Magnetic resonance imaging contrast agents: theory and application to the central nervous system

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The theoretical aspects of magnetic resonance (MR) imaging contrast agents are reviewed, and their current applications to the central nervous system (CNS) and their future applications are discussed. Profound differences exist between contrast agents used for MR imaging and computerized tomography (CT). In MR imaging, the contrast agents are not imaged directly but rather act on adjacent protons to shorten $T_1$ and $T_2$ relaxation times. This in turn results in signal intensity changes. The lanthanide metal, gadolinium, in the form of gadopentetate dimeglumine, has been found to be both safe and efficacious as the only currently approved contrast agent for MR imaging.

Magnetic resonance imaging revolutionized the detection and treatment of disease affecting the brain and spine. Initially, it was thought that signal characteristics on MR imaging would allow differentiation of specific pathology. It was soon found that MR studies were able to detect more abnormalities but were less able to characterize them. The recent development of contrast agents for MR imaging has allowed this modality to surpass CT for the evaluation of most CNS lesions.

At present, contrast-enhanced MR imaging is generally accepted as the study of choice for evaluating acoustic neurinomas, pituitary lesions, meningeal disease, primary and secondary brain tumors, active multiple sclerosis, intradural spinal neoplasms, intramedullary spinal disease, and postoperative states in both the spine and brain. Even when contrast-enhanced CT can detect the same abnormalities, evaluation of the lesions in multiple planes on MR imaging can sometimes yield invaluable information, especially prior to surgery. Future developments of contrast material for MR imaging include non-gadolinium compounds, intrathecal contrast media, cerebral blood flow and volume evaluation, and, possibly, antibody-labeled contrast agents.

KEY WORDS • magnetic resonance imaging • contrast medium • gadolinium • central nervous system lesion • brain neoplasm

The recent Food and Drug Administration (FDA) approval of gadopentetate dimeglumine (Magnevist),* also formerly known as gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA), paves the way for contrast-enhanced magnetic resonance (MR) imaging to become a significant form of neuroimaging. Numerous studies have already indicated that postcontrast MR imaging is superior to all other modalities, including noncontrast-enhanced MR for certain conditions. This review examines the theoretical aspects of MR contrast enhancement, the specific properties of gadolinium (Gd) as a contrast agent, the present indications for Gd-DTPA in clinical practice, and the future prospects for contrast-enhanced MR imaging.

Theoretical Aspects of MR Contrast Agents

Magnetic resonance spin-echo signal intensity depends on the equation:

$$I = (H)f(v)[e^{-TR/T_2}][1 - e^{-TR/T_1}],$$

where $I$ is signal intensity, $H$ is hydrogen or proton density, and $f(v)$ is a function of both the speed and fraction of protons moving through the imaged region. Alterations of the following factors will increase signal intensity: shortened $T_1$, prolonged $T_2$, increased proton density, or a change in flow function. Agents which alter these parameters will alter contrast. The $T_1$ and $T_2$ relaxation times are the easiest parameters to manipulate. To understand how agents alter $T_1$ and $T_2$, one must be familiar with the principles of magnetism.

Magnetism

Magnetism results when a charged particle is in motion; for example, proton/electron spinning, electron

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* Gadopentetate dimeglumine supplied by Berlex Imaging, Wayne, New Jersey.
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Fig. 1. Relationship of induced magnetism with an external magnetic field. Diamagnetic agents (D) have a weak negative magnetism while paramagnetic agents (P) have a positive magnetic effect. Superparamagnetic materials (SP) achieve a much greater positive magnetization than do paramagnetic materials. The arrows indicate that all three substances lose their magnetization completely when the external applied field is turned off. Ferromagnetic substances (F) retain positive magnetism even when the external field returns to zero (point a).

Magnetic susceptibility is the ability of a substance to become magnetized when placed in an external field. This can be quantified as a ratio of induced magnetization in the substance to that of the external field (Fig. 1). Magnetic susceptibility induces proton relaxation, resulting in contrast enhancement.

Magnetic behavior can be classified into four categories: diamagnetic, paramagnetic, ferromagnetic, and superparamagnetic (Fig. 1). Almost all tissues are diamagnetic and have very weak negative susceptibility because they have paired electrons and therefore induce very little change in the local field. Compounds with unpaired electrons have a positive magnetic dipole moment and are either paramagnetic, ferromagnetic, or superparamagnetic. In an applied magnetic field a positive magnetic moment is induced in these compounds resulting in an attractive force. When the external field is removed, paramagnetic molecules resume random orientation, resulting in a net magnetization of zero. Paramagnetic agents include chromium, manganese (Mn), copper, Gd, organic free radicals, and molecular oxygen. These are the most clinically interesting molecules since they are positive contrast agents and are water-soluble and therefore can be injected intravenously.

Ferromagnetic substances retain a net magnetism after the external field is returned to zero. This is due to grouping of paramagnetic atoms or molecules into a crystal. With closely spaced molecules the dipole moments align parallel to each other. Ferromagnetic substances include iron (Fe), nickel, and cobalt.

Superparamagnetic substances are composed of “micro” ferromagnetic particles. They have a much greater magnetic susceptibility than paramagnetic substances because of their crystalline structure. When an external magnetic field is removed, however, they become ran-
domly oriented similar to paramagnetic molecules and thus retain no magnetization. The particulate nature of superparamagnetic substances makes them useful for imaging the reticuloendothelial system. Proton Relaxation Enhancement and Signal Intensity

As previously mentioned, a change in $T_1$ and $T_2$ relaxation times will result in an alteration of signal intensity. Substances with strong magnetic susceptibility, such as paramagnetic agents, alter the local magnetic field within an external field, resulting in proton relaxation enhancement. The $T_1$ relaxation time is shortened when the fluctuating magnetic fields match the Larmor frequency and facilitate the transition between high- and low-energy spin states. The fluctuating magnetic fields are created by the paramagnetic molecular tumbling and electron motion. The $T_2$ relaxation time is shortened because inhomogeneities in the local magnetic field cause rapid dephasing of the transverse magnetization of local protons. A non-uniform field causes protons to precess at different frequencies with loss of transverse-phase coherence.

Proton relaxation enhancement shortens both $T_1$ (increase in signal) and $T_2$ (decrease in signal) relaxation times. These are conflicting changes in signal intensity. However, $T_1$ effects predominate at lower, pharmacological concentrations of paramagnetic substances while $T_2$ shortening predominates at higher levels (Fig. 2). $T_2$ shortening with the subsequent decrease in signal is the dominant effect of superparamagnetic and ferromagnetic substances with their much higher magnetic susceptibility.

In clinical neuroimaging, the aim is to achieve signal enhancement by utilizing small doses of paramagnetic agents with predominant $T_1$ shortening effects. It is important to realize that the increase in signal on a $T_1$-weighted image is not due to the paramagnetic agent itself but to the agent's effect on neighboring protons. Unlike the situation with iodinated contrast in computerized tomography (CT), increasing the dose of contrast medium will eventually lead to negative rather than positive enhancement when $T_2$ shortening effects predominate (Fig. 2).

Clinical Contrast Agents

Soluble paramagnetic species include transitional metal complexes, the lanthanide (rare earth) complexes, organic free radicals, and molecular oxygen. The transitional metals are strongly paramagnetic because the 3d orbit contains unpaired electrons. Examples of transition metals include Mn and copper. The lanthanide metals are paramagnetic because of unpaired electrons in the 4f orbit. The most clinically relevant ion in this series is Gd with seven unpaired electrons. It is one of the strongest paramagnetic ions. The greater the number of unpaired electrons, the stronger the magnetic moment, and therefore the greater the relaxation potential tends to be. Since these metal cations are very toxic, the metal is united with a ligand or chelated into a metal complex which is nontoxic. Diethylenetriaminepenta-acetic acid (DTPA), ethylenediaminetetra-acetic acid (EDTA), and tetraazacyclododecane tetra-acetic acid (DOTA) combined with Gd, Mn, Fe, and chromium have been investigated as parenteral agents. Gadopentetate dimeglumine, the chelate of DTPA with Gd, is the only potentially useful imaging substance at present approved by the FDA.

Comparison of Gd complexes has shown that Gd-DTPA has greater $T_1$ relaxivity (17%) and contrast enhancement (45%) than Gd-DOTA. Although Gd-DOTA has much greater in vitro stability (10²) than Gd-DTPA (10²) or Gd-EDTA (10¹), both Gd-DTPA and Gd-DOTA have a much greater safety index than iodinated contrast-enhanced CT. A Belgian study has recently shown Gd-DOTA to be safe and efficacious in clinical studies of central nervous system (CNS) lesions in 38 patients. Gadolinium-EDTA is almost as toxic as free Gd, which may be related to a greater amount in the form of free Gd ion due to Gd-EDTA's lower formation constant.

Nitroxide stable free radicals are organic molecules with an unpaired electron which is shielded from bonding by bulky alkyl groups. Like Gd compounds, nitroxides have the advantage of low acute animal toxicity and the potential for conjugation with target-specific agents. They have been used successfully in some animal studies as contrast agents.

Gadopentetate Dimeglumine: Physical Properties

Gadolinium is chelated to DTPA because the free ion is very toxic. There is no detectable in vivo disso-

![Graph showing Gadolinium-DTPA concentration versus signal intensity for T₁-weighted (T₁W) and T₂-weighted (T₂W) pulse sequences on a 1.0-tesla system. The relationship is nonlinear, with a decrease in signal at high concentrations. (Adapted from Runge VM, Schaible TF, Goldstein HA, et al: Gd-DTPA clinical efficacy. Radiographics 8:147-159, 1988, with permission.)
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ciation of the ion from DTPA, due to the high forma-
tion constant \(10^{23}\) of the compound.\(^79\) As a dimeglu-
mine salt, Gd-DTPA has an osmolality of 1940 mOsm/ kg, six times that of plasma.

Gadolinium is distributed in the intravascular and extracellular fluid compartments.\(^79\) It does not cross the blood-brain barrier or cell membranes because of its charge, high molecular weight, and hydrophilic nature. Gadolinium-DTPA is excreted by glomerular filtration, with 83% being eliminated within 6 hours. Minimal excretion occurs via the gastrointestinal tract.

Gadolinium-DTPA has shown very low toxicity in both animal and clinical trials.\(^44,56,59,64\) The 50% lethal dose (\(LD_{50}\)), measuring the acute intravenous toxicity in animals, is 5 to 15 mmol/kg. This is 50 to 150 times the 0.1 mmol/kg dose in clinical patients, as opposed to a safety index (animal \(LD_{50}/clinical\) dose) of 10 for iodinated contrast medium. It is also a very poor activ-
or of the complement system, which is thought to play a role in the induction of anaphylactoid reactions.

There have been no significant adverse effects with Gd.\(^44,56,59,64\) The incidence of adverse reactions related to Gd-DTPA is as follows: headache 5%, nausea 3.4%, vomiting 2%, and irritation at site of injection 2%; all other reactions have occurred in less than 1% of cases (which includes two cases of hypotension in a study of 442 subjects). One study\(^59\) noted a similar percentage of adverse reactions (21%) occurring in both the 60 patients receiving Gd-DTPA and the 28 receiving placebo (\(p > 0.99\)). A transient rise in the serum Fe and bilirubin levels in some patients is thought to be due to a minimal increase in hemolysis by the spleen because of Gd-DTPA-induced changes in the erythrocyte membrane. No mutagenic or teratogenic effects have been seen at levels up to 1.0 mmol/kg. Studies have shown Gd-DTPA to be safe and efficacious for imaging of the brain\(^13,56,59,64\) and spine,\(^67,76\) and in pediatric patients.\(^2,19,49\)

In the United States, gadopentetate dimeglumine was approved by the FDA for imaging of the brain in June, 1989, for the spine in May, 1989, and in pediatric patients aged 2 years or older in August, 1989.

The effectiveness of Gd-DTPA as a contrast agent is determined by several factors. These include its hydration number, magnetic moment, correlation time, and its proximity to water protons.\(^5,56\) Compared to other substances, Gd-DTPA is one of the most suitable choices in each of these respects. Gadolinium is one of the few metals ions which still allows access of water molecules to the ion after chelation. With chelation, however, the effective proton relaxation enhancement decreases. The concentration of Gd-DTPA must be about twice as high as free Gd to produce the same proton relaxation enhancement.\(^79\)

Parameters determining signal enhancement include paramagnetic concentration, pulse sequence, and field strength, as well as the choice of paramagnetic agent. Although the Gd-enhanced relaxation of both \(T_1\) and \(T_2\) results in opposite effects on signal intensity, the increased signal from shortened \(T_1\) relaxation predominates on \(T_1\)-weighted (short repetition time (TR), short echo time (TE)) spin-echo sequences and at lower concentrations of Gd. At the recommended dose of 0.1 mmol/kg, these \(T_1\) effects are dominant. At concentrations, such as in the dependent portion of the urinary bladder, \(T_2\) effects predominate with loss of signal from the urine (Fig. 2).\(^52\) Therefore, the contrast agent dosage is important for obtaining optimal studies. The optimal TR for a spin-echo pulse sequence is one between the \(T_1\) of the tissue before and after contrast enhancement.

Comparison of Gd-DTPA with iodinated agents shows many similarities but a few important differences. Both Gd-DTPA and iodinated contrast medium have similar molecular weight and pharmacokinetics with rapid intravascular and extracellular compartment distribution as well as excretion primarily by the kidneys. Both will enhance intracranial lesions when the blood-brain barrier is broken. However, a much smaller dose of Gd-DTPA is needed, which results in a much greater safety index and a relative paucity of side effects. Runge, et al.\(^52\) suggested that Gd-DTPA-enhanced MR imaging is more sensitive than iodinated contrast-enhanced CT at detecting early disruption in the blood-brain barrier.

**Clinical Applications: The Brain**

**Enhancement of Normal Brain Structures**

Knowledge of normal contrast patterns is important to differentiate normal from pathological enhancement and to confirm adequate enhancement with Gd-DTPA (see Figs. 5, 7, 8, and 9).

The intracranial contents with an intact blood-brain barrier do not enhance with Gd-DTPA. The following structures have an incomplete barrier and routinely show enhancement: pituitary gland, infundibulum, intracavernous portions of the third through sixth cranial nerves, cavernous sinuses, choroid plexus, and the reti-

nal choroid.\(^33\) Peak enhancement is at 3 minutes, but enhancement persists for approximately 1 hour. The pineal, falc cerebri, tentorium, and walls of the large vessels show enhancement inconsistently. Enhancement is seen in small vessels, usually venous. Rapidly flowing blood (in arteries) is imaged as a signal-void area which does not enhance. There is a 5% quantitative increase in the signal of gray matter after injection of Gd that cannot be visualized qualitatively. Inner and middle ear structures, including the facial nerve, do not normally take up contrast medium.\(^13,33\) Extracranially, the mucosa of the paranasal sinuses, nasopharynx, and oropharynx consistently show enhancement with Gd-DTPA.\(^4,21,29,59,64\)

**Overview of Clinical Utilization**

Gadolinium-DTPA has the potential to increase de-
tection of intracranial lesions, improve diagnostic abil-
ity, and reduce imaging time. Five reports\(^13,21,29,59,64\) involving 283 patients have shown that Gd-DTPA-
enhanced MR studies provided additional information in up to 50% of patients when compared to precontrast MR images. Gadolinium-DTPA increased the contrast of lesions, helped distinguish tumor from edema and normal brain, differentiated intra-axial from extra-axial lesions, and improved differential diagnosis. A blinded retrospective MR study of 55 lesions confirmed that postcontrast MR images improved diagnostic accuracy, particularly of metastases and meningiomas, as compared to the precontrast T1- and T2-weighted MR studies, with a decrease in false negatives from 8.6% to 0.7%. The authors also substantiated that contrast-enhanced MR imaging was better than noncontrast MR studies at distinguishing approximate tumor boundaries from edema.

Since Gd-DTPA is functionally similar to iodinated contrast material, enhancement patterns are similar. Gadolinium-DTPA MR images may show enhancement slightly earlier and more frequently than contrast-enhanced CT. A greater number of lesions may be seen with Gd-DTPA in patients with active multiple sclerosis, metastases, hemangioblastomas, meningial lesions, ventricular abnormalities, pituitary adenomas, and intracanalicular neurinomas. However, CT remains the best modality to diagnose calcified lesions and small calvarial abnormalities.

Some predictions for contrast-enhanced MR imaging have been overly optimistic. Postcontrast T1-weighted images have a lower sensitivity in general than precontrast T2-weighted images. T2-weighted studies are very sensitive to changes in tissue water content which may be due to minimal disruption of the blood-brain barrier. Gadolinium-DTPA, like iodinated contrast material, is a macromolecule which will accumulate in the extravascular space only if there is a significant breakdown in the blood-brain barrier. Thus, postcontrast T1-weighted images are generally used in conjunction with T2-weighted images for screening purposes. For example, inactive multiple sclerosis plaques often do not enhance with contrast medium. Nevertheless, detection of these lesions on the T2-weighted sequence is often very important, particularly in the initial diagnosis.

As with iodinated contrast material, Gd-DTPA may obscure certain types of pathology. On contrast-enhanced T1-weighted images, hemorrhage within a lesion may be missed (Fig. 3). Enhancing skull-base lesions, such as glomus tumors or bone metastases, may be obscured by the adjacent bright signal of fat or bone marrow. While it was originally feared that lesions which are normally visible on T2-weighted images by virtue of their prolonged T2 relaxation times may become isointense to brain with Gd-induced T2 shortening, this appears to be a rare situation.

As stated previously, the dosage of contrast medium is important for obtaining optimal studies. The optimal dose for imaging intracranial tumors in a comparison study of 11 patients has been found to be 0.1 mmol/kg. If one-half of this dose is used, there is inadequate tumor enhancement. A 0.2 mmol/kg dose is safe and may be useful in selected cases such as metastases, but is greater than the current recommended dose.
Pathological Conditions

Primary Brain Tumors. Gadolinium-DTPA enhancement represents the site of breakdown of the blood-brain barrier and not necessarily the tumor margin. Microscopic tumor is known to occur within areas of edema in patients with high-grade gliomas. Contrast is helpful in separating “gross” tumor margins from surrounding edema, a differentiation which is often difficult on noncontrast MR images (Fig. 3). This may be important for surgical planning and for posttherapeutic evaluation. Enhancement patterns are variable, similar to CT. Noncontrast T2-weighted studies are more sensitive, especially for the nonenhancing gliomas. Stack, et al., reported that 40 primary brain tumors all showed an increased signal on T2-weighted images, whereas six lesions were poorly identified on Gd-DTPA-enhanced T1-weighted images. Gadolinium-DTPA-enhanced MR imaging has detected subependymal spread of a glioma missed with contrast-enhanced CT.

Metastases. Contrast-enhanced MR imaging is equal to or better than contrast-enhanced CT in the evaluation of intracranial metastases: more lesions are detected with better contrast. This is particularly true of lesions adjacent to bone such as leptomeningeal metastases and of punctate metastases. In a study of 50 consecutive patients with suspected intraparenchymal metastases imaged with MR and CT studies (both contrast-enhanced), short-TR contrast-enhanced MR images showed more lesions in eight patients. Contrast-enhanced T1-weighted studies can be more sensitive than noncontrast T1-weighted images for imaging small sites of blood-brain barrier breakdown without significant edema. In six patients from this same series, short-TR postcontrast MR images detected metastases not seen on noncontrast MR (Fig. 4). Punctate metastases, particularly in the gray matter, can be more easily detected after Gd administration; these lesions often appear isointense under all sequence parameters if contrast material is not employed. In addition, noncontrast T2-weighted images can be equivocal because the nonspecific signal abnormalities in the periventricular area and white matter often found in older patients can mask metastases. Finally, if several metastases are adjacent to each other, contrast-enhanced MR imaging is much better at discriminating the actual number of lesions than noncontrast MR imaging. Without contrast enhancement, the copious edema associated with metastases often obscures small lesions. Since neurosurgical resection of single intraparenchymal metastases is sometimes performed, administration of Gd can be essential in the MR evaluation. Although most metastases may be detected at 5 minutes postinjection, the peak detection time may be 30 minutes or longer after injection.

Metastatic lesions to the skull were investigated by West and colleagues in 14 patients and 60 control subjects. The normal intradiploic space shows a wide variability in signal intensity due to fatty marrow, vascular spaces, and focal cortical bone. There is generally some symmetry of the intradiploic space from side to side, although it is inhomogeneous. The signal intensity of the calvaria changes with age. Bone marrow in young children appears as a uniform hypointense signal within the calvaria and clivus. After the age of 7 years, children exhibit increasing fatty infiltration of the marrow. Thus, the signal intensity within the calvaria or clivus becomes more hyperintense on short-TR images.

The normal diploic space does not enhance except for diploic venous channels and dura related to parachionian granulations. Calvarial metastases generally enhance with Gd-DTPA but, since the intradiploic
FIG. 5. Magnetic resonance images of a tentorial meningioma. Left: The meningioma (arrow) is isointense with gray matter on this short-TR/TE coronal image. It is not easily seen and impossible to differentiate from an intra-axial lesion. Right: With Gd-DTPA enhancement, the lesion is easily detected and definitely extra-axial. There is normal enhancement of the choroid plexus (large arrow) and pineal (small arrow).

Extra-Axial Tumors. Because extra-axial tumors are often isointense with normal brain on multiple pulse sequences, noncontrast MR imaging can be less sensitive than contrast-enhanced imaging by CT or MR study. Enhancement occurs immediately post-injection and persists for at least 1 hour. Gadolinium-DTPA enhancement may occasionally obscure lesions (such as glomus tumors or chordomas) which are adjacent to the bright signal of the nasopharynx or bone marrow. Computerized tomography remains the best imaging modality for demonstrating calcification, hyperostosis, and bone erosion.1,6,21,27,64

Gadolinium-DTPA-enhanced MR studies of meningiomas have significant advantages over noncontrast MR images and contrast-enhanced CT scans in four areas (Fig. 5): 1) contrast-enhanced MR imaging is the best modality for evaluating difficult regions such as the planum sphenoidale, parasellar area, and the foramen magnum; 2) since arteries and patent venous sinuses can be seen coursing through or adjacent to these tumors on contrast-enhanced MR images, vascular displacement and encasement is easily noted; 3) multiplanar evaluation may provide important additional information for the surgeon; and 4) dural extension (en plaque meningioma) may be better detected, especially on slightly delayed studies when contrast washes out of the normal dura (however, differentiation of tumor from reactive change may be difficult).1,21,27,64

Large neurinomas can be easily detected on either contrast-enhanced CT or MR imaging, with or without contrast enhancement. Acoustic neurinomas smaller than 1.5 cm are better seen on MR images than CT scans (Fig. 6). Several studies indicate that MR imaging is equal to or more successful than air-cisternography CT for detecting acoustic neurinomas.10,65 The use of postcontrast MR imaging was evaluated by Curati, et al.,10 in 10 patients with 12 presumed acoustic neurinomas (three surgically proved). Computerized tomography detected only five of the 12 lesions; the lesions not detected were usually less than 1.5 cm in diameter. Air-cisternography CT was positive in five of six patients who underwent this type of procedure. Magnetic resonance imaging was positive in all cases; the detection rate with noncontrast MR studies was equivalent to that after contrast enhancement; However, the lesions were markedly more conspicuous. In another study by Stack, et al.,65 involving 20 patients with 21 acoustic neurinomas, all five tumors less than 8 mm in diameter could only be detected on CT with air cisternography. Noncontrast MR images detected all 21 tumors, although three were visualized poorly. Contrast-enhanced MR imaging clearly delineated the tumor and distinguished it from the surrounding structures in all 21 patients, improving confidence of diagnosis. Eighteen acoustic neurinomas were confirmed surgically. These studies by Curati, et al., and Stack, et al., have demonstrated that with low-strength magnet systems, postcontrast MR imaging appears to be better than CT, and equivalent or better than CT with air cisternography or precontrast MR imaging. Since magnets of high field strength yield better resolution, the proportional benefit of contrast-enhanced MR imaging over noncontrast MR studies is less certain. However, the general feeling throughout the neuroradiology community is that postcontrast MR imaging is a great benefit for small lesions, regardless of the field strength. In addition to a potential increased detection rate, the increase in clarity of the lesion leads to improved ob-
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server confidence in the diagnosis. Thus, contrast-enhanced MR imaging appears to be the best type of study for small intracanalicular acoustic neurinomas, small facial-nerve and other neurinomas, and recurrent tumors.  

Pituitary Adenomas. Macroadenomas are well visualized on noncontrast MR studies. After Gd administration, they will enhance; however, extension into the cavernous sinus may be masked on postcontrast MR studies.  

Microadenomas can also be visualized on noncontrast MR studies. After Gd administration, they will enhance; however, extension into the cavernous sinus may be masked on postcontrast MR studies.  

Doppman and colleagues used a 1.5-tesla magnet and Gd-DTPA for MR evaluation of eight patients with surgically proven adrenocorticotrophic hormone-secreting microadenomas. Microadenomas were found in five of the eight patients at surgery. Tumor was found in the other three only after hemihypophysectomy and microscopic examination. Noncontrast as well as post-contrast MR studies were negative in these three; there was one false-positive contrast-enhanced MR image. Three microadenomas were imaged both by noncontrast and postcontrast MR images. The contrast-enhanced MR images detected two microadenomas not found by noncontrast MR studies.  

Newton, et al., examined 11 patients with surgically proven microadenomas. Noncontrast MR studies correctly identified the lesion in two of six patients with Cushing's disease, in three of four patients with hyperprolactinemia, and in a single patient with acromegaly. Contrast-enhanced MR imaging correctly detected another two patients with Cushing's disease and an additional patient with hyperprolactinemia. In the one false-positive examination of a patient with Cushing's disease (wrong site identified) obtained by both noncontrast and postcontrast MR imaging, contrast-enhanced CT and venous sampling were better at localizing the correct side of the tumor. These studies concluded that contrast-enhanced MR imaging is indicated for evaluating microadenomas if the noncontrast MR study is normal. However, incidental nonfunctioning cysts or adenomas in patients with Cushing's disease can lead to false-positive results.  

There are two time periods to image pituitary microadenomas with Gd-DTPA: 1) immediately (3 min-
FIG. 7. Magnetic resonance images of a hyperprolactin pituitary microadenoma: short-TR/TE coronal images of the pituitary glands. Left: Noncontrast image showing subtle enlargement of the left side of the gland without a focal signal abnormality. Right: Gadolinium-enhanced study, obtained immediately postinjection, clearly identifying the hypointense microadenoma with a hyperintense center on the left side of the gland (black arrows). It is easy to measure the size of the 6-mm microadenoma on this study. The adjacent normal pituitary tissue (white arrows) is markedly enhanced. There is normal enhancement of the cavernous sinus more laterally.

utes postinjection) when the microadenoma enhances to a very limited extent compared to the adjacent normal pituitary gland and therefore the tumor appears hypointense (Fig. 7); and 2) delayed (55 minutes postinjection) when there is delayed enhancement of the microadenoma and mild decrease in the enhancement of the normal pituitary resulting in relative hyperintensity of the microadenoma. In practical terms, imaging of microadenomas after injection of contrast medium should be performed immediately and must be accomplished quickly. Acquisition parameters for rapid postcontrast pituitary MR studies are still in a state of transition. If no abnormality is seen in a patient strongly suspected of having a microadenoma, a delayed image can be performed approximately 1 hour after contrast injection, as recommended by Dwyer, et al., although other investigators have not found delayed examinations to be helpful.

Meningeal Disease. Gadolinium-DTPA may mildly enhance normal meningeal structures. In a series of 20 patients without meningeal disease, Sze, et al., found fine linear enhancement of normal meninges in short segments, especially in the parasagittal and anterior portions of the cranium. Plain MR imaging and contrast-enhanced CT are comparatively insensitive to meningeal disease. Recent findings suggest that Gd-DTPA-enhanced MR images are more sensitive at detecting tumors and inflammatory and traumatic changes of the leptomeninges. While subtle enhancement adjacent to the skull may not be seen on postcontrast CT scans, these changes are easily detected with MR imaging (Fig. 8).

Mathews, et al., evaluated experimental bacterial meningitis in four dogs with postcontrast CT and MR studies. Computerized tomography demonstrated abnormal enhancement in only one of the four animals, 28 hours after induction of meningitis; however, MR imaging was able to demonstrate abnormal enhancement in all four dogs between 13 and 29 hours after inoculation. The areas of abnormal enhancement on the MR images were found to demonstrate severe inflammatory changes histologically. In areas that were mildly inflamed at pathological examination, there was no abnormal enhancement on MR evaluation. Complications of meningitis such as ventriculitis and cerebritis were more effectively demonstrated on MR images than CT scans. Unenhanced MR images were not useful in detecting meningitis.

Sze, et al., found abnormal meningeal enhancement in 52 of 175 contrast-enhanced MR studies of the brain. Twenty-two patients had carcinomatosis meningitis, 14 cases were postoperative or posttraumatic, while other etiologies included infection, sarcoid-
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When dura adjacent to the skull was involved, contrast-enhanced MR imaging demonstrated abnormal meningeal enhancement better than postcontrast CT because bone obscures adjacent contrast enhancement on CT. Contrast-enhanced CT was equal to contrast-enhanced MR imaging in detection of meningeal nodules.

Postoperative Lesions. Residual or recurrent tumor in patients who have undergone surgery may be difficult to detect and differentiate from postoperative changes on MR imaging. Contrast-enhanced MR imaging has had a major impact on these cases, regardless of the etiology of the original tumor. In a study of 15 postoperative patients, Bird, et al., reported six patients in whom postcontrast MR studies showed recurrent tumor not identified on the noncontrast MR images (Fig. 9).

A few studies have evaluated the temporal evolution of MR enhancement in the postoperative state. As with postcontrast CT, MR enhancement in the hypervascular brain parenchyma adjacent to the resection can be seen postoperatively for several months. Contrast-enhanced MR imaging differs from contrast-enhanced CT in two ways, however. First, contrast enhancement is often seen slightly earlier and somewhat later than in postcontrast CT. Second, as hemorrhage evolves, it becomes hyperintense on MR imaging and thus is more easily confused with Gd-DTPA contrast enhancement, whereas on CT, hemorrhage at the resection site often presents less of a problem after the first few days since the blood becomes isodense. For these reasons, in the immediate postoperative situation, it is important to perform Gd-DTPA MR imaging even sooner than postcontrast CT.

Initially, during the first few days after an operation, very little MR enhancement is seen at the operative site. However, after several days, thin linear enhancement is noted at the edge of the resected tissue. This linear appearance is difficult to confuse with tumor. With time, however, the enhancement can become progressively nodular and can be easily confused with tumor. From approximately 5 or 6 days to several months after surgery, enhancement that is seen at the operative site can be due to either tumor or to postoperative change. During this time, it is difficult to differentiate one from the other. In the chronic postoperative condition, enhancement at the postoperative site fades; however, the time course for this evolution differs between postcontrast CT and postcontrast MR imaging. With postcontrast CT, enhancement due to surgical change is generally not seen after 6 months; with contrast-enhanced MR imaging, however, enhancement is often seen 6 to 8 months postoperatively. Therefore, contrast-enhanced MR evaluation for possible residual or recurrent tumor must be viewed with skepticism if performed within 8 months after an operation.

Infection. Contrast enhancement of cerebral infections is similar on both CT and MR imaging. Animal studies suggest that Gd-DTPA enhances more conspicuously and at an earlier stage in the development of subdural hematoma, subacute infarction, or adjacent skull or parenchymal metastasis. Compared with the short linear enhancement seen normally, abnormal meninges demonstrated longer segments of enhancement which were sometimes nodular and more peripheral (that is, away from the parasagittal region). Abnormal enhancement was seen in up to two-thirds of patients with proven leptomeningeal carcinomatosis.
cerebritis; this has been observed as early as 1 day postinoculation in two of five dogs. Contrast enhancement was more easily detectable at 10 minutes than at 2 minutes after Gd-DTPA injection.

Multiple Sclerosis. Enhancement in multiple sclerosis is thought to be due to breakdown of the blood-brain barrier in active lesions. Enhancement of lesions on MR studies has been correlated with clinical symptoms in patients with active disease. Gadolinium-DTPA can often separate active from nonenhancing inactive disease as opposed to noncontrast T2-weighted images (Fig. 10). On long-TR images, both appear as areas of high signal. Gadolinium-enhanced MR is probably more sensitive than contrast CT. Grossman, et al., reported enhancement in all of nine symptomatic patients studied with Gd-DTPA as opposed to four of the same nine studied with contrast-enhanced CT. Most lesions were seen on the immediate postinjection images, although some became more visible on delayed studies. A follow-up study by Grossman, et al., in 13 of these patients found that multiple sclerosis lesions are dynamic, with both active (enhancing) and inactive (nonenhancing) lesions showing marked changes on serial MR studies.

Research by Kuharik, et al., complements the findings by Grossman and colleagues. Experimental allergic encephalomyelitis, a demyelinating disease with similarities to multiple sclerosis, was induced in two of 12 dogs by Kuharik’s group. During the acute phase, periventricular white matter lesions were imaged on T2-weighted MR images. These lesions enhanced with Gd-DTPA and were found to represent new active plaques of demyelination at necropsy. One dog had pathologically proven subacute demyelinating lesions, 6 weeks old. While these subacute plaques were indistinguishable from the acute lesions using long-TR studies, postcontrast examinations were able to separate the nonenhancing subacute lesions from the enhancing acute lesions. As clinical symptoms resolved, enhancement of lesions disappeared.

Infarction. Noncontrast T2-weighted MR imaging is more sensitive to early infarction than CT or postcontrast MR imaging. T2-weighted MR studies are very sensitive to the increase in water content seen acutely in ischemic tissue. After several days, capillaries lacking an intact blood-brain barrier are seen at the periphery of an infarct. Although enhancement by Gd-DTPA has been seen as early as 16 hours experimentally and 22 hours in patients, clinically the abnormal appearance is seen best several days after infarction and usually persists up to 6 to 8 weeks. Postcontrast MR imaging can detect infarctions earlier and with better enhancement than postcontrast CT but may not yield any more significant information than CT.

The enhancement pattern may help with the differential diagnosis of lesions seen on noncontrast MR imaging. This is especially true in separating chronic infarcts or asymptomatic white matter lesions (often called “UBO’s” or “unidentified bright objects”) which do not enhance from lesions with active disruption of the blood-brain barrier, such as subacute infarctions, neoplasms, or inflammatory lesions.
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Skull-Base Lesions. Skull-base lesions are sometimes difficult to image on CT scans since the bone at the skull base may obscure or mask pathology. Sagittal or direct coronal planes are often the most optimal means of imaging skull-base lesions, yet they can be difficult to obtain with routine CT scanning. Due to its multiplanar capability, MR imaging has been particularly useful in these situations. Although contrast can obscure lesions adjacent to fat, recent reports indicate that contrast-enhanced MR studies can be more useful than noncontrast MR studies in some cases involving the skull base.

In a report on 27 patients with extracranial head and neck lesions, Robinson and colleagues described three conditions in which Gd-enhanced MR imaging was more useful than noncontrast MR studies. First, perineural tumor spread at the level of the skull base was better seen in one patient. Second, Gd-enhanced studies more accurately documented neoplasm extending to the leptomeninges in three patients. Third, tumor could be more easily differentiated from inflammatory disease of the nasal and paranasal sinuses in four of their patients.

Daniels, et al., reported Gd-enhancement in nine of 10 patients who had facial-nerve paralysis but no facial-nerve tumors. Three of the four patients had idiopathic Bell’s palsy and the other six had facial-nerve paralysis after temporal bone surgery. Thus, the authors stressed that enhancement of the intratemporal facial nerve is a nonspecific finding and can be seen with inflammatory changes as well as with tumors. This type of information could not be acquired on noncontrast MR or contrast-enhanced CT examinations.

Vogl, et al., examined 26 patients with paragangliomas comparing postcontrast CT with noncontrast and postcontrast MR studies. There were 16 glomus jugulare tumors, three glomus tympanicum tumors, and seven carotid body tumors in their study. They claimed that, in three of five tumors less than 1.5 cm in size, contrast MR imaging was able to detect tumors not seen on nonenhanced MR studies. They found that MR imaging was better than CT because it displayed anatomy, vascularity, and tumor delineation better in all cases except the three with glomus tympanicum tumors. However, it was not stated whether the detection rate for CT and MR imaging was the same.

Dynamic contrast-enhanced MR studies using gradient echo imaging can help confirm the diagnosis of very vascular lesions such as paragangliomas by their typical enhancement-versus-time profile. Skull-base lesions such as meningiomas, clivus chordomas, pituitary lesions, or even primary brain tumors may all be detected on noncontrast MR studies or postcontrast CT scans. However, the combination of contrast enhancement with the multiplanar capacity of MR imaging can often yield invaluable information, especially in preoperative cases. Computerized tomography still remains the best method for detecting bone abnormalities at the skull base.

Clinical Applications: The Spine

Postcontrast CT studies of the spine have always been plagued by bone artifact which often masks enhancement. With the development of contrast agents for MR imaging, an exquisite way now exists to evaluate the enhancement properties of the spine and its contents without interference by bone. Enhancement patterns of normal spinal structures and of extradural, intradural extramedullary, and intramedullary disease are reviewed in this section.

Enhancement of Normal Spinal Structures

The most marked enhancement is seen in slow-flowing vascular structures, especially the epidural and basivertebral plexus (Fig. 11 right). However, these enhance inconsistently. The blood-CNS barrier is responsible for visualization of little to no enhancement within the spinal cord and intradural segments of the nerve roots. Once the nerve roots exit the thecal sac, they often enhance and in fact the dorsal root ganglion enhances markedly. Minimal quantitative enhancement of the vertebral bone marrow, ligamentum flavum, and adjacent muscle occur, but these are not generally detectable.

Extradural Disease

Neoplastic Disease. Unenhanced MR images are excellent at detecting tumor involvement of the vertebrae as well as the epidural space. Contrast MR studies may obscure pathology and thus are not indicated as the initial study of choice. On unenhanced MR, vertebral body lesions are detected as low-intensity regions surrounded by the increased signal intensity of normal fat-containing marrow. Enhancement of spinal lesions with Gd is extremely variable. Depending on the degree of enhancement, lesions either remain hypointense to normal marrow or become isointense or hyperintense. The variability of enhancement can occur with different lesions even in the same patient. Gadolinium becomes a liability when the detectable low-intensity lesion enhances to become isointense with the surrounding marrow and is thus obscured (Fig. 11). The same considerations apply to tumor within the epidural space. Depending on the degree of enhancement, tumor may become isointense with either the adjacent vertebral bone marrow or the adjacent epidural fat (Fig. 11).

In certain situations, however, Gd may be helpful during MR evaluation of extradural tumors. These advantages include: 1) characterizing unusual epidural lesions; 2) evaluating regions of more aggressive tumor for biopsy; 3) indicating areas of cord compression; and 4) possibly evaluating tumor response to therapeutic intervention. Contrast enhancement can be useful in more fully characterizing epidural lesions. For example, differentiation of intervertebral disc herniation from epidural tumor adjacent to a narrowed disc on noncontrast MR imaging is occasionally difficult. Since discs...
and disc fragments generally do not enhance on immediate postcontrast scans, tumor can be distinguished by its enhancement.66

The administration of contrast material can also help in MR-guided biopsy. Contrast uptake may often be localized to only a portion of the vertebral body. It is thought that these areas of Gd enhancement indicate regions of more active tumor involvement. In our experience, biopsy of the enhancing portion of the abnormal vertebral body has been more successful than biopsy of the nonenhancing regions.71

Cord compression due to diffuse epidural tumor, especially in patients with a narrow spinal canal, is occasionally better delineated on an enhanced rather than unenhanced MR image. The nonenhancing cord is highlighted against enhancing tumor. However, high-quality long-TR images or gradient echo studies may provide comparable information.

Contrast enhancement may be useful as an index of tumor response to treatment. Berry, et al.,1 noted that prostatic carcinoma metastatic to the skull failed to enhance on MR imaging after radiation therapy. We have noted similar findings in spinal metastases which have been irradiated. Presumably, tumor that is responsive to radiation therapy becomes poorly vascularized and thus does not enhance. We have also noted cases with the reverse condition where tumor which was unresponsive to radiation therapy continues to show enhancement.

Degenerative Changes and Disc Disease. Modic and colleagues66 have noted several types of MR signal intensity changes of vertebral bodies associated with degenerative disc disease. The early stage consists of decreased signal intensity compared to adjacent marrow on short-TR images and increased signal intensity on long-TR images (type 1 degenerative changes). It is believed that these findings are due to edema, inflammation, and fibrovascular changes. Enhancement by Gd often occurs at this stage and is usually mild.31,67 One should not mistake this enhancement for tumor or infection. Later stages of degenerative disease result in an increased signal intensity on short-TR images and an isointense to slightly hyperintense signal on long-TR studies (type 2 degenerative changes). This is thought to be due to replacement of the early changes with fatty marrow. No enhancement is seen during this stage.

Unenhanced MR images are superb for evaluating disc herniation. Gadolinium is occasionally helpful when one wants to improve the delineation of a disc herniation since the epidural veins will enhance and outline disc protrusions.7 Degenerative disc, herniated disc, and free disc fragments do not generally enhance on immediate postcontrast scans but can show mild

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**Fig. 11.** Magnetic resonance images of metastases from a colon carcinoma. Left: Short-TR/TE sagittal image revealing multiple foci of hypointensity within the vertebral bodies (contrasted by adjacent normal hyperintense fatty marrow) consistent with known metastatic disease. Extension of the tumor at L-5 to the epidural space (arrow) is also appreciated. Center: Long-TR/TE cardiac-gated sagittal image demonstrating hyperintensity of the vertebral body metastases. Right: Gadolinium-DTPA-enhanced short-TR/TE sagittal image displaying varying degrees of enhancement of lesions. Some mildly enhancing lesions remain hypointense to normal marrow. Other lesions, especially at L-5, enhance enough to become isointense to the adjacent marrow. These isointense lesions would not be detected if the contrast-enhanced examination had been the only study performed. The epidural tumor also enhances to a similar extent as the adjacent tumor-infiltrated body of L-5. The enhancing thin line continuing in the anterior epidural space from L-5 superiorly to L-4 (arrowhead) may represent displaced enhancing epidural veins or extension of tumor. (Reprinted from Sze G, Krol G, Zimmerman RD, et al: Gadolinium-DTPA: malignant extradural spinal tumors. Radiology 167:217-233, 1988, with permission.)
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FIG. 12. Magnetic resonance (MR) images of a case of failed-back syndrome. Upper Left: Short-TR/TE axial image 6 months postsurgery disclosing a large low-intensity region on the left at the operation site. Upper Right: Postcontrast short-TR/TE axial image demonstrating enhancement of only the rim (arrows) of the mass. The remainder of the mass appears as an area of low intensity. The patient underwent repeat surgery and a large disc fragment was found. Lower: Short-TR/TE axial MR images obtained 3 months later, when the patient developed recurrent pain. The precontrast image (left) again reveals a low-intensity mass in the same position as previously noted. The postcontrast image (right) demonstrates homogeneous enhancement of this lesion, consistent with scar formation. The nerve root sleeve passes through the center of the scar.

enhancement on delayed images. Occasionally, enhancement is seen due to granulation tissue in the disc space.

The “failed-back” syndrome is one example of a situation in which contrast-enhanced MR imaging is the diagnostic modality of choice. Although postcontrast CT and noncontrast MR imaging can often detect abnormal tissue within the spinal canal displacing normal fat in the postoperative back, characterizing the abnormality is more difficult; differentiating scar from disc material is reported to be reliable in 67% to 100% of cases. A blinded prospective study by Hueftle, et al., reported 17 patients with failed-back syndrome who had surgical findings correlated with precontrast and postcontrast MR studies. When contrast MR images were compared to precontrast MR studies, specificity increased from 71% to 100%. Other reports have confirmed these findings of improved differentiation of scar versus disc herniation (Fig. 12). On immediate postcontrast studies, disc and disc fragments generally do not enhance, while scar generally enhances markedly. Inflamed nerve roots can also enhance.

Injection. Gadolinium enhancement may provide supplementary information for spinal osteomyelitis and discitis. Noncontrast MR images show classic findings of spinal infection consisting of loss of disc-space height, destruction of adjacent endplates, and signal abnormalities involving the disc and adjacent vertebral bone marrow. Gadolinium enhances inflamed tissue and granulation tissue surrounding the infection. Epidural inflammatory changes generally show enhancement. Most importantly, Gd can show extension of infection into the epidural space; even when an abscess does not itself enhance on MR imaging, extension of the disease can still be well demonstrated by enhancement of the inflamed overlying epidural veins.

Intradural Extramedullary Disease

Neoplastic Disease. Unlike MR evaluation of extradural disease, Gd is essential for MR studies evalu-
FIG. 13. Spinal imaging in a case of drop metastases from a cerebral glioblastoma. Upper Left: This noncontrast short-TR/TE sagittal magnetic resonance (MR) image is negative except for poor definition of the conus and proximal nerve roots. In retrospect, very vague nodules may be present in the subarachnoid space. Upper Center and Right: These non-contrast long-TR sagittal MR images are also equivocal. There may be a suggestion of high intensity near the conus. Lower Left: Postcontrast short-TR/TE sagittal MR image showing an enhancing subarachnoid tumor encasing the nonenhancing distal spinal cord, causing the total block seen on the myelogram (lower right). In addition, multiple other drop metastases are clearly seen. Lower Right: Myelogram confirming the presence of multiple nodules and total block at the level of the conus. (Reprinted from Sze G, Abramson A, Krol G, et al. AJNR 9:153-163, 1988, with permission.)

Gadolinium-DTPA enhancement helps to distinguish intramedullary lesions from extramedullary disease. Lesions detected on noncontrast MR studies, such as schwannomas and meningiomas, are more conspicuous with enhancement. Lesions invisible on non-contrast MR images strongly enhance and are detectable with Gd. Sze, et al.,58 evaluated 12 patients with intradural extramedullary disease, most of whom had leptomeningeal spread of tumor. Of the 11 patients who had a myelogram, three had normal or equivocal studies. Nine of the 12 patients had normal or equivocal noncontrast MR images using short- as well as long-TR pulse sequences. In contradistinction, contrast MR studies using short-TR pulse sequences demonstrated marked contrast enhancement of lesions in nine patients, often depicting nodules which were 2 to 3 mm in size. The one normal postcontrast MR study was in a patient with a normal myelogram who had leukemia confirmed by cerebrospinal fluid (CSF) studies.

There are several reasons why small intradural extramedullary tumors and leptomeningeal tumor are poorly seen on noncontrast MR studies.68 These include the following. 1) The CSF often has elevated levels of protein while leptomeningeal tumor often has a high water content. Both of these factors result in a decrease in the difference between the $T_1$ and $T_2$ relaxation times of the lesions from those of the surrounding CSF. 2) Meningiomas and neural-sheath tumors are often isointense to the cord or CSF on multiple sequences. While large tumors are usually detected, small lesions may be masked by adjacent cord or CSF. 3) Lesions both in the brain and spinal cord are often associated with edema. It is often the edema and not the lesion which is detected on MR imaging. However, there is usually no edema detectable with intradural extramedullary lesions. 4) Artifact due to many types of motion can
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degrade imaging and decrease lesion detection rate in
the spine. Movement and CSF pulsation are constant
problems. Since Gd markedly enhances intradural extramedullary lesions, even very small nodules, one can
understand why postcontrast MR studies represent the
diagnostic modality of choice. We prefer short-TR images before and after the administration of Gd. Long-TR images may not be necessary. Enhancement of intradural extramedullary disease is best on the immediate postcontrast study.

**Inflammatory Disease.** Chronic arachnoiditis can lead to adhesions with resulting clumping of nerve roots and distortion of the thecal sac. These changes can be seen on unenhanced MR studies. Although mild or even moderate enhancement of inflamed and matted nerve roots has been seen, poor enhancement in many cases of severe arachnoiditis may also be found. For most cases, contrast-enhanced MR imaging will not be more advantageous than noncontrast MR studies. Myelography is probably still the most sensitive imaging modality for detecting early arachnoiditis, while noncontrast MR imaging and myelography are equivalent for moderate to severe arachnoiditis.

Enhancement can also occur in infectious conditions involving the subarachnoid space. We have noted Gd enhancement of nerve roots in syphilitic and pyogenic bacterial meningitis.

**Vascular Disease.** There has been a limited amount of material published regarding diagnosis of spinal dural arterial venous fistulas on postcontrast MR studies. Enhancement of abnormal medullary veins has sometimes been the only finding on MR images in such cases; however, the "gold standard" at the present time is still myelography and spinal angiography. Gadolinium has been shown to enhance regions of ischemia or infarction within the cord which are secondary to spinal arterial venous malformations.

**Intramedullary Disease**

**Neoplastic Disease.** Magnetic resonance imaging has revolutionized the evaluation of spinal cord tumors. Most reports indicate that Gd improves characterization and delineation of tumors rather than detection. However, Dillon, et al., have recently reported four of 13 cases in which detection occurred only after contrast enhancement. Two of the four patients had recurrent tumor. Contrast-enhanced MR imaging is equal to or better than noncontrast MR studies. Gadolinium is most helpful in cases of focal masses, such as hemangioblastomas and metastases, and helps to separate the solid portion of the tumors from the adjacent edema. Cysts are often associated with primary cord tumors. Gadolinium can help to differentiate the solid tumor from the associated cyst (Figs. 15 and 16).

Intramedullary tumors almost always enhance with contrast material on MR imaging. Six studies describing a total of 75 patients with spinal cord tumors noted contrast enhancement for all tumors except two, an astrocytoma and a cavernous hemangioma. The

**FIG. 14.** Magnetic resonance imaging of a surgically proven spinal neurofibroma. **Upper:** Consecutive noncontrast short-TR/TE sagittal images depicting an apparent widening of the distal cord and conus. **Center:** Postcontrast short-TR/TE sagittal images demonstrating a well-defined enhancing mass, consistent with a neurofibroma. **Lower:** Postcontrast short-TR/TE axial image confirming the intradural extramedullary location of this lesion.
FIG. 15. Magnetic resonance imaging of breast carcinoma metastasis to the spinal cord. **Left and Center:** These noncontrast short-TR/TE (left) and long-TR/TE (right) sagittal images of the cervical cord cannot depict the exact location of the lesion. **Right:** Postcontrast short-TR/TE sagittal image demonstrating a focal enhancing lesion consistent with an intramedullary metastasis. The finding of the focal lesion enabled radiation therapy to be directed at the metastasis itself, sparing the remainder of the cord.

Majority of lesions were ependymomas and astrocytomas, with a smaller proportion of hemangioblastomas and metastases. There is usually marked enhancement of a well-circumscribed lesion in those cases of hemangioblastomas and metastases. Heterogeneous or variable enhancement can be seen with ependymomas and astrocytomas, although as a general rule ependymomas enhance more homogeneously. It is interesting to note that, while up to one-half of gliomas of the brain do not enhance, almost all gliomas of the cord enhance regardless of grade. In fact, 54 of 55 spinal cord gliomas reported from six studies enhanced with contrast material. One may extrapolate these data to mean that the probability of the presence of a spinal cord glioma is significantly lessened if no enhancement is seen. If a cyst is seen within the cord, Gd is an excellent means of differentiating a benign syrinx from one associated with a tumor.

**Non-Neoplastic Disease.** Enhancement within the cord on MR imaging is not specific for tumor. Infarction, active multiple sclerosis plaques, and transverse myelitis can also result in uptake of contrast material within the spinal cord. In a study of five patients with spinal multiple sclerosis, Gd-DTPA enhancement on MR studies paralleled the degree of symptomatology in the two patients with clinically active disease.

**Future Applications**

Future applications for MR contrast agents are developing in two directions: 1) new uses for an accepted agent (Gd-DTPA), and 2) development of new contrast agents. Dynamic scanning and fat-suppression MR imaging are two areas of research where Gd-DTPA may make a major contribution. Preliminary results show enhancement of lesions by Gd-DTPA with gradient echo fast scanning. This may be the future technique for dynamic scanning and decreasing scanning times. These fast scanning techniques are also currently more easily coupled with the use of three-dimensional Fourier transform imaging. With fat-suppression techniques, one does not need to worry about masking contrast enhancement by fat. Potential uses include skull-base, orbital, and spinal extradural evaluation.
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**FIG. 16.** Magnetic resonance imaging of a low-grade cervical astrocytoma. **Left:** Precontrast short-TR/TE sagittal image disclosing extensive enlargement of the cervical cord. **Right:** The postcontrast short-TR/TE sagittal image, however, shows enhancement of the nidus of the tumor. While tumor undoubtedly extends beyond the area of enhancement, Gd-DTPA depicts the region of the most active tumor. Low-grade gliomas of the spinal cord enhance much more frequently than low-grade gliomas of the brain.

In addition to gadopentetate dimeglumine, a number of other contrast agents incorporating Gd are being investigated in clinical trials including Gd-DOTA, non-ionic Gd-DTPA-bis (methylamide) also known as gadolinium-DTPA-BMA, and the non-ionic gadolinium 1,4,7 tris (carboxymethyl)-10-(2’hydroxypropyl) 1,4,7,10 tetra-azacyclododecane or gadolinium HP-DO3A. The non-ionic substances have the theoretical advantage of improved safety; however, the lack of significant side effects of gadopentetate dimeglumine may make this advantage negligible.

The contrast agents used in clinical practice for CT and MR imaging are useful because they do not pass through the blood-brain barrier except when it is damaged. There are new contrast agents on the horizon which have different pharmacokinetics. Intravascular agents have been used to explore blood pool and perfusion properties. Gadolinium-DTPA linked to serum albumin or dextran is retained in the intravascular space and results in enhancement of the entire blood pool. Albumin-(Gd-DTPA) has been used to obtain MR angiography. Paramagnetic and superparamagnetic agents can also be used to evaluate the intravascular space. Perfusion agents have the potential for measuring intravascular volume and for improving evaluation of stroke and vascular lesions.

Reticuloendothelial system agents may prove to be useful in specific clinical circumstances involving spinal bone marrow. These agents include superparamagnetic iron oxide crystals and Gd-labeled liposomes. One could postulate a situation where these agents would be more useful than Gd-DTPA, such as in distinguishing between a neoplastic versus a traumatic vertebral compression fracture.

An area of ongoing investigation is the development of target-specific contrast agents. The potential for such agents is immense. In addition to improving detection of lesions, one could also characterize the type of neoplastic process and ultimately treat the disease on a microscopic level. Difficulties, however, have arisen with development of tumor-specific antibody contrast agents.

Lipophilic contrast agents which can cross cell membranes and the blood-brain barrier could be used to evaluate brain function. One substance, Mn mesoporphyrin, has already been used for enhancing experimental gliomas. These substances may never achieve clinical importance because of their toxicity.

In addition to intravenous administration, contrast agents can also be injected intrathecally. Early investigations have already found that intrathecal administration of these contrast agents can enhance the CSF.

This approach could be used to evaluate arachnoid cysts, epidermoid tumors, intrathecal adhesions, and CSF leaks.

**Conclusions**

Gadopentetate dimeglumine is a safe and efficacious paramagnetic contrast agent. In certain conditions, Gd-DTPA-enhanced MR imaging is either the study of choice or provides additional helpful information. In the head, contrast MR is useful in the evaluation of intracranial metastases, pituitary microadenomas, acoustic neurinomas, meningeal disease, primary brain tumors, and some skull-base lesions. In spinal imaging, Gd injection is indicated routinely in MR diagnosis of the failed-back syndrome or when intradural and intramedullary lesions are suspected. Future potential directions in the utilization of MR contrast agents include dynamic scanning, MR angiography, intrathecal contrast, cerebral blood flow and volume evaluation, and antibody-labeled contrast agents.

**References**

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