Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy

D.J. Loes, MD; A. Fatemi, MD; E.R. Melhem, MD; N. Gupte, BSc; L. Bezman, MD, MPH; H.W. Moser, MD; and G.V. Raymond, MD

Abstract—*Background:* X-linked adrenoleukodystrophy (X-ALD) has variants with widely different outcomes, hampering clinical counseling and evaluation of therapies. *Objective:* To evaluate the degree to which MRI patterns can predict lesion progression. *Methods:* Two hundred six boys and men with cerebral X-ALD (median age 12.2 years, mean age 18.5 years, age range 1.7 to 73.8 years) were studied. In 140 individuals, follow-up MRI were available. Data after bone marrow transplantation (BMT) were excluded. The patterns of MRI abnormalities were subdivided into five groups based on the anatomic location of the initial T2 signal hyperintensity (pattern 1: parieto-occipital white matter, pattern 2: frontal white matter, pattern 3: corticospinal tract, pattern 4: cerebellar white matter, pattern 5: concomitant parieto-occipital and frontal white matter). The X-ALD MRI Severity Scale, a 34-point scale previously described, was used in the analysis. *Results:* Pattern 1 patients had rapid progression if contrast enhancement was present and if the MRI abnormality manifested at an early age. The latter was also true for pattern 2 patients. Based on these variables, predictive formulas were constructed for these two patterns using multiple regressions. MRI progression was much slower in pattern 3 and 4 patients, whereas in the few pattern 5 patients, it was more rapid than in any other of the patterns. Patterns 1 and 5 occurred mainly in childhood, patterns 2 and 4 in adolescence, and pattern 3 in adults. *Conclusions:* MRI progression in X-ALD depends on patient age, initial MRI Severity Scale score, and anatomic location of the lesion. When used in combination, these data aid the prediction of disease course and the selection of patients for BMT.

NEUROLOGY 2003;61:369–374

X-Linked adrenoleukodystrophy (X-ALD) is a progressive disorder that involves the nervous system, adrenal cortex, and testes.[1] It is associated with the accumulation of very long chain fatty acids (VLCFA) and can be diagnosed reliably by abnormally high VLCFA levels in plasma.[2] The gene deficient in X-ALD, *ABCD1*, codes for a peroxisomal membrane protein that is a member of the ATP binding cassette transporter superfamily.[3] The clinical manifestations of X-ALD range widely from the childhood cerebral form (CCER), leading to severe disability and death by 10 years of age, to the milder adult form, adrenomyeloneuropathy (AMN), which is compatible with survival to the eighth decade.[1,4] CCER affects about 40% of patients and involves the parieto-occipital white matter most frequently, whereas AMN is found in about 45% of affected males and involves mainly the spinal cord.[5] Within these two major categories are a series of intermediate subgroups that vary with respect to the degree and location of cerebral involvement.[6] The prognostic significance of these subgroups is still poorly understood. The various phenotypes co-occur often within the same family and do not correlate with the nature of the gene mutation[7] or the severity of the biochemical abnormality.[2]

The inability to predict outcome limits severely the capacity to counsel and to evaluate and select therapeutic interventions. To overcome this limitation, we have explored the role of neuroimaging studies as prognostic markers. We have reported recently that a MRI severity score, designed specifically for X-ALD,[8] correlates with the severity of neuropsychological and neurologic involvement and, when combined with age, provides information of prognostic significance in X-ALD.[9] The MRI score progression also correlates strongly with survival.[9] In a separate study, we demonstrated that the presence of perilesional contrast enhancement has a profoundly negative effect on prognosis.[10]

The aim of the current study was to determine whether different brain MRI lesion patterns predict the course of cerebral X-ALD. Based upon lesion location, five distinct patterns were identified. In three of the patterns, progression was rapid, while a relatively benign course was demonstrated in two. A formula was developed that combines these new data with the two previously described MRI variables and

From Suburban Radiology Consultant Ltd. (Dr. Loes), Minneapolis, MN; Kennedy Krieger Institute (Drs. Fatemi, Bezman, Moser, and Raymond) and School of Public Health (N. Gupte), Johns Hopkins Medical Institutions, Baltimore, MD; and Department of Radiology (Dr. Melhem), University of Pennsylvania, Philadelphia.

Supported by grants HD10981 and M0RR11 from the NIH and contract LM 9-3537 from the National Library of Medicine.

Received January 22, 2003. Accepted in final form May 5, 2003.

Address correspondence and reprint requests to Dr. G.V. Raymond, Kennedy Krieger Institute, 707 N. Broadway, Rm. 500L, Baltimore, MD; e-mail: raymond@kennedykrieger.org

patient age. This formula was found to enhance predictive power with respect to the progression of the MRI abnormality.

Methods. *Participants.* The study group was derived from patients with proven biochemical defect for X-ALD seen at the Kennedy Krieger Institute (KKI) and the Johns Hopkins Hospital (JHH) between 1987 and 2001. Two hundred six male patients with cerebral X-ALD defined by an MRI score of ≥0.5 were enrolled into the study. Follow-up MRI were available in 140 patients. None of these patients received bone marrow transplantation (BMT) during the follow-up period. Dietary treatment with a 4:1 mixture of glyceryl trioleate and glyceryl trierucate (Lorenzo's oil) was not an exclusion criterion.

MRI protocol. Eighty percent of the MRI examinations were performed at KKI or JHH. The remaining MRI were sent from other institutions. The exams included at a minimum sagittal T1-weighted spin echo imaging (with repetition time [TR] ranging from 500 to 600 milliseconds, depending on the scanner's gradient capabilities, and echo time [TE] between 15 and 25 milliseconds) and axial double-echo spin echo imaging (TR between 2,500 and 3,500 milliseconds, depending on scanner, and TE1 at 20 and TE2 at 30 milliseconds). Contrast-enhanced axial T1-weighted spin echo imaging (TR 500 to 600/TE 15 to 20 milliseconds) studies had been performed in 40 of the 140 on whom follow-up studies were available. We reported previously the baseline and last follow-up evaluations in these 40 patients.[10] For the purpose of the current study, we also evaluated the MRI at 73 intermediate time points in this group that had not been included in the previous study. The MRI of these patients were classified as contrast positive in the presence of gadolinium enhancement (T1-weighted spin echo MR hyperintensity within or adjacent to the lesion after 0.10 mmol/kg gadopentetate dimeglumine administration) or as contrast negative.

All studies were reviewed by at least two physicians experienced in X-ALD using the MRI Severity Scale scoring method (table). Reviewers were blinded to the neurologic findings. For the assessment of disease progression, the first abnormal MRI exam was used as a reference for all subsequent examination.

Pattern definition. The patterns of MRI abnormalities were subdivided into five groups based on the anatomic location of the lesion. Primary involvement of white matter in the parieto-occipital lobe or splenium of corpus callosum was defined as pattern 1 (figure 1, a), whereas involvement of the frontal lobe or genu of corpus callosum was defined as pattern 2 (see figure 1, b). When the frontopontine or corticospinal projection fibers were the primary affected location, the lesion was defined as pattern 3 (see figure 1, c). Pattern 4 was defined as primary cerebellar white matter involvement (see figure 1, d) and pattern 5 as combined parieto-occipital and frontal white matter involvement (see figure 1, e). In six patients, the abnormalities did not conform to any of these patterns (one patient had unilateral temporal involvement and five had diffuse global white matter involvement representing late stage of disease).

Follow-up analysis. In the group with multiple MRI studies, assessment of progression was based on the increase of the MRI severity score during the follow-up period (ΔMRI score/follow-up time). The Kruskal–Wallis test was used to detect significant differences of mean progression values between the first three patterns. Multiple regression analyses were performed to measure the effect of age and initial abnormal MRI score on follow-up MRI score in each pattern. Follow-up time was used as a covariate in the analysis, and a model for the follow-up MRI score after 1 year was calculated. In the largest group (pattern 1), a sufficient number of gadolinium MRI studies were available so that this information could be included as a covariate in the analysis. The StatView software package (SAS Corp., Cary, NC) was used for descriptive statistics and the nonparametric tests, whereas STATA (Stata Corp., College Station, TX) was used for the multiple regression analysis.

Results. Interobserver reliability for the MRI severity score was high ($r = 0.98$), and rare disagreement between the two reviewers was resolved by consensus.

Table *MRI Severity Scale*

Parieto-occipital WM (maximum 4)
Anterior temporal WM (maximum 4)
Frontal WM (maximum 4)
Periventricular
Central
Subcortical
Local atrophy
Corpus callosum (maximum 5)
Splenium
Body
Genu
Splenium atrophy
Genu atrophy
Visual pathway (maximum 4)
Optic radiations
Meyer's loop
Lateral geniculate body
Optic tract
Auditory pathway (maximum 4)
Medial geniculate body
Brachium to inferior colliculus
Lateral lemniscus
Pons
Projection fibers (maximum 2)
Internal capsule
Brainstem
Cerebellum (maximum 2)
White matter
Atrophy
Basal ganglia (maximum 1)
Global atrophy (maximum 4)
Mild
Moderate
Severe
Brainstem

This MRI Severity Scale has been designed specifically for X-linked adrenoleukodystrophy[8] and has been shown to correlate with severity of neurologic deficits and to be predictive of disease progression.[9] Different brain regions are considered in the MRI severity score. Each area is scored as 0 if normal, 0.5 if unilateral involvement, and 1 if the lesion or atrophy is bilateral. The maximum severity score is 34; a score of ≥1 is considered abnormal.

WM = white matter.

MRI pattern frequency and relation to age. Figure 2 shows the distribution of patterns in relation to age. Eighty patients were younger than 10, 43 patients between 10 and 16, and 83 patients older than 16 years at the time of initial abnormal MRI scan. Whereas 80% of patients under 10 years of age presented with pattern 1, the overall frequency of this pattern was somewhat less common in the older patients. For the group as whole, 137

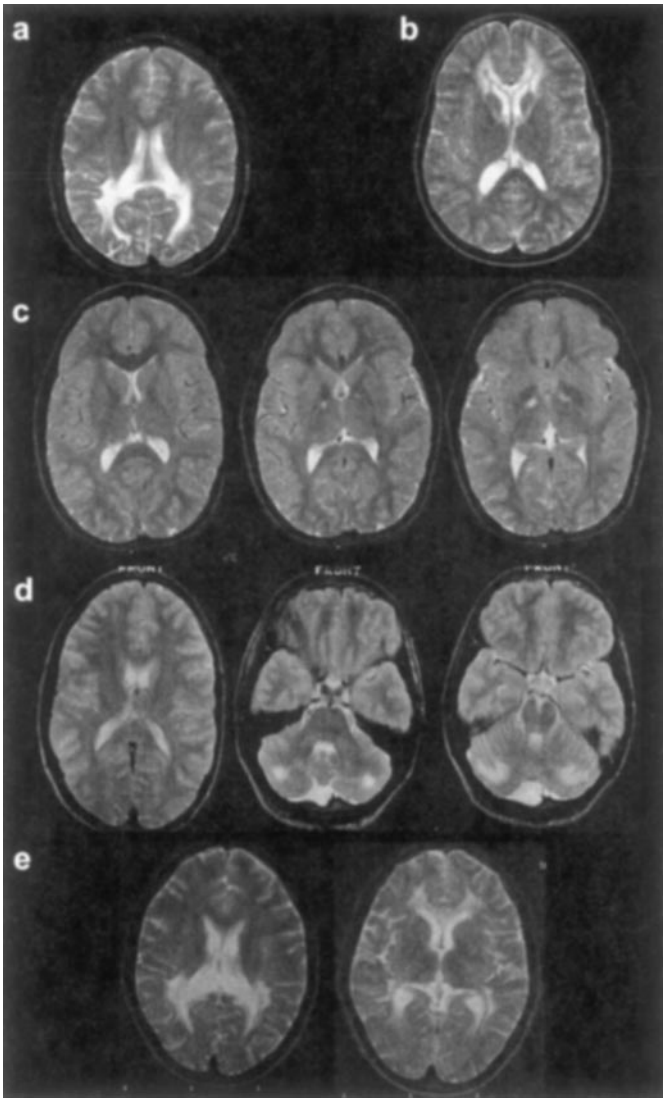

Figure 1. Different patterns recognized in male patients with cerebral X-linked adrenoleukodystrophy. (a) Pattern 1: white matter in the parieto-occipital lobe or splenium of corpus callosum; (b) pattern 2: white matter in the frontal lobe or genu of corpus callosum; (c) pattern 3: primary involvement of frontopontine or corticospinal projection fibers without affection of periventricular white matter; (d) pattern 4: primary involvement of cerebellar white matter; (e) pattern 5: combined but separate initial involvement of frontal and parieto-occipital white matter.

(66%) patients presented with pattern 1, 32 (15.5%) with pattern 2, 24 (12%) with pattern 3, 2 (1%) with pattern 4, and 5 (2.5%) with pattern 5. The mean MRI severity score of the whole cohort was 6 ± 0.4 (SE). The median age was 12.2 years (mean 18.5 years) at the time of the first abnormal MRI examination, with a range from 1.7 to 73.8 years. As shown in figure 3, the pattern 1 and 5 groups were on average the youngest, whereas patterns 2 and 4 presented mostly during adolescence and pattern 3 during adulthood.

Follow-up studies. In the 140 patients with follow-up MRI series, the average duration of follow-up was 3.51 years, ranging from a minimum of 59 days to 11.1 years. Eighty-eight patients of this group presented with pattern 1, 24 with pattern 2, 20 with pattern 3, 2 with pattern 4, 4

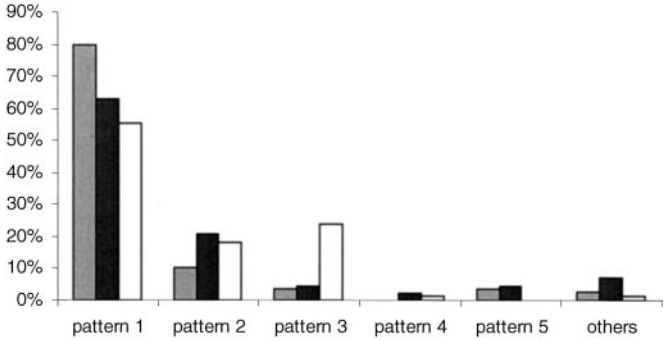

Figure 2. Frequency of the pattern presentation at first abnormal MRI, subdivided according to age (gray columns = <10 years; black columns = 10 to 16 years; open columns = 16 years of age). In most instances, the age at first MRI reflects the age at onset of symptoms. Patterns 1 and 2 are most frequent in children and adolescents, with the "classic" pattern 1 by far the most common, particularly in those who manifest before 10 years of age. Pattern 3 is most common in those who manifest in adulthood.

with pattern 5, and 2 patients with advanced global white matter involvement. Of the 40 patients with contrast studies, 34 presented with pattern 1, 3 with pattern 2, 2 with pattern 3, and 1 patient was in a late disease stage. The median follow-up time of this subgroup was 1 year (mean 11 months, range 59 days to 4.3 years).

Progression of MRI abnormality.

1. The mean progression of the MRI score per year was nearly the same for patterns 1 and 2 (figure 4). It was lower in patients with pattern 3 (0.4 ± 0.15 [SE]; Kruskal–Wallis test, $p = 0.001$). One of the two patients with pattern 4 did not show MRI progression over 26 months, whereas the score in the second patient had increased by only 1.5 points over 3 years. The four patients with pattern 5 showed very rapid progression with a mean MRI score increase of 11.2 ± 0.75 (SE) over 1 year.
2. Re-evaluation of the previously published data on the 40 patients with contrast studies confirmed our previous reports that progression was much more rapid in

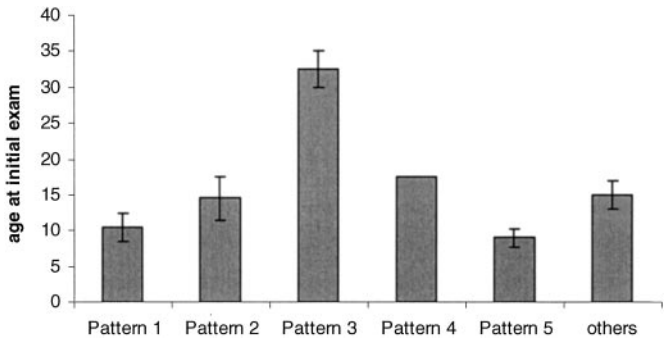

Figure 3. Mean ages at initial examination in various patterns. The "classic" pattern 1 presents most commonly in the youngest patients, with the second most frequent pattern 2 presenting at a slightly older age. Pattern 3, which involves the frontopontine and corticospinal projection fibers, presents in adulthood. Bars indicate SEM.

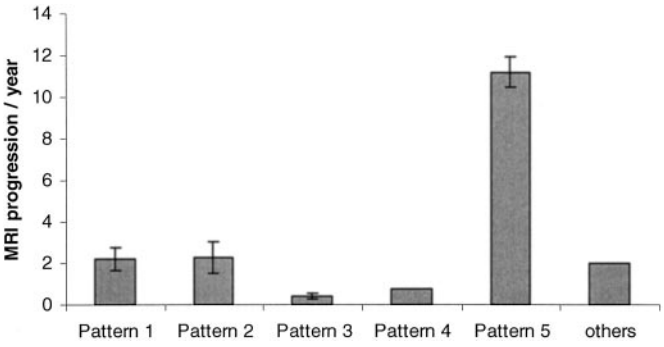

Figure 4. Mean rate of progression of the MRI Severity Scale score[8] (severity score/number of follow-up years) in different pattern groups. Progression rates for patterns 1 and 2 are relatively rapid and similar, whereas progression in pattern 3 patients is slow. Progression in pattern 5 patients (simultaneous posterior and anterior presentation) is extremely rapid. Bars indicate SEM. Note that pattern 4 and the "others" group include only two patients each and the pattern 5 group only five.

the contrast-positive group (50/113 follow-up MRI examinations; 44%): In this group, MRI progression was detected in 45 (90%) follow-up exams, whereas in the contrast-negative group (63 follow-up MRI; 56%), MRI severity score increased only in 7 (11%) patients.

Multiple linear regression analyses. Because of the large group size, the analysis was most complete in the pattern 1 patients:

Pattern 1: In the 34 patients who underwent contrast studies, we constructed a model based on age (regression coefficient = -0.07 ± 0.02 [SE], $p = 0.006$), MRI severity score (regression coefficient = 1.05 ± 0.02 [SE], $p < 0.0001$) at initial exam, and presence or absence of gadolinium enhancement around lesion (regression coefficient = 2.28 ± 0.32 [SE], $p < 0.0001$) as independent variables. These covariates explained 96% of the variability of MRI progression after 1 year. Based on this analysis, we developed a formula that predicts the follow-up MRI severity score after 1 year: predicted MRI score after 1 year = 2.28 enhancement − 0.07 initial age + 1.05 initial MRI score + 0.87 ("enhancement": perilesional gadolinium enhancement around the lesion was defined as 1, the absence of this phenomenon as 0).

Pattern 2: Disease progression was more rapid in patients who were 13 years old or younger compared with those who were older than 13. It was not possible to analyze the effect of contrast enhancement in patients with this pattern because of the small number of contrast studies that were available for this group. A formula was developed that accounted for 79% of the variability of MRI progression after 1 year. The covariates in this model were the age subgroup (<13 and ≥13 years old; regression coefficient = -4.4 ± 2.3 [SE], $p = 0.05$) and MRI severity score (regression coefficient = 2.1 ± 0.27 [SE], $p < 0.0001$) at initial examination: predicted MRI score after 1 year = 2.1 initial MRI score − 4.4 age subgroup − 0.48 (age subgroups: 0: <13 years, and 1: ≥13 years old).

Pattern 3: In this group, there was no significant effect of age or MRI severity score at initial exam on the progression of disease. Only 3 of the 20 (15%) patients had an increase of the MRI severity score of >2. One of these three patients developed progressive disease (MRI score increase from 1 to 10.5) over a 5.7-year period. The mean increase of the MRI severity score over 1 year was only 0.44 ± 0.16 (SE).

Pattern 4 and 5 groups were too small for multiple regression analysis. However, as mentioned above, the mean MRI progression was slow in pattern 4 but very rapid in pattern 5.

Discussion. We report the relative frequency of various MRI patterns of brain involvement in a large group of cerebral X-ALD patients and the rate at which the MRI abnormality increased in each. We find that pattern 1 patients had serious prognosis if contrast enhancement was present and if the MRI abnormality manifested at an early age. The latter was also true for patients with pattern 2. MRI progression was much slower in pattern 4 and 5 patients. Progression in the few patients with pattern 5 was more rapid than in any other of the patterns. A formula that includes the pattern aspect in combination with two previously described MRI variables and patient's age was developed. This information will aid in counseling and increases the capacity to evaluate and select therapeutic interventions in X-ALD.

Cerebral X-ALD is the most severe X-ALD phenotype and develops in approximately 40% of patients.[1] MR findings either predate cerebral symptoms or appear to develop at the same time as patients become symptomatic.[11,12] Pattern 1 (posterior white matter involvement) has been reported to be the most common pattern, with a frequency of 80% in several studies,[6,8] including our own.[8] This value was based mainly on studies of boys with CCER who were younger than 10. Although we confirm that 80% of the boys in this age group do present with pattern 1, this pattern occurred in only 63% of those between 10 and 16 years old and in 55% of those older than 16 (see figure 2). Frontal involvement was the second most common pattern of cerebral X-ALD in the 10- to 16-year-old patients. The projection fiber involvement (pattern 3) is most common in the adult group.

Multiple linear regression analyses were applied to develop formulas that predict follow-up MR severity scores at 1 year after the initial MRI study. The formula to predict progression in pattern 1 patients is especially useful as it accounts for 96% of all variability. The contrast data and, to a lesser extent, age were the major determinants of disease progression in this pattern. The contrast data effectively divided this pattern into two groups. The group with contrast enhancement progressed rapidly, whereas the group without contrast enhancement progressed much more slowly. The positive contrast enhancement most likely is a marker of the acute demyeli-

nating inflammatory process, as shown in pathologic studies.[13]

The predictive value of the formula for the pattern 2 group patients is less powerful than for pattern 1. Owing to the small number of available contrast studies, this item could not be included in the regression model. It has been reported that patients with the frontal white matter involvement progress less rapidly than those with pattern 1.[6] In the current study, the overall mean progression of the MRI severity score was almost equal in both patterns. Further analysis of pattern 2 patients showed that MRI progression varies with patient age. Progression was more rapid in patients under 13 years old, whereas patients 13 years or older showed progression only when the MRI severity score was ≥ 5. In the other studies, the patients with pattern 2 were older than those with pattern 1. We believe that these age differences account for the discrepancy between those observations and ours.

What is referred to here as pattern 3, namely, the isolated involvement of the projection fibers, was initially observed in a CT study and designated as ALD type II.[14] A major finding of the current study is that pattern 3 has a more benign course than that associated with patterns 1 and 2 and that it presents at a later age. The more common posterior (pattern 1) and anterior (pattern 2) patterns showed nearly identical yearly MRI score progression rates, whereas pattern 3 progressed at one-eighth of that rate (see figure 4). In 5 children and 15 adults with pattern 3, the MRI score had not increased at follow-up examinations. Only one of the pattern 3 patients, an adult in his late thirties, went on to develop symptomatic cerebral disease. Clinically, 13 of the pattern 3 patients presented with symptoms characteristic for the "pure" AMN phenotype, which, according to Powers et al.,[5,15] is a noninflammatory dying-back axonopathy and differs fundamentally from the inflammatory myelinopathy in patients with demyelinating cerebral lesions. The relative lack of progression in the pattern 3 patients may reflect this difference.

The two pattern 4 patients with primary cerebellar involvement presented in their late teenage years, and the MRI abnormalities were nonprogressive. Pattern 5 patients who had combined but separate frontal and parieto-occipital lesions at an early age progressed very rapidly, suggesting that this is a particularly ominous pattern.

The findings reported here are relevant to the selection of therapeutic interventions. Once cerebral symptoms become clinically apparent, the majority of patients have a rapidly progressive downhill course, resulting in a vegetative state or death.[1] The only current effective treatment for cerebral X-ALD is BMT.[16] Selection of patients who can benefit from BMT depends upon careful analysis of the stage of the disease process. Because of the high morbidity/mortality, which ranges up to 36%,[16-18] the procedure is recommended only in children and adolescents with early and progressive MRI disease.[18] It is not recommended for patients who do not have MRI or clinical evidence of brain involvement, because about 50% of these patients will not develop the severe cerebral form of the disease even without treatment.[9] BMT is also not recommended in patients who already have advanced cerebral involvement, because the risk of morbidity/mortality in these patients is high and the likelihood of achieving a meaningful quality of life is low.[16] The challenge is to identify those patients who are at risk of rapid disease progression at a time when brain involvement is still at an early enough stage so that BMT can achieve long-term stabilization and benefit. Although the presence of some degree of MRI brain abnormality is an essential requirement, it is not sufficient for this recommendation, because some patients with abnormal MRI remain stable without BMT, as shown in this study and in previous reports by others.[19] The predictive formula presented here may help identify those patients who are at low risk of progression and in whom BMT should be considered only with a great deal of caution.

Several new therapies for X-ALD have been proposed, including dietary therapy, lovastatin, phenylbutyrate, and gene therapy, and controlled trials are planned here and elsewhere.[22] Evaluation of therapies is hampered by the great and unpredictable variability in the natural history of X-ALD. The information presented here provides a degree of predictive capacity, namely, the prediction of MRI progression over a 12-month period in untreated patients. This will aid statistical evaluation of therapeutic interventions.

A limitation of this study is that the follow-up period is short and thus cannot predict long-term outcome. It is essential that research aimed to identify the trigger for rapidly progressive cerebral X-ALD will be continued so that this devastating process can be detected early. Search for modifier genes and environmental factors is in progress.[20,21] It is likely that inclusion of new emerging neuroimaging techniques such MR spectroscopic imaging and diffusion tensor and magnetization transfer MR techniques will further increase predictive power. Biochemical changes on MR spectroscopy have been shown to precede MRI abnormalities and appear to be predictive.[23-25] When a larger series of patients have been studied, we plan to include these measurements in our formula.

References

1. Moser HW, Smith KD, Watkins PA, Powers J, Moser AB. X-linked adrenoleukodystrophy. In: Scriver CR, Beaudet AL, Valle D, Sly WS, eds. The metabolic basis of inherited disease. 8th ed. New York: McGraw-Hill, 2001:3257–3302.
2. Moser AB, Kreiter N, Bezman L, et al. Plasma very long chain fatty acids in 3,000 peroxisome disease patients and 29,000 controls. Ann Neurol 1999;45:100–110.
3. Mosser J, Lutz Y, Stoeckel ME, et al. The gene responsible for adrenoleukodystrophy encodes a peroxisomal membrane protein. Hum Mol Genet 1994;3:265–271.

4. van Geel BM, Bezman L, Loes DJ, Moser HW, Raymond GV. Evolution of phenotypes in adult male patients with X-linked adrenoleukodystrophy. Ann Neurol 2001;49:186–194.
5. Powers JM, DeCiero DP, Ito M, Moser AB, Moser HW. Adrenomyeloneuropathy: a neuropathologic review featuring its noninflammatory myelopathy. J Neuropathol Exp Neurol 2000;59:89–102.
6. Aubourg P. X-linked adrenoleukodystrophy. In: Moser HW, ed. Handbook of clinical neurology. New York: Elsevier Science, 1996:447–472.
7. Kemp S, Pujol A, Waterham HR, et al. ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. Hum Mutat 2001;18:499–515.
8. Loes DJ, Hite S, Moser H, et al. Adrenoleukodystrophy: a scoring method for brain MR observations. AJNR Am J Neuroradiol 1994;159: 1761–1766.
9. Moser HW, Loes DJ, Melhem ER, et al. X-Linked adrenoleukodystrophy: overview and prognosis as a function of age and brain magnetic resonance imaging abnormality. A study involving 372 patients. Neuropediatrics 2000;31:227–239.
10. 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.
11. Aubourg P, Sellier N, Chaussain JL, Kalifa G. MRI detects cerebral involvement in neurologically asymptomatic patients with adrenoleukodystrophy. Neurology 1989;39:1619–1621.
12. Aubourg P, Adamsbaum C, Lavallard–Rousseau MC, et al. Brain MRI and electrophysiologic abnormalities in preclinical and clinical adrenomyeloneuropathy. Neurology 1992;42:85–91.
13. Powers JM, Liu Y, Moser AB, Moser HW. The inflammatory myelinopathy of adreno-leukodystrophy: cells, effector molecules, and pathogenetic implications. J Neuropathol Exp Neurol 1992;51:630–643.
14. Di Chiro G, Eiben RM, Manz HJ, Jacobs IB, Schellinger D. A new CT pattern in adrenoleukodystrophy. Radiology 1980;137:687–692.
15. Powers JM, DeCiero DP, Cox C, et al. The dorsal root ganglia in adrenomyeloneuropathy: neuronal atrophy and abnormal mitochondria. J Neuropathol Exp Neurol 2001;60:493–501.
16. Shapiro E, Krivit W, Lockman L, et al. Long-term effect of bone-marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. Lancet 2000;356:713–718.
17. Malm G, Ringden O, Anvret M, et al. Treatment of adrenoleukodystrophy with bone marrow transplantation. Acta Paediatr 1997;86:484–492.
18. Peters C, Shapiro E, Ziegler R, et al. The worldwide hematopoietic cell transplantation experience for cerebral X-adrenoleukodystrophy. In: Peters C, ed. Correction of genetic diseases by transplantation. London: Cogent Trust (in press).
19. Korenke GC, Pouwels PJ, Frahm J, et al. Arrested cerebral adrenoleukodystrophy: a clinical and proton magnetic resonance spectroscopy study in three patients. Pediatr Neurol 1996;15:103–107.
20. Smith KD, Kemp S, Braiterman LT, et al. X-Linked adrenoleukodystrophy: genes, mutations, and phenotypes. Neurochem Res 1999;24:521–535.
21. Lombard–Platet G, Savary S, Sarde CO, Mandel JL, Chimini G. A close relative of the adrenoleukodystrophy (ALD) gene codes for a peroxisomal protein with a specific expression pattern. Proc Natl Acad Sci USA 1996;93:1265–1269.
22. Moser HW, Bezman L, Lu SE, Raymond GV. Therapy of X-linked adrenoleukodystrophy: prognosis based upon age and MRI abnormality and plans for placebo-controlled trials. J Inherit Metab Dis 2000;23:273–277.
23. Pouwels PJ, Kruse B, Korenke GC, Mao X, Hanefeld FA, Frahm J. Quantitative proton magnetic resonance spectroscopy of childhood adrenoleukodystrophy. Neuropediatrics 1998;29:254–264.
24. Kruse B, Barker PB, van Zijl PC, Duyn JH, Moonen CT, Moser HW. Multislice proton magnetic resonance spectroscopic imaging in X-linked adrenoleukodystrophy. Ann Neurol 1994;36:595–608.
25. Eichler FS, Barker PB, Cox C, et al. Proton MR spectroscopic imaging predicts lesion progression on MRI in X-linked adrenoleukodystrophy. Neurology 2002;58:901–907.