

T2 Relaxation Measurements in X-linked Adrenoleukodystrophy Performed Using Dual-echo Fast Fluid-attenuated Inversion Recovery MR Imaging

Elias R. Melhem, Theodore F. Gotwald, Ryuta Itoh, S. James Zinreich, and Hugo W Moser

Summary: The purpose of this study was to determine whether dual-echo fast fluid-attenuated inversion recovery MR imaging and corresponding T2 brain maps can show different zones in the affected white matter of patients with cerebral X-linked adrenoleukodystrophy. Ten male patients with cerebral X-linked adrenoleukodystrophy underwent imaging performed using dual-echo fast fluid-attenuated inversion recovery and dual-echo conventional spin-echo MR sequences. Corresponding T2 relaxation maps of the brain were generated. On the basis of dual-echo fast fluid-attenuated inversion recovery images and T2 maps, the affected white matter could be divided into two distinct zones in four patients with cerebral X-linked adrenoleukodystrophy.

In cerebral X-linked adrenoleukodystrophy, three different pathologic zones (Schaumberg's zones) are described in affected white matter: an outermost zone typified by myelin destruction with preservation of axons (Schaumberg's zone 1), an intermediate zone that contains perivascular lymphocytic infiltrates in addition to myelin destruction (Schaumberg's zone 2), and a central zone, which is typically irreversible, characterized by axonal destruction, astrogliosis, and cavitation with absence of oligodendroglia, myelin, and inflammatory cells (Schaumberg's zone 3) (1, 2). White matter injury in zones 1 and 2 may be reversible and has been the prime target for therapeutic intervention. MR imaging has been effective in showing different zones in affected white matter that may correspond to characteristic pathologic zones (3). Conventional dual-echo MR imaging has been shown to provide T2 values in brain tissue that strongly correlate with clinically impractical

16-echo sequence measurements (4). Recently, normative T2 values of brain tissue obtained from dual-echo fast fluid-attenuated inversion recovery (FLAIR) imaging correlated favorably with conventional spin-echo imaging (5). The reported advantages of dual-echo fast-FLAIR imaging include shorter acquisition times, less motion, fewer susceptibility-related artifacts, and reduced contamination of the T2 values by CSF signal (5). Our purpose was to determine whether dual-echo fast-FLAIR MR imaging and corresponding T2 brain maps show different zones in affected white matter of patients with cerebral X-linked adrenoleukodystrophy.

Methods

Ten male patients with biochemically proved X-linked adrenoleukodystrophy and mild neurologic disability (including personality changes and visual and auditory deficits) were prospectively included in the study. The average age of the patients was 7 years, with a range from 2 to 13 years. Institutional review board approval and informed consent from all patients were obtained.

MR imaging was performed using a 1.5-T MR system with a maximum gradient capability of 23 mT/m and a slew rate of 103 mT/m. All images of the brain were acquired using a standard quadrature head coil operating in receive mode. Each MR examination of the brain included a dual-echo fast-FLAIR sequence (6000/58, 160/4 [TR/first TE_{eff}, second TE_{eff}/excitations]; inversion time, 2000 ms; three gradient echoes per RF echo; 16 RF refocusing periods; acquisition time, 5 min 24 s) and a dual-echo conventional spin-echo MR sequence ([3000/30, 100/1; acquisition time, 7 min 42 s). Both sequences were matched for section orientation (section number, 22; section thickness, 5 mm; intersection gap, 1 mm; matrix, 182 × 256; field of view, 24 cm). The dual-echo fast-FLAIR and dual-echo conventional spin-echo MR images of the 10 participants were evaluated by a neuroradiologist for the presence of white matter disease and for their ability to show zonal differences in signal intensity.

The images from both sequences were transferred to a UNIX workstation (SUN Enterprise 5500; Sun Microsystems, Mountain View, CA). Numerical calculations and imaging displays were made using IDL (Interactive Data Language; Research Systems, Boulder, CO). For each section, pixel-by-pixel T2 maps (Fig 1) were generated according to the following equation:

$$T2 \text{ value} = (TE2 - TE1)/\text{Ln}(SI1/SI2)$$

where SI1 and SI2 represent signal intensity from the first and second echo images, respectively.

Regions of interest were placed in the normal-appearing white matter and the affected white matter, guided by visually

Address reprint requests to Elias R. Melhem, MD, Department of Radiology and Radiological Sciences, The Johns Hopkins Medical Institutions, 600 North Wolfe Street, Baltimore, MD 21287.

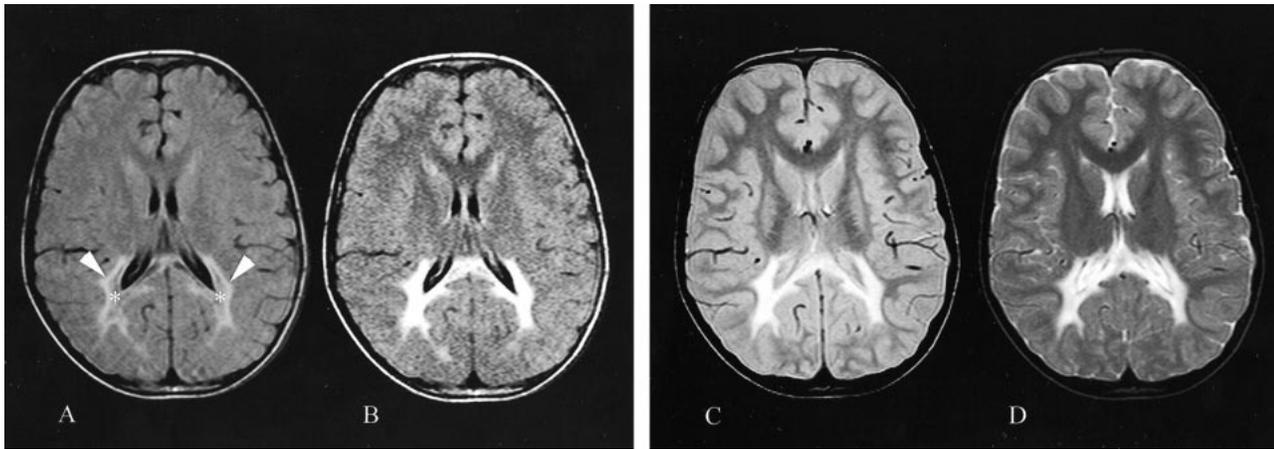


FIG 1. Images of a 13-year-old male patient with X-linked adrenoleukodystrophy.

A, Axial first echo fast FLAIR image (6000/58 [TR/first TE_{eff}]; inversion time, 2000 ms).

B, Axial second echo fast FLAIR image (6000/160 [TR/second TE_{eff}] inversion time, 2000 ms).

C, Axial first echo conventional spin-echo MR image (3000/30 [TR/first TE]).

D, Axial second echo conventional spin-echo MR images (3000/100 [TR/second TE]) of the brain, obtained at the level of the lateral ventricles, show symmetrical and confluent abnormal signal intensity in the deep white matter of the both parietooccipital lobes and splenium of the corpus callosum. The peripheral (arrowheads) and central (asterisks) zones are most distinct on the first echo fast-FLAIR image.

apparent signal intensity differences on the MR images. T2 values were measured from regions of interest copied onto corresponding T2 maps derived from dual-echo fast-FLAIR and dual-echo conventional spin-echo MR images. For each participant, the T2 values from the normal-appearing white matter and affected white matter were averaged over the multiple sections that covered the cerebral hemispheres.

Using commercially available statistical software (Statview; SAS institute Inc., Cary, NC), repeated measures analysis of variance and paired Bonferonni/Dunn post hoc analyses were performed to compare average T2 values in the different white matter zones. The T2 values in normal-appearing white matter were compared with the published normal range at 1.5 T (6–8). Correlation between T2 values obtained from dual-echo fast FLAIR and dual-echo conventional spin-echo MR images was calculated using Pearson correlation coefficient. For all statistical analyses, the significance level for differences was set at $P < .05$.

Results

In four patients, the first echo of the dual-echo fast-FLAIR sequence showed two distinct zones in the affected white matter (Figs 1A and 2A). The peripherally located zone showed increased signal intensity compared with normal-appearing white matter, and the centrally located zone showed decreased signal intensity compared with normal-appearing white matter. These zones were difficult to distinguish on the dual-echo conventional spin-echo MR images and on the second echo fast-FLAIR images (Fig 1). In each of six patients, there was only one zone (increased signal intensity compared with normal-appearing white matter in the affected white matter on all MR sequences.

Among the four patients with two distinct zones, the average T2 values were 135.3 ± 12.8 ms (FLAIR) and 104.4 ± 3.5 ms (conventional spin-echo) in the zone of increased signal (peripheral zone) and 329.0 ± 62.2 ms (FLAIR) and $207.4 \pm$

33.8 ms (conventional spin-echo) in the zone of decreased signal intensity (central zone). The average T2 values from the two zones were different ($P < .0167$). For each of six patients with one zone of affected white matter, the T2 values ($137.4 + 9.7$ ms [FLAIR] and 107 ± 5.5 ms [conventional spin-echo]) were not different from those of the hyperintense zone (peripheral zone) in the four patients with two zones each ($P = .32$). The average T2 values in normal-appearing white matter (79.8 ± 3.7 ms [FLAIR] and 69.8 ± 3.3 ms [conventional spin-echo]) were within the published normal range (68–95 ms). There was a very strong correlation between the average T2 values from dual-echo fast-FLAIR and dual-echo conventional spin-echo sequences ($r = 0.93$) for both normal-appearing white matter and affected white matter.

Discussion

Currently, the burden of quantifying CNS disease load and identifying reversibility in cases of X-linked adrenoleukodystrophy lies primarily on MR imaging. The ability of the various MR-based imaging techniques (anatomic, functional, or metabolic) to differentiate between zones of reversible and zones of irreversible white matter disease and to identify early white matter derangement is of the essence (9).

In this study, dual-echo fast-FLAIR MR imaging (specifically the first echo) showed two distinct zones in the affected white matter of four patients with X-linked adrenoleukodystrophy, which may correspond to well-established irreversible and potentially reversible pathologic zones. However, this radiologic-pathologic correlation requires confirmation if dual-echo fast-FLAIR imaging is to as-

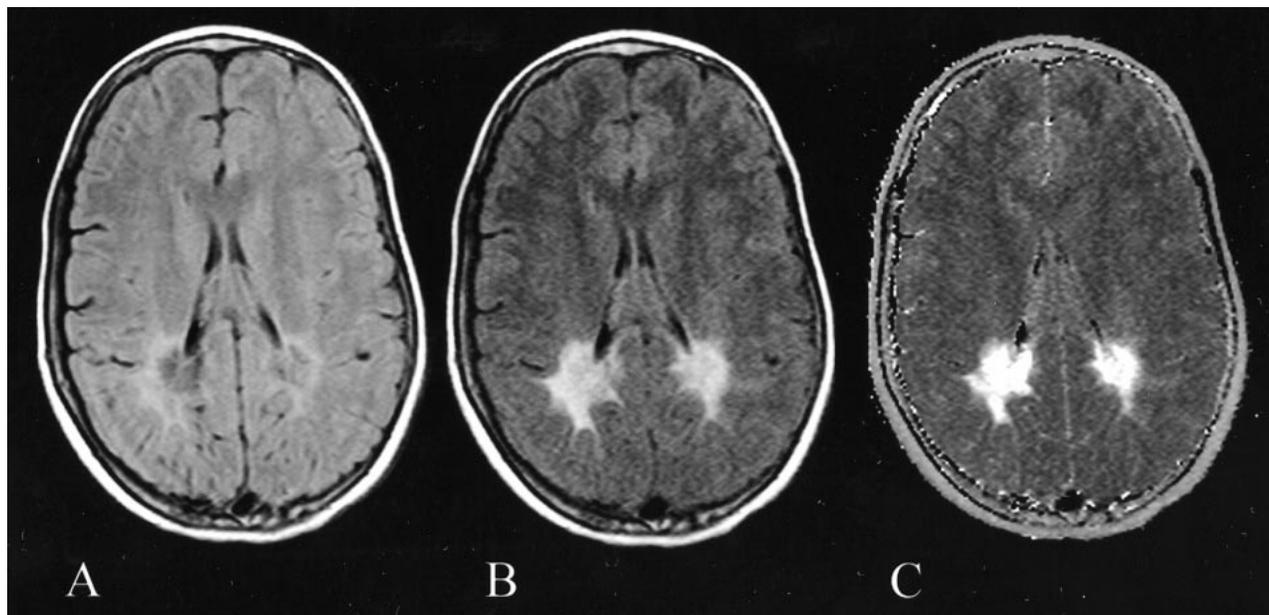


FIG 2. Images of an 8-year-old male patient with X-linked adrenoleukodystrophy.

A, Axial view first echo fast-FLAIR image (6000/58 [TR/first TE_{eff}]; inversion time, 2000 ms).

B, Axial view second echo fast-FLAIR image (6000/160 [TR/second TE_{eff}]; inversion time, 2000 ms).

C, Corresponding T2 maps of the brain, obtained at the level of the lateral ventricles, show symmetrical and confluent abnormal signal intensity in the deep white matter of the both parietooccipital lobes. Note that regions of highest signal intensity on the T2 map (ie, highest T2 values) correspond to the central zone of low signal intensity on the first echo FLAIR image.

sume an important role in differentiating between pathologic zones.

The low signal intensity in the central zone within the affected white matter on first echo fast-FLAIR images is probably due to marked prolongation of T1 relaxation, approaching that of CSF. The low signal is the result of short effective TE (58 ms) and CSF-nulling inversion pulse (10). On the other hand, the central zone is hyperintense on the second echo fast-FLAIR images because of marked prolongation of T2 relaxation, which is emphasized by the long effective TE (160 ms).

For the remaining six patients, the absence of central low signal intensity on the first echo fast-FLAIR images and the moderate prolongation of T2 relaxation may imply that axonal destruction, astrogliosis, and cavitation have not yet occurred in potentially reversibly affected white matter. This again awaits radiologic-pathologic confirmation. Determination of T2 values in the affected white matter of patients with cerebral X-linked adrenoleukodystrophy provides a quantitative measure that is intrinsic to the diseased white matter and devoid of MR weighting effects. These intrinsic measures allow normalization across participants and MR imagers and help better define thresholds for segmentation algorithms. The ability to normalize becomes critical for conducting multicenter trials (necessary for uncommon diseases such as adrenoleukodystrophy). Furthermore, once spatial matching between pathologic zones and T2 value zones is confirmed, we anticipate an improvement in the correlation between disease burden, as defined by MR imaging, and clinical disability. Also,

if future work shows the ability of dual-echo fast-FLAIR images and T2 maps to distinguish between reversibly and irreversibly affected white matter, these maps may provide a better guide for experimental therapies.

A limitation of our study is the lack of contrast-enhanced T1-weighted MR images of the participants. The presence of contrast enhancement in affected white matter has been attributed to the inflammatory process in Schaumbert's zone 2 and has been shown to be a predictor of disease progression (11). Combining contrast-enhanced T1-weighted MR imaging and dual-echo fast FLAIR MR imaging with corresponding T2 maps may improve *in vivo* delineation of the different pathologic zones.

It is important to emphasize that the two MR imaging sequences implemented in this study do not fully account for the multiexponential nature of the T2 decay in brain tissue or for the effects of molecular diffusion, stimulated echoes, and magnetization transfer on the T2 relaxation values (12, 13). However, multiple echo MR imaging sequences designed for accurate *in vivo* T2 relaxation measurements remain impractical for clinical use because of time and brain coverage constraints (4). Additionally, for the purpose of generating total brain T2 maps of our patients with X-linked adrenoleukodystrophy, we feel restricted to dual-echo MR imaging. Furthermore, the effects of molecular diffusion, stimulated echoes, and magnetization transfer on T2 relaxation values are influenced by the type of MR read-out implemented. This is the likely reason for the wide range of published nor-

mative brain T2 values and the differences in T2 values of both affected white matter and normal-appearing white matter generated from the two dual-echo techniques used in this study (5).

Conclusion

On the basis of dual-echo fast-FLAIR imaging and T2 maps, the affected white matter can be divided into distinct zones in patients with cerebral X-linked adrenoleukodystrophy.

References

1. Schaumburg HH, Powers JM, Raine CS, Suzuki K, Richardson EP Jr. **Adrenoleukodystrophy: a clinical and pathological study of 17 cases.** *Arch Neurol* 1975;32:577-591
2. Powers JM. **The pathology of peroxisomal disorders with pathogenetic considerations.** *J Neuropathol Exp Neurol* 1995;54:710-719
3. Melhem ER, Breiter SN, Ulug AM, Raymond GV, Moser HW. **Improved tissue characterization in adrenoleukodystrophy using magnetization transfer imaging.** *AJR Am J Roentgenol* 1996;166:689-695
4. Duncan JS, Bartlett P, Barker GJ. **Technique for measuring hippocampal T2 relaxation time.** *AJNR Am J Neuroradiol* 1996;17:1805-1810
5. Melhem ER, Whitehead RE, Bert RJ, Caruthers SD. **MR imaging of the hippocampus: measurement of T2 with four dual-echo techniques.** *Radiology* 1998;209:551-555
6. Bottomley PA, Foster TH, Argersinger RE, Pfeifer LM. **A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1-100 MHz: dependence on tissue type, NMR frequency, temperature, species, excision, and age.** *Med Phys* 1984;11:425-448
7. Bottomley PA, Hardy CJ, Argersinger RE, et al. **A review of 1H nuclear magnetic resonance relaxation in pathology: are T1 and T2 diagnostic?** *Med Phys* 1987;14:1-37
8. Rydberg JN, Riederer SJ, Rydberg CH, Jack CR. **Contrast optimization of fluid-attenuated inversion recovery (FLAIR) imaging.** *Magn Reson Med* 1995;34:868-877
9. Melhem ER, Barker PB, Raymond GV, Moser HW. **X-linked adrenoleukodystrophy in children: review of genetic, clinical, and MR imaging characteristics.** *AJR Am J Roentgenol* 1999;173:1575-1581
10. Ashikaga R, Araki Y, Ono Y, et al. **Appearance of normal brain maturation on fluid-attenuated inversion-recovery (FLAIR) MR images.** *AJNR Am J Neuroradiol* 1999;20:427-431
11. Melhem ER, Loes DJ, Georgiades CS, Raymond GV, Moser HW. **X-Linked adrenoleukodystrophy: the role of contrast-enhanced MR imaging in predicting disease progression.** *AJNR Am J Neuroradiol* 2000;21:839-844
12. Crawley AP, Henkelman RM. **Errors in T2 estimation using multislice multiple-echo imaging.** *Magn Reson Med* 1987;4:34-47
13. Whittall KP, Mac Kay AL, Graeb DA, Nugent RA, Li DK, Paty DW. **In vivo measurement of T2 distributions and water contents in normal human brain.** *Magn Reson Med* 1997;37:34-43