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Gd-DTPA in Clinical MR of the Brain: 1. Intraaxial Lesions

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Over 35 intraaxial lesions in 15 patients suspected of having intracranial tumors were studied with MR before and after injection of Gadolinium-DTPA (Gd-DTPA). Diseases included primary and metastatic brain tumors, plaques of multiple sclerosis, occult arteriovenous malformations, lymphoma, toxoplasmosis, and pituitary adenoma. The precontrast T2-weighted sequence (SE 2000/30, 60) was found to be most sensitive in detecting intraaxial lesions, showing 17 lesions that were not seen on the post-Gd-DTPA T1-weighted sequence (SE 500/30). In one case of multiple sclerosis, several lesions seen on the pre-Gd-DTPA study on T2-weighted images faded after injection of Gd-DTPA (due to T2 shortening). In two patients with large metastatic foci, other small metastatic lesions were seen better after Gd-DTPA on both T1- and T2-weighted sequences. Four other patients with only one focal-enhancing lesion and one patient with multifocal lesions on T1-weighted images actually had a much larger single glioma depicted on pre-Gd-DTPA T2-weighted images. In a patient with AIDS, a ring-enhancing lesion thought to be an abscess proved to be lymphoma. The cryptic arteriovenous malformations enhanced but showed more characteristic findings, such as hemorrhage, on pre-Gd-DTPA studies. Our experience suggests that Gd-DTPA may not improve sensitivity of MR in the detection of intraaxial lesions. However, functional aspects of brain disease, such as the presence of perfusion of a lesion and active breach of the blood-brain barrier, are depicted well with Gd-DTPA and are vital for proper diagnosis in many instances.

Early limitations of MR included relatively long study times, suboptimal characterization of disease and its chronicity, perceived inability to separate tumor from edema, and, on occasion, suboptimal sensitivity. CT had similar problems in its early stages, with suboptimal sensitivity being the most unacceptable problem but the one most easily remedied through the use of preexisting iodinated contrast agents. The impact of such contrast agents on CT provided a historical precedent for the development of paramagnetic contrast agents. Gadolinium-DTPA (Gd-DTPA) was the first such substance to be tested for human use in European trials, with the brain and spinal cord as early targets [1–3]. Enthusiasm for this agent's utility is evident in these early trials. The first American clinical trials of Gd-DTPA have been completed and the initial results of tolerance, toxicity, and efficacy from the phase II multicenter trial have been reported [4]. This and the following article (5] elucidate the clinical experience with Gd-DTPA from a referral center for neurologic disease where MR had been used routinely by neuroradiologists for 4 years prior to the introduction of this agent.

Subjects and Methods

Thirty patients at the University of California, San Francisco (UCSF), were enrolled in a multicenter clinical trial of Gd-DTPA under the guidelines of the Food and Drug Administration, the Human Research Committee at UCSF, and the commercial developer of the product (Berlex Laboratories, New Jersey). Fully informed consent was obtained from every patient.

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TABLE 1: **Clinical Data in 13 Patients with Definitive Diagnosis**

Age	Gender	Clinical Symptoms	Histology
Primary Brain Tumors			
55	M	Progressive difficulty in verbal fluency	Anaplastic astrocytoma
53	M	Grand mal seizures	Multicentric anaplastic astrocytoma
42	M	Grand mal and focal seizures	Anaplastic astrocytoma
34	M	Grand mal seizures	Anaplastic astrocytoma
56	M	History of astrocytoma treated by radiation; homonymous hemianopsia	Radionecrosis residual astrocytoma
32	M	Petit mal seizures	Anaplastic astrocytoma
Secondary Brain Tumors			
59	F	Sensory seizures	Adenocarcinoma metastasis
62	M	Left arm weakness and dysarthria	Adenosarcoma metastasis
53	F	History of breast carcinoma; left hemiparesis	Breast carcinoma* metastasis
Miscellaneous Lesions			
43	M	Altered mental status; AIDS	Lymphoma and toxoplasmosis
37	M	History of seminoma; multifocal neurologic signs	Multiple sclerosis*
53	F	Visual flashes; hearing loss	Cryptic arteriovenous malformation
31	M	Incidental discovery; head trauma	Pituitary adenoma

* Denotes clinical diagnosis only.

The enrollment requirements included strong suspicion of intracranial tumor (based either on CT studies or clinical criteria) in adult patients. Women of child-bearing age were excluded. Following a battery of baseline laboratory studies [4], MR was performed before and after the intravenous administration of Gd-DTPA (0.1 mmol/kg), at 0.35 T with dual spin-echo (TE 30, 60 msec) sequences using TR of 2000 msec (sequence A) and 500 msec (sequence B). The order of sequences was A/B, B/A/B/A/B, with Gd-DTPA delivered after the first A/B pair. The image matrix was 256 × 256, or 128 × 128 when the patient's condition necessitated a more rapid study. The imaging time for an A/B pair at a matrix of 128 was 13 min; at a matrix of 256, it was 26 min. Slices were contiguous and 5 or 10 mm in thickness, depending on the anatomic region of interest. Quantitative measurements of tissue intensity were carried out before and after administration of Gd-DTPA by circumscribing a region of interest with an interactive cursor. This procedure allowed calculation of T1 and T2 relaxation values in normal and pathologic foci. The quantitative aspects of the intraaxial lesions considered here are reported elsewhere as part of an overall study [6].

Visual evaluation of the degree of enhancement in the intraaxial lesions considered here was scored on a 0–2 scale by two of the authors (MBZ, IB), with 0 = no enhancement, 1 = equivocal enhancement, 2 = definite enhancement. The same scoring scale was used to judge the ability of MR before and after the injection of Gd-DTPA to separate tumor from edema, identify focal cyst or necrosis, and provide a site for biopsy, if applicable. Finally, an overall judgment was made regarding the effects of Gd-DTPA on the general diagnostic efficacy of MR. The effect was judged positive if this agent improved sensitivity or made the lesion easier to see, or if it helped characterize the disease process. For all these judgments, *both* A and B sequences before Gd-DTPA administration were used and compared with both sequences after the agent was given.

Results

Fifteen of the 30 patients enrolled in the study had over 35 intraaxial lesions. The patient tolerance and toxicity data relative to Gd-DTPA administration is the subject of the multicenter report [4] and will not be considered here. The variety of diseases encountered are listed in Table 1. Histologic proof of the diagnosis was available in 11 of the 15 patients. In two others with multifocal lesions, the diagnosis was based on the imaging studies and on definitive clinical criteria (multiple sclerosis, metastases). Two patients with a focal MR abnormality are being followed with no firm diagnosis to date. Therefore, 13 patients with an established diagnosis form the basis of this study. Five of the patients were on steroid therapy when undergoing the imaging study. No correlation between enhancement or lack thereof and such therapy was noted in this small group of patients (only one patient on steroids had a nonenhancing lesion). Overall, almost half (17) of all the lesions detected with MR showed

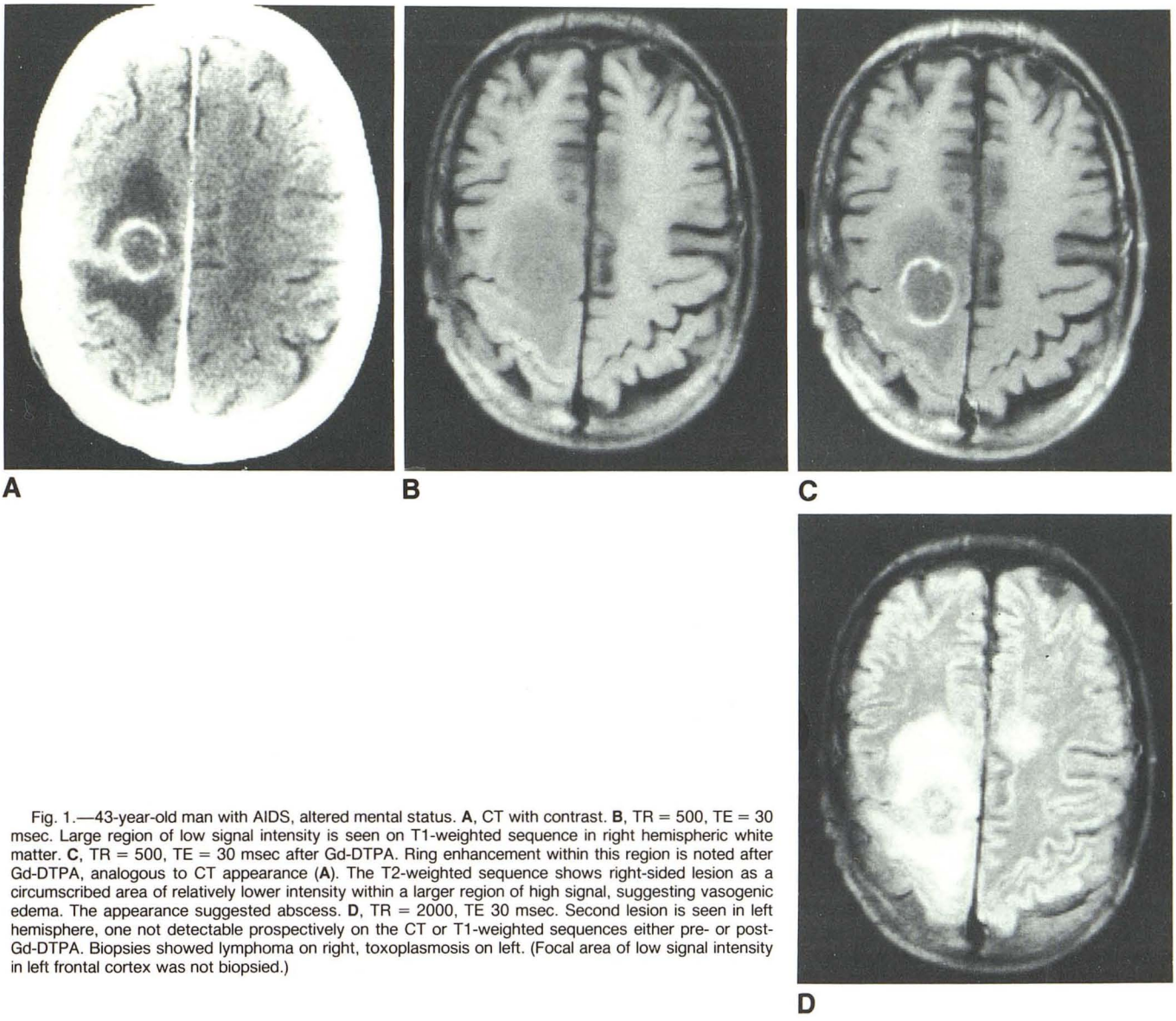

Fig. 1.—43-year-old man with AIDS, altered mental status. **A**, CT with contrast. **B**, TR = 500, TE = 30 msec. Large region of low signal intensity is seen on T1-weighted sequence in right hemispheric white matter. **C**, TR = 500, TE = 30 msec after Gd-DTPA. Ring enhancement within this region is noted after Gd-DTPA, analogous to CT appearance (**A**). The T2-weighted sequence shows right-sided lesion as a circumscribed area of relatively lower intensity within a larger region of high signal, suggesting vasogenic edema. The appearance suggested abscess. **D**, TR = 2000, TE 30 msec. Second lesion is seen in left hemisphere, one not detectable prospectively on the CT or T1-weighted sequences either pre- or post-Gd-DTPA. Biopsies showed lymphoma on right, toxoplasmosis on left. (Focal area of low signal intensity in left frontal cortex was not biopsied.)

no definite enhancement with Gd-DTPA. However, 10 of these were demyelinating plaques in a single patient with multiple sclerosis. The agent's effects on overall diagnostic capability was judged as positive in two of 15 patients and negative in two others.

Detection of Enhancement

Prior to Gd-DTPA injection, the T2-weighted sequence (sequence A) was the most sensitive in detecting focal lesions within the brain, showing 17 such lesions that were not seen (score 0 or 1) on the post-Gd-DTPA, T1-weighted sequence (sequence B). The lesions missed on post-Gd-DTPA sequence B included the majority of the plaques in the patient with multiple sclerosis (only 10 of which were counted for the purpose of this study), the lesions of toxoplasmosis and primary cerebral lymphoma (Fig. 1) in the patient with AIDS, two foci of astrocytoma in a patient with multicentric astrocytoma, one large infiltrating temporal astrocytoma in which only a punctate focus enhanced with Gd-DTPA on sequence B, a large parietal astrocytoma involving the thalamus (Fig. 2), the major component of a diffusely infiltrating astrocytoma in which a subfrontal and posterior parietal focus of enhancement was seen, and a frontal astrocytoma in which a punctate hemorrhagic focus was noted. In a minority of these cases, minimal (equivocal) increase in signal intensity (score 1) was faintly visible on the post-Gd-DTPA sequence B when the pre-Gd-DTPA sequence was available for side-by-side comparison.

The optimal sensitivity of the T2-weighted sequence A was maintained after injection of Gd-DTPA with two notable exceptions. Several of the multiple sclerosis plaques seen on the pre-Gd-DTPA T2-weighted sequence A disappeared on

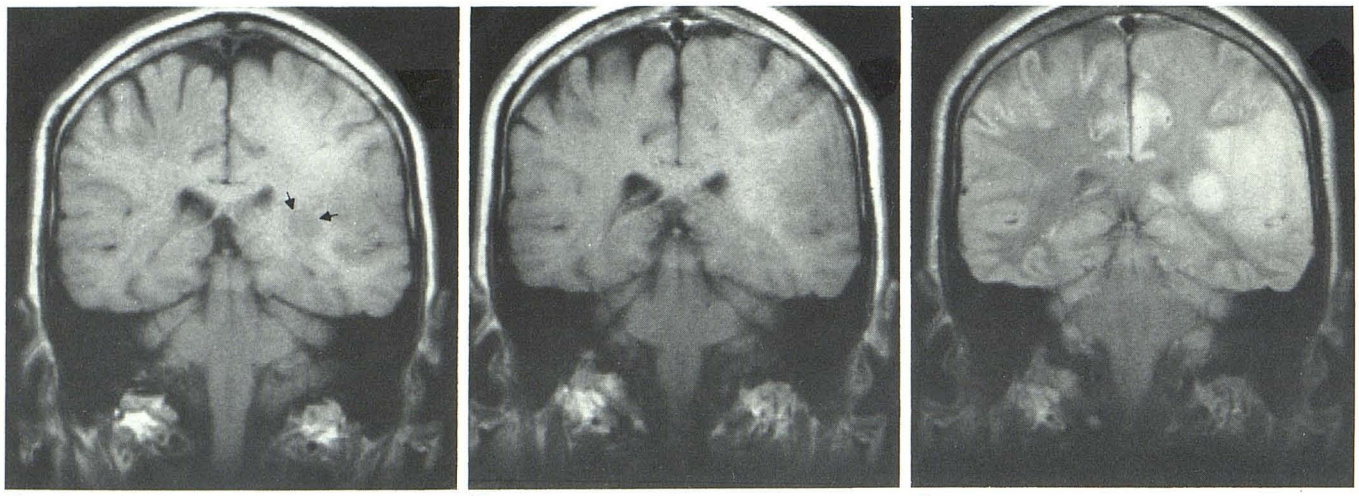

Fig. 2.—55-year-old man with progressive difficulty in verbal fluency; astrocytoma. **A**, TR = 500, TE = 30 msec. Small region of lower intensity (*arrows*) and subtle cortical mass effect is seen on T1-weighted sequence prior to Gd-DTPA. **B**, TR = 500, TE = 30 msec after Gd-DTPA. Administration of Gd-DTPA yields no obvious enhancement of the lesion. **C**, TR = 2000, TE = 30 msec. T2-weighted sequence shows circumscribed area of high signal intensity with even brighter nidus in its deep portion corresponding to low-intensity focus seen in **A**.

that sequence after injection of Gd-DTPA (Fig. 3) because of shortening of T2 relaxation values [6]. The intensity of one, focal, hyperintense site within an astrocytoma faded on the T2-weighted sequence A post-Gd-DTPA when compared with that pre-Gd-DTPA sequence.

Gd-DTPA did improve the sensitivity of both A and B sequences in two of the three patients with metastatic disease (adenosarcoma, adenocarcinoma). Both patients exhibited a single enhancing lesion on CT. The pre-Gd-DTPA MR (sequences A and B) showed a single lesion in one patient and two lesions in the other patient. In both patients, an additional punctate focus of enhancement post-Gd-DTPA was noted on sequences B and A (Fig. 4).

Of the remaining cases, Gd-DTPA-enhanced lesions on T1-weighted sequence B were also detected pre-Gd-DTPA in a patient with multiple breast metastases, in an AIDS patient with cerebral lymphoma (whose toxoplasmosis lesions did not enhance—see Fig. 1), in a patient with multifocal familial occult arteriovenous malformations (Fig. 5), and in a patient with a large pituitary tumor. In all cases that had enhancement, the phenomenon was detectable on the first T1-weighted sequence after injection; however, several multiple sclerosis plaques and two punctate metastatic foci showed more conspicuous enhancement after a 20-min delay.

Characterization

In four of the patients (two with metastases, one with lymphoma, and one with treated astrocytoma), CT showed definite segmentation of the lesion into an enhancing component surrounded by low density—an appearance strongly suggestive of tumor surrounded by edema. In all four cases, the combination of sequence A and B pre-Gd-DTPA also indicated such segmentation. In some cases, the very low intensity focus on T1-weighted sequence B corresponded to the enhancing central component on CT, while T2-weighted sequence A showed the extensive surrounding high intensity consistent with edema (Fig. 4). Post-Gd-DTPA sequence B showed enhancement corresponding to that of CT in these cases. In others, the T2-weighted sequence A showed diffuse high signal intensity, suggesting edema in a vasogenic pattern, circumscribing a garland-shaped low-intensity center (Fig. 1).

Cystic or necrotic components in these intraaxial lesions were identifiable by low-intensity foci on T1-weighted sequence B, and Gd-DTPA offered little to their characterization other than the delayed increase in intensity of the central nidus of such lesions when compared with their periphery.

Hemorrhagic foci within tumors and the occult arteriovenous malformations could be identifed only on the pre-Gd-DTPA pair of sequences based on the high signal intensity of such foci on both A and B sequences. After Gd-DTPA, distinguishing the hemorrhagic focus from an enhancing one was not possible (Fig. 5).

The pattern of enhancement offered little advantage over the morphologic pattern of the lesion before Gd-DTPA. For example, prior to biopsy, the lymphoma lesion in the AIDS patient was thought more likely to represent an abscess based on the ring-enhancing pattern with both CT and MR sequence B. Enhancement in a homogenous or garland-shaped manner was seen in primary as well as metastatic lesions. Thus, in any individual case, these patterns were not predictive of the disease. Although multifocal enhancement with Gd-DTPA did significantly alter the diagnostic differential in two patients with metastatic foci, such multifocal enhancement post-Gd-DTPA would have negatively altered the differ-

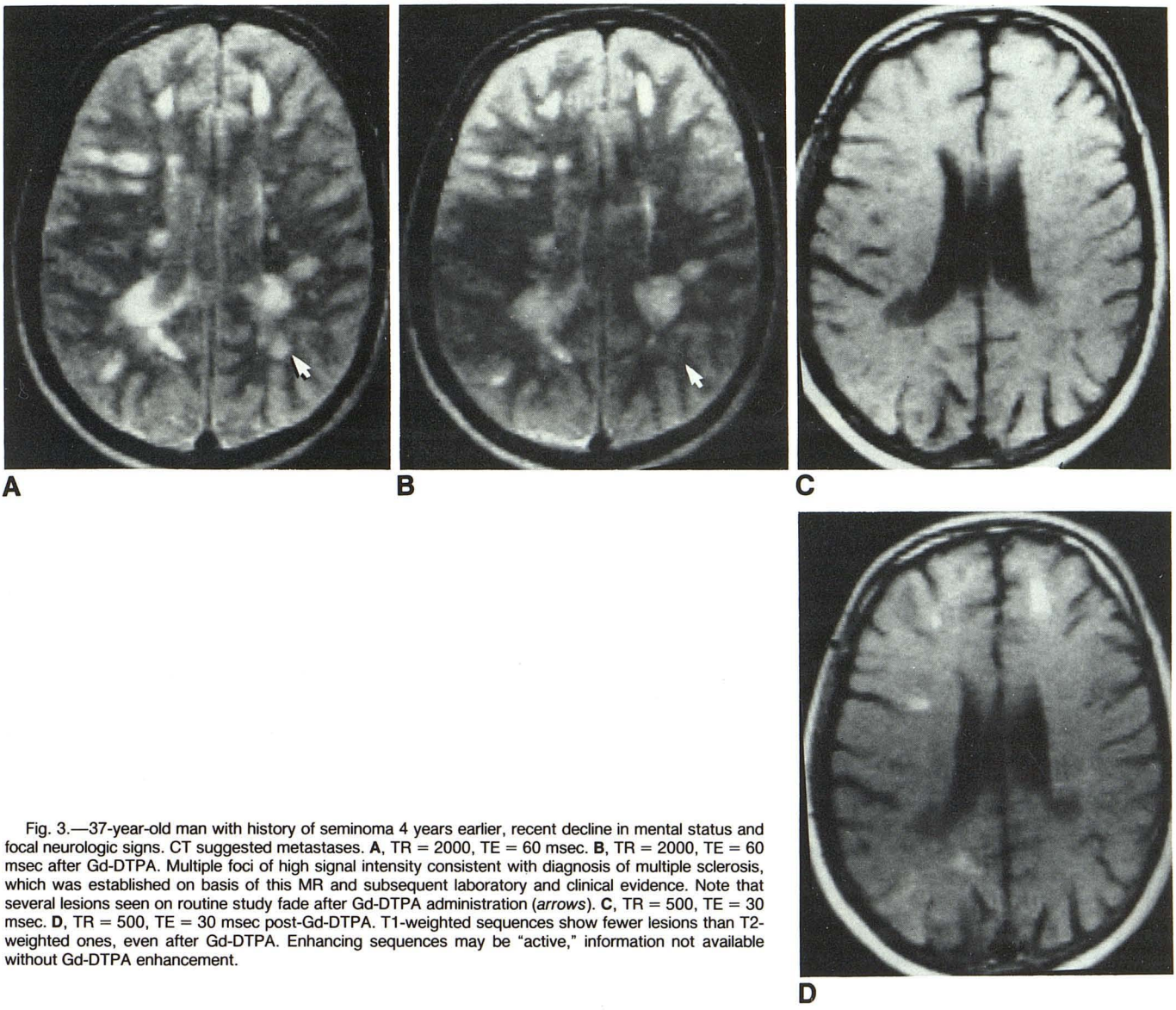

Fig. 3.—37-year-old man with history of seminoma 4 years earlier, recent decline in mental status and focal neurologic signs. CT suggested metastases. **A**, TR = 2000, TE = 60 msec. **B**, TR = 2000, TE = 60 msec after Gd-DTPA. Multiple foci of high signal intensity consistent with diagnosis of multiple sclerosis, which was established on basis of this MR and subsequent laboratory and clinical evidence. Note that several lesions seen on routine study fade after Gd-DTPA administration (*arrows*). **C**, TR = 500, TE = 30 msec. **D**, TR = 500, TE = 30 msec post-Gd-DTPA. T1-weighted sequences show fewer lesions than T2-weighted ones, even after Gd-DTPA. Enhancing sequences may be "active," information not available without Gd-DTPA enhancement.

ential considerations in three patients with primary astrocytomas were it not for the picture of nonenhancing contiguous infiltration seen with the T2-weighted sequence A.

Discussion

The superiority of T2-weighted sequences in the detection of intraaxial brain disease when compared with Gd-DTPA-enhanced T1-weighted sequences as documented by the limited experience reported here is easily understood in light of the pathophysiology of brain disorders. Contrast agents for CT, as well as Gd-DTPA, are large molecules that require both intact perfusion and gross active disruption of the blood–brain barrier (BBB) for their accumulation within the diseased tissues. However, only minimal BBB breakdown may be needed for water to leak out into abnormal tissue. Such water accumulation may predate the more severe BBB disruption needed for leakage of larger proteins across this barrier [7]. Water is an inherent contrast-enhancing substance for T2-weighted images. Indeed, increased water may be seen in diseased tissues (such as demyelinated plaques) even when no active BBB breakdown is present. MR's superior sensitivity to increased tissue water compared with contrast-enhanced CT is well documented and accounts for its diagnostic advantage (8]. Given the pathophysiology of BBB breakdown, then, it is implausible that Gd-DTPA would accumulate in a site that did not also contain abnormal amounts of water. Such sites routinely yield a high signal on T2-weighted sequences. The two "missed" metastatic lesions prior to Gd-DTPA in this series run counter to the above analysis. However, they were both punctate and subject to partial volume

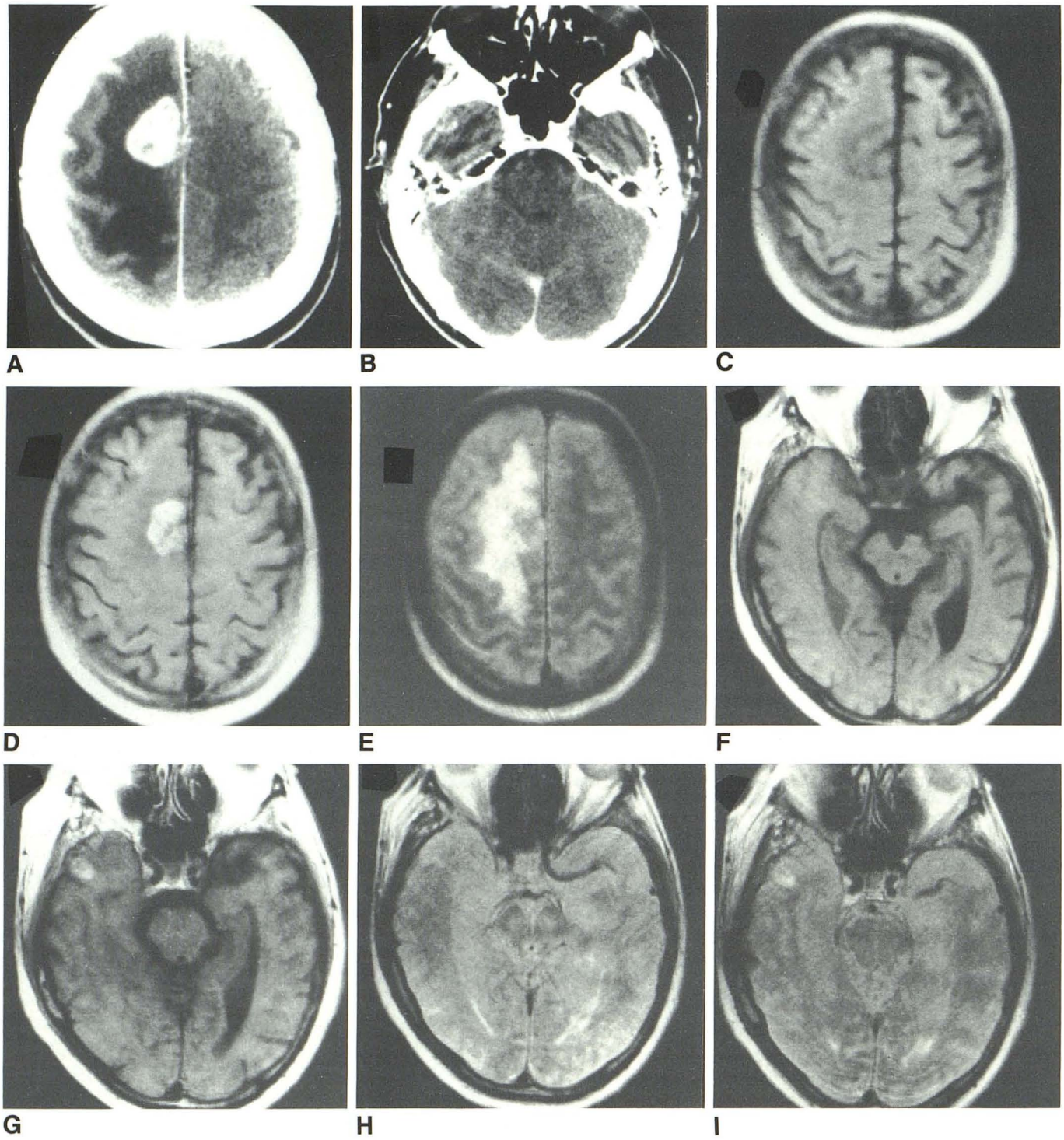

Fig. 4.—62-year-old man with left arm weakness and dysarthria progressing over 3 weeks. **A**, CT shows enhancing lesion in right hemispheric white matter, surrounded by low density. **B**, CT section of temporal lobes degraded by streak artifact. **C**, TR = 500, TE = 30 msec. **D**, TR = 500, TE = 30 msec after Gd-DTPA. Lesion enhances. **E**, TR = 2000, TE = 60 msec. Localization of lesion and differentiation from surrounding edema are possible on pre-Gd-DTPA sequences (**C**, **E**). Primary tumor was suspected. **F**, TR = 500, TE = 30 msec. **G**, TR = 500, TE = 30 msec after Gd-DTPA. **H**, TR 2000, TE = 60 msec. **I**, TR 2000, TE = 60 msec after Gd-DTPA. Temporal focus seen after Gd-DTPA (**G**, **I**) is not visible on CT (**B**) or on sequences before Gd-DTPA (**F**, **H**). Note slight differences of slice orientation, indicating patient motion between pre- and post-Gd-DTPA sequences. On biopsy of large lesion, adenosarcoma was found.

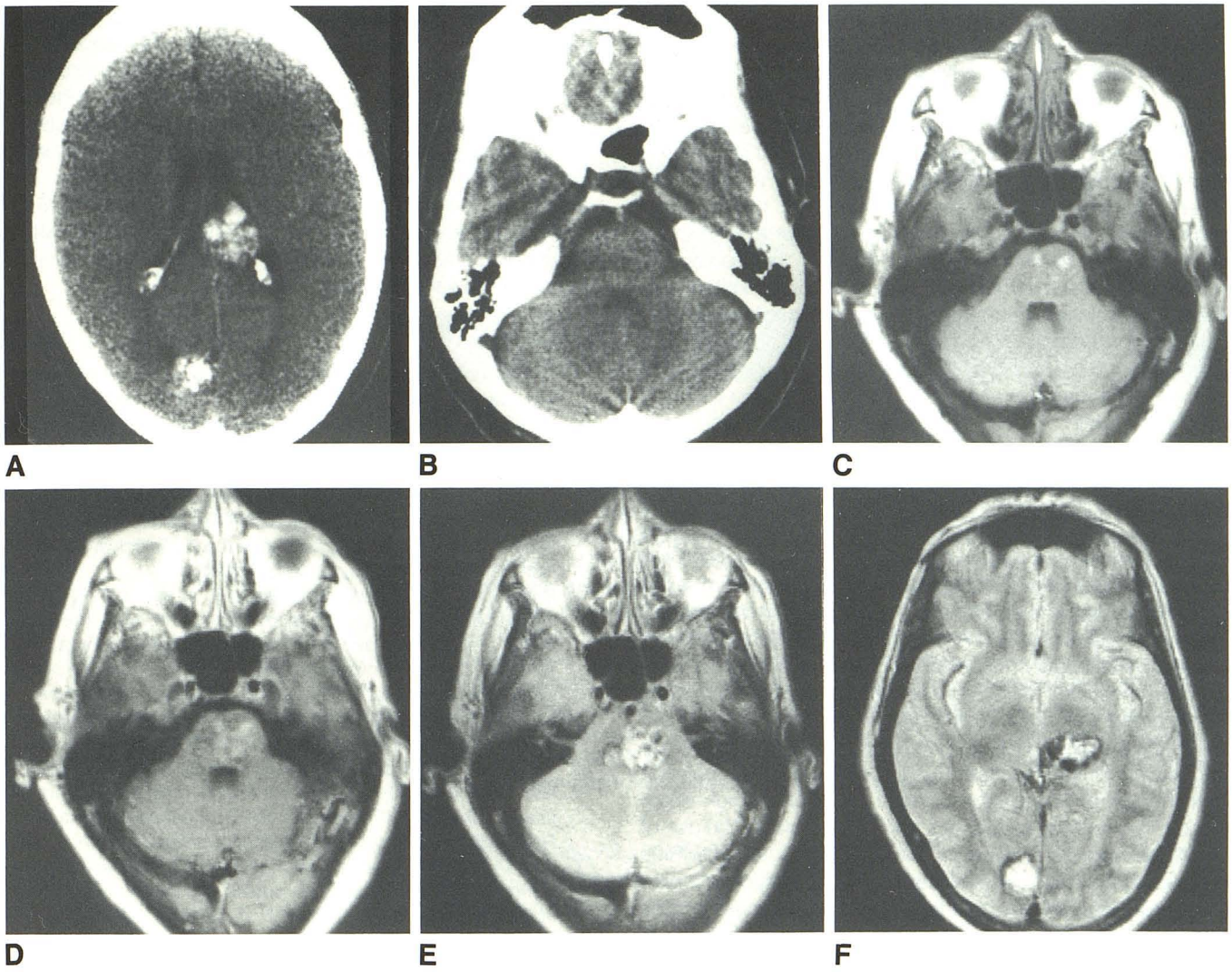

Fig. 5.—53-year-old woman with visual flashes, hearing loss. **A**, **B**, CT shows two partially calcified lesions; one in left thalamus, one in right occipital cortex. Brainstem appears normal. Angiography was negative. **C**, TR = 500, TE = 30 msec. MR shows third lesion in brainstem, missed with CT. High-intensity foci on T1- and T2-weighted sequences suggested subacute bleeding in lesion. Lack of brainstem signs or symptoms suggested occult arteriovenous malformations; biopsy of occipital lesion confirmed this. **D**, TR = 500, TE = 30 msec post-Gd-DTPA. Enhanced MR cannot distinguish foci of enhancement from foci of hemorrhage. **E**, TR = 2000, TE = 60 msec. **F**, TR = 2000, TE = 60 msec. T2-weighted sequences pre-Gd-DTPA show all three lesions with regions of signal void suggesting calcification, although hemosiderin deposition accounting for signal void cannot be excluded.

effects in patients who moved slightly between the pre- and postcontrast sequences. Our results are affected, of course, by the pulse sequences used and by the selected population. The inclusion of 10 demyelinating plaques in one patient heavily weighted the nonenhancing lesions. Also, the relatively large number of primary brain tumors in our material should be noted.

A major difference between the use of contrast agents in CT and their use in MR is documented. In CT, the greater the concentration of iodine in the abnormal tissue, the greater its enhancement. In MR, too much Gd-DTPA may produce an unwanted effect of decreasing the T2 relaxation time, which causes signal decay, as opposed to the typical signal enhancement based on more rapid T1 relaxation produced by appropriate amounts of the agent (Fig. 3).

Given the observed results, the expectation that Gd-DTPA might speed up the MR procedure obviating T2-weighted sequences will not be realized. Another early expectation—based on an analogy with CT—that contrast would significantly improve sensitivity, is also not entirely fulfilled. However, as in the case of two of our patients with metastatic disease, punctate foci of BBB breakdown may be more conspicuous after Gd-DTPA. It should be noted that slice thickness of 10 mm and the slight motion of the patients between the pre- and post-Gd-DTPA sequences detracted from a truly rigorous analysis of the comparison. It does conform to the CT analogy, however, in that early generation CT scanners with less than optimal image quality were those that especially benefited from a contrast agent.

The role of Gd-DTPA in helping to characterize disease was limited. When enhancement was seen, however, definite evidence of perfusion into and BBB breakdown around the

lesion was obtained. Such information is analogous to that obtained with contrast-enhanced CT. Both techniques can mask the presence of underlying hemorrhage if contrast-only studies are performed. The separation of tumor and edema is inaccurate on CT or MR even when a focal-enhancing lesion surrounded by low density is seen. All that is shown is the site of greatest BBB disruption, not tumor margins. Another observation dispels the misconception that contrast enhancement correlates with tumor margins (or the degree of malignancy). A number of tumors (both in this series and elsewhere) either did not enhance at all or exhibited only select foci of enhancement within a much larger tumor mass, despite their malignancy.

In view of this limited early experience, it is perhaps premature to discuss the eventual rational use of Gd-DTPA in MR of the brain. Certain preliminary points can be made, however. It is an open question whether Gd-DTPA will be used as liberally as iodinated agents are in CT for initial screening studies. The optimal sensitivity of T2-weighted sequences will ensure their routine use unless new, more sensitive sequences are developed. Nevertheless, when the information that Gd-DTPA can provide is needed, its use will significantly aid the characterization of disease on MR images. The major role for Gd-DTPA will likely be the identification of active BBB disruption, especially in patients who are known to have underlying CNS disease. Thus, once the screening T2-weighted sequence shows abnormalities, a T1-weighted sequence with Gd-DTPA may well be obtained to characterize the activity of the process. For example, in the population over the age of 65, a high incidence of abnormal high-signal foci on T2-weighted sequences is known to exist. The use of Gd-DTPA may be routine in this age group when MR is ordered to look for metastases, recent infarction, or some other process that disrupts the BBB. Such active processes should enhance on T1-weighted sequences, differentiating them from the underlying chronic high-signal foci on T2-weighted sequences. Of course, if hemorrhage (e.g., hypertensive stroke) is in the differential diagnosis, both a pre- and post-Gd-DTPA T1-weighted sequence may be needed. Gd-DTPA may be used when searching for pituitary microadenomas. The lack of a BBB in the pituitary will allow enhancement of its extracellular space and show the hypercellular or cystic microadenoma as a nonenhancing focus. In patients with previously diagnosed infection or tumor who are undergoing therapy, Gd-DTPA will be useful during follow-up in evaluating response to therapy, identifying new foci within surrounding edema, or separating such foci from demyelination due to radiation therapy.

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