Neuroimaging in Multiple Sclerosis

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1. Introduction

Multiple sclerosis (MS) is a chronic disabling autoimmune disorder of the central nervous system histopathologically characterized by inflammation, multifocal demyelination, axonal damage and neuronal loss. Focal intensive demyelination and white matter infiltration by lymphocytes and mononuclear cells are pathological hallmarks of the disease (Ferguson et al., 1997; Lucchinetti et al., 2000).

Complementary to the clinical evaluation, conventional magnetic resonance imaging (cMRI) plays a prominent role for diagnosis and assessment of patients with multiple sclerosis. It provides reliable detection and quantitative estimation of focal white matter lesions in vivo. Modern criteria involve MRI parameters for the diagnosis of MS and for predicting conversion to clinically definite MS in patients who present with a first clinical episode (eg, unilateral optic neuritis) suggestive of disease onset. A diagnosis of multiple sclerosis is based on showing disease dissemination in space and time and excluding other neurological disorders that can clinically and radiologically mimic multiple sclerosis. However, neurological impairment of patients with MS is poorly associated with the lesion load observed on conventional MRI scans. The discrepancy between clinical and conventional MRI findings in MS is explained, at least partially, by the low sensitivity of conventional MRI in the detection of grey-matter involvement and diffuse damage in white matter.

In order to overcome these limitations new uses of conventional MRI methods have evolved and nonconventional MRI techniques have been developed. These advances are expected to help in understanding the underlying disease processes and the accumulation of irreversible disability and therefore are promising tools in studies of disease evolution and clinical trials.

Optical coherence tomography (OCT) -a new, sensitive and non-invasive transpupillary imaging method- is able to provide accurate and quantitative measurements of axonal loss in retina and therefore holds promise as a biomarker for neurodegeneration in MS.

This chapter reviews the use of cMRI techniques to diagnosis and follow-up of patients with MS. It also summarizes the evolving non-conventional MRI and non-invasive optical techniques, which are sensitive to different aspects of MS pathology and are promising to further increase our understanding of disease pathophysiology and the mechanisms accounting for the accumulation of irreversible disability.

2. MRI and the diagnosis of multiple sclerosis

Since multiple sclerosis is a histopathological diagnosis, clinical criteria have been developed for the diagnosis of MS during life. Initial diagnostic criteria were based on clinical features alone to show disease dissemination in space and in time (Schumacher et al., 1965). The introduction of MRI in clinical practice resulted in improved investigation of multiple sclerosis (Young et al., 1981). Paraclinical evidence to support clinical findings in cases of diagnostic uncertainty was first proposed by Poser and colleagues (Poser et al., 1983). Given that MRI is the most sensitive paraclinical test and that comparable MRI abnormalities may be found in a variety of other diseases and in healthy volunteers, criteria have been developed by which MRIs can be classified as suggestive of multiple sclerosis or not (Fazekas et al., 1988; Paty et al., 1988; Barkhof et al., 1997; Tintore et al., 2000).

With the increased availability of MRI scanners and the high sensitivity and ability of MRI to provide evidence for disease dissemination in both space and time, subsequent consensus criteria relied on MRI findings to complement clinical and other paraclinical data for the diagnosis of MS (McDonald et al., 2001). The 2001 McDonald diagnostic criteria for multiple sclerosis included MRI evidence of dissemination in space (DIS) and dissemination in time (DIT), which allowed a diagnosis of multiple sclerosis to be made in patients with clinically isolated syndrome (CIS) (McDonald et al., 2001). The DIS criteria were those developed for brain MRI by Barkhof and colleagues (1997) and Tintore and colleagues (2000), in addition to allowing one spinal-cord lesion to substitute for a brain lesion. Evidence for DIT requires either a gadolinium enhancing lesion after at least 3 months from CIS onset, or a new T2 lesion developing on a scan subsequent to a reference scan obtained at least 3 months after CIS onset (Table 1).

The incorporation of MRI findings to the diagnostic criteria improved the ability to diagnose MS and exclude alternative diagnoses. Apparently MRI started to play a prominent role in establishing a firm and clear diagnosis of multiple sclerosis and predicting conversion to clinically definite MS in patients who present with a first clinical episode (eg, unilateral optic neuritis) suggestive of disease onset. The necessity of early and accurate diagnosis became particularly important with the advent of disease modifying treatments. Subsequently, the McDonald criteria were revised in 2005 by Polman and colleagues, to simplify their use and increase their sensitivity while maintaining their specificity. These revised criteria strengthen the use of spinal cord lesions in MS diagnosis, allowing a spinal cord lesion to substitute for an infratentorial brain lesion. In 2006, new simpler imaging criteria were proposed with similar high specificity for clinically definite MS (CDMS) and increased sensitivity (Swanton et al., 2006), in which DIS requires at least one T2 lesion in at least two of four locations (juxtacortical, periventricular, infratentorial, and spinal-cord) and DIT requires a new T2 lesion on a follow-up scan. Thereafter, new data and consensus underlined the need to simplify the revised McDonald Criteria in order to improve their comprehension and utility. Accumulating evidence resulted recently in specific recommendations for revisions to the McDonald Criteria. These proposals concerned the use and interpretation of imaging criteria for DIS and DIT and were based on the simplified criteria of Swanton and colleagues (Polman et al., 2011). The 2010 revisions to the McDonald Criteria simplify the diagnostic process with fewer required MRI examinations, allowing a more rapid diagnosis of MS, with preserved or improved specificity and sensitivity

compared with past Criteria (Table 2). However, even these latest revisions do not address issues of lesion morphology except to emphasize the importance of Gd enhancement and insufficiently deal with lesion location. Distribution and morphology provide important clues to the suspected nature of the detected lesions. In addition, misapplication of the McDonald criteria can lead to misdiagnosis in subjects without relevant clinical symptoms. Therefore, a diagnosis of MS based on incidental findings on MRI alone, should be avoided (Polman et al., 2011).

Clinical Presentation	Additional Data Needed
• 2 or more attacks (relapses) • 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
• 2 or more attacks • 1 objective clinical lesion	Dissemination in space, demonstrated by: • MRI • or a positive CSF and 2 or more MRI lesions consistent with MS • or further clinical attack involving different site
• 1 attack • 2 or more objective clinical lesions	Dissemination in time, demonstrated by: • MRI • or second clinical attack
• 1 attack • 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space demonstrated by: • MRI • or positive CSF and 2 or more MRI lesions consistent with MS *and* Dissemination in time demonstrated by: • MRI • or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	Positive CSF *and* Dissemination in space demonstrated by: • MRI evidence of 9 or more T2 brain lesions • or 2 or more spinal cord lesions • or 4-8 brain and 1 spinal cord lesion • or positive VEP with 4-8 MRI lesions • or positive VEP with <4 brain lesions plus 1 spinal cord lesion *and* Dissemination in time demonstrated by: • MRI • or continued progression for 1 year

Table 1. 2001 McDonald diagnostic criteria for multiple sclerosis (from McDonald et al., 2001; with permission)

Clinical Presentation	Additional Data Needed
• 2 or more attacks (relapses; exacerbations) [1] • 2 or more objective clinical lesions or • Objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack [2]	None[3]
• 2 or more attacks[1] • Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: • 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) [4] or • Await a further clinical attack[1] implicating a different CNS site
• 1 attack[1] • Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or • Await a second clinical attack[1]
• 1 attack[1] • Objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: For DIS: 1 or more T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) [4] or • Await a second clinical attack[1] implicating a different CNS site; and For DIT: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or • A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or • Await a second clinical attack[1]

Clinical Presentation	Additional Data Needed
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: [4] • Evidence for DIS in the brain based on 1 or more T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions • Evidence for DIS in the spinal cord based on 2 or more T2 lesions in the cord • Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

[1] An attack is defined as patient-reported or objectively observed events typical of an acute inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection.

[2] Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Historical evidence for 1 past attack can include events with symptoms and evolution characteristic for a prior inflammatory demyelinating episode; at least 1 attack, however, must be supported by objective findings.

[3] No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria.

[4] Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

Table 2. The 2010 McDonald Criteria for Diagnosis of MS (from Polman et al., 2011; with permission)

2.1 Characteristic findings on conventional MRI techniques

Hydrogen protons of water are highly abundant in our body. Conventional MRI measures alterations in tissue water content and dynamics by proton excitation, thus enabling visualization of edema, inflammation, demyelination and axonal damage in MS lesions. Conventional MRI techniques include T2-weighted, fast fluid-attenuated inversion recovery (FLAIR), and T1-weighted imaging with and without gadolinium (Gd) administration.

In routine evaluation of patients with suspected or known MS, the most useful image acquisition clinical protocols for cMRI are axial dual spin-echo or single late echo T2-weighted imaging, axial and sagittal FLAIR, and pre- and post-gadolinium (Gd)-enhanced axial spin-echo T1-weighted imaging (Bakshi et al., 2004). On cMRI scans, detected MS lesions are presented as hyperintensities on T2- weighted images, hypointensities on T1-weighted images, and Gd-enhancing foci on postcontrast images.

2.1.1 T2-weighted imaging

T2-weighted MRI is sensitive in detecting white matter lesions. In T2-weighted images, MS lesions appear as bright areas against a gray or more neutral background; this hyperintesity reflects an increase in water content and thus is not specific for the underlying pathology.

The T2 hyperintense lesions represent processes ranging from edema and inflammation to demyelination, remyelination, Wallerian degeneration, axonal loss and gliosis (Fillipi & Agosta, 2009; Markovic-Plese & McFarland, 2001). Once detected, a lesion typically persists in the T2 hyperintense stage for many years. The techniques that are commonly used for the identification of T2 hyperintense lesions are conventional spin echo, fast spin echo, and fluid-attenuated inversion recovery (FLAIR) (Filippi et al., 2006). FLAIR imaging is a technique that suppresses the CSF signal, being more sensitive to periventricular and cortical/juxtacortical lesions and less sensitive to infratentorial lesions than T2-weighted MRI (Bakshi et al., 2001).

Given the lack of specificity of hyperintensities on T2-weighted MRI, lesion location and morphology plays a prominent role in distinguishing demyelinating lesions from the common and incidental presence of non-specific white-matter abnormalities, microvascular ischemia, or enlarged perivascular spaces (Fig. 1). MS lesions are primarily found in white matter but also in gray matter and usually affect the periventricular regions, corpus callosum, juxtacortical gray-white matter junction in the white matter, and infratentorial brain regions (brain stem, middle cerebellar peduncles and cerebellar white matter in the posterior fossa) (Bakshi et al., 2004; Barkhof et al., 1997). In some cases, direct involvement of the cerebral cortex also may be apparent (Bakshi et al., 2001). Corpus callosum is commonly affected in MS due to the large amount of myelinated fibres it contains. Callosal demyelinating lesions are usually multiple, small, nodular and characteristically involve callosal-septal interface. Infratentorial lesions are considered specific for multiple sclerosis and are typically located at the surface of the pons, the base of the fourth ventricle, and in the intra-axial trigeminal tract. It is important to note however that they can also be found in small-vessel disorder, with characteristic involvement of the central part of the pons (Kwa et al., 1997). Demyelinating lesions are larger (> 3mm) than punctuate non-specific white matter abnormalities associated with migraine and microvascular ischemia. Characteristically, they have an ovoid shape and appear perpendicular to the long axis of the ventricles in the axial plane. These typical MRI findings reflect the histopathological findings in multiple sclerosis. The periventricular lesions, especially in the corpus callosum, and the ovoid abnormalities with extensions (Dawson' fingers) into the adjacent white matter correlate with the perivenular distribution of multiple sclerosis plaques (Gean-Marton et al., 1991).

Between 50% and 90% of MS patients show hyperintense T2 lesions in the spinal cord, more frequently located in the cervical and the thoracic area (Lycklama et al., 2003; Agosta & Filippi, 2007). Cord lesions are usually located peripherally, occupy less than one half of the cord cross-sectional area and rarely involve more than two contiguous vertebral segments in length. Acute lesions may be associated with cord swelling. The presence of characteristic spinal cord abnormalities on MRI increases both sensitivity and specificity to the diagnosis of MS (Fillipi & Agosta, 2009).

In 50–70% of patients presenting with CIS clinically silent MRI lesions suggestive of MS are found. The extent of T2 lesions on brain MRI in CIS patients can predict the future risk of MS. The majority of CIS patients with T2 abnormalities (56–88%), develop clinically definite MS (CDMS) after prolonged (7–14 years) follow-up, whereas a minority of those with normal MRI (approximately 20%) have a risk for conversion to definite MS (Barkoff et al., 1997; Tintoré et al, 2006). Moreover, brain T2 hyperintense lesion load early in the clinical course of MS is also a predictor of long-term disability (Di Filippo et al., 2010).

(a) Axial FLAIR image showing typical ovoid periventricular hyperintense MS lesions
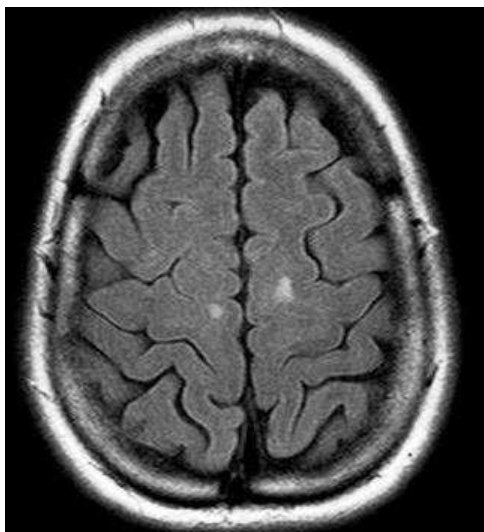
(b) Axial FLAIR scan revealing juxtacortical lesions
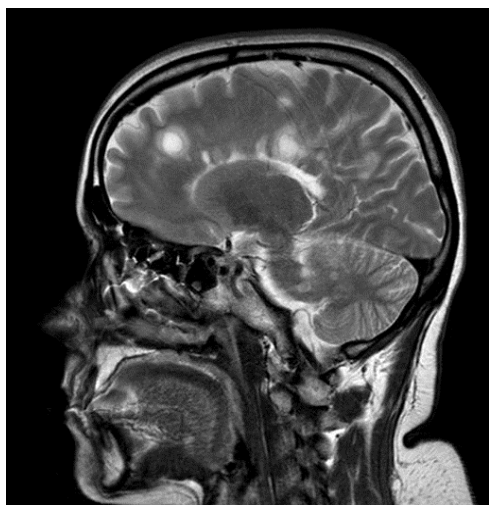
(c) Sagittal T2-weighted image demonstrating lesions in the corpus callosum and periventricular white matter with characteristic extensions (Dawson's fingers)
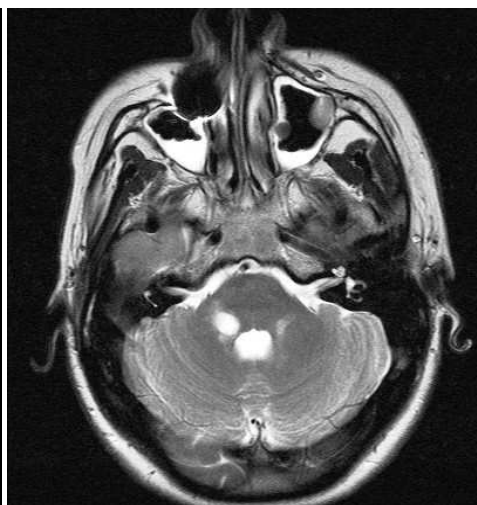
(d) Axial T2 scan showing characteristic infratentorial involvement

Fig. 1. (a-d). Axial and sagittal FLAIR and T2 images showing common sites of MS involvement.

2.1.2 T1-weighted imaging

On noncontrast T1-weighted images (T1-WI), most T2 brain lesions are isointense in white matter; however, some are hypointense (van Walderveen et al., 1998). These hypointense lesions may be acute and reversible within 6 months or chronic (referred to as black holes) (Fig. 2). The acute T1 hypointense lesions are likely to represent oedema and inflammation or demyelination with subsequent remyelination whereas the chronic ones severe demyelination and irreversible axonal loss (Bagnato et al., 2003; Brex et al., 2000; Filippi et al., 2001; Van Walderveen et al., 1998). The percentage of newly formed hypointense lesions that do revert to isointensity varies between 20 and 60% (van Waesberghe et al., 1998). Larger size of the lesions, longer duration of Gd-enhancement and ring enhancement are associated with the development of persistent T1- hypointense black holes (Mineboo et al., 2005). T1 hypointense lesions correlate better with clinical evolution and disability than T2 lesions and therefore may be a useful biomarker of progressive tissue damage in established MS (Truyen et al., 1996). By contrast to chronic cerebral lesions, chronic spinal cord lesions are isointense on T1-weighted images (Fillipi & Agosta, 2009).
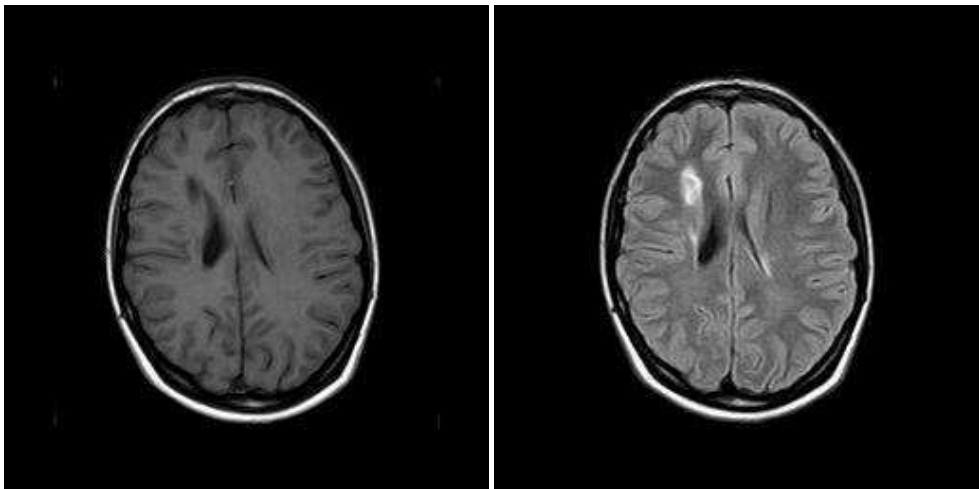
a) Axial T1-weighted noncontrast MRI showing a chronic hypointensity in the right frontal periventricular white matter

(b) Corresponding hyperintensity on FLAIR scan.

Fig. 2. (a-b) A chronic black hole in a 32-year-old woman with relapsing-remitting MS

2.1.3 Postcontrast T1-weighted imaging

On T1-weighted scans, gadolinium injection enables detection of lesions with active inflammation and blood–brain barrier (BBB) disruption, as it is normally excluded from the brain by the BBB. Gd-enhancing lesions on T1-WI typically correspond to areas of high signal intensity on T2-WI and, in some instances, low signal intensity on T1-WI that stem from edema and demyelination (Zivadinov & Cox, 2007). There are various patterns of gadolinium enhancement in MS lesions that usually persists for 2 – 6 weeks (Cotton et al., 2003): homogeneous, heterogeneous, punctuate, ring, open ring enhancing and tumor-like (Fig. 3). Among them, the incomplete or open-ring morphology (Fig. 3a) is particularly

characteristic of MS lesions (Masdeu et al., 1996). Compared with homogeneously enhancing plaques, ring-enhancing lesions are larger and have a shorter duration of enhancement (Minneboo et al., 2005). Concentric ring enhancing lesions with central contrast pallor appear in areas of heightened local inflammation (Rovira et al., 1999).

Results of serial MRI studies demonstrate that enhancement usually precedes or accompanies the appearance of most new lesions on T2-WI in all disease subtypes, even in primary-progressive MS (Molyneux et al., 2001). However, Gd- enhancement is more commonly seen in patients with relapsing-remitting (RRMS) than in patients with primary or secondary progressive MS (Thompson et al., 2000) and is considered sensitive to disease activity and predictive of future clinical relapses. Enhancing lesions do not correlate with long-term disability (Kappos et al., 1999), with the exception of ring-enhancing plaques that are usually suggestive of a more aggressive form of MS. Ring-enhancement is associated with severe tissue damage, persisting hypointense T1 lesions and subsequent development of cerebral atrophy (Morgen et al., 2001; Bagnato et al., 2003; Minneboo et al., 2005;). Enhancing lesions are less frequently seen in the cord (Fig. 3b) than in the brain (Filippi & Agosta, 2009).
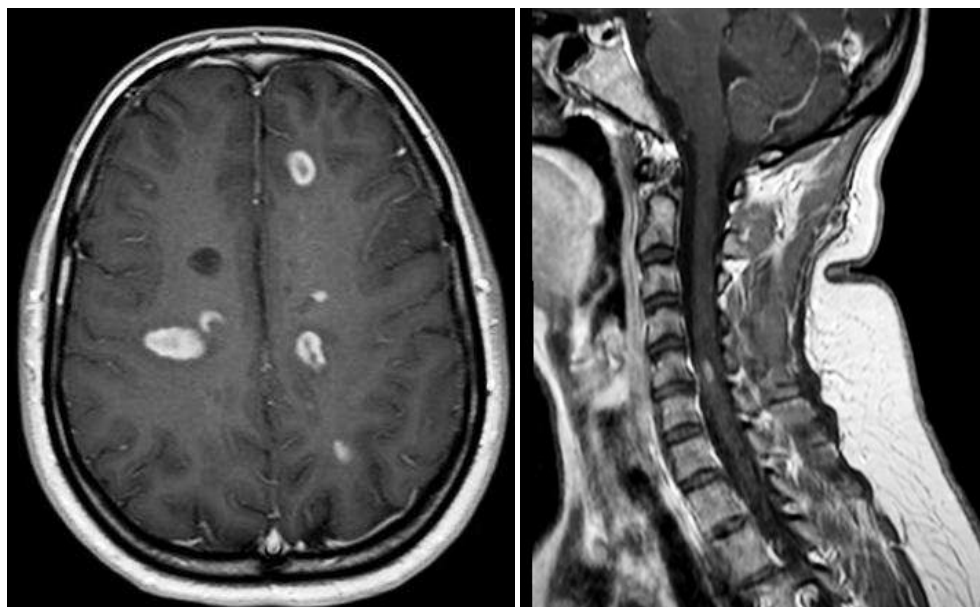
(a) Puctuate, homogeneous, and ring enhancing brain lesions

(b) Spinal enhancing lesion

Fig. 3. Characteristic patterns of enhancement on T1-weighted scans

2.2 Conventional MRI characteristics suggesting alternative diagnoses

Although existing diagnostic criteria for multiple sclerosis have emphasized that alternative explanation for the clinical presentation must be considered and excluded before a diagnosis of MS can be made, they mainly focus on early diagnosis of patients presenting with a first clinical episode suggestive of MS (e.g., unilateral optic neuritis, internuclear

ophthalmoplegia, partial myelopathy). Incorporated data from magnetic resonance imaging are used as prognostic for the subsequent development of clinically definite MS, rather than diagnostic (McDonald et al., 2001; Polman et al., 2005, 2011). However, the increased availability of MRI scanners and the sensitivity of this technique in showing asymptomatic lesions of multiple sclerosis, have revealed difficulties in the application of existing MRI criteria, the most common of which is the incidental presence of non-specific white-matter abnormalities on MRI scans of patients who have headache, vertigo or a variety of other common disorders and the inability to differentiate these lesions from those that are typical for MS. Recognition of MRI features that are not suggestive of MS or even suggestive of another disorder is essential, as it underlines the need for extensive evaluation of patients presenting with such abnormalities in order to avoid misdiagnosis.

A set of MRI signs (red flags), which suggest alternative conditions that mimic MS has been defined by the European MAGNIMS group (Charil et al., 2006). It is important to note however that these red flags (Table 3) should be considered in the appropriate clinical context in order to exclude the most common alternatives (Miller et al., 2008).

The distribution of lesions is an important parameter that should be considered in the differential diagnosis of demyelinating lesions. In hypoxic-ischemic diseases lesions follow arterial anatomy, such as borderzone or watershed lesions, lacunes, multifocal basal ganglia lesions and cortical infarcts whereas in multiple sclerosis are perivenular (Enzinger et al., 2006). Moreover, the corpus callosum is not usually involved in hypoxic-ischemic diseases, due to its rich blood supply; on the contrary, this is commonly affected in MS due to the large amount of myelinated fibres it contains, with characteristic involvement of callosal-septal interface (Gean-Marton et al., 1991). Infratentorial lesions are uncommon in small-vessel disorder, but when they occur they are typically located in the central part of the pons (Kwa et al., 1997). The predominance of lesions located at the cortical or subcortical areas, as well as the coexistence of brain infarcts, calcification, or haemorrhages are usually suggestive of systemic immune mediated diseases with CNS involvement, small-vessel vasculitides, or antiphospholipid antibody syndrome (either primary or secondary to systemic immune-mediated diseases). In these disorders, enhancing lesions and T1 black holes are much less common than in multiple sclerosis (Theodoridou & Settas, 2008). Extensive brainstem and basal ganglia lesions that can be associated with swelling and enhancement in the acute phase and that can shrink or disappear at follow-up may be a manifestation of Behçet's disease (Lee et al., 2001). Bilateral and symmetric white-matter lesions are other important features against the diagnosis of multiple sclerosis. Although adult forms of leucodystrophies, such as adrenoleucodystrophy, metachromatic leucodystrophy, and Krabbe disease may have a MRI pattern resembling that of MS, white-matter lesions tend to be bilateral and symmetric (Barkhof & Scheltens, 2002). Diffuse and confluent symmetrical T2-weighted hyperintensities in the deep and periventricular white matter with characteristic involvement of the external capsules and temporal poles are considered highly specific for cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) and may distinguish it from MS (Andreadou et al., 2008; O'Sullivan et al., 2001; Singhal et al., 2005). Moreover, the cortex, corpus callosum and infratentorial regions (except the pons) are rarely affected in CADASIL (Singhal et al., 2005). Furthermore, the presence of multiple microhaemorrhagic foci, which can be seen on gradient-echo images, is another characteristic feature of CADASIL (Dichgans et al., 2002). Another feature pointing against the diagnosis of MS is significant asymmetry of the white-matter abnormalities, which is usually suggestive of ipsilateral carotid disease (Andreadou et al., 2010; Barkhof & Scheltens, 2002).

Brain white matter	Disease
Normal	NMO (absent or few lesions), ATM
Lesions	
Morphology	
Large lesions	AMS (sometimes confluent and perilesional oedema), BCS (concentric whorls of alternating rings of enhancement), PACNS (with mass effect)
Poorly defined lesion margins	ADEM
Absent or rare Dawson fingers	ADEM
Absent MRI activity at follow-up	ADEM
Isolated lesions with ring enhancement (often complete)	Abscesses
Mass effect	Abscesses
Large lesions with absent or rare mass effect	PML
Multiple bilateral microhaemorrhagic foci	CADASIL, SVD
Haemorrhages	PACNS
Infarcts	SID, PACNS, SVD
Distribution	
Substantially asymmetric distribution of lesions	Ipsilateral carotid disease
Extensive and bilateral periventricular abnormalities in isolation	B12D, ACD
Symmetrically distributed lesions	ADEM, AFL
Absent or rare corpus callosum and periventricular lesions	ADEM
Frequent sparing of corpus callosum and cerebellum	SVD, CADASIL
Lesions in the centre of corpus callosum, sparing the periphery	Susac's syndrome
T2-hyperintensity of the temporal pole, U- fibres at the vertex, external capsule and insular regions	CADASIL
Predominance of lesions at the cortical/subcortical junction	SID
Diffuse WM involvement	NBD, encephalitis (HIVE), SVD, CADASIL
Cerebral venous sinus thrombosis	NBD
Large and infiltrating brainstem lesions	NBD
Pontine lacunar infarcts	CADASIL, SVD
Anterior temporal and inferior frontal lobe involvement, associated with enhancement or mass effect	Encephalitis (HSE)
Multifocal, asymmetrical lesions starting in a juxtacortical location and progressively enlarging	PML
Pattern of enhancement	
Simultaneous enhancement of all lesions	ADEM, PACNS, sarcoidosis

Punctiform parenchymal enhancement	PACNS, sarcoidosis, NBD
Cortical grey matter Cortical/subcortical lesions crossing vascular territories Prevalent involvement versus white matter Infiltrating lesions that do not remain in grey or white matter boundaries	MELAS Encephalitis Abscesses
Deep grey matter Bilateral lesions Lacunar infarcts T1-hyperintensity of the pulvinar Multiple discrete lesions in the basal ganglia and thalamus Large and infiltrating basal ganglia lesions Infiltrating lesions without respecting grey-matter or white-matter boundaries T2-hyperintense lesions in the dentate nuclei	ADEM (at the grey–white-matter junction), CADASIL CADASIL, SVD FD Susac's syndrome NBD Abscesses AFL (CTX)
Spinal cord Large and swelling lesions Diffuse abnormalities in the posterior columns	NMO (with corresponding T1 hypointensity), ADEM, ATM, Sjogren's syndrome B12D, ACD
Other Absence of optic-nerve lesions Hydrocephalus Dilation of Virchow-Robin spaces Meningeal enhancement Regional atrophy No "occult" changes in the NAWM Diffuse lactate increase on brain MRS	PML Sarcoidosis HHC, PACNS Susac's syndrome, PACNS, NBD, meningitis, Lyme disease, sarcoidosis HHC (hippocampus and amygdala), NBD (brainstem) NMO, Lyme disease, SID (except in NSLE) MELAS

ACD=acquired copper deficiency. ADEM=acute disseminated encephalomyelitis. AFL=adult forms of leucoencephalopathies. AMS=acute multiple sclerosis (Marburg type). ATM=acute transverse myelitis. B12D=vitamin B12 deficiency. BCS=Balo's concentric sclerosis. CTX=cerebrotendinous xanthomatosis. FD=Fabry's disease. HHC=Hyperhomocysteinaemia. HIVE=HIV encephalitis. HSE=herpes simplex encephalitis. MELAS=mitochondrial encephalopathy with lactic acidosis and stroke-like episodes. MRS=magnetic-resonance spectroscopy. 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 leucoencephalopathy. SID=systemic immune-mediated diseases. SVD=small-vessel disease.

Table 3. MRI characteristics suggestive of alternative conditions that mimic MS (adapted from Charil et al., 2006; with permission).

By contrast to MS where MRI-detectable spinal cord lesions can be found in the majority of patients with established disease (Lycklama et al., 2003; Agosta and Filippi, 2007), spinal cord abnormalities are not observed in patients with hypoxic-ischemic disease and are rarely reported in other immune-mediated disorders (Bot et al, 2002), and progressive multifocal leucoencephalopathy (Yousry et al., 2006). Another characteristic pointing against the diagnosis of MS is the complete disappearance of spinal cord lesions in systemic immune-mediated diseases after steroid or immunosuppressive treatment (Rovaris et al., 2000). Moreover, incidental spinal cord hyperintense foci do not occur with ageing (Lycklama et al., 2003). Therefore, cord MRI is helpful in patients with normal or equivocal brain MRI and in those more than 50 years old (Agosta & Filippi, 2007). Longitudinally extensive spinal cord involvement (usually three or more segments), affecting primarily the central part of the spinal cord on axial sections, is typically seen in neuromyelitis optica. Moreover, NMO myelopathy is often associated with swelling and T1 hypointensity in the acute and chronic stages (de Seze et al., 2002; Wingerchuk et al., 2007).

The pattern of enhancement is another useful distinctive characteristic. Simultaneous enhancement of multiple white-matter lesions is usually observed in neurosarcoidosis and primary angiitis of the CNS (PACNS). Moreover, meningeal enhancement should raise the suspicion of PACNS, neurosarcoidosis or neuroBehçet's disease (Campi et al., 2001; Zajicek et al., 1999).

It is important to note that when these MRI features 'not suggestive' of multiple sclerosis are used along with the existing MS diagnostic criteria, they minimize the chance of false positive diagnoses and facilitate the correct diagnosis of other disorders. Therefore, it is suggested to be taken into account in the diagnostic work-up of patients suspected of having MS. In the presence of at least one MRI 'red flag', appropriate additional tests should be performed. However, in cases of equivocal findings, follow-up with repeated imaging will be needed to establish a firm diagnosis (Charil et al., 2006)

3. MRI and disease progression

Recognition of the neurodegenerative aspects of MS has rendered the development of techniques to measure disease progression essential. Since conventional MRI is sensitive in detecting disease activity, it has routinely been used to ameliorate not only the accuracy of multiple sclerosis diagnosis but also the prognosis. Conventional MRI assessment of lesions on non-contrast T1-weighted and T2-weighted scans, and on gadolinium-enhanced T1-weighted images is now routinely used to monitor the disease course and detect therapeutic effects (Zivadinov & Leist, 2005). However, measures like the lesion volume and the number of gadolinium-enhancing and T2 lesions, are weakly associated with the clinical status and have insufficient sensitivity and specificity to reveal the extent of histopathological changes occurring in MS. Persistent T1 hypointense lesions can predict development of disability better than the previously mentioned lesion-based MRI measures (Zivadinov & Leist, 2005) as they are mainly associated with more advanced pathological processes of the disease, i.e. axonal loss, Wallerian degeneration and gliotic changes (Bakshi et al., 2004; Stevenson et al., 2004). Moreover, brain and spinal cord atrophy have been shown to be powerful predictors of clinical impairment and disease progression. Additionally, newer nonconventional MRI techniques that become increasingly available hold significant promise to improve monitoring of MS. Accumulating evidence suggests that metrics derived from non-cMRI techniques correlate better with disability compared to conventional measures.

3.1 Detection of subclinical disease activity

Conventional MRI can be used as a valuable tool for the assessment of disease progression, as it provides objective and sensitive measures of MS activity. In patients with RRMS and SPMS, disease activity is detected 5–10 times more frequently on cMRI scans than with clinical assessment of relapses (Filippi & Agosta, 2010). Despite the sensitivity of T2-weighted images to reveal disease activity and lesions over time (Molyneux et al., 1998), no significant correlation between MRI findings and clinical progression has been demonstrated, except in patients with very early disease (Rovaris et al., 2003). Indeed, both brain T2 hyperintense lesion load early in the clinical course and early progression of T2 burden of MS have been associated with the development of long-term disability (Brex et al., 2002). However, T2 lesion load measurement is not appropriate for the assessment of the advanced stages of the disease (Li et al., 2006). Although differences in T2 lesion load among different MS phenotypes have been consistently reported, being higher in SPMS in comparison to benign MS, RRMS, and PPMS, no significant relationship between T2 lesion load and disability has been demonstrated (Filippi & Agosta, 2010).

Gd enhancement occurs in almost all new lesions in patients with RRMS or SPMS and can be sometimes detected even before the onset of clinical symptoms (Filippi & Agosta, 2010). The number of enhancing lesions increases shortly before and during clinical relapses and predicts subsequent MRI activity (Molyneux et al., 1998, Kappos et al., 1999). The burden of MRI activity has been shown to be associated with the subtype of the disease, being higher in RRMS and SPMS in comparison with PPMS and BMS (Kappos et al., 1999). Moreover, patients with SPMS and severe disability show a lower incidence of enhancing lesions when compared to those with mildly disabling RRMS (Filippi et al., 1997). However, a moderate correlation has been demonstrated between the degree of clinical disability and the mean frequency of enhancing lesions in patients with RRMS and SPMS (Filippi & Agosta, 2010).

T1 black holes and CNS atrophy are useful markers of progressive tissue damage and clinical evolution in established MS. In patients with either RRMS or SPMS, the increase in T1 lesion volume (LV) over time correlates significantly with progressive cerebral atrophy and the change in EDSS score (Sailer et al., 2001; Truyen et al., 1996). Moreover, in patients with CIS, baseline T1 hypointense lesion number and volume are strong predictors of the severity of executive dysfunction (Summers et al., 2008).

3.2 Detection of brain and spinal cord atrophy

Since the initial MRI studies in MS, marked atrophy of the brain has been found to be an important feature of the advanced stages of the disease (Filippi & Agosta, 2010). Subsequently, it was recognised as an early phenomenon that progresses over the disease course. Thus, conventional MRI has been used to measure atrophy of the brain tissue, whole or segmented in white matter (WM) and gray matter (GM). Cerebral volume loss is associated with changes in normal appearing white matter and grey matter (Ge et al., 2000; Horakova et al., 2009). It occurs in all MS subtypes (even in CIS) with a rate of 0.5-1% per year and is closely related to disability (Anderson et al., 2006; Bermel & Bakshi, 2006). Moreover, brain atrophy develops in different structures in the different clinical phenotypes of the disease: ventricular enlargement is predominant in RRMS, whereas cortical atrophy is more pronounced in the progressive forms of the disease (Pagani et al., 2005). The most atrophic cortical regions have been consistently found to be the frontal, temporal and parietal lobes (Filippi & Agosta, 2010). GM atrophy rate has been found to increase with

disease progression, whereas WM atrophy rate has been reported to remain constant (Fisher et al., 2008). Atrophy of the deep gray matter has been also observed in MS, especially in the posterior basal ganglia and the thalamic regions (Bermel & Bakshi, 2006; Carone et al., 2006; Filippi & Agosta, 2010; Henry et al., 2008). Measurement of atrophy in selected pathways, such as the corpus callosum and the corticospinal tract, may also improve the in vivo monitoring of MS progression (Martola et al., 2007). In addition, spinal cord atrophy, more pronounced in the progressive forms of MS, has been reported (Rovaris et al., 2001). It should be mentioned, however, that reduction of the cervical cord size can be observed in the early stages of MS (Brex et al., 2001). CNS atrophy reflects the destructive component of the MS disease process and contributes to irreversible neurological impairment.

Recent advances in volumetric MRI with the use of parallel imaging techniques may improve the use of atrophy metrics as outcome measures in clinical trials of MS therapies. It should be mentioned however, that the anti-inflammatory effect of MS treatments can reduce brain volume (a phenomenon called pseudoatrophy effect), and consequently affect atrophy measurements (Zivadinov et al., 2008). Advances in neuroimaging may help separate true atrophy from pseudoatrophy with the use of methods that can distinguish axonal loss from transient changes in water content.

3.3 MRI in disease management and evaluation of treatment outcomes

Since MRI provides information essential in monitoring disease activity and severity of multiple sclerosis, it is a critical component of disease management. In addition to the relapse rate and progression on EDSS, MRI variables play an essential role in determining the short and long-term effects of MS treatments, since the approval of the first therapy for MS by the Food and Drug Administration in 1993 (Rovaris, 2008; Bates, 2011; Freedman, 2011). Short-term and long-term clinical trial results have indicated that currently available disease-modifying therapies (DMTs) are effective in reducing MRI disease activity (Bates, 2011; Freedman, 2011). Moreover, reduction in MRI-detected lesion burden is used as supportive to the clinical findings to show reduction in disease activity. Brain MRI activity is determined as the number of new or enlarging T2-hyperintense lesions and Gd-enhancing lesions, whereas the MRI burden of the disease includes the T2-lesion volume and the T1-hypointense LV.

Accumulating evidence suggests that MRI-derived metrics could be used to define treatment options and strategies in individual patients with MS (Beck et al., 2002; Rudick et al., 2004). In RRMS, the accumulation of two or more new T2-hyperintense lesions during a two-year period has been demonstrated to predict poor treatment response more reliably than the persistence of clinical relapses and the presence of enhancing lesions (Rudick et al., 2004). In CIS, the subgroup of patients with enhancing lesions at baseline showed a trend for greater treatment benefit than patients without (Beck et al., 2002). However, only the integration of clinical and MRI data can be considered a reliable approach for the work-up of patients receiving disease-modifying treatments.

Recently, clinical trials have incorporated cerebral volume measurement to determine the efficacy of novel treatments (Bermel & Bakshi, 2006). However, the current inability to separate true atrophy from pseudoatrophy limits the use of atrophy measures at present. Advances in MRI technology might contribute to a better correlation between clinical and MRI findings, and thus provide relevant information to improve prognosis and predict therapeutic response.

4. Nonconventional MRI techniques

Conventional MRI is unable to disclose the extent of the damage because of its limited sensitivity to structural changes outside the focal lesions and its lack of specificity to the heterogeneous features of the disease. The hyperintense lesions on T2-weighted images represent nonspecific tissue alterations as they reflect changes in water content caused by a variety of processes including edema, inflammation, demyelination, remyelination, Wallerian degeneration, gliosis and axonal loss. Furthermore, neurological impairment of patients with MS is poorly associated with the lesion load observed on conventional MRI scans (Filippi & Agosta, 2010). During the past decade, other nonconventional MRI techniques-including proton MR spectroscopy, magnetization transfer MRI, diffusion tensor MRI, double inversion recovery sequences, high-field and ultrahigh-field MR imaging, techniques employing cellular MR contrast agents, and functional MRI-have been developed to overcome these limitations, improve the sensitivity and specificity in the detection of MS lesions and characterize and quantify the heterogeneous pathological substrates of the disease. Issues encountered in emerging clinical application of these methods will be addressed.

4.1 Magnetic resonance spectroscopy

Conventional MRI describes the physical characteristics of a region of tissue relative to surrounding regions by measuring alterations in tissue water content and dynamics by proton excitation. Proton MR Spectroscopy (^{1}H-MRS) is a non invasive method that depicts the chemical properties of a region of brain tissue by investigating other proton-containing cellular metabolites. It provides information on tissue metabolism and function of a selected brain area volume relative to surrounding regions. Therefore it could be used to study biochemical changes occurring in lesions and normal appearing white matter over the course of MS (De Stefano et al., 2007). ^{1}H-MRS could also be used as a diagnostic tool, although it has not yet moved to clinical practice.

Various compounds can be detected using ^{1}H-MRS. At long echo times four major resonance peaks are revealed from (a) choline-containing phospholipids (Cho), (b) creatine and phospho- creatine (Cr), (c) N-acetyl-aspartate (NAA), and (d) lactate (Lac) methylgroup. NAA, normally present in axons and neurons, reflects neuronal/axonal integrity and therefore appears to be a sensitive biomarker of disease progression (Narayana, 2005). A decline in NAA levels in MS, with correlation with disability, has been shown in several studies. Reduced NAA was observed in lesions, cortical GM and NAWM in early RRMS (Kapeller et al., 2001; Chard et al., 2002). Decrease in NAA levels in chronic WM lesions has been reported in RRMS, SP and PPMS (Davie et al., 1997). Moreover, chronic lesions have higher NAA signal intensities in patients with BMS than those in patients with SPMS, indicating a more efficient tissue integrity recovery in patients with less severe disability (De Stefano et al., 2007). Transient changes in NAA levels in acute MS plaques have been also reported (Narayama et al, 1998). Decreases in NAA concentrations are also known to occur in the NAWM of MS patients (Caramanos et al., 2005). Furthermore, significant reduction in whole-brain NAA levels was found, more pronounced in older than younger patients (Gonen et al., 2000).

Cho and Lac reflect cell membrane metabolism. Increases in these metabolites are considered as chemical correlates of acute inflammatory or demyelinating changes. Indeed, increases in Cho and Lac resonance intensities have been found in acute MS lesions (Davie

et al., 1994; De Stefano et al., 1995). In large, acute demyelinating lesions, decreases of Cr have also been seen (De Stefano et al., 1995).

^{1}H-MRS studies with shorter echo times can detect additional metabolites, such as lipids and myoinositol (mI), which are also regarded as markers of progressing myelin damage. Increase of levels of myoinositol, which is mainly localised in astrocytes, has been shown in early MS (Capeller et al., 2001; De Stefano et al., 1995) and also in chronic lesions, indicating neuronal injury and ongoing astrogliosis (Srinivasan et al., 2005). Amino acids acting as neurotransmitters, such as glutamate, glutamine, and GABA (γ-aminobutyric acid), can also be measured. Glutamate levels were found to be increased in acute lesions (Srinivasan et al., 2005). A reduced concentration of glutamate and glutamine in the cortical GM of patients with PPMS has been found (Sastre-Garriga et al., 2005), which was significantly correlated with the EDSS score. Recently, the concentration of glutathione, a marker of oxidative status, was measured by ^{1}H-MRS at 7.0 T and was found decreased in the NAWM and gray matter of MS patients compared to healthy controls (Srinivasan et al., 2010).

MRS may provide insight into MS pathogenesis, evaluate the severity of MS and follow disease evolution and therefore is becoming a useful tool in the understanding of the disease. Moreover, MRS measures of brain metabolites seem to be better predictors of clinical disability than is conventional MRI.

4.2 Magnetization transfer imaging

Magnetization transfer (MT) is a physical phenomenon in which protons of two or more environments with different magnetic resonance properties exchange magnetization. MT MRI measures quantitatively the continuous exchange of magnetization in the brain tissue between macromolecular bound protons (i.e. protons associated with myelin, cell membranes and proteins) and protons in adjacent free water molecules, thus allowing the calculation of an index, the MT ratio (MTR). Diminution of this index denotes a decreased capacity of the bound protons to exchange magnetization with the surrounding ''free'' water (Filippi & Agosta, 2007). The reduction of MTR values in focal lesions is considered as a marker of the extent of tissue damage, primarily associated with demyelination (Schmierer et al., 2004; van Buchem et al., 1996). The relative specificity of MTR to myelin density has been demonstrated by post-mortem imaging and histopathological studies that did not reveal any significant association with axonal density or gliosis (Schmierer et al., 2004).

Voxel-based analysis of MTR changes can provide indirect information about demyelination and remyelination in MS lesions (Chen et al., 2007). Changes of MTR of individual lesion voxels, as well as the mean normalized MTR over all lesion voxels during and after contrast enhancement have been reported (Chen et al., 2008). The mean normalized MTR of Gd-enhancing lesions was significantly decreased at the time of lesion enhancement, partially recovered over the subsequent four months, and then appeared to stabilize. Moreover, enhancing lesions were found to have different MTR values, according to their size, pattern, and duration of enhancement. Specifically, MTR was lower in ring-enhancing lesions than in homogeneously enhancing lesions (Silver et al., 1998) and in lesions with longer duration of enhancement (Filippi et al., 1998a), suggesting more severe demyelination. Furthermore, evolution of the mean normalized MTR of individual lesions shows considerable heterogeneity ranging from partial recovery or stability that suggest remyelination, to decline over time that suggests ongoing demyelination (Chen et al., 2008).

In addition to increased specificity, MTI may also offer increased sensitivity for studies of MS. Focal changes in magnetization transfer were reported to precede the appearance of gadolinium-enhancing lesions (Filippi et al., 1998b). Moreover, microscopic damage in normal-appearing brain tissues was shown on MTI before the development of T2 lesions on cMRI scans (Laule et al., 2003).

Decreased MTR has also been found in normal appearing brain tissue (NABT), in both gray (Ge et al., 2001; Dehmeshki et al., 2003) and white matter (Santos et al., 2002), of patients with established MS. These abnormalities are more pronounced in patients with the progressive forms of MS and tend to worsen over time (Filippi & Rocca, 2007). Moreover, reduced NABT MTR has been found in patients at presentation with CIS, with significant prognostic value for the subsequent evolution to clinically definite MS (Miller et al., 2005). NAWM and NAGM MTR abnormalities have been found to correlate with clinical disability (Ge et al., 2001; Santos et al., 2002) and cognitive impairment (Ranjeva et al., 2005).

MTI metrics have several limitations that include lack of specificity to the various MS pathological substrates and lack of standard magnetisation transfer data acquisition protocols across different scanners (Horsfield et al., 2003). Improvement of the quantification and specificity of MTI with the use of new analysis methods (Chen et al., 2008) may render this technique a reliable tool not only for studies of disease evolution, but also for diagnostic purposes in every day clinical practice.

4.3 Diffusion weighted and diffusion tensor imaging

Diffusion weighted (DWI) and diffusion tensor imaging (DTI) provide information about the tissue fibers by measuring the motion of tissue water molecules in vivo (Rovaris et al., 2005). The mobility of water molecules is diminished in highly organized tissue, like white and gray matter, and consequently, the apparent diffusion coefficient (ADC) is lower in those tissues than in free water. Pathological processes that alter tissue organization can result in abnormal water motion, thus modifying ADC values. Tissue damage in MS, mainly demyelination and axonal degeneration, results in abnormal water motion, and therefore in alteration of the ADC values. Diffusion abnormalities may precede Gd-enhancement in hyperacute MS lesions.

Diffusion tensor imaging (DTI) is a valuable technique based on the fact that diffusion of water molecules within white matter is much greater along the fibres than across them. The diffusion tensor is a mathematical description of the magnitude and predominant direction of water molecules movement (anisotropy) in the three-dimensional space. As the diffusion ellipsoid provides a description of the diffusion tensor, the individual components of the diffusion ellipsoid (called eigenvalues) can also be assessed separately. These components are the longitudinal or axial diffusivity (LD or AD), which is the principal eigenvalue of the DT, and the transverse or radial diffusivity (TD or RD) that is the average of the second and third eigenvalues of the DT. Quantitative DTI parameters, such as the fractional anisotropy (FA), which is a normalized measure of the degree of anisotropy, the mean diffusivity (MD), that is the averaged diffusion for detecting WM alterations, and the longitudinal and transverse diffusivities of the diffusion tensor are considered valuable tools in the assessment of focal and widespread white matter tissue damage in patients with MS. FA was found to be decreased (Werring et al., 1999) whereas MD was consistently shown to be increased in MS plaques as well as in normal appearing white matter of MS patients (Lowe

et al., 2006). However, FA values have been found to be increased in intracortical MS lesions, possibly reflecting intralesional loss of dendrites and activation of microglia (Poonawalla et al., 2008). Transverse diffusivity, which refers to the diffusion across fibers, is believed to be a specific marker for axonal loss and demyelination associated with MS (Oh et al., 2004; Lowe et al., 2006; Henry et al., 2003). Relative increase of TD has been shown in MS, correlating with demyelination and axonal loss (Song et al., 2005). This finding suggests that fragmented or missing myelin permits greater diffusion of water molecules across fibers. Moreover, quantitative variables derived from DTI were found to correlate with clinical disability (Filippi & Agosta, 2010).

Fiber tractography is a diffusion technique based on the directional movement of water, which allows the generation of non-invasive three-dimensional images of white matter fiber tracts. It is a promising method for in vivo segmentation of the major WM tract fiber bundles in the brain (Mori et al., 2002). In MS patients, DT MRI tractography can be used to segment clinically eloquent WM pathways, such as the corticospinal tracts, the corpus callosum, and the optic radiations and holds promise in enabling visualization and quantification of the degree of axonal loss and demyelination in vivo. However, the application of DTI tractography in MS is limited by the presence of both focal and diffuse alterations of tissue structure, which cause a decrease in anisotropy and consequently an increase in uncertainty of the primary eigenvector of the DT (Pagani et al., 2007). Using DT MRI tractography, a study in patients with optic neuritis showed reduced connectivity values in both left and right optic radiations compared with controls, possibly attributed to trans-synaptic degeneration secondary to optic nerve damage (Ciccarelli et al., 2005). DT MRI tractography has been also used to identify NAWM fibers at risk for degeneration, when they intersect T2-visible lesions (Simon et al., 2006). A recent study found increased interthalamic connectivity in patients with early MS as measured by DTI and tractography when compared with control subjects, suggesting a possible reactive structural reorganization of the fiber tracts within the thalami (Tovar-Moll et al., 2009).

Technical improvements of tensor models may allow better description of water diffusion in more complex architectures such as those with crossing fiber tracts, better segmentation of fiber bundles and better understanding of the relationship between tissue structure and function.

4.4 Double inversion recovery imaging

Double inversion recovery (DIR – i.e. two inversion times are used to suppress the signal from both white matter and cerebrospinal fluid) is a novel imaging method that has markedly improved the sensitivity of MRI to detect cortical lesions in vivo (Geurts et al., 2005). Cortical demyelination is an important part of the disease process, especially in more advanced stages (Kutzelnigg et al., 2005), and may contribute to the accumulation of irreversible disability in MS (Calabrese et al., 2009a,b; Calabrese et al., 2010; Roosendaal et al., 2009). Despite improvement, at present only a small number of cortical gray matter lesions can be detected with this technique, compared with pathological studies (Calabrese et al., 2007; Geurts et al., 2008).

Cortical lesions have been detected in all the major MS clinical phenotypes, including patients with CIS suggestive of MS (Calabrese et al., 2009a, b). Remarkably, cortical lesions are more frequently seen in patients with secondary progressive MS than in those with CIS

or RRMS. Moreover, patients with early RRMS have a greater number of lesions than patients with benign MS (Calabrese et al., 2009a). Longitudinal studies have shown that new cortical lesions continue to form in patients with early RRMS (Calabrese et al., 2009a), and in those with the progressive disease phenotypes over 1 to 2-year periods of follow-up (Calabrese et al., 2009b; Roosendaal et al., 2009). Cortical lesion burden has been associated with progression of disability over the subsequent 2 to 3 years in patients with different disease phenotypes (Calabrese et al., 2009b), as well as with the severity of cognitive impairment in patients with RRMS (Roosendaal et al., 2009).

DIR sequences at 1.5 T have not been established as yet into the clinical routine probably because of the relatively low signal-to-noise ratio values due to the application of two inversion pulses, longer acquisition times and higher propensity of artefacts. DIR applications at higher magnetic field strengths may overcome these major problems (Wattjes & Barkhof, 2009).

4.5 Functional MRI

Functional MRI (fMRI) is a non-invasive neuroimaging method that enables visualisation not only of the detailed anatomy but also of brain function. It is used to identify changes in brain activation in response to various stimuli and in the resting state. The fMRI signal reflects blood oxygenation level-dependent (BOLD) alterations associated with activation of neural tissue. This mechanism permits the detection of changes in the relationship between blood flow and local oxygen consumption. Upon initiating a task, neural activity in the involved brain region results in increased blood flow and consequently in increased total blood oxygen content (Logothetis et al., 2001; Ogawa et al., 1990). The increased blood oxygen produces an increase in the MRI signal, thus allowing demonstration of abnormal patterns of brain activation caused by tissue injury.

fMRI is not used clinically for the diagnosis of MS; rather it is used to provide insight into disease progression. The most common finding in fMRI studies is increased extent or strength of activation of functional tissue in MS patients compared with controls, implying compensatory processes or reorganization of neuronal activation (Lee et al., 2000; Penner et al., 2003; Reddy et al., 2000; Rocca et al., 2005). At the initial stages of the disease, an increased recruitment of the areas normally involved in the performance of a given task, such as the primary sensorimotor cortex and the supplementary motor area is shown (Rocca et al., 2003). At later stages, bilateral activation of these regions is first observed, followed by a widespread recruitment of additional areas, which are usually recruited by healthy subjects in the performance of more complex or novel tasks (Rocca et al., 2005). Similarly, fMRI studies investigating various cognitive domains in MS patients have shown altered patterns of cortical activation (Audoin et al., 2003; Staffen et al., 2002; Hillary et al., 2003; Li et al., 2004; Cader et al., 2006). Moreover a relationship between cortical activation and fatigue has been shown in several studies suggesting that the underlying mechanism of this common but poorly understood symptom may be the deficiency of neuronal compensation (Filippi et al., 2002; White et al., 2009).

Functional connectivity MRI (resting-state fMRI) is a newer fMRI method that measures low frequency oscillations (0.01–0.1 Hz) in BOLD signals across the whole brain during rest, thus enabling measurement of functional interactions between brain regions (Cordes et al., 2000). Since it studies the strength of network between anatomically separated brain regions, it is

considered a promising method to explore disconnectivity effects in MS (van den Heuvel & Hulshoff Pol, 2010). Indeed, decreased levels of functional connectivity of regions of the primary motor network have been reported in patients with MS (Lowe et al., 2008).

Since studies with fMRI have demonstrated consistently functional cortical changes in all MS subtypes, this method can be used to assess the role of brain plasticity and cortical adaptive changes in limiting the clinical manifestations of demyelination and tissue loss in MS and therefore explain the discrepancy between clinical and cMRI findings.

4.6 High and ultrahigh-field MRI

Magnet field strengths higher than 1.5 Tesla (T) improve image resolution, signal-to-noise ratio and chemical shift. Therefore application of high-field MRI on conventional and quantitative MRI methods offers advantages on brain imaging in MS, as it may give new insights into the microstructural damage and functional reorganization (Wattjes & Barkhof, 2009). In patients with established MS, high-field MRI has resulted in a higher detection rate of T2 (Wattjes et al., 2009) and gadolinium-enhancing brain (Sicotte et al., 2006) but not spinal cord (Stankiewicz et al., 2009) lesions at 3.0T compared with 1.5T. In CIS patients, however, 3.0T imaging did not substantially affect evidence for disease dissemination in space (Wattjes et al., 2008).

Ultrahigh-field MRI (referred to as imaging at field strength of 7 Tesla or more) provides improved brain lesion load quantification and characterization of the pathological features of MS lesions. It is also likely that detection of GM and spinal cord abnormalities could be improved by ultrahigh-field MRI (Kangarlu et al., 2007).

Both high-field and ultra-high field MRI can improve 1H-MRS by providing better quantification of metabolites in lesions and the normal-appearing brain tissue (white and gray matter) (Srinivasan et al., 2004, 2005, 2009). Magnetisation transfer MRI, diffusion tensor MRI, and fMRI studies in MS may also benefit from higher field strengths (Bakshi et al., 2008; Wattjes & Barkhof, 2009). Indeed, subtle damage in the NAWM and NAGM Ceccarelli ea al., 2007), as well as diffuse microscopic damage in the absence of macroscopic MS lesions in the thalamus and basal ganglia has been detected by the use of high-field MRI (Tovar-Moll et al., 2009). Finally, higher field MRI might be important for studying iron deposition in the grey matter of patients with MS, which has been postulated to contribute to neurotoxicity (Stankiewicz et al., 2007).

4.7 New MR contrast agents

Conventional MRI allows follow-up of lesion development in time and space. Although in clinical practice the number of hyperintense lesions on T2-weighted MRI is considered as a biomarker of disease activity in MS, they represent nonspecific tissue alterations. Commonly, the identification of gadolinium-DTPA (Gd) enhancing lesions on T1-weighted scans is considered as evidence for acute inflammation and disruption of the BBB. Gd, a lanthanide chelate, is an extracellular contrast agent that requires relatively high local concentration to achieve sufficient contrast on MRI. Gadofluorine M (Gf), a new Gd-based agent, has been shown in in-vivo experimental studies to have a much higher sensitivity than Gd-DTPA in detecting disruption of the BBB on T1-weighted MRI (Bendszus et al., 2008).

The development and application of novel MR contrast agents allowing cellular and targeted molecular imaging hold promise in exploring inflammation and its regulation by

cell adhesion molecules in MS. Contrast media composed of iron particles [super-paramagnetic particles of iron oxide (SPIO) and ultrasmall particles of iron oxide (USPIO)] are more sensitive compared to Gd-containing agents at similar tissue concentrations (Liu & Frank, 2009). The size of SPIO particles is 50–150nm whereas that of USPIO particles is approximately 10–50nm. These particles are partly phagocytosed by circulating macrophages upon injection. When circulating macrophages are attracted to inflammatory lesions, they can be detected in vivo by MRI, since in tissue iron particles shorten both the T1 and T2 relaxation time (Vellinga et al., 2008). Several recent studies support the aspect that SPIO/USPIO enhanced MRI allows cellular neuroimaging (Baeten et al., 2008; Chin et al., 2009). Preliminary studies in RRMS patients have shown that some lesions may enhance only with Gd, others only with USPIO, and others with both. Moreover, the same lesions can change their pattern of enhancement over time (Vellinga et al., 2008). Furthermore, USPIO-enhanced MRI may not only disclose a greater number of 'active' MS lesions but may also detect subtle and diffuse inflammatory activity in MS patients not visible on conventional T2-weighted MR sequences and unrelated to Gd-DTPA enhancement (Vellinga et al., 2009).

Additionally, novel cellular MR contrast agents such as polyfluorinated nanoemulsions or activatable paramagnetic sensors and emerging molecular imaging approaches might give new insights into the MS inflammatory process. Myeloperoxidase (MPO) is one of the most abundant enzymes secreted by inflammatory cells and, thus, may serve as a marker of macrophage inflammation. It has been recently shown in an animal model of EAE that myeloperoxidase activity in inflamed tissues can be detected and labelled in vivo by a myeloperoxidase sensitive ''smart'' molecular imaging probe (JW Chen et al., 2008).

Transferring cellular and targeted molecular imaging approaches from in-vitro to in-vivo MRI and subsequently in clinical use holds promise for exploring MS neuroinflammation in the future.

5. Optical techniques

5.1 Optical coherence tomography (OCT)

Optical coherence tomography (OCT) is a new, sensitive, non-invasive, transpupilary method that allows direct imaging and quantification of the retinal nerve fibre layer (RNFL), which is principally composed of unmyelinated axons. By using an optical interferometer in conjunction with a low-coherence light source, OCT detects light reflections within a tissue and provides in vivo cross-sectional images at near microscopic resolution (Hrynchak & Simpson, 2000; Huang et al., 1991). Recent advances in OCT allow differentiation of major retinal layers and analysis of tissue thickness and volume with a resolution of about 3 μm (Ko et al., 2004).

Because the retina is the only place where a tissue layer made up of axons can be imaged directly, and the retina and optic nerve are often affected by MS, OCT can be used to assess the impact of MS on the retina by measuring the RNFL thickness and macular volume. The reductions of RNFL thickness and macular volume are associated with axonal loss and secondary retinal ganglion cell loss, respectively. Therefore, OCT shows promise in the detection, assessment and monitoring of neurodegeneration in MS (Barkhof et al., 2009; Petzold et al., 2010).

RNFL thinning has been detected with OCT about 3 months after acute optic neuritis. Moreover, continuing axonal loss in the affected eye for at least 12 months after optic

neuritis has been found, more pronounced the first 6 months after injury (Costello et al., 2008). In addition, OCT has been shown to be predictive of a clinical outcome (poor visual recovery) (Costello et al., 2006). A recent meta-analysis of time domain OCT showed RNFL thinning in MS patients, both with and without a history of optic neuritis, more pronounced after optic neuritis (Petzold et al., 2010). The estimated RNFL thinning in patients with MS has been found to be greater than the extent expected in normal ageing and has been attributed to retrograde trans-synaptic degeneration and progressive loss of retinal ganglion cells, in addition to the more pronounced thinning observed in case of optic neuritis (Petzold et al., 2010). Furthermore, thinning of the RNFL in MS without optic neuritis was found to correlate with visual and neurological functioning, as well as with paraclinical data (Trip et al., 2005, 2006; Villoslada et al., 2008).

Macular volume loss has also been reported in patients with MS compared with controls, correlating with loss of RNFL (Burkholder et al., 2009; Trip et al., 2006). Recently, a subgroup of MS patients with primary retinal pathology characterized by predominant macular thinning has been described with the use of OCT, in whom there appears to be disproportionate thinning of the inner and outer nuclear retinal layers independent of optic nerve pathology. Moreover, these patients were shown to have accelerated disability progression, implying that this primary process may be associated with a more aggressive form of MS (Saidha et al., 2011).

OCT could be used for analysis of neurodegeneration in MS as well as for monitoring of treatment effects in trials of neuroprotective strategies in MS. Moreover, the integration of OCT into MS research could allow insights into the structure–function relations, thus improving our understanding of the pathophysiology of the disease.

6. Conclusion

Advances in neuroimaging have improved our ability to diagnose and monitor MS and have provided insight into the pathophysiology of the disease. Conventional MRI of the central nervous system plays a prominent role in establishing the diagnosis of MS and in differentiating MS-mimics and demyelinating disease subtypes. Moreover, it allows an earlier and accurate diagnosis of the disease, as it can support or even replace some clinical criteria. Early diagnosis is essential to allow earlier therapeutic intervention that appears to be beneficial on delaying the accumulation of irreversible neurologic damage and consequent disability.

In addition cMRI is a useful tool for monitoring disease progression as it is a sensitive imaging biomarker that detects pathological changes prior to the onset of clinical symptoms. Conventional MR scans are effective in detecting clinically silent new white matter inflammatory lesions. In particular, Gd-enhancing lesions are predictive of future clinical relapses. Therefore, cMRI is routinely used for detection of subclinical disease activity and for decisions regarding treatment in individual patients. Moreover, most clinical trials involving new treatments use MRI parameters as outcome measures to show therapeutic effectiveness. Besides Gd-enhancing and T2 lesions, CNS atrophy measurements are being increasingly used as primary MRI end point in clinical trials as they have been shown to be powerful predictors of clinical impairment, disease progression, and the accumulation of long-term physical and neuropsychological disability.

MRI serves also as a research tool in the study of MS. However, cMRI metrics have a limited ability to accurately determine the full extent of inflammatory and neurodegenerative

pathological processes in MS. The discrepancy between clinical and MRI evolution in MS patients, often referred to as the "clinical–MRI paradox", has led to a growing interest in advanced techniques that can detect the presence of cortical lesions, subtle changes in the normal appearing white and gray matter, as well as adaptive functional changes that limit the clinical consequences of disease-related injury. The development and application of novel MR methods of acquisition and postprocessing aim to provide a more accurate characterization of tissue injury including demyelination, remyelination and axonal damage. These advanced approaches give also insights into the functional and metabolic consequences of MS. Additionally, the combined analysis of different magnetic resonance techniques, sensitive toward different aspects of MS, is likely to improve our understanding of the mechanisms responsible for the accumulation of irreversible neurological deficits in the disease. Emerging applications of these tools may also be useful in measuring the effect of therapies. Beyond MRI, novel imaging approaches such as OCT show promise in detecting and monitoring neurodegeneration in MS. Nevertheless, the new techniques and analysis procedures need to be refined and validated before they can be properly integrated into clinical research and practice. Until that time cMRI metrics will continue to play an important role in clinical practice and in clinical trials. Overuse of MRI in clinical practice, however, should be avoided. It is important to keep in mind that clinical judgment remains essential in the management of the disease and that careful interpretation of the MRI data is needed to avoid misdiagnosis.

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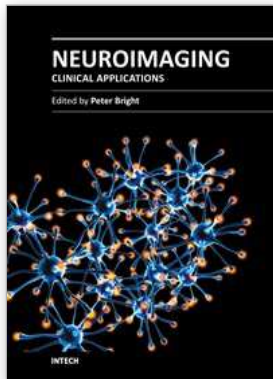
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Modern neuroimaging tools allow unprecedented opportunities for understanding brain neuroanatomy and function in health and disease. Each available technique carries with it a particular balance of strengths and limitations, such that converging evidence based on multiple methods provides the most powerful approach for advancing our knowledge in the fields of clinical and cognitive neuroscience. The scope of this book is not to provide a comprehensive overview of methods and their clinical applications but to provide a "snapshot" of current approaches using well established and newly emerging techniques.

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