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Time-Dependent Changes in Image Contrast in Brain Tumors After Gadolinium-DTPA

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Time-dependent changes in the contrast enhancement of tumor tissue, tumor necrosis, perifocal edema, and normal brain tissue after IV injection of 0.1 mmol gadolinium-DTPA/kg body weight were studied with spin-echo technique (SE 800/35) in 15 patients with intracranial tumors. Using a region of interest technique, we determined the signal-intensity values of these tissues before and at fixed times up to 68.5 min after administration of the contrast agent. In tumor tissue, the 8.5 min postinjection (p.i.) scan showed a significant increase in signal intensity. The signal intensity of the tumor tissue remained significantly higher than precontrast levels throughout the entire period of observation, decreasing only slightly toward the end of the examination (48.5 and 68.5 min p.i.). Central tumor necrosis exhibited a delayed uptake of the contrast agent, with a maximum signal intensity between 48.5 and 68.5 min p.i. In perifocal edema and normal brain tissue, slight increases in signal intensity after injection of gadolinium-DTPA were measured (statistically significant in the case of edema). This effect, however, was not visually detectable. The present study shows that after one injection, scans with excellent tumor visualization can be obtained between 8.5 and 38.5 min p.i. and with diagnostically valid enhancement at least up to 68.5 min p.i.

MR imaging is becoming increasingly important in the diagnosis of cerebral disorders, [1–5]. Despite the high level of contrast, which is one of the prime advantages of MR as compared with CT, there are various clinical situations in which a contrast agent may be required. It may for example be difficult, especially in the case of brain tumors, to differentiate between the tumor and the perifocal edema, even using various pulse sequences [6–9]. On the basis of the experiences with CT, several authors view this as an indication for an MR-specific contrast medium [1, 9].

Paramagnetic substances can be used as MR contrast agents. Owing to their strong local magnetic fields, they reduce the relaxation times of the surrounding tissue [10]. With appropriate imaging sequences, the decrease in T1 relaxation time after administration of a paramagnetic substance results in an increase in the intensity of the signal.

Various paramagnetic substances (e.g., gadolinium, magnesium, manganese, and iron) have already been used as contrast-enhancing agents in animals [11–15]. To reduce their toxicity, these substances are normally used in the form of complexes created by chelation with certain ligands. Among the substances tested in animals, gadolinium-DTPA (Gd-DTPA) has received the most attention, both because of its good tolerance and its strong magnetic moment. In the meantime it has become the first MR contrast medium (Gd-DTPA, Schering AG, Berlin) to be tested in clinical trials [16, 17]. The first investigations in patients with intracranial tumors showed that IV administration of Gd-DTPA can increase tumor intensity, resulting in decisively improved differentiation between tumor and perifocal edema [18–24].

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The purpose of the present study of 15 patients with intracranial tumors was to investigate the time-dependence of changes in signal intensity of various intracranial tissues after administration of Gd-DTPA.

Subjects and Methods

Nine female and six male patients (aged 26–71 years) with intracranial tumors were examined before and after intravenous injection of Gd-DTPA. The tumors included 11 cases of primary cerebral neoplasms and four cases of intracranial metastases. The diagnoses were based on the clinical findings and on the results of plain and contrast-enhanced CT. Histologic confirmation was available in 12 cases (Table 1).

A precondition for enrollment in the study was an intracranial tumor showing contrast enhancement on CT. All CT examinations (Somatom 2, Somatom DR 2, EMI 1010 head scanner) were performed within 1 week prior to the MR investigations.

As Gd-DTPA is an investigational drug, a strict protocol was to be adhered to in performing each examination. Therefore, patients whose general condition was poor or who showed elevated serum creatinine or bilirubin levels were excluded from the study, as were all female patients of child-bearing age and patients below 18 years of age. Each of the patients was given detailed information, both oral and written, on the purpose of the study; and written, informed consent to perform MR with Gd-DTPA was obtained in all cases.

MR was performed using a whole-body nuclear magnetic resonance tomograph with a field strength of 0.35 T (Siemens Magnetom). The signal is transmitted via a head coil (internal diameter = 25 cm) capable of 1×1 mm nominal spatial resolution in the imaging plane. The slice thickness was 10 mm. In accordance with the CT examinations, a transverse scanning plane was chosen.

To find a representative slice position, we scanned with multiple-slice spin-echo (SE) sequences using a double-echo technique with a pulse repetition time (TR) of 1600 ms and echo delay times (TE) of 35 and 70 ms (SE 1600/35 and SE 1600/70). A 256×256 matrix and two averages were used. Scanning time for this sequence is about 14 min. After the representative slice position was established, we scanned in this position with the sequence SE 800/35. Then Gd-DTPA was injected. The postcontrast scans in the representative slice were likewise performed with the sequence SE 800/35, beginning at 5, 15, 25, 35, 45, and 65 min p.i., respectively. Henceforth we will refer to the postcontrast scans in terms of the temporal midpoint of each scan based on a scanning time of about 7 min (i.e., 8.5, 18.5, 28.5, 38.5, 48.5, and 68.5 min p.i.).

The contrast medium used was an aqueous, stable solution of the di-N-methylglucamine salt of the DTPA complex of gadolinium (Scher-ing AG, Berlin) in a concentration of 0.5 mol/l. 0.1 mmol/kg body weight (0.2 ml/kg) was injected intravenously into the cubital vein via a plastic in-dwelling cannula (Abbocath-T 18 G) at an injection rate of approximately 10 ml/min. Immediately after injection of the contrast agent, the catheter was rinsed with 5 ml of saline solution and closed off.

The signal intensities of tumor tissue—presumably necrotic portions of the tumor—perifocal edema, and normal brain tissue before and after administration of the contrast agent were measured in the pre- and postcontrast SE 800/35 images. The quantitative assessment was performed by determining the signal intensities at the DMSC display (Siemens, Erlangen) using a region-of-interest (ROI) technique. The display allows for mean value measurements of SI of a given number of pixels included in a circular region. The region is defined by line column and area.

The signal-intensity measurements in tumor tissue were done in the enhancing portion of the lesion. When the tumor tissue was not

directly visible in the precontrast scans, the ROI was positioned on the basis of the postcontrast scans using anatomic structures as a guide.

The measurements in presumed necrotic tissue were made in those portions of the tumor that showed reduced density in plain CT scans and a lower increase in density immediately after the contrast injection than did the surrounding contrast-enhanced tumor structures.

The measurements of signal intensity in perifocal edema were performed in those areas that were hyperintense in the SE 1600/70 scans but that did not display signal-intensity increases on the SE 800/35 scans after injection of Gd-DTPA. The signal intensity of normal brain tissue was measured in the white matter.

The actual size of the different ROIs varied because we chose to evaluate the largest, most homogeneous ROI possible. The pre- and postinjection measurements of the signal intensity of a given structure in a given patient were always made with the same size ROI in a corresponding part of the lesion. The signal intensity was measured in arbitrary units ranging from 0 to 4096.

Each of the signal-intensity values was related to the signal intensity of a simultaneously measured external standard, consisting of a cylindrical plastic tube (diameter = 2.5 cm, length = 8 cm) that contained a solution of Gd-DTPA of known concentration. This tube was attached to the inside of the head coil in such a way that the transverse scans of the head also imaged a cross section of the sample. The signal intensity of the external standard was likewise determined by an ROI technique.

The purpose of referring the signal-intensity values in tissue to the signal intensity of the external standard was to neutralize temporary instrument-dependent deviations. Correction factors for each of the individual signal-intensity values in tumor, necrotic tissue, edema, and brain were obtained by dividing the signal intensity of the external standard at each scan time by the arithmetic mean of the signal-intensity values obtained for the external standard in the SE 800/35 scans performed in each patient. The signal-intensity values for tumor, necrotic tissue, edema, and normal brain—which were measured in the scan at a certain time—were then multiplied by the respective correction factor to obtain the corrected signal-intensity values used for the quantitative evaluation.

To describe the changes in contrast enhancement produced by Gd-DTPA in a given tissue, we also calculated the difference between the pre- and postcontrast signal-intensity values for a given structure (Δ SI).

In our results, we give the median signal-intensity values and the median signal-intensity differences for all patients, and additionally list the highest and lowest values.

For tumor, "necrotic" tissue, perifocal edema, and normal brain tissue, we compared signal intensity at each postcontrast scan time with the corresponding precontrast value, using Wilcoxon's test for paired differences. The level of significance chosen was $p < 0.05$. For pathologic tissues—i.e., tumor, necrotic tissue, and edema—we also compared the signal-intensity values at the various postcontrast scan times with one another, again using Wilcoxon's test for paired differences at probability $p < 0.05$.

In addition, we assessed the effects of the contrast agent visually. The criteria for this assessment were the degree of contrast enhancement and the contour of the contrast-enhanced structure.

Results

Tumor Tissue

Before administration of Gd-DTPA, the median signal intensity of tumor tissue was 575 (327–1268) (lowest–highest

TABLE 1: Summary of Patient Data

Case No.	Age/Gender	Diagnosis	Histology	Average Signal Intensity Increase (%)
1	67/M	Glioblastoma	+	164
2	68/M	Glioblastoma	—	137
3	71/M	Glioblastoma	+	155
4	26/F	Ganglioglioma	+	150
5	58/F	Meningioma	+	141
6	66/F	Meningioma	—	117
7	65/F	Meningioma	+	112
8	50/F	Meningioma	+	116
9	46/F	Meningioma	+	134
10	63/F	Neurinoma	+	164
11	59/F	Pituitary adenoma	+	135
12	71/M	Metastasis (colon carcinoma)	+	125
13	47/F	Metastasis (bronchial carcinoma)	—	111
14	65/M	Metastasis (bronchial carcinoma)	+	147
15	50/M	Metastasis (unknown primary tumor)	+	214

Note.—Diagnoses were established by CT and confirmed in 12 patients histologically (+ = confirmatory; — = not done).

TABLE 2: Signal Intensity (SI) Values on Pre- and Postcontrast Scans

	Time Post-Injection (min)						
	Precontrast	8.5	18.5	28.5	38.5	48.5	68.5
Tumor	^a 575 ^b (327/1268) ^c <i>n</i> = 15	813* (500/1758) <i>n</i> = 13	821* (537/1740) <i>n</i> = 15	843* (529/1724) <i>n</i> = 14	829* (547/1711) <i>n</i> = 14	814* (549/1650) <i>n</i> = 15	811* (551/1624) <i>n</i> = 14
Necrosis	590 (316/675) <i>n</i> = 7	674* (393/856) <i>n</i> = 6	644* (401/919) <i>n</i> = 7	627* (429/903) <i>n</i> = 6	636* (453/911) <i>n</i> = 6	636* (448/937) <i>n</i> = 7	671* (479/939) <i>n</i> = 7
Edema	586 (345/1105) <i>n</i> = 10	634 (335/1152) <i>n</i> = 9	620* (358/1148) <i>n</i> = 10	640 (353/1160) <i>n</i> = 9	650 (360/1118) <i>n</i> = 9	631* (362/1144) <i>n</i> = 10	670* (360/1150) <i>n</i> = 9
Normal brain	618 (331/1292) <i>n</i> = 14	646 (346/1380) <i>n</i> = 13	621 (358/1382) <i>n</i> = 14	674 (348/1401) <i>n</i> = 13	613 (364/1350) <i>n</i> = 13	629 (368/1380) <i>n</i> = 14	671 (366/1395) <i>n</i> = 13

Note.—Number of measurements varies at different time points because of technical problems, patient movement, etc.

^a Median value of SI

^b (Lowest/highest value of SI)

^c *n* = number of measurements

* Significantly different from precontrast value (*p* < 0.05)

value). This increased to 813 (500–1758) in the first postcontrast scan at 8.5 min p.i. Median signal-intensity values remained at levels of between 811 and 843 throughout the rest of the examination (Table 2).

As regards the differences in signal intensity (Δ SI) in tumor tissue 8.5 min after administration of Gd-DTPA, the median value of signal-intensity increases was 196 (116–490).

The maximum Δ SI of 241 at 28.5 and 38.5 min p.i. was followed by a slight decrease to 228 (74–407) at 48.5 min p.i. and to 223 (33–409) at 68.5 min p.i. (Table 3, Fig. 1).

Statistical analysis showed all the postcontrast signal-intensity values to be significantly higher than the precontrast values. Comparison of the postcontrast values with one another showed that values obtained at 8.5, 18.5, 28.5, and up to 38.5 min p.i. did not differ significantly from one another, whereas both the 48.5 and 68.5 min values showed significant decreases of signal intensity as compared to the 38.5 min p.i. value.

The individual analysis of each case showed that after injection of Gd-DTPA there was an initial increase of signal-intensity values in tumor tissue in all cases. Thereafter, however, the individual time course of signal intensity varied after 8.5 min p.i., and no consistent pattern of time course was found in tumors of one type (e.g., glioblastomas, meningiomas).

After the initial increase, signal intensity remained almost unchanged or showed a slight decrease throughout the entire postcontrast period in seven tumors (patients 1, 3, 4, 6, 11, 12, and 14). In two patients, tumor tissue displayed increases of signal intensity in the second half of the postcontrast period (patients 5 and 15), whereas in the remaining six cases signal intensity markedly decreased toward the end of the examination (patients 2, 6, 8, 9, 10, and 13).

As regards the visual assessment, there was a marked increase in tumor signal intensity from the first postcontrast scan onward in all the patients (Figs. 2–4). Corresponding to

TABLE 3: Signal Intensity Differences (Δ SI) Between Pre- and Postcontrast MR Scans

	Time Post-Injection (min)					
	8.5	18.5	28.5	38.5	48.5	68.5
Tumor	^a +196	+232	+241	+241	+228	+223
	^b (+116/+490)	(+59/+472)	(+78/+456)	(+118/+443)	(+74/+407)	(+33/+409)
Necrosis	+70	+74	+111	+137	+132	+163
	(+32/+181)	(+30/+244)	(+47/+228)	(+68/+236)	(+31/+262)	(+66/+284)
Edema	-2	+24	+11	+13	+22	+24
	(-32/+75)	(-18/+94)	(-29/+91)	(-6/+72)	(-21/+76)	(-2/+93)
Normal brain	+10	+7	+19	+23	+26	+32
	(-82/+88)	(-92/+90)	(-78/+109)	(-77/+90)	(-62/+98)	(-100/+103)

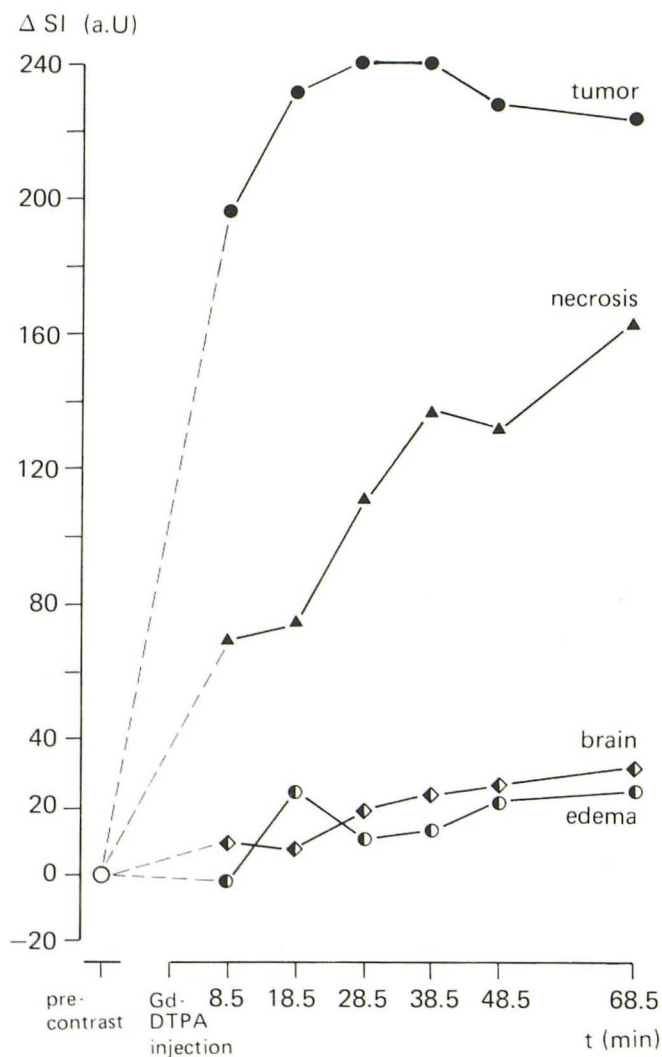
^a Median value of Δ SI^b (Lowest/highest value of Δ SI)

Fig. 1.—Time-dependent changes in image contrast in intracranial tumors. Differences between pre- and postcontrast MR signal intensity values (Δ SI) calculated for tumor, "necrotic" tissue, edema, and normal brain in 15 patients with intracranial tumors. The differences in signal intensity are given as median values.

the quantitative findings, tumor enhancement in some of the patients appeared to be constant throughout the postinjection period (Fig. 3) and to show a decrease in others (Figs. 2 and 4). At the beginning of the postcontrast period, the margin of

the contours became less defined and it was more difficult to distinguish borderlines between the tumor and the adjacent brain tissue or surrounding edema.

"Necrotic" Tissue

In seven of the patients the tumor showed central necrosis (patients 1, 3, and 11–15). The median signal intensity for necrotic tissue in precontrast scans was 590 (360–675). After injection of Gd-DTPA the median signal-intensity values were all higher than those prior to injection (Table 2). In all patients, the maximum signal intensity for necrotic tissue was measured at either 48.5 or 68.5 min p.i.

At 8.5 min p.i., the Δ SI value was 70 (32–181). It rose continuously throughout the rest of the examination period, reaching 163 at 68.5 min p.i. Only the 48.5 min Δ SI value of 132 was lower than the previous one at 38.5 min (Table 3, Fig. 1).

All postcontrast signal-intensity median values were significantly higher compared with the precontrast median value (Table 2). Comparison of the postcontrast values with one another revealed that signal intensity at 48.5 min p.i. was significantly higher than at 18.5 and 28.5 min, and that the value at 68.5 min p.i. was significantly higher than those at 8.5, 18.5, and 28.5 min.

Visual assessment also showed that the signal intensity of the central necrotic tissue increased with time (Fig. 2). At the beginning, contrast enhancement was observed mainly in the peripheral areas of the necrotic tissue, whereas later contrast enhancement was seen in the central parts as well.

Edema

Ten of the tumors exhibited perifocal edema (patients 1–5, 10, and 12–15). The median signal intensity of perifocal edema in precontrast scans was 586 (345–1105). The median signal-intensity values for the postcontrast scans were in the range of 620 to 670 (Table 2).

As regards the Δ SI values, all the postcontrast scans—with the exception of that at 8.5 min p.i.—had a Δ SI of 11 to 24 (Table 3, Fig. 1).

Statistical comparison of pre- and postcontrast values showed the increases in signal intensity at 18.5, 48.5, and 68.5 min p.i. to be significant (Table 2). Comparison of the

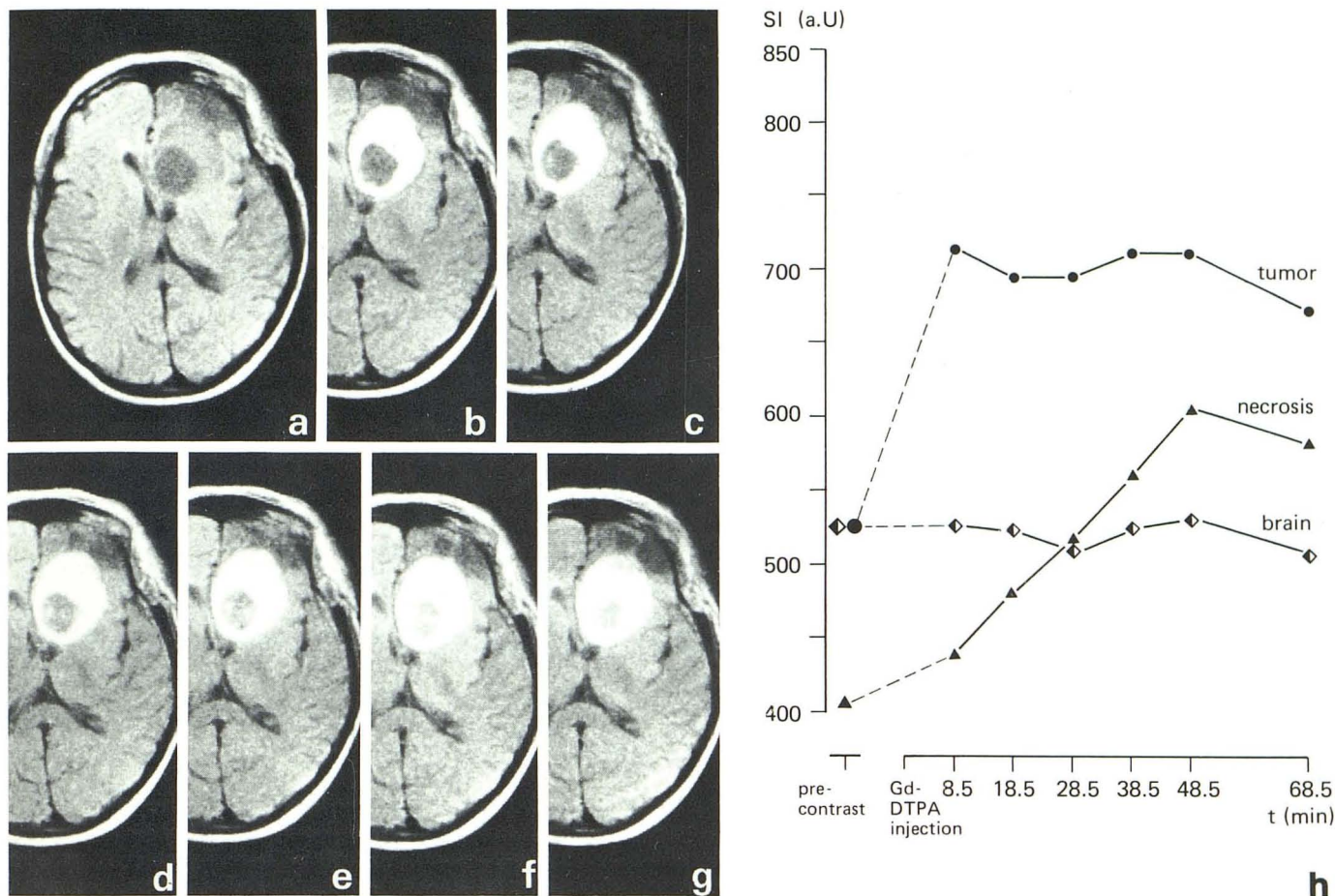


Fig. 2.—Recurrent pituitary adenoma (case 11). Series of MR scans before injection (a), 8.5 min post-injection (p.i.) (b), 18.5 min p.i. (c), 28.5 min p.i. (d), 38.5 min p.i. (e), 48.5 min p.i. (f), and 68.5 min p.i. (g) displays strong increase in image contrast in ring-shaped tumor after gadolinium-DTPA injection. There

is delayed signal-intensity enhancement in central "necrotic" tissue. Part h represents quantitative data in same patient. (Parts a and b reprinted with permission. See ref. 24.)

postcontrast values with one another revealed no statistically significant differences.

Visually, these increases of signal intensity after administration of Gd-DTPA could not be detected (Fig. 3).

Normal Brain Tissue

Before administration of the contrast agent, the median signal intensity for normal brain tissue was 618 (331–1292). After injection of Gd-DTPA, we found median signal-intensity values of between 613 and 674 (Table 2) at the different time points.

The median values of Δ SI after administration of the contrast medium ranged from 7 to 32 (Table 3). Statistical analysis revealed no significant differences between pre- and postcontrast SI values (Table 2). Visual assessment likewise revealed no effect of Gd-DTPA on the signal intensity of normal brain tissue (Figs. 2–4).

Discussion

The choice of sequence parameters is known to have a considerable effect on contrast in MR [25, 26]. With MR-

specific contrast media such as Gd-DTPA it is possible to influence T1, T2, and proton density and thus change image contrast [11–15, 18–24]. Unlike the changes of signal intensity produced by varying the sequence parameters, in which case signals from all tissues are changed accordingly, the use of a contrast agent may change signal intensity only in certain regions according to its tissue distribution.

Both animal experiments and clinical studies have shown that the pharmacokinetics of Gd-DTPA are basically similar to those of the known X-ray contrast media [15, 27, 28].

By virtue of the blood-brain barrier, the brain represents a special case as regards the distribution of substances that, like conventional X-ray contrast media or Gd-DTPA, are highly hydrophilic and have a molecular weight of 500 or more [29]. Only after the blood-brain barrier has been disrupted is it possible for contrast-agent molecules to diffuse into the interstitial space. Thus, like conventional X-ray contrast agents, Gd-DTPA acts as a marker for lesions of the blood-brain barrier [12, 30, 31]. While it has no relevant effect upon the signal produced by normal brain tissue, it brings about localized signal increases in lesions with an impaired or absent blood-brain barrier. Thus, malignant cerebral tumors (e.g.,

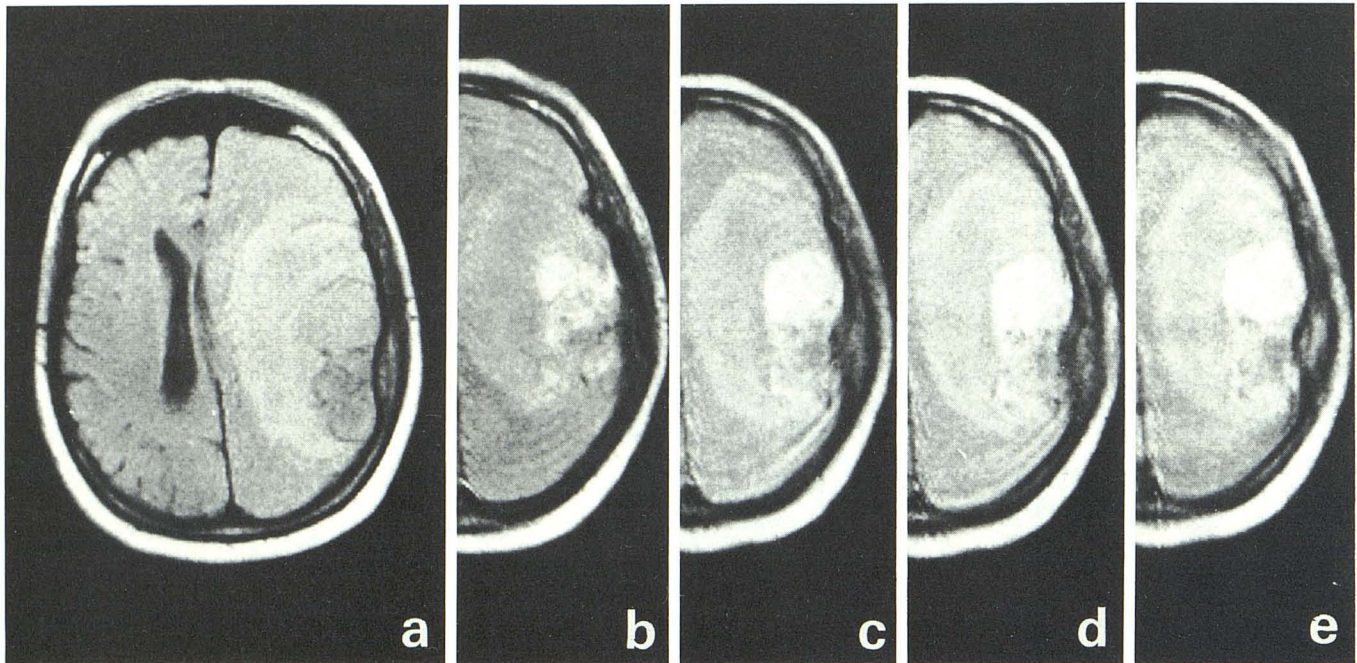
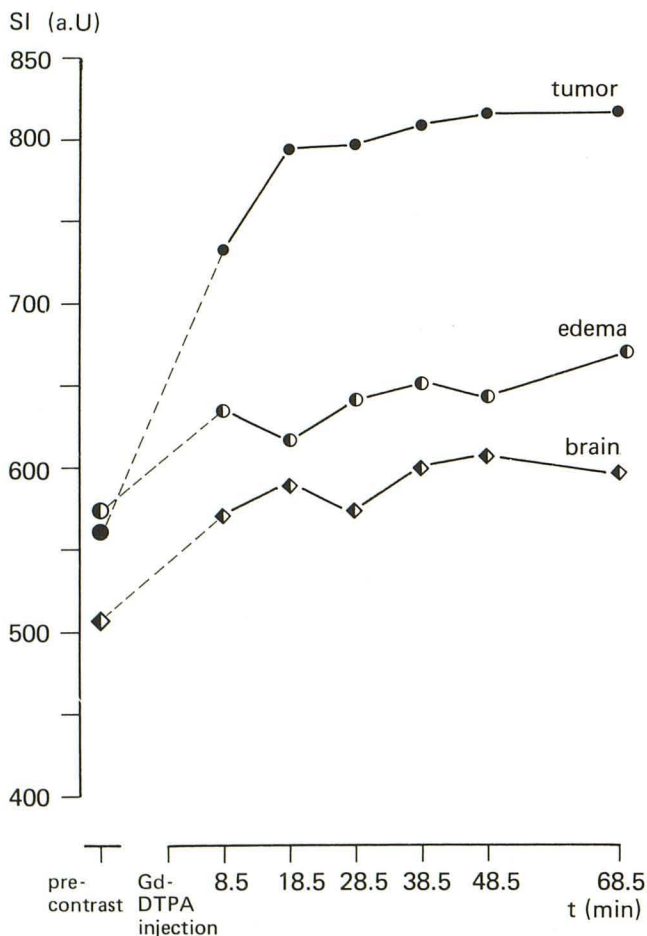


Fig. 3.—Meningioma of the convexity (case 5). Series of MR scans before injection (a), 8.5 min post-injection (p.i.) (b), 18.5 min p.i. (c), 38.5 min p.i. (d), and 68.5 min p.i. (e) displays slow increase in signal intensity in inhomogeneous tumor. Part f represents quantitative data in same patient.



glioblastomas) with altered vascular structures and other intracranial tumors (e.g., meningiomas, neurinomas, adenomas) of extracerebral origin, which possess no blood-brain barrier, exhibit contrast enhancement after administration of Gd-DTPA [18–23].

In the tumor tissue of the patients studied, the first post-contrast scan at 8.5 min p.i. showed a statistically significant increase in signal intensity above the precontrast level. Toward the end of the postcontrast phase there was a drop in signal intensity, which was likewise significant. As compared with precontrast values, however, signal intensity remained significantly elevated throughout the post-injection period investigated. Corresponding to these figures, the best tumor visualization with high contrast was seen in the early post-contrast scans.

The gradual increase in signal intensity produced by Gd-DTPA in the central "necrotic" area occurred somewhat later than the marked increase in vital tumor tissue. Since the signal intensity of vital tumor tissue decreased toward the end of the observation period while that of necrotic tissue was at its peak in the later scans, both tissues were therefore best differentiated on the early postcontrast scans.

The fact that conventional X-ray media and Gd-DTPA exhibit similar physicochemical and pharmacokinetic properties leads us to expect that CT and MR will show parallels as regards the time-dependent contrast enhancement of brain tumors. And, in fact, within certain limits, our results are in keeping with those in CT as reported in the literature. Thus, Lange et al. [32] reported that in 64 of 75 brain tumors, density values reached a maximum 5 to 15 min p.i. Only 11

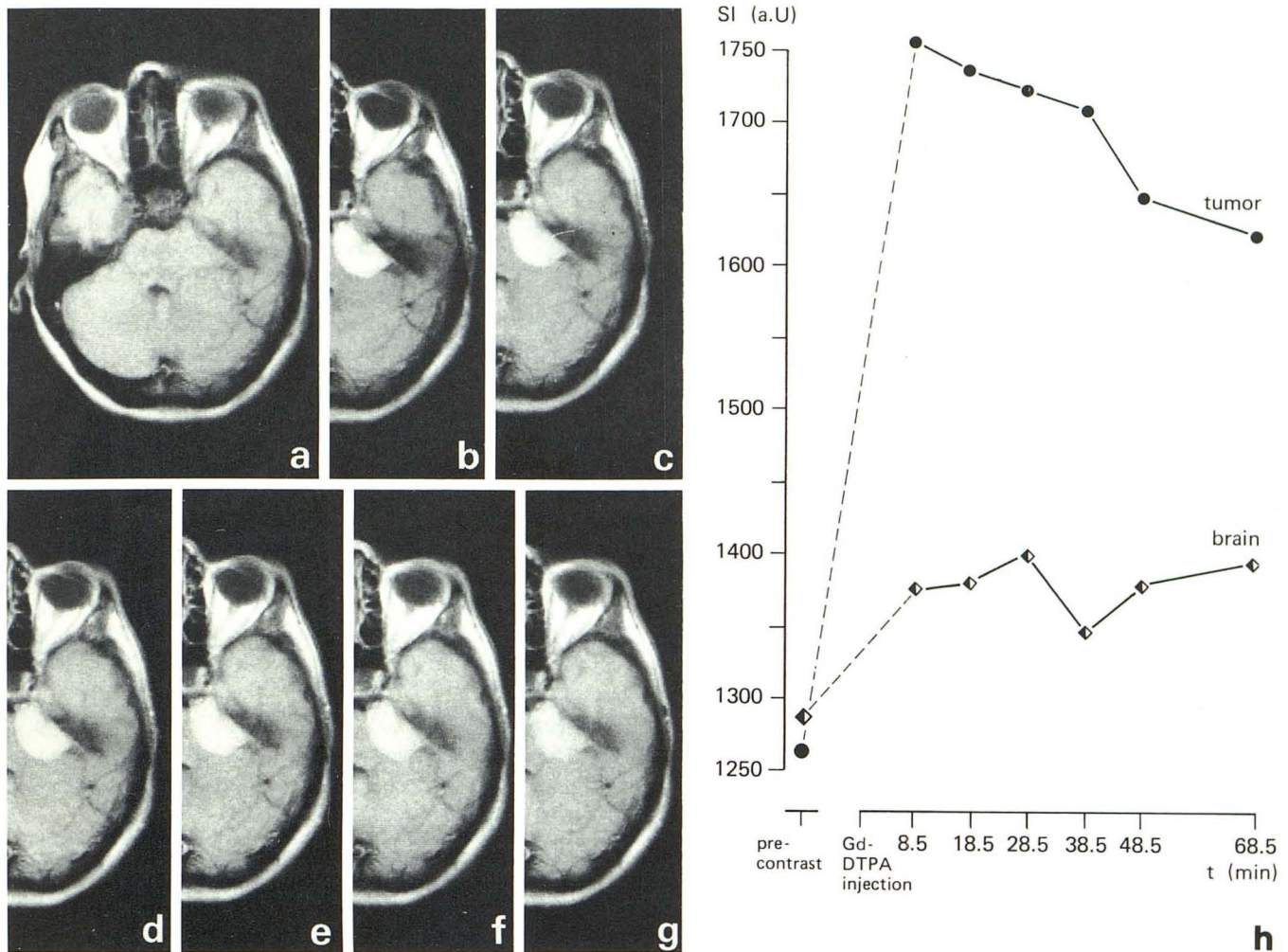


Fig. 4.—Meningioma of right cerebellopontine angle (case 9). Series of MR scans before injection (a), 8.5 min post-injection (p.i.) (b), 18.5 min p.i. (c), 28.5 min p.i. (d), 38.5 min p.i. (e), 48.5 min p.i. (f), and 68.5 min p.i. (g) displays

strong signal-intensity enhancement of tumor on early postcontrast scans followed by rapid decrease in tumor enhancement on later postcontrast scans. Part h represents quantitative data in same patient.

tumors exhibited maximum densities on later scans, which were taken between 15 and 60 min p.i.

Likewise, it is reported that in CT the accumulation of contrast medium in necrotic tissue takes place later than in the vital portions of the tumor. According to Norman et al. [33], maximum density values for central necrotic tissue in contrast-enhanced CT were found 20 to 60 min p.i.

The different kinetics of contrast agents in vital and necrotic tumor tissue can be explained in part by differences in vascularization. According to Norman et al. [33], necrotic tissue in comparison with vital tissue is a second compartment that equilibrates at a slower rate.

In CT, infusion of contrast medium is accompanied by only a slight density increase in perifocal edema [34], and, here again, there are analogies to MR. After administration of Gd-DTPA, quantitative evaluation revealed a slight, though diagnostically irrelevant, increase in edema signal intensity.

Concerning the effect of Gd-DTPA on signal intensity of normal brain tissue, the results published so far are conflicting. In animals, normal brain tissue showed unchanged [12] or elevated [31] signal-intensity values. Carr et al. [21] reported that in patients with brain tumors normal brain displayed little or no evidence of enhancement after administration of Gd-DTPA, whereas changes were seen in arteries, veins, and sinuses.

In the present study, only insignificant signal-intensity increases in normal brain tissue were found. This effect was not visually recognizable, however, and was therefore diagnostically irrelevant.

In conclusion we found that the already reported diagnostic usefulness of Gd-DTPA in brain tumors is based on the favorable pharmacokinetic behavior of Gd-DTPA, which does not cross the intact blood-brain barrier. Based on the time-dependent behavior of signal intensity in brain tumors and

accompanying pathologies (e.g., necrosis, edema) the best scanning time was determined to be between 8.5 and 38.5 min p.i. Postcontrast scans performed at an early stage after administration of contrast medium have the advantage of revealing the contours of an enhancing tumor more clearly, and the contrast between vital tumor and presumed necrotic regions is greater than in later images. However, on later images contrast still is sufficient to obtain images of the tumor in various planes using various sequences without having to administer a second dose.

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