_1	Isointense or hypointense	Isointense with progressive hypointensity
T_2	Hyperintense, may resolve over months	Hyperintense
Mass effect	Only in large lesions	Not typical. PML-IRIS may show mass effect
Contrast enhancement	Acute lesions enhance. Nodular or incomplete ring	40–50% enhancement. Variable pattern—linear, nodule, punctate or peripheral

FLAIR, fluid-attenuated inversion recovery; IRIS, immune reconstitution inflammatory syndrome.

Adapted from Yousry. *Ann Neurol* 2012.

characterization, and we perform axial T_2^* gradient echo sequences of the cervical spine on all our MS protocols.

A smaller percentage of new spinal cord lesions demonstrate enhancement following gadolinium administration—61% compared with 94% of brain lesions in one study—and its value is still under consideration.²⁴ The updated imaging guidelines recommend that the spinal cord should be imaged directly after contrast-enhanced brain imaging, to prevent the need for additional contrast administration and to reduce repeated attendances to the department.¹⁸

Disease-modifying drugs and progressive multifocal leukoencephalopathy

DMDs used in active relapsing MS are effective in reducing the frequency and severity of MS attacks. One of the most effective of these is natalizumab, a recombinant monoclonal (Ig)-G4 antibody directed at $\alpha 4b1$ and $\alpha 4b7$ integrins, which are cell adhesion molecules. The effect of integrin blockade is decreased T-cell migration into the CNS.²⁵ Phase III trials demonstrated clinical efficacy and superiority compared with interferon-B or

glatiramer acetate.^{5,26} Up to 37% of patients were free of clinical and radiological disease activity after 2 years.⁵ Natalizumab is generally well tolerated with a low incidence of immediate adverse events. However, in 2005, three patients were reported to have developed PML while on natalizumab.²⁷ As of September 2016, 698 cases of PML associated with natalizumab had been confirmed and incidence has reached 4.18 per 1000 patients treated (Biogen MedInfo. Available from: <https://medinfo.biogen.com>; Accessed September 2016). PML has additionally been occasionally reported in patients taking dimethyl fumarate and fingolimod (other disease-modifying therapies for MS).^{28–30}

Progressive multifocal leukoencephalopathy

PML is an opportunistic infection pathologically characterized by lytic infection of oligodendrocytes and astrocytes by the JCV, a double-stranded DNA polyomavirus. JCV is ubiquitous and a large percentage of the population carries it as an asymptomatic latent infection.³¹ CNS infection can occur in patients who are immunosuppressed including with DMDs, following a complex reactivation and virus replication whereby latent JCV mutates to a neurotropic variant.^{32,33}

A positive anti-JCV antibody status is a risk factor for developing PML during natalizumab treatment, although patients who are serologically negative may still carry the virus, can periodically display low levels of viraemia and have very occasionally developed PML.³⁴ Prior use of immunosuppressants and duration of natalizumab therapy, especially beyond 2 years, are additional risk factors for the development of PML.⁹

American Academy of Neurology consensus statements mandate that diagnosis can be made from brain biopsy, or more commonly from clinical findings combined with JCV DNA in CSF, typically supported by typical imaging findings.^{35,36} Cognitive deficits are the most common clinical feature of PML, although presentation is often heterogeneous with focal and non-focal neurological deficits.³⁷ This may lead to early symptoms of PML being attributed to an MS relapse or exacerbation. Therefore, in the context of a JCV seropositive patient on natalizumab treated longer than 2 years presenting with new neurological symptoms, there should be a high index of suspicion for PML. CSF can occasionally be negative in early cases, particularly in patients who are asymptomatic with only MRI-based suspicion. Serial scanning and lumbar puncture supported by detailed and frequent clinical assessment is sometimes required to achieve definite diagnosis.³⁸

Natalizumab-associated PML has a mortality rate of 22% when picked up at the time of symptoms which is lower than the HIV-AIDS related form, although surviving patients can have significant morbidity.³⁹ Older patients and those with poorer baseline function have a worse prognosis. PML screening may lead to an earlier diagnosis at an asymptomatic stage with a better functional outcome.¹¹

Imaging characteristics of leukoencephalopathy

Attempting detection, particularly of pre-symptomatic PML on MRI can be difficult owing to the overlap of imaging findings with MS lesions. Recognized imaging characteristics of PML include one or more foci of T_2 /FLAIR hyperintensity in a sub-cortical location involving U-fibres with an ill-defined border towards the white matter but a well-delineated border towards the grey matter.⁴⁰ White matter involvement is typically peripheral, although periventricular white matter involvement does not exclude PML.³⁵ Lesions vary in shape and coalesce as they increase in size. Larger lesions may show a “granular” appearance on T_2 weighted imaging, which reflects focal areas of demyelination.⁴⁰ Lesion sizes of >3 cm are more likely to be associated with PML than MS. T_1 weighted imaging typically shows PML lesions to be hypointense.⁴¹

The frontal lobes are most affected, followed by the parietal and occipital lobes. Callosal involvement has been reported, although isolated lesions are rare.⁴⁰ Deep grey matter structure involvement can occur, with the thalami more frequently involved than the basal ganglia.⁴² Cortical involvement is increasingly recognized,⁴³ and in a multivariate model proposed by Wijburg et al,⁴⁴ cortical grey matter involvement along with punctate T2 lesions predicted for PML over MS lesions. Posterior fossa involvement is well recognized and “crescent”-shaped lesions involving the middle cerebellar peduncles can be seen

and are not typical for MS lesions.⁴⁵ Approximately 30% of PML lesions may show enhancement or other signs of inflammation, and the enhancement pattern is varied and may be patchy, nodular, linear or peripheral.⁴⁶

Restricted diffusion can be seen on DWI sequences, although this may be less common with early or asymptomatic disease.⁴⁶ In the early stages of disease, DWI shows high signal owing to swollen and dying oligodendrocytes.⁴⁷ Treatment commencement results in the lesion rim losing its DWI hyperintensity, and over time the lesion becomes hypointense owing to tissue destruction. Apparent diffusion coefficient values rise with progressive white matter injury, in keeping with more irreversible damage.⁴⁸ This evolution of DWI signal changes is essential in monitoring disease progression and treatment response (Figure 2).^{48,49}

Progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome

Treatment of natalizumab-associated PML is by rapid drug removal, usually by plasma exchange. This can hasten PML-IRIS which may worsen symptoms and is associated with significant negative effects on patient outcome.⁵⁰ IRIS was originally described in patients with AIDS who paradoxically deteriorated on starting highly active antiretroviral therapy.⁵¹ In patients who do not receive plasma exchange on discontinuation of natalizumab, PML-IRIS occurs 90 days after the final dose, reflecting the time taken for the biological effects of the drug to clear.⁵² PML-IRIS carries a mortality of up to 30%.¹¹

PML-IRIS is characterized by an increase in size of pre-existing PML lesions. Oedema, cerebral swelling and mass effect may be seen, imaging features which are not typical for PML.³⁵ The most prominent imaging finding is that of contrast enhancement, with variable, irregular, ill-defined contrast enhancement patterns described.⁴⁰ Patchy enhancement was most frequently located within the periphery of the PML lesions, which is attributed to active lytic JCV infection within preserved myelin.^{47,53} Punctate enhancement with a perivascular distribution, outside of the main PML lesion, is another sign of PML-IRIS (Figure 3).⁵³

Natalizumab rebound

Another recently recognized phenomenon is that of natalizumab rebound, where a patient develops a severe inflammatory response greater than that of their usual typical relapse severity within approximately 3 months of natalizumab cessation.⁵⁴ This rebound phenomenon has been reported in up to 40% of patients after discontinuation of natalizumab.^{12,55} This provides another reason for clinicians to be vigilant when patients stop treatment. Typical imaging appearances are of new enhancing and non-enhancing lesions, which may be greater in number than in a normal MS relapse episode.^{2,10,55}

Suggested imaging surveillance protocol

Given that prompt detection and treatment of PML in the pre-symptomatic phase has been shown to improve outcomes^{56–58} and limits permanent brain damage before immune reconstitution,³⁷ appropriate surveillance of patients taking natalizumab is essential. Various studies have shown that MRI is able

Figure 2. A patient with known multiple sclerosis (MS) on treatment with natalizumab presented with progressive changes in behaviour. Coronal fluid-attenuated inversion recovery (FLAIR) imaging (a, b) shows an ill-defined focus of high signal within the medial left frontal lobe (solid arrows), without restricted diffusion on diffusion-weighted imaging/apparent diffusion coefficient (c, d). A repeat MRI scan performed 6 weeks later shows enlargement of the pre-existing left frontal lobe lesion (e and f, solid arrows). There is also faint punctate contrast enhancement at the posterior aspect of the lesion (h, dashed line). A new ill-defined high T_2 /FLAIR lesion is also now seen within the left temporal lobe (f, dotted line). Findings are consistent with progressive multifocal leukoencephalopathy. Pre-existing MS lesions within both centrum semiovale are noted.

to detect PML-related changes 3–4 months prior to development of symptoms^{58–60}

An expert group has proposed a surveillance protocol, stratifying patients into one of three risk groups based on anti-JCV antibody status: JCV negative, JCV positive with index <1.5 and JCV positive with index >1.5 . Those with an index value of ≥ 1.5 have a relatively low risk within the first 24 months (1.17/1000), but this increases to 1 in 113 after 24 months. Therefore, these patients with higher risk should have more regular MRI monitoring for PML than those with lower risk.⁵⁷ Since JCV antibody status can change over time, it is recommended that antibody testing should be repeated every 6 months and MRI surveillance frequency adjusted if JCV becomes positive or if the index increases above 1.5.⁵⁷

The MRI surveillance strategy has been incorporated by the European Medicines Agency for the natalizumab label update. It is recommended that all patients be imaged prior to starting natalizumab and at least annually. The frequency of repeat imaging for those patients who are anti-JCV antibody positive and have been on treatment for 18 months increases to a minimum of 6 monthly for those with an index value of ≤ 1.5 and at least 3–4 monthly for those with a value ≥ 1.5 . While the risk of natalizumab-associated PML increases after 24 months, the opinion of the expert group is that more frequent imaging at

18 months would aid detection of asymptomatic PML.⁵⁷ This early detection would facilitate prompt treatment cessation and further treatment.

A proposed abbreviated PML surveillance imaging protocol includes 3D or 2D FLAIR and DWI sequences⁴³ but not post-contrast imaging, as fewer than 50% of early PML lesions demonstrate contrast enhancement.⁴⁰ A protocol which avoids the use of contrast is important owing to the increasingly recognized phenomenon of gadolinium deposition within the brain in patients who have had multiple contrast-enhanced MRIs. Long-term effects of this deposition have yet to be determined.⁶¹ However, it would be prudent to avoid gadolinium-based contrast agents wherever possible, particularly in those younger patients who may have large numbers of contrast-enhanced scans to assess for active disease.

There are implications of increased frequency of MRI monitoring of these patients. As of September 2016, 161,300 patients worldwide had received natalizumab (Biogen MedInfo. Available from: <https://medinfo.biogen.com>). In the UK, there are an estimated 107,740 people with MS and an estimated 5110 new diagnosed cases a year.⁶² Our department currently has 109 patients on natalizumab, with an estimated prevalence of MS at 2740 patients, or 3.97%. Extrapolated across the UK, this suggests a rough estimate of approximately 4286 patients treated

Figure 3. Axial fluid-attenuated inversion recovery (a, b) and contrast-enhanced T_1 weighed images (c, d) of a 54-year-old patient with patients with relapsing-remitting multiple sclerosis being treated with natalizumab longer than 3 years at the time of progressive multifocal leukoencephalopathy (PML) diagnosis (a, c) and at the time of PML- immune reconstitution inflammatory syndrome (IRIS) (b, d). The PML lesion at the time of the diagnosis shows typical PML lesion characteristics without any mass effect or perilesional oedema (closed head arrows). At the PML-IRIS stage, the immune reconstitution causes substantial inflammation leading to multifocal contrast enhancement inside and outside of the main PML lesion (d, open head arrows) and swelling, mass effect and perilesional oedema (c, open head arrows).

with natalizumab. Given that 57.1% of patients in a study by Plavina et al⁶³ fell into the higher risk category with an index ≥ 1.5 , 2443 patients would require frequent surveillance MRI scans. As natalizumab is well tolerated with a reduced relapse rate and reduced risk of sustained disability progression, its use in clinical practice will increase.⁵ If these patients at higher risk required 3 scans per year as is suggested, nearly 7500 extra MRI scans per year could be generated from natalizumab surveillance alone. If surveillance protocols were extended to include those patients on other DMDs such as fingolimod and dimethyl fumarate (currently 144 and 272 patients, respectively, in our department), then UK radiology departments would have serious difficulty in scanning and providing reports for these patients. Certainly, PML surveillance scans would have to be

performed by non-neuroradiology specialist radiologists. Therefore, suspicion for and accurate detection of MRI findings in PML will no longer be the preserve of the neuroradiologist and should be at the forefront of any radiologist who reports follow-up MRI scans on patients with MS on DMDs.

CONCLUSION

The use of MRI in the diagnosis and surveillance of MS and treatment-related complications is evolving with new MRI techniques and more DMDs available to clinicians. The most recent revision to the McDonald Criteria has simplified MS diagnosis while maintaining sensitivity and specificity and allows the diagnosis of MS on a single MRI scan. This allows earlier diagnosis and treatment.

More widespread use of newer DMDs will require improved surveillance *via* clinical assessment, MRI and more frequent assessment of anti-JCV antibody status, in order to accurately and promptly detect related complications such as PML, PML-IRIS and rebound episodes. The anti-JCV antibody status provides a quantitative measure of risk related to whether patients should continue with natalizumab treatment

or not and stratifies them into distinct follow-up protocols. More regular repeat MRI scans as part of a surveillance protocol will provide radiology departments logistical challenges as more patients commence natalizumab therapy and effective strategies should be put in place in order to provide clinicians and patients with an effective surveillance programme.

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