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*AJNR Am J Neuroradiol* 1987, 8 (6) 1045-1048

<http://www.ajnr.org/content/8/6/1045>

This information is current as  
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# MR of Acute Experimental Allergic Encephalomyelitis

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**Acute experimental allergic encephalomyelitis, an animal model of CNS inflammatory and demyelinating disease, was produced in guinea pigs and imaged with MR. Correlation of histopathology with MR revealed acute mononuclear perivascular inflammatory changes and edema corresponding to the high-intensity abnormalities observed on long repetition time (TR) images.**

**Our results suggest that in acute multiple sclerosis the high intensity noted on long TR images may be secondary to associated inflammatory changes rather than to demyelination.**

Experimental allergic encephalomyelitis (EAE) is an autoimmune inflammatory disease of the CNS that was first described nearly 50 years ago [1]. In its acute form it appears to be an exact model of acute disseminated encephalomyelitis, and perhaps of acute exacerbations in multiple sclerosis (MS) [2–4]. Chronic and relapsing EAE is considered by many to be a model for MS, since pathologically it is marked by inflammation, edema, gliosis, and demyelinating lesions of different ages as well as being characterized by a relapsing and/or chronic clinical course [4–6].

MR is extremely effective for imaging lesions in MS, but few studies have correlated pathologic findings with imaging results (CT or MR) [7–9]. This study investigates the feasibility of imaging guinea pigs with EAE, as well as correlates the MR findings with histopathology in an effort to understand the cause of the high-intensity signal seen on long repetition time (TR) MR scans.

## Materials and Methods

Twenty-seven outbred Hartley albino guinea pigs weighing between 300–500 g were sensitized with homologous spinal cord in complete Freund's adjuvant (CFA). Spinal cord (1 g) was homogenized with an equal volume of saline (1 ml) and then emulsified with an equal volume of CFA containing 10 mg/ml of *Mycobacterium tuberculosis* (heat-killed, H37Ra) for a total volume of 4 ml. Each animal received 0.5 ml divided into five subcutaneous sites of injection (0.1 ml per injection site) [10].

The guinea pigs were examined daily beginning on the sixth day after sensitization. Since we were interested in studying early lesions in this initial feasibility study, animals had MR scans on the first to third day of clinical illness (11–14 days postsensitization). Clinical illness was characterized by weight loss, difficulty with righting, ataxia, varying degrees of paralysis (hind limb or quadriplegia), and urinary and fecal incontinence.

The guinea pigs were anesthetized with intramuscular ketamine (35 mg/kg) and xylazine (5 mg/kg) just before MR. The study was performed on a 1.4-T MR scanner with a 31-cm bore, which has been previously described [11]. Separate RF coils were used for receiving and transmitting. These were designed to provide a high degree of field homogeneity. The transmitter (6.5 in. diameter) was a variation on the "birdcage" design of Hayes et al. [12]. The receiver was of the type described by Joseph and Fishman [13], and although only 3 in. in diameter, had negligible inhomogeneity over the region of the animals' brains. The technique

Received January 13, 1987; accepted after revision May 29, 1987.

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**AJNR 8:1045–1048, November/December 1987**

0195–6108/87/0806–1045

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used a  $128 \times 128$  pixel matrix with a pixel size of 0.4 mm and a field of view of 5.2 cm. Spin-echo images—using a TR of 200 msec, echo time (TE) of 10 msec, and number of averages (NAV) equal to 2—were obtained in the coronal planes for localization (Fig. 1). When the proper imaging planes were selected, multiple 3-mm-thick coronal slices using long TR spin-echo images were made with a TR of 2000 msec, TE of 100 msec, and NAV of 2. Additionally, inversion recovery (IR) images were made in the coronal plane using a TR of 2000 msec and times to inversion (TI) of 800–1000 msec. Limitations on imaging time did not always allow IR images to be obtained for every animal. MR was performed on guinea pigs sensitized with spinal cord in CFA and control animals (nonsensitized). The images were read independently of the pathologic studies. Because of technical limitations only cerebral hemispheres were imaged, thus precluding clinical pathologic correlation.

After imaging, the guinea pigs were sacrificed and autopsies were performed. The CNS was placed in neutral buffered formalin. Routine H and E and Luxol Fast Blue stains were done on sections of forebrain, cerebellum, and brainstem as well as the spinal cord. The histology was read on coded slides with degree and areas of involvement determined independently of the MR results. After MR and pathologic examinations, correlative localization studies were performed in an unblinded manner.

## Results

Twenty-seven animals were sensitized with homologous spinal cord in CFA. Two additional unsensitized animals were

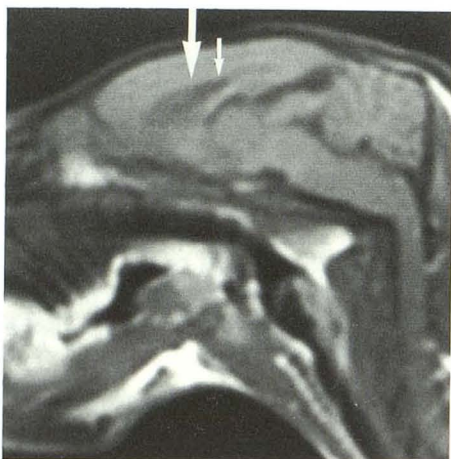
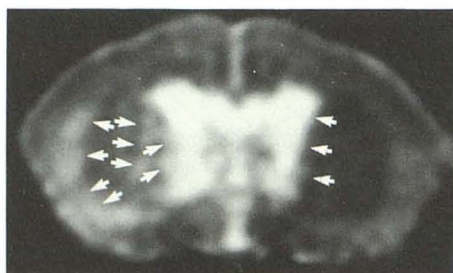
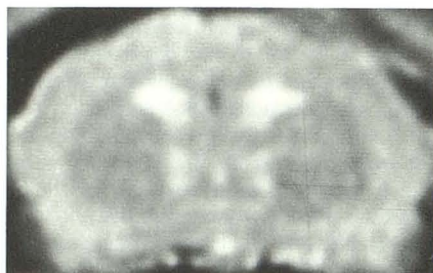


Fig. 1.—Sagittal spin-echo image (TR = 200 msec, TE = 15 msec, number of averages = 2). Large and small arrows indicate approximate coronal planes of Figures 2 and 3, respectively.



A



B

Fig. 2.—A, Guinea pig with acute experimental allergic encephalomyelitis demonstrating areas of high intensity in right globus pallidus/putamen complex, periventricular region, and subcortical region (arrows). TR = 2000 msec, TE = 100 msec, number of averages = 2.

B, Comparison image in approximately the same region using same parameters in a control animal.

imaged as controls and did not exhibit signs of neurologic dysfunction. Nine of the 27 animals did not develop clinical EAE although minor histopathologic changes were noted at necropsy. Of the 18 animals who developed fulminant clinical EAE, four animals died before they could be imaged. Six of the remaining 14 animals had definite abnormalities on long TR images. These consisted of high-intensity abnormalities predominantly affecting the white matter, basal ganglia, periventricular, and cortical-subcortical regions (Figs. 2A and 3A). The remaining eight animals with clinically definite EAE had equivocal high-intensity changes on long TR images (Fig. 4). The two control animals showed no abnormalities on the long TR images (Figs. 2B and 3B). IR images, when performed, were normal.

The pathologic changes consisted of mononuclear perivascular inflammation and edema, as well as ventriculitis, choroiditis, and meningitis (Fig. 5). White-matter lesions sometimes but not always had modest associated demyelination (Fig. 6). High-intensity abnormalities were observed additionally in areas that were devoid of myelin (globus pallidus/putamen complex) (Fig. 5C). All definite lesions on long TR images could be correlated with the inflammatory changes observed pathologically. As noted, demyelination was not prominent in the white-matter lesions and was obviously absent in gray-matter lesions. Occasional swollen astrocytes were seen but no gliosis (astrocyte proliferation) was noted in these acute lesions. We were less successful in correlating equivocal MR changes and definite pathologic abnormalities (eight animals).

## Discussion

The rapid development of MR has provided a powerful technique for noninvasively imaging the results of immunological inflammatory diseases occurring in EAE. Imaging of this well-studied model of demyelinating disease may aid in elucidating the origin of the signal-intensity changes present on MR in patients with MS. In our study, six of 27 sensitized animals with acute EAE demonstrated definite high-intensity abnormalities on long TR images (Figs. 2A and 3A). These high-intensity lesions were characterized histologically by inflammation and edema (Figs. 5 and 6). Interestingly, frank demyelination and gliosis were inconspicuous or absent. The larger lesions (greater than four cell layers thick) or relatively confluent lesions in the cerebral hemisphere were correlated with abnormalities observed on MR. The clinical severity as



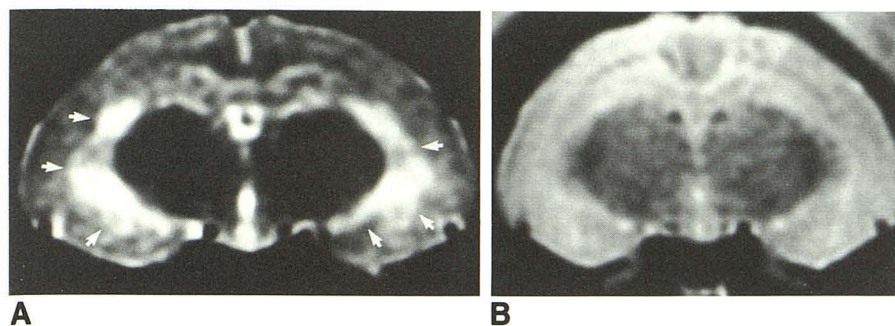


Fig. 3.—A, Another guinea pig with acute experimental allergic encephalomyelitis. Note high-intensity abnormalities in external capsule bilaterally (arrows). TR = 2000 msec, TE = 100 msec, number of averages = 2. The globus pallidus/putamen complex appears hypointense, possibly secondary to heterogeneous susceptibility related to iron deposition.

B, Similar section through a control animal using same parameters.

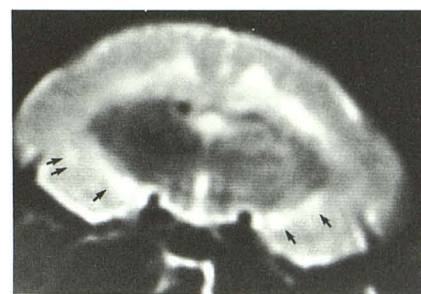


Fig. 4.—Coronal image of animal with equivocal lesions (arrows). TR = 2000 msec, TE = 100 msec, number of averages = 2.

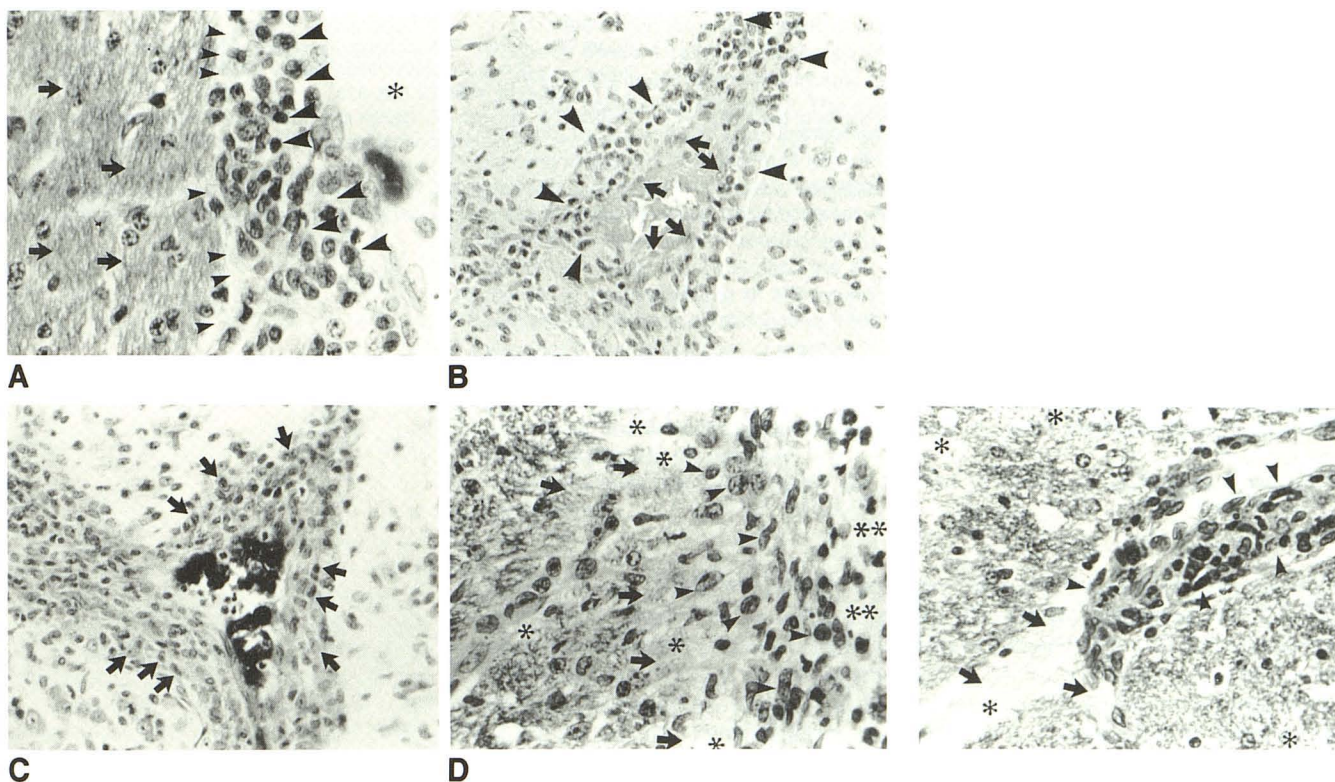


Fig. 5.—Histopathology of animal shown in Figure 2.

A, Mononuclear inflammatory lesion in periventricular white matter (large arrowheads). Asterisk is on lateral ventricle. There is minimal demyelination within inflammatory lesion and a small amount immediately adjacent (lateral) to the inflammatory cells (small arrowheads). Normal myelin is noted lateral to infiltrate and myelin loss (arrows).

B, Large perivascular mononuclear infiltrate in gray matter (arrowheads). Arrows indicate venule wall. This section is from the globus pallidus/putamen complex. H and E  $\times 200$  original magnification.

C, Large perivascular region also from globus pallidus/putamen complex. The lack of any Luxol Fast Blue staining in deep gray matter shows that this is a nonmyelinated area. This is in contrast to Figure 5D, in which loss of myelin is from a myelinated region. Arrows indicate perivascular inflammatory cells.

D, Subcortical inflammatory infiltrate (arrowheads) with mild demyelination (arrows). Edema is indicated by asterisks.

Fig. 6.—Luxol Fast Blue stain shows inflammatory infiltrate in region of external capsule (arrowheads) and small amount of myelin loss (arrows). This corresponds to image in Figure 3A. Edema is indicated by asterisks.

well as the histologic picture was similar to that of other investigators as well as to our own previous experience [4, 10]. Technical limitations precluded spinal cord and brainstem imaging. Thus, the correlation of MR and pathologic findings

was only possible for those animals with gross cerebral lesions. This may account for the discrepancy between the number of imaged animals with clinical EAE (14) and the number of animals with definite cerebral lesions (six). Stewart



et al. [14] described MR abnormalities in two monkeys with EAE, but pathologic studies of those lesions were not reported.

Our results indicate that in animals with acute EAE the abnormal high-intensity regions observed on long TR images correspond to regions of inflammation and edema rather than primarily to demyelination or gliosis. The implication of this data is that the high-signal abnormality on long TR images in patients with acute MS is the result of inflammation and edema rather than demyelination. This makes intuitive sense as well, since the edema and inflammation will increase both the proton density and T2 relative to uninvolved white matter. This study indicates that high-intensity abnormalities in white matter should not glibly be attributed to primary loss of myelin. Moreover, it demonstrates the feasibility of imaging EAE in guinea pigs with MR and the importance of histopathologic-MR correlation in interpreting MR images.

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