

MRI Contrast Agents

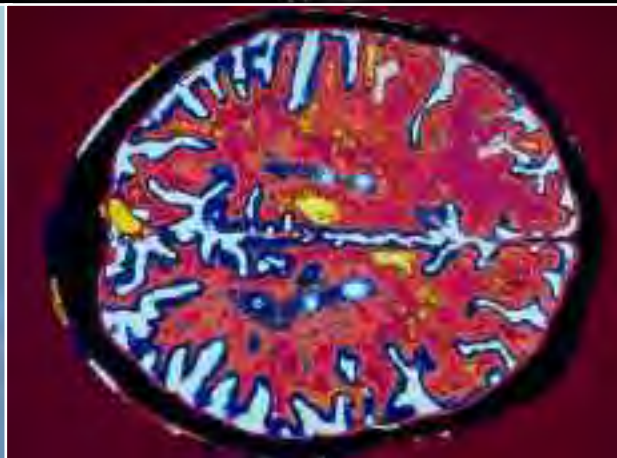
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Imaging of brain tumours and metastases

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Imaging with contrast media – an introduction

Tim Leiner, MD, PhD

The state of the art of imaging techniques is presented, bringing out the advantages and risks of these procedures. Modern imaging is so well regarded that the risks of allergy to iodinated and gadolinium-based contrast agents may be overlooked. Use of these techniques is growing rapidly.

Introduction

Medical imaging is one of the fastest growing disciplines in the hospital. The average radiology department has seen the number of procedures growing at 5–10% annually over the last decade, and the end of this growth is certainly not in sight. The growth in use of imaging has been paralleled by a rapid increase in the use of medical contrast agents. It is important to realise that contrast agents – while very safe in general – are sometimes associated with severe side effects, depending on the class of agents used. In this article a short introduction to the most commonly used imaging techniques is given, with emphasis on the role of contrast agents.

General principles of imaging techniques

X-ray imaging

X-ray-based imaging refers to procedures performed under fluoroscopic guidance such as small or large bowel imaging or coronary and peripheral vascular angiography as well as any form of computed tomography (CT). Contrast agents used in X-ray-based imaging techniques are barium or iodine-based. Barium agents are only used to visualise the gastrointestinal tract, so the vast majority of contrast-enhanced X-ray procedures are performed using iodinated contrast agents. It is estimated that for CT scans over half of all examinations are enhanced using iodinated contrast agents. The purpose of these agents is to increase soft tissue contrast, as the densities of un-enhanced soft tissues are very similar. Dynamic enhancement patterns can also give valuable clues with regard to the differential diagnosis, and

this finding is often used in daily practice for instance to differentiate between different kinds of liver lesions.

It is well known that iodinated contrast agents have the potential to adversely affect renal function, i.e. to cause contrast-induced nephropathy (CIN), especially in patients whose renal function is already compromised. However, careful selection of patients and taking preventive measures such as pre-hydration and, if needed, premedication, make these agents well tolerated in everyday clinical practice. For an up-to-date overview of this topic the reader is referred to the recent meta-analysis on this subject by Kelly et al. who found that N-acetylcysteine is more renoprotective than pre-hydration alone [1]. Allergic-like reactions also comprise a substantial part of the adverse effects associated with the administration of iodinated contrast agents, although with the widespread switch to non-ionic agents the frequency has dropped substantially. Singh et al. provide an excellent overview of iodinated contrast media and their adverse reactions [2].

Ultrasonography

Ultrasonography is a safe and cheap imaging modality that is very widely used as the first choice of imaging method throughout the world. In ultrasonography, grey scale values as seen in the image are related to the acoustic impedance of different tissues. Because of the inherently high contrast between different tissues as visualised with ultrasonography contrast agents are not often used in clinical practice. Contrast agents used for ultrasonography are gas-filled

bubbles giving rise to a (transient) high signal in the vasculature of the organ of interest due to increased back-scatter. The main indication for their use is to characterise the vascular supply of focal lesions in soft tissues such as the liver. Emerging indications are the characterisation and follow-up of tumour microvasculature in the context of focal liver disease and breast and prostate tumours [3].

The adverse effects of ultrasound contrast agents are primarily back pain, headache, urticaria, and rarely anaphylactic reactions (estimated rate of 1 per 10,000) [4]. However, the safety of echocardiographic contrast agents has been the subject of discussion since the FDA issued a ‘black box’ warning for the agents Definity and Optison in October 2007, contraindicating their use in patients with worsening or unstable heart failure, acute myocardial infarction or serious ventricular arrhythmias and in conditions that cause pulmonary hypertension, based on the occurrence of 11 deaths, four of which were caused by cardiac arrest occurring during or within 30 minutes of their use. However, these events occurred over a period of six years and causality was not clear. The FDA reviewed these guidelines in May 2008 and replaced the extended contraindications with warnings after recognising the favourable risk/benefit ratio for these contrast agents and the potential risks of alternative procedures. Current contraindications to the use of echocardiographic contrast agents are right to left or bidirectional cardiac shunts, hypersensitivity to perflutren, intra-arterial injection and, for Optison

only, hypersensitivity to blood or albumin. Thirty minutes of monitoring is required only for patients with pulmonary hypertension and unstable cardiopulmonary diseases [5].

Magnetic resonance imaging

The most versatile modern method of imaging is no doubt magnetic resonance imaging (MRI). MRI is unequalled in the variety and kinds of imaging contrasts that can be generated. In its conventional, most well-known form, MRI soft tissue contrast is based on the phenomenon of relaxation parallel T1 and perpendicular T2 to a strong external magnetic field after radiofrequency stimulation. By manipulating sequence parameters different sequences (also known as weightings) can be generated [6]. Furthermore, in contrast to CT and ultrasonography, MRI is not only capable of imaging 'anatomy' but also physiological processes such as flow, perfusion and diffusion.

There are many MR contrast agents and the reader is referred to the review paper by Bellin [7] for an overview of the class of extracellular gadolinium-based contrast agents which comprise virtually all of the agents used today.

In general, MR contrast agents increase the relative difference between tissues by altering the relaxation times. *Positive* contrast agents cause a reduction in the T1 relaxation time (increased signal intensity on T1 weighted images). They are typically small molecular weight compounds containing as their active element gadolinium, manganese or iron and appear bright on MRI. All of these elements have unpaired electron spins in their outer shells and long relaxivities. Some typical contrast agents such as gadopentetate dimeglumine, gadodiamide, gadoteridol, gadobutrol, gadoxetic acid and gadoterate meglumine are used for the central nervous system and the complete body; mangafodipir trisodium and gadoxetic acid are specially used for lesions of the liver. *Negative* contrast agents (appearing predominantly dark on MRI) are small particulate aggregates

often termed superparamagnetic iron oxide (SPIO). These agents produce predominantly spin-spin relaxation effects (local field inhomogeneities), which result in shorter T1 and T2 relaxation times. SPIOs and ultra-small superparamagnetic iron oxides (USPIO) usually consist of a crystalline iron oxide core containing thousands of iron atoms and a shell of polymer, dextran, polyethylene glycol, and produce very high T2 relaxivities. USPIOs smaller than 300 nm cause a substantial T1 relaxation and T2 weighted effects are predominant. A special group of negative contrast agents (appearing dark on MRI) are perfluorocarbons. The hydrogen atoms responsible for the signal in MRI are replaced by fluorine atoms. These agents are the subject of research and not available clinically at present.

Since the late 1980s many toxicological and pharmacokinetics studies have been conducted by the major contrast vendors with various gadolinium-based contrast agents (GBCA). An extremely favourable safety profile was found in all of these studies. Therefore, the recent discovery of the association between administration of GBCA and nephrogenic systemic fibrosis (NSF) came as a surprise to almost everyone involved, although in retrospect it may not be so surprising. To date, over 200 million patients have been dosed and adverse effects of any kind were very rare, until the discovery of NSF.

NSF is a rare, idiopathic systemic fibrosing disorder and is characterised clinically by pain, dermatopathy and joint contractures. NSF affects the skin, skeletal muscle, oesophagus, lungs, heart and kidneys. The first suggestion of the link between GBCA and NSF, published by Grobner et al. three years ago [8], has sparked intense interest in this subject, illustrating just how important MR contrast media are today. It is now clear that NSF is a condition that almost exclusively affects patients with severely limited renal function. However, surprisingly little is known about the exact pathogenesis of the disease, and who exactly are at risk for developing the disease.

The discovery of NSF has been unfortunate for patients, and particularly patients with acute or chronic kidney disease (CKD) with severely impaired renal function. Worldwide, regulatory agencies have issued warnings on the use of GBCA in patients with severe kidney dysfunction (CKD stages 4 and 5) [9], which has led to the virtual cessation of use of contrast-enhanced MRI in this vulnerable patient group [10].

Relative merits and shortcomings of imaging techniques

For CT the drawbacks include the relatively higher rate of adverse events associated with contrast media administration and the use of ionizing radiation. Although recent technical developments with regard to multi-detector row technology have addressed many of the concerns regarding radiation, the rapid rise in the number of CT procedures has partially offset these gains again.

Ultrasonography's advantages are many. The technique is widely available, cheap and images are obtained in real time at very high spatial resolution. Disadvantages are the relatively high rate of uninterpretable studies, which is primarily a function of the expertise of the person performing the examination, as well body type, and improper preparation for the exam, i.e. not fasting prior to abdominal imaging.

For MRI the main limitations are cost and availability. A typical MRI examination takes about 30–60 minutes depending on the indication. Also, because of higher equipment and maintenance costs, MRI is much more expensive compared to other imaging modalities. It is also important to realise that not all patients are good candidates for MRI. Patients who suffer from claustrophobia or who cannot lie still in the magnet, or patients with ferromagnetic implants such as pacemakers and aneurysm clips are poor candidates, and are better served with CT or ultrasonography.

MRI – the preferred technique?

From the above discussion it becomes

clear that despite their strengths all imaging modalities have drawbacks. It is important to realise that in clinical practice all techniques are routine employed and no single imaging modality can be fully replaced by another. Despite this caveat, it is safe to say that MRI is probably the most versatile imaging modality due to sheer amount of anatomical and physiological information that can be obtained.

Furthermore, the great advantage of MRI is the entirely non-destructive nature of the imaging process, making the technique of special interest when radiation exposure is of concern, such as in paediatric patients or when imaging especially radiosensitive organs such as the gonads or breast.

Despite the risks associated with administration of gadolinium-based contrast agents it very important to realise that risk is relative, not absolute. Not only is the risk of NSF with GBCA-MRI small compared to the risk of CIN with iodinated CT, but also in comparison with risk of severe allergic reactions with iodine and allergic reactions with GBCA. The concern about NSF has masked our concerns for GBCA's other potential adverse effects. A survey of major American centres published in 1999 by Murphy et al. indicated an inci-

dence of severe allergic reactions to GBCA of approximately 20 cases per million doses administered [11]. This is about 10-fold greater than the incidence of NSF, not to mention the risk of making an incorrect diagnosis because the most appropriate imaging study was not done.

In conclusion, nowadays there are many alternatives available to the referring clinician when it comes to imaging. Basic knowledge of imaging modalities and the contrast media that are used enable patient care to be optimised.

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Image augmentation in MRI – critical factors in selecting optimal contrast agents

Nicoletta Anzalone, MD

Contrast-enhanced magnetic resonance imaging has become a standard technique for diagnosis and disease management across a wide range of conditions. Choosing between the numerous gadolinium-based contrast agents now available requires an understanding of their different properties and how these relate to safety and efficacy.

The past 20 years has seen a huge expansion in the use of contrast agents in magnetic resonance imaging (MRI). The resulting improvement in diagnostic accuracy and sensitivity has made contrast-enhanced MRI a standard procedure in the management of an increasing number of diseases. Most of the MRI contrast agents approved for human use contain gadolinium (Gd), a paramagnetic element of the lanthanide series. Gd-based contrast agents (GBCAs) are positive contrast agents that result in increased signal intensity on T1-weighted images. The first of these, gadopentetate dimeglumine (Magnevist) was approved for clinical use in whole-body MRI in 1988 and a further eight GBCAs have since become available (see Table 1). In order to optimise the workflow in a radiology department, it is desirable that most patients can be diagnosed with one preferred contrast agent. Weighing up the options requires a good understanding of the properties of the different compounds and what these mean for the safety of the patient and the quality of the image.

Characteristics of the available Gd-based contrast agents

GBCAs are low-molecular-weight complexes in which

the Gd ion is chelated into either a linear or a macrocyclic structure (see Table 1). The linear agents are commonly further categorised, based on the net charge of the complex, into non-ionic and ionic agents. These three categories of GBCA differ in terms of their stability, i.e. their propensity to release the Gd from the chelate. *In vitro* studies have shown that the macrocyclic chelates (gadobutrol (Gadovist), gadoterate meglumine (Dotarem) and gadoteridol (ProHance)) are the most stable, whereas non-ionic linear chelates (gadoversetamide (OptiMARK) and gadodiamide (Omniscan)) are the least stable [1].

GBCAs can also be divided into protein-binding and non-protein-binding categories. The majority of the extracellular

GBCAs show negligible protein binding, meaning that they have a low tendency to modulate enzyme activities and, thus, have a good tolerability profile. One exception is gadobenate dimeglumine (MultiHance), which exhibits weak, reversible binding to serum albumin. This weak protein-binding plays a role in increasing the T1 relaxivity of this agent but is also implicated in reduced tolerability, giving a higher frequency of nausea/vomiting compared with the non-protein-binding agents [2, 3].

Safety considerations

With more than 200 million doses of GBCAs administered worldwide to date, there is an extensive base of experience in terms of safety and tolerability. In general, GBCAs are well tolerated, with adverse reactions being mostly mild to moderate and transient in nature. The most frequent side effects observed are nausea, vomiting, urticaria and headache. Post-marketing assessments suggest a low frequency of adverse drug reactions with most GBCAs (<1%) [2–6]. Although a direct comparison cannot be drawn between these post-marketing studies, some clear differences between the agents can be observed. For example, nausea/vomiting and headache seem to occur less frequently with gado-

Table 1: Gadolinium-based contrast agents

Organ specific/ blood pool	Extracellular			
	Linear ionic		Linear non-ionic	Macrocyclic
	0.25 M	0.5 M	0.5 M	0.5 M
	Gadoteric acid (Primovist [®])	Gadobenate dimeglumine (MultiHance [®])	Gadoversetamide (OptiMARK [®])	Gadoteridol (ProHance [®])
	Gadopentetate	Gadoterate dimeglumine (MultiHance [®])	Gadodiamide (Omniscan [®])	Gadoterate meglumine (Dotarem [®])
Example of a linear molecule (gadopentetate dimeglumine)				Example of a macrocyclic molecule (gadobutrol)

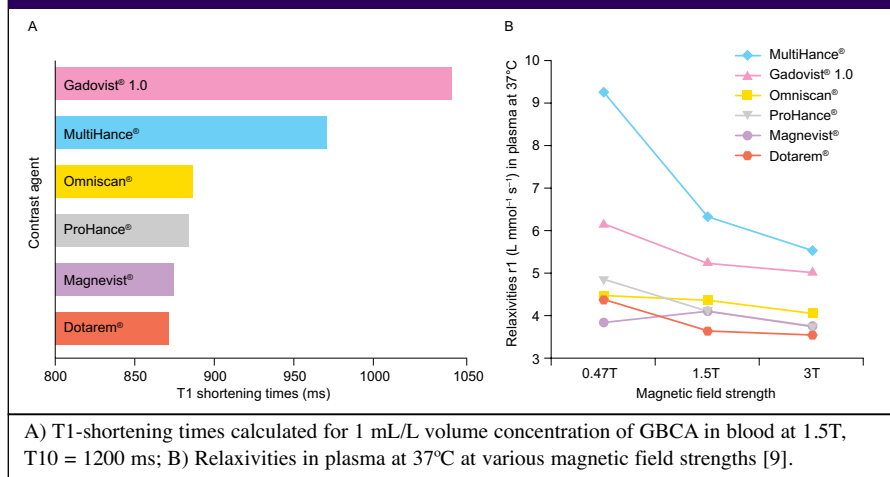
butrol (0.31%) than with gadobenate dimeglumine (0.56%) [2, 3].

With the increasing use of contrast-enhanced MRI, nephrogenic systemic fibrosis (NSF) has emerged as a rare but debilitating potential side effect of GBCAs in patients with severe renal insufficiency. This condition is thought to be due to accumulation of free Gd ions in skin and other tissues. Studies in rats have shown that non-ionic linear agents result in high Gd concentrations in the skin and are more likely to be associated with NSF-like skin lesions [7, 8]. These results are consistent with clinical observations; following a thorough evaluation of all available data on NSF and GBCAs, the EMEA Committee for Medicinal Products for Human Use has classified gadoversetamide, gadodiamide and gadopentetate dimeglumine into a single high-risk group [9], although for gadoversetamide and gadodiamide the risk appears higher compared to gadopentetate dimeglumine based on physicochemical properties and animal studies. These agents should not be used in patients at risk of NSF (patients with severe renal dysfunction, in liver transplant patients and newborn babies) [9]. Agents in the intermediate-risk group include gadofosveset, gadoxetic acid and gadobenate dimeglumine, whereas the low-risk group comprises gadobutrol, gadoteridol and gadoterate meglumine. Agents in these two groups should be used at the minimum recommended dose in patients at risk of NSF [9].

Efficacy considerations

The ability of a contrast agent to increase the intensity of the MRI signal in T1 sequences is determined by how efficiently it is able to shorten T1 relaxation time. This in turn depends on the relaxivity of the agent and its concentration at the region of interest. In a study comparing the relaxivities of all commercially available GBCAs in plasma, the highest relaxivity at all field strengths was produced by gadobenate dimeglumine, followed by gadobutrol (see Figure 1B) [10].

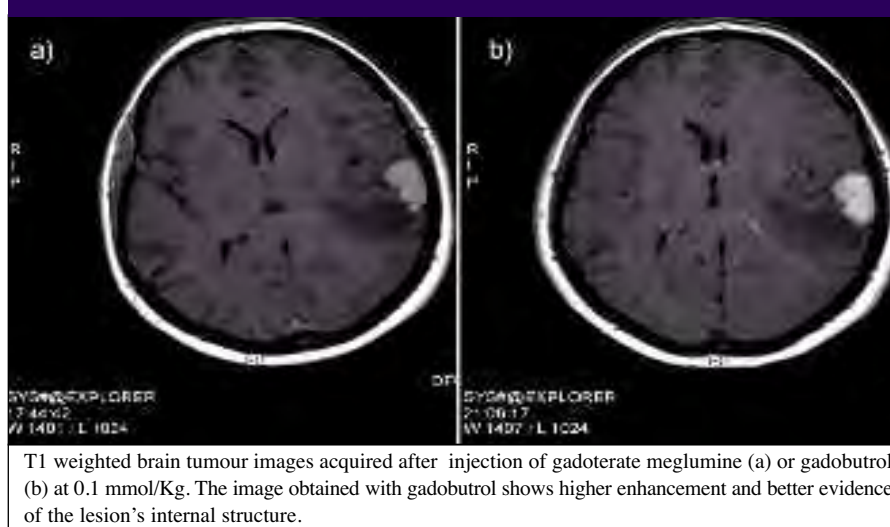
Figure 1: Relaxivity and T1-shortening of gadolinium-based contrast agents



Concentration at the region of interest is affected by many factors, including the location of the region, the injection rate, the total injected dose and the concentration of the Gd solution. With the exception of gadobutrol, all the extracellular agents are formulated at a concentration of 0.5 M. Because of its low osmolarity and low viscosity, gadobutrol can be formulated at 1.0 M, double the standard concentration. This high concentration allows for injection of a smaller volume of agent, providing the highest T1 relaxivity per volume, and therefore the greatest increase in T1-shortening per volume, of any contrast agent (see Figure 1A). It also produces a more

defined bolus that may be less likely to diffuse before arriving at the target area, thus retaining a high local concentration resulting in improved image contrast (see Figure 2). The advantage of the higher concentration of Gd in gadobutrol for brain tumour imaging had been demonstrated in a study in a rat model comparing gadobutrol at 0.1 mmol/kg of body weight with equivalent doses of gadoterate meglumine or gadopentetate dimeglumine. Gadobutrol resulted in superior contrast enhancement at 3T, providing a higher signal-to-noise ratio and significantly improving the contrast-to-noise ratio ($p < 0.0001$) [11].

Figure 2: Gadobutrol is good for brain imaging



Clinical impact

The impact of the different properties discussed above can be illustrated by reference to studies evaluating the diagnostic utility of different GBCAs in a clinical setting. For example, a recent study assessed the effectiveness of 1.0 M gadobutrol compared with 0.5 M gadopentetate dimeglumine, each dosed at 0.1 mmol/kg bodyweight, for the detection of brain metastases in 27 candidates for gamma knife radiosurgery [12]. In 12 patients, the diagnostic performance of MRI was better with gadobutrol than with gadopentetate dimeglumine; with improved lesion conspicuity in 10 patients and detection of additional lesions in two. In the remaining patients, the agents demonstrated equivalent effectiveness. Thus, a major benefit resulting from the high concentration and high relaxivity of gadobutrol may be an improvement in the visualisation of small metastatic brain lesions, which frequently go undetected. Improved imaging of brain lesions with gadobutrol was also demonstrated in a study using perfusion-weighted imaging at 3T, to detect intracranial space-occupying lesions in 11 patients [13]. Compared with gadopentetate dimeglumine, gadobutrol resulted in significantly greater delineation between grey and white matter and significantly better demarcation of highly vascularised tumour tissue. Cranial gadolinium-enhanced MRI is also important in the diagnosis and monitoring of multiple sclerosis (MS). In a study in 30 patients with MS, significantly more brain lesions were detected using 0.1 mL/kg (0.2 mmol/kg) of gadobutrol compared with 0.1 mL/kg (0.1 mmol/kg) of gadopentetate dimeglumine [14]. Importantly, the detection of lesions only visible with gadobutrol resulted in a change in clinical management in six of the 30 patients in this study.

Conclusion

In conclusion, currently available extracellular GBCAs can be divided into three groups based on physicochemical

properties: non-ionic linear agents (gadodiamide and gadoversetamide), ionic linear agents (gadopentetate dimeglumine, gadobenate dimeglumine and gadoxetate) and macrocyclic agents (gadobutrol, gadoteridol and gadoterate dimeglumine). The safety and tolerability of these agents is generally good with small differences in the incidence of some side effects, possibly influenced by differences in protein binding. The less stable non-ionic linear agents, which are more likely to release free Gd, have been associated with higher NSF risk in patients with renal failure. The efficacy of the agents to enhance image contrast is determined by both relaxivity and concentration. The two agents with the highest relaxivity are gadobenate dimeglumine and gadobutrol, but only gadobutrol combines this high relaxivity with a high concentration of Gd in the formulated product together with highest stability as a macrocyclic compound.

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Pharmaceutical and safety aspects of gadolinium-based contrast agents



Martin A Sieber, PhD

A contrast agent can substantially improve the diagnostic quality of magnetic resonance imaging. Gadolinium-based contrast agents are a very similar class of pharmaceuticals. But they differ in two important aspects, the complex stability and the ability to enhance the MRI signal intensity.

Magnetic resonance imaging (MRI) provides excellent soft tissue images. For several diagnoses, however, a contrast agent (CA) can substantially improve the diagnostic quality. For example, the use of Gadovist as a contrast agent increased the metastatic brain lesions detected in 53% of patients compared to unenhanced MRI procedures, leading to a change in therapy for 20% of patients [1]. Therefore, contrast agents are used in 30–40% of MRI examinations. Unlike iodinated CAs used for X-ray imaging, MRI contrast agents can provide negative and

positive contrast. The principal of MRI contrast agents works by changing the magnetic moment. Therefore, only paramagnetic elements or molecules can be used as contrast agents. Gadolinium-, manganese- and iron-containing agents are used for contrast-enhanced clinical MRI imaging. Iron causes a negative contrast and is therefore called a negative contrast agent. Gadolinium and manganese usually causes a signal increase and are therefore called positive CAs.

Structural and functional aspects

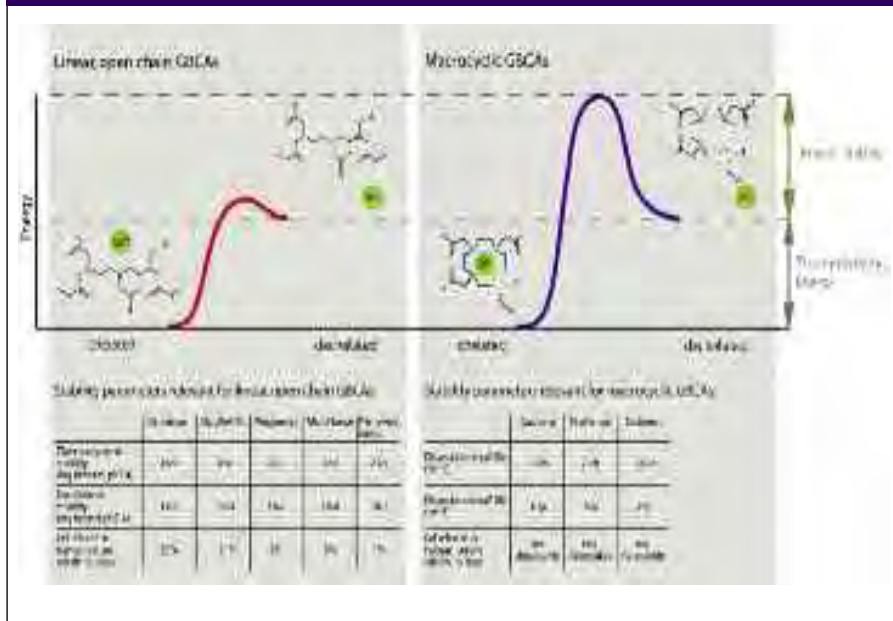
Since IV application of manganese- and

iron-based CA do not play a clinically relevant role, this article will focus on the pharmaceutical and safety aspects of gadolinium-based contrast agents (GBCAs). Several agents have been approved since the first GBCA, Magnevist, was approved in 1988. All GBCAs contain a central Gd^{3+} ion complexed by a ligand. They are prepared by chelating Gd_2O_3 with their respective ligands. Based on the molecular structure of those ligands, GBCAs can be divided into two classes: the linear open chain class and the macrocyclic class. In all complexes, the central Gd^{3+} ion is coordinated by the ligand at eight of the

Table 1: Physical aspects of GBCAs marketed in Europe

Structural class	Non-ionic linear		Ionic linear			Macrocyclic		
	Trade name	Omniscan	OptiMARK	Magnevist	MultiHance	Primovist/Eovist	Gadovist	ProHance
Generic names	Gadodiamide	Gado- versetamide	Gadopentetate dimeglumine	Gadobenate dimeglumine	Gadoxetate	Gadobutrol	Gadoteridol	Gadoterate dimeglumine
	GD-DTPA- BMA	Gd-DTPA- BMEA	Gd-DTPA	Gd-BOTA	Gd-EOB- DTPA	Gd-BT- DO3A	Gd-HP- DO3A	Gd-DOTA
Concentration [mol/L]	0.5	0.5	0.5	0.5	0.25	1.0	0.5	0.5
Excess ligand	5.0%	10.0%	0.1%	0%	0.5%	0.1%	0.1%	0%
R_1 Relaxivity at 3T in plasma at 37°C [Lmmol ⁻¹ s ⁻¹]	4.0	4.5	3.7	5.5	6.2	5.0	3.7	3.5
Viscosity [mPa*s]	1.4	2.0	2.9	5.3	1.19	3.7	1.3	2.0
Osmolality [mOsm/kg H ₂ O]	790	1,100	1,960	1,970	668	1,910	630	1,350
Excretion	renal	renal	renal	renal, 4-5% hepatobiliary	50% renal; 50% hepatobiliary	renal	renal	renal
Manufacturer	GE	Covidien	Bayer Schering Pharma	Bracco	Bayer Schering Pharma	Bayer Schering Pharma	Bracco	Guerbet

Figure 1: Stability aspects of GBCAs



The upper panel depicts the energy level for linear open chain (left) and macrocyclic (right) GBCAs. Please notice the additional activation energy needed for chelating and dechelating of macrocyclic agents, due to steric hindrance. Therefore the complex stability of macrocyclic GBCAs is best described by the kinetic dissociation half-life. The complex stability of linear open chain GBCAs is best described by the thermodynamic stability or conditional stability constant (lower panel). These theoretical considerations are also reflected for example by the difference in Gd³⁺ release under physiological conditions [7].

CAs, since GBCAs are used at significantly lower doses and volumes (5–20 mL) compared to iodinated CAs (100–300 mL). For example, the osmotic load per kg body weight is significantly lower after the administration of GBCAs compared to low osmolar iodine CAs.

Pharmacokinetics

All GBCAs have a low molecular mass of about 500 Da, are extremely hydrophilic complexes and are excreted unmetabolised in the urine. They have similar pharmacokinetic properties with similar plasma half-lives, and, due to their small size, extracellular GBCAs are excreted almost exclusively by passive glomerular filtration through the kidneys with neither secretion nor reabsorption. However, protein binding GBCAs are also excreted to varying degrees by the hepatobiliary route (MultiHance 3–4% and Primovist/Eovist 50%). The specific uptake of Primovist/Eovist by hepatic anion transporters greatly facilitates the detection of liver lesions [4].

nine coordination sites of the Gd³⁺ ion. One coordination site of the Gd³⁺ ion interacts with a proton of a water molecule, which is essential for its signal enhancement mechanism. GBCAs are mainly used for influencing the so-called T1 shortening. This effect depends on the relaxivity and the concentration. R₁ relaxivity best describes the efficacy to increase the signal enhancement for the most important T1 imaging sequences by the GBCAs. The GBCAs exhibit similar paramagnetic effects, with Gadovist (5.0 Lmmol⁻¹s⁻¹ at 3 T in serum) showing the highest R₁ relaxivity and Dotarem the lowest R₁ relaxivity (3.5 Lmmol⁻¹s⁻¹ at 3T in serum) for the non-protein binding GBCAs (see Table 1). Gadovist has, due to the higher concentration, also the highest T1 shortening per volume [2]. The relaxivity of the GBCAs is also dependent on the magnetic field strength, temperature, protein binding and surrounding [2].

The majority of GBCAs are formulated at a concentration of 0.5 M. One exception is Gadovist, a macrocyclic agent formulated at a concentration of 1.0 M. Therefore, Gadovist possesses double the relaxivity per volume compared to all the other agents. This higher volume relaxivity is helpful for fast magnetic resonance angiography or dynamic and functional studies, such as brain or tumour perfusion [3]. GBCAs are typically approved for IV administration at a concentration of 0.1–0.3 mmol/kg body weight, depending on the product and the label in the respective country. For example, Gadovist is approved in Europe for CNS examinations in a dose up to 0.3 mmol/kg body weight. All GBCAs are formulated as hypertonic solutions with an osmolality between 630–1970 mOsm/kg and viscosities between 1.3–5.3 mPa*s (see Table 1). In general, the physicochemical properties of GBCAs are of less importance for their safety compared to the iodinated

In patients with normal renal function, the plasma half-life of GBCAs is about 70–100 min, with about 98% excreted within 24 hours post injection. In a patient with chronic kidney disease, however, the circulation time of these agents is prolonged, with plasma half-lives of up to 30 hours in severe renal impairment [5]. Therefore, exposure of a patient to GBCAs depends not only on the administered dose but also on the renal status of the patient.

Complex stability

When assessing the complex stability of different GBCAs, they are classically compared on the basis of the thermodynamic stability constant (log K_{therm}), valid at pH 14, or the conditional stability constant (log K_{cond}), calculated for pH 7.4 on the basis of log K_{therm}. This consideration, however, neglects kinetic stability differences. This parameter is especially relevant when considering the complex stability of macrocyclic

GBCAs (Gadovist, ProHance and Dotarem). Due to their rigid ring structure and steric hindrance, these GBCAs are generally considered to be kinetically inert (see Figure 1). Therefore, the thermodynamic stability constant and the conditional stability constant are of lesser relevance for the macrocyclic GBCAs [6].

Although all of these agents have a very high level of complex stability, there are differences in complex stability within the linear, open chain group (see Figure 1). For example, the two non-ionic compounds (Omniscan and OptiMARK) are considerably less stable than the ionic linear agents (Magnevist, MultiHance and Primovist/Eovist) [6]. The different complex stability of linear, open chain group is most adequately described by the thermodynamic stability or conditional stability constant. In chemical terms, those differences in complex stability are easy to understand given that the lower negative charge (3-) of the non-ionic linear agents results in a weaker electrostatic interaction with the positive Gd^{3+} ion (3+) than the ligands of the ionic linear agents (5-). The non-ionic, linear compounds are formulated with a considerable amount of Gd free, calcium-bound ligand in order to reduce the occurrence of free Gd^{3+} ions *in vivo*.

These theoretical considerations led to the grouping of GBCAs into three classes with regard to the complex stability (macrocyclic, ionic linear and non-ionic linear GBCAs), which is supported by experiments *in vitro* and *in vivo*. For example, in human serum, 10-fold higher Gd^{3+} is released from the non-ionic linear GBCAs than from the ionic linear GBCAs *in vitro*, whereas no Gd^{3+} release could be observed from any of the macrocyclic GBCAs [7]. Various studies in rodents have shown that the highest Gd values were measured after administration of the least stable agents, while the lowest Gd levels are observed after administration of the

most stable agents [6, 8]. Preclinical data is also in agreement with studies in humans, where significantly lower Gd concentrations were observed in hip bone biopsies after administration with a macrocyclic GBCA compared to administration with a non-ionic linear GBCA [9]. The data strongly suggests that exposure to Gd not only depends on the administered dose but also on the complex stability of the chosen agent.

Tolerance to GBCAs

Generally, GBCAs are very well tolerated and have established an excellent safety profile. For example, in six prospectively planned surveillance studies conducted with Gadovist, including 14,422 patients, the overall incidence of one adverse drug reaction (ADR) was about 0.55% [10]. There have been no major differences in the incidence rate of ADRs between GBCAs reported. Furthermore, the lower volume and lower dose administered are most likely the reason that GBCAs have a lower incidence of renal complications compared to iodinated CAs.

Recently, IV administration of GBCAs has been linked to nephrogenic systemic fibrosis (NSF), which has been diagnosed in patients with severe renal impairment (glomerular filtration rate <30 mL/min/1.73 m²) and in patients with acute renal insufficiency of any severity due to hepato-renal syndrome or in the perioperative liver transplantation period*. Most of the reported cases have been in patients receiving haemodialysis or peritoneal dialysis [11]. NSF is a severe systemic disease typically characterised by fibrosis of the skin and connective tissues with an increase in CD34 positive fibroblast-like cells and a considerable increase in collagen bundles on the cellular level [11].

Most of the cases reported in the literature to date have been associated with the administration of one specific agent, the non-ionic linear Omniscan,

but there have been reports involving other agents [12, 13]. Based on the currently prevailing theory that Gd dissociated from the underlying chelate may play a role in the development of NSF, as well as on the results of animal and *in vitro* studies, it is believed that, complex stability is an important consideration in attempting to understand the pathogenesis of NSF [14].

Conclusion

While GBCAs, as a group, share several common characteristics, they differ in complex stability and in their ability to enhance the MRI signal intensity. Macrocyclic GBCAs (Gadovist, Prohance and Dotarem) have the lowest likelihood to release Gd under clinical conditions, while the non-ionic linear GBCAs (Omniscan and OptiMARK) have highest likelihood. Minor differences exist in regards to signal enhancement, with Gadovist demonstrating the highest level and Dotarem the lowest level of signal enhancement for the non-protein binding GBCAs.

*Bayer has recently received a few reports of possible NSF in patients who were reported to have mild to moderate renal impairment. As these reports contained limited information, Bayer is attempting to obtain the information necessary to allow the reports to be properly evaluated.

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Imaging of brain tumours and metastases



Professor Marco Essig, MD; Lars Gerigk

Magnetic resonance imaging is the most sensitive method for diagnosing brain tumours. Modern protocols allow further insights into their pathophysiology.

The goals and requirements for brain tumour imaging are complex and involve making a differential diagnosis subsequently resulting in a diagnosis, while accurate lesion grading is needed in the case of tumour description. Imaging is also involved in the decision-making process for therapy and precise planning of surgical or radiotherapeutic interventions. Neuroimaging techniques are also essential for monitoring of (residual) disease and possible therapy related side effects.

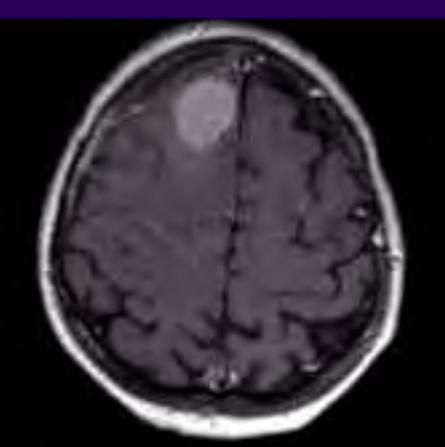
Due to the high tissue contrast and the non-invasive nature of the method, magnetic resonance imaging (MRI) is accepted as the most sensitive method for diagnosing brain tumours [1]. The exclusion of a possible brain tumour is one of the most common indications for neuroimaging using MRI.

The classification of brain tumours is still controversial, and includes classification by location or histology. The most common classification is that of the World Health Organization (WHO) summarised in the so-called 'Blue Book' [2]. Brain tumours are categorised into primary versus secondary tumours, based on the tissue of origin, and intra-axial versus extra-axial tumours based on the origin of growth [3]. The most common primary intra-axial tumours are neuroepithelial tumours including astrocytomas, oligodendrogliomas, mixed gliomas and other more rare neuronal-glioma tumours with the glioblastoma multiforme as the most common brain tumour [4]. Meningiomas are the most common primary extraaxial tumours [5] and account for about 20% of all brain tumours. In adults, however, secondary, metastatic brain lesions far

outnumber primary tumours with a high incidence in systemic cancers such as lung and breast [6].

The MRI protocol to assess brain tumours includes unenhanced T1-, T2- and FLAIR-weighted sequences followed by contrast studies in T1 weighting. The unenhanced T1-weighted sequences are used to rule out intraleSIONAL bleeding or visualisation of e.g. melanin, which is frequently found in metastases of melanoma (see Figure 1).

Figure 1: Haemorrhage in a melanoma metastases



T1 Spin-Echo imaging presents high signal of the lesion, indicating the presence of methaemoglobin.

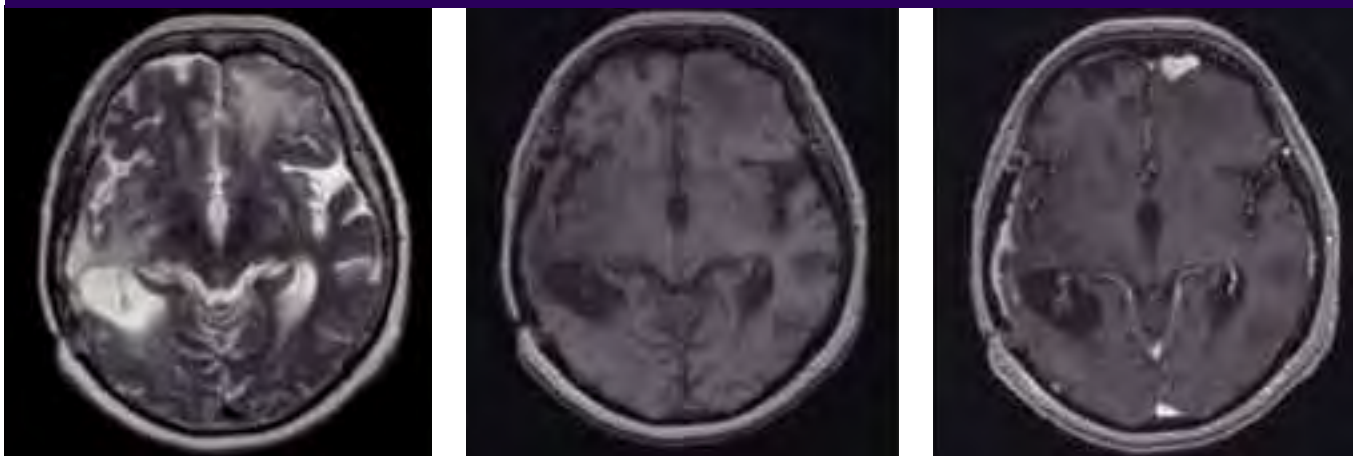
T2-weighted Fast SE sequences and FLAIR is used to display the margins of a tumour and its surrounding oedema [7, 8]. In uncooperative patients a motion insensitive acquisition should be used [9]. Contrast enhancement studies are mandatory in the assessment of patients with cerebral tumours. The standard dose employed for MRI of the CNS is 0.1 mmol/kg body weight although numerous studies have shown that lesion

detection may be improved with the use of higher doses and dedicated sequences [10, 11]. Contrast enhanced MRI helps in distinguishing tumours from other pathologic processes, and is better to depict signs of tumour response to therapy, such as change in size, morphology and degree of contrast material enhancement (see Figure 2). The sequences after contrast media should at least include two planes of T1-weighted sequences, and, if possible, a volumetric sequence, e.g. 3D T1-weighted imaging to allow for reconstruction in different planes and volumetric assessment of the lesions.

Due to the presence of the Blood-Brain-Barrier (BBB) the current available MR contrast media do not leak into the brain tissue [12]. Substances with a molecular weight higher than 180 daltons (Da), which include all available imaging contrast media, generally cannot cross the BBB. In intraaxial primary tumours, mainly gliomas, the BBB can be compromised by neovascularisation and direct damage due to tumour ingrowth. In secondary, metastatic intraaxial tumours and extraaxial tumours the vessels are different from normal cerebral vasculature and have no or strongly disturbed BBB [13,14]. Those entities normally have a strong enhancement pattern presenting the whole tumour as enhancing mass.

Contrasting material enhanced MRI is the accepted standard of reference for assessment of the integrity of the blood-brain barrier. Compared with contrast-enhanced computed tomography, MRI with gadolinium-based contrast agents is far more sensitive and depicts even subtle disruptions of the BBB that are caused by a variety of noxious agents, neoplastic or inflammatory processes, or ischaemic stress [15].

Figure 2 a-c: MRI of a patient with frontal enhancing tumor (Meningeoma)



T2 shows oedema in the frontal and temporal lobe with no circumscribed tumorous lesion. After contrast media application (0.1 mmol of gadobutrol, Gadovist, Bayer Healthcare) the lesion in the frontal lobe is well circumscribed and could be demarcated from the oedema. Note also the enhancement of the meninges in the temporo-parietal region.

Figure 2d: Using a standard contrast media (Dotarem, Guerbet)



Using a standard contrast media (Dotarem, Guerbet) the enhancement is less pronounced and the meningeal enhancement not as obvious. This intraindividual comparative study shows the importance of the use of high quality contrast media for the patient safety and security of diagnosis.

The use of gadolinium contrast media is therefore standard in the assessment of cerebral tumours (see Figure 2).

In the past few years a number of advanced, non enhanced and contrast enhanced MRI techniques have been developed that provide new insights into the pathophysiology of brain tumours, mainly gliomas. These techniques include MR-spectroscopy (MRS), perfusion MRI [16], dynamic contrast enhanced (DCE) MRI [16] and diffusion tensor MR. The contrast perfusion MRI

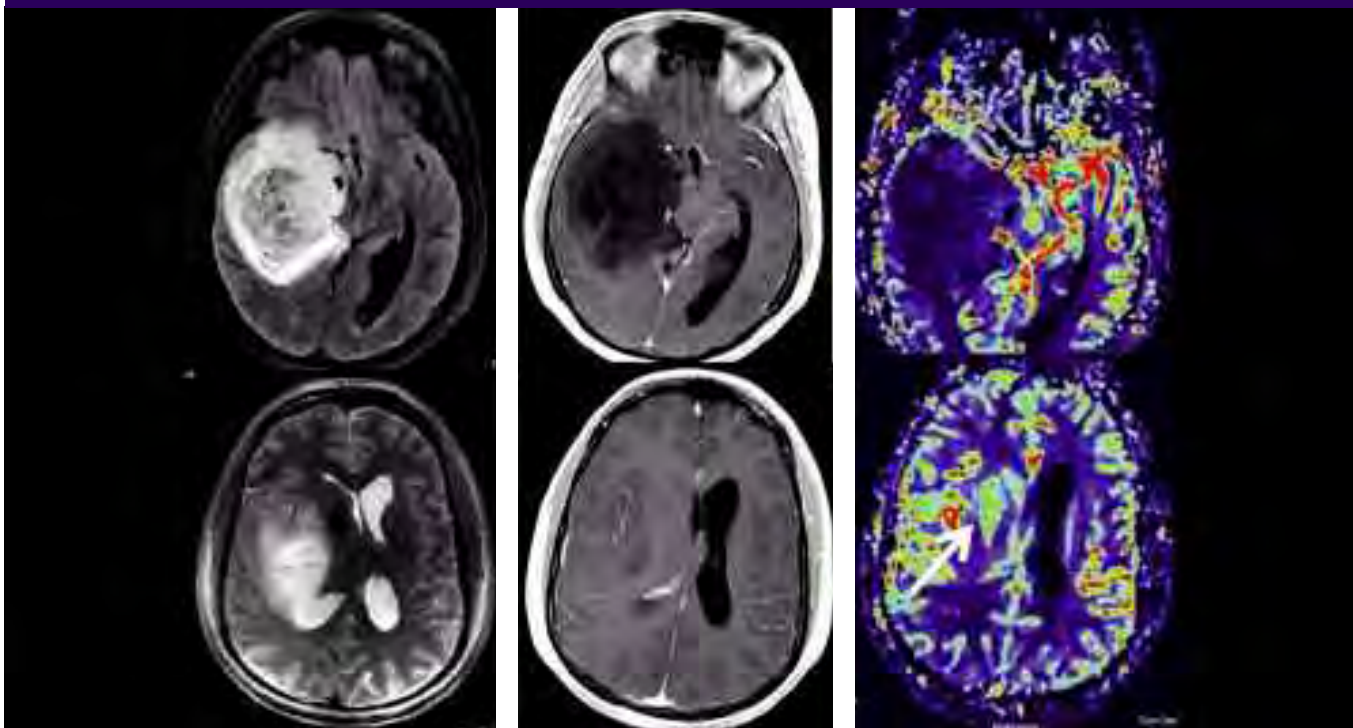
technique is now recognised as an important new means for assessing tumour grading and follow up of various treatment strategies (see Figure 3). Another of these techniques, dynamic contrast enhanced MRI, is also gaining acceptance for the same purposes. Perfusion-weighted imaging (PWI) in brain tumours has benefits for three major fields: differential diagnosis, biopsy planning, and treatment monitoring. The basic principle of PWI using dynamic susceptibility-weighted contrast-enhanced MRI is as follows: The first-pass of a contrast bolus, e.g. 0.1 mmol of Gadovist, in brain tissue is monitored by a series of T2*-weighted MR images. The susceptibility effect of the paramagnetic contrast agent leads to a signal loss that can be converted, using the principles of the indicator dilution theory, into an increase of the contrast agent concentration. From these data, parameter maps of cerebral blood volume (CBV) and cerebral blood flow (CBF) can be derived. Regional CBF and CBV values can be obtained by region-of-interest analysis. Our experience of brain tumour differentiation is that PWI has superior diagnostic performance in predicting glioma grade and in differentiating glioblastoma from other tumour entities (metastases, meningiomas, and CNS-lymphomas) when compared to spectroscopic imaging and dynamic contrast-enhanced MRI [16]. Correct grading of gliomas has

significant clinical impact, because adjuvant therapy after surgery is usually administered to high-grade but not low-grade gliomas.

Perfusion-weighted imaging can easily be incorporated as part of the routine clinical evaluation of intracranial mass lesions due to the relatively short imaging and data processing times and the use of a standard dose of contrast agent. Thus, PWI together with conventional MRI should be regarded as the test of choice to diagnose and monitor brain tumours before, during, and after therapy.

Conclusion

The use of contrast media is essential in MRI for the diagnostic work-up of patients with cerebral tumours. The hospital pharmacist should have a basic understanding about the availability of different contrast media with different properties and potential. The contrast in the final images is influenced by the dosage of the contrast agent, the used MR field strength and the application strategy. In modern neuroimaging protocols, however, functional contrast enhanced techniques such as PWI, MRS and DCE allow further insights into the pathophysiology of cerebral tumours and provide information that complements the superb morphological assessment with standard imaging techniques.

Figure 3: Large glioma in a 34-year-old patient

T2 (A-B) presents a large heterogenous tumour in the right temporo-parietal and frontal region.

T1 GRE after contrast media (0.1 mmol/kg of Gadobutrol) (C-D) did not show any contrast enhancement within the tumour.

Perfusion MRI – CBF maps (E-F) present a low perfused caudal part of the tumour indicating a low grade lesion, but with an increased perfusion in the upper frontal area of the tumour (arrow) indicating a high grade (WHO III) lesion.

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Gadolinium-enhanced magnetic resonance imaging in multiple sclerosis

Àlex Rovira Cañellas, MD

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.

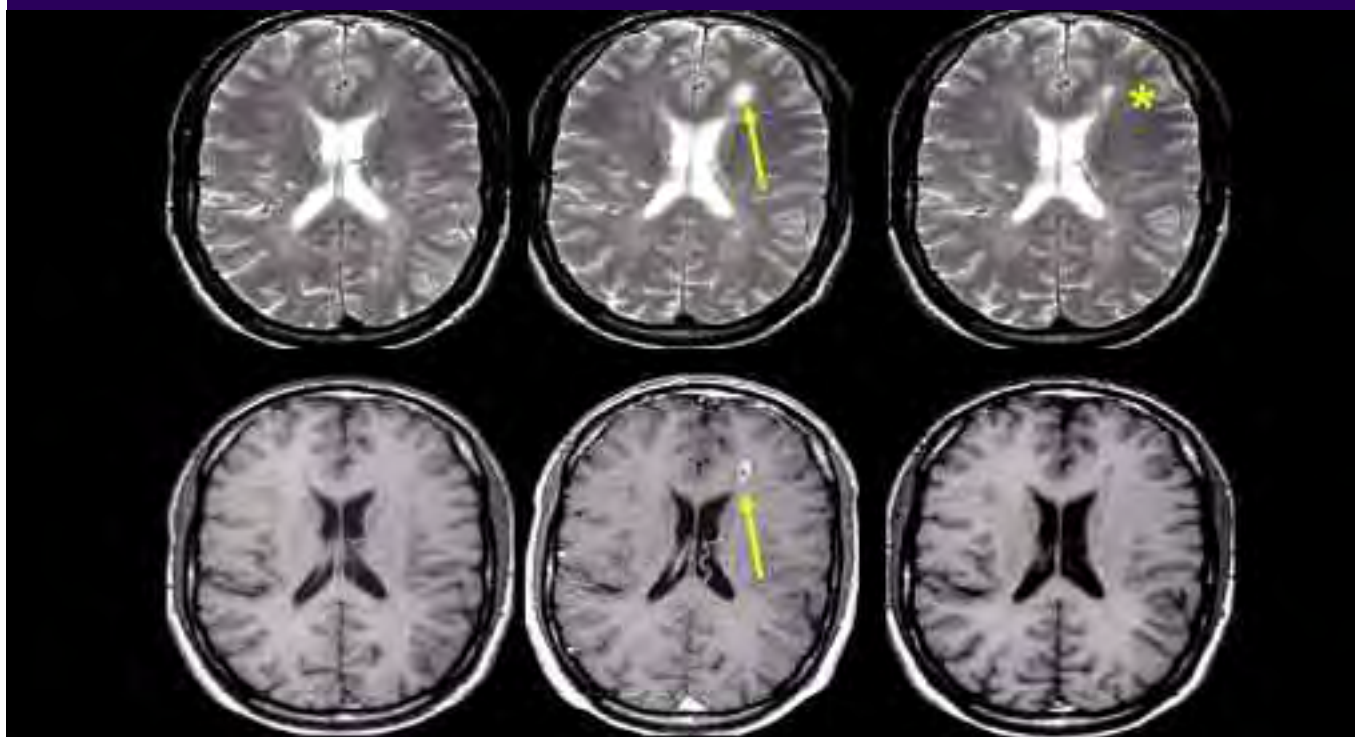
Gadolinium-based contrast agents in MS

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 subclinical 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 relaxivity ($9.7 \text{ mM}^{-1}\text{s}^{-1}$ instead of $4.3\text{--}5.6 \text{ mM}^{-1}\text{s}^{-1}$), 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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