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# Magnetization Transfer and Diffusion Tensor MR Imaging of Acute Disseminated Encephalomyelitis

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*BACKGROUND AND PURPOSE:* **Patients with acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) have a similar pattern of abnormalities on conventional MR images. We used magnetization transfer and diffusion tensor MR imaging to quantify normal-appearing brain tissue and cervical cord disease in patients with ADEM and to compare findings with those in healthy volunteers and patients with MS.**

*METHODS:* **Brain dual-echo, T1-weighted magnetization transfer, and diffusion tensor images were obtained in eight patients with ADEM, in 10 patients with MS, and in 10 healthy volunteers. Fast short-tau inversion recovery, T1-weighted, and magnetization transfer cervical cord images were also obtained. We identified lesions on the images and quantified their volumes. We performed histogram analysis of the magnetization transfer ratio (MTR) and average mean histogram analysis of the diffusivity ($\bar{D}$) in normal-appearing brain tissue and MTR in the cervical cord.**

*RESULTS:* **Histogram analysis of normal-appearing brain tissue in patients with MS showed significantly lower MTRs and peak positions and significantly higher $\bar{D}$ averages compared with those in patients with ADEM. Patients with MS had significantly lower MTRs and $\bar{D}$ peak heights and significantly higher average $\bar{D}$ compared with those in healthy volunteers. Between patients with ADEM and control subjects, normal-appearing brain tissue MTR and $\bar{D}$ histogram metrics did not differ significantly. Cervical cord MTRs did not differ between control subjects and patients with ADEM, whereas the average MTR and histogram peak position was significantly lower in patients with MS than in the other groups.**

*CONCLUSION:* **Outside the acute phase of disease and as opposed to what happens in MS, the normal-appearing brain tissue and cervical cord in patients with ADEM are spared in the pathologic process.**

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the CNS that develops acutely or subacutely in a close temporal relationship to an infectious illness or vaccination (1–4). The neurologic picture of ADEM usually reflects a multifocal but monophasic involvement of the CNS, with full or marked clinical recovery in most cases (1–4). Although multiple sclerosis (MS) results in recurrent episodes that are disseminated in both time and place, in most cases MR images reveal a similar pattern of multifocal white matter abnormalities in both ADEM and MS (3–8). Consistent with the more typical clinical evolution of ADEM, findings of two longitudinal studies with serial MR imaging have shown that, as opposed to what usually happens in MS (9), ADEM lesions tend to partially or completely resolve and, more importantly, new lesion formation rarely occurs (5, 8). However, MS causes multiple white matter abnormalities that are visible on T2-weighted images and also more subtle changes in the normal-appearing brain tissue (10–13) and cervical cord (14, 15). The aim of this study was to determine whether, and to what extent, such subtle changes are present in patients with ADEM by comparing magnetization transfer and diffusion tensor MR imaging findings in these patients with findings in healthy volunteers and patients with MS.

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**TABLE 1: Clinical, laboratory, and MR imaging findings in patients with ADEM at presentation**

| Patient No./ Age(y)/Sex | Main Clinical Features | Clinical Outcome | MR Imaging Findings at Presentation | MR Imaging Findings at ≥6 Mo | CSF Findings |
|---|---|---|---|---|---|
| 1/47/M | Confusion, left hemiparesis | Complete recovery | Multiple brain WM lesions | Complete resolution of lesions | Not obtained |
| 2/22/M | Tetraparesis, urine retention | Complete recovery | Multiple brain and spinal cord WM lesions, one hyperintense lesion in the left thalamus | Marked but incomplete resolution of brain lesions, complete resolution of cord lesions | Cells increased, OB |
| 3/21/F | Drowsiness, right hemiparesis | Complete recovery | Multiple brain WM lesions, one hyperintense lesion in the left basal ganglia | Incomplete resolution of lesions | Cells and protein level increased |
| 4/37/F | Confusion, left hemiparesis | Almost complete recovery | Multiple brain WM lesions | Incomplete resolution of lesions | Cells increased |
| 5/31/F | Drowsiness, right hemiparesis | Complete recovery | Multiple brain WM lesions | Complete resolution of lesions | Normal |
| 6/40/F | Paraparesis, urine retention | Complete recovery | Multiple brain and spinal cord WM lesions | Marked but incomplete resolution of brain and cord lesions | Cells and protein level increase, OB |
| 7/22/M | Drowsiness, diplopia, tetraparesis, ataxia | Complete recovery | Multiple brain WM lesions | Incomplete resolution of lesions | Protein level increased |
| 8/51/M | Ataxia, paraparesis | Marked improvement | Multiple brain and spinal cord WM lesions | Incomplete resolution of brain and cord lesions | Protein level increased, OB |

Note.—OB indicates oligoclonal bands; WM, white matter.

## Methods

### *Patients*

One of the authors (M.F.) reviewed the case records of patients with a diagnosis of ADEM, suspected MS, optic neuritis or neuropathy or both, or myelitis or myelopathy or both. We classified patients as having ADEM if they had all of the following: 1) a close temporal relationship between a CNS white matter syndrome and an infective illness or vaccination, 2) a pattern of multifocal lesions on the brain MR images obtained at clinical presentation, and 3) no evidence of new lesion formation on MR images obtained at least 6 months after the clinical onset of the disease (5).

According to these criteria, eight patients with ADEM were identified and included in the current study. They included four women and four men, (mean age, 33.8 years [SD, 11.8]); median duration of the disease, 2.5 years [range, 1–9 years]). In seven cases, the neurologic manifestations were preceded by a nonspecific respiratory infection, and in one, by a flulike syndrome. In three patients, spinal cord MR images were obtained at presentation, and T2-weighted images showed multiple hyperintense lesions. After treatment with steroids, six patients had a complete clinical recovery within 3 months of disease onset, and two had a marked but partial recovery and minor residual neurologic deficits. None of the patients had a subsequent clinical exacerbation. Further clinical, MR imaging, and laboratory details of these patients are given in Table 1.

Two control groups were identified. The first consisted of 10 healthy volunteers (five women, five men) with no history of neurologic disorders and normal findings at neurologic examination. Their mean age was 33.4 years (SD, 11.3). The second consisted of 10 patients (five woman, five men) with clinically definite relapsing-remitting MS (16). Only patients with MS who were relapse- and steroid-free for at least 3 months before study entry were included. Also, their conventional MR images had to depict no more than 20 lesions, but they had to have enough lesions to meet the criteria of Fazekas et al (17). These criteria were used for two reasons: first, to select patients with MS who had MR images that matched, as closely as possible, those of patients with ADEM outside the acute phase of the disease (5, 8); and, second, to select patients with MS and typical MR images. Their mean age was 33.5 years (SD, 8.8), the median disease duration was 4.0 years (range, 1–7 years), and the median Expanded Disability Status Scale score (18) was 2.0 (range, 1.0–6.0). Local ethics committee approval and written informed consent from all the subjects were obtained before study initiation.

### *Brain MR Imaging*

The following sequences were performed in all subjects during a single imaging session with a 1.5-T unit: 1) dual-echo turbo spin-echo sequence (3300/16 and 98 [TR/TE]; echo train length, five); 2) 2D gradient-echo sequence (640/12; flip angle, 20°) with and without an off-resonance radio-frequency saturation pulse (offset frequency, 1.5 kHz; gaussian envelope duration, 7.68 ms; flip angle, 500°); and 3) pulsed-gradient spin-echo echo-planar sequence (interecho spacing, 0.8; TE, 123), with diffusion gradients applied in eight noncollinear directions, with a maximum b factor in each direction of 1044 s/mm$^2$. To optimize the measurement of diffusion, only two b factors were used: approximately 0 and 1044 s/mm$^2$ (19). Fat saturation was performed by using a train of four radio-frequency binomial pulses to prevent chemical shift artifact. For dual-echo and gradient-echo imaging, 24 contiguous interleaved axial images were acquired with a 5-mm section thickness, 256 × 256 matrix, and 250 × 250-mm field of view. The sections were positioned in a plane running parallel to a line that joins the most inferoanterior and inferoposterior parts of the corpus callosum (20). For the echo-planar sequence, 10 5-mm-thick images were acquired, with the same orientation as

that of the other images; the second to last caudal section was positioned to match the central sections of the other image sets. These central sections are less affected by the distortions due to $B_0$ field inhomogeneity, which can affect image coregistration. A 128 × 128 matrix and 250 × 250-mm field of view were used.

### *Cervical Cord MR Imaging*

With a tailored cervical-spine phased-array coil for signal reception, the following sequences were used to image the cervical cord in all subjects: 1) fast short-tau inversion recovery (fast-STIR) sequence (2288/60/110 [TR/TE/TI]; echo train length, 11; field of view, 280 × 280 mm; matrix size, 264 × 512; number of signals acquired, four), 2) T1-weighted spin-echo (500/12; field of view, 245 × 280; matrix size, 192 × 256; number of signals acquired, two), and 3) 2D gradient-echo sequence (640/10; flip angle, 20°; field of view, 280 × 280 mm; matrix size, 224 × 256, number of signals acquired, two) with and without the same saturation pulse used in the brain. With the fast-STIR and T1-weighted sequences, eight sagittal images were obtained with a 3-mm section thickness and a 0.3-mm intersection gap. With the gradient-echo sequence, 20 contiguous axial images were obtained.

### *Postprocessing of Brain MR Images*

A single experienced observer (M.I.) who was unaware of the patient's identity performed all MR image postprocessing. Hyperintense lesions were identified on dual-echo images, and lesion volumes were measured by using a segmentation technique based on local thresholds (21). After the two gradient-echo images were coregistered by using a surface-matching technique based on mutual information (22), magnetization transfer ratio (MTR) images were derived pixel by pixel, as previously described (10). Extracerebral tissue was removed from the MTR maps by using the same technique as that used for lesion segmentation (21), and the resulting images were coregistered with the T2-weighted images (22). Echo-planar images were first corrected for distortion induced by eddy currents by using an algorithm that maximizes mutual information between the diffusion-unweighted and diffusion-weighted images (22). Then, the diffusion tensor was calculated for each pixel by using a linear fit of the data (23). From the tensor, the mean diffusivity $\bar{D}$ was derived for every pixel. The diffusion images obtained with a b value of 0 (T2 weighted but diffusion unweighted) were interpolated to the same matrix as that of the T2-weighted images and coregistered with the T2-weighted images (22). The registration parameters were then used to transform the $\bar{D}$ maps, which were aligned exactly with the diffusion-weighted images obtained with a b value of 0. The next step consisted of automatic transference of lesion outlines onto the MTR and $\bar{D}$ maps and calculation of average lesion MTR and $\bar{D}$ values. To study the MTR and $\bar{D}$ characteristics of the normal-appearing brain tissue, pixels belonging to lesions were nulled, and MTR and $\bar{D}$ histograms of normal-appearing brain tissue data were created as previously described (10, 24). To correct for the between-subject differences in brain volume, each histogram was normalized by dividing the height of each bin by the total number of pixels contributing to the histogram. For each histogram, the following measures were derived: the relative peak height (ie, the proportion of pixels with the most common MTR and $\bar{D}$ values), the peak location (ie, the most common MTR and $\bar{D}$ values), and the average MTR and $\bar{D}$ values.

### *Postprocessing of Cervical Cord MR Images*

The same observer reviewed the fast-STIR images to identify lesions. Once the lesions were identified, they were classified according to their length relative to the spacing of the vertebral bodies and also as lesions that occupied or did not occupy the entire cord cross-sectional area. Whether the cord morphology was altered by the presence of lesions (ie, cord swelling or atrophy) and whether the lesions identified on the fast-STIR images were hypointense on the T1-weighted images were also noted. With the two gradient-echo images obtained with and without the saturation pulse, MTR maps were derived as previously described (14). MTR histograms were derived from results in the entire cervical cord in all subjects. The same MTR histogram metrics that were computed in the brain were measured in the cervical cord.

**TABLE 2: Brain lesion volume, MTR, and $\bar{D}$ in the patients with ADEM and patients with MS**

| Finding | Patients with ADEM | Patients with MS |
|---|---|---|
| Lesion volume on T2-weighted image (mL) | 2.5 (0.0–16.4) | 5.1 (0.4–16.0) |
| Lesion MTR (%) | 38.2 (31.5–43.2) | 37.2 (31.5–40.6) |
| Lesion $\bar{D}$ ($\times 10^{-3}$ mm$^2$/s) | 0.97 (0.82–1.30) | 0.93 (0.82–1.03) |

Note.—Data are the means; data in parentheses are the ranges.

### *Statistical Analysis*

One-way analysis of variance was used to compare MTR and $\bar{D}$ histogram-derived metrics among the three groups. Post hoc analysis was performed by using the two-tailed Student *t* test for nonpaired data. To compare MTR and $\bar{D}$ histogram-derived metrics between patients with ADEM and those with MS, an analysis of variance corrected for lesion volume on T2-weighted images was used.

## Results

### *Brain MR Imaging Findings*

No abnormalities were seen on any of the images obtained in the healthy volunteers. In Table 2, lesion volume on T2-weighted images, mean lesion MTR, and $\bar{D}$ values are reported for patients with ADEM and those with MS. None of these MR quantities was significantly different between the two groups. In Table 3, mean MTR and $\bar{D}$ histogram-derived metrics in patients with ADEM, those with MS, and healthy control subjects are reported. Although no significant difference between patients with ADEM and healthy volunteers was found, average normal-appearing brain tissue MTRs ($P < .001$) and peak positions ($P < .001$) on the MTR histogram were lower and average normal-appearing brain tissue $\bar{D}$ values were higher ($P = .03$) in patients with MS than in those with ADEM. All of these differences remained significant after we corrected for lesion volume on T2-weighted images. (On the normal-appearing brain tissue histogram, *P* values were as follows: average MTR, $P < .001$; MTR peak position, $P = .001$, and average $\bar{D}$, $P = .05$.) Patients with MS had decreased MTR and increased $\bar{D}$ values in normal-appearing brain tissue compared with the corresponding quantities in the white matter of healthy volunteers (Table 3).

### *Cervical Cord MR Imaging Findings*

No abnormalities were seen on any of the images in healthy volunteers. Seven lesions were seen on the

**TABLE 3: MTR and $\bar{D}$ histogram metrics in NABT in healthy volunteers, patients with ADEM, and patients with MS**

| Finding | Control Subjects | Patients with ADEM | Patients with MS | *P* Value | |
|---|---|---|---|---|---|
| | | | | Patients with ADEM vs Patients with MS | Control Subjects vs Patients with MS |
| MTR (%) | 40.6 (1.4) | 41.3 (1.24) | 38.6 (1.08) | <.001 | .003 |
| MTR peak height | 117.7 (13.0) | 105.6 (19.2) | 104.4 (14.3) | >.05 | .05 |
| MTR peak position (%) | 35.7 (1.7) | 36.8 (1.5) | 33.2 (1.7) | <.001 | .007 |
| $\bar{D}$ ($\times 10^{-3}$ mm$^2$/s) | 0.93 (0.05) | 0.92 (0.03) | 0.98 (0.06) | .03 | .009 |
| $\bar{D}$ peak height | 110.7 (12.5) | 97.3 (19.0) | 89.9 (11.0) | >.05 | <.001 |
| $\bar{D}$ peak position ($\times 10^{-3}$ mm$^2$/s) | 0.77 (0.04) | 0.75 (0.02) | 0.77 (0.04) | >.05 | >.05 |

Note.—Data are the means; data in parentheses are the SDs. No significant difference between control subjects and patients with ADEM was found.

**TABLE 4: MTR histogram metrics in cervical cord tissue in healthy volunteers, patients with ADEM, and patients with MS**

| Finding | Control Subjects | Patients with ADEM | Patients with MS | *P* Value | |
|---|---|---|---|---|---|
| | | | | Patients with ADEM vs Patients with MS | Control Subjects vs Patients with MS |
| MTR (%) | 45.7 (2.3) | 43.7 (2.5) | 39.2 (3.2) | .005 | <.001 |
| MTR peak height | 69.6 (27.7) | 67.8 (10.3) | 65.4 (14.9) | >.05 | >.05 |
| MTR peak position (%) | 40.8 (2.3) | 39.0 (4.0) | 34.3 (2.6) | .008 | <.001 |

Note.—Data are the means; data in parentheses are the SDs. No significant difference between control subjects and patients with ADEM was found.

fast-STIR images in patients with ADEM, and 12 were seen on the images in patients with MS. None of these lesions was longer than two vertebral segments, was hypointense on T1-weighted images, occupied the entire cross-sectional area of the cord, or was associated with cord atrophy or swelling. In Table 4, cervical cord MTR histogram-derived metrics in patients with ADEM and MS and in healthy volunteers are reported. No significant difference was found between patients with ADEM and healthy control subjects in any of the MTR quantities on the histograms. On the contrary, the average cervical cord MTR and peak position on the histogram were lower in MS patients than in patients with ADEM and in healthy volunteers (Table 4).

## Discussion

MS results not only in macroscopic lesions that are visible on conventional MR images but also microscopic changes in normal-appearing brain tissue (8–11). Normal-appearing brain tissue changes have been found in all of the clinical phenotypes of the disease (10), including those in patients with clinically definite MS and no visible abnormalities on T2-weighted images (25) and the clinically isolated syndromes that are suggestive of MS (26). This finding is absent in patients with Devic neuromyelitis optica (15), another CNS demyelinating disease, and in patients with other neurologic conditions associated with multiple brain abnormalities on T2-weighted images (27–29). To our knowledge, no previous investigators have studied this aspect in patients with ADEM. The present findings show that all MTR and $\bar{D}$ histogram-derived metrics in the normal-appearing brain tissue in patients with ADEM are similar to those of age- and sex-matched healthy control subjects, whereas the average MTR and peak position were significantly higher and average $\bar{D}$ was significant lower than those of patients with MS. These findings suggest that, at least outside the acute phase of the disease, the pathologic process of ADEM is confined to lesions that are visible on T2-weighted images, and it does not affect (at least in a way that is detectable with available quantitative MR technology) the relative proportions of intra- and extracellular water (which should decrease the MTR) and the structural barriers that restrict water molecular motion (which should increase $\bar{D}$). Since in vivo magnetization transfer and diffusion tensor MR studies of MS have revealed that variable degrees of normal-appearing white matter changes may precede lesion formation in MS (30–33), our findings agree with those of previous longitudinal studies of conventional MR imaging that revealed that new lesion formation is an extremely unlikely event in patients with ADEM outside the acute phase of the disease (5, 8).

Patients with MS were carefully selected not only for age and sex distributions similar to those of patients with ADEM but also for conventional MR images that matched those of the latter group as closely as possible. This selection is important for two reasons. First, it provided an additional guarantee of a fully blinded assessment of MTR and $\bar{D}$ abnormalities. Second, it reduced the likelihood that the normal-appearing brain tissue differences between patients with ADEM and those with MS were due to the latter group of patients having more T2-weighted images. We are aware that the strategy we used cannot exclude an unintentional sampling of normal-appearing white matter around MS macroscopic lesions, which have MTR values that are known to be

lower than those of normal-appearing white matter away from such lesions (34). Although not proven, $\bar{D}$ values also are likely to change with increasing distance from lesions on T2-weighted images. Also, we are aware that wallerian degeneration of axons traversing the lesions that are visible on T2-weighted images can contribute to the development of normal-appearing brain tissue changes (10, 35). Although our inclusion criteria for patients with MS were designed to select patients with relatively low lesion loads on conventional MR images, they had lesion loads that were larger than those of patients with ADEM. Nevertheless, differences in MTR and $\bar{D}$ histogram-derived metrics remained significantly different even after we corrected for lesion volumes on T2-weighted images. In addition, these lesion volumes were not significantly different between the two groups of patients, and perhaps they were too low to affect normal-appearing brain tissue histograms a great deal. This possibility also agrees with the observation that, although lesions were detected on T2-weighted images obtained in patients with ADEM but not on those obtained in healthy volunteers, the two groups had similar MTR and $\bar{D}$ histogram characteristics.

As in the brain (5, 8), we observed lesion resolution and no new lesion formation in the cervical cord in the three patients with ADEM in whom cervical cord MR images were obtained at presentation. This finding likewise supports the notion that time dissemination of CNS lesions is rare in ADEM. Although we were able to study a limited number of ADEM lesions in the cervical cord, all were undistinguishable from those typically seen in MS (36). In fact, they were shorter than two vertebral segments, were isointense on T1-weighted images, did not occupy the entire cross-sectional area of the cord, and did not alter cord morphology. These findings confirm that distinction of the two conditions, even with extensive CNS assessment with conventional MR imaging, might be challenging.

In the present study, we also assessed the overall cervical cord damage in the two conditions by using MTR histograms. As in the brain, cervical cord MTR histogram metrics were not significantly different between patients with ADEM and healthy control subjects, whereas cervical cord average MTR and peak position on the histogram were significantly different than those from patients with MS. Although patients with MS had more lesions than did patients with ADEM, the amount of tissue involved with macroscopic disease is not likely to be very different. (Seven lesions were seen in patients with ADEM, and 12 were seen in those with MS; all were relatively small.) Therefore, one possible explanation for this finding is more severe damage to the normal-appearing white matter of the cord in patients with MS. This explanation agrees with the results of previous MS studies (14, 37) and with the results of the analysis of the normal-appearing brain tissue in patients with ADEM.

We recognize that we selected our ADEM cases by using a set of criteria that had an unproven ability to discriminate between ADEM and MS. However, at present, no better clinical criteria for diagnosing ADEM are available (3, 4). We also selected our patients retrospectively, and this approach might have influenced our results. However, we think this is a minor issue in the present study for two reasons. First, we extensively reviewed all cases in which a diagnosis of ADEM would have been possible by using a predefined set of criteria. Second, at present and with whatever criteria, a diagnosis of ADEM can be made only after the onset of the symptoms (5, 8) when an alternative diagnosis of MS can be reasonably excluded. In the present study, we also did not assess normal-appearing brain tissue and cervical cord changes in patients with ADEM at presentation. Therefore, we can not definitively rule out that reversible changes can occur in the CNS normal-appearing tissue in the acute phase of ADEM, when a differential diagnosis with MS is more compelling. Sublethal axonal injury can occur in the normal-appearing tissue distant from lesions that are visible on T2-weighted images obtained in patients with MS, and they can cause MR spectroscopic changes (38). As a consequence, similar changes arguably can occur in patients with ADEM at presentation. Nevertheless, although quantitative MR studies of the normal-appearing brain tissue and cord tissue in patients with ADEM at presentation are warranted to clarify this issue, sublethal axonal injury is unlikely to cause modifications in the relative proportions of intra- and extracellular water and in the size of water-filled spaces that are large enough to cause MTR and $\bar{D}$ changes comparable to those seen in MS (10–12, 14, 15, 24).

## Conclusion

These findings show that, outside the acute phase of the disease and opposed to what happens in MS, the normal-appearing brain tissue and cervical cord of patients with ADEM are spared in the pathologic process.

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