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Gadolinium-DTPA and MR Imaging of Pituitary Adenoma: A Preliminary Report

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Gadolinium-DTPA MR imaging (Gd-MR), unenhanced MR imaging, and contrast-enhanced CT studies were compared prospectively in six patients with surgically confirmed pituitary adenomas and three patients without sellar pathology to determine the utility of Gd-MR in the diagnosis of pituitary adenoma. In normal patients, the pituitary gland, cavernous sinus, and infundibulum enhanced by T1 shortening after gadolinium. In adenoma patients, two of four focal lesions identified with contrast-enhanced CT were identified with Gd-MR, and one was identified with unenhanced MR. The earliest short repetition-time sequence performed after gadolinium injection was best for focal lesion detection. Normal cavernous sinus enhancement by gadolinium made identification of cavernous sinus extension of adenoma difficult. Infundibulum displacement was better seen with contrast-enhanced CT (two vs one); however, unenhanced and Gd-MR were better than contrast-enhanced CT for demonstrating chiasmal compression (four vs three). Contrast-enhanced CT, Gd-MR, and plain MR were equally able to identify gland enlargement, sellar floor erosion, and abnormalities of the diaphragma sellae.

In this preliminary series, we found Gd-MR to be promising for imaging adenomas; however, modifications in Gd-MR technique including thinner slices and immediate scanning after gadolinium injection are necessary for the best detection of focal lesions.

Several recent series describing the MR appearance of pituitary adenoma have confirmed the utility of MR in defining and localizing macroadenomas [1-6]. Although the mass effect and displacement of adjacent structures caused by macroadenomas are well seen, the macroadenoma itself is not distinguishable from the normal pituitary gland. Microadenomas have been demonstrated with MR, but no series has convincingly shown that MR is equivalent to or superior to contrast-enhanced CT for the detection of microadenomas. Indeed, focal lesions seen readily with contrast-enhanced CT may be inapparent with MR [6, 7].

Gadolinium DTPA/dimeglumine is an IV paramagnetic contrast agent that has utility in differentiating tumor from edema in intracranial tumors [8-10]. Its efficacy in defining pituitary adenomas is largely unknown. In this series, a preliminary prospective study was completed in an attempt to determine the role of gadolinium DTPA/dimeglumine and MR in diagnosis of pituitary adenoma.

Subjects and Methods

Six patients (four women, two men, 21-73 years old) with clinical, laboratory, enhanced CT, and surgical proof of pituitary adenoma and three patients without evidence of sellar pathology (one woman, two men, 25-37 years old) were evaluated with pre- and postgadolinium MR scans. All patients were evaluated as part of a phase III investigational drug protocol (Berlex, Inc.) with approval by the Human Investigations Committee and informed patient consent.

Gadolinium DTPA/dimeglumine (Berlex, Inc.) is a paramagnetic contrast agent evaluated in clinical trials as a phase III investigational drug for patients with intracranial tumors. Prior studies with gadolinium demonstrated a favorable margin of safety compared with other

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contrast agents. Gadolinium DTPA/dimeglumine is excreted in the urine without metabolic conversion. Its primary use is in enhancement of tissue abnormalities (tumor, inflammation, infarcts) by shortening the T1 (spin-lattice) relaxation time of hydrogen nuclei [11-13].

Gadolinium DTPA/dimeglumine was administered intravenously (0.1 mmol/kg) after preliminary clinical, laboratory, and neurologic evaluations. Additional laboratory studies, and clinical and neurologic examinations were completed 24 hr after injection. Patients tolerated gadolinium DTPA well, and no significant ill effects or permanent sequelae were seen.

MR examinations were completed before and after gadolinium with timing of scans and pulse sequences set by protocol and using a 1.5-T superconducting magnet (Philips) operating at 0.5 T. Spin-echo pulse sequences included pre- and postgadolinium studies with a short repetition time (TR) of 550 msec and echo time (TE) of 30 and 60 msec and a long TR (TR = 2000 msec, TE = 30 and 60 msec). One adenoma patient was studied with a fast-field echo sequence with a TE of 13 msec and TR of 250 msec before gadolinium, and as the first sequence after gadolinium injection. In this patient, the long TR postgadolinium sequence was omitted. Coronal 5-mm multislice (0- to 1-mm tissue gap) images with two acquisitions were completed through the sella. Adenoma patients were studied with two postinjection studies taken for each of the TR = 550 and TR = 2000 sequences. The postinjection time of each sequence was defined as the midpoint of that acquisition. The first TR = 550 sequences in patients with adenomas were acquired with a mean postinjection time of 16 min (range, 5-31 min); the mean time between the first and second TR = 550 sequence was 30 min (range, 15-53 min). The first TR = 2000 sequences were acquired with a mean postinjection time of 28 min (range, 18-40 min); the mean time between the first and second TR = 2000 sequences was 28 min (range, 12-50 min).

All adenoma patients had an enhanced CT study before the MR examinations; 1.5- to 2-mm collimation was used, which demonstrated abnormalities compatible with adenoma. Five patients were studied with direct coronal scans; one elderly patient who could not tolerate a direct coronal study was evaluated with axial images only. The three patients without sellar pathology had abnormal axial enhanced CT scans for intracerebral neoplasia and no evidence of pituitary abnormality.

Enhanced CT, Gd-MR, and plain MR parameters evaluated included gland height, presence of a focal lesion, size of focal lesion, infundibulum position, configuration of the diaphragma sellae, cavernous sinus invasion, and sellar floor erosion. For comparison purposes,

a generally convex diaphragma sellae with a normal gland height (less than 9.7 mm) was considered normal [14-16].

All adenoma patients underwent transsphenoidal exploration. Operative notes were used for an estimate of the size and location of adenoma, location of normal gland, and status of the sellar floor. The cavernous sinus was not explored as part of a transsphenoidal procedure; thus, no operative confirmation is available for the status of the cavernous sinus. All adenomas are histologically confirmed and graded for degree of cellular pleomorphism, perivascular exudation, calcification, and true hemorrhage within the adenoma (scale: absent, equivocal, 1+ to 4+).

Results

In the three patients without sellar pathology, the pituitary gland on plain MR appeared homogeneous and had an intensity approximately equivalent to that of cortex. After gadolinium injection, the cavernous sinus, pituitary gland, and infundibulum increased in intensity consistent with T1 shortening on all pulse sequences (Fig. 1). On the earliest postgadolinium study (mean, 3.5 min after injection) in patients without sellar disease, the intensity of pituitary gland varied from slightly hyper- to slightly hypointense compared with the adjacent enhancing portions of the cavernous sinus. The pituitary gland, infundibulum, and cavernous sinus were isointense with one another on the second and later gadolinium studies as late as 90 min after gadolinium. No focal lesions or sellar pathology were detected.

Three patients with microadenomas (mean diameter, 7.9 mm) were evaluated (Table 1). All three had focal hypodense lesions on enhanced CT. These correlated with the surgical site of the microadenoma. One prolactin-secreting adenoma, one ACTH-secreting adenoma, and one growth-hormone-secreting adenoma were in this group. On plain MR, one microadenoma resulted in a focal lesion that was hypointense to normal gland on a heavily T1-weighted sequence (TR = 250 msec, TE = 13 msec). This lesion was slightly hyperintense to normal gland on the TR = 550 msec, TE = 30 msec sequence, but increased further in intensity on the TR = 2000 msec, TE = 30 msec sequence, indicating a long T1. In addition, its intensity increased with later echoes, suggesting a long T2, as confirmed by region-of-interest measurements.

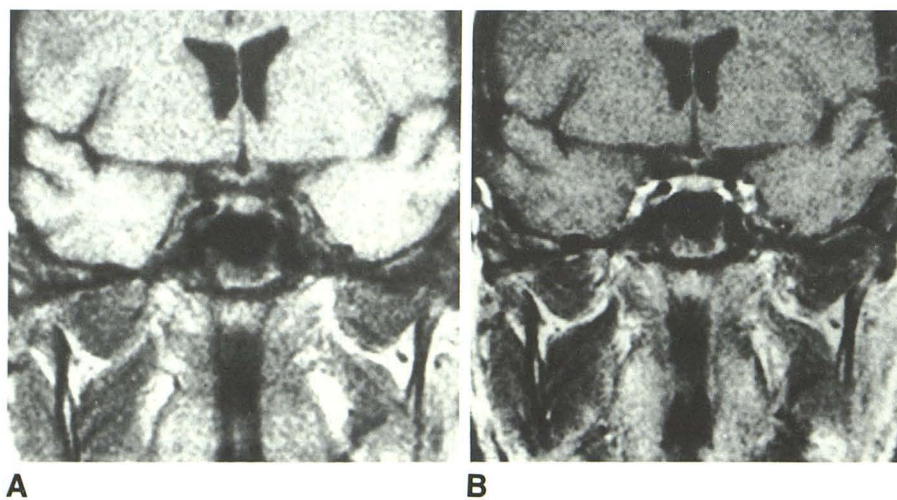


Fig. 1.—A, Unenhanced MR image (TE = 30 msec, TR = 550 msec) of sella in patient with no evidence of sellar pathology.

B, After gadolinium administration (TE = 30 msec, TR = 550 msec). Normal pituitary gland, cavernous sinus, and infundibulum enhanced by T1 shortening.

TABLE 1: Comparison of Sellar Abnormalities Detected by Contrast-Enhanced CT, Gadolinium MR, and Unenhanced MR

Abnormality	Hormone Secreted						Total
	Micro-adenoma			Macro-adenoma			
	PRL	ACTH	GH	PRL	NF	GH	
Size (mm)	9	7	9	12	20	20	
Focal lesion:							
Contrast-enhanced CT	+	+	+	+	—	—	4
Gadolinium MR	+	+	—	—	—	—	2
Unenhanced MR	+	—	—	—	—	—	1
Sellar floor erosion:							
Contrast-enhanced CT	—	—	—	+	+	+	3
Gadolinium MR	—	—	—	+	+	+	3
Unenhanced MR	—	—	—	+	+	+	3
Abnormal diaphragma sellae:							
Contrast-enhanced CT	+	+	—	+	+	+	5
Gadolinium MR	+	+	—	+	+	+	5
Unenhanced MR	+	+	—	+	+	+	5
Cavernous sinus invasion ^a :							
Contrast-enhanced CT	—	—	—	—	+	I	1
Gadolinium MR	—	—	—	—	+	—	1
Unenhanced MR	—	—	—	—	I	—	0
Infundibulum displacement:							
Contrast-enhanced CT	+	—	—	+	—	—	2
Gadolinium MR	—	+	—	—	—	I	1
Unenhanced MR	—	+	—	—	—	I	1
Chiasmal compression:							
Contrast-enhanced CT	—	—	—	+	+	+	3
Gadolinium MR	+	—	—	+	+	+	4
Unenhanced MR	+	—	—	+	+	+	4

Note.—PRL = prolactin; ACTH = adrenocorticotrophic hormone; GH = growth hormone; NF = nonfunctioning; + = positive; - = negative; I = indeterminate.

^a Cavernous sinus extension was suspected on one or more study but was not proven surgically.

This lesion contained microscopic foci of old hemorrhage without evidence of cystic necrosis; however, the long T1 and T2 on MR indicated either that minimal hemorrhage was present or that it was obscured by volume-averaging of adjacent nonhemorrhagic tissue. At 19 min after gadolinium, this lesion remained hypointense while the surrounding normal gland enhanced by T1 shortening on the fast-field echo sequence (TE = 13 msec, TR = 250 msec) (Fig. 2). The other microadenoma patients had homogeneous sellar contents that were approximately isointense with cortex on unenhanced MR. After gadolinium, one additional focal lesion was identified as a hypointense lesion in contrast to the enhancing normal gland on the first postgadolinium short TR sequence (19 min after injection) (Fig. 3). The two focal lesions identified on initial short TR postgadolinium studies were not visible on delayed short or long TR postgadolinium images. On the later sequences, the focal lesions and pituitary gland were isointense with one another and approximately isointense with the cavernous sinus.

Three patients were evaluated with macroadenomas 12–20 mm in diameter (Table 1). Adenoma types included prolactin-secreting (one), growth-hormone-secreting (one), and nonfunctioning (one). Of these, only one resulted in a discrete focal hypodense lesion on contrast-enhanced CT; it correlated surgically with a 12-mm adenoma. The sellar contents were

enlarged in all cases, and two patients had enlargement of the cavernous sinus suggesting cavernous sinus invasion.

On unenhanced MR, gland enlargement was visible in all three macroadenomas, with the intrasellar contents approximately isointense with cortex on all sequences. No focal lesions were identified. After gadolinium, the intrasellar contents, cavernous sinus, and infundibulum enhanced, with no detectable differences in intensity between adenoma and normal gland on short or long TR sequences (Fig. 4). Gadolinium enhancement resulted in increased contrast between sellar and cavernous sinus tissues and adjacent CSF and brain parenchyma; thus, the mass effect of sellar lesions was more apparent. In one patient with slight enlargement of the cavernous sinuses bilaterally on enhanced CT, the cavernous sinuses were unremarkable on plain MR and Gd-MR. In the second patient, unilateral cavernous sinus invasion suspected on enhanced CT correlated with asymmetry in appearance of the cavernous sinus on plain MR and Gd-MR (Fig. 5). This asymmetry was more apparent before gadolinium than afterward because of normal enhancement of the cavernous sinus.

After evaluation of the MR findings, calculations of the change in T2 were made (calculated with region-of-interest intensity measurements at 30 and 60 msec) for adenoma, normal gland, gray matter, and white matter vs time after gadolinium injection. A decrease in T2 of adenoma was identified on early sequences in all patients, with the final T2 value always less than the pregadolinium value (Fig. 6). No consistent change was identified in T2 of gray or white matter or of normal gland after gadolinium.

Changes in intensity vs time on short TR sequences were plotted with a region-of-interest cursor for adenoma and for normal gland. On early postinjection studies, the intensity of normal gland and adenoma increased consistent with shortening of T1. On later sequences, the intensity of gland and adenoma decreased or stabilized in four patients. In one patient the intensity of adenoma increased to 35 min after injection; however, later studies were not performed.

In this series, only one patient had received bromocriptine therapy; this was discontinued about 3 months before MR and CT examination. This adenoma was indistinguishable by CT, plain MR, Gd-MR, of histology from other lesions in the study.

An attempt was made to correlate the MR appearance with histologic characteristics of the adenoma. It has been suggested that perivascular exudation, a perivascular accumulation of fluid that eventually leads to fibrosis, is related to the bromocriptine effect [17–19]. This was equivocally present in five patients, four of whom were never treated with bromocriptine. One patient with 2+ perivascular exudation histologically had not received bromocriptine. No correlation could be made between the degree of perivascular exudate histologically and the pre- or postgadolinium MR intensity of adenoma. Confirmed hemorrhage within adenoma was identified histologically in two cases; neither of these adenomas had characteristic MR findings expected for subacute or chronic hemorrhage, presumably because of the small amount of hemorrhage present or volume-averaging of adjacent nonhemorrhagic tissue. The degree of cellular pleomorphism was variable and resulted in no consistent change in MR intensity.

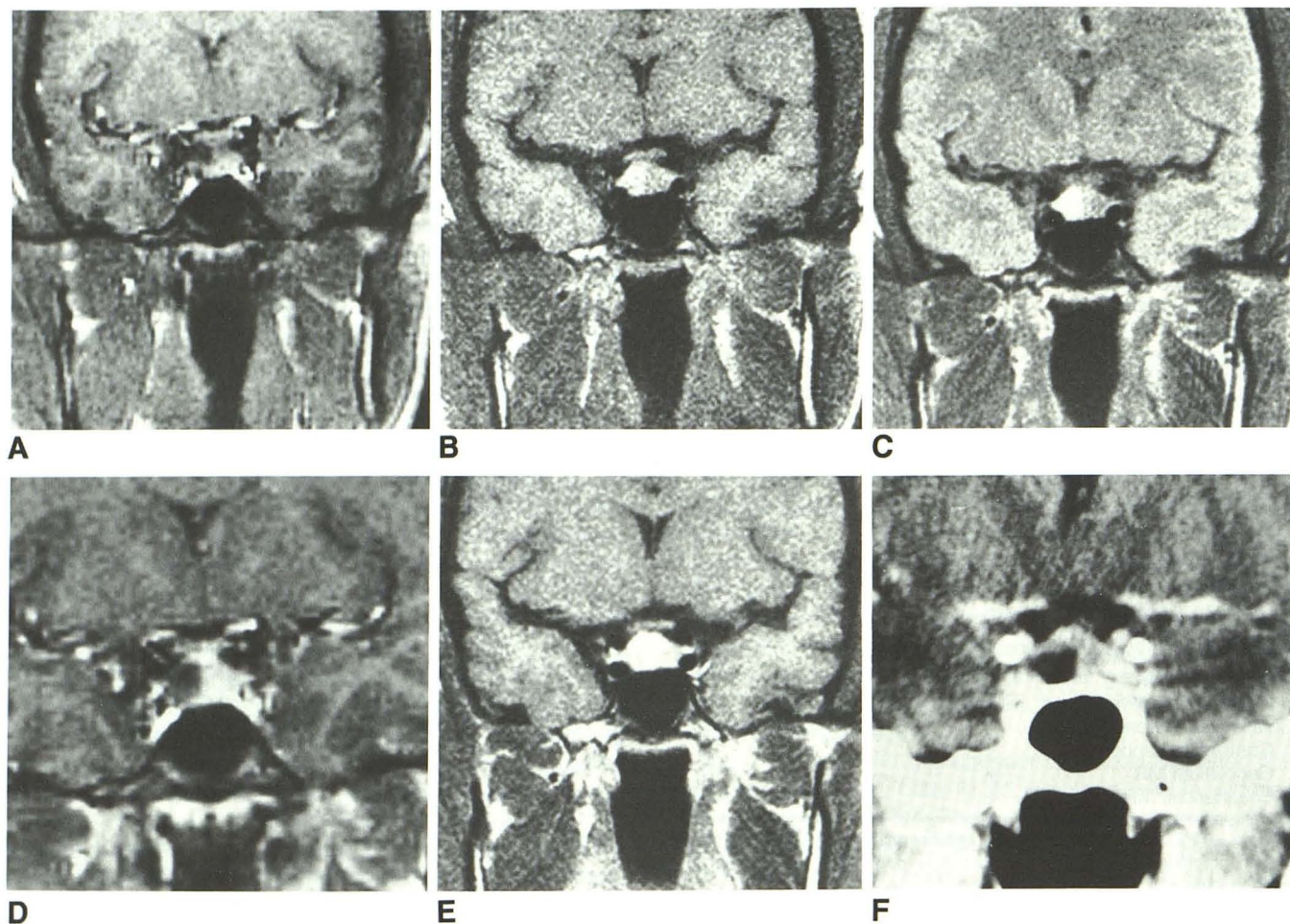


Fig. 2.—A, Unenhanced MR image (TE = 13 msec, TR = 250 msec). Hypointense focal lesion.
 B, Unenhanced image (TE = 30 msec, TR = 550 msec). Lesion is slightly hyperintense relative to normal gland.
 C, TE = 30 msec, TR = 2000 msec. Increased intensity indicates long T1. Focal lesion also increased in intensity with lengthening of TE (TE = 30–60 msec), indicative of long T2 (not shown).
 D, Fast-field echo sequence (TE = 13 msec, TR = 250 msec) 19 min after injection of gadolinium. Focal lesion is nonenhancing lesion relative to enhancing normal gland.
 E, 34 min after gadolinium (TE = 30 msec, TR = 550 msec). Focal lesion seen previously is seen no longer.
 F, Contrast-enhanced CT shows discrete right-sided focal lesion.

ties. No calcification was detected histologically, and none was suspected on MR or CT.

Discussion

Experience is limited with high-resolution MR vs CT or surgery of proven pituitary adenomas, particularly of microadenomas. Early reports were encouraging for the imaging of macroadenomas [1–5]; however, these studies were largely performed with 10-mm slices and a sagittal or axial plane. With higher resolution MR examinations (2- or 5-mm slices, coronal positioning), greater lesion definition and more accurate depiction of the extent of disease are achieved [6, 7]. For macroadenoma evaluation, mass effect and chiasmal compression from large adenomas are apparent on MR. The normal pituitary gland, however, is indistinguishable from adenomatous tissue.

Demonstration of microadenomas is difficult with MR. Al-

though lesions readily apparent on enhanced CT have also been identified with MR, we and others have encountered false-negative MR studies in patients with definite lesions on enhanced CT [6, 7] and false-negative enhanced CT examinations in proven microadenoma [20, 21]. In addition, in our experience MR has added little to the evaluation of patients with suspected microadenoma who have normal or inconclusive enhanced CT studies [6].

Iodinated contrast material has proven helpful in the evaluation of pituitary lesions with CT because the pituitary gland is outside the blood-brain barrier. Immediately after administration of intravascular contrast material, the normal pituitary gland enhances more rapidly than some adenomas [22], resulting in a focal hypodense lesion on enhanced CT. With delayed imaging, a discrete focal lesion may become isodense with the normal pituitary gland [22]. In the absence of a focal hypodense lesion, high-resolution, thinly collimated enhanced

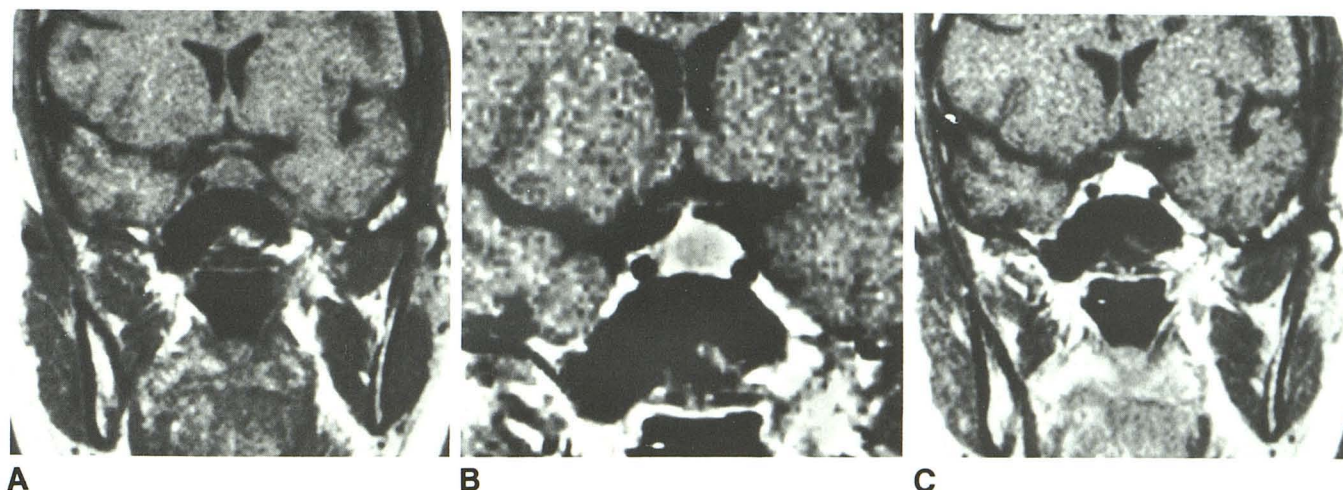


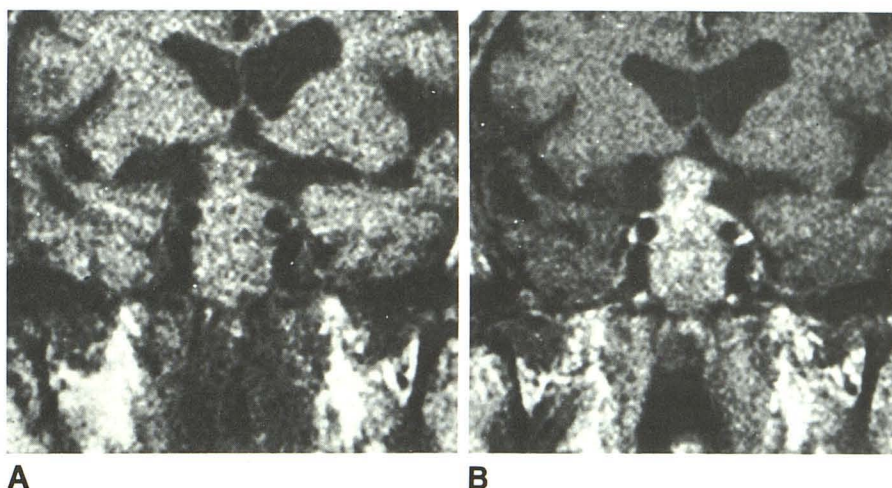
Fig. 3.—A, Unenhanced MR image (TE = 30 msec, TR = 550 msec) fails to show focal lesion, although slightly hypodense focal lesion had been seen on contrast-enhanced CT. Mass effect, gland enlargement, and right infundibulum displacement are apparent.

B, Early gadolinium MR image 19 min after injection (TE = 30 msec, TR = 550 msec) shows subtle midline hypointense focal lesion.

C, Later sequence (TE = 30 msec, TR = 550 msec). Focal lesion is no longer apparent.

Fig. 4.—A, Unenhanced MR image (TE = 30 msec, TR = 550 msec). Mass effect and extension into suprasellar cistern and sphenoid sinus are apparent in this macroadenoma.

B, After gadolinium (TE = 30 msec, TR = 550 msec). Contrast between adenoma and adjacent brain in suprasellar cistern is increased. In addition, adenomatous tissue in sphenoid sinus has enhanced.



CT images permit visualization of subtle mass effect (focal convexity of the diaphragma sellae, infundibular displacement, or sellar floor erosion).

Gadolinium DTPA/dimeglumine is a paramagnetic contrast agent with utility in enhancement by T1 shortening of tissues with a disrupted blood-brain barrier or those outside the blood-brain barrier. Gadolinium DTPA/dimeglumine is handled in vivo similarly to iodinated contrast material; thus gadolinium would be expected to improve the accuracy of MR for adenoma detection. Coronal gadolinium MR examinations in patients without apparent sellar disease in this series confirmed the enhancement by T1 shortening of the normal pituitary gland, infundibulum, and cavernous sinus.

Key questions concerning Gd-MR for the diagnosis of adenoma include its use in detecting focal lesions, cavernous sinus invasion, chiasmal compression, and diaphragma sellae

abnormalities. In addition, the safety of Gd-MR and its role in the differential diagnosis of sellar masses must be determined.

In this series Gd-MR failed to demonstrate one of three microadenomas that were recognizable with enhanced CT; however, this may reflect the technique of examination rather than an inherent limitation of gadolinium. The two focal lesions that were detectable with gadolinium MR became isointense with normal gland on delayed images, as expected from enhanced CT studies [22]. This delay in gadolinium enhancement of adenoma compared with normal gland on early studies suggests that MR imaging immediately after gadolinium injection might improve detection of focal lesions by preferential early enhancement of the surrounding normal gland and delayed gadolinium uptake in adenoma, as is seen with iodinated contrast material. In addition, by protocol in this study, 5-mm slices were used; these relatively thick slices

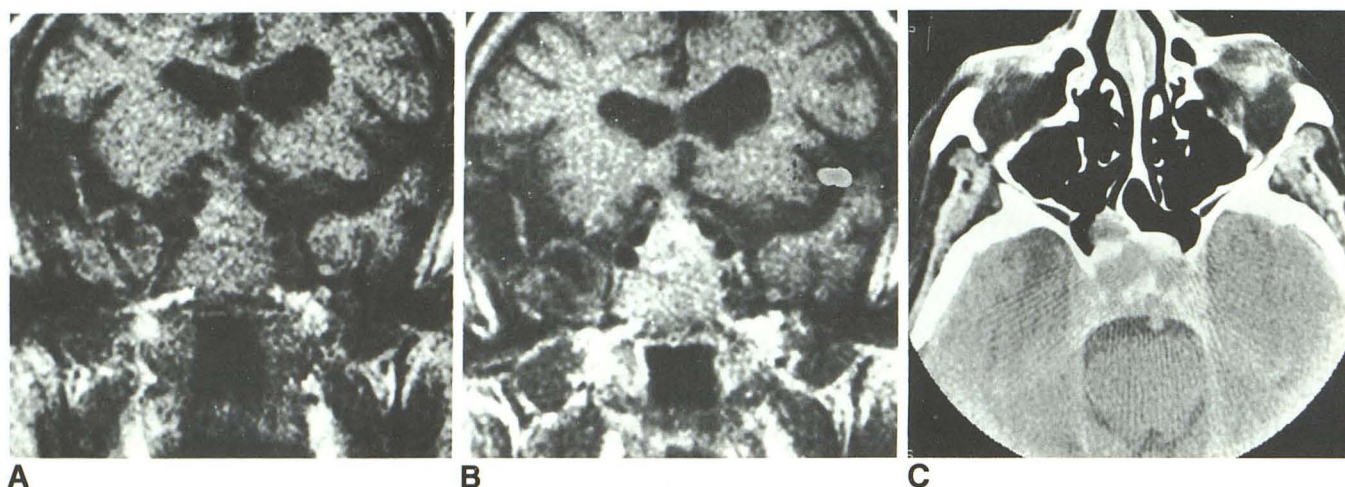


Fig. 5.—A, Unenhanced MR image (TE = 30 msec, TR = 550 msec) shows asymmetry of right cavernous sinus anteriorly. B, After gadolinium (TE = 30 msec, TR = 550 msec). Enhancement of cavernous sinus and adenoma renders asymmetry on right more difficult to appreciate. C, Axial contrast-enhanced CT scan (2 mm) shows greater adenoma extension into sphenoid sinus and anterior cavernous sinus on right.

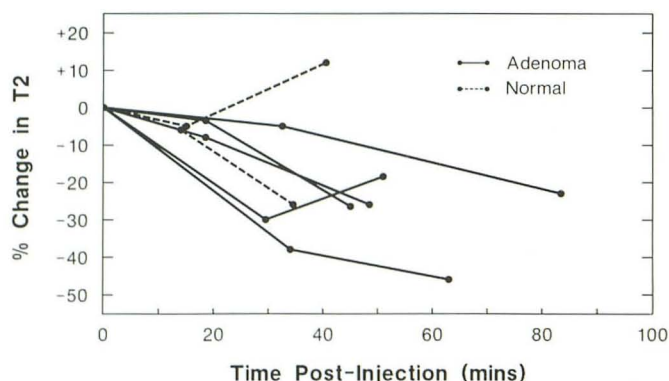


Fig. 6.—Percentage change in T2 is plotted (y axis) against time after gadolinium injection (x axis) for adenoma and normal pituitary gland.

could mask small lesions because of averaging of adjacent tissues. The major effect of gadolinium is T1 shortening; hence, a very strongly T1-weighted sequence should optimize the paramagnetic contrast achieved with gadolinium. This was confirmed in one patient in whom a fast-field sequence with a very short TE and TR on the first postgadolinium study convincingly demonstrated a focal nonenhancing microadenoma contrasted against the enhanced normal gland. A stronger magnetic field (that is, 1.5 T) might also be advantageous for focal lesion detection because of the improved signal-to-noise ratio.

Gd-MR and plain MR were diagnostically equivalent for evaluation of gland size, infundibulum position, and sellar floor abnormalities. Gd-MR resulted in greater contrast between the intrasellar contents and adjacent CSF and brain; thus, the extent of a macroadenoma was more apparent. Gadolinium enhancement of both the normal cavernous sinus and ade-

noma rendered invasion by adenoma more difficult to identify in one case.

With Gd-MR, no focal lesions were identified that were not detected by enhanced CT. In part this may have been from a delay between gadolinium administration and scanning, although, based on enhanced CT studies [20, 21], proven adenomas frequently result in few or no radiographic abnormalities. An adenoma is a benign proliferation of a normal cell type encountered in the pituitary gland; thus, it is reasonable that an adenoma might be similar to normal gland in intensity, attenuation, and degree of contrast enhancement with iodinated contrast material or gadolinium DTPA.

Gadolinium DTPA/dimeglumine is probably safer than iodinated contrast material because of the reduced osmotic load, chelation with DTPA, and the low dose administered. Gd-MR also eliminates radiation and the difficult coronal positioning required with enhanced CT. Disadvantages of MR for sellar studies include a loss in signal resulting in a noisy image, particularly with short TR thin slices, sensitivity to patient motion, and variable signal effects from calcium.

An attempt was made to explain the variable appearances of adenomas on pre- and postcontrast MR on the basis of histologic information. Subacute or chronic hemorrhage was suspected in one patient because of hyperintensity on all spin-echo pulse sequences. This MR appearance was misleading, however, and actually reflected a persistent T2 influence caused by a TE of 30 msec. A second patient with histologic hemorrhage had no MR characteristics typical of hemorrhage, perhaps due to the small amount of hemorrhage present or averaging with nonhemorrhagic tissue. Other histologic characteristics and prior bromocriptine therapy had no identifiable correlation with pre- or postgadolinium MR intensities.

In summary, this small preliminary series raises many questions concerning the role of Gd-MR in the diagnosis of pituitary adenoma. Gd-MR examinations were performed according to

an investigational protocol designed primarily for intraaxial lesions; thus, pulse sequences and timing of images were probably not the best for adenoma detection. Very strongly T1-weighted sequences and minimal delay between gadolinium administration and scanning may improve focal lesion detection. Immediate postinjection scanning might also permit differentiation between cavernous sinus invasion by adenoma and normal cavernous sinus enhancement by gadolinium. The role of Gd-MR for differential diagnosis of sellar lesions has yet to be determined. At this early stage of investigation, no conclusive comparisons can be made between Gd-MR and enhanced CT for adenoma diagnosis and detection; however, our preliminary observations are encouraging and warrant further study.

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