Neuroradiological evaluation of demyelinating disease

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Abstract: Central nervous system inflammatory demyelinating disease can affect patients across the life span. Consensus definitions and criteria of all of the different acquired demyelinating diseases that fall on this spectrum have magnetic resonance imaging criteria. The advances of both neuroimaging techniques and important discoveries in immunology have produced an improved understanding of these conditions and classification. Neuroimaging plays a central role in the accurate diagnosis, prognosis, disease monitoring and research efforts that are being undertaken in this disease. This review focuses on the imaging spectrum of acquired demyelinating disease.

Keywords: demyelinating disease, multiple sclerosis, MRI, neuroimaging

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Background

Magnetic resonance imaging (MRI) has become a critically important tool in diagnosis and differentiation of different demyelinating disorders. Prognosis, disease monitoring and treatment changes are often based on the combination of clinical symptoms and neuroimaging findings. MRI is the most commonly used imaging modality as it offers high-resolution images in a noninvasive and safe method, without exposing patients to ionizing radiation. The multitude of available pulse sequences provides unparalleled structural and even functional information that allows investigation of different pathological tissue properties. Since the introduction of MRI, this technique has truly altered the approach to demyelinating diseases, including that of multiple sclerosis (MS) [Noseworthy *et al.* 2000]. The latter is the most common demyelinating disease in adults and leads to significant morbidity and disability within the population. Neuroimaging has played an increasing role in the diagnosis of MS since its initial incorporation in the 2001 McDonald's criteria [McDonald *et al.* 2001] and subsequent revisions [Polman *et al.* 2005, 2011]. In predicting conversion risk from the presentation with clinically isolated (demyelinating) syndrome (CIS), MRI measures have been shown to play a large role [Barkhof *et al.* 1997; Brex *et al.* 2002; Morrissey *et al.* 1993; O'Riordan *et al.* 1998]. Also, there has been increasing recognition of MRI patterns typical for MS, meeting imaging criteria in the absence of any clinically related symptoms, also known as radiologically isolated syndrome (RIS), which over time has the potential to evolve into clinically definite MS [Lebrun *et al.* 2009; Okuda *et al.* 2009; Siva *et al.* 2009]. In other demyelinating or neuro-inflammatory diseases MRI has been incorporated as well into diagnostic criteria, including neuromyelitis optica (NMO) [Wingerchuk *et al.* 1999, 2006], transverse myelitis [Transverse Myelitis Consortium Working Group, 2002], pediatric MS [Callen *et al.* 2009b] and acute disseminated encephalomyelitis (ADEM) [Tenembaum *et al.* 2007].

However, there is a clear discrepancy between the clinical course of the disease and the 'severity' of the appearance of the disease on MRI, also known as the clinicoradiological paradox [Barkhof, 2002]. This has become apparent even in recent subanalyses of data from several clinical studies; the exclusive use of MRI derived surrogate markers of disease activity in clinical trials in its current state was disputed based on its lack of correlation with clinical outcomes [Daumer *et al.* 2009]. Advances in the MRI acquisitions are revealing aspects of MS beyond visibility on conventional imaging techniques. The expectation is that once validated, such new sequences

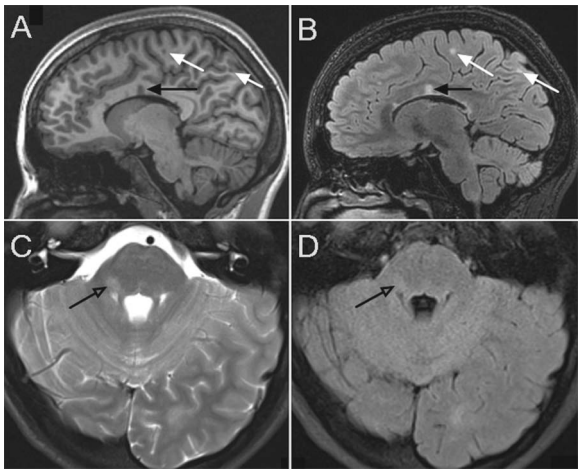

Figure 1. Lesions in subject with relapsing remitting MS. Top images are sagittal images with corpus callosum lesions (black arrows) and juxtacortical lesions on the T1 weighted image (A) and T2 FLAIR weighted image (B). Bottom images clearly demonstrate the improved sensitivity of posterior fossa lesion detection (open arrow) on standard T2 weighted images (C) over T2 FLAIR (D).

gradually will be incorporated into future clinical trials.

In this review we discuss routinely available MRI sequences, their current role in diagnosis, management and disease monitoring of MS and other acquired inflammatory demyelinating diseases, including NMO and ADEM. In addition, we will briefly review some advanced MRI sequences, currently mostly utilized in research studies. We will first review typical imaging features of CIS and MS. Subsequently we briefly review some of the other acquired demyelinating diseases.

Imaging appearance of typical lesions in MS

Although MS is a demyelinating disease that predominantly affects the white matter, anywhere within the central nervous system (CNS) different pathologies can be detected.

White matter lesions

T2 weighted imaging. The hallmark lesions of demyelinating disease are within the white matter of the brain. The classical sequences that visualize MS plaques *in vivo* are T2 weighted imaging (T2WI) acquisition techniques, where lesions are sensitively detected with a hyperintense signal change (Figures 1C and 2A). However, the specificity of detecting the underlying pathology is poor. These lesions typically remain hyperintense over time [Paty and Li, 1993]. It can be difficult to make a clear distinction on T2WI alone between demyelination and other pathological features associated with demyelinating disease (e.g. remyelination, inflammation, edema, Wallerian degeneration, axonal loss) or with other diseases (e.g. cell infiltration, neoplasm, infection, etc.). All of these can have similar hyperintense characteristics on T2WI. The most common T2WI sequences used in clinical practice are fast spin echo (FSE)-based techniques and fluid attenuation inversion recovery (FLAIR). In the latter acquisition technique, an additional inversion recovery pulse is used to suppress signal arising from cerebrospinal fluid (CSF). Owing to the increased tissue contrast in this sequence, it has improved detection of cerebral hemispheric lesions, especially increased sensitivity to the detection of juxtacortical lesions [Filippi *et al.* 1996] (Figure 1B and 2B). The improved tissue contrast of FLAIR images makes it overall easier to spot lesions at the first glance, probably one of the reasons why this sequence is often preferred over standard T2 weighted sequences by practicing neurologists. Often forgotten, they come with a major shortcoming, which is the relative decreased sensitivity to detect posterior fossa lesions [Gawne-Cain *et al.* 1997; Stevenson *et al.* 1997] (Figure 1C and D). Such infratentorial lesions are common in MS and CIS and one of the main reasons to continue to include standard T2WI in the evaluation of possible demyelinating disease. The location of T2 weighted hyperintense lesions is of great importance from the diagnostic perspective in MS. It can help differentiate MS from its numerous mimics and is one of the main reasons why lesion location is prominently featured in the diagnostic criteria of MS [McDonald *et al.* 2001; Polman *et al.* 2005, 2011]. These criteria will be reviewed in further detail later. The most frequently seen lesions are located periventricularly, which have a unique feature in MS where seemingly arising from the ventricle with the main axis almost perpendicular to the main axis of the lateral ventricle [Gean-Marton *et al.* 1991; Offenbacher *et al.* 1993], also known as Dawson's fingers.

There are multiple factors that contribute to what has been called the clinicoradiological or 'MRI paradox': there is a limited weak correlation between standard T2 lesion load and clinical disability. In early relapsing–remitting (RRMS) this

correlation is slightly stronger [Molyneux *et al.* 1998; O'Riordan *et al.* 1998; Sailer *et al.* 1999; Zivadinov and Leist, 2005] and when the disability scale is extended to include higher Expanded Disability Status Scale (EDSS) scores, this correlation does not seem to plateau [Caramanos *et al.* 2012]. Part of this is discrepancy is the location and biological features of lesion recovery that do not have great imaging differentiating factors as remyelinated lesions can have an indistinct appearance on T2WI. In advanced MS the multifocal T2 lesions can 'merge' and become confluent and at the same time brain atrophy has been shown to progress [Pirko *et al.* 2007]. Owing to the combination of these, the lesion load may actually decrease in advanced cases, another potential reason of the paradox.

T1 weighted imaging. T1 weighted scans can be quite unimpressive compared with T2WI in many patients. On first observation, these images may almost appear entirely normal in MS in such patients. However, in some patients many of the typical T2 hyperintense signal change has a T1 hypointense imaging characteristic [Uhlenbrock and Sehlen, 1989], the so-called 'T1 black holes'. This phenomenon can be seen in two instances with largely independent mechanisms.

(1) Acute T1 black holes are seen in an early transient stage in lesion formation [Bagnato *et al.* 2003; Levesque *et al.* 2005]. Cellular infiltration in emerging lesions and associated 'focal edema' are thought to be the pathological correlate. These often resolve [Brex *et al.* 2001; Losseff *et al.* 2001a].
(2) However, approximately 30% of T1 'black holes' will persist, becoming a lifelong present feature [Ciccarelli *et al.* 1999; van Waesberghe *et al.* 1999] (Figure 1A). When persistent, these are thought to represent more severe tissue loss with areas of axonal injury [Bitsch *et al.* 2001; van Walderveen *et al.* 1998], the degree of hypointensity correlated best with axonal density [Bitsch *et al.* 2001]. The most hypointense black holes can have little to no remaining neuronal tissue [van Waesberghe *et al.* 1999]. However, in most cases the signal intensity is higher than CSF in these areas, indicating persistence of (some) CNS tissue.

On advanced MRI, T1 black holes have low magnetization transfer ratios (MTRs) associated with them (even lower than in T1 isointense lesions) [Hiehle *et al.* 1995]. On MRS, the hallmark of chronic black holes is severely decreased N-acetlyaspartate (NAA) [Brex *et al.* 2000]. These are additional indicators of more profound tissue damage in these lesions. This seems to correlate better with clinical disability, as in contrast to T2WI lesion load, T1 black hole load correlates better with chronic disability [Truyen *et al.* 1996; van Walderveen *et al.* 1995, 2001; Zivadinov and Leist, 2005].

Gadolinium contrast enhancement. Gadolinium enhancement (Figure 1D) is considered the hallmark of 'active lesions' as it represents the presence of inflammatory infiltrates through leakage of the blood–brain barrier (BBB). Where most lesions noted on noncontrast T2WI and T1 weighted imaging are chronically present, gadolinium contrast-enhanced lesions (CELs) provide a 'time-stamp' for recent or ongoing inflammatory activity. Gadolinium enhancement is typically observable in the first 4–6 weeks of lesion formation [Cotton *et al.* 2003; Miller *et al.* 1988]. Very rarely, it is detectable beyond 2–3 months, which should raise the concern for alternative diagnoses (neoplasm, [neuro]sarcoidosis, etc.). Chelated gadolinium is the most commonly used contrast material and is detected as a T1 hyperintense signal change. Spontaneous T1 hyperintensity on conventional spin-echo-based T1 weighted studies have been reported [Janardhan *et al.* 2007; Zhou *et al.* 2010], therefore correlation between pre- and post-contrast administrated T1 weighted images should be made. There are alternative iron oxide nanoparticle-based contrast agents that can give hypointense signal changes on T2* weighted imaging, but most of these are experimental and with limited use in human studies [Dousset *et al.* 2006; Pirko *et al.* 2004, 2005; Vellinga *et al.* 2008].

Important factors in the appearance of CELs (sensitivity) are the dose and delay between administration and scanning time in addition to imaging parameters (e.g. slice thickness, field strength, use of 'sensitizing' magnetization transfer pulse [Silver *et al.* 1999]). Typical recommended doses are 0.1 mmol/kg, and a delay of minimal 5 minutes. Between administration and obtaining the T1 weighted post-contrast images, often another noncontrast sensitive sequence is obtained. With the increasing use of gadolinium a linkage between nephrogenic systemic fibrosis and administration of gadolinium was made, most strongly correlated with poor kidney

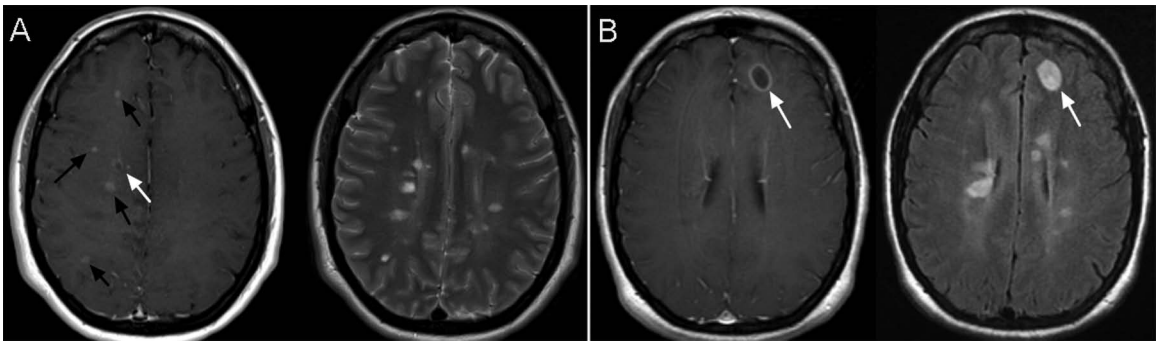

Figure 2. Variety of contrast enhancing lesions in a patient with RRMS during a clinical relapse. (A) shows numerous small, nodular contrast enhancing lesions (black arrow) and a small ring enhancing lesion (white arrow) in a T1 weighted post contrast image (left image), correlating to the hyperintensities on T2 weighted images (right image). Images in (B) show a larger ring enhancing lesion in the right frontal lobe on the T1 weighted post gadolinium contrast images (left image) with multiple older lesions appearing on FLAIR imaging (right image).

function, the reason to screen for this prior to administration of gadolinium [Sadowski *et al.* 2007]. In cases of limited estimated glomerular filtration rate (eGFR), caution should be applied in the use of gadolinium-based contrast agents [Colletti, 2008; Haemel *et al.* 2011].

It deserves mention that, similar to other lesion-based clinicoradiological discordances, in many cases the presence of enhancement will not result in an obvious new clinical relapse. As a matter of fact, presence of gadolinium enhancement is 5–10 times more common than clinical observation alone [Thompson *et al.* 1992]. This increased sensitivity to recent disease activity is the main reason that gadolinium-enhanced lesion-based quantitative metrics have been used as surrogate markers of outcome measures in clinical trials of MS therapies. While efficiently capturing recent inflammatory activity, these lesions also do not correlate well with disability on longitudinal studies. The mean number of CELs in the first 6 months after the diagnosis of MS showed only a weak correlation with disability 1 and 2 years later [Kappos *et al.* 1999]. In biopsy-proven demyelinating disease, also no such association was found between ring CELs and disability [Lucchinetti *et al.* 2008]. CELs are not single predictors of subsequent relapses and many factors, including overall clinical course, imaging appearance and temporal changes in addition to most importantly patient preference is what should guide decision making regarding treatment change. This is one of the most important features for the practicing neurologist, treatment changes are made based on disease activity overall and not the appearance of imaging features alone at this point.

In progressive forms of MS, contrast enhancement can be present, albeit with much lower incidence. In secondary progressive MS (SPMS), CELs are rarely seen and often are not observed at all [Kidd *et al.* 1996; Tubridy *et al.* 1998]. In primary progressive MS (PPMS), CEL have been reported in as low as approximately 5% of cases [Thompson *et al.* 1991]. This is thought to occur more frequently in the earlier stages of the disease, in the first 5 years of PPMS as high as 40% of patients may have associated cerebral CELs [Ingle *et al.* 2005].

The physical appearance of CELs can take many different forms. The differential diagnosis of ring enhanced lesions is wide and includes gliomas, metastases, abscesses, etc. Demyelinating CELs can appear as homogenously enhanced lesions, heterogeneous/nodular pattern or with (open) ring enhanced patterns [Grossman *et al.* 1986, 1988; Miller *et al.* 1988; Thompson *et al.* 1992; Thorpe *et al.* 1996] (Figure 2). In the case of the very specific open ring enhancement pattern, the opening is typically outward, towards the cortex [Masdeu *et al.* 1996, 2000]. Ring enhanced lesions are often larger and can have specific imaging features, including shorter duration of enhancement [Minneboo *et al.* 2005], low signal intensity on apparent diffusion coefficient (ADC) [Leist *et al.* 2001] and MTR [Morgen *et al.* 2001]. There are some reports on the evolution into T1 black holes and the association with the development of brain atrophy [Bagnato *et al.* 2003].

Tumefactive demyelinating white matter lesions

A small subset of patients will initially present with unusually large or tumefactive solitary or

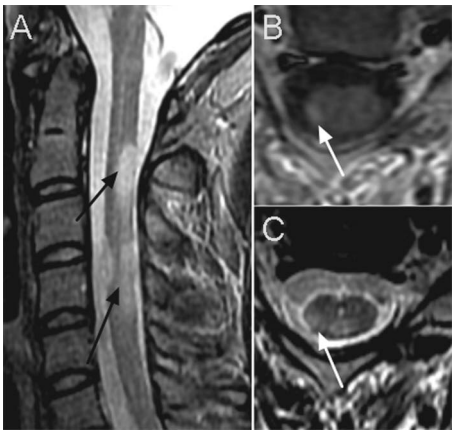

Figure 3. Typical spinal cord lesions in a patient with RRMS. On the sagittal STIR sequence (A) multiple ovoid lesions (black arrows) are seen extending across one vertebral segment. The images on the right show axial cuts of the same individual, showing the typical pattern of ovoid lesion in the right dorsolateral aspect of the cervical spinal cord (white arrow). (B) post gadolinium contrast T1 weighted image, (C) T2 weighted image.

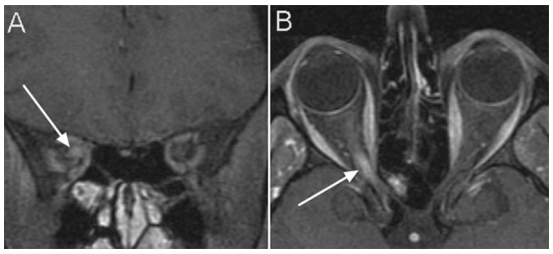

Figure 4. Post gadolinium fat saturated T1 weighted images showing contrast enhancement and thickening of the optic nerve (white arrows) on coronal (A) and axial image (B).

multiple demyelinating lesion. These typically have contrast enhancement patterns as described above and the differentiating between the potential diagnoses is even more pressing as entirely different treatment pathways and prognosis follow. Other similar appearing lesions primarily include primary brain neoplasms (e.g. high-grade gliomas), metastatic malignancies and abscess. Biopsies are often obtained to complete the evaluation of these atypical lesions as differentiation on imaging presentation alone often is not sufficient. Efforts to differentiate using magnetic resonance spectroscopy (MRS) has not been proven helpful thus far. MRS of tumefactive demyelinating lesions may show elevated choline and decreased NAA peak in addition to lactate and lipid peaks, similar findings have been seen in neoplastic lesions [Saindane *et al.* 2002]. Changes in MRS patterns over time may be suggestive of demyelinating etiology [Butteriss *et al.* 2003]. Some had reviewed specific diagnostic algorithms [Al-Okaili *et al.* 2007] to incorporate perfusion MRI, diffusion weighted imaging and conventional MRI. Other subtle imaging findings can include the presence of a similar T2 hypointense rim and a pattern of open ring enhancement favoring demyelination. The hypointense borders are thought to correlate with the location of macrophages in these lesions, but are not specific. However, a recent correlation study between histopathology and MRI findings of tumefactive demyelinating disease found that distinguishing appearance of tumefactive lesions include appearance on the ADC maps of diffusion weighted imaging [Abou Zeid *et al.* 2012]. The behavior of peripheral ADC patterns at the lesion edge was found to have significant peripheral diffusion restriction in demyelination, compared with abscesses and tumors ($p = 0.006$); whereas central restriction was only seen in abscesses.

Spinal cord lesions

Spinal cord lesions (Figure 3) are prominently present in MS and are commonly not fully investigated. As reviewed later, the significance of spinal cord involvement is also underlined in the newly revised diagnostic criteria of MS [McDonald *et al.* 2001; Polman *et al.* 2005]. The best way to detect spinal cord lesions are T2 weighted short tau inversion recovery (STIR) and FSE sequences. On sagittal scans, smaller MS lesions can be missed and opposed to NMO, these rarely extend longitudinally beyond one spinal cord segment. When imaging quality and patient factors permit (e.g. movement, obesity), axial cord images commonly show smaller lesions with involvement of small sections anywhere within the spinal cord, commonly affecting the posterior or lateral aspects. This typically is around a quarter to half of the axial cord slice surface area, with both white and gray matter involvement. STIR imaging is often used to increase the sensitivity of spinal cord lesion detection [Bot *et al.* 2000]. These images also provide fat suppression, which may be useful in optic nerve imaging as well [Campi *et al.* 2000; Moseley *et al.* 1998]. Similar to T1 black holes that are most commonly found in the cerebral white matter, T1 hypointense signal changes can be found in the spinal cord [Losseff *et al.* 2001b]. In progressive forms of MS, where the clinical picture is predominated by myelopathic symptoms, subtle cord

atrophy and increasing cord lesion load may be the only MRI manifestations.

Optic nerve lesions

The optic nerve is frequently involved in demyelinating disease and optic neuritis (ON) can be seen as CIS or as part of MS, ADEM or NMO. The diagnosis of ON is clinical with most frequently gradual worsening of visual acuity, color perception and associated eye pain. Imaging findings can be supportive, best demonstrated with dedicated orbital/optic nerve imaging (Figure 4). The most significant contribution of imaging at initial presentation with isolated ON is evaluation with brain MRI. The overall conversion risk to MS in the optic neuritis treatment trial (ONTT) was approximately 50% in 15 years after initial presentation with ON [Brodsky *et al*. 2008]. When brain MRI findings were incorporated, risk stratification revealed that approximately 75% of patients converted when brain lesions were present, where only 25% of patients with a normal MRI developed MS in that time frame. Advanced imaging methods such as diffusion tensor imaging have been used to study ON as well and only have been described to possibly predict outcome [Naismith *et al.* 2009, 2010], without any clear diagnostic advantage.

Subcortical gray matter lesions

On standard T2 weighted images, hypointensities have been observed and described in the thalamus and deep gray nuclei [Bakshi *et al.* 2001, 2002; Bermel *et al.* 2005; Grimaud *et al.* 1995; Tjoa *et al.* 2005]. The presence of such lesions seems to correlate with specific imaging outcomes such as brain atrophy, and with clinical outcome measures, including an increased likelihood for cognitive dysfunction, fatigue and disability. In addition, quantitative volumetric MRI metrics in these regions seem to correlate with similar clinical outcomes [Batista *et al.* 2012; Benedict *et al.* 2009]. Although not yet conclusively proven, pathological iron deposition seems to play a role in this, further supported by imaging features using susceptibility weighted imaging [Haacke *et al.* 2007; Hagemeier *et al.* 2012].

Cortical gray matter lesions

Whereas T2WI sequences are very sensitive in detecting demyelinated white matter lesions, they are relatively insensitive in the detection of cortical gray matter pathology. The presence of pathological abnormality within the cortex in MS has been discussed since the early descriptions by Charcot. A recent study investigating pathological samples obtained from biopsies of demyelinating white matter lesions found that in 38% of the specimens cortical demyelination was present *en route* to the biopsy core [Lucchinetti *et al.* 2011]. Lesions can be located in subpial, intracortical or leukocortical areas and even meningeal inflammation can be seen in early phases of the disease [Popescu and Lucchinetti, 2012]. Together with inflammatory demyelinating lesions in the cortex, over time there has been substantial evidence for advanced brain and cortical atrophy developing over time with MRI-based studies. Interestingly, these changes are more typically associated with clinical outcomes [Pirko *et al*. 2007; Zivadinov and Leist, 2005].

The detection of cortical lesions is so far the most sensitive of the T2 weighted inversion recovery techniques, including FLAIR and the recently developed double inversion recovery (DIR) acquisition techniques. DIR, which will be reviewed in further detail in the advanced imaging section, has an increased sensitivity of detecting cortical lesions compared with FLAIR, although in a recent pathology and MRI correlation study, this sensitivity was only 18% compared with the gold standard, histopathology [Seewann *et al.* 2012]. Part of this is that the greatest sensitivity is to detecting leukocortical or juxtacortical lesions, where the vast majority of intracortical and subpial cortical lesions remain undetected.

Imaging findings of other demyelinating diseases

The differential diagnosis of typical imaging findings of MS is large. As reviewed above, one of the most important features in detecting typical MS lesions is location. In contrast to MS lesions, nonspecific lesions due to small vessel ischemia and migraines tend to spare the U-fibers (juxtacortical lesions) and the hallmark periventricular locations of demyelinating disease. In addition, the nonspecific white matter lesions of such etiologies are typically absent in the infratentorial brain, with the exception of rare pontine lesions that can be seen in small vessel ischemic disease. Spinal cord lesions are typically not seen in small vessel ischemic disease, underlining the importance of diagnostic use of spinal cord imaging to assess demyelinating disease [Bot *et al.* 2002].

Table 1. Table summarizing important entities in the differential diagnosis of MS and potential 'red flags' in the misdiagnosis of MS.

Brain white matter	Disease	Cortical gray matter	Disease
Normal	NMO (absent or few lesions), ATM	Cortical/subcortical lesions crossing vascular territories	MELAS
Large lesions	AMS (can be confluent with perilesional edema), BCS, PACNS (with mass effect)	Infiltrating lesions that do not remain in gray or white matter boundaries	Abscess
Symmetrically distributed lesions	ADEM, AFL	Prevalent involvement *versus* white matter	Encephalitis
Poorly defined lesion margins	ADEM, pattern III MS	**Deep gray matter**	
Absent MRI activity at follow-up	ADEM	Bilateral lesions	ADEM (GM-WM junction), CADASIL
Involvement temporal pole, vertex U-fibers, external capsule, insula.	CADASIL	Lacunar infarcts	CADASIL, SVD
Bilateral microhemorrhagic foci	CADASIL, SVD, AHEM/AHLE, PACNS	T1-hyperintensity of the pulvinar	FD
Frequent sparing of CC and cerebellum	CADASIL, SVD	Multiple discrete lesions in the basal ganglia and thalamus	Susac's syndrome
Predominant CC involvement	Susac's syndrome	Large and infiltrating basal ganglia lesions	NBD
Enhancement of all lesions	ADEM, PACNS, sarcoidosis	Infiltrating lesions without respecting gray-matter or white-matter boundaries	Abscesses
Infarcts	SID, PACNS, SVD	T2-hyperintense lesions in the dentate nuclei	AFL (CTX)
Punctate parenchyma enhancement	PACNS, sarcoidosis, NBD	**Spinal cord**	
Predominance of lesions at the cortical/subcortical junction	SID	Large and swelling lesions	NMO, ADEM, ATM, Sjögren's syndrome
Diffuse white matter involvement	NBD, encephalitis, SVD, CADASIL	Diffuse posterior column abnormalities	B12D, ACD
Cerebral venous sinus thrombosis	NBD	**Other**	
Infiltrating (large) brainstem lesions	NBD	No 'occult' changes in the NAWM	NMO, Lyme disease, SID (except in NSLE)
Anterior temporal and inferior frontal lobe involvement, associated with enhancement or mass effect	Encephalitis (HSE)	Pontine lacunar infarcts	CADASIL, SVD
Isolated lesions with ring enhancement (often complete)	Abscess	Dilation of Virchow–Robin spaces	HHC, PACNS
Mass effect	Abscess, metastasis, malignancy, tumefactive MS	Diffuse lactate increase on brain MRS	MELAS
Progressively enlarging lesions, asymmetric lesions (juxtacortical origin)	PML	Meningeal enhancement	Susac's syndrome, PACNS, NBD, meningitis, Lyme disease, sarcoidosis
Large lesions, absent or rare mass effect	PML	Hydrocephalus	Sarcoidosis

(Continued)

Table 1. (Continued)

Brain white matter	Disease	Cortical gray matter	Disease
Extensive and bilateral periventricular abnormalities in isolation	B12D, ACD	Absence of optic-nerve lesions	PML
		Regional atrophy	HHC (hippocampus and amygdala), NBD (brainstem)

ACD, acquired copper deficiency; ADEM, acute disseminated encephalomyelitis; AFL, adult forms of leukoencephalopathies; AMS, acute multiple sclerosis (Marburg type); ATM, acute transverse myelitis; B12D, vitamin B12 deficiency; BCS, Balo's concentric sclerosis; CNS, central nervous system; CTX, cerebrotendinous xanthomatosis; FD, Fabry's disease; HHC, hyper homocystinemia; HIVE, HIV encephalitis; HSE, herpes simplex encephalitis; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MRS, magnetic resonance spectroscopy; MS, multiple sclerosis; NAWM, normal-appearing white matter; NBD, Behçet's disease with CNS involvement; NMO, neuromyelitis optica; NSLE, neuropsychiatric systemic lupus erythematosus; PACNS, primary angiitis of the CNS; PML, progressive multifocal leukoencephalopathy; SID, systemic immune-mediated disease; SSP, subacute sclerosing panencephalitis; SVD, small-vessel disease.

A workshop of the European MAGNIMS (Magnetic Resonance Network in Multiple Sclerosis) defined 'MRI red flags' derived from evidence-based findings and expert opinion [Charil *et al*. 2006]. Table 1 summarizes some of the identified MRI features that are suggestive of specific other pathologies and in the appropriate clinical setting should trigger consideration of work up targeted to other etiologies.

Neuromyelitis optica

The diagnostic criteria of NMO have been established after recognition that this was more than a variant of MS and now is recognized as a separate disease entity with an entirely different epidemiology, pathology and radiographic appearance. The breakthrough has been the discovery of a serum marker (NMO-IgG) against aquaporin 4 (AQP-4) [Lennon *et al.* 2004, 2005]. Although highly specific (>99%) [McKeon *et al.* 2009; Waters *et al.* 2012], sensitivity of the serological disease marker remains around 70% and depends on the performed laboratory method [Waters *et al.* 2012]. This is reflected in the revised diagnostic criteria; it remains a clinical diagnosis with ancillary support of radiographic and serological features. These criteria [Wingerchuk *et al.* 2006] include the presence of (1) clinical history of both ON and transverse myelitis, with (2) two out of the three supporting criteria (MRI evidence of longitudinally extensive transverse myelitis in >3 vertebral segments, brain MRI is nondiagnostic for MS at onset, or positive NMO-IgG testing).

NMO spinal cord lesions demonstrate a 'swollen cord' appearance with mass effect. Not uncommonly initially this would raise the question of neoplastic or ischemic disease. The lesions are longitudinally extensive (defined as stretching over >3 vertebral segments) and in most typical circumstances involve over half of the area on axial cuts (Figure 5A and B). This often distinguishes readily from MS-like lesions, which are smaller lesions as reviewed earlier. NMO lesions more often have central cord involvement and can affect both gray and white matter within the spinal cord. In addition, optic nerve lesions also have a tendency to be more extensive in length, often crossing the optic chiasm, a feature not commonly seen in MS-related ON. MS and NMO both have the presence of demyelination on histopathology. However, in NMO lesions there is

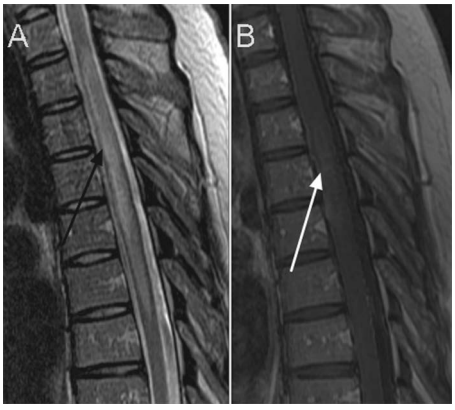

Figure 5. Spinal cord lesions in a patient with neuromyelitis optica (NMO). These images very nicely demonstrate the longitudinally extensive involvement of the spinal cord in this disease. In this patient this extended over a region of 5 vertebral segments as seen on the sagittal STIR image (A), with in affected area a faint, heterogeneous hyperintense signal change after gadolinium contrast administration on sagittal T1 image (B).

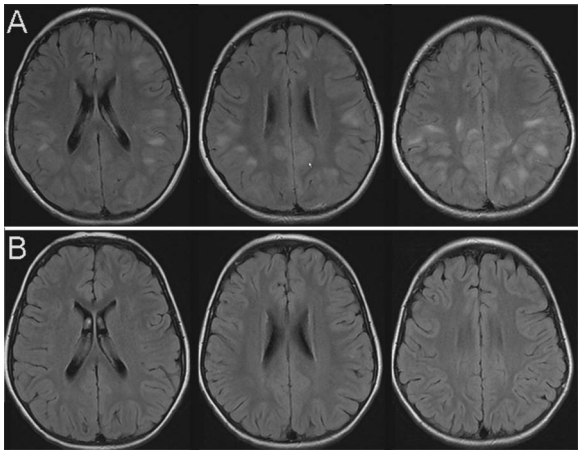

Figure 6. Images of acute disseminated encephalomyelitis (ADEM) in a pediatric patient. The T2 FLAIR axial images were acquired during the symptomatic phase of the disease (A) with typical poorly demarcated lesions with white matter and grey matter involvement. There was no contrast enhancement of any of these lesions (not shown). On follow up imaging three months later (B) no residual signal change is noted.

generally more tissue destruction than what is seen in MS lesions, resulting in some features of the characteristic imaging appearance. Related to that is the finding that on average it seems that NMO attacks can be associated with more significant disability after a single attack. It is critical to differentiate NMO from MS as commonly used therapies for MS (interferon β) have been reported to possibly worsen the clinical course of NMO [Kim *et al.* 2012; Shimizu *et al.* 2010].

One of the most important revisions was to no longer exclude the presence of brain lesions as these were described to be frequently present in NMO [Pittock *et al.* 2006a, 2006b]. Cerebral white matter findings could even meet imaging criteria for MS, but more often are fairly nonspecific in imaging characteristics and confined to regions known to be rich in AQP-4 [Pittock *et al.* 2006b]. These typically include periventricular regions of the third (diencephalic) and fourth ventricle (brainstem). In comparison with MS, where abnormalities are found in the unaffected white and gray matter (normal-appearing white matter [NAWM] and normal-appearing gray matter [NAGM]), such abnormalities are not commonly found in NMO and if present seem to be in areas involved in connection to the active disease, e.g. corticospinal tract or optic radiation [Filippi *et al.* 1999b; Pichiecchio *et al.* 2012; Yu *et al.* 2007].

Acute disseminated encephalomyelitis

ADEM is an immune-mediated inflammatory demyelinating disorder that often is preceded by infection or vaccination and usually behaves as a monophasic disease [Leake *et al.* 2004; Torisu *et al.* 2010]. The diagnosis of ADEM has not been as rigidly reviewed and revised as those of MS and NMO. Part of this is the low incidence of the disease and its variable clinical presentation and course. While ADEM can occur at any age it is most commonly encountered in the pediatric age group. An international pediatric study group proposed clinical criteria [Krupp *et al.* 2007]. Part of one of the main distinguishing clinical features of ADEM that was included most commonly in clinical criteria [Krupp *et al.* 2007] is the presence of encephalopathy. In addition to a variable degree of encephalopathy, both clinical and imaging findings need to be consistent with polyfocal demyelinating disease. Around the same time another study group that focused more on presentation at older age (>15 years) proposed similar diagnostic criteria that could differentiate from MS: clinical symptoms atypical for MS, absence of oligoclonal bands (OCBs), and gray matter involvement [de Seze *et al.* 2007].

Neuroimaging of ADEM has multiple characteristic features. Brain parenchymal abnormalities are typically large, multiple, bilateral but asymmetric, poorly demarcated, areas of increased signal on T2-weighted and FLAIR sequences which can affect both white and gray matter (Figure 6). Gray matter involvement can be neocortical or deep gray matter (thalamus, basal ganglia). Brainstem and cerebellum are commonly involved [Callen *et al.* 2009a; Ketelslegers *et al.* 2010; Tenembaum *et al.* 2007]. Associated edema, swelling and localized mass effect can be seen in larger lesions. Enhancement is not commonly encountered (10–30%), can be marginal and/or nodular in distribution. Four imaging patterns have been proposed based on evaluation of pediatric patients with ADEM [Tenembaum *et al.* 2002,2007] These categories included ADEM with (1) multifocal numerous small (<5 mm) lesions, (2) large, confluent white matter lesions with frequent edema and mass effect, (3) bithalamic involvement, and (4) acute hemorrhagic encephalomyelitis (AHEM) [Tenembaum *et al.* 2002]. The latter is with T2* hypointensity within areas of T2 hyperintense signal change. In pediatric patients, spinal cord involvement has been reported to potentially include long segments (>3 vertebral segments) [Tenembaum *et al.* 2007; Yiu *et al.* 2009] that are NMO-IgG negative [Banwell *et al.* 2008].

Follow-up imaging often documents resolution of the signal change abnormalities and the development of additional lesions are not compatible with a monophasic course of ADEM. Complete resolution of lesions can occur in up to half of patients with ADEM, however residual hyperintensities on T2WI likely represent gliosis and demyelination [Dale *et al.* 2000].

Pathologically, ADEM is different from MS and shows a striking perivenular inflammatory demyelination [Wingerchuk and Lucchinetti, 2007; Young *et al.* 2010]. The risk of development of MS has varied significantly in the last few decades, partly due to variable inclusion criteria that were applied. Initially, this risk was estimated to be as high as 20–30% [Mikaeloff *et al.* 2004, 2007; Tenembaum *et al.* 2002, 2007]. Using MRI to refine diagnostic criteria better to distinguish between pediatric MS and ADEM suggested the presence of two out of the following three criteria to distinguish MS from ADEM: (1) absence of a diffuse bilateral lesion distribution pattern; (2) presence of T1 hypointense lesions; (3) presence of two or more periventricular lesions. On imaging appearance alone, this was found to be 81% sensitive and 95% specific[Callen *et al.* 2009a], later confirmed by others [Ketelslegers *et al.* 2010]. Using these and the more stringent clinical criteria, a recent prospective population based study in Canada revealed conversion rates of MS in ADEM in pediatric patients as low as 3.3% [Banwell *et al.* 2011].

The role of MRI in diagnostic criteria of MS

Relapsing–remitting multiple sclerosis

Since the first international consensus criteria for MS that incorporated MRI criteria (also known as McDonald criteria) [McDonald *et al.* 2001], two subsequent revisions [Polman *et al.* 2005, 2011] have reflected the increased role of MRI in the diagnostic process. These criteria are based on the 'dissemination in space' and 'dissemination of time' in MS. Although MS-related pathology and MRI change can be seen anywhere in the CNS, the most commonly encountered location remains the periventricular white matter, where ovoid lesions are often observed (Dawson's fingers). In addition to periventricular (1) lesions, juxtacortical (2), infratentorial (3) and spinal cord lesions (4) are specifically included in the 2010 dissemination in space criteria. With these current criteria, the presence of lesions in any of two of these four locations meets the 'dissemination in space' criteria.

The criterion for dissemination in time was simplified in most recent 2010 revision of the McDonald criteria. Where previously either new enhanced or nonenhanced new lesions needed to develop between two defined time points, now the diagnosis can be made within one single scan. Simply, the presence of asymptomatic CELs and nonenhanced T2 hyperintense lesions fulfill the prior requirement of lesions developing over a minimum of 3 months. Thus, one single MRI is sufficient to establish dissemination in time. The importance of imaging findings in the different stages of lesion formation come from prior studies showing that these findings hold up in early stages of MS and conversion of CIS [Montalban *et al.* 2010; Rovira *et al.* 2009]. The only caveat to such measures of increasing sensitivity (capturing disease earlier) is that it can be at the cost of specificity. Special care should be maintained in interpreting scans: the prior mentioned persisting gadolinium-enhanced 'lesions' can include other inflammatory pathologies (e.g. sarcoidosis) or occasionally observed structural anomalies (e.g. venous angiomas) could erroneously conclude that dissemination in time could be present or only related to MS. MS remains a clinical diagnosis with data derived from clinical history, neurological examination supplemented by ancillary support from both laboratory and MRI. It can and will not fully be replaced by any one of these components alone.

Primary progressive multiple sclerosis

PPMS typically presents as a slowly progressive myelopathy. As reviewed earlier, MRI features of PPMS include a cord predominant lesion pattern with minimal to no CELs in comparison with RRMS. The current (in 2010 revised) MS criteria were further simplified and require 1 year of slow clinical progression, and two out of the following three findings: (1) limited evidence of DIS in the brain (with one or more periventricular, juxtacortical and infratentorial lesion); (2) evidence of DIS in the cord with two or more characteristic T2 weighted lesions; (3) positive CSF (OCB elevation and/or IgG Index elevation).

Clinically isolated syndrome

The initial presentations of MS include well-characterized subacute onset demyelinating syndromes that can include either ON, transverse myelitis, or isolated brainstem/cerebellar syndromes, but the

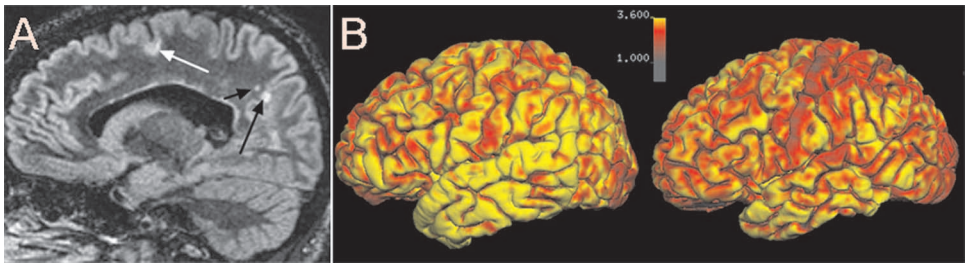

Figure 7. (A) Sample image of double inversion recovery imaging (DIR) demonstratting the presence of leukocortical lesion (white arrow) and typical white matter lesions (black arrows). Image (B) shows a sample of cortical thickness measurements using Freesurfer (software available on http://surfer.nmr.mgh.harvard.edu) showing a sample of a healthy control (left image) and a patient with RRMS. The color bar representing the cortical thickness goes from thin (red) to thicker cortex (yellow) measurements.

differential diagnosis can be broad. CIS is when there is a single clinical event that is demyelinating in nature, where the clinical and MRI criteria for dissemination in time are not met. The clinical presentation of CIS immediately raises the question whether this represents a first episode of MS and what to expect in terms of prognosis and risk of relapse. The question of evaluation of the risk of conversion to MS has been studied extensively and these studies have contributed to the revision of some of the MRI criteria to allow earlier diagnosis of MS. The most sensitive measure has been the presence of typical MS lesions on MRI at time of presentation. Most of this knowledge comes through the series of longitudinal studies from the National Hospital in London, UK and were confirmed in (usually smaller) studies [Brex *et al.* 2002; Chard *et al.* 2003; Fisniku *et al.* 2008; Morrissey *et al.* 1993; O'Riordan *et al.* 1998]. This has established that at different time points in follow up, the conversion risk of developing MS was significantly higher when other CNS lesions were present. It has become evident that most of the conversion takes place in the first few years after the initial demyelinating event. These time points were 1 year (30% *versus* 0%), 5 year (65% *versus* 3%), 10 year (83% *versus* 11%), 14 year (88% *versus* 19%) and 20 years (82% *versus* 21%). Part of some of this fluctuation is the availability of follow up [Fisniku *et al.* 2008]. Those that converted with an unremarkable MRI at presentation typically had a milder course of the disease. The follow up at the last time point (20-year follow up) [Fisniku *et al.* 2008] addressed the disability rate and in those that had converted to MS, there was a significant correlation between T2 lesion volume and EDSS, most evident in the first 5 years. This study established that change in lesion volume at earlier time points are correlated with disability at 20 years. There statistical significant difference in the rate of lesion growth over the duration of the study was 0.80 cm^3/year in those patients who continued in a relapsing–remitting course, and 2.89 cm^3/year in those who developed SPMS.

Radiologically isolated syndrome

RIS is an entity when the typical MRI findings of MS can be seen in entirely asymptomatic patients. These MRIs are often obtained in the work up of unrelated diseases, e.g. headache, head injury, etc. When upon further historical or and/or laboratory investigations, no other evidence can be found for demyelinating disease or other explanatory diagnoses, this finding is commonly labeled as the RIS. This is somewhat of a misnomer as patients by definition do not have any 'syndrome', there is no constellation of symptoms that would fit with CIS or MS. Thorough evaluation investigating other etiologies is often warranted. There is evidence that a subgroup of these patients will develop clinically definite MS, over as long as 10 years [Lebrun *et al.* 2009; Okuda *et al.* 2009; Siva *et al.* 2009]. In one of these series (n = 44), radiological evidence for new lesion formation was seen in 59%, only 22.8% had clinical symptoms and 'converted' to CIS or MS [Okuda *et al.* 2009]. The presence on initial imaging of CELs [Okuda *et al.* 2009] or asymptomatic spinal cord lesions [Okuda *et al.* 2011] have been reported to be predictors of clinical conversion to either CIS or MS. Extensive cognitive testing demonstrated similar cognitive abnormalities in the patients with RIS as compared with patients with MS [Lebrun *et al.* 2010]. Cases of RIS need radiological and clinical follow up and treatment decisions should be dependent on radiological or clinical conversion. Further efforts to improve the understanding of this entity are ongoing.

Advances in MRI in demyelinating disease

Both MRI acquisition and post-processing of MRI data have gone through tremendous improvements in the recent years. It is beyond the scope of this paper to review all research MRI sequences and processing techniques in a comprehensive matter, as currently many of these are not yet available for routine clinical practice. Despite the advances that have been made, not many have made it into clinical practice. The validation of such improved acquisitions or analysis tools in the solution to the discrepancy between clinical outcome and imaging findings will greatly advance diagnostic and therapeutic decision points. Some of the main hurdles to implementation in clinical practice are that many of these methods require pulse sequences and post-processing software that is often not installed in the standard package of MRIs. In addition, the post-processing steps are often time and labor intensive, requiring significant computational power and interpretation and can be clouded by fairly easily introduced artifacts. We will briefly highlight some of the potential advances in evaluation with the most commonly used techniques.

Volumetric studies of the brain and spinal cord have been important in detecting ongoing and early presence of atrophy in MS. Atrophic changes are most pronounced in progressive stages of advanced MS, but are detectable even in the earliest stages of the disease [Sastre-Garriga *et al.* 2004, 2005; Tiberio *et al.* 2005] (Figure 7B). In addition, atrophy keeps progressing even when new lesion formation or gadolinium enhancement are no longer detectable in progressive MS, and is overall at least partially independent of lesion load in most studies [Anderson *et al.* 2007; Fox *et al.* 2000; Jasperse *et al.* 2007; Losseff *et al.* 1996; Miller *et al.* 2002]. Studies have shown that this is strongly correlated with clinical disability [Bermel and Bakshi, 2006; De Stefano *et al.* 2007; Kutzelnigg and Lassmann, 2005; Simon, 2006; Zivadinov and Bakshi, 2004]. Improvements in automated methods to generate volumetric assessments have resulted in different software applications to study this in an organized method. In clinical practice the application is still somewhat limited despite the ready availability of this software, there have been no great studies where this is implemented in outcome measures of clinical therapeutic intervention trials. MS-related atrophy includes both gray and white matter loss, with the potential predominance of gray matter atrophy emerging in more recent studies [Pirko *et al.* 2007; Zivadinov and Cox, 2007].

High field strength MRI has become increasingly available. These have become more widely available. Many institutions have 3 T scanners, with up to 7 T or higher becoming available in a smaller number of centers. Current FDA approval for clinical use goes up to 4 T, making the others currently only useful for research purposes with local IRB approval. The energy absorption in tissue is higher and sequences need to be specifically designed to allow the desired acquisition techniques without crossing the specific absorption rate (SAR). These sequences have been generally without described adverse events. Higher field strength results in higher signal-to-noise ratio, enabling higher-resolution acquisitions in shorter time. Along with that comes the potential of improved contrast-to-noise ratio. In MS, research studies applying higher field strength MRIs have resulted in some interesting studies, although validation of many will have to come with time. There has been the potential for improved lesion detection in white and cortical gray matter [de Graaf *et al.* 2012; Mistry *et al.* 2011; Nielsen *et al.* 2012], deep gray matter pathology [Lebel *et al.* 2012] and unusual imaging features of white matter lesions with persistent ring phase white matter lesions [Bian *et al.* 2012] all potentially provide additional insight in the pathology of MS, where clinical application may be still far out.

Magnetization transfer imaging (MTI) was first performed in MS patients in 1992 [Dousset *et al.* 1992]. An additional saturation pulse is directed at macromolecules such as myelin and subsequent transfer of magnetization to the mobile proton pool is measured. It allows the influence of these macromolecules on the local environment to be studied, thus providing a sensitive marker for tissue integrity. In lesions, the MTR is decreased proportional to the degree of tissue abnormality. In NAWM and NAGM it has been shown that the MT ratio is altered, reflecting nonlesional pathology [Chen *et al.* 2005; Filippi *et al.* 1999a; Laule *et al.* 2003; Rovaris *et al.* 2003; Santos *et al.* 2002]. Changes in NAWM and NAGM are often detectable very early in MS, and correlate at least moderately with future disability according to most [Rovaris *et al.* 2003; Santos *et al.* 2002; Traboulsee *et al.* 2002] but not all studies [Rocca *et al.* 2008]. MTR signal intensity may normalize as part of normal lesion evolution [Filippi and Rocca, 2004; Inglese *et al.* 2005] or may remain decreased [Dousset *et al.* 1998; Inglese *et al.* 2005; Oreja-Guevara *et al.* 2006]. The potential normalization is thought to reflect underlying tissue repair (remyelination) [Barkhof *et al.* 2003]

and could be used potentially in studies investigating therapeutics addressing remyelination and regeneration.

Diffusion tensor imaging has found similar changes within the NAWM and NAGM. By measuring the relative displacement of free water it provides information on the directional migration of water along and perpendicular to nerve fibers. This provides a marker of white matter integrity as this is altered in injured nerve fibers. This is often measured in fractional anisotropy (FA) and mean diffusivity measures along the nerve fibers (axial diffusivity), perpendicular to the nerve fibers (radial diffusivity) or mean diffusivity measures. This method is similar to measuring changes of restricted diffusion commonly used in other pathologies (such as ischemic strokes), but in diffusion tensor imaging more gradient directions are applied, which allows for more accurate vector measurement, which is used to calculate diffusivity measures and FA. The latter is a mathematical value that describes whether the overall direction of the diffusion is linear. When the direction of movement is uniformly in the same direction (highly organized tissue in one direction) the FA is larger. When movement in all directions is equal, e.g. free water), the FA approaches zero. Therefore, white matter has higher FA values than gray matter and is highest in areas of organized parallel fiber bundles. In MS, FA values have been reported to be lower. This goes for lesional areas, NAWM and NAGM [Ciccarelli *et al.* 2001, 2003, 2005; Griffin *et al.* 2001; Werring *et al.* 1999]. These subtle changes can be present in the earliest stages of MS, even in pediatric patients [Tillema *et al.* 2012; Vishwas *et al.* 2009].

Double inversion recovery imaging was introduced relatively recently. The acquisition is similar to FLAIR with an additional inversion recovery pulse compared with FLAIR. These are calibrated to suppress signal arising from both CSF and white matter. The sequence has an inherent low SNR, but excellent CNR, leaving better visibility of white matter pathology and cortical lesions (Figure 7A). It has mostly been described in studies improving the detection of cortical lesions, but there is great interrater variability when different acquisition parameters are used [Geurts *et al.* 2011]. In a recent study comparing DIR with the gold standard, histopathology, while it did have improved detection compared with FLAIR, but still only had a sensitivity of 18% [Geurts *et al.* 2005; Seewann *et al.* 2012].

Conclusions and future directions

MRI has become the single most important paraclinical biomarker of demyelinating diseases and these are routinely used in the diagnostic process, prognosis, disease and treatment monitoring of inflammatory and demyelinating diseases. A growing body of imaging research, using advanced acquisition and post-processing techniques, has revolutionized the understanding of these diseases. Despite these enormous advances, the relative lack of specificity of standard MRI techniques and lack of clear correlation between these measures and clinical outcome stress the need for further research in this field. No paraclinical diagnostic modality can replace solid clinical judgment using all available sources, but MRI has been and will continue to represent an important supplement to the decision-making process. Validation of newer imaging acquisitions will continually result in gradual changes in the implementation of MRI in clinical practice.

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