Role of Contrast-enhanced Magnetic Resonance Imaging in Multiple Sclerosis

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Abstract

Magnetic resonance imaging (MRI) is an important diagnostic tool in different central nervous system (CNS) disorders including brain cancer and cerebrovascular, inflammatory and neurodegenerative diseases. The most commonly used MRI contrast agents are gadolinium-based compounds that have been successfully employed in combination with T1-weighted sequences to detect and monitor focal disease-related abnormalities. These gadolinium-based contrast agents facilitate the visualisation of areas of blood brain barrier disruption, show good performance in diagnostic procedures and present a favourable safety profile. In multiple sclerosis (MS), conventional MRI, including T2-weighted and gadolinium-enhanced T1-weighted sequences, is pivotal to diagnose and to monitor disease activity and progression. Advanced magnetic resonance (MR) techniques and new contrast agents are currently being developed to improve the ability to identify CNS structural and functional abnormalities in MS, which may better correlate with and predict the clinical course of the disease.

Keywords

Magnetic resonance imaging (MRI), gadolinium-based contrast agents, multiple sclerosis (MS)

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Magnetic Resonance Imaging in Multiple Sclerosis

Since its introduction to medical practice in the 1980s, magnetic resonance imaging (MRI) has become an indispensable imaging technique. It exploits differences in relaxation times (T1 and T2) between nuclei that have an odd number of nucleons (protons and neutrons) – usually hydrogen protons from water molecules present in bodily tissues. When these nuclei are subjected to a homogeneous magnetic field and stimulated by radiofrequency pulses they return to an equilibrium state at different relaxation rates generating variable resonance signals. Differences between water-containing tissues affect the relaxation rates and allow the generation of an image revealing structural differences within these tissues. Initially used for chemical and physical analyses, it rapidly evolved into a fundamental medical imaging procedure that revealed to be particularly useful in the detection of lesions of the central nervous system (CNS).[1] This high-resolution technique allows detection of focal and diffuse abnormalities in the white and grey matter and has become an established tool in the diagnosis of multiple sclerosis (MS) at clinical centres worldwide. It has also proved valuable in monitoring disease activity and progression, and treatment response in the research setting.[2]

Gadolinium-based compounds markedly decrease the T1 relaxation time of adjacent mobile water protons. As a result, after intravenous gadolinium administration, there is a locally increased signal on T1-weighted images from CNS tissues where, normally, there is no blood brain barrier (e.g., the circumventricular organs, meninges and choroid plexus) or where it is abnormally compromised or even absent. This occurs in many types of tumoural, inflammatory and infective lesions.

Longitudinal and cross-sectional magnetic resonance (MR) studies have shown that contrast-enhancement occurs in almost all new MS plaques in patients with relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS). This enhancement correlates with altered blood brain barrier permeability in the setting of acute perivascular inflammation, discriminating acute active from chronic inactive lesions (see *Figure 1*). The gadolinium enhancement varies in size and shape, and usually lasts from a few days to weeks with an average duration of three weeks. New contrast-enhancing lesions are nearly always associated with a hyperintense lesion in the same location on T2-weighted images. The extent of these new T2 lesions usually contract over time (three–five months) and their intensity is reduced as oedema resolves and some tissue repair occurs, leaving

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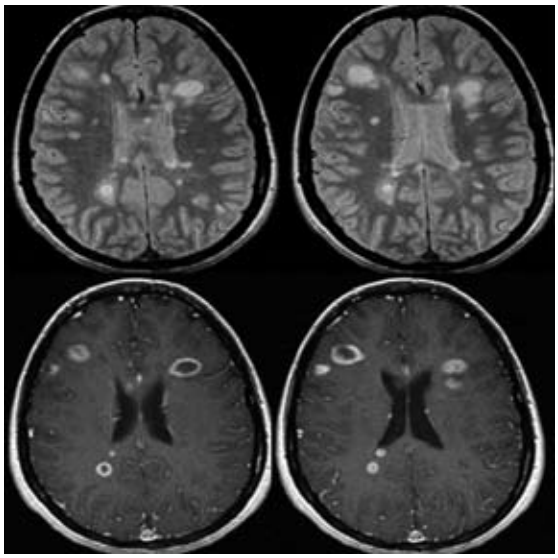
Table 1: Imaging McDonald and Magnetic Imaging in Multiple Sclerosis Criteria for Diagnosing Multiple Sclerosis

	2001 McDonald Criteria[3]	2005 Revised McDonald Criteria[4]	2010 Revised McDonald Criteria[7] (Based on MAGNIMS Criteria[5])
Dissemination in space	At least three of the following: • ≥1 contrast-enhanced lesion or ≥9 T2 lesions • ≥1 juxtacortical lesion • ≥3 periventricular lesions • ≥1 infratentorial lesion Note: 1 spinal cord (SC) lesion can be counted as a brain lesion	At least three of the following: • ≥1 contrast-enhanced lesion or ≥9 T2 lesions • ≥1 juxtacortical lesion • ≥1 infratentorial lesion • ≥3 periventricular lesions Note: • An SC lesion can replace an infratentorial lesion • An enhancing SC lesion is equivalent to an enhancing brain lesion • Any number of SC lesions can be included in total lesion count	At least two of the following: • ≥1 juxtacortical lesion • ≥1 infratentorial lesion • ≥1 periventricular lesion • ≥1 SC lesion All lesions in symptomatic regions excluded in brainstem and SC syndromes
Dissemination in time	• ≥1 contrast-enhanced lesion ≥3 months after initial event; or • ≥1 new T2 lesion compared to a prior scan obtained >3 months after CIS onset	• ≥1 contrast-enhanced lesion ≥3 months after initial event; or • ≥1 new T2 lesion on a follow-up scan compared to a prior scan obtained >30 days after CIS onset	Simultaneous presence of: • Asymptomatic enhanced and non-enhanced lesions at any time; or • A new T2 lesion on follow up MRI irrespective of timing of baseline scan

CIS = clinically isolated syndrome; MAGNIMS = magnetic imaging in multiple sclerosis; MRI = magnetic resonance imaging.

Figure 1: Transverse T2-weighted and Gadobutrol-enhanced T1-weighted Brain Magnetic Resonance Images Obtained from a Patient with Relapsing-Remitting Multiple Sclerosis



Transverse T2-weighted (upper row images) and gadobutrol-enhanced T1-weighted (lower row images). Multiple white matter lesions are identified on the T2-weighted images, some of them showing contrast enhancement reflecting disease activity.

a much smaller T2 permanent 'footprint' of the prior inflammatory event (see *Figure 2*).

Presence of new active lesions is commonly used as an efficacy outcome in clinical trials of disease-modifying therapies (DMTs), as well as for establishing an early diagnosis of the disease.

Because no single clinical feature or diagnostic test suffices to diagnose MS, various diagnostic criteria have been proposed for this purpose in the last years, based on the clinical or paraclinical demonstration of demyelinating lesions disseminated in space and time. The 2001 McDonald diagnostic criteria, based on a series of studies that followed the natural course of disease and established correlations of pathophysiological features with MRI findings, aimed to offer specific and sensitive imaging guidelines for an accurate diagnosis (see *Table 1*).[3] These recommendations were revised in 2005 based on new clinical evidences, which attempted to simplify the criteria for dissemination in time and to better define the role of MRI of the spinal cord for demonstrating dissemination in space.[4] More recently, the European Multicenter Collaborative Research Network on MRI in MS, (MAGNIMS), proposed new criteria for both dissemination in space and time, which could be demonstrated on a single MRI obtained at any time after symptoms onset, simplifying the diagnostic process by requiring fewer MRI examinations and as a consequence allowing an earlier diagnosis and treatment[5,6] (see *Table 1*). These recommendations and the results of other studies[5,6] were incorporated in the 2010 revised McDonald criteria,[7] which also introduced new guidelines for differential diagnosis and on the application of the criteria in paediatric, Asian and Latin American populations. Recent studies confirmed the superior sensitivity of the 2010 McDonald criteria in the diagnosis of paediatric MS.[8,9]

Several recommendations concerning scan acquisition (imaging parameters, slice thickness, patient positioning, field strength, frequency and post-injection timing of scanning), image analysis and structured reporting have been made in an attempt to standardise MRI protocols in research studies and clinical practice.[10–12] For monitoring disease activity and progression, conventional MRI techniques such as proton-density and T2-weighted sequences (spin echo and fluid-attenuated inversion recovery [FLAIR]) and contrast-enhanced T1-weighted sequences are the modalities of choice given their high sensitivity in assessing disease burden and new lesion formation. Nevertheless MRI-based treatment response assessment still presents some acquisition and interpretation challenges (i.e. availability of a pre-treatment MRI scan, optimisation and standardisation in MRI acquisition and analysis), as well as some limitations due to the fact that this technique does not suffice to explain the entire spectrum of the disease process (particularly the neurodegenerative component of the disease), leading to a mismatch between clinical and MRI efficacy of approved treatments. Therefore, MRI

Table 2: Summary of Magnetic Resonance Imaging Contrast Agents Currently Available and their Applications, Benefits and Precautions[17,19,20,64]

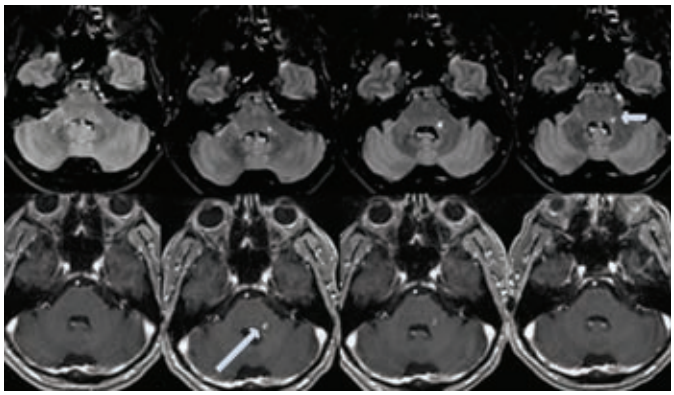
Agent	Availability	Applications	Distinctive Properties	Main Safety Concerns	Select Studies in MS
GBCAs – Blood Brain Barrier Damage					
Macrocyclic Contrast Agents					
Gadoterate meglumine (Dotarem)	Europe Japan Latin America	CNS, MRA, whole body indications	Macrocyclic, ionic High stability	Low NSF risk Anaphylactic-like reactions Hypersensitivity reactions	RRMS[45]
Gadobutrol (Gadovist/Gadavist)	Europe US, Asia Latin America	CNS, MRA liver, kidney, whole body indications	Macrocyclic High stability, non-ionic High concentration Highest T1 shortening	Low NSF risk Hypersensitivity reactions	CIS, RRMS[35]
Gadoteridol (ProHance)	Europe, US Japan	CNS, MRI	Macrocyclic, non-ionic High stability	Low NSF risk Hypersensitivity reactions	MTI[65] and SWI[49] studies in RRMS
Gadofluorine M	Not approved	Originally developed for MRL, nerve imaging[66]	Macrocyclic, ionic Strong binding to serum albumin and ECM proteins Accumulation in inflammatory-demyelinating lesions in spinal cord, brain and optic nerve Faecal and renal excretion	Non-toxic in mice[67] and rabbits[68]	Animal MS model[37,38]
Linear Contrast Agents					
Gadobenate dimeglumine (MultiHance)	Europe, US Asia	Liver, CNS, MRA	Linear, ionic Hepatobiliary and renal excretion Highest T1 and T2 relaxivity Weak plasma protein binding	Medium NSF risk Hypersensitivity reactions Vomiting, nausea	Small-scale study of perfusion imaging of brain tumours, MS lesions, neurolupus, abscesses and stroke[69]
Gadoxetate disodium (Primovist/Eovist)	Europe, US Asia, Japan	Liver dynamic imaging	Linear, ionic Hepatic and renal excretion	Medium NSF risk Hypersensitivity reactions	None
Gadofosveset trisodium (Ablavar)	US, Australia Withdrawn in Europe	MRA For aortoiliac occlusive disease (with known or suspected peripheral vascular disease)	Linear, ionic Reversible strong plasma protein binding Long intravascular enhancement	Medium NSF risk Hypersensitivity reactions	None
Gadopentetate dimeglumine (Magnevist)	Europe, US Japan, Asia Latin America	CNS, MRA (excluding the heart), whole body indications	Linear, ionic	High NSF risk Hypersensitivity reactions	Magnetisation transfer subtraction technique used in the evaluation of plaques in the acute phase of RRMS;[70] PPMS[71]
Gadodiamide (Omniscan)	Europe, US Japan, Asia	CNS, body (intrathoracic [noncardiac], intra-abdominal, pelvic and retroperitoneal regions)	Linear, non-ionic, low stability	High NSF risk Spurious hypercalcaemia Free Gd release Hypersensitivity reactions	Dosing study in RRMS and SPMS;[56] therapy monitoring in RRMS[72]
Gadoversetamide (OptiMARK)	Europe, US	Liver, CNS	Linear, non-ionic agent, low stability	High NSF risk Spurious hypercalcaemia Free Gd release	None
IOBCAs – Cellular Infiltration and Blood Brain Barrier Damage					
Ferumoxide (Endorem/Feridex)	Europe, US Japan	Liver, delayed-phase imaging	SPIO Enhanced T2 relaxation	Slow drip infusion Higher rate of CV events (hypotension) Anaphylactic-like reactions	Animal MS model[73-75]
Ferucarbotran (Resovist/Supravist)	Europe, Japan Australia	Liver, dynamic and delayed-phase imaging MRA, X-ray, ultra-sound	SPIO Enhanced T2 and T1 relaxation Ready-to-use formulation More favourable safety profile	IV administration	RRMS, PPMS[43]
Ferumoxtran-10 (Sinerem/Combidex)	Marketing authorisation application withdrawn in Europe	MRA Lymph nodes metastases	USPIO Enhanced T2 and T1 relaxation Long plasma half-life	High rate of false positives	RRMS[45]

Table 2: (continued)

Agent	Availability	Applications	Distinctive Properties	Main Safety Concerns	Select Studies in MS
MBCAs – Potentially Blood Brain Barrier Damage					
Mangafodipir trisodium (Teslascan)	Marketing authorisation application withdrawn in Europe, Discontinued in the US	Liver, pancreas MRI	Faecal and renal excretion	Cellular toxicity	Currently under evaluation in healthy volunteers and in patients with MS (NCT01326715)[76]

CIS = clinically isolated syndrome; CNS = central nervous system; CV = cardiovascular; ECM = extracellular matrix; GBCA = gadolinium-based contrast agent; Gd = gadolinium; IOBCA = iron oxide-based contrast agent; IV = intravenous; MBCA = manganese-based contrast agent; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MRL = magnetic resonance lymphography; MS = multiple sclerosis; MTI = magnetisation transfer imaging; NSF = nephrogenic systemic fibrosis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPIO = super paramagnetic iron oxide; SPMS = secondary progressive multiple sclerosis; SWI = susceptibility-weighted imaging; USPIO = ultra-small super paramagnetic iron oxide.

Figure 2: Transverse T2-weighted and Gadobutrol-enhanced T1-weighted Brain Magnetic Resonance Images Obtained Serially at Monthly Intervals from a Patient with Multiple Sclerosis



Transverse T2-weighted (upper row) and gadobutrol-enhanced T1-weighted (lower row) images. Observe formation of a new plaque in the brainstem showing transient contrast uptake (long arrow). With cessation of inflammatory activity, the T2 lesion decreased in size, but left a persistent hyperintense footprint on the T2-weighted image (short arrow).

findings should not be used as the primary source of information on disease progression or as a standalone measure to determine treatment decisions in clinical practice;[2,11] however, they correlate well with response to treatment with interferon-ß and the level of short-term disability,[13,14] and are used as surrogates of disease activity, in parallel with clinical markers, in the research setting.[10,12]

Despite its limitations, MRI has also been evaluated for prognostic purposes and for predicting treatment response. A prospective longitudinal study of patients who presented with clinically isolated syndrome (CIS) and were followed for 20 years showed a moderate correlation between initial T2 lesion load and the level of disability during the first five years,[15] and a 10-year follow-up of patients with primary progressive MS (PPMS) identified T2 lesion spatial location as an important, independent contributor to disability.[16] Recent data have shown that the simultaneous presence of relapses or increased disability and active lesions (either new T2 or contrast-enhancing lesions) on a brain MRI scan performed within the first 12 months after initiating a DMT significantly predicts the risk of having a poor response to the treatment in the following years.[17] Nevertheless there is still not enough evidence to support the use of MRI for predicting treatment response in individual patients, which would make possible the identification of poor responders to DMTs who would greatly benefit from switching therapy early during the course of the disease.[18]

Contrast Agents – Benefits and Limitations

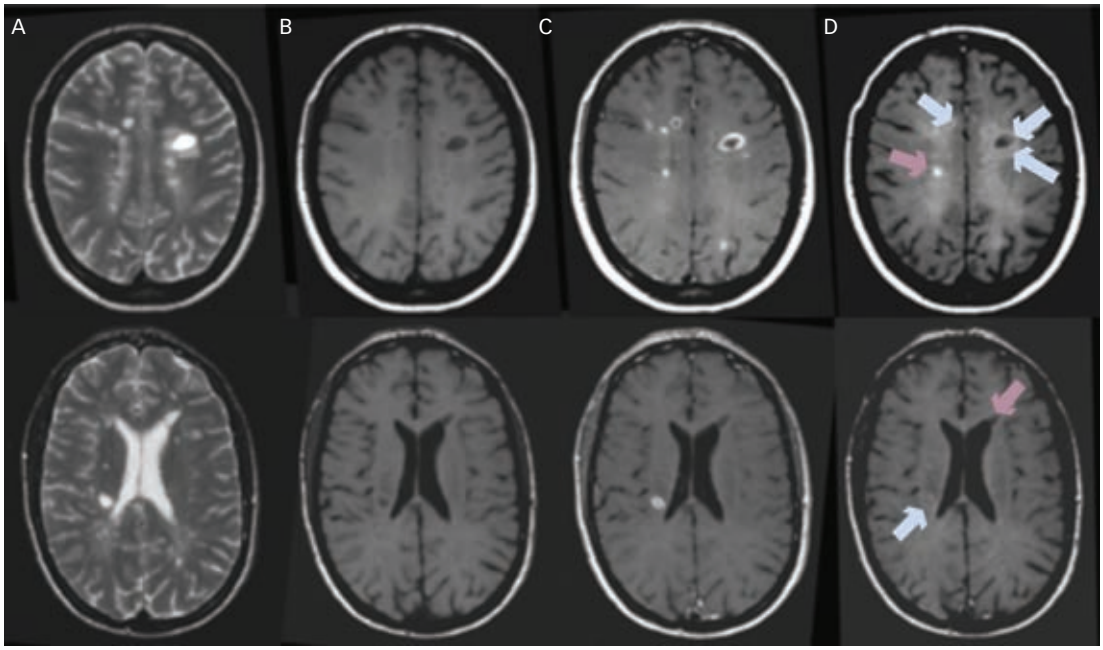
Gadolinium (Gd)-based contrast agents (GBCAs), routinely used in MRI for the identification and characterisation of different types of CNS lesions, transiently highlight newly forming MS lesions on the basis of blood brain barrier leakage and are used as markers of neuroinflammation. They are administered intravenously and are characterised by low toxicity, rapid renal clearance and an extracellular biodistribution.

GBCAs differ in their overall charge, magnetic properties, stability and ligand structure (See *Table 2*).[19] Most of the agents show comparable performance given their similar T1 and T2 relaxivities,[17,20] but gadobenate dimeglumine, gadobutrol and gadofosveset show double relaxivities at all magnetic field strengths;[17] this results in superior lesion enhancement.[17,21] Several other factors not directly related to the chemical structures of the compounds are also known to affect enhancement, namely dose, delay between injection of agent and scanning, MR field strength, and characteristics of image acquisition.[22]

In general, GBCAs present a favourable safety profile. Reports of increased risk of nephrogenic systemic fibrosis (NSF) in patients with renal disease associated with their use, particularly of non-ionic linear agents,[23] led to specific recommendations for restricting use of these agents in patients with severe renal failure, whether or not on dialysis.[24,25] Gadobutrol, gadoterate meglumine and gadoteridol show lower levels of Gd release into the serum (see *Table 2*).[19] This has resulted in their categorisation as low-risk agents by European Medicines Agency (EMA) in 2009[26] which has been recently reconfirmed by the European Society of Urogenital Radiology (ESUR) guidelines.[27]

Gadobutrol, a non-ionic, macrocyclic, extracellular contrast agent, shows good performance in diagnostic procedures and has a favourable safety profile,[28] even in paediatric patients,[29] being well tolerated in patients with renal, hepatic and cardiovascular disease.[30] Gadobutrol performed better than gadoterate meglumine in the qualitative and quantitative evaluation of neoplastic brain lesions in several studies[31,32] and a single dose of gadobutrol was noninferior to double dose gadoteridol in the detection of brain metastases.[33] However, a recent comparative study of brain tumours showed higher detail and enhancement for gadobenate dimeglumine versus gadobutrol when the agents were administered at equivalent doses.[34] Gadobutrol is the only GBCA combining both features: high relaxivity and T1 shortening to yield high efficacy and macrocyclic structure for higher stability and lower Gd release. The effects of doubling the dose of gadodutrol and increasing the time after the dose is given before conducting MRI scans is being investigated in an ongoing study conducted at the Vall d'Hebron

Figure 3: Example of Magnetic Resonance Imaging Scans from a Patient with Multiple Sclerosis Obtained with Both Gadolinium and USPIO Contrast Agents



Cross-sectional patterns of lesion enhancement. A) Pre-Gd T2 spin-echo images showing multiple periventricular lesions. B) Pre-Gd T1-W images showing hypointensity of some of the lesions. C) Post-Gd T1-W images show that several lesions enhanced with Gd in focal and ring-like patterns. D) Post-USPIO T1-W images show different patterns of USPIO-enhancement: purple arrow upper row: focal USPIO-enhancement; blue arrows upper row: ring-like USPIO-enhancement; blue arrow bottom row: change to isointensity of a previously hypointense lesion as seen on pre-contrast T1-W images (see B); purple arrow bottom row: a hypointense lesion that remains hypointense on post-USPIO images. Gd = gadolinium; T1-W = T1-weighted; USPIO = ultra-small super paramagnetic iron oxide. Source: Reprinted with permission from Vellinga et al., 2008.[27]

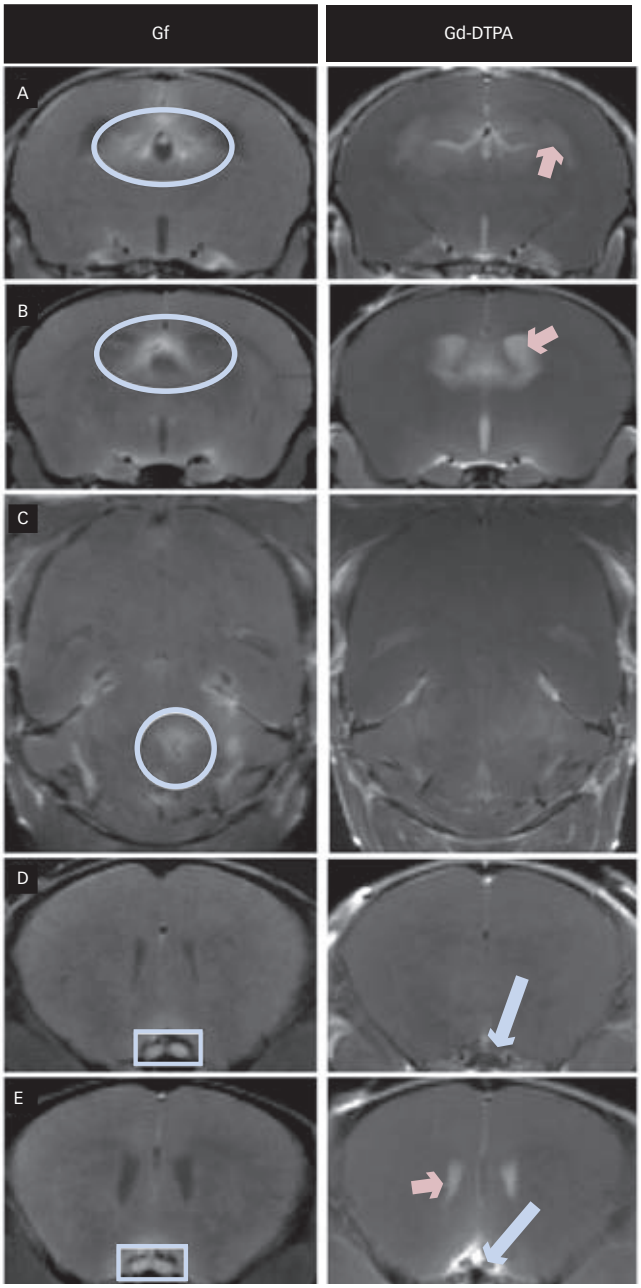
University Hospital in Barcelona that includes 118 patients with either CIS or RRMS. Four sets of contrast-enhanced T1-weighted sequences are performed on each patient, five and 15 minutes after a single (0.1 mmol/kg) and a cumulative double (0.1 + 0.1 mmol/kg) dose of gadobutrol. Preliminary results obtained from the first 52 patients showed that significantly more active lesions were seen in RRMS compared with CIS.[35] The cumulative double dose increased the detection of patients with active lesions from 3 to 7 % over the single dose; however, delaying the scan from five to 15 minutes also increased the active lesion detection after either single or double dosing.

Although GBCAs are the agents of choice for the identification of active lesions on MRI, the field would strongly benefit from new highly specific and sensitive contrast media, either based on Gd chemistry or with new underlying biochemical mechanisms. Animal studies show the potential of a new Gd-chelate, gadofluorine M, in targeting neuroinflammation (see *Table 2*). This tracer, originally conceived for magnetic resonance lymphography applications, accumulates in degenerating nerve fibres highlighted on T1-weighted sequences in an established rat model of demyelinating disease induced by lysolecithin, and the degree of enhancement correlates with the demyelination level, as shown by quantitative MRI and histological analysis.[36] Remarkably, most of the lesions are not depicted by conventional T2-weighted and gadopentetate–dimeglumine-enhanced T1-weighted sequences in murine models of experimental autoimmune encephalomyelitis (EAE) (see *Figure 3*).[37, 38] Likewise, a new fluorescent Gd-based contrast agent targeting myelin produced exciting results in several murine demyelination disease models, which could eventually enable distinction between tissue myelination status and inflammation, providing the MS community with a much needed strong correlation with disease progression. Staining with this highly specific myelin imaging compound (MIC) corresponded to intensely myelinated white matter and was significantly reduced in myelin-deficient shiverer mice and in L-α-lysophosphate- and cuprizone-induced demyelination rat models.[39]

Iron oxide-based paramagnetic particles also exhibit high sensitivity in the detection of active MS lesions (see *Table 2*). Super paramagnetic iron oxide (SPIO) and ultra-small super paramagnetic iron oxide (USPIO) contrast agents identify regions of macrophage hyperactivity, known to be crucial in lesion development, in rat models of EAE[40-42] and can highlight inflammation areas without signal changes on T2-weighted images, which may or may not be enhanced by Gd (see *Figure 4*).[43] Their sustained enhancement versus that obtained with Gd suggests a distinct mechanism for macrophage infiltration and inflammation in acute active lesions,[44] which may pave the way towards an understanding of interpatient variability in the pathological manifestations of the disease. Following the encouraging results of the above mentioned animal studies and an exploratory study involving patients with both PPMS and RRMS, a small-scale study in patients with RRMS confirmed the distinct and complementary role of USPIO-enhancement in lesion detection versus traditional GBCAs that reflect increases in blood brain barrier permeability.[45] USPIO-enhanced macrophage infiltration is being evaluated in an ongoing clinical trial as a prognostic marker in patients with CIS (NCT01567553).

Interestingly, iron oxide particles have been conjugated to an anti-VCAM antibody and used to quantify pre-symptomatic lesions in a mouse model of MS.[46] Binding of the conjugated contrast agent identified regions of leukocyte infiltration not seen by Gd-enhancing T1-weighted sequences and correlated significantly with increasing disability. Likewise, SPIO particles bound to T-cell-specific antibodies against CD3 recognised leukocyte infiltration in the same murine model of MS,[47] and active inflammation regions were successfully labelled with an experimental, highly sensitive myeloperoxidase-activated paramagnetic

Figure 4: Detection of Inflammatory Lesions in a Mouse Model of Multiple Sclerosis by Gadofluorine M



Coronal (A, B, D, E) and axial (C) T1- weighted images are depicted 24 hours after gadofluorine (Gf) injection (left column) and immediately after gadopentetate dimeglumine (Gd-DTPA) injection (right column). Periventricular pathology was better assessable applying Gf (A and B: ovoid). The disruption of the blood-cerebrospinal fluid (CSF) barrier frequently caused leakage of contrast agent into the CSF (A, B, E: purple arrows), initially obscuring periventricular lesions. A parenchymal midbrain lesion is shown as example of a lesion (C: encircled) that was not seen with Gd-DTPA. Visualisation of optic neuritis (D and E: square) was markedly improved by Gf, since neighbouring intravascular signal prohibited the unambiguous determination on Gd-DTPA-enhanced images (D and E: blue arrows). Source: From Wuerfel et al., 2010.[38]

probe,[48] suggesting that cellular-targeted and inflammation-induced molecular enhancement is feasible.

Finally, mangafodipir is an MRI contrast agent containing manganese that has been approved for MRI scans of the liver and pancreas. Its safety and effectiveness are currently being evaluated in a small-scale Phase I study enrolling patients with MS and healthy volunteers. Participants will be randomly assigned to an eye- or brain-imaging group (NCT01326715) with the specific goals of determining whether mangafodipir can detect tissue damage in the retina, optic nerve and brain, as well as its effects on the basal ganglia on follow-up.

Non-conventional and Advanced Magnetic Resonance Techniques in Multiple Sclerosis

The sensitivity of MRI has made it a valuable routine clinical examination method for MS, providing significant advantages in the assessment of lesion activity and progression compared with previous imaging techniques such as computed tomography.

Despite this sensitivity and diagnostic value, conventional MRI underestimates the damage that occurs in the so-called normal appearing brain tissue (both white and gray matter), and has limited pathological specificity, being unable to assess the degree of the underlying pathologic substrate (edema, inflammation, demyelination, remyelination, reactive gliosis, and axonal loss) which contribute differently to the development of permanent disability. In recent years, great effort has been dedicated to developing new MRI techniques and imaging analysis methods, which improve the sensitivity in detecting cortical lesions and can selectively assess and predict the neurodegenerative component of MS pathology and monitor the reparative mechanisms. These techniques, which include global and regional measures of CNS atrophy, susceptibility-weighted imaging (SWI), double inversion-recovery sequences, diffusion tensor imaging, (DTI) magnetisation transfer imaging (MTI), proton magnetic resonance spectroscopy and functional MRI, have increased our understanding of the pathogenesis of the disease, and have provided significant insights into the structural and cellular basis of MS, with subsequent impact on treatment response monitoring and prediction.[2]

SWI showed comparable specificity in the detection of active plaques versus contrast-enhanced MRI and can provide quantitative assessment of iron deposition both in the white matter and basal ganglia.[49] Double inversion recovery (DIR) sequences have made possible the visualisation of cortical lesions with higher sensitivity compared with T2-FLAIR sequences in patients with RRMS, SPMS and CIS, but still needs to be validated in the clinical setting. Additional studies will confirm whether cortical lesions may have diagnostic value in CIS patients and function as predictors of disease progression and long-term disability.[50]

Although DTI and MTI can quantify focal and diffuse tissue changes, the correlation of these structural abnormalities with pathophysiological features has not completely been established. However, these MRI techniques may prove useful in monitoring the progression of grey and white-matter damage and its potential reversal with new pharmacological interventions targeting demyelination and axonal loss instead of inflammation.[2] Nevertheless, MTI has proven to be sensitive to changes in myelin content in murine species.[51]

High-field (3-4 Tesla) and ultra-high-field (4-7 Tesla) MRI have provided additional details of the lesions, particularly regarding evidence for abnormal patterns of iron deposition in macrophages and vessels.[52-54] Moreover, ultra-high-field MRI has the potential to increase sensitivity in the identification of cortical lesions, which are often not detected by conventional MRI.[55] While higher doses of GBCAs[56,57] and delay of scanning time after injection of the contrast agent combined with the application of an off-resonance saturated magnetic transfer pulse increases the ability to detect active MS lesions,[22] 3T magnetic fields increase the ability to detect Gd-enhancing lesions when

compared with 1.5T fields, allowing for visualisation of early events in lesion formation.[58] Despite this obvious advantage, current limitations to widespread use of high- and ultra-high-field MRI involve technical issues (e.g. installation and image acquisition), cost (i.e. of the equipment itself and in shielding, to ensure safety) and physiological tolerability thersholds.[59] Also, its usefulness in terms of allowing earlier diagnosis is still under question.[60]

By contrast, functional MRI has yielded promising results regarding visualisation of CNS functional reorganisation in patients with MS at different stages of disease and could be used as a monitoring tool in the assessment of the efficacy of therapies that promote neuroplasticity.[2]

Proton magnetic resonance spectroscopy (^{1}H-MRS) is particularly valuable for assessing the neurodegenerative component of MS, which is known to occur from the early phases, through the quantitative assessment of the amino acid *N*-acetylaspartate, considered a marker of neuronal/axonal function and density. Other metabolites, such as choline, myo-inositol, creatine, glutamate, lipids, and lactate which play a significant role in the pathophysiology and repair mechanisms of MS, have also been proposed as markers of metabolic abnormalities. In addition to detection of changes in levels of the above-mentioned metabolites, recent studies have reported changes in other metabolites, such as citrulline and glutathione, which could be considered markers of demyelination of oxidative stress in the cell.[61,62]

MRI has undergone rapid advances over the past three decades to become a fundamental clinical diagnostic imaging tool.[63] Contrast-enhanced MRI has contributed to the characterisation of the pathophysiology of MS and provides an early and accurate diagnosis. With the development of new and improved DMTs, reliable assessment tools are needed to inform treatment strategies, avoiding the damage and costs associated with pharmacological agents of limited efficacy, to predict treatment responses and to even elucidate the mechanisms of lesion formation and progression. Contrast-enhanced MRI will therefore increasingly assume these roles.

The results obtained in the specific research settings described above raise hope for future implementation of advanced MRI-based imaging techniques in clinical practice. The foreseeable future will bring physicians and patients standardised protocols and further validated imaging tools that will benefit patients with MS tremendously. Increased use of contrast agents in MRI and the availability of new contrast media are likely to enable MS physicians to monitor disease progression, indicating where treatments should be maintained or changed, thus improving patient outcomes. ■

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