Background: Various studies have demonstrated abnormal neuropsychological function in boys with the childhood cerebral phenotype of X-linked adrenoleukodystrophy. Not much is known about the cognitive function of neurologically asymptomatic boys with X-linked adrenoleukodystrophy who have normal brain magnetic resonance imaging results.

Objective: To describe the cognitive profile of 52 neurologically asymptomatic boys with X-linked adrenoleukodystrophy (mean ± SD age, 6.7 ± 3.6 years).

Methods: Neuropsychological tests included evaluation of IQ (full-scale IQ, verbal IQ, and performance IQ), 5 major cognitive domains (language, visuospatial skills, perception, visuomotor or graphomotor skills, memory, and attention or executive function), adaptive skills, and academic achievement. Standardized z scores relative to age-appropriate published norms were generated. Association between age and cognitive performance was evaluated using nonparametric Spearman rank correlation and robust median regression adjusting for full-scale IQ and socioeconomic status.

Results: All but 4 patients had normal cognitive function. There was a negative correlation between age and visual perception as well as age and visuomotor skills after adjustment for full-scale IQ and socioeconomic status.

Conclusions: This study provides, to our knowledge, the first evidence of overall normal cognitive function in neurologically and radiologically normal boys with X-linked adrenoleukodystrophy, indicating no evidence of neurodevelopmental abnormalities despite the inherent ABCD1 mutation. Subtle deterioration with age was observed in some functional domains. This suggests that prevention and timely institution of therapy can potentially preserve cognitive function seen in patients with the cerebral X-linked adrenoleukodystrophy phenotype. X-linked adrenoleukodystrophy should be considered a candidate disorder for neonatal screening.

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X-LINKED ADRENOLEUKODYSTROPHY (X-ALD) is a neurodegenerative disorder affecting the nervous system, adrenal cortex, and testes due to a defect in ABCD1, which codes for a peroxisomal membrane protein, a member of the ATP-binding cassette transporter superfamily. The accumulation of saturated very long-chain fatty acids is the principal biochemical abnormality in X-ALD, and demonstration of abnormally high very long-chain fatty acid levels in plasma is the most frequently used diagnostic assay.

X-linked adrenoleukodystrophy is expressed in a variety of clinical phenotypes with and without cerebral demyelination. The childhood cerebral phenotype of X-ALD usually manifests in the first 10 years of life. Psychological and behavioral abnormalities have considerable prognostic significance, and in many cases, they initially resemble attention-deficit/hyperactivity disorder. Abnormalities in performance IQ (PIQ) and executive function have been demonstrated in patients with childhood cerebral adrenoleukodystrophy, most of whom had extensive posterior white matter changes. The corpus callosum, parieto-occipital lobes, and temporal lobes are most commonly involved in X-ALD. The abnormalities of these regions lead to abnormal processing of visual and auditory input. It is not known whether there are inherent cognitive abnormalities in patients with X-ALD owing to the nature of the biochemical and genetic defect when inflammatory demyelination is not demonstrable. To our knowledge, cognitive function in patients with X-ALD without any obvious white matter changes has not been evaluated previously. One study that included 8 neurologically asymptomatic boys suggested normal cognitive profiles with subtle ab-
neuropsychological function but also tried to combine the available normative data over the widest applicable age range. The obtained scores were transformed into age-adjusted z scores using the published norms.

The effect of socioeconomic status (SES) on intellectual function, especially verbal and language skills, is well established. We used the Index of Social Position by Hollingshead to assess the SES of the families of patients included in the study to analyze its association with neuropsychological function across the broad age range at which each was used. The obtained scores were used to evaluate the association between age and performance on neuropsychological testing (the absolute index of Social Position score was used for adjustment instead of the SES category). A P value of .05 or less was considered statistically significant.

### RESULTS

#### OVERALL PERFORMANCE ON NEUROPSYCHOLOGICAL TESTING

Table 2 summarizes the evaluation for the entire cohort. The IQ subsets (FSIQ, verbal IQ [VIQ], and PIQ), global z scores, and performance on the 5 cognitive function domains were within normal limits for 49 patients and were abnormal in 3. Figures 1, 2, 3, and 4 demonstrate performance on IQ subsets and major cognitive function domains.

Four patients showed significant abnormality in 1 or more domains. Patient 1 was aged 5.2 years, with significant abnormalities in FSIQ and VIQ; his age-appropriate z score for FSIQ was −2.13, and his VIQ z score was −2.73. He also showed significant abnormalities in the language domain (z score = −2.59) and Vineyard Adaptive Behavior Scales (adaptive behavior composite z score = −2.67; communication domain z score = −3.00; daily living skills subscale z score = −2.73; and socialization domain z score = −2.47). His PIQ and performance on other functional domains were within normal limits. Patient 2 was aged 12.8 years. He showed significant abnormality in the executive function domain (z score = −2.04), his PIQ placed in the low average range, and his VIQ and FSIQ were placed within normal limits. His performance in all of the other functional domains was within normal limits. Patient 3 was aged 2.6 years; he showed significantly poor performance in the visual perception domain (z score = −3.40). He showed no abnormalities on VIQ, which was the only other evaluation the patient could complete (VIQ z score = 0.50). He did not complete testing for PIQ (therefore, the FSIQ could not be completed), visual perception, memory, and executive domains. Patient 4 was aged 2.4 years and had significant abnormality in the Vineland Adaptive Behavior Scales domain-testing activities of daily living (z score = −2.00). This patient had no abnormalities in any other tested cognitive domain.

### ASSOCIATION BETWEEN AGE AND NEUROPSYCHOLOGICAL PERFORMANCE

There was no association between age and FSIQ, PIQ, or VIQ after adjusting for SES. There was a significant negative association between visual perception as well as age and visuomotor skills after adjustment for FSIQ and SES (for visual perception, β = −0.15, P = .02; for visuomotor skills, β = −0.12, P = .005). There was no association between attention or executive function, memory, and language z scores with age after adjustment for FSIQ and SES.

### COMMENT

This study demonstrates an overall normal cognitive profile in asymptomatic boys with X-ALD who have no detectable abnormalities on conventional brain MRI. Forty-eight patients demonstrated normal-for-age performance on neuropsychological testing. Four patients had moderate deficits in verbal skills, the visuomotor domain, and adaptive behavior. Such variations may also occur in a normal population. It is not certain whether they can be attributed to X-ALD. Thus, for the tested cohort as a whole, we did not detect cognitive deficiencies using standard testing procedures, suggesting a normal neurodevelopmental process despite the inherent defect of ALDP (a protein encoded by the mutant gene in X-ALD).
Table 1. Tests Used in the Neuropsychological Assessment of Cognitive Functional Domains

<table>
<thead>
<tr>
<th>Cognitive Functional Domain</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability</td>
<td>Stanford-Binet Intelligence Scale–Fourth Edition (ages 2-3 y)</td>
</tr>
<tr>
<td></td>
<td>WPPSI-R (ages 3-5 y)9</td>
</tr>
<tr>
<td></td>
<td>WISC-R (2 subjects) or WISC-III (ages ≥6 y)10</td>
</tr>
<tr>
<td>Adaptive skills</td>
<td>Vineland Adaptive Behavior Scales–Interview Edition (global adaptive behavior composite, communication, daily living skills, socialization, and motor skills domain scores) (ages &lt;5 y)17</td>
</tr>
<tr>
<td>Academic achievement</td>
<td>Woodcock-Johnson Tests of Achievement–Revised</td>
</tr>
<tr>
<td>Language</td>
<td>Vocabulary, comprehension, information, and similarities subtests of the WPPSI-R, WISC-R, WISC-III, and Stanford-Binet Intelligence Scale–Fourth Edition9,10</td>
</tr>
<tr>
<td></td>
<td>Expressive vocabulary and riddles subtests of the K-ABC (ages 2.5-6 y)12</td>
</tr>
<tr>
<td></td>
<td>Peabody Picture Vocabulary Test (ages ≥2.5 y)13</td>
</tr>
<tr>
<td></td>
<td>Woodcock-Johnson Tests of Achievement–Revised picture vocabulary subtest (ages ≥2.5 y)</td>
</tr>
<tr>
<td></td>
<td>Clinical Evaluation of Language Fundamentals–Revised oral directions subtest (ages ≥6 y)</td>
</tr>
<tr>
<td></td>
<td>McCarthy verbal fluency (ages 2.5-6 y) and letter (FAS) and category fluency (ages ≥6 y) subtests</td>
</tr>
<tr>
<td>Visual perception/visuomotor or visual reasoning</td>
<td>Picture completion, picture arrangement, and symbol search subtests of the WPPSI-R, WISC-R, and WISC-III as applicable</td>
</tr>
<tr>
<td>Visuomotor or constructional</td>
<td>Benton Judgment of Line Orientation and Facial Recognition Tests (ages ≥6 y)14</td>
</tr>
<tr>
<td></td>
<td>K-ABC magic windows subtest (ages 2.5-5 y)12</td>
</tr>
<tr>
<td></td>
<td>K-ABC gestalt closure subtest (ages 2.5-6 y)2</td>
</tr>
<tr>
<td></td>
<td>Woodcock-Johnson Tests of Achievement–Revised visual closure subtest (ages ≥6 y)</td>
</tr>
<tr>
<td></td>
<td>K-ABC matrix analogies subtest (ages ≥5 y)12</td>
</tr>
<tr>
<td></td>
<td>Raven Colored Progressive Matrices (ages 6-8 y)</td>
</tr>
<tr>
<td></td>
<td>Standard Progressive Matrices (ages ≥8 y)</td>
</tr>
<tr>
<td></td>
<td>Triangles subtest of the K-ABC (ages ≥4 y), copying subtest of the Stanford-Binet Intelligence Scale–Fourth Edition, geometric designs subtest of the WPPSI-R, and coding subtest of the WISC-R and WISC-III</td>
</tr>
<tr>
<td></td>
<td>Developmental Test of Visuomotor Integration (ages ≥3 y)</td>
</tr>
<tr>
<td></td>
<td>Rey-Osterrieth Complex Figure copy subtest (ages ≥6 y)15</td>
</tr>
<tr>
<td>Memory</td>
<td>Purdue Pegboard Test (ages ≥2.5 y)16</td>
</tr>
<tr>
<td></td>
<td>Number recall subtest of the K-ABC (ages 2.5-6 y) or digit span subtest of the WISC-R or WISC-III (ages ≥6 y)</td>
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<tr>
<td></td>
<td>Memory-for-sentences subtest of the Stanford-Binet Intelligence Scale–Fourth Edition (ages ≥2.5 y) or sentences subtest of the WPPSI-R</td>
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<tr>
<td></td>
<td>Bead memory subtest of the Stanford-Binet Intelligence Scale–Fourth Edition (ages ≥2.5 y)</td>
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<tr>
<td></td>
<td>Woodcock-Johnson Tests of Cognitive Ability–Revised picture recognition subtest (ages ≥6 y)</td>
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<tr>
<td></td>
<td>Buschke Selective Reminding Test or California Verbal Learning Test (ages ≥6 y)</td>
</tr>
<tr>
<td></td>
<td>Rey-Osterrieth Complex Figure delayed recall subtest (ages ≥6 y)15</td>
</tr>
<tr>
<td>Executive functions</td>
<td>Developmental Test of Visuomotor Integration (ages ≥2.5 y)</td>
</tr>
<tr>
<td>(not performed in children aged &lt;3 y)</td>
<td>WISC-R or WISC-III mazes subtest.16 Test of Variables of Attention, Rey-Osterrieth Complex Figure copy subtest,16 delayed recall organization subtest, and California Verbal Learning Test clustering and repetition subtest (ages ≥6 y)</td>
</tr>
<tr>
<td></td>
<td>FAS letter fluency (ages ≥7 y)</td>
</tr>
<tr>
<td></td>
<td>Stroop Color and Word Test (ages ≥7.5 y)</td>
</tr>
</tbody>
</table>


There was an inverse correlation between age and performance in visuomotor and visual perception domains. It may be that some decline in cognitive performance might surface later with increasing age; however, definitive implications of this apparent association cannot be made in a cross-sectional study. Despite the weak negative age association, the standardized z scores remained within normal limits. Alternatively, the negative association could be owing to the better ability to characterize cognitive performance for older children because of the greater sensitivity of the testing instrument; thus, the weak negative association could be an artifact of the wider standard deviations observed in the younger subset mainly owing to inherent inadequacies of the evaluation tools.

Table 2. Summary Measures for Performance on Neuropsychological Testing in a Cohort of 52 Asymptomatic Boys With X-linked Adrenoleukodystrophy Who Had Normal Brain Magnetic Resonance Imaging Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (Median; Range)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>6.7 ± 3.6 (6.2; 2.1-14.6)</td>
</tr>
<tr>
<td>Full-scale IQ</td>
<td>104 ± 13.6 (104; 68-127)</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>101 ± 14.4 (102; 59-125)</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>106 ± 12.9 (107; 77-132)</td>
</tr>
<tr>
<td>Language domain z score</td>
<td>0.06 ± 0.92 (0.06; -2.59 to 3.43)</td>
</tr>
<tr>
<td>Visual perception domain z score</td>
<td>0.28 ± 0.83 (0.20; -1.00 to 2.00)</td>
</tr>
<tr>
<td>Visuomotor domain z score</td>
<td>-0.08 ± 0.86 (-0.08; -3.39 to 1.65)</td>
</tr>
<tr>
<td>Mean memory domain z score</td>
<td>0.09 ± 0.70 (0.09; -1.44 to 1.33)</td>
</tr>
<tr>
<td>Executive domain z score</td>
<td>-0.12 ± 0.74 (-0.15; -2.04 to 1.50)</td>
</tr>
</tbody>
</table>
There are numerous studies that have demonstrated neuropsychological abnormalities in patients with the cerebral phenotype of X-ALD; however, it is not clear whether these patients would have normal cognitive development in the absence of these cerebral abnormalities. All of the patients in our cohort had normal conventional MRI results. However, this does not rule out the presence of more subtle abnormalities. Studies that use magnetic resonance spectroscopy and diffusion-tensor imaging may show abnormalities in the regions that appear normal on conventional MRI. Asymptomatic boys with X-ALD and other phenotypes of X-ALD with normal brain MRI results and no evidence of obvious inflammatory demyelination have been shown to have reduced N-acetylaspartate levels, suggesting subtle neuroaxonal abnormalities that are not detectable on conventional MRI. The observed subtle decrease (or failure to grow) in performance within some cognitive functional domains may be owing to axonal structural abnormalities not visible on conventional MRI that might be demonstrable with the use of specialized imaging modalities such as magnetic resonance spectroscopy and diffusion-tensor imaging, which were not included in this analysis. Studies combining cognitive evaluation with specialized magnetic resonance methodologies such as spectroscopy may serve as sensitive markers and aid in predicting disease progression. However, even if the abnormalities were present in our cohort, they do not ap-
pear to have an effect on standard tests of cognitive function.

The presence of normal cognitive function in most boys with X-ALD whose conventional MRI results are normal, combined with the encouraging results of early therapeu-
tic interventions, suggests that X-ALD should be viewed as a candidate disorder for neonatal screening. Recent studies from our group provide evidence that di-
etary therapy with Lorenzo’s oil has a preventive effect in asymptomatic patients with normal MRI results and that patients with X-ALD with impaired adrenal reserve can be identified and treated before they develop overt Addison disease. The follow-up study by Peters et al24 shows a favorable outcome (92% 5-year survival rate) of hematopoietic cell transplantation in patients with X-ALD who receive the transplant when the inflammatory brain disease is still in its early stages. The 3-pronged management approach discussed earlier can help improve the prognosis of X-ALD. Furthermore, the risk of developing cerebral disease is not constant with increasing age. Prior to age 7 years, the risk of cerebral disease is approximately 40%. It diminishes progressively after that age, and it is less than 10% after age 15 years.25 Thus, early identification of at-risk subjects is of great importance. Our demonstration that cognitive function is intact in young asymptomatic patients indicates that there is a substantial therapeutic “window of opportunity” and strengthens the rationale for neonatal screening.

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