

Gadolinium-enhanced magnetic resonance imaging in multiple sclerosis



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Magnetic resonance imaging has a major role in the overall diagnostic scheme of multiple sclerosis as well as in selecting patients for immunomodulatory treatment, monitoring disease activity, and predicting treatment response.

Multiple sclerosis (MS) is a chronic, persistent inflammatory-demyelinating disease of the central nervous system (CNS), characterised pathologically by areas of inflammation, demyelination, axonal loss, and gliosis scattered throughout the CNS with a predilection for the optic nerves, brainstem, spinal cord, and cerebellar and periventricular white matter, although cortical and subcortical gray matter damage is also prominent.

Relapsing forms of MS account for 85% of all MS. This clinical form typically presents as an acute clinically isolated syndrome (CIS) attributable to a monofocal or multifocal CNS demyelinating lesion. Over the years, patients usually experience episodes of acute worsening of neurologic function followed by complete recovery (relapsing-remitting [RR] course). After several years of the RR course, more than 50% of untreated patients will develop progressive disability with or without occasional relapses, minor remissions, and plateaus (secondary progressive [SP] course). As long as the aetiology of MS remains unknown, causal therapy and effective prevention are not possible. Immunomodulatory drugs such as beta-interferon, glatiramer acetate, mitoxantrone and natalizumab can alter the course of the disease, particularly in the RR form, by reducing the number of relapses and accumulated lesions seen on magnetic resonance imaging (MRI), and by influencing the impact of the disease on disability. Patients with the SP form of MS, continuing relapses of activity, and pronounced progression of disability may also benefit from immunomodulatory or immunosup-

pressive therapy, see also articles in *Eur J Hosp Pharm Prac.* 2007;13(1):17-22 and *Eur J Hosp Pharm Prac.* 2007;13(3):72-3.

Conventional MRI techniques, such as T2-weighted sequences and gadolinium-enhanced T1-weighted sequences, which are highly sensitive for detecting MS plaques, have become established as the most important paraclinical tool for diagnosing MS, and for understanding the natural history of the disease and monitoring the efficacy of treatments.

Gadolinium-based contrast agents in MS

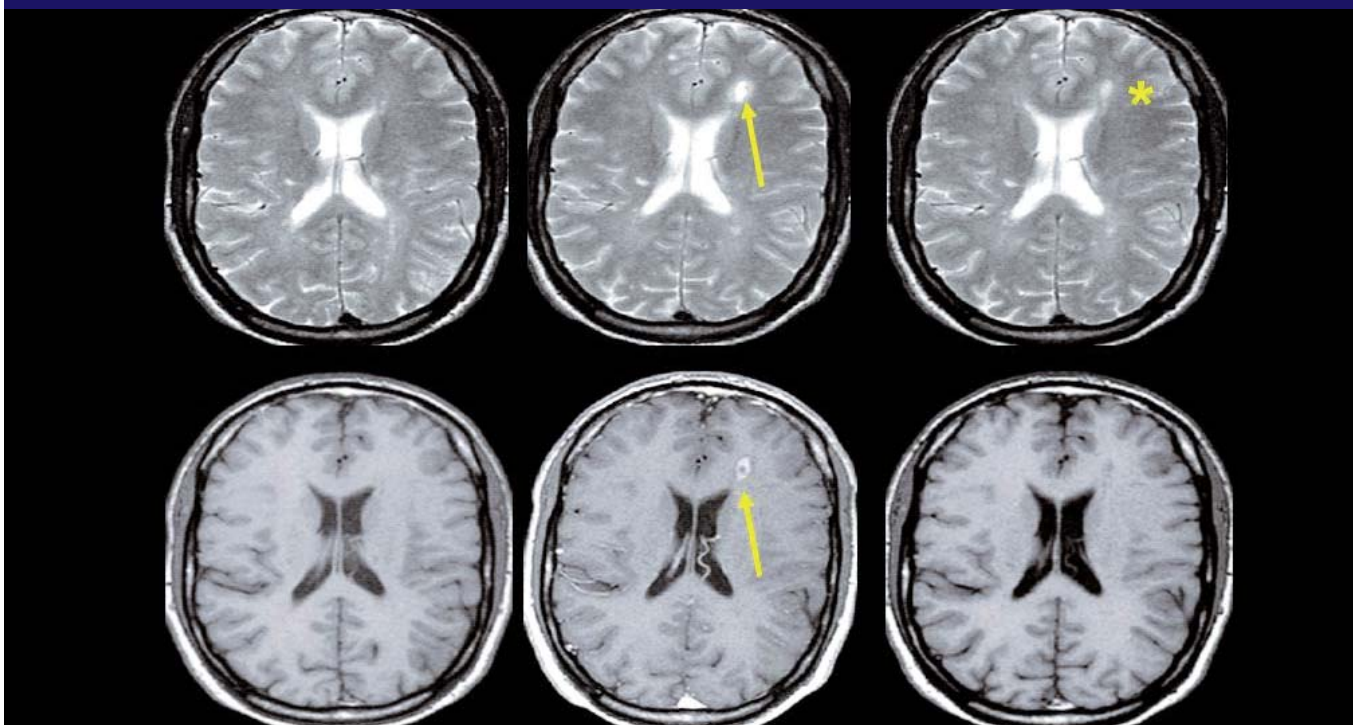
Gadolinium (Gd) is a rare element of the lanthanide series, with strong paramagnetic properties. Because free gadolinium is highly toxic, it must be bound to other molecules (chelate) in the contrast-agent solution. These gadolinium agents, which are the most widely used contrast agents for MRI, are characterised by low toxicity, high thermodynamic and kinetic stabilities, rapid renal clearance and an extracellular biodistribution [1]. However, a severe late adverse reaction following administration in patients with severe kidney disease (nephrogenic systemic fibrosis) has been recently reported [2].

Gadolinium administration markedly decreases the T1 relaxation time of adjacent mobile water protons. As a result, after IV 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 the barrier is abnormally compromised or even absent, as occurs in many types of lesions. This is

the case of active MS lesions, in which enhancement correlates with altered blood brain barrier permeability in the setting of acute perivascular inflammation.

In MS patients gadolinium-enhanced T1-weighted imaging is highly sensitive in detecting inflammatory activity. This technique detects disease activity 5 to 10 times more frequently than clinical evaluation of relapses, suggesting that most of the enhancing lesions are clinically silent. Longitudinal and cross-sectional MR studies have shown that the formation of new MS plaques is often associated with contrast enhancement, mainly in the acute and relapsing stages of the disease (see Figure 1). The gadolinium enhancement varies in size and shape, and usually lasts from a few days to weeks, although this time period is shortened by steroid treatment [3]. Focal enhancement can be detected before abnormalities appear on unenhanced T2-weighted scans, and can reappear in chronic lesions with or without a concomitant increase in size. Although enhancing lesions also occur in clinically stable MS patients, their number is much greater when there is concomitant clinical activity. Contrast enhancement is a relatively good predictor of further enhancement and of subsequent accumulation of T2 lesions, but shows no (or a weak) correlation with progression of disability and development of brain atrophy. Subclinical disease activity with contrast-enhancing lesions is 4 to 10 times less common in the spinal cord than the brain, a fact that may be partially explained by the large volume of the brain as compared with spinal cord.

Figure 1: Relapsing-remitting MS with new plaque formation



Transverse T2-weighted (upper row) and contrast-enhanced T1-weighted (lower row) brain MR images obtained serially at monthly intervals. Observe formation of a new plaque in the left frontal white matter showing transient contrast uptake (arrow). With cessation of inflammatory activity, the T2 lesion decreased in size, but left a persistent hyperintense footprint on the T2-weighted image (*).

Role of gadolinium-enhanced MRI in the initial diagnosis

An early and accurate diagnosis of MS in CIS patients is essential to relieve uncertainty, provide prognostic counselling, and consider MS disease-modifying treatments that have partial efficacy at this earliest clinical stage 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 three main principles: 1) demonstration of disease dissemination in space (DIS), 2) demonstration of disease dissemination in time (DIT), and 3) reasonable exclusion of alternative explanations for the clinical presentation.

These principles, codified in 1983 by the Poser committee [4], specified that the diagnosis of clinically definite MS could be based on either: 1) occurrence of two attacks and clinical evidence of two lesions, or 2) two attacks and clinical evidence of one lesion plus paraclinical

evidence of a second lesion. MRI was not considered at that time, since it was then a new, untested technique.

In 2001, new diagnostic criteria were proposed that incorporated a precisely defined role for MRI [5]. The 2001 McDonald criteria and the revised 2005 version [6] integrated MRI criteria into the scheme to demonstrate dissemination of demyelinating lesions both in space and time. To demonstrate DIS, brain MR scans must meet the Barkhof-Tintoré criteria [7, 8], in which a threshold of at least three of the following four features must be seen:

- one gadolinium-enhancing lesion or nine T2 hyperintense lesions if gadolinium-enhancing lesions are not present
- at least one infratentorial lesion
- at least one juxtacortical lesion and at least three periventricular lesions.

When three of these four parameters are not fulfilled, the presence of two or more sub-clinical lesions consistent with MS on brain

MRI, plus CSF detection of oligoclonal bands or a raised IgG index are required to demonstrate DIS. Dissemination in time can be demonstrated with MRI when new lesions have developed after the clinical onset. This can be a gadolinium-enhancing lesion on a scan obtained more than three months after a CIS if it is not associated with the initial clinical event, or a new T2 lesion on a brain MR scan compared to a reference scan done at least 30 days after the onset of the initial clinical event.

Role of gadolinium-enhanced MRI in predicting treatment response

Interferon beta and glatiramer acetate (GA) are the most widely used and accepted treatments for RR MS. Clinical trials with these immunomodulatory agents in this clinical phenotype have shown an evident effect in reducing clinical and MRI disease activity (new T2 or gadolinium-enhancing lesions), and progression of disability. Nevertheless, the response to these treatments in patients with MS is very heteroge-

neous. MS patients treated with interferon beta or GA who continue to experience clinical and MRI activity are considered non-responders, but actually, it is difficult to establish whether an individual patient is responding to treatment and to what degree. Recent data have shown that the simultaneous presence of relapses or increased disability and active lesions on brain MRI (either new T2 or contrast-enhancing lesions) significantly predicts the risk of having a poor response to interferon beta treatment in the following years [9]. This information is especially important nowadays, when new second-line treatments, such as natalizumab, are available for treating MS. Although these agents are more effective than first-line treatments, they have a lower safety profile. Hence, it is fundamental to identify non-responders early to optimise MS therapy and facilitate rational evidence-based therapeutic decisions.

Methods to increase the sensitivity of gadolinium-enhanced MRI

Several methods have been proposed to increase the sensitivity of gadolinium-enhanced MRI for detecting disease activity in routine clinical practice [10-12]. These include:

- The introduction of a minimum 20-minute delay between gadolinium injection and scanning, with the aim of maximising the signal changes derived from increased blood-brain barrier permeability.
- The use of high gadolinium doses (0.3 or 0.2 instead of 0.1 mmol/kg body weight) or gadolinium agents having a high concentration (1 M instead of 0.5 M) or markedly high *in vivo* T1 relaxation (9.7 mM⁻¹s⁻¹ instead of 4.3–5.6 mM⁻¹s⁻¹), with the purpose of boosting the decreased T1 relaxation time effect.
- The use of magnetisation transfer saturation pulses, which improve the conspicuity of gadolinium-enhancing lesions by reducing the signal of the surrounding brain parenchyma.

There is now considerable evidence that a combination of two or more of these differ-

ent strategies, e.g. delayed scanning combined with higher doses of gadolinium can result in a significant increase in sensitivity compared to the standard technique [13].

In addition to these strategies, high field MRI (3.0T) offers higher gadolinium-enhancing lesion detection rates when compared to 1.5T [14]. This greater detection can be explained by the fact that T1 (longitudinal) relaxation time is significantly elevated (by approximately 40%) in the white matter at 3.0T when compared to 1.5T, increasing the T1 shortening effect of gadolinium-based contrast media and resulting in a higher post-contrast signal of enhancing tissues.

Conclusion

Due to its unique sensitivity in detecting disease activity, gadolinium-enhanced MRI is extremely valuable not only for achieving an early diagnosis of MS, but also in selecting patients for immunomodulatory treatment and monitoring disease activity. Recent data also support the value of gadolinium-enhanced MRI in predicting treatment response. The use of cost-effective strategies that increase the sensitivity of gadolinium-enhanced MRI for detecting disease activity might improve our capability in the initial diagnosis and in monitoring treatment for the disease.

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