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Gd-Enhanced MR Imaging of Acute and Chronic Experimental Demyelinating Lesions

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Experimental allergic encephalomyelitis, a demyelinating disease with marked similarity to multiple sclerosis, was produced in two of 12 dogs. All dogs were studied with serial MR imaging. T1- and T2-weighted MR images were obtained both before and after IV Gd-DTPA. Multiple, new periventricular white matter demyelinating lesions were observed after each clinical episode of the disease. Like multiple sclerosis, the acute lesions of experimental allergic encephalomyelitis on T2-weighted MR images were indistinguishable from the older, more chronic lesions. However, after Gd-DTPA, there was bright paramagnetic enhancement of the acute lesions and, in one animal, no enhancement of the chronic lesions on T1-weighted MR images. At necropsy, the differences in the MR paramagnetic enhancement correlated well with the relative histologic age of the demyelinating lesions.

Our results suggest that MR with Gd-DTPA may be used to differentiate acute, active demyelinating lesions from the more chronic, inactive lesions in this animal model.

Experimental allergic encephalomyelitis (EAE) is a well established animal model for human demyelinating diseases, particularly multiple sclerosis (MS) [1-8]. The disease is produced by inducing a cell-mediated hypersensitivity response to the myelin of the CNS with subsequent demyelination. The distribution, gross and histopathologic appearance of the CNS lesions, as well as the clinical course of EAE closely resembles MS [1-8].

MR imaging has dramatically improved the diagnostic evaluation in patients with MS [9, 10]. With MR, one can assess the number, size, and location of the MS lesions. However, MR has not previously been proved to reliably differentiate acute active MS lesions from chronic plaques. Recently, Grossman et al. [10] described paramagnetic enhancement of MS lesions present in patients with new clinical symptoms, thus suggesting a means by which active MS lesions may be distinguished.

The purpose of this project was to (1) determine if the canine form of EAE is a useful animal model for human demyelinating diseases in relation to its neuropathologic and MR appearance; (2) observe the changes in the demyelinating lesions over the course of the disease with MR; and (3) determine if Gd-DTPA can be used with MR to differentiate acute from chronic demyelinating lesions as assessed by specimen correlation.

Methods and Materials

Experimental Model

Induction of the canine form of EAE was attempted in 12 mongrel dogs, each weighing approximately 20 kg, by using the method described by Summers et al. [4]. The canine cervical spinal cord was emulsified in physiological saline to give a 50% weight/volume suspension. The thick emulsion was mixed with an equal volume of Freund's complete adjuvant (Sigma, no. F-5881). Each dog was inoculated subcutaneously along the back at

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five different sites with the spinal cord–adjuvant mixture for a total of 1 ml. The injections were repeated every 15 days or until the disease developed. Once signs of the disease occurred, no additional injections were given. The dogs were observed daily for neurologic signs typical of EAE: gait ataxia, progressive paralysis, and blindness. Dogs were imaged within 24 hr of such signs, and were otherwise scanned at approximately 10-day intervals.

MR Imaging

A 1.5-T superconducting Picker MR imager was used with a 20-cm field of view, a 192×192 matrix with two repetitions, and a 5-mm section thickness. Images were obtained in the axial plane with the dog lying supine after sedation with 5 ml of ketamine intramuscularly. The head was placed within a knee surface coil for improved resolution. T1-weighted SE pulse sequences were 600/20 (TR/TE), and T2-weighted SE pulse sequences were 2000/90.

The MR examinations were obtained first without and then with Gd-DTPA, which was administered as an IV bolus injection at a dose of 0.2 mmols/kg. The dogs were scanned 10 min after the injection. All dogs in the study had MR scans prior to EAE induction to exclude any previously existing cranial pathology.

Neuropathology

The dogs that acquired EAE were to be sacrificed during either (1) the acute phase of EAE, which was defined as 0–5 days after the onset of neurologic signs, or (2) the chronic phase of EAE, defined as more than 4 weeks after the onset of neurologic signs and after partial or complete remission of those signs. The animals were killed with an overdose of thiopental. The brains were removed intact and fixed in 10% buffered formalin. They were cut axially at 5-mm sections in approximately the same plane as the MR images. These sections were inspected for gross lesions. Histologic whole brain sections were cut at 10 μ m and stained with H and E and with Smith's myelin stain.

Results

Experimental Model

We attempted to induce EAE in 12 dogs, of which most received multiple injections and were observed for at least 30 days (range, 30–114 days). Of the 12 dogs studied, only two (dogs 3 and 6) developed EAE (17%). Both animals showed clinical signs of EAE 12 days after the first injection. No additional injections were given. The initial sign was gait ataxia, which progressed rapidly to extremity paralysis or weakness. In dog 6, the neurologic deficit was maximal for 10 days and resolved completely over the next 14 days. The dog did well over the next 36 days, both in appearance and behavior, until 72 days after EAE induction. At this time, the animal again developed acute, diffuse neurologic signs, representing a second acute episode of EAE.

Dog 6 was sacrificed on day 73 postinduction, which was considered to be during both an acute phase of EAE (1 day after the onset of the second episode of neurologic signs) and a chronic phase of EAE (60 days after the onset of the initial neurologic signs). Dog 3 died during the acute phase of EAE on day 12 postinduction (day 1 of neurologic signs).

MR Imaging

MR examinations were performed within 12 hr of the acute neurologic signs (day 12 postinduction for dogs 3 and 6). The pre-Gd T1-weighted MR images did not reveal any abnormalities. However, pre-Gd T2-weighted images did show multiple small, focal regions of high signal in the periventricular and deep white matter of the cerebrum and cerebellum (Figs. 1A and 1B). After the administration of Gd-DTPA these same lesions were found to exhibit bright paramagnetic enhancement on the T1-weighted images (Figs. 1C and 1D). On day 30 postinduction (day 18 of the disease), dog 6 was observed to have persistent but slowly resolving paralysis. The white matter lesions on pre-Gd T2-weighted images appeared slightly larger and better defined. Faint paramagnetic enhancement was noted on post-Gd T1-weighted images. By day 56 postinduction (day 44 of the disease) all neurologic deficits had completely resolved. MR images at this time demonstrated no change in the appearance of the multiple white matter abnormalities on pre-Gd T1- and T2-weighted images. On post-Gd T1-weighted images, however, no enhancement was observed (Fig. 2). This animal continued to be neurologically intact until day 72 postinduction (day 60 of the disease) when the dog was found to be completely quadriplegic and severely obtunded. This exacerbation was considered the second episode of EAE. MR examination performed at that time revealed multiple, new high-signal subcortical and periventricular white matter lesions on the pre-Gd T2-weighted images (Figs. 3A and 3B, *arrow*). The white matter lesions from the previous (first) episode of EAE appeared unchanged and indistinguishable in appearance from the new-onset (second-episode) lesions on pre-Gd T2-weighted images (Figs. 3A and 3B, *arrowheads*). Post-Gd T1-weighted images demonstrated bright enhancement of the new, second-episode lesions (Fig. 3C, *arrows*). Again, no enhancement of the older, first-episode lesions was observed.

Neuropathology

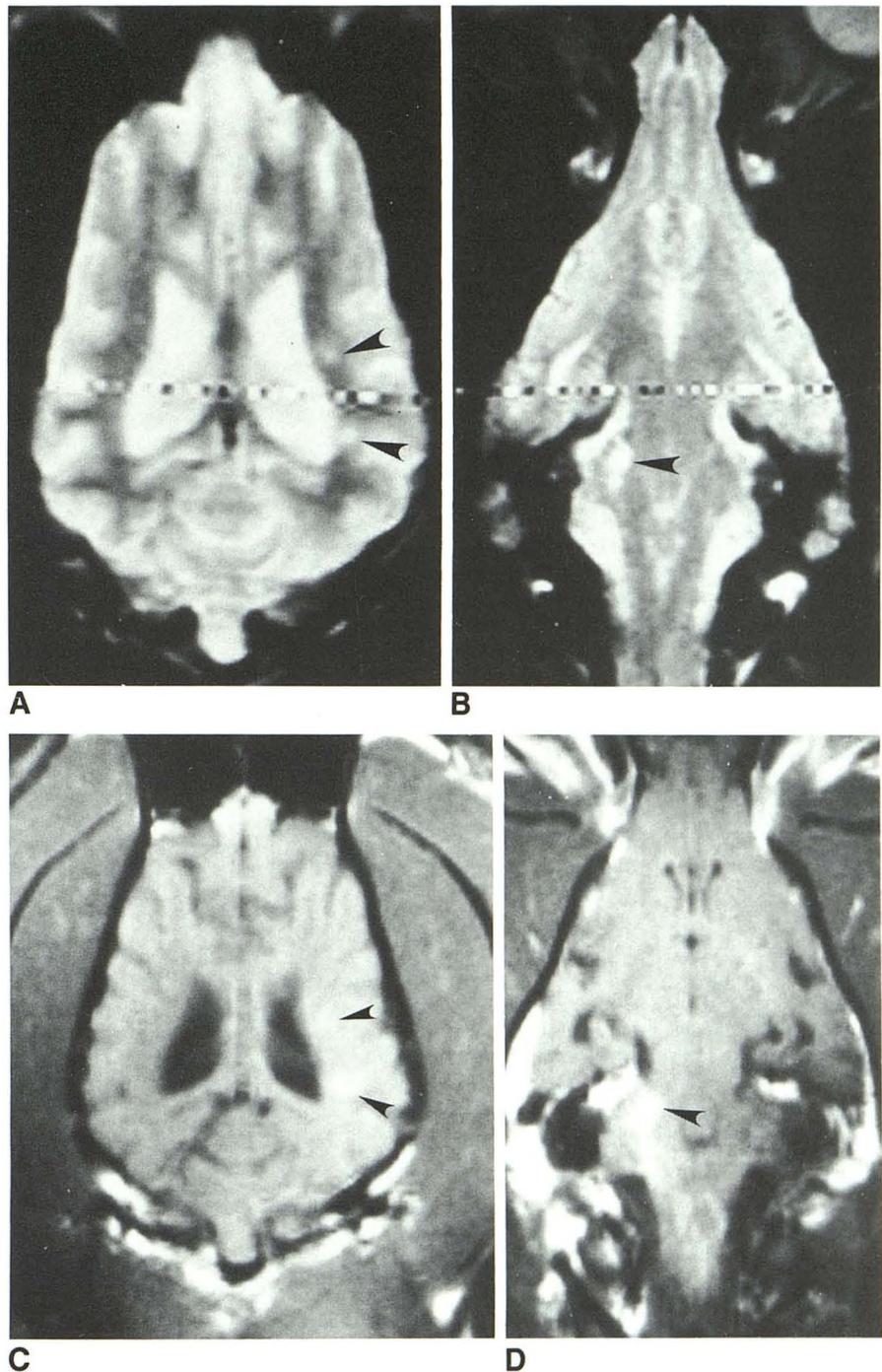
Dog 3 died during the acute phase of EAE (day 12 postinduction, day 1 of the disease), and dog 6 was sacrificed 24 hr after the onset of the second episode of EAE (acute phase, second episode). At the time of necropsy, dog 6 was also clinically fully recovered from the first episode of EAE (day 61 of the disease). These lesions were stable, clinically silent, and considered chronic-phase EAE.

Gross examination of the brain axial sections revealed a few small foci of necrosis, which correlated with the larger high-signal lesions seen on the pre-Gd T2-weighted images (Fig. 4). Many of the smaller lesions noted on the MR examinations were not identified grossly. These same lesions were, however, seen after whole-section myelin staining with a high degree of correlation to the T2-weighted images (Fig. 5). H and E stained sections of the lesions observed on MR during the acute phase of the disease demonstrated a well organized perivascular cellular infiltration consisting of small lymphocytes and polymorphonuclear neutrophils (Fig. 6A). Myelin

Fig. 1.—Dog 6, day 12 postinjection (day 1 of the disease). Neurologic: hind-leg paralysis, foreleg weakness, mildly obtunded.

A and B, Pre-Gd T2-weighted MR image 2000/90. Multiple small, indistinct high-intensity lesions (*arrowheads*) in left periventricular (A) and right cerebellar (B) white matter.

C and D, Post-Gd T1-weighted MR image 600/20. Paramagnetic enhancement (*arrowheads*) of white matter lesions seen on T2-weighted images in A and B; left periventricular (C) and right cerebellar (D) white matter.



stained sections of these lesions showed the characteristic perivascular demyelination (Fig. 6B). These foci were therefore characterized as acute demyelinating lesions.

Histologic examination of the chronic-phase (>60 days old) lesions revealed a disorganized diffuse cellular infiltration consisting of macrophages and plasma cells with the persistence of some lymphocytes. These lesions were believed to be subacute to early chronic demyelinating lesions. Truly chronic lesions in which gliosis had become marked were not seen. This process may take many months to occur.

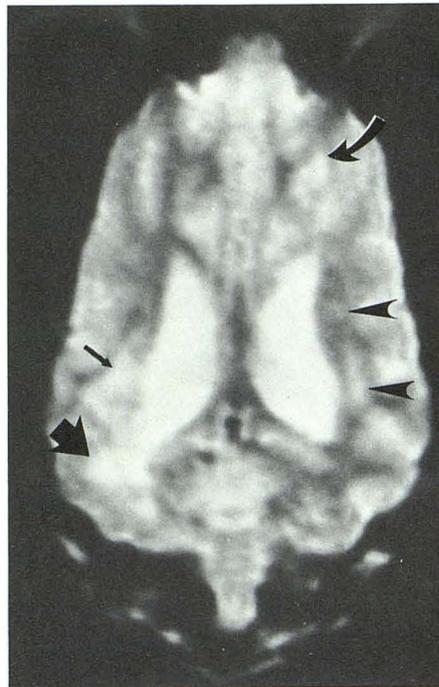
Discussion

EAE was first described in 1933 and has become one of the most extensively studied experimental autoimmune diseases [1–8, 11]. EAE is a cell-mediated delayed hypersensitivity response that develops to the myelin basic protein (MBP) present in mammalian neural tissues [2–4, 7]. MBP is a neuroantigen that stimulates peripheral T-lymphocytes in the regional draining lymph nodes near the site of the subcutaneous injection [2]. These activated lymphocytes circulate,

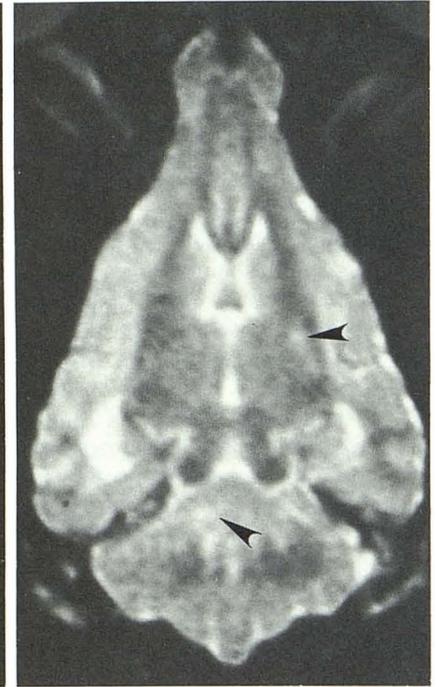


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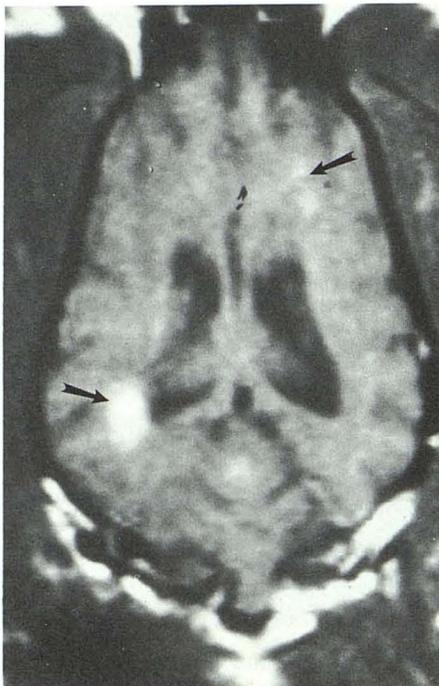
Fig. 2.—Dog 6, day 56 postinjection (day 44 of the disease). Neurologic: complete resolution of all neurologic deficits. Post-Gd T1-weighted MR image 600/20. No paramagnetic enhancement of white matter lesions observed earlier.



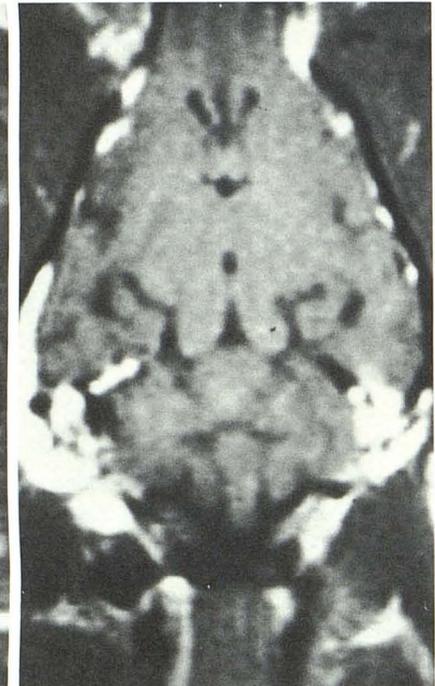
A



B



C



D

Fig. 3.—Dog 6, day 72 postinjection (day 60 of the disease). Neurologic: new onset of complete quadriplegia, severely obtunded (second episode of EAE, day 1).

A and B, Pre-Gd T2-weighted MR image 2000/90. Multiple new high-signal white matter lesions; right occipital subcortical lesions (*large arrow, A*) confluent with right periventricular lesion (*small arrow, A*); left frontoparietal subcortical lesion (*curved arrow, A*). White matter lesions from previous (first) episode of EAE are unchanged (*arrowheads, A and B*).

C and D, Post-Gd T1-weighted MR image 600/20. Bright enhancement of the new (second-episode) lesions (*arrows*); right periventricular and left frontoparietal white matter (C). Again, no enhancement was observed of the older, first-episode, EAE lesions (left periventricular and right cerebellar).

encountering MBP in the myelin sheaths of the CNS. A hypersensitivity response is induced with the accumulation of acute inflammatory cells in the neural perivascular spaces. Demyelination then proceeds either by direct cytotoxic effects on the myelin-producing cells or by localized production of cytotoxic antibodies, or both [2-4].

The relapsing form of EAE resembles MS in many ways. Surviving EAE animals demonstrate marked reversibility of symptoms. The preferred periventricular anatomic sites of demyelinating lesions with perivascular cellular infiltrates and demyelination as well as the sera and CSF immunoglobulin changes are also similar to MS [2, 3]. The canine form of this

Fig. 4.—Gross brain, dog 6. 5-mm axial sections. *Arrowhead* points to region of abnormal white matter seen on MR. Focal necrosis left periventricular white matter after relatively chronic-phase EAE.

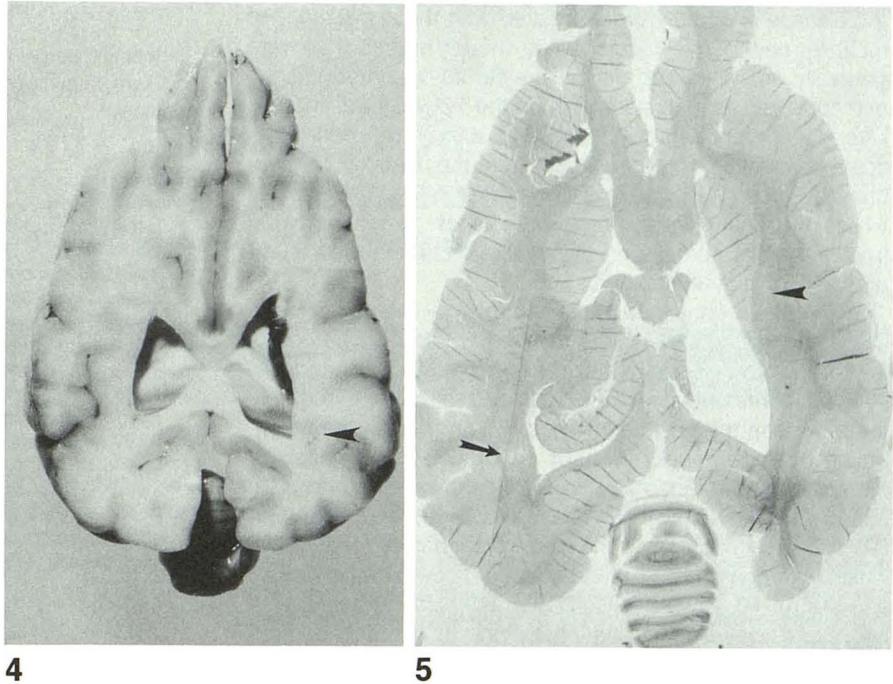


Fig. 5.—Myelin stain, dog 6. 10- μ m sections. *Arrow* points to acute-phase EAE lesions with patchy demyelination of right periventricular white matter. *Arrowhead* points to a relatively chronic-phase EAE lesion, left periventricular white matter.

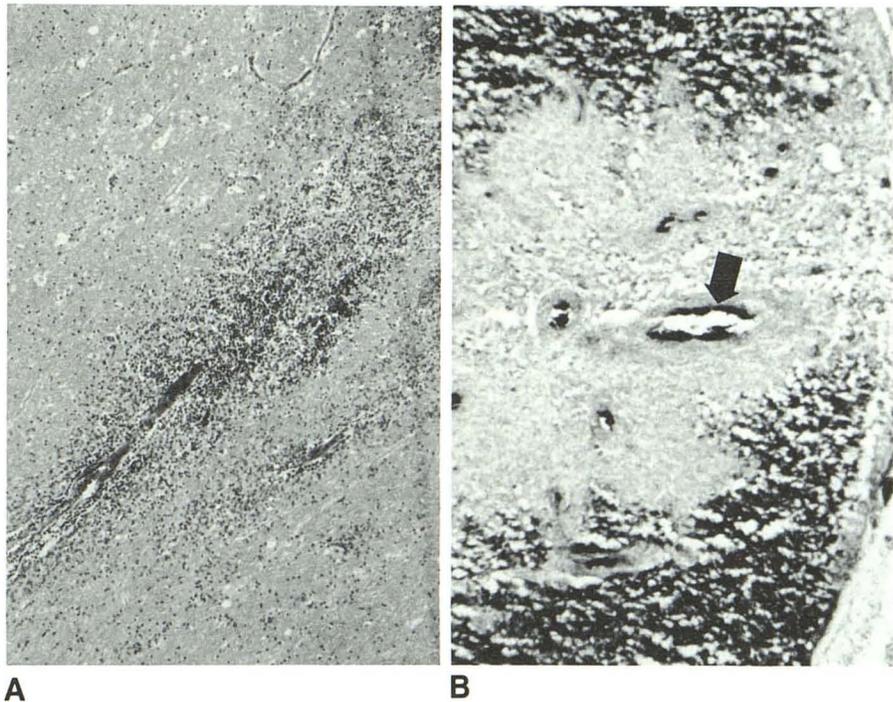


Fig. 6.—Neurohistopathology acute-phase EAE lesions, dog 6. 10- μ m sections.

A, H and E stain. Well organized, perivascular cellular infiltration by polymorphonuclear neutrophils and lymphocytes.

B, Myelin stain. Perivascular demyelination about a venule (*arrow*).

disease was chosen for its morphologic/pathologic resemblance to human MS and for the experimental animal's large brain size, which allowed for reproducible lesion imaging in the living animal.

MR is exquisitely sensitive in detecting white matter abnormalities, particularly on the T2-weighted images. These high signal abnormalities are nonspecific, but in MS patients, the

periventricular lesions in conjunction with a typical clinical history and spinal fluid abnormalities allow definitive diagnosis of the disease [12]. Unfortunately, MR examinations have not been able to differentiate acute, active MS lesions from chronic, inactive plaques [10].

EAE in our animal closely resembled MS in disease course and in MR appearance of the lesions. The clinical episodes of

the disease in dog 6 were correlated with the appearance of multiple, new periventricular white matter lesions that were generally not visualized on the pre-Gd T1-weighted images and appeared as high signal foci on the T2-weighted images. Like MS, the appearance of these lesions on MR during the acute phase was indistinguishable from the relatively chronic-phase lesions. This situation is illustrated in Figs. 3A and 3B, where the acute lesions (*arrows*) cannot be differentiated from the more chronic, 60-day-old lesions (*arrowheads*) on pre-Gd T2-weighted images.

MR contrast enhancement is obtained by the use of paramagnetic agents, such as Gd-DTPA. The Gd³⁺ ions possess seven unpaired electrons that impart a relatively strong magnetic moment on the ion. This produces a local magnetic field that shortens the relaxation times, T1 and T2, of the neighboring hydrogen nuclei [13–20]. IV Gd-DTPA is exclusively extracellular and does not normally cross the blood-brain barrier [13–15, 18–20]. It is these properties that make Gd-DTPA useful in assessing the blood-brain barrier breakdown, which commonly occurs in the acute or active lesions of EAE and MS [6, 10, 21]. After Gd-DTPA, the histologically classified acute-phase demyelinating lesions in our dog demonstrated bright paramagnetic enhancement on the T1-weighted images (Fig. 3C, *arrows*). These same lesions were thought to be clinically active, causing the animals neurologic deficits. Over the next 3–4 weeks, the neurologic deficits resolved and the white matter lesions began to lose their paramagnetic enhancement. Histologically classified subacute/early-chronic-phase demyelinating lesions, which occurred more than 60 days after the onset of the disease, did not exhibit enhancement on the post-Gd T1-weighted images (Figs. 3C and 3D). These lesions were considered clinically silent with an apparent reestablishment of the blood-brain barrier. This difference in the paramagnetic enhancement characteristics may allow the separation between the acute, active demyelinating lesions and the relatively chronic, inactive lesions.

Our research complements the work of Grossman et al. [10] in which paramagnetic enhancement was observed in MS lesions thought to be active. Tissue specimens of these lesions were, however, not available for gross and histologic analysis of lesion age or activity. Our study suggests a relationship between the relative age of the EAE demyelinating lesions and the presence of paramagnetic enhancement. More specifically, we have demonstrated in one animal that the demyelinating lesions of EAE evolve over time from acute paramagnetic enhancing foci to chronic nonenhancing plaques. Because of the marked similarities between EAE and MS, we believe a similar phenomenon can be expected during MS lesion evolution.

In conclusion, the results from our current investigation suggest that MR with Gd-DTPA may be used to differentiate acute from chronic demyelinating lesions in this animal model. We believe the EAE animal model closely resembles MS in its MR appearance and provides a unique opportunity to observe the MR evolution of demyelinating lesions with gross and histologic specimen correlation. Finally, these findings may assist in the interpretation of MR with paramagnetic contrast in human demyelinating diseases.

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REFERENCES

- McFarlin DE, McFarland HF. Multiple sclerosis. *N Engl J Med* 1982;307:1183–1188, 1246–1251
- Rowe MJ. Experimental allergic encephalomyelitis: a review. *Bull Los Angeles Neurol Soc* 1969;34(1):55–66
- Lisak RP, Behan PO. Experimental autoimmune demyelinating diseases: experimental allergic encephalomyelitis and experimental allergic neuritis. *Biomed Pharmacother* 1975;22:81–87
- Summers BA, Greisen HA, Appel MJ. Canine distemper and experimental allergic encephalomyelitis in the dog: comparative patterns of demyelination. *J Comp Pathol* 1984;94:575–589
- Ferraro A, Cazzullo CL. Chronic experimental allergic encephalomyelitis in monkeys. *J Neuropathol Exp Neurol* 1948;7:235–260
- Alvord EC. Summary and concluding remarks. In: Kiess MW, Alvord EC, eds. "Allergic" encephalomyelitis: experimental allergic encephalomyelitis and its relation to other diseases of man and animals. Chicago: Thomas, 1959:518–557
- Wisniewski HM, Keith AB. Chronic relapsing experimental allergic encephalomyelitis: an experimental model of multiple sclerosis. *Ann Neurol* 1977;1:144–148
- Wolf A, Kabat EA, Bezer AE. The pathology of acute disseminated encephalomyelitis produced experimentally in the rhesus monkey and its resemblance to human demyelinating disease. *J Neuropathol Exp Neurol* 1947;6:333–357
- Sheldon JJ, Siddharthan R, Tobias J, Sheremata WA, Soila K, Viamonte M. MR imaging of multiple sclerosis: comparison with clinical and CT examinations in 74 patients. *AJR* 1985;145:957–964
- Grossman RI, Gonzalez-Scarano F, Atlas SW, Galetta S, Silberg DH. Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology* 1986;161:721–725
- Rivers TM, Schwentker FF. Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys. *J Exp Med* 1935;61:689–703
- Carr DH, Brown J, Bydder GM, et al. Gadolinium-DTPA as a contrast agent in MRI: initial clinical experience in 20 patients. *AJR* 1984;143:215–224
- Weinmann HJ, Brasch RC, Press WR, Wesbey GE. Characteristics of gadolinium-DTPA complex: a potential NMR contrast agent. *AJR* 1984;142:619–624
- Brasch RC, Weinmann H-J, Wesbey GE. Contrast-enhanced NMR imaging: animal studies using gadolinium-DTPA complex. *AJR* 1984;142:625–630
- Goldstein EJ, Burnett KR, Hansell JR, et al. Gadolinium-DTPA (an NMR proton imaging contrast agent): chemical structure, paramagnetic properties and pharmacokinetics. *Physiol Chem Phys Med NMR* 1984;16:97–104
- Runge VM, Clanton JA, Lukehart CM, Partain CL, James AE. Paramagnetic agents for contrast-enhanced NMR imaging: a review. *AJR* 1983;141:1209–1215
- Runge VM, Clanton JA, Price AC, et al. The use of Gd-DTPA as a perfusion agent and marker of blood-brain barrier disruption. *Magn Reson Imaging* 1985;3:43–55
- Grossman RI, Joseph PM, Wolf G, et al. Experimental intracranial septal infarction: magnetic resonance enhancement. *Radiology* 1985;155:649–653
- Runge VM, Clanton JA, Price AC, et al. Evaluation of contrast-enhanced MR imaging in a brain-abscess model. *AJNR* 1985;6:139–147
- Farlow MR, Markand ON, Edwards MK, Stevens JC, Kolar OJ. Multiple sclerosis: magnetic resonance imaging, evoked responses, and spinal fluid electrophoresis. *Neurology* 1986;36:828–831
- Vinuela FV, Fox AJ, Debrun GM, Feasby TE, Ebers GC. New perspectives in computed tomography of multiple sclerosis. *AJNR* 1982;3:277–281, *AJR* 1982;139:123–127