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. 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). The principal biochemical defect is the accumulation of saturated very-long-chain fatty acids in tissues. 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. Progression of demyelination is systematic, striking earliest and most severely in the splenium and genu of the corpus callosum. 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. However, we have found that approximately 20% of adult patients with adrenomyeloneuropathy without initial clinical brain involvement develop additional cerebral demyelination. 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. 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-
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. 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 pat-
tern) was noted. Progression of the lesion burden was defined
as an increase in the Loes score by more than 1 point and as-
essed 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 stud-
ies 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±3 years (mean±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 cortico-
spinal tract involvement but had other white matter les-
ions (group 3). The age at first MR imaging study, du-
ration of follow-up, and the Loes scores are listed in the
Table and the eFigure (available at http://www.archneurol.
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 an-
terior and posterior pattern, and 7 had isolated involve-
ment 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

<table>
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<th>Group No.*</th>
<th>Progression</th>
<th>No. of Patients</th>
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<th>Duration of Follow-up, y</th>
<th>Loes Score, Points</th>
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<td>8 ± 6</td>
<td>2 ± 1</td>
<td>11 ± 9</td>
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</table>

*Groups are described in the “Categorization” subsection of the “Methods” section.
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 ± SD rate of progression for the group overall was 0.6 ± 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 ± 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 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 ± 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.

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 ± SD, 2.2 ± 0.55 and 2.3 ± 0.75 points/y for the posterior and anterior patterns, respectively). 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. 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. 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. These findings may well rep-
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. 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, 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 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.
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.\textsuperscript{15,16} 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.\textsuperscript{17-19} 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.\textsuperscript{20} Genes that encode for other peroxisomal membrane proteins (eg, \textit{ALDR}, \textit{PMP70}, and \textit{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.

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.

Contrast enhancement and proton MR spectroscopy are powerful tools in predicting disease progression.\textsuperscript{21,22} Unfortunately, the historical data we analyzed were limited regarding this pertinent information as well as detailed 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.\textsuperscript{23} 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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Additional Information: The eFigure is available at http://www.archneurol.com.

REFERENCES


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.


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