

Clinical Application of Gadolinium-DTPA, A Magnetic Resonance Contrast Agent, for Evaluation of the Central Nervous System

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Abstract

Gadolinium-DTPA dimeglumine, a magnetic resonance contrast agent, was evaluated in 51 patients with known intracranial pathology. Patients were studied with both T_1 weighted and T_2 weighted spin echo pulse sequences prior to and following the intravenous injection of gadolinium-DTPA. This contrast agent is primarily an enhancer of increased blood brain barrier permeability and thus, Gd-DTPA behaves very similar to conventional iodinated contrast agents used for CT scanning. One major difference, however, between gadolinium-DTPA and CT contrast agents is the fact that the vascular compartment including normal arterial structures and AV malformations are usually not enhanced with gadolinium-DTPA. However, some contrast enhancement was noted in areas of slow flow including normal veins, especially the cavernous sinus.

Review of pathologic cases revealed that the MRI scan done following Gd-DTPA

2 Contrast Agent

The first contrast agent to be introduced for use with clinical MR imaging is gadolinium diethylenetriamine pentaacetic acid dimeglumine (Gd-DTPA) [Schering AG, Berlin] which is a chelate of gadolinium (Gd), a rare earth metal of the lanthanide series^{10~12}). Although Gd is toxic in elemental form, this chelated form of Gd is a stable complex with very low toxicity when injected intravenously. The LD₅₀ is approximately 10 mM/kg and compares favorably with the LD₅₀ for conventional x-ray contrast agents of approximately 18 mM/kg¹⁰). Gd-DTPA has pharmacological properties which are nearly identical to conventional iodinated radiographic contrast material such as meglumine diatrizoate and it is rapidly excreted into the urine with a half life of approximately 20 minutes^{10,13}).

3 Imaging Characteristics

Paramagnetic substances such as gadolinium-DTPA alter the MR signal by causing a decrease in the relaxation time of water protons. At the low blood and tissue concentrations of Gd-DTPA achieved in clinical practice, there is a preferential effect on the T_1 relaxation time with a measurable decrease of this parameter, and a negligible effect on the T_2 relaxation time. This results in an increased signal intensity on the MR image. The effect is most pronounced on T_1 weighted images such as inversion recovery sequences and spin echo sequences with a short TR and short TE¹⁴).

In high concentrations paramagnetic substances also cause a significant decrease of T_2 relaxation time and this effect can be dominant^{7),15}). In this case, the result is a decrease or a complete absence of signal intensity on the image since the marked shortening of T_2 relaxation time causes very rapid decay of the transverse magnetization vector and prevents rephasing of the spins following the 180° refocusing pulse. This effect is present with all imaging sequences and can be best seen in human studies as decreased signal within the bladder and renal collecting systems¹²) since gadolinium, which is primarily secreted through the kidneys, is present in high concentration in these areas.

4 Methods

There were 51 patients in our series who were studied with magnetic resonance (MR) scans both before and after the injection of Gd-DTPA. All patients were entered into an investigative protocol approved by the Committee for Human Research and a signed, informed consent was obtained from each patient. One of the requirements for entry into this study was that the

patient have a CT or MRI demonstrated intracranial abnormality prior to receiving Gd-DTPA.

All MRI scans were performed on a Diasonics MT/S scanner (Diasonics, Inc., Milpitas, CA, USA) operating at a field strength of 0.35 Tesla. Patients were studied with T_1 , spin density and T_2 weighted images performed immediately prior to the injection of 0.1 mM/kg Gd-DTPA. These same sequences were obtained beginning three minutes following the injection of gadolinium and continuing serially with repetition of these sequences up to one hour post injection. The T_1 weighted images were obtained with a spin echo pulse sequence utilizing a TR of 500 msec and a TE of 28-30 msec. The spin density and T_2 weighted images were spin echo sequences with multiple echoes consisting of a TR of 1500-2000 msec and TE's of either 28 and 56 msec or 30, 60 and 90 msec. Most of the examinations were done with a 10 mm slice thickness, although a few studies were done using slice thicknesses of 5 mm.

Detailed analysis of the pre- and serial post-contrast MR images was done. Data was tabulated for presence or absence of enhancement within the primary abnormality, the presence of new information about the primary lesion, the detection of additional lesions and the presence and pattern of enhancement within normal, anatomical structures. Since there were no normal patients in our series, data for normal enhancement was obtained by evaluating structures that were not related to the primary pathology in each patient.

All but three of our patients (48 of 51) had good quality CT scans performed within a few days of the MRI study and these were compared to determine if the enhancement patterns of CT and MR with Gd-DTPA were similar and, also to determine if either study provided more diagnostic information.

5 Results and Discussion

1 The Normal Enhancement Pattern

The physiologic basis of contrast enhancement within the brain with gadolinium-DTPA is related to increased permeability of the blood brain barrier. This has been well demonstrated in animal experiments by both Brasch¹⁵⁾ and Runge¹⁶⁾ and this effect is similar to that found with contrast enhancement on CT scans¹⁷⁾. However, there are two important differences between MRI contrast enhancement with gadolinium-DTPA versus CT contrast enhancement with iodinated radiographic agents. First is the fact that CT with contrast, in addition to the blood brain barrier effect, also demonstrates enhancement of the intravascular space including blood vessels, AV malformations and aneurysms. This is not usually the case with MRI contrast since flow related phenomena result in unique changes on the MR image without contrast. This often results in markedly decreased or absent signal in areas of rapid flow. It should be pointed out that gadolinium has been observed to cause mild increased signal in some areas of slow flow¹⁸⁾; however, this effect is usually variable and of doubtful clinical significance. The one exception was in the cavernous sinus which consistently demonstrated intense contrast enhancement following injection

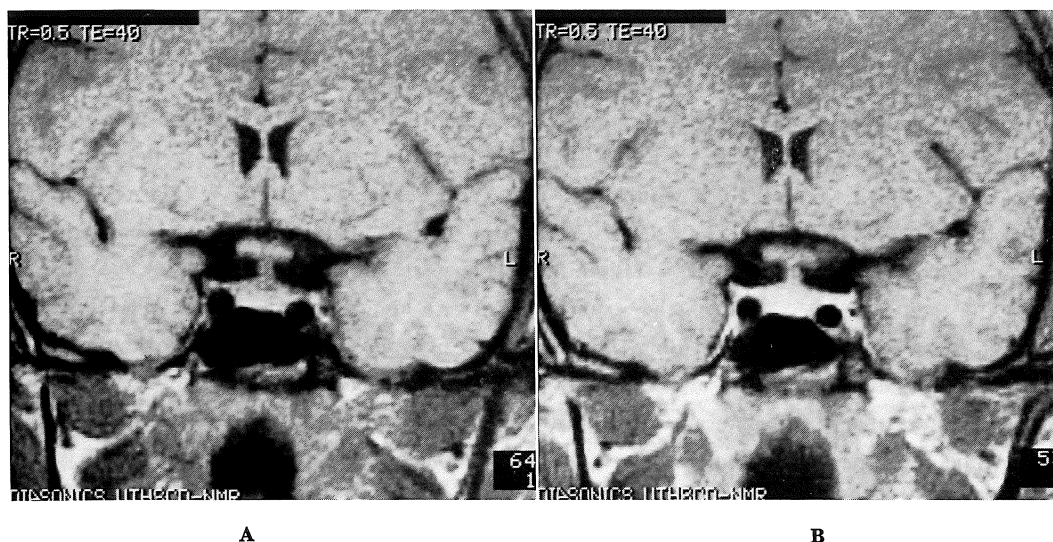


Fig. 1 A: Baseline, pre-contrast MR scan (TR 500, TE 40 msec) shows the normal pituitary gland and cavernous sinus to be approximately isointense with the surrounding brain tissue.
B: Post-contrast T_1 weighted MR image (TR 500, TE 40 msec) of the same patient shows good enhancement of both the pituitary gland and the cavernous sinus.

of Gd-DTPA (Fig. 1).

The second major difference between MR and CT contrast images is the fact that, unlike the interaction of x-ray photons with iodine, the gadolinium contrast agent is not visualized directly on the MR image. Rather, what is shown are the indirect effects of gadolinium as it shortens the relaxation time of the mobile protons. Thus structures which do not normally possess any significant intrinsic signal, such as ligaments and dura, would not be expected to demonstrate a signal increase following injection of gadolinium.

In comparing the normal pattern of enhancement within the head on both CT and MR, there are several similarities as well as some notable differences. Several areas within the brain which do not possess a blood brain barrier show contrast enhancement with gadolinium. These include the pituitary gland and pituitary stalk, the pineal gland and the choroid plexus (Fig. 2). Areas of **rapid flow**, such as arteries at the base of the brain, do not show any enhancement on the MR image although they are well seen on contrast CT. However, areas of **slow flow**, including the sagittal sinus and the superficial cerebral veins, show variable patterns of mild to moderate enhancement due to shortening of the T_1 relaxation time of blood. This can only be demonstrated in areas of slow flow.

A notable difference between CT and MR enhancement involves the falx and tentorium. Although these structures intensely enhance on the CT scan they are not visualized on the MR

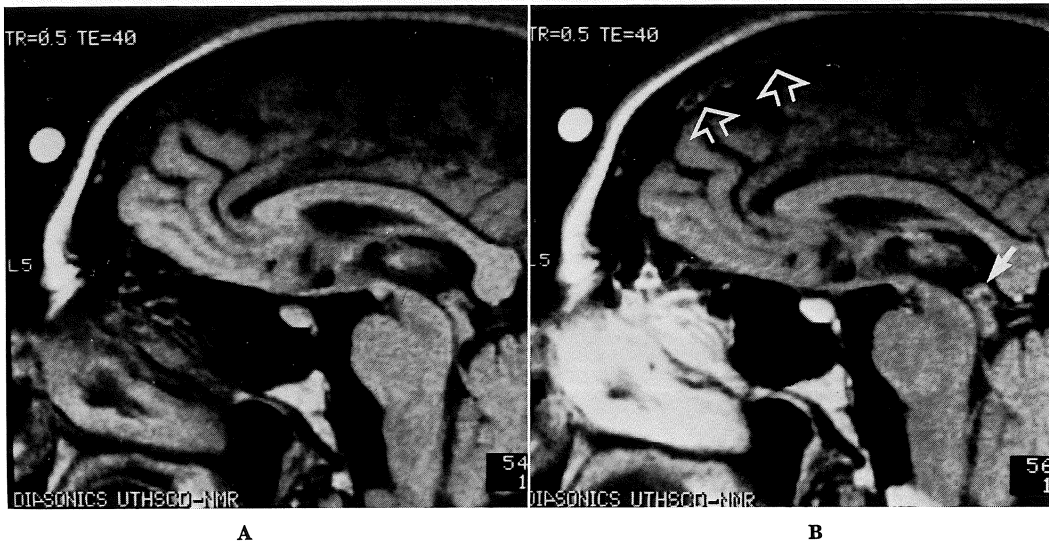


Fig. 2 Pattern of normal enhancement with gadolinium-DTPA

- A:** Sagittal T_1 weighted image (TR 500, TE 40 msec) done prior to the injection of contrast material.
B: Repeat sequence with the same parameters done three minutes following injection of gadolinium-DTPA. There is intense enhancement within the pituitary gland and the nasal mucosa. Increased signal intensity can also be seen in the small pineal gland (arrow). Note also normal enhancement within parasagittal veins (open arrows).

study with Gd-DTPA. The reason for this is felt to be due to the fact that the dura is a fibrous structure and has a low concentration of mobile protons. Thus, the falx and tentorium do not demonstrate measurable MR signal on the pre-contrast study as evidenced by the fact that these structures are not seen on baseline MR images. Therefore, they would not be expected to demonstrate signal on the post-contrast study. If signal is seen within these structures following Gd-DTPA injection, it is an abnormal situation and has been demonstrated in cases where there has been tumor infiltration or en plaque growth of meningioma along the falx (Fig. 3)¹⁸.

MR with Gd also demonstrates prominent enhancement within several extracranial structures including the nasal mucosa (Fig. 2), the mucosa of the paranasal sinuses, and mucosa within the oropharynx and nasopharynx (Fig. 4). These structures also show enhancement on CT with the exception of sinus mucosa which cannot be seen on CT due to its intimate attachment to the overlying bone. The presence of MR enhancement in these areas indicates that Gd-DTPA may prove to be a useful contrast agent for evaluation of extracranial lesions of the head and neck. However, at present our investigative protocol does not allow us to examine these patients with Gd-DTPA and so confirmation of this hypothesis must await future investigations.

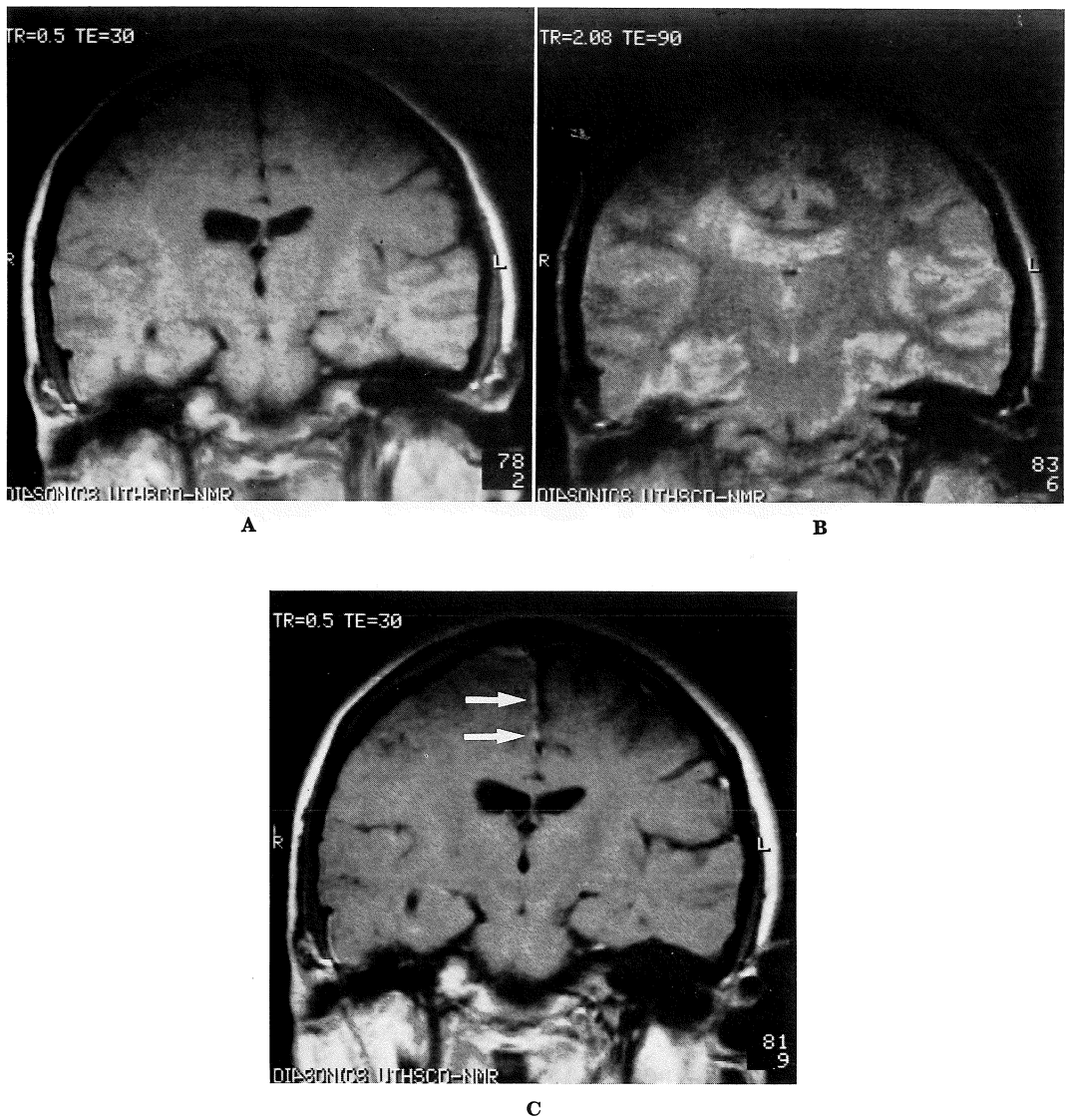


Fig. 3 Patient with a parietal parasagittal meningioma

- A:** Coronal T_1 weighted scan (TR 500, TE 30 msec) shows effacement of the cerebral sulci in the parasagittal region and interhemispheric fissure on the right side.
- B:** T_2 weighted image at the same level (TR 2080, TE 90 msec) shows increased signal intensity within the deep white matter of the cerebral hemisphere representing edema secondary to the patient's meningioma. The interhemispheric fissure does not show any evidence of abnormality.
- C:** Post-contrast T_1 weighted image (TR 500, TE 30 msec) now shows contrast enhancement within the anterior portion of the right parasagittal meningioma and en plaque extension of the tumor along the falx (arrows).

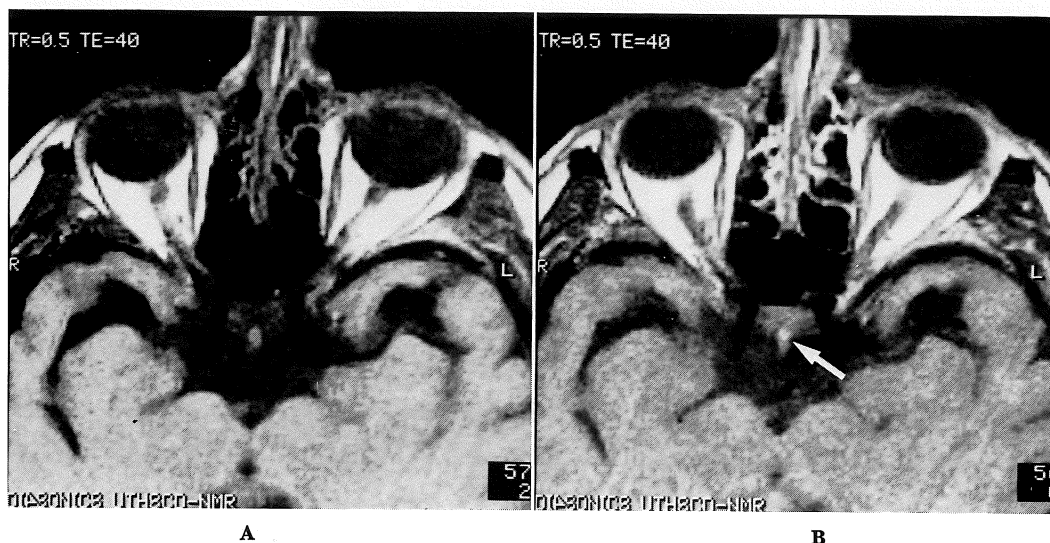


Fig. 4 A: Pre-contrast, axial T_1 weighted image (TR 500, TE 400 msec) through the level of the orbits and ethmoid sinuses shows good demonstration of the normal anatomy of this region.
B: Post-contrast scan with same imaging parameters now shows marked enhancement within the mucosa of the ethmoid sinus air cells. Note also mild enhancement within the pituitary stalk (arrow).

2 Gadolinium in Intracranial Pathology

In evaluating the abnormalities in our patients, we sought to answer several questions. First, is the contrast agent safe in clinical practice? Secondly, did the gadolinium study add significant new information which would increase either the sensitivity of MRI, the specificity, or both? Thirdly, did the MRI study with Gd-DTPA provide the same information as the post-contrast CT scan? Finally, which imaging sequences are needed to provide an optimal study and to get the maximum information?

From the combined early experience of a number of research centers it appears that gadolinium-DTPA is a very safe contrast agent^{(11), (12), (19-21)}. We have had no significant untoward reactions from the injection of contrast material. No patient experienced any subjective symptoms such as nausea, vomiting or flushing. There were no significant changes in respiration, pulse or blood pressure either during or immediately following the injection and no anaphalactoid reactions were encountered. Other investigators have had similar experiences and, to the best of our knowledge, there has been no significant reaction to the use of gadolinium-DTPA.

We carefully analyzed our series of patients to determine if gadolinium-DTPA added diagnostic utility. All of the patients in our series had MR or CT demonstrated abnormalities prior to entry into the study protocol. There were 41 patients who had intracranial tumors and the remain-

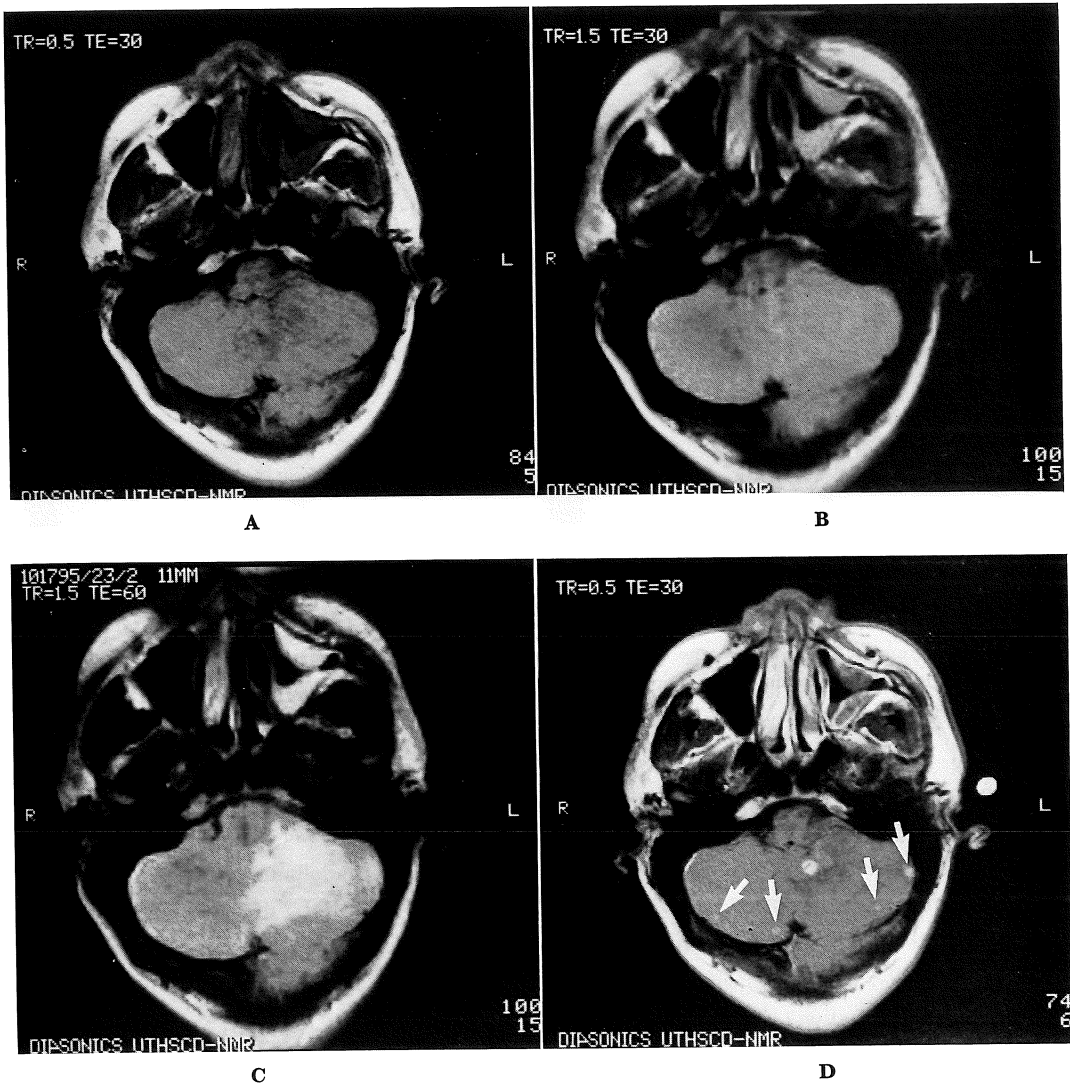


Fig. 5 Pre-contrast MR images of the posterior fossa

- A:** T_1 weighted image (TR 500, TE 30 msec) shows distortion of the left cerebellar hemisphere and ill-defined low signal intensity in the left paravermian region.
- B, C:** Spin density (TR 1500, TE 30 msec) and moderate T_2 weighted (TR 1500, TE 60 msec) images show infiltrative type pattern of increased signal intensity with a long T_2 relaxation time characteristic of intracerebellar edema.
- D:** Post-contrast T_1 weighted image (TR 500, TE 30 msec) permits clear separation between the tumor nodule in the left paravermian region and the large area of edema shown on the pre-contrast T_2 weighted images in B and C. In addition, multiple additional enhancing lesions are seen in both cerebellar hemispheres (arrows). At surgery, these proved to be hemangioblastomas. A contrast enhanced CT scan done prior to the MR image (not illustrated) showed only the largest lesion in the left paravermian region.

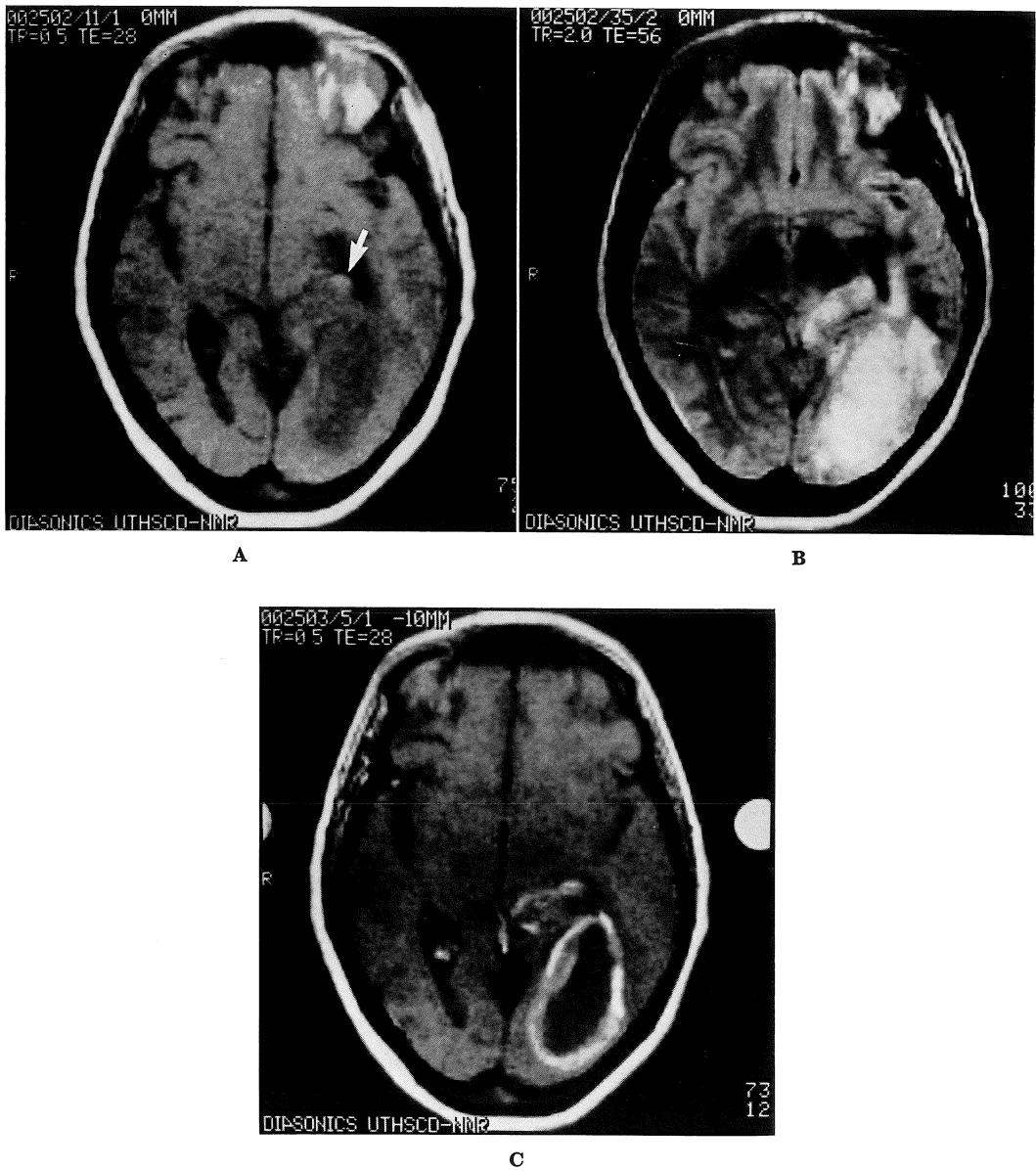


Fig. 6 Glioblastoma multiforme

- A:** Pre-contrast T_1 weighted image (TR 500, TE 28 msec) shows ill defined area of low density in the left occipital region with anterior displacement of the left atrial trigone. Small area of increased signal in the trigonal area (arrow) probably represents a small hemorrhage within the mass.
- B:** Pre-contrast T_2 weighted image (TR 2000, TE 56 msec) shows a large area of increased signal roughly corresponding to the low intensity abnormality on the T_1 weighted image in A.
- C:** Post-contrast T_1 weighted image (TR 500, TE 28 msec) three minutes post injection of gadolinium-DTPA shows enhancing, irregular ring-like pattern which is characteristic for a glioblastoma.

ing 10 patients had a variety of diagnoses including 2 patients with inflammatory disease, 2 with cerebral infarctions, 2 with AV malformations, 2 with postoperative changes, 1 patient with a thrombosed aneurysm, and 1 patient with a calcified intracranial lesion of undetermined etiology. Forty patients demonstrated enhancement on the MR study following the injection of gadolinium-DTPA while the remaining 11 patients did not. Among the patients who showed enhancement, Gd-DTPA often added valuable information in determining the extent of a mass and enabling separation of the mass from surrounding edema^{19),22)}. MR has been disappointing in its ability to separate the nidus of a lesion from perifocal edema in many cases^{23),25)}. In our series there were 17 patients (33%) where it was not possible to determine the boundaries between the lesion and perifocal edema but this was easily determined after the injection of gadolinium (Fig. 5). There was one case with an intraventricular and intracerebral hemorrhage which demonstrated the hemorrhage on the T_1 weighted pre-contrast examination and hemorrhage plus surrounding edema on the T_2 weighted images done pre-contrast. Following the injection of gadolinium, a small area of enhancement was seen adjacent to the hemorrhage and distinct from the perifocal edema. Angiographically this proved to represent a small AV malformation and the contrast enhancement was presumably related to pooling and stasis of blood within the vascular sinusoids of the AVM.

Magnetic resonance imaging is generally recognized as extremely sensitive for the detection of intracranial abnormalities. We therefore were quite surprised in reviewing our series of patients when we found that new lesions were detected following injection of Gd-DTPA in 14 of our 51 patients (27%). These new lesions included 2 patients with metastatic carcinoma in whom additional lesions were demonstrated, 2 patients with multiple hemangioblastomas where several were not seen pre-gadolinium, suprasella seeding from a pineal region germinoma in one case, and 6 cases of leptomeningeal or dural abnormalities which were seen only on the post-contrast MR study. Two of these meningeal cases were proven at surgery to represent leptomeningeal spread of malignant tumor and two patients had en plaque extension of a meningioma along the falx (Fig. 3). Thus, based on our experience, it appears that gadolinium can add increased sensitivity to the MR method in a significant portion of cases.

Although gadolinium-DTPA demonstrates areas of increased permeability of the blood brain barrier and thus is a non-specific contrast agent, it nevertheless provides an added dimension of information that can be used to further characterize a lesion and narrow the differential diagnostic possibilities. This proved especially useful in three types of tumors, namely, meningiomas, glioblastomas, and intracerebral metastases^{26),27)}. In these cases the MR enhancing pattern was often very similar to the characteristic findings that are seen with contrast enhanced CT scans. Of the 6 glioblastomas in our study, all demonstrated abnormal MR scans on their baseline studies. Four of the 6 lesions were poorly defined due to the presence of perifocal edema and none of the 6 patients showed characteristics within the mass which would allow the proper diagnosis to be made on the pre-contrast study. Following the injection of gadolinium-DTPA, all 6 glioblastomas show-

ed excellent contrast enhancement and 4 of the lesions showed the typical, irregular, ring-like pattern of enhancement which is commonly seen on CT and which is characteristic for glioblastoma (Fig. 6).

There were 8 meningiomas in our study and 7 of these lesions were nearly isointense with the underlying brain on both T_1 and T_2 weighted images obtained prior to injection of Gd. All 8 cases demonstrated abnormal baseline scans but in the 7 isointense cases, the lesions were demonstrated by a combination of either mass effect and/or intracerebral edema and a firm diagnosis of meningioma could not be made. One lesion was hyperintense on the T_2 image and, in this case, the appropriate diagnosis and the extent of the lesion could be determined on the pre-contrast study. Following the injection of gadolinium-DTPA, all 8 meningiomas demonstrated excellent contrast enhancement (Fig. 7). The characteristic pattern of an intensely enhancing, extra-axial mass based against a dural surface enabled the correct diagnosis of meningioma to be made in all cases. In one case, despite the fact that the sagittal sinus was patent, the post-contrast study demonstrated tumor extension into the sinus that was not detected on the baseline scan. Two meningiomas also demonstrated en plaque growth along the falx on the post-contrast study that was subsequently proven at surgery.

Prior to our experience with Gd-DTPA, we often obtained contrast enhanced CT studies to obtain complementary information about an abnormality detected on a baseline MRI scan. We were interested as to whether or not this combination of studies could substitute for MRI done with Gd-DTPA by providing the same information. In general, there was good correlation of the presence, pattern of enhancement, and degree of intensity between the contrast CT scan and that seen on the post-gadolinium MR study. However, among the 48 patients who had CT scans available for comparison, there were 12 cases in which additional abnormalities were seen on the post-contrast gadolinium study which were not seen on either the post-contrast CT study or the baseline MRI study. It must be pointed out that in 2 of these cases either no contrast was given for the CT scan or the optimal view (i.e., direct coronal) was not obtained with the CT study. Nonetheless, if we eliminate these 2 cases, there were 10 cases (21%) in which findings on the post-contrast MR study were not visible, even in retrospect, on good quality, contrast enhanced CT scans. This indicates that increased information is obtainable from MR with contrast compared to CT with contrast. Among these patients were two cases in which additional metastatic lesions were found and two cases with multiple hemangioblastomas in which additional tumors were identified (Fig. 5). This group also included the 6 cases of meningeal abnormalities, none of which were seen on the contrast enhanced CT studies (Fig. 8).

Finally, we attempted to determine what imaging sequences proved most useful in evaluating the gadolinium studies. The T_1 weighted images showed the gadolinium enhancement best. Although inversion recovery sequences provide excellent T_1 weighting and have been shown to provide excellent definition of Gd enhancement^(14),28), we preferred to use spin echo techniques with a short TR (500 msec) and short TE (30 msec) because of their efficiency in imaging speed

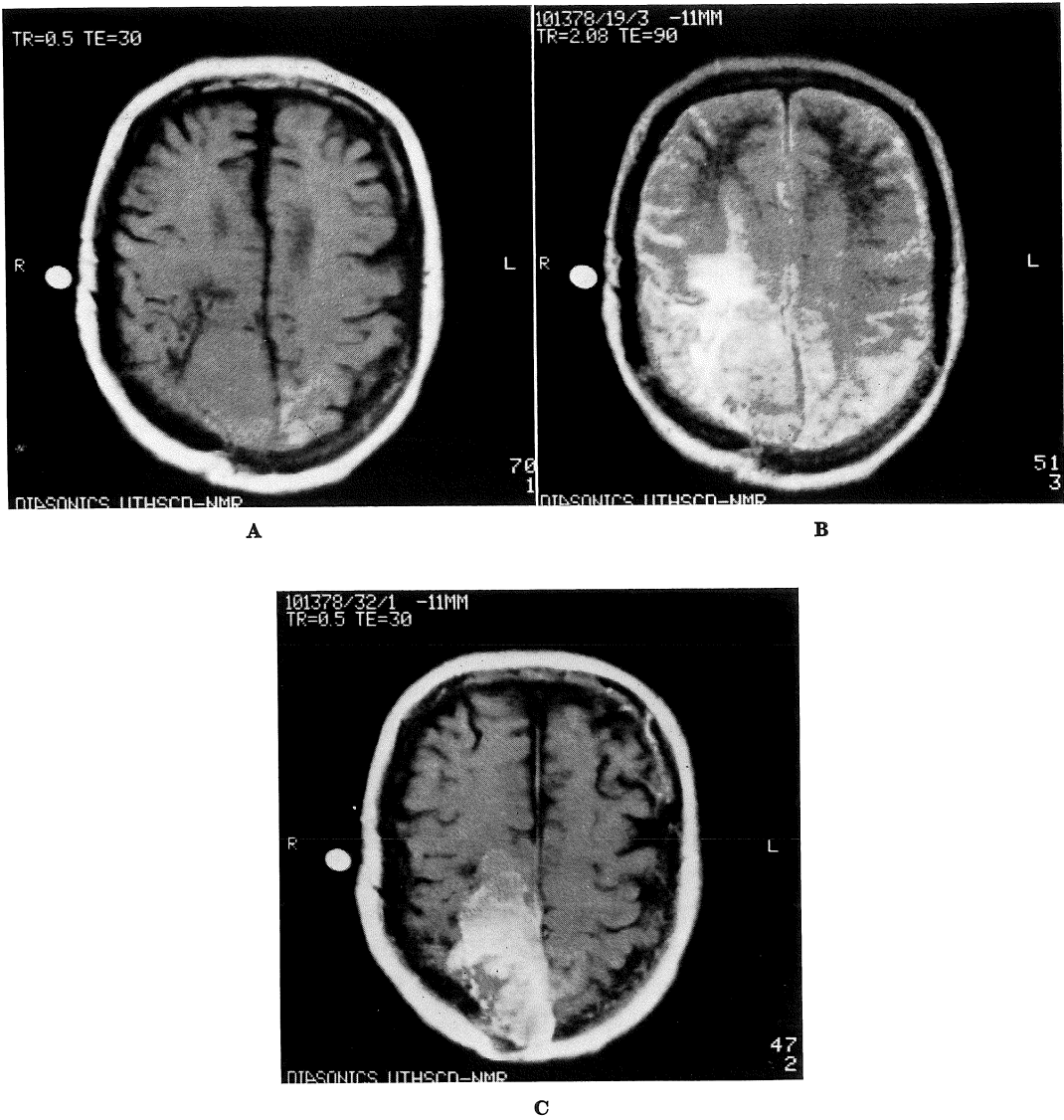


Fig. 7 Parasagittal meningioma

A, B: Pre-contrast T_1 (TR 500, TE 30 msec) and T_2 weighted images (TR 2080, TE 90 msec) demonstrate an ill-defined mass in the right occipital region that is nearly isointense with the surrounding grey matter. Intracerebral edema in the right hemisphere is also noted on the T_2 weighted image. The tumor margins are poorly outlined and the full extent of the tumor cannot be accurately determined.

C: Post-contrast T_1 weighted image (TR 500, TE 30 msec) now demonstrates prominent, irregular enhancement within this recurrent meningioma. The exact extent and margins of the tumor can be defined. In addition, tumor extension along the falx is also identified as abnormal enhancement within this structure. This was not recognized on either the pre-contrast MR studies or a CT scan done with contrast.

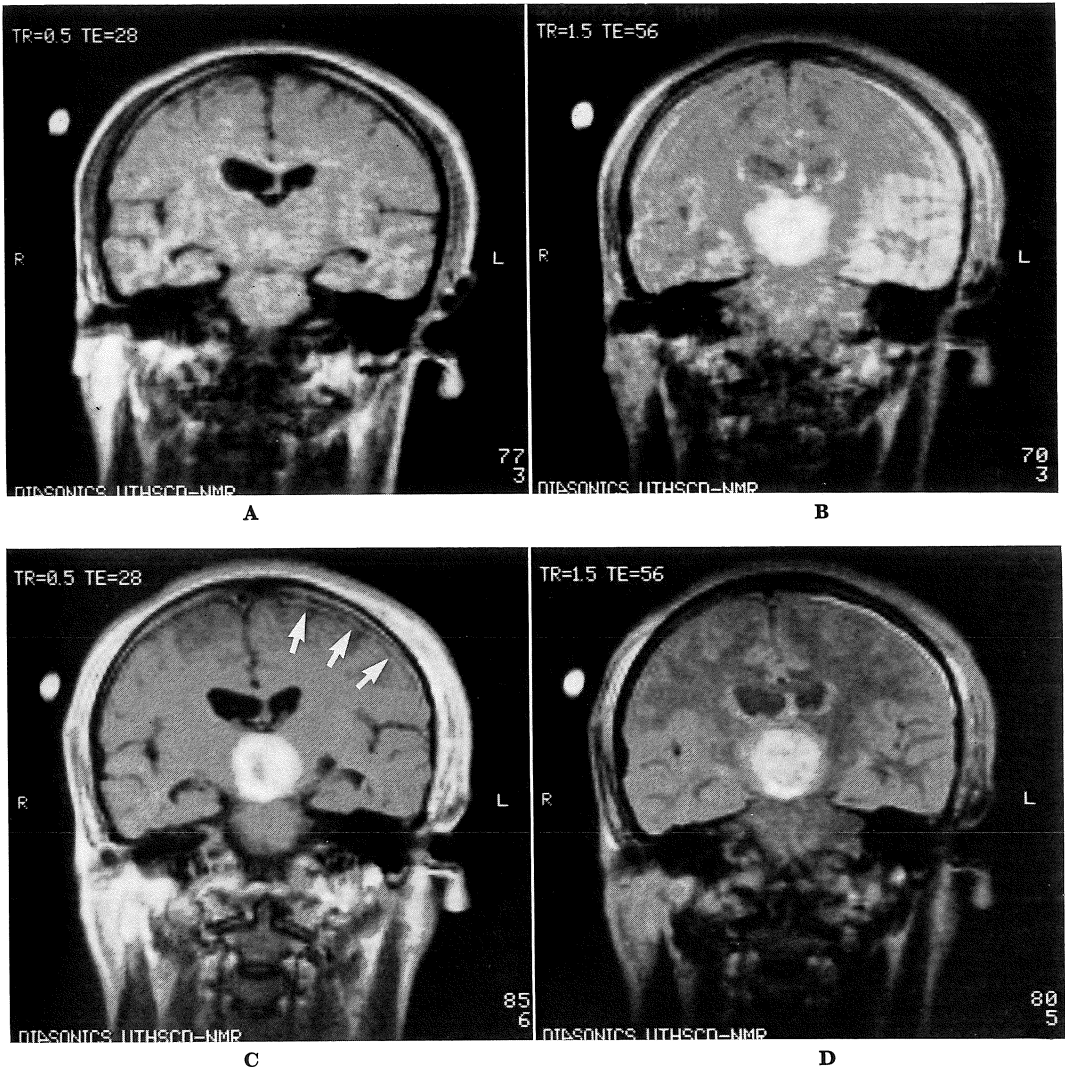


Fig. 8 Leptomeningeal spread of glioblastoma

- A, B:** Pre-contrast T_1 (TR 500, TE 28 msec) and T_2 weighted images (TR 1500, TE 56 msec) shows a mass within the third ventricle and diencephalon. Curvilinear bright and dark lines paralleling the inner table of the skull on both sides on the T_2 weighted image represents phase encoding artifacts secondary to slight patient motion.
- C:** Post-contrast T_1 weighted image (TR 500, TE 28 msec) now shows good enhancement within the diencephalic mass. There is a faint area of increased signal along the surface of the left cerebral hemisphere (arrows) which was not present on the pre-contrast T_1 image in A.
- D:** Post-contrast T_2 weighted image (TR 1500, TE 56 msec) now shows obvious area of abnormally increased signal over the surface of the left cerebral hemisphere. This is better shown on the T_2 weighted image than on the T_1 weighted image probably secondary to addition of T_1 and T_2 effects from the gadolinium and the tumor. This represents a glioblastoma with spread over the leptomeningeal surface of the left hemisphere.

and the ability to obtain more multislice sections. We also found, however, that it was useful to perform a T_1 weighted sequence before the injection of gadolinium to determine what portions of a lesion enhance and what portions might have a short T_1 relaxation time on the baseline study due to hemorrhage or fat within the lesion, such as illustrated in Figure 6A of a patient with hemorrhage within a glioblastoma. This baseline comparison study proved especially useful for cases in which there was only minimal contrast enhancement on the post-gadolinium study. Finally, it was necessary in all cases to have a T_2 weighted sequence in order to define perifocal edema which is often not visible or poorly visible on the T_1 weighted images. The T_2 sequence is also necessary to demonstrate lesions which do not show enhancement on the post-gadolinium T_1 studies.

We encountered four cases in our series in which the T_2 weighted image post-contrast injection showed enhancement better than the T_1 weighted image. In all cases the lesions showed minimal contrast enhancement on the T_1 weighted images but showed unequivocal, moderately intense signal on the post-contrast images obtained with a long TR sequence that was not present on the long TR baseline images (Fig. 8). This enhancement effect was best appreciated on the long TR (1500–2000 msec) and short TE (30 or 60 msec) images which are spin density weighted or mildly T_2 weighted. We feel that this result is due to the addition of the T_1 effects from Gd together with a minimal increase in either T_2 or spin density within the lesion. For example, if there is a slightly prolonged T_2 relaxation time within the lesion that is not significantly altered following the injection of gadolinium and, at the same time, the T_1 relaxation time is mildly decreased post-gadolinium, then the addition of the shortened T_1 with the minimally prolonged T_2 results in a more marked signal increase on the spin density weighted image. Thus, in those cases in which the gadolinium enhancement is minimal or equivocal on the post-contrast T_1 weighted image, it may be useful to also obtain a post-contrast T_2 study. Otherwise, the recommended protocol, at this point in our experience, consists of T_1 and T_2 weighted sequences obtained pre-contrast together with a post-contrast T_1 weighted sequence.

6 Conclusion

Based on early clinical trials, it appears that gadolinium will prove to be a clinically useful contrast agent for magnetic resonance imaging of the central nervous system. In our series, the use of gadolinium-DTPA caused a significant increased sensitivity of the MR study as evidenced by the fact that new abnormalities were found in 27% of our cases. Furthermore, MRI performed with Gd-DTPA adds an additional dimension of information about a lesion which helps characterize the abnormality and thus adds specificity to the diagnosis. MR with Gd has also proved useful in the separation of a mass from perifocal edema in nearly 30% of our cases. The MR study performed with Gd-DTPA was also able to provide more diagnostic information to the baseline MR study than was possible by combining routine MR with contrast enhanced CT.

Gadolinium-DTPA is a first generation contrast agent which enhances areas of increased blood brain barrier permeability. No doubt in the future we will see more sophisticated contrast agents which can target specific organs and/or specific disease processes. With the development of such agents, which may take the form of compounds bound to monoclonal antibodies or to biochemical precursors, it will be possible to further improve the specificity of the MR technique.

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