

# Magnetic Resonance Imaging Detection of Lesion Progression in Adult Patients With X-linked Adrenoleukodystrophy

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**Background:** An inherited disorder, X-linked adrenoleukodystrophy (X-ALD) is known to cause progressive inflammatory demyelination.

**Objective:** To analyze the adult pattern of disease progression in X-ALD.

**Design, Setting, and Patients:** We retrospectively assessed magnetic resonance (MR) images obtained in adult patients who had developed cerebral disease between January 1, 1985, and December 31, 2005. We identified 103 adult patients with X-ALD with lesions on their MR images. Of these, 56 had serial MR examinations at least 1 year apart and were included in this study.

**Main Outcome Measure:** Progression of X-ALD lesions on MR images.

**Results:** On initial presentation, 17 patients with X-ALD had corticospinal tract lesions without splenium or genu involvement, 24 had symmetric corticospinal tract lesions with additional involvement of the splenium or genu, and 15 did not have corticospinal tract involvement but had other white matter lesions. In 18 of 21 patients with progressive lesions, corticospinal tract involvement preceded or occurred concurrently with progressive inflammatory demyelination.

**Conclusions:** Brain MR imaging abnormalities in adults with X-ALD progress slower than those reported in childhood. The involvement of the corticospinal tracts is prominent and may at times represent a variant course of progressive inflammatory demyelination.

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**X**-LINKED ADRENOLEUKODYSTROPHY (X-ALD) is a peroxisomal disorder affecting the nervous system, adrenal cortex, and testes.<sup>1</sup> It is caused by a defect in the *ABCD1* gene, which has been mapped to Xq28 and codes for a peroxisomal membrane protein (ALD protein).<sup>2,3</sup> The principal biochemical defect is the accumulation of saturated very-long-chain fatty acids in tissues.<sup>4,5</sup> There is a wide range in phenotypic expression. In childhood, a severe inflammatory reaction associated with accumulation of very-long-chain fatty acids in brain lipids causes cerebral demyelination.<sup>6,7</sup> Progression of demyelination is systematic, striking earliest and most severely in the splenium and genu of the corpus callosum.<sup>8</sup> Isolated corticospinal tract involvement seen in the adult has not been observed in the child. Early symptoms include attention-deficit disorder, behavioral changes, and impairment of visual acuity and hearing. Within 3 years, most patients are in a persistent vegetative state or have died.

In adulthood the disease manifests as adrenomyeloneuropathy, a spastic paraparesis that is due to a chronic axonopathy of the spinal cord. In most cases, adult patients with X-ALD show symmetric corticospinal tract lesions that are thought to follow a benign course and lack progression.<sup>9</sup> However, we have found that approximately 20% of adult patients with adrenomyeloneuropathy without initial clinical brain involvement develop additional cerebral demyelination.<sup>10</sup> Recently, diffusion tensor imaging showed that occult tract-specific microstructural changes occur in patients with pure adrenomyeloneuropathy who have normal findings on conventional brain magnetic resonance (MR) imaging.<sup>11</sup> It is unclear whether axonal degeneration and cerebral demyelination emerge in X-ALD independently of each other and whether progression of cerebral demyelination in the adult patient resembles that in the child. We set out to analyze the pattern of regional lesion progression visible on MR images in adult patients with X-ALD. The goal was to determine whether progres-

**Table. Magnetic Resonance Imaging Progression and Lesion Location in Adult Adrenoleukodystrophy**

Group No.*	Progression	No. of Patients	Mean $\pm$ SD			
			Initial Age, y	Duration of Follow-up, y	Loes Score, Points	
					Initial	Follow-up
1	No	12	35 $\pm$ 12	3 $\pm$ 2	2 $\pm$ 2	2 $\pm$ 2
	Yes	5	35 $\pm$ 6	7 $\pm$ 3	2 $\pm$ 1	13 $\pm$ 7
2	No	11	25 $\pm$ 15	4 $\pm$ 5	9 $\pm$ 4	9 $\pm$ 4
	Yes	13	31 $\pm$ 11	5 $\pm$ 3	7 $\pm$ 4	11 $\pm$ 6
3	No	12	22 $\pm$ 18	9 $\pm$ 6	3 $\pm$ 2	3 $\pm$ 2
	Yes	3	15 $\pm$ 5	8 $\pm$ 6	2 $\pm$ 1	11 $\pm$ 9

\*Groups are described in the "Categorization" subsection of the "Methods" section.

sion of lesions noted on MR images differed in the adult compared with the child with X-ALD.

## METHODS

### SUBJECTS

We retrospectively analyzed MR images of patients with a proved biochemical defect for X-ALD who were older than 18 years and seen at the Kennedy Krieger Institute and The Johns Hopkins Hospital, Baltimore, Md, between January 1, 1985, and December 31, 2005. Patients were only included if a T2-weighted or a fluid-attenuated inversion recovery signal abnormality was present on their initial MR image and if they had serial MR imaging studies at least 1 year apart. None of these patients had received bone marrow transplantation in childhood, and none was receiving long-term regimented dietary therapy (Lorenzo's oil).

### MRI PROTOCOL

Eighty percent of the MR imaging examinations were performed at the Kennedy Krieger Institute or The Johns Hopkins Hospital. The remaining MR images were sent from other institutions. Several patients received their follow-up MR imaging at the Massachusetts General Hospital. The examinations included at least a sagittal T1-weighted spin echo image (repetition time, 500-600 milliseconds; echo time, 15-25 milliseconds) and an axial double-echo spin echo image (repetition time, 2500-3500 milliseconds; echo time 1, 20 milliseconds; echo time 2, 30 milliseconds). Contrast-enhanced axial T1-weighted spin echo imaging studies (repetition time, 500-600 milliseconds; echo time, 15-20 milliseconds) had been performed in 9 of the patients for whom follow-up studies were available.

### CATEGORIZATION

To distinguish the adult pattern of corticospinal tract involvement from the childhood pattern of splenium and/or genu involvement, we classified patients according to the presence or absence of corticospinal tract lesions and the presence or absence of splenium and/or genu involvement on the initial MR image. Lesions were evaluated on sagittal T1-weighted, axial T2-weighted, and proton density images. Results of this evaluation led to the following 3 groups: group 1 exhibited corticospinal tract involvement without splenium and/or genu involvement; group 2, corticospinal tract involvement in the presence of splenium and/or genu involvement; and group 3, absence of corticospinal tract involvement but presence of other

white matter lesions. Patients with isolated genu or splenium lesions were included in this last group.

The lesion burden was assessed in separate readings by 2 physicians (D. Loes and D. Lin) experienced in X-ALD using the X-ALD MR imaging Severity Scale (Loes score), a 34-point scale previously described.<sup>8</sup> The Severity Scale score is based on a point system derived from the location and extent of disease and the presence of focal and/or global atrophy, and was calculated for each MR image in our study. The involvement of the genu (anterior pattern) vs the splenium (posterior pattern) was noted. Progression of the lesion burden was defined as an increase in the Loes score by more than 1 point and assessed in all 3 groups.

## RESULTS

Of 158 adult patients with X-ALD in our database, we identified 103 with lesions on their MR images. Fifty-six of these patients had serial MR imaging studies at least 1 year apart and formed the basis of our study. Fifty-eight patients in our database had an initial normal MR images and were followed up with serial MR imaging studies at least 1 year apart. Of these patients with normal MR images, only 3 (5%) showed progression on the MR imaging. None of them developed a Loes score of more than 3 points in the course of  $5 \pm 3$  years (mean  $\pm$  SD). On the initial MR image, 17 patients had corticospinal tract lesions without splenium and/or genu involvement (group 1). Twenty-four patients had symmetric corticospinal tract lesions with additional involvement of the splenium or genu (group 2). Fifteen patients did not have corticospinal tract involvement but had other white matter lesions (group 3). The age at first MR imaging study, duration of follow-up, and the Loes scores are listed in the **Table** and the eFigure (available at <http://www.archneurology.com>).

### GROUP 1

In group 1, 12 patients had stable lesions and 5 patients showed lesion progression. Of the patients with stable lesions, 3 had a posterior pattern, 2 had a combined anterior and posterior pattern, and 7 had isolated involvement of the posterior limb of the internal capsule (**Figure 1**). Four of the 12 patients were in a vegetative state or dead by the end of the study, whereas the others

remained clinically stable. Of the patients with progressive lesions, 3 had a posterior pattern, 1 had a combined anterior and posterior pattern, and 1 had isolated involvement of the posterior limb of the internal capsule. Corticospinal tract lesions preceding diffuse demyelination within the corpus callosum is illustrated in **Figure 2**. On average, these patients showed progression by 1 point every 10 months (range, 4-18 months). The mean  $\pm$  SD rate of progression for the group overall was  $0.6 \pm 0.9$  points/y. All of the patients with lesion progression had died by the end of the study.

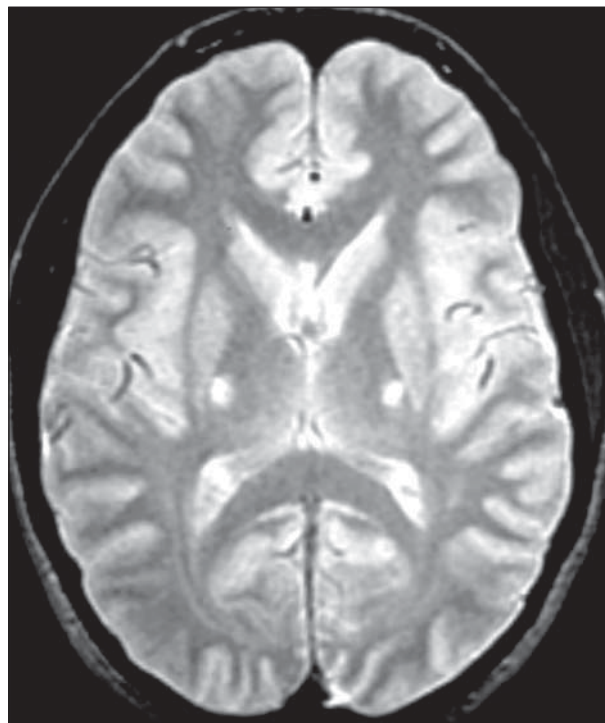
## GROUP 2

In group 2, 11 patients had stable lesions and 13 patients showed lesion progression. Two of these patients had only subtle corpus callosum involvement, with lesions visible on T2-weighted or on fluid-attenuated inversion recovery but not T1-weighted images. Of the patients with stable lesions, 7 had a posterior pattern, and 4 had a combined anterior and posterior pattern. Four of the patients with a posterior pattern had died by the end of the study, whereas the other 11 remained clinically stable. Of the 13 patients with progressive lesions, 8 had a posterior pattern, 1 had an anterior pattern, and 4 had a combined anterior and posterior pattern. On average, these patients showed progression by 1 point every 10 months (range, 3-12 months). The mean rate of progression for the group overall was  $1.0 \pm 1.6$  points/y. Ten of the 13 patients with lesion progression had died by the end of the study.

## GROUP 3

In group 3, 12 patients had stable lesions and 3 had progressive lesions. Among the patients with stable lesions, 10 had a lesion within the splenium (**Figure 3**). In 7 of these patients, we were able to demonstrate that the initial lesion had been detected in childhood or adolescence (average age, 12 years; age range, 7-17 years). In the other 3 patients, the first MR imaging study had been performed in adulthood (25, 59, and 60 years of age) and had shown the lesion at that time. One patient had an isolated cerebellar lesion and another had an isolated pontine lesion. All of these patients were clinically stable.

Among the patients with progressive lesions, 2 had developed their first lesion in the splenium during adolescence. One of them showed progression to the posterior pattern by 22 years of age, while the other developed a combined anterior and posterior lesion pattern as well as lesions in his cerebellum and internal capsule by 24 years of age. The third patient with progressive lesions had developed his first lesion in the genu of the corpus callosum at 9 years of age. By 23 years of age, he showed progression into the subcortical frontal white matter as well as the anterior limb of the internal capsule. On average, these patients showed progression by 1 point every 11 months (range, 4-19 months). The mean rate of progression for the group overall was  $0.4 \pm 0.9$  points/y. The 2 patients who had developed splenium lesions during adolescence had died by the end of the study, whereas the third patient remained clinically stable.



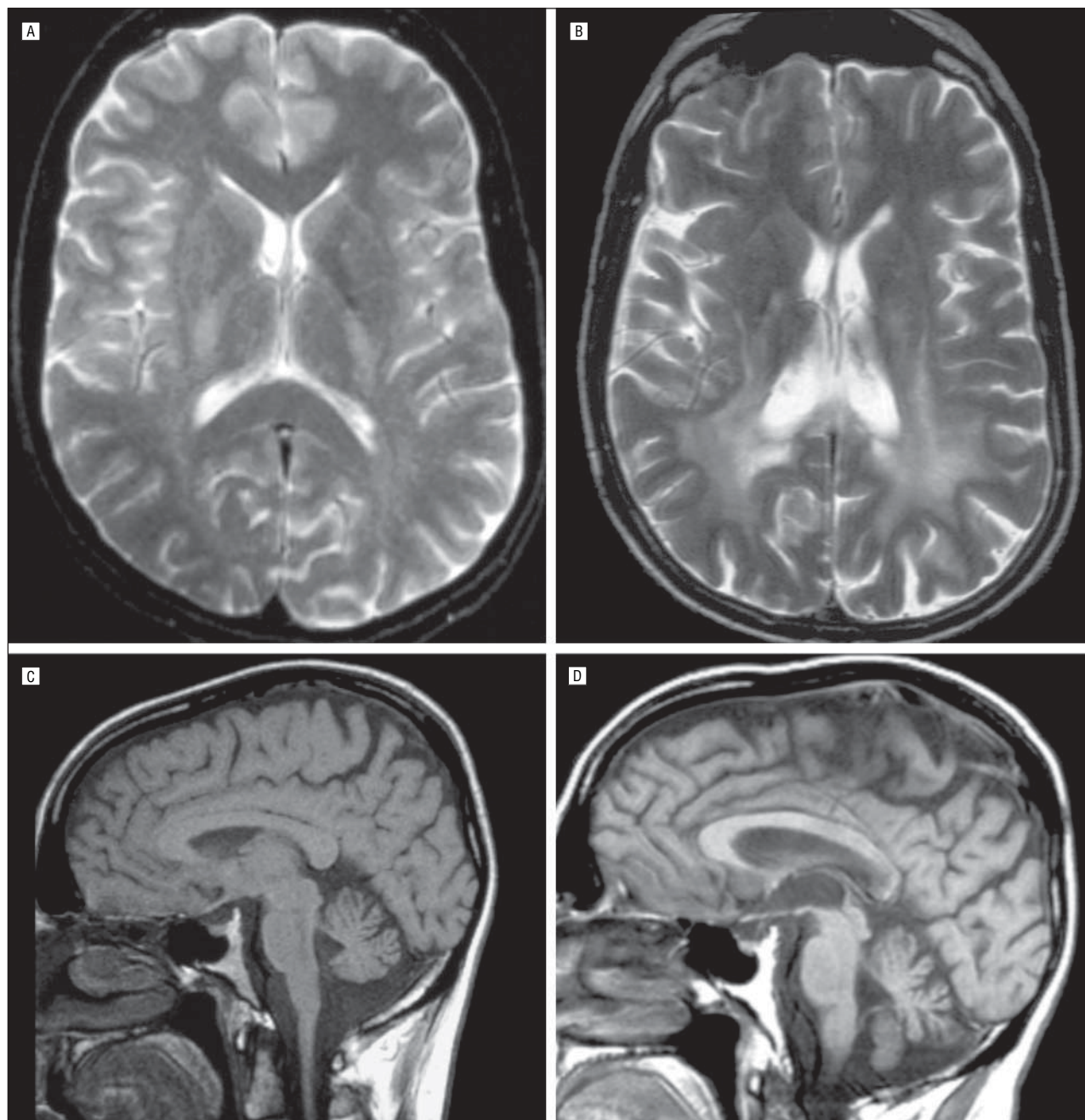
**Figure 1.** A T2-weighted axial magnetic resonance imaging study of a 24-year-old man with adrenomyeloneuropathy shows a stable lesion with primary involvement of the corticospinal projection fibers without affecting the periventricular white matter.

## COMMENT

In this study we present the natural MR imaging history of brain findings in adult patients with X-ALD. Forty-two (75%) of 56 adult patients with MR imaging lesions show corticospinal tract involvement, and 21 (50%) of these 42 patients show lesion progression. We find the rate of lesion progression in adults to be slower than that previously reported in children (mean  $\pm$  SD,  $2.2 \pm 0.55$  and  $2.3 \pm 0.75$  points/y for the posterior and anterior patterns, respectively).<sup>9</sup> Our data show that 18 (86%) of the 21 patients with lesion progression have initial corticospinal tract involvement. This is in marked contrast to the childhood form of the disease and has not been reported previously. In our patient population, we found only 3 adult patients in whom isolated lesions in the genu or the splenium had preceded lesion progression. In all 3 of these patients, we were able to demonstrate that the initial lesion developed in childhood or adolescence.

Involvement of the corticospinal tract has been recognized as the most common MR imaging pattern in adult patients with X-ALD but was thought to follow a benign course and lack progression.<sup>9</sup> Because of the slow degeneration of these tracts demonstrable by MR imaging, this has been thought to represent a “dying-back” mechanism of these long tracts, possibly due to a defective axonal protein transport secondary to metabolic alterations of the perikarya.<sup>12</sup> Several studies have noted the symmetric demyelination within the entire pyramidal tract, as well as in ascending tracts such as the medial lemnisci, the spinocerebellar tracts, or the medial parts of the posterior fasciculi.<sup>12,13</sup> These findings may well rep-



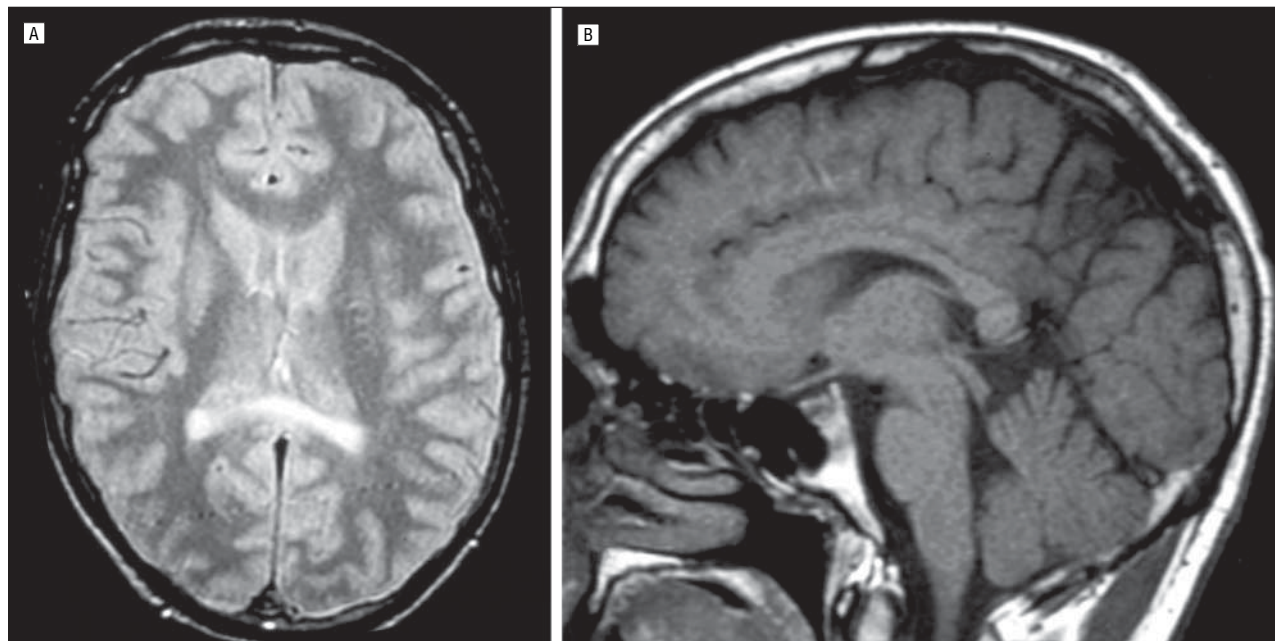


**Figure 2.** Magnetic resonance imaging study shows progression of a lesion in a 38-year-old man with adrenomyeloneuropathy. Axial T2-weighted (A) and sagittal T1-weighted (C) images demonstrate the lesions in the long fiber tract system (posterior limb of the internal capsule and the Meyer loop) with the absence of involvement of the splenium. Ten years later, this patient shows diffuse lesions throughout the corpus callosum with affected splenium visible on the axial (B) and sagittal (D) images.

resent the pathologic basis of the corticospinal tract involvement seen in our group 1.

The occurrence of severe and rapid progressive demyelination is being increasingly recognized in adult patients with X-ALD.<sup>10</sup> The adult patient who is neurologically asymptomatic and the patient with symptoms of adrenomyeloneuropathy are at high risk of developing cerebral demyelination. Although the pattern of severe white matter lesions and brain atrophy has been reported before,<sup>14</sup> the evolution of these lesions had not been investigated. Our longitudinal evaluation demonstrates that, unlike childhood cerebral ALD, adult patients with ALD rarely show initial lesions in the splenium

or the genu of the corpus callosum. Instead, the pattern of diffuse demyelination evolves from or along with the long fiber tract system (Figure 2). This observation implies that progressive inflammatory demyelination can occur alongside the known axonopathy of adulthood. At times, the inflammatory lesions can appear as direct extensions of the corticospinal tract lesion, blurring the boundaries between the 2 most common phenotypes in X-ALD. It remains unclear whether corticospinal tract involvement is a signature of adrenomyeloneuropathy (ie, wallerian degeneration) or whether it could be a variant pattern of inflammatory demyelination.



**Figure 3.** Magnetic resonance (MR) imaging study shows a stable lesion in the splenium of a 20-year-old man with X-linked adrenoleukodystrophy. Proton density-weighted axial (A) and sagittal T1-weighted (B) images are shown. The lesion had been apparent on the initial MR image at 13 years of age.

Furthermore, we were surprised to find a number of adult patients with stable periventricular lesions that had initially developed as lesions in the splenium and genu in childhood (Figure 3). The conventional thinking has been that these lesions progress rapidly in childhood unless halted by bone marrow transplantation.<sup>15,16</sup> Clearly, not all patients with cerebral ALD of childhood show progression in the classic fashion. Although bone marrow transplantation seems to be the only treatment that may halt the progression of cerebral demyelination, our study demonstrates that stabilization and prolonged survival may reflect the natural course of the disease in some patients. Further studies will be necessary to determine what controls the progression rate of these continuous symmetric lesions.

The differential vulnerability of individual fiber tracts with age suggests the contribution of developmental factors. Incorporation of very-long-chain fatty acids into cell membranes is known to impair cell function.<sup>17-19</sup> Analogously, the long-term incorporation of very-long-chain fatty acid-laden lipids in the axonal membranes may cause an axonopathy in X-ALD, and boys with ALD may be too young to manifest the axonopathy that only becomes apparent in adulthood. It had been suggested that a modifier gene determines the phenotypic expression of X-ALD.<sup>20</sup> Genes that encode for other peroxisomal membrane proteins (eg, *ALDR*, *PMP70*, and *PMP70R*) may form heterodimers with the X-ALD gene product, the ALD protein, and trigger the process of demyelination. Other possible modifying factors are immunologic or environmental. Our findings might have implications in the search for modifying factors; they indicate a specific temporal and spatial sequence of events in cerebral X-ALD.

Contrast enhancement and proton MR spectroscopy are powerful tools in predicting disease progression.<sup>21,22</sup> Unfortunately, the historical data we analyzed were limited regarding this pertinent information as well as de-

tailed clinical examinations. Most of our patients with lesion progression on MR images (17 of 21) were in a vegetative state or dead by the end of our study, supporting the previous observation that the MR imaging Severity Scale score correlates strongly with survival.<sup>23</sup> We are currently performing longitudinal prospective studies using proton MR spectroscopy and contrast administration in patients with adrenomyeloneuropathy and will determine whether these tools are predictive of the clinical course as in the childhood form of the disease.

Characteristics of brain lesions in X-ALD are the continuous growth and symmetry that provide evidence for a systematic process. Our study suggests that the vulnerability of specific fiber tracts changes with age. This may offer clues to the inciting factors of injury and the pathogenesis of this devastating disease. The specific temporal and spatial sequence of events described in this report affects considerations regarding the disease mechanism, as well as the timing of therapeutic interventions in the adult patient with X-ALD.

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**Author Contributions:** *Study concept and design:* Eichler, Mahmood, and Moser. *Acquisition of data:* Mahmood, Loes, Bezman, and Raymond. *Analysis and interpretation of data:* Eichler, Mahmood, Lin, and Moser. *Drafting of the manuscript:* Eichler and Raymond. *Critical revision of the manuscript for important intellectual content:* Eichler, Mahmood, Loes, Bezman, Lin, Moser, and Raymond. *Statistical analysis:* Mahmood and Bezman. *Administrative, technical, and material support:* Mahmood, Loes, and Raymond. *Study supervision:* Moser and Raymond.

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**Additional Information:** The eFigure is available at <http://www.archneurol.com>.

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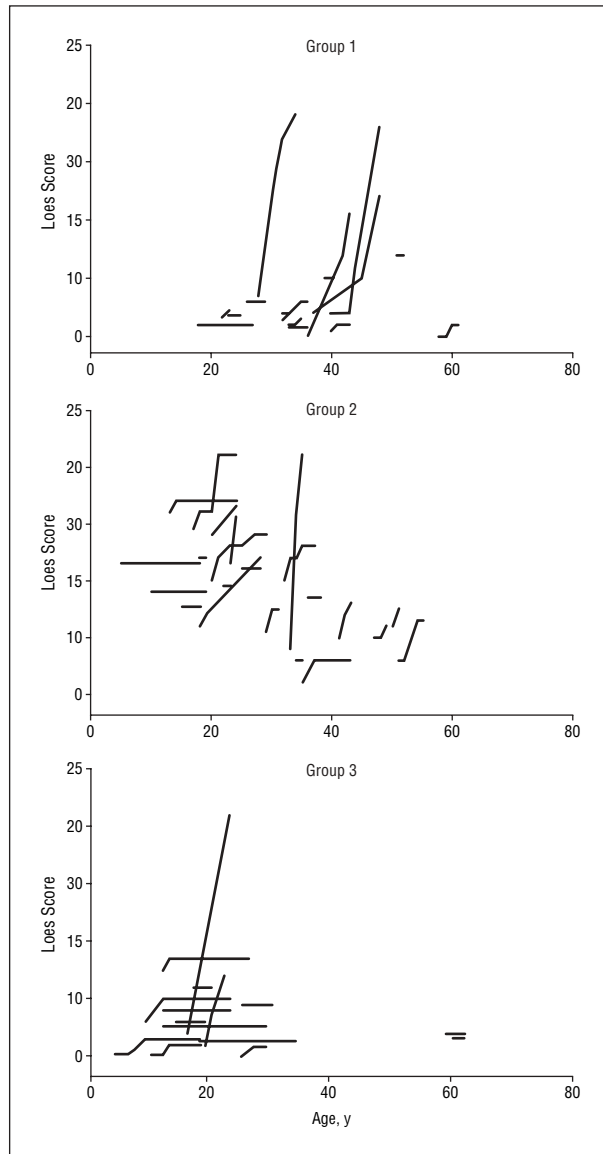
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## Announcement

**Trial Registration Required.** In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Neurology* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as <http://ClinicalTrials.gov>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of *Archives of Dermatology* (2005;141:76-77). Also see the Instructions to Authors on our Web site: [www.archneurol.com](http://www.archneurol.com).





**eFigure.** Progression of Loes scores in groups 1, 2, and 3 by age. The groups are described in the “Categorization” subsection of the “Methods” section.