Dyke Award: Gd-DTPA-Enhanced MR Imaging of Experimental Bacterial Meningitis: Evaluation and Comparison with CT

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Gd-DTPA-Enhanced MR Imaging of Experimental Bacterial Meningitis: Evaluation and Comparison with CT

Vincent P. Mathews[1]
Michael A. Kuharik[1]
Mary K. Edwards[1]
Peter G. D'Amour[1]
Biagio Azzarelli[2]
R. Gerald Dreesen[1]

Gd-DTPA-enhanced MR images of experimental bacterial meningitis were obtained after *Staphylococcus aureus* was inoculated directly into the cisterna magna of four dogs. Each animal was studied with both unenhanced and enhanced MR and CT with Gd-DTPA and meglumine iothalamate, respectively. The enhancement patterns resulting from these techniques were compared and images were correlated with histopathology. All animals demonstrated abnormal leptomeningeal enhancement on MR with Gd-DTPA, but only one of four dogs exhibited abnormal contrast enhancement on CT. In these animals Gd-DTPA-enhanced MR also identified complications of meningitis, such as ventriculitis and cerebritis, more effectively than CT did. Unenhanced MR was not helpful in identifying meningitis. Histologic evaluation demonstrated that the abnormal areas of contrast enhancement on MR and CT correlated with inflammatory cell infiltration. However, some regions of mild leptomeningitis, ependymitis, and cerebritis identified histologically did not demonstrate abnormal enhancement.

Since the animal model used was clinically and pathologically similar to human meningitis, we propose that Gd-DTPA-enhanced MR will subsequently be found more effective than unenhanced MR and IV contrast-enhanced CT for demonstrating meningitis and its complications in humans.

Uncomplicated bacterial meningitis is an infectious process in which organisms and exudate are confined to the CSF spaces and the leptomeninges [1]. The diagnosis of acute bacterial meningitis is based on the clinical presentation and laboratory CSF findings [2]. The development of CT has provided a noninvasive means of imaging the intracranial manifestations of meningitis. More important, CT has been shown effective in evaluating the complications of meningitis such as hydrocephalus, cerebritis, abscess, subdural empyema or effusion, ventriculitis, and infarction [3–9]. Other authors have indicated that CT may be valuable in predicting eventual neurologic outcome in meningitis patients [6, 7]. Contrast-enhanced CT is recommended for these patients since it may reveal areas of involvement not detected with plain CT. Meningeal, cisternal, or parenchymal enhancement may be seen after contrast administration [3, 7, 10].

More recently, MR imaging of meningitis has been described [10, 11]. Although not yet reported, paramagnetic contrast agents have been predicted to demonstrate abnormal MR enhancement in meningitis [12].

The purpose of this study is to evaluate MR of experimental bacterial meningitis and its complications using an established canine model and the paramagnetic agent gadolinium(Gd)-DTPA. The paramagnetic enhancement patterns observed on MR were compared with CT images and correlated with histopathology.

Materials and Methods

Experimental Model

Using a modification of a previously described model [13], we induced bacterial meningitis in four mongrel dogs each weighing between 10 and 22 kg. One milliliter of a saline suspension

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[1] Department of Radiology, University Hospital, 926 W. Michigan, Indianapolis, IN 46223. Address reprint requests to M. K. Edwards.

[2] Department of Pathology, University Hospital, Indianapolis, IN 46223.

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of *Staphylococcus aureus* (*S. aureus*), containing approximately 10^9 organisms, was injected into the cisterna magna. Intramuscular ketamine provided sedation for inoculation and imaging. The animals were observed closely for clinical signs of meningitis.

Imaging Techniques

CT (General Electric 9800) was performed both with and without IV contrast (2.2 ml/kg 60% meglumine iothalamate). High-resolution 5-mm axial sections were obtained with the CT scanner operating at 120 kVp and 140 mA. Enhanced scans were acquired 5 min after IV contrast injection.

A 1.5-T superconducting MR imager (Picker International) was used with a 28-cm internal diameter head coil. Images were acquired in the axial and coronal planes using a 5-mm slice thickness, 256 × 256 matrix, two repetitions, and a 20-cm field of view. The pulse sequences used were a spin-echo format with 600/26 for T1-weighted images and 2000/90 for T2-weighted images. Motion artifact suppression technique (MAST) was used with the T2-weighted sequence and allowed the acquisition of only a single echo. T1- and T2-weighted images were obtained before Gd-DTPA administration and T1-weighted images were acquired 5 min after the IV injection of Gd-DTPA at a dose of 0.2 mmol/kg. MR was performed immediately after CT. CT and MR, with and without iodinated contrast and Gd-DTPA, respectively, were obtained before and at intervals ranging from 13 to 134 hr after the induction of meningitis. Specifically, the animals were imaged after inoculation as follows: dog 1 at 28 hr, dog 2 at 15, 40, and 64 hr, dog 3 at 15 and 134 hr, and dog 4 at 15 hr.

Pathologic Examination

CSF was sampled and analyzed prior to bacterial inoculation. After inoculation, CSF was obtained at the time of imaging and examined for cell count and protein as well as cultured for bacterial growth. Animals were sacrificed at different intervals ranging from 15 to 135 hr after inoculation, immediately following the imaging procedures. The brains were fixed in formalin for a minimum of 2 weeks and then cut at 5-mm intervals either in the axial or coronal plane. Representative sections were obtained for histology. Examination was performed on 10-μm-thick sections of paraffin-embedded material. The sections were stained with hematoxylin and eosin (H and E).

Results

Experimental Model

Meningitis was confirmed in all four animals by the clinical observation of lethargy, nuchal rigidity, and varying degrees of gait disturbance as well as the development of CSF leukocytosis and protein elevation. CSF cultures were positive for *S. aureus* growth.

CT and MR

CT scans were degraded variably by streak artifacts caused by the relatively thick canine skulls. Because of these artifacts, changes in ventricular size associated with meningitis were not appreciated by CT. Abnormal contrast enhancement was evaluated by comparing scans before and after inoculation. Twenty-eight hours after the induction of meningitis, one of four animals demonstrated abnormal contrast enhancement by CT. This enhancement was mild in nature and was located in the posterior fossa (Figs. 1A and 1B).

MR images prior to the induction of meningitis were normal in the four animals. Pre-Gd-DTPA T1- and T2-weighted images revealed increased ventricular size in each of the infected animals but did not demonstrate signal abnormality of the leptomeninges or cisterns. On the post-Gd-DTPA T1-weighted images, abnormal enhancement was observed in all four animals between 13 and 29 hr after inoculation. Bright paramagnetic enhancement of the posterior fossa meninges, basal cisterns, and/or superficial cerebellar and brainstem parenchyma developed in all four animals (Figs. 1C and 1D). At the same time, supratentorial leptomeningeal enhancement occurred in only two of four dogs. One of these dogs exhibited diffuse gyriform enhancement suggesting underlying cerebritis (Fig. 2). Another animal (dog 3) demonstrated subependymal paramagnetic enhancement of the third and lateral ventricles on the post-Gd-DTPA T1-weighted image 134 hr after induction of infection, suggesting the development of ventriculitis (Figs. 3A–3C). The pre-Gd-DTPA T2-weighted image of this animal demonstrated abnormal irregular bright signal in the subependymal region of the lateral ventricles (Fig. 3D).

Neuropathology

After necropsy, all four animals were found to have the characteristic inflammatory cell infiltration of the leptomeninges seen in meningitis (Fig. 4). In all dogs the underlying superficial cortex was also mildly inflamed. In each animal, areas of abnormal paramagnetic enhancement observed on the post-Gd-DTPA T1-weighted image correlated with severe inflammatory changes histologically. However, areas of less intense meningeal inflammation at necropsy did not demonstrate abnormal enhancement on MR. In addition, two dogs (1 and 2) had mild ependymitis histologically without associated Gd-DTPA enhancement. However, at necropsy dog 3 demonstrated very severe ependymitis with subependymal cerebritis and choroid plexus inflammation (Fig. 5). These findings correlated well with the pattern of abnormal paramagnetic enhancement on the T1-weighted images (Figs. 3B and 3C).

Discussion

Bacterial meningitis develops in humans when the causative organism reaches the leptomeninges via the bloodstream, by direct extension from an adjacent infection, or by traumatic inoculation [2]. The method of direct inoculation used in this study, although artificial, effectively produced clinical, laboratory, and histologic findings identical to those in naturally acquired disease [2].

CT has been used primarily to detect complications associated with meningitis [3–7, 9]. The actual meningeal involvement by the infection, however, has only been inconsistently demonstrated by CT as areas of contrast enhancement. The proposed mechanisms for enhancement with iodinated contrast include the presence of contrast in dilated and engorged

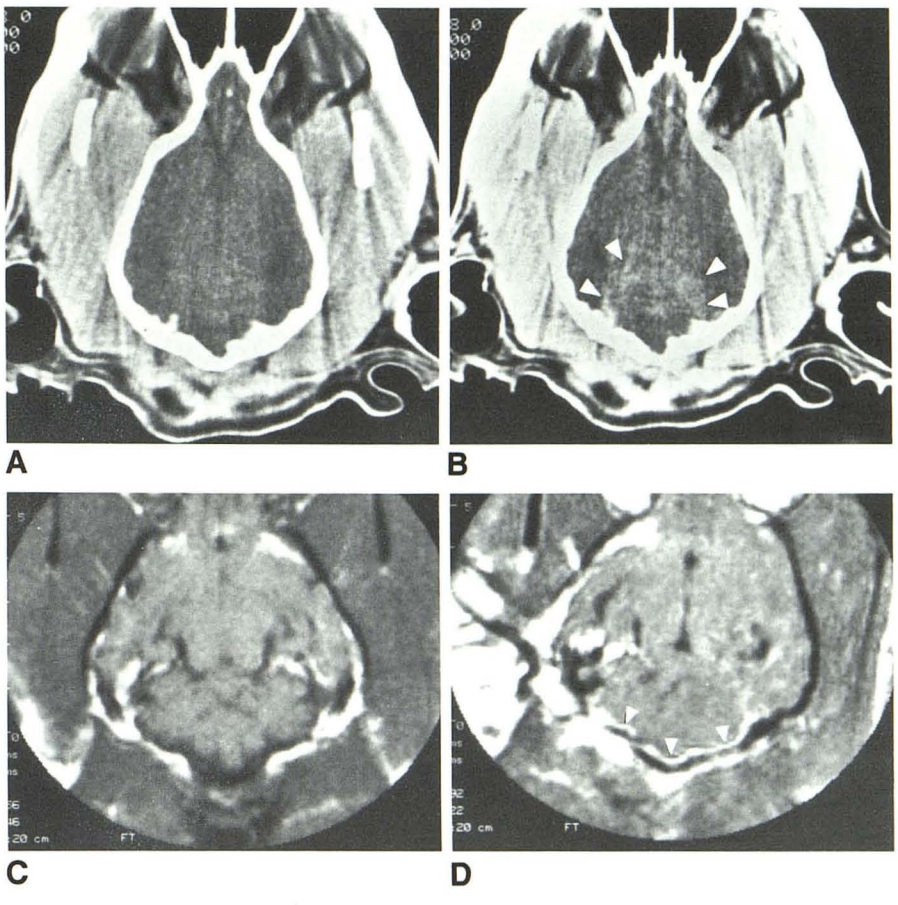


Fig. 1.—Dog 1.
***A*, Unenhanced CT scan obtained 27 hr after inoculation is unremarkable.**
***B*, Contrast-enhanced CT scan obtained at the same time as *A* demonstrates mild posterior fossa enhancement (*arrowheads*).**
***C*, Unenhanced 600/20 T1-weighted image of the animal imaged in *A* and *B* obtained before the induction of meningitis.**
***D*, Post-Gd-DTPA 600/20 T1-weighted image 1 hr after *A* and *B* and at a similar level to *C* shows abnormal enhancement of meninges surrounding cerebellum (*arrowheads*).**

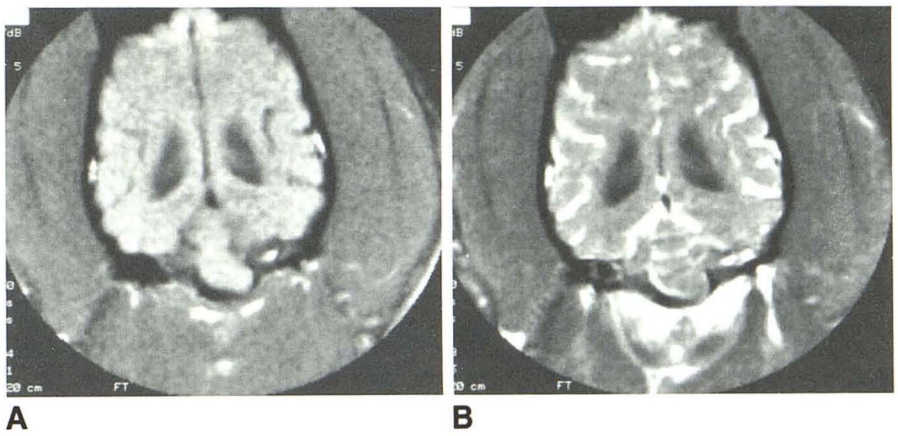
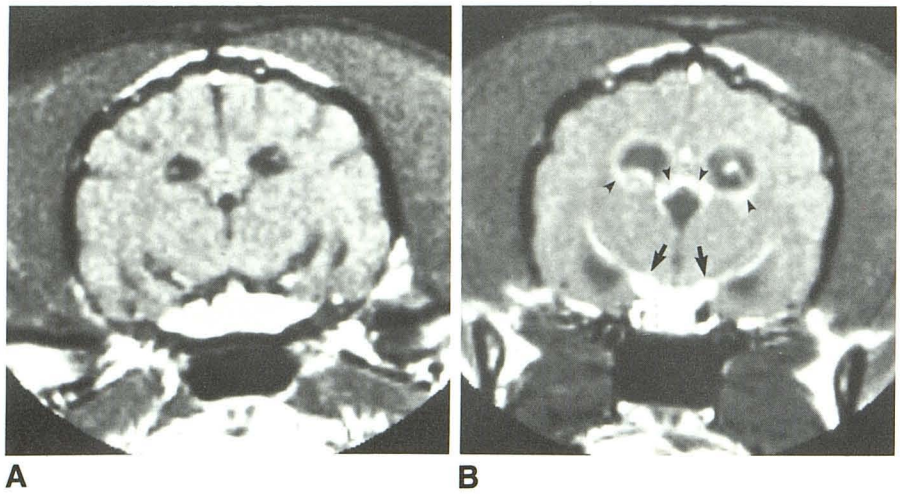


Fig. 2.—Images of dog 2 obtained 15 hr after bacterial inoculation.
***A*, Pre-Gd-DTPA 600/26 T1-weighted image shows mild hydrocephalus.**
***B*, Post-Gd-DTPA 650/26 T1-weighted image exhibits marked meningeal and cortical enhancement both supratentorially and infratentorially.**

leptomeningeal vessels and abnormal function of the blood-meningeal barrier resulting from inflammation near these vessels [3, 6, 14]. The term blood-meningeal barrier refers to that portion of the blood-brain barrier formed by capillaries of the leptomeninges [3].

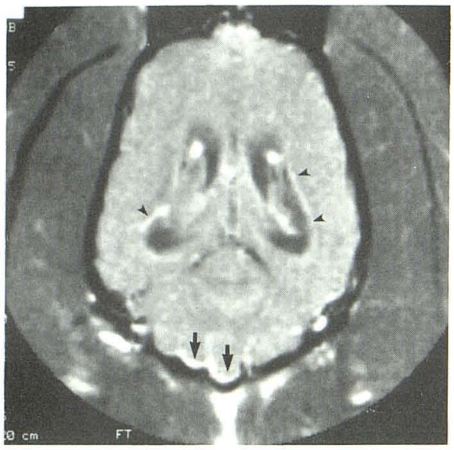
Gd-DTPA has previously been shown to function similarly to water-soluble, iodinated contrast agents and to produce abnormal enhancement in CNS infections [15–17]. However, while flowing blood reliably enhances with contrast-enhanced CT, the arterial and capillary vascular space inconsistently enhances with Gd-DTPA-enhanced MR [18]. Therefore, blood-meningeal barrier abnormalities rather than contrast material in vessels are more likely to be responsible for the reproducible leptomeningeal MR contrast enhancement observed in this study.

In our cases of experimental meningitis, post-Gd-DTPA T1-weighted images more consistently exhibited abnormal enhancement than did contrast-enhanced CT. The extent of meningeal inflammation was also more accurately depicted by Gd-DTPA-enhanced MR than by contrast-enhanced CT. In one case of ventriculitis, Gd-DTPA-enhanced T1-weighted images demonstrated marked ependymal enhancement



A

B



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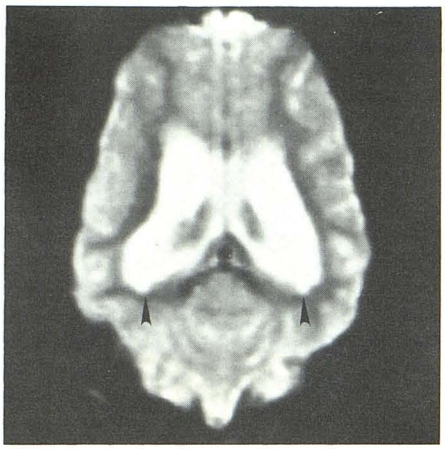

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Fig. 3.—Dog 3.

***A*, Post-Gd-DTPA 500/26 coronal T1-weighted image before induction of meningitis reveals no abnormal areas of enhancement.**

***B*, Post-Gd-DTPA 650/26 coronal T1-weighted image 5 days after onset of meningitis demonstrates dilatation of lateral and third ventricles as well as abnormal contrast enhancement of the ventricular lining (*arrowheads*) and basal cisterns (*arrows*).**

***C*, Post-Gd-DTPA 600/26 axial T1-weighted image at same time as *B* exhibits abnormal ventricular (*arrowheads*) and posterior fossa (*arrows*) enhancement.**

***D*, Pre-Gd-DTPA 2000/90 axial T2-weighted image obtained just prior to *B* and *C* demonstrates mild contour irregularity (*arrowheads*) of lateral ventricles posteriorly. Signal in the meningeal region is unchanged from premeningitis images.**

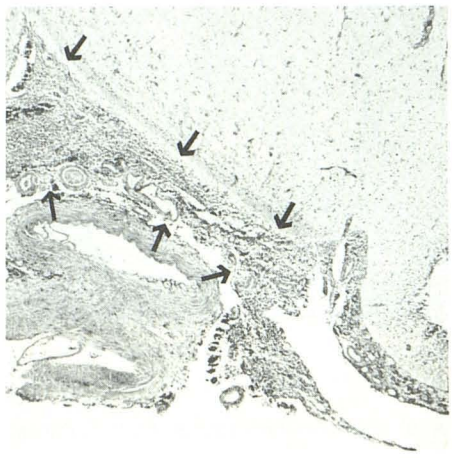

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Fig. 4.—Photomicrograph illustrates extensive acute inflammatory infiltrates confined primarily to the leptomeninges (*arrows*). (H and E, ×40)

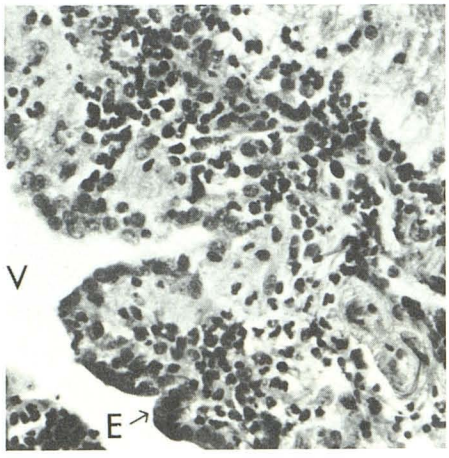

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Fig. 5.—Photomicrograph demonstrates extensive acute inflammatory infiltrates in subependymal region. V = lateral ventricle. E = ependyma. (H and E, ×400)

whereas contrast-enhanced CT was unremarkable. These observations are probably the result of the superior anatomic detail and greater tissue contrast afforded by MR relative to CT. These advantages are especially beneficial around the brainstem and areas adjacent to cortical bone where contrast enhancement on CT may be obscured. However, Gd-DTPA may, for as yet undetermined reasons, be more sensitive in delineating blood-brain barrier abnormalities than iodinated contrast.

Pathologic examination of the animals in this study demonstrated that areas of contrast enhancement on both CT and MR images correlated with inflammatory cell infiltration. This has been assumed to be the case in CT of meningitis, but histologic correlation with CT or MR has not been previ-

ously disclosed. The value of CT in demonstrating the extent of infection in meningitis [6] and ventriculitis [9] has been reported. In our animal model Gd-DTPA-enhanced T1-weighted images revealed inflammatory meningeal and ependymal processes more effectively than did contrast-enhanced CT. However, Gd-DTPA-enhanced MR is not completely accurate in depicting CNS inflammation, as indicated by the histologic demonstration of areas of leptomeningitis, cerebritis, and ventriculitis that did not enhance after Gd-DTPA administration. These areas of inflammation were mild, however, whereas regions of more intense inflammation corresponded more closely to paramagnetic contrast enhancement on MR. This suggests that there may be a threshold of inflammation above which there is enough disruption of the blood-meningeal barrier to permit the visualization of Gd-DTPA enhancement. Nevertheless, as MR is improved, the disparity between diagnostic imaging and histology may further diminish.

The observation that unenhanced T1- and T2-weighted images were not helpful in detecting meningitis is notable. Peripheral extension of white-matter MR signal such that it appeared to merge with marrow signal has been described in meningitis [11] but was not seen in our cases. In the case of severe ventriculitis T2-weighted images revealed irregular contour of the lateral ventricles, which may be a helpful sign in making this diagnosis. Irregularity of ventricular margins has previously been described in some CT cases of ependymitis [20]. Mild degrees of ventriculitis and cerebritis were also not identified with T2-weighted or unenhanced T1-weighted images.

The clinical usefulness of MR in the management of patients with meningitis remains to be determined. The delineation of the extent of meningeal involvement may be important when evaluating patients with delayed response to therapy. Persistent meningeal inflammation or the development of ventriculitis may be illustrated in these patients and, on the basis of our results, will likely be more effectively depicted with Gd-DTPA-enhanced T1-weighted images than with contrast-enhanced CT or unenhanced MR. Previous investigation has indicated that MR may be more effective than CT in detecting the early stages of abscess formation [16, 17], which may also complicate meningitis. Other authors studying brain abscess have suggested that the greater inherent tissue contrast of MR relative to CT as well as the higher therapeutic safety index of Gd-DTPA compared with iothalamate allows one to obtain more information from Gd-DTPA-enhanced MR than from contrast-enhanced CT [21]. This argument can be applied to the imaging of meningitis and its complications as well.

Conclusions

Gd-DTPA-enhanced MR demonstrated abnormalities characteristic of meningitis with far greater frequency than did contrast-enhanced CT. While others have found ventricular dilatation to be the most common CT abnormality in meningitis [20, 22], meningeal and cisternal MR contrast enhancement with Gd-DTPA was just as common as hydrocephalus in our meningitis model. In this study Gd-DTPA-enhanced T1-weighted images were superior to contrast-enhanced CT scans not only in the detection of meningeal involvement but also in the identification of complications such as cerebritis and ventriculitis. Unenhanced MR was not helpful in identifying meningitis in these animals but it did detect some complications of meningitis such as hydrocephalus and ventriculitis. Since the animal model of meningitis used produced clinical and pathologic responses similar to those in human meningitis, we propose that Gd-DTPA-enhanced MR will prove more effective than contrast-enhanced CT and unenhanced MR for demonstrating meningeal inflammation as well as the complications of meningitis in humans.

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