Adrenoleukodystrophy
New Approaches to a Neurodegenerative Disease

X-linked adrenoleukodystrophy (X-ALD), which was first described in 1923, was viewed until 1976 as a rare and inexorably fatal neurodegenerative disorder that affected boys. The genetic defect and biochemical abnormalities have now been defined. Ongoing research has resulted in new findings: (1) there is a wide range of phenotypic expression. At least half of patients with X-ALD are adults with somewhat milder manifestations, and women who are carriers may become symptomatic. X-ALD is often misdiagnosed as attention-deficit/hyperactivity disorder in boys and as multiple sclerosis in men and women, and is not an uncommon cause of Addison disease; (2) the incidence of X-ALD, estimated to be 1:17,000 in all ethnic groups, approximates that of phenylketonuria; (3) noninvasive and presymptomatic diagnosis and prenatal diagnosis are available; family screening and genetic counseling are key to disease prevention; and (4) new therapies, applied early, show promise. Neonatal screening is likely to become available, and a wider awareness of X-ALD and its various modes of presentation permit new proactive approaches to this distressing disorder.

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a slowly progressive paraparesis in adults and is now referred to as "adrenomyeloneuropathy" (AMN). The pathological basis of AMN is a noninflammatory distal axonopathy that involves the long tracts of the spinal cord and, to a lesser extent, the peripheral nerves. Adrenomyeloneuropathy confined to the spinal cord tracts and peripheral nerves and without radiological evidence of diffuse cerebral involvement is referred to as "pure AMN." Approximately 20% of patients with pure AMN also develop inflammatory cerebral involvement. This group is referred to as "AMN-cerebral." X-ALD can also manifest as Addison disease without evidence of neurological involvement. Such patients are referred to as the "Addison-only" phenotype.

The table shows the great variability of phenotypic expression as well as the wide range of disorders for which X-ALD has been mistaken. In children and adolescents, it is often misdiagnosed as an attention-deficit/hyperactivity disorder (ADHD), and in adults as multiple sclerosis. Screening for VLCFA in at-risk relatives is identifying an increasing number of asymptomatic males with X-ALD. Women who are carriers may develop an AMN-like syndrome, but cerebral involvement and adrenal insufficiency are rare.

**Diagnosis**

In the past, the diagnosis of X-ALD had often been delayed, at times until a decade or more after symptoms began or even not until after death. This is unfortunate, because therapies could have been offered, and the opportunity for timely genetic counseling was lost. Lack of awareness of X-ALD and of the wide range of the phenotypic expression of X-ALD has been the most frequent cause of delay.

The plasma VLCFA assay is the recommended diagnostic procedure in males. Plasma VLCFA levels are increased on the day of birth. The assay provides a rapid distinction between X-ALD and all other conditions it can mimic. It is particularly important that the assay be performed in all males with idiopathic Addison disease and in men with progressive paraparesis. The early symptoms of childhood cerebral ALD are difficult to distinguish from the much more frequent ADHD. While it is not practical to screen all boys with ADHD for X-ALD, the assay should be performed when there are unusual or progressive features. It is crucially important to screen at-risk family members of known patients with X-ALD. This screen should include the extended family—hundreds of asymptomatic boys have been identified in this way.

Plasma VLCFA levels are increased in women who are heterozygous for X-ALD, but false-negative test results can occur. DNA-based diagnosis in carriers is reliable and is recommended as the diagnostic assay in women. After the DNA mutation in an X-ALD kindred has been defined, heterozygotes can be identified accurately and rapidly by determining whether the mutation is present in at-risk women. Levels of VLCFA are increased in cultured amniocytes and chorion villus cells, which has permitted prenatal identification of hundreds of affected male fetuses, but confirmation by DNA analysis is recommended.

Brain magnetic resonance imaging (MRI) often shows characteristic, but not totally specific, changes in the cerebral forms of X-ALD. Brain MRI is often normal in patients with pure AMN and in heterozygotes. Spinal cord MRI in patients with AMN shows nonspecific cord atrophy, but magnetization transfer permits quantification.

**Treatment**

Three modes of therapy are available at this time. They improve the prognosis of X-ALD significantly when offered in the early stages of the illness, but a definitive cure does not yet exist.

**Adrenal Replacement Therapy.** Adrenal hormone replacement therapy must be provided for the more than 70% of male X-ALD patients who have adrenal insufficiency. Patients with impaired adrenal reserve can be identified and treated at 6 to 12 months of age. This can prevent a potentially life-threatening adrenal crisis, which in the past contributed to significant morbidity and mortality, and improves general well-being. However, there is currently no definitive evidence that steroid replacement therapy slows neurological progression.

**Lorenzo’s Oil Therapy.** Lorenzo’s oil is a 4:1 mixture of glyceryl-trioleate and glyceryl-trierucate, which normalizes plasma VLCFA levels in X-ALD patients within 4 weeks. While Lorenzo’s oil therapy does not alter the progression after the onset of cerebral disease, recent data suggest that it may significantly reduce the risk of developing cerebral disease. Carefully supervised Lorenzo’s oil therapy is recommended for asymptomatic boys with X-ALD who have a normal MRI result, particularly those who are younger than 8 years, and can now be provided as part of a research protocol. This must be combined with adrenal hormone replacement therapy as indicated and monitoring of brain MRI. Patients who show early evidence of cerebral involvement should be considered for hematopoietic stem cell transplantation (HSCT). A placebo-controlled trial evaluating therapeutic efficacy of Lorenzo’s oil in patients with pure AMN is now in progress.

**Hematopoietic Stem Cell Transplantation.** Hematopoietic stem cell transplantation has been shown to be of long-term benefit in the inflammatory cerebral forms of X-ALD. Peters et al have analyzed the outcome in 126 patients and found that this varied greatly with the severity of the process at the time of HSCT. An excellent outcome (92% 5-year survival) was achieved in boys in whom the involvement was still mild (performance IQ >80 and limited MRI abnormality). For patients with more advanced disease, the mortality and quality of life outcomes were unfavorable and the procedure is not recommended. It is also not recommended for asymptomatic patients with normal MRI findings, because half of them may never develop the cerebral forms of X-ALD (it is not known whether HSCT benefits patients with pure AMN). The

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## X-Linked Adrenoleukodystrophy (X-ALD) Phenotypes

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Total ALD, %</th>
<th>Symptoms/Signs</th>
<th>Age at Presentation, y</th>
<th>Misdiagnosed as</th>
<th>Diagnostic Test</th>
<th>Follow-up Tests</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic (MRI normal)</td>
<td>Increasing None</td>
<td>0 to ≥10</td>
<td>Normal</td>
<td>Monitor MRI and adrenal function; family screening</td>
<td>Lorenzo’s oil, adrenal HRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic (MRI abnormal)</td>
<td>Increasing None (cognition normal)</td>
<td>2 to ≥10</td>
<td>Other white matter disorders</td>
<td>VLCFA, brain MRI</td>
<td>Neurological and neuropsychological testing, adrenal function</td>
<td>HSCT, adrenal HRT</td>
<td></td>
</tr>
<tr>
<td>Addison disease only (MRI normal)</td>
<td>20 (decreases with age) Primary adrenocortical insufficiency, normal neurology, MRI normal</td>
<td>0 to ≥10</td>
<td>Other causes of Addison disease</td>
<td>VLCFA</td>
<td>Monitor MRI, neurological and neuropsychological testing</td>
<td>Lorenzo’s oil, adrenal HRT</td>
<td></td>
</tr>
<tr>
<td>Addison disease only (MRI abnormal)</td>
<td>1 Primary adrenocortical insufficiency</td>
<td>0 to ≥10</td>
<td>Other causes of Addison disease</td>
<td>VLCFA, brain MRI</td>
<td>Neurological and neuropsychological testing, MRI</td>
<td>HSCT, adrenal HRT</td>
<td></td>
</tr>
<tr>
<td>Cerebral (mild) without AMN*</td>
<td>45 Behavior changes, school failure, dementia, audiovisual</td>
<td>3-10 (common) 11-21 (intermediate) ≥21 (rare) ADHD, psychological disorder, Asperger syndrome, autism</td>
<td>VLCFA, brain MRI</td>
<td>Neurological and neuropsychological testing, MRI</td>
<td>HSCT, adrenal HRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral (severe) without AMN*</td>
<td>2-3 Dementia, psychoses, paralysis, epilepsy, loss of vision, loss of speech, bulbar palsy</td>
<td>5 to adulthood</td>
<td>Other neurodegenerative diseases, brain tumor, psychosis, epilepsy</td>
<td>VLCFA, brain MRI</td>
<td>Adrenal function, neurological and neuropsychological testing, family screening</td>
<td>Adrenal HRT, general support</td>
<td></td>
</tr>
<tr>
<td>Pure AMN†</td>
<td>35 Paraparesis, sphincter disturbances, sensory changes, incoordination, pain, impotence</td>
<td>28 (SD, 0) Multiple sclerosis, progressive spastic paraparesis, cervical spondylosis, osteoarthritis, back injury, ALS, “triple A syndrome”</td>
<td>VLCFA</td>
<td>Brain MRI, adrenal function, MT5; SSEP, family screening</td>
<td>Adrenal HRT, possibly Lorenzo’s oil,† physical therapy</td>
<td></td>
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</tr>
<tr>
<td>Cerebral AMN†</td>
<td>15 (increases with age) Like pure AMN plus dementias, behavioral disturbances, psychoses, epilepsy, aphasia, visual loss, bulbar palsy</td>
<td>28 (SD, 9) Other causes, dementia, other neurodegenerative diseases, brain tumor, schizophrenia, Alzheimer disease, cerebrovascular disease, epilepsy, alcoholism, drug dependency</td>
<td>VLCFA, brain MRI</td>
<td>As in pure AMN plus neurological and neuropsychological testing, EEG, psychiatry, family screening</td>
<td>Adrenal HRT, general support, possibly HSCT§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar</td>
<td>2-3 Ataxia, brainstem</td>
<td>Childhood; adolescence</td>
<td>Olivopontocerebellar degeneration</td>
<td>VLCFA, brain MRI</td>
<td>Adrenal function, neurological testing, family screening</td>
<td>Adrenal HRT, physical therapy</td>
<td></td>
</tr>
</tbody>
</table>

| Females Heterozygous for ALD |              |                |                       |                 | DNA (LCFA) |                |                   |
| Asymptomatic (normal neurology) | 50 (estimated)* | None | Any age | Neurological examination and adrenal function, monitor MRI, family screening | Genetic counseling, general support |
| Heterozygotes (symptoms or neurological abnormalities) | 50 (estimated)** | Paraparesis, sphincter disturbances, leg pain, sensory disturbances, incoordination, fatigue | Rare in women younger than 30 y | DNA (LCFA) | Adrenal function, MT5, SSEP, family screening | Genetic counseling, physical therapy, adrenal HRT, possibly Lorenzo’s oil,† general support |

* Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ALS, amyotrophic lateral sclerosis; DNA, ABCD1 mutation analysis; AMN, adrenomyeloneuropathy; EEG, electroencephalogram; HRT, hormone replacement therapy; HSCT, hematopoietic stem cell transplant; MRI, magnetic resonance imaging; MTS, magnetization transfer MRI cervical cord; SSEP, somatosensory evoked potential; VLCFA, very long chain fatty acid assay in plasma.
** See Peters et al. for distinction between mild and severe cerebral forms.
† Placebo-controlled trial in progress.
§ HSCT being considered for mild cerebral AMN.
‡ False-negative test results can occur.

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“window of opportunity” for HSCT is narrow. Half or more of the patients with cerebral forms who are diagnosed when they became symptomatic no longer meet the criteria for HSCT at diagnosis. Neurologically asymptomatic boys who are identified by screening at-risk relatives of known patients or those with idiopathic Addison disease have the best chance of benefiting from HSCT.

Prevention

In the absence of a definitive treatment strategy, timely identification of carriers and genetic counseling are imperative. Women heterozygous for X-ALD can be identified accurately by mutation analysis or pedigree analysis (daughters of X-ALD men are obligate heterozygotes). Studies of chorion villus sampling or amniocentesis permit accurate prenatal identification of affected male fetuses. Preimplantation diagnosis of X-ALD is now available and offers an important new alternative for women who are carriers.

Future Directions

Unlike many other inherited metabolic disorders, X-ALD does not compromise cognitive development; hence, appropriate management improves the chances of a meaningful and productive life. This, combined with the severity of the untreated illness, the encouraging effects of therapy applied in the early stages, and its relatively high incidence, provides compelling rationale for neonatal screening. Methods to accomplish this are now under investigation and are likely to become available. New methods of therapy, such as gene therapy and new pharmacological approaches, are being developed and some are being tested in animal models. Neonatal screening will make it possible to provide therapies to all patients before their nervous system has been damaged. Advances in therapy and prevention are taking place concurrently and will lessen the burden of this devastating disorder.

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REFERENCES