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**Index terms:**

Acquired immunodeficiency syndrome (AIDS), 10.2068  
Brain, atrophy, 10.83  
Brain, diseases, 10.87  
Brain, infection, 10.2068  
Brain, white matter, 10.87  
Magnetic resonance (MR), magnetization transfer contrast, 10.121417

**Radiology 1999;** 210:539-543

**Abbreviations:**

AIDS = acquired immunodeficiency syndrome  
FLAIR = fluid-attenuated inversion recovery  
HIV = human immunodeficiency virus  
PML = progressive multifocal leukoencephalopathy  
WML = white matter lesions

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Guarantor of integrity of entire study, T.E.; study concepts and design, T.E., L.C.; definition of intellectual content, T.E., L.C.; literature research, T.E.; clinical studies, L.C., M.W., H.A., M.L.Y., E.S.; data acquisition and analysis, T.E., I.W.; statistical analysis, T.E.; manuscript preparation, T.E., L.C.; manuscript editing, T.E.; manuscript review, T.E., L.C., M.W.

# Progressive Multifocal Leukoencephalopathy and Human Immunodeficiency Virus-associated White Matter Lesions in AIDS: Magnetization Transfer MR Imaging<sup>1</sup>

**PURPOSE:** To determine the magnetization transfer features of progressive multifocal leukoencephalopathy (PML) and human immunodeficiency virus (HIV)-associated white matter lesions (WML) (hereafter, HIV-WML) on magnetic resonance (MR) images obtained in patients with acquired immunodeficiency syndrome (AIDS).

**MATERIALS AND METHODS:** Conventional MR imaging and magnetization transfer MR imaging were performed in 21 AIDS patients with 42 areas of white matter hyperintensity on MR images (13 patients had 25 PML lesions, eight patients had 17 WML). The magnetization transfer ratio was calculated for each lesion.

**RESULTS:** Compared with normal-appearing white matter (magnetization transfer ratio = 47.9%), both PML and HIV-WML showed reduced magnetization transfer ratio. The magnetization transfer ratio was significantly lower in PML lesions (magnetization transfer ratio = 26.1%) than in HIV-WML (magnetization transfer ratio = 38.0%,  $P < .0001$ ), and there was no overlap in the magnetization transfer ratio between PML lesions and HIV-WML. The separation in magnetization transfer ratio between the two lesion types was valid for lesions as small as 0.5 cm<sup>2</sup>.

**CONCLUSION:** The larger reduction in magnetization transfer ratio for PML lesions is most likely due to demyelination, whereas the reduction in HIV-WML may be associated primarily with gliosis. PML lesions appear to cause strong reductions in magnetization transfer ratio early in the course of disease. Magnetization transfer MR imaging is a noninvasive tool that improves the differentiation between PML and HIV-WML in patients with AIDS.

Magnetic resonance (MR) imaging is the preferred diagnostic technique for the evaluation of patients with acquired immunodeficiency syndrome (AIDS) who have neurologic symptoms. Whereas MR imaging is very sensitive in detecting brain abnormalities, it lacks specificity with respect to the degree of brain injury and may not be able to differentiate between gliosis, demyelination, and edema. Some of these problems might be resolved with magnetization transfer MR imaging, a relatively new contrast mechanism that promises to be more specific for myelin destruction than is T2-weighted MR imaging.

Magnetization transfer makes it possible to observe and quantify the exchange of magnetization between water molecules bound to macromolecules (bound water pool) and a free (unbound) water pool. Because of (dipolar) interactions between the two water pools, magnetization may be transferred from the bound to the unbound water pool, eventually changing the observable MR signal from the protons of the free pool (1). In the brain, magnetization transfer is very low for cerebrospinal fluid, moderate for gray matter, and highest for white matter. It has been suggested that the high magnetization transfer of

white matter reflects the high concentration of myelin (1–4). As a result, demyelinating lesions, such as multiple sclerosis plaques (2,3,5) or progressive multifocal leukoencephalopathy (PML) lesions (6,7), cause dramatic reductions in magnetization transfer.

The purpose of this study was to examine the magnetization transfer features of two frequently observed white matter abnormalities in patients with AIDS. The first type of lesions is nonspecific, well-defined white matter lesions (WML) frequently found in the brain of AIDS patients without known opportunistic infections. These human immunodeficiency virus (HIV)-associated WML (hereafter, HIV-WML) may be associated with the direct sequelae of HIV and are often nonspecific (8), but they appear to occur more frequently in patients with more advanced AIDS. PML is another common cause of white matter abnormalities in patients with AIDS, affecting 2%–7% of all AIDS patients (9–13). PML is caused by infection of oligodendrocytes by JC virus; low CD4+ cell count (<100 cells per microliter) is postulated to permit reactivation of latent JC virus (14). PML lesions produce characteristic WML on MR images as well as histopathologic examination (12,15–21); however, atypical features are common (12,19,22–25).

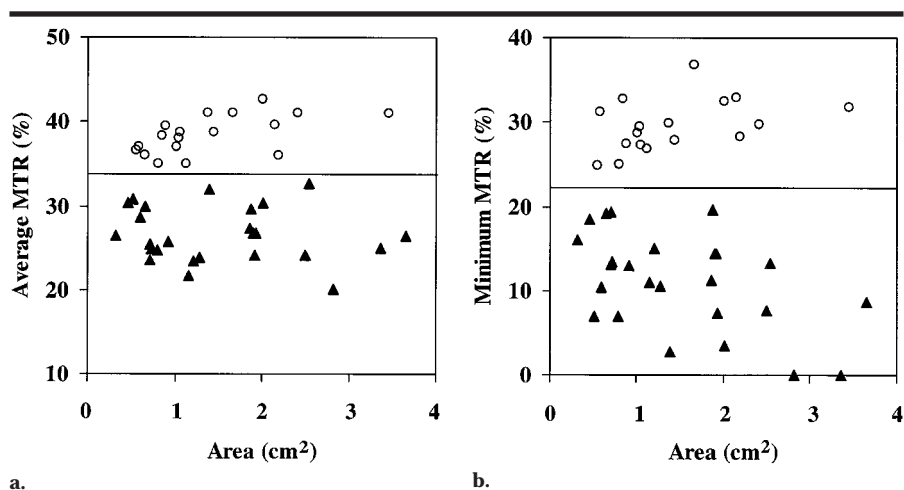
Because PML is a demyelinating disease, we hypothesized that PML lesions would lead to greater reduction in magnetization transfer than would HIV-WML. If this is correct, then magnetization transfer would be useful for improving the differential diagnosis of PML and HIV-WML in patients with AIDS. Furthermore, our goal was to determine whether the magnetization transfer values of the lesions are dependent on the size of the lesions.

## MATERIALS AND METHODS

### Patients and Lesions

We prospectively studied 21 AIDS patients with findings in clinical variables and imaging studies consistent with either PML or HIV-WML.

Disease in 13 patients (age range, 33–57 years) was diagnosed as PML, on the basis of characteristic clinical signs and course, typical MR imaging and MR spectroscopy patterns (25,26), and polymerase chain reaction for JC virus DNA in the cerebrospinal fluid. Six of the PML patients had positive cerebrospinal fluid-polymerase chain reaction for JC virus DNA, and two more patients underwent brain biopsy to confirm the diagnosis of PML. At the time



**Figure 1.** Graphs depict dependence of (a) average and (b) minimum magnetization transfer ratio (MTR) values on lesion size and lesion type. There is no overlap in magnetization transfer ratios between HIV-WML (○) and PML lesions (▲) ( $P < .0001$  for both variables). In the PML group, one lesion with an area of 11.6 cm<sup>2</sup> is not shown.

of MR imaging, the PML patients had a median duration of PML-related symptoms of 3 months (range, 1–36 months), a median duration of HIV diagnosis of 52 months (range, 1–135 months), and an average CD4 count of 110 cells per microliter  $\pm$  135 (SD) (range, 2–420 cells per microliter).

Disease in eight patients, aged 35–54 years, was diagnosed as HIV-WML. Patients with HIV-WML were asymptomatic, and cerebrospinal fluid showed no signs of bacterial, fungal, or viral infections (with negative polymerase chain reaction for JC virus DNA and negative polymerase chain reaction for cytomegalovirus). In the HIV-WML group, the median duration of HIV diagnosis was 108 months (range, 0.5–174.0 months), and the average CD4 count was 221  $\pm$  220 (range, 20–668; median, 135) cells per microliter.

Lesions with an area greater than 0.5 cm<sup>2</sup> were included in the analysis. Twenty-five lesions were analyzed in the PML group and 17 in the HIV-WML group. All HIV-WML were well-defined hyperintense lesions in the centrum semiovale on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images. Oral or written informed consent was obtained from all patients before MR imaging. The protocol was approved by the institutional review board.

### MR Imaging

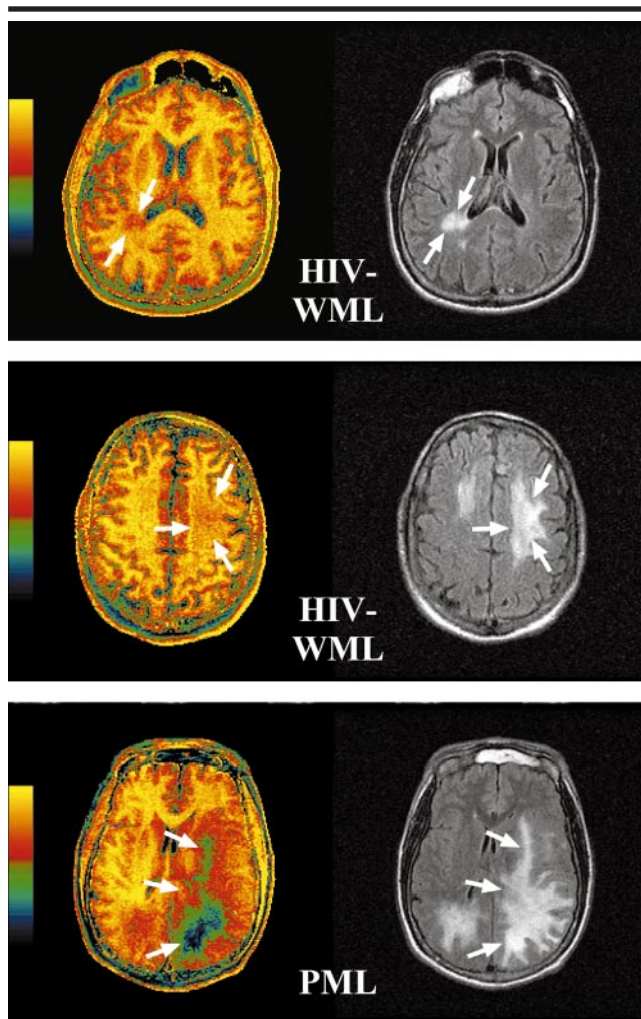
MR imaging was performed on a 1.5-T imager (GE Medical Systems; Milwaukee, Wis) equipped with the SR120 echoplanar imaging hardware. Conventional

MR imaging consisted of sagittal T1-weighted imaging (repetition time msec/echo time msec = 500/11, 5-mm section thickness, 2-mm gap, 24-cm field of view), axial fast double spin-echo imaging (4,000/17, 102; 5-mm section thickness; contiguous; 24-cm field of view), and optimized axial FLAIR imaging (11,000/142/2,600 [inversion time msec], 5-mm section thickness, contiguous, 24-cm field of view) (27).

Magnetization transfer MR imaging was performed with an axial T1-weighted spin-echo sequence (11/650, 5-mm section thickness, contiguous, 24-cm field of view, 4-minute imaging time) that was performed both with and without off-resonance saturation pulses. The offset frequency of the magnetization transfer pulses was 600 Hz.

### Image Analysis

Image analysis was performed on a workstation (Alpha; Digital Equipment, Nashua, NH) by means of programs (Interactive Data Language, or IDL; Research Systems, Boulder, Colo) customized specifically for the analysis of magnetization transfer data sets. Data for images with ( $M_1$ ) and without ( $M_0$ ) magnetization transfer-saturation pulses were sent to the workstation. For each pixel, the magnetization transfer ratio (MTR) was calculated as the difference in signal intensity between the images without and with magnetization transfer, divided by the signal intensity on images without magnetization transfer:  $MTR = (M_0 - M_1)/M_0$ . The result was displayed as a color-coded map of the magnetization transfer ratio.



**Figure 2.** Magnetization transfer ratio maps (left) and corresponding FLAIR images (right) of two HIV-WML (top and middle) and PML lesions (bottom). Despite similar appearances on the FLAIR images, the magnetization transfer ratios of the lesions (arrows) are markedly different. The HIV-WML show only moderate, and relatively homogeneous, reductions in magnetization transfer ratio, whereas the PML lesions exhibit areas of very low magnetization transfer ratio. This difference in the magnetization transfer ratio appearance is probably due to the fact that PML is a demyelinating disease, whereas myelin is relatively intact in HIV-WML. The same magnetization transfer ratio color scale is used for both lesions; bright yellow corresponds to the highest magnetization transfer ratio value of 52%.

To draw regions of interest, the magnetization transfer ratio maps were aligned (ie, shifted and scaled) on the computer with the anatomic images. Each lesion was manually outlined on the FLAIR images. If a lesion was visible on several sections, the region of interest was defined on the section that showed the most severe abnormalities in the magnetization transfer ratio. Because magnetization transfer ratio in the lesions was usually heterogeneous, the average and minimum values were determined for each lesion. The area of each region of

interest (in square centimeters) was also recorded.

### Statistical Analysis

Statistical analyses were performed (STATVIEW; Abacus, Berkeley, Calif). An unpaired Student *t* test was used to determine the statistical significance of differences between the magnetization transfer ratios in PML lesions and HIV-WML. The relationship between magnetization transfer ratio and lesion size or duration of PML was evaluated by means of linear

regression analysis. A *P* value below .05 was considered statistically significant. All group averages were reported as the mean  $\pm$  SD.

## RESULTS

The dependence of the magnetization transfer ratio on the lesion type and lesion size is shown in Figure 1. There was no overlap in either the minimum or average magnetization transfer ratios. As a result, the difference in the two magnetization transfer ratio measures between the two groups was highly significant ( $P < .0001$  for both variables). However, minimum magnetization transfer ratios showed better separation between the groups than did the average magnetization transfer ratios (Fig 1). The average magnetization transfer ratio in PML lesions was  $26.1\% \pm 4.0$  and in HIV-WML  $38.0\% \pm 2.6$ ; the average minimum magnetization transfer ratios were  $10.0\% \pm 5.9$  and  $29.1\% \pm 3.2$ , respectively. In comparison, the magnetization transfer ratio of normal-appearing white matter was  $47.9\% \pm 2.2$ . The magnetization transfer ratio separated PML lesions from HIV-WML for even the smallest lesions studied.

When the minimum or average magnetization transfer ratio for each PML lesion was plotted versus lesion age, no correlation was observed between the two variables. In contrast, the minimum but not the average magnetization transfer ratio of PML lesions was inversely related to the lesion size ( $r = -0.41$ ,  $P = .04$ , Fig 1). One very large lesion with an area of  $11.6 \text{ cm}^2$  was excluded from this analysis; inclusion of this lesion improved the correlation ( $r = 0.49$ ,  $P = .01$ ). In the HIV-WML group, the average but not the minimum magnetization transfer ratio correlated with the lesion size ( $r = 0.51$ ,  $P = .03$ ).

Typical FLAIR images and magnetization transfer ratio maps in two patients with HIV-WML are shown in Figure 2. Both MR images showed a well-defined hyperintense white matter lesion in the centrum semiovale. There was no enhancement on the gadolinium-enhanced images. The magnetization transfer ratio in both lesions was mildly reduced.

Figure 2 also shows a FLAIR image and a magnetization transfer ratio map of a large PML lesion in the left parietal white matter and of a smaller PML lesion in the right parietal white matter. The two lesions spared the gray matter and were hyperintense, similar to HIV-WML, on

the FLAIR images. There was no enhancement on the gadolinium-enhanced images. However, the magnetization transfer ratio in the larger lesion was markedly reduced, with an average magnetization transfer ratio of 21.7% (minimum, 3.4%); the average and minimum magnetization transfer ratios of the smaller lesion were 26.4% and 8.7%, respectively. These two lesions, similar to most other PML lesions studied, exhibited lowest magnetization transfer ratio in the center of the lesion, with a radial increase in the magnetization transfer ratio toward normal values.

## DISCUSSION

Findings in our study demonstrate that considerable difference exists between the magnetization transfer characteristics of PML lesions and HIV-WML in patients with AIDS. PML lesions are characterized by very low magnetization transfer ratio values (mean, 26.1%), compared with that for normal white matter (mean, 47.9%). In contrast, HIV-WML show only moderate decreases in magnetization transfer ratio (mean, 38.0%). It is important to note that all HIV-WML in our study were well-defined hyperintense lesions in the centrum semiovale on T2-weighted or FLAIR images (Fig 2). Consequently, magnetization transfer MR imaging may be useful for differentiating PML lesions from nondemyelinating hyperintense white matter abnormalities in patients with AIDS, even if both types of lesions have similar appearance on T2-weighted MR images. This is important since not all PML lesions in patients with AIDS show typical radiologic features such as a subcortical white matter location and lack of enhancement after injection of contrast material (12,19,28). Atypical features, such as posterior fossa location, enhancement with gadolinium, atrophy, involvement of deep gray matter, and widespread punctate abnormalities, have been described by several authors (12,19,22-25). In a recent MR study of 20 PML patients, we found that 50% had posterior fossa lesions, and 20% had lesions that enhanced with contrast material (25). In these atypical cases, the quantitative magnetization transfer ratio value might be used to support or refute a possible diagnosis of PML.

The observed difference in the magnetization transfer ratio abnormalities between PML and HIV-WML most likely reflects differences in pathophysiology. PML is caused by infection of oligodendrocytes by the JC virus, which produces

demyelinating lesions seen at neuropathologic examination and MR imaging (12,15-21). In contrast, the histopathologic characteristics of HIV-associated brain injury include the presence of macrophages, microglia nodules, multinucleated giant cells, reactive astrogliosis, and perivascular lymphocytic infiltration. PML lesions are characterized by marked demyelination and marked magnetization transfer ratio decreases, whereas HIV-WML are primarily nondemyelinating and exhibit only moderate magnetization transfer ratio reductions. This fact supports the concept that the high magnetization transfer ratio of normal white matter is facilitated by the presence of myelinated axons (1-4).

Our results confirm those in previous reports of magnetization transfer studies in PML patients. In a group of HIV-positive patients with either PML or HIV-WML, Dousset et al (29) observed a larger reduction in the magnetization transfer ratio of PML lesions (average magnetization transfer ratio = 22%) compared with that of HIV-WML (average magnetization transfer ratio = 40%). Gillams et al (30) also reported reduced magnetization transfer ratio in seven patients with "HIV leukoencephalopathy"; unfortunately, the investigators did not quantify magnetization transfer ratio, and they pooled patients with PML and HIV-WML. In a case report, Kasner et al (6) presented the case of a patient with PML, and found that the magnetization transfer ratio in the PML lesion was approximately 40% lower than that in normal white matter and that the reduced magnetization transfer ratio remained unchanged at 3 and 9 months after the initial presentation. In an atypical case of PML, Ng et al (7) also observed reduced magnetization transfer ratio in a PML lesion. In summary, findings in our study, in accordance with all prior observations, demonstrate that PML lesions show significantly greater reduction in magnetization transfer ratio than do HIV-WML.

The magnetization transfer ratio features of PML lesions appear similar to those of lesions in patients with multiple sclerosis, another demyelinating disease. In more than 200 multiple sclerosis plaques, Dousset et al (3) and Grossman (31) found an average magnetization transfer ratio of 62% compared with normal white matter (3,31). Tomiak et al (32) found that multiple sclerosis lesions aged less than 1 year had a significantly lower magnetization transfer ratio than older lesions (age, >1 year), and they concluded that the magnetization transfer

ratio might be potentially useful in determining the age of these lesions. In a study by Gass et al (5), the magnetization transfer ratio was inversely correlated with clinical disability. Taken together, these findings suggest that magnetization transfer MR imaging may be useful to subcategorize multiple sclerosis lesions and to follow up patients during drug treatment and may have prognostic value (31). In contrast, our findings in PML lesions studied cross-sectionally in time did not demonstrate a statistically significant correlation between magnetization transfer ratio and lesion age; this is mostly due to a relatively large variation in magnetization transfer ratio among new lesions (age,  $\leq 2$  months). This variation may be due to differences in the rate of disease progression among patients. For example, some of our patients experienced fulminant progression of PML with very low magnetization transfer ratio values within 1-2 months after disease onset, whereas disease in other patients progressed much more slowly and exhibited considerably lower magnetization transfer ratio decreases in the same time period.

One of the current limitations of the use of the magnetization transfer ratio as an adjunct diagnostic test in white matter diseases in AIDS is that to our knowledge no data are available on the magnetization transfer ratio features of WML due to other diseases, such as viral infection due to cytomegalovirus, herpes simplex, or varicella zoster. However, since these viral infections generally do not cause extensive demyelination, as seen in PML, one would predict that the reduction in magnetization transfer ratio in these other viral lesions may be only moderate.

Another potential pitfall of magnetization transfer MR imaging is that early PML lesions may exhibit only moderate decreases in the magnetization transfer ratio and thus appear similar to that of HIV-WML. However, there was no overlap between the magnetization transfer ratios of the 25 PML lesions and the 17 HIV-WML analyzed in our study. Therefore, the diagnostic accuracy of the magnetization transfer ratio in differentiating PML from HIV-WML appears to be well over 90%. Importantly, the separation between PML lesions and HIV-WML was maintained even in relatively small lesions with areas as small as 0.5 cm<sup>2</sup>. Thus, it appears that PML lesions cause severe reductions in the magnetization transfer ratio rapidly and that some of these lesions at early stages may be detected even when disease in the patients is asymptomatic. However, these issues will have to be

addressed in future longitudinal studies. Longitudinal studies also may be able to help resolve the important question whether there is a lower magnetization transfer ratio threshold that would indicate irreversible damage to the brain tissue.

Findings in our study show significant differences in the magnetization transfer ratio abnormalities between PML lesions and HIV-WML. Therefore, magnetization transfer MR imaging is a noninvasive tool that may allow differentiation between PML and HIV-WML in patients with AIDS. Future longitudinal studies will be required to assess whether magnetization transfer MR imaging is also valuable for predicting disease progression and for monitoring therapy in patients with PML.

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