Proton MR Spectroscopy and Neuropsychological Testing in Adrenoleukodystrophy

V. Rajanayagam, M. Balthazor, E. G. Shapiro, W. Krivit, L. Lockman, and A. E. Stillman

PURPOSE: To determine early signs of disease in patients with childhood-onset cerebral adrenoleukodystrophy (COCALD) with the use of proton MR spectroscopy. METHODS: Eleven children with posterior COCALD involvement and three children with anterior COCALD involvement were studied with single-voxel proton MR spectroscopy and neuropsychological testing. Findings were compared with those in five healthy control subjects. RESULTS: Areas of abnormal T2 signal intensity in children with COCALD showed abnormal metabolite ratios relative to those of control subjects as follows: decreased N-acetylaspartate (NAA)/Creatine (Cr) and NAA/Choline (Ch) and increased Ch/Cr. Metabolite ratios from normal-appearing brain regions in the same patients also were abnormal, with reduced NAA/Cr and NAA/Ch and increased Ch/Cr values. The mean metabolite ratios in normal-appearing regions were between those in the abnormal regions and those found in the control subjects. Statistical comparison of these ratios with neuropsychological test scores, which are specific for anterior and posterior brain functions, showed a significant correlation with the abnormal metabolite ratios. Our results indicate that the normal-appearing brain regions in these patients are metabolically abnormal. CONCLUSION: Proton MR spectroscopy could be a useful noninvasive tool to evaluate extent of disease in patients with COCALD.

Index terms: Adrenoleukodystrophy; Children, diseases; Magnetic resonance, spectroscopy


Adrenoleukodystrophy (ALD) is a cerebral degenerative disease that affects predominantly the white matter (1–5). Boys with childhood-onset cerebral ALD (COCALD) have a mean age of onset of 7 years, with demyelination and deterioration progressing rapidly to death over an average of 3 to 4 years. No biochemical test distinguishes between these forms or reflects the degree of deterioration (1, 6). Abnormalities on magnetic resonance (MR) images correlate well with neuropsychological measures (7). However, detection of objective changes on MR images to ascertain disease progression is difficult (8).

Proton MR spectroscopy has also been used to identify the different levels of cerebral metabolites present in abnormal brain regions in patients with ALD (9–12). Metabolite ratios of patients with ALD differ from those of control subjects. MR spectroscopy has shown promise in the monitoring of disease course and treatment, and metabolite ratios from abnormal brain regions also correlate well with the clinical status of patients with ALD (12).

We present the MR spectroscopic metabolite data accumulated from abnormal and normal-appearing white matter in a small cohort of patients with COCALD.

Materials and Methods

The patient group consisted of 14 children, 4 to 13 years old, with the biochemical defect for ALD and with abnormal anterior and posterior regions of white matter on MR images. Of these 14 patients, 11 had posterior involvement and three had anterior involvement. Four patients...
had nearly normal MR imaging studies, with only mild involvement in the posterior regions. Five male control subjects (age range, 8 to 35 years) also were studied. These control subjects were not age matched, as the primary changes in the metabolite ratios occur predominantly in the first 2 years of life (13, 14). In addition, and as observed by others, we did not find any significant differences in the metabolite ratios between the child and adult control subjects. Informed consent was obtained from the parents of the patients before the examinations. Nine children were sedated (2 to 6 mg/kg pentobarbital sodium) and monitored using pulse oximetry and an apnea monitor during the MR examination.

All MR studies were done on a 1.5-T imaging unit equipped with shielded gradients and a quadrature head coil. MR imaging consisted of axial, coronal, and sagittal T1-weighted sequences (600/14/2 [repetition time/echo time/excitations]) and axial T2-weighted sequences (2500/45,90/2). This was followed by MR spectroscopy, in which the spectra were acquired using the double spin-echo sequence (15). Single-voxel (2 × 2 × 2 cm³) water-suppressed spectra were acquired from occipital and frontal white matter regions that appeared both normal and abnormal on MR images. MR spectra from two regions of interest (ROI) were obtained from each patient. Fourteen examinations of abnormal regions (three anterior and 11 posterior) and 12 examinations of normal-appearing regions (nine anterior and three posterior) were performed. The ROIs were prescribed from axial, coronal, and sagittal T1-weighted images. After global and localized shimming, water suppression was optimized and water-suppressed spectra were acquired for each ROI. Water suppression was achieved by application of chemical-shift selective pulses with a bandwidth of 60 Hz followed by gradient spoiling of the excited magnetization. An echo time of 135 enabled the detection of lactate and also simplified spectral overlap, which enabled the acquisition of reliable peak area measurements. Localized spectra were acquired with parameters of 1600/135/256, a 1000-Hz sweep width, and 1024 complex points. The residual water signal was removed by means of time-domain filtering and then apodized and zero-filled to 2048 points before Fourier transformation to obtain the metabolite spectra. The spectra were manually phase corrected then baseline corrected, and the relative peak areas of N-acetylaspartate (NAA), total creatine (Cr), and choline-containing compounds (Ch) were determined by spectral peak fitting. The metabolite peak areas were not corrected for T1 and T2 differences.

Yearly neuropsychological tests measuring cognitive, nonverbal, verbal, memory, and attention functions were administered to all our patients with COCALD. Previous research has shown that performance IQ scores from the Wechsler tests of intelligence (16, 17) are particularly sensitive to posterior abnormalities commonly associated with ALD (18). This sensitivity is due to the varied demands on visual processing associated with performance IQ tasks. All subtests, including the optional mazes subtest, were administered. In addition, the test of vari-
and 2.14, 1.81, and 1.18, respectively. A small amount of lactate was visible in the posterior region (Figure 2B). The mean values of the metabolite ratios from normal-appearing regions in 12 patients are also listed in Table 2. These values were between those of the control subjects and those from the abnormal regions. The differences between the values in the control subjects and those in the abnormal regions were statistically significant. The differences between the abnormal regions and the normal-appearing regions were also statistically different. The \( P \) values were at the lower end of significance, with that for Ch/Cr being .06.

**Table 1: Comparison of metabolite ratios in control subjects and patients with COCALD who had abnormal and normal-appearing brain regions at MR imaging**

<table>
<thead>
<tr>
<th></th>
<th>NAA/Cr</th>
<th>NAA/Ch</th>
<th>Ch/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects (n = 5)</td>
<td>2.17 ± 0.09</td>
<td>2.00 ± 0.09</td>
<td>1.09 ± 0.04</td>
</tr>
<tr>
<td>Abnormal regions (n = 14)</td>
<td>1.49 ± 0.17</td>
<td>1.12 ± 0.16</td>
<td>1.52 ± 0.11</td>
</tr>
<tr>
<td>( P ) value*</td>
<td>.005</td>
<td>.0004</td>
<td>.006</td>
</tr>
<tr>
<td>Normal-appearing regions (n = 12)</td>
<td>1.91 ± 0.07</td>
<td>1.58 ± 0.10</td>
<td>1.26 ± 0.06</td>
</tr>
<tr>
<td>( P ) value†</td>
<td>.02</td>
<td>.004</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>( P ) value‡</td>
<td>.03</td>
<td>.02</td>
<td>.06</td>
</tr>
</tbody>
</table>

Note—All values are presented as the mean plus or minus one standard error.

* Comparison of controls and patients with abnormal regions.
† Comparison of controls and patients with normal-appearing regions.
‡ Comparison of abnormal and normal-appearing regions in patients.

**Comparison of MR Spectroscopic Data and Neuropsychological Data**

Neuropsychological tests were administered to every patient during the same visit. Table 2 lists correlation coefficients from abnormal regions of patients with posterior involvement of COCALD disease. Performance IQ correlated with all three metabolite ratios. Six individual subtests that make up the performance IQ score were evaluated separately, and the picture arrangement subtest was the only one that correlated significantly with all three metabolite ratios. Scores on the mazes test showed significant correlation with
NAA/Cr and NAA/Ch ratios. No significant correlations were found with the TOVA measures. For these same patients, MR spectra from normal-appearing anterior regions were correlated with neuropsychological measures, and two measures of the TOVA showed significant correlation with the metabolite ratios. NAA/Cr and NAA/Ch ratios from the normal-appearing anterior regions showed significant correlation with a measure of reaction time. One measure of vigilance, omission errors, correlated significantly with Ch/Cr. No significant correlation was found between performance IQ score and metabolite ratios from these normal-appearing anterior regions. The correlation coefficients are listed in Table 2.

**Discussion**

Proton MR spectroscopy has been used to study X-linked ALD, and several studies have reported differences in metabolite ratios as compared with those in healthy control subjects, including a decrease in NAA/Cr and NAA/Ch ratios and an increase in the Ch/Cr ratio together with the presence of lactate (10–12). Previous studies have also shown that MR spectroscopic data correlate well with the clinical severity of disease (12). All these studies were focused on abnormal cerebral regions as depicted on MR images. Our study demonstrates the potential of proton MR spectroscopy to delineate abnormal cerebral regions in patients with ALD before the appearance of abnormal intensity patterns on MR images.

It has been shown previously that the metabolite ratios from abnormal cerebral regions are different from those in healthy control subjects; that is, NAA/Cr and NAA/Ch are decreased and Ch/Cr is increased (10–12). A decrease in NAA and an increase in Ch are common in patients with ALD. The decrease of NAA is due to loss of neurons (21) and the increase in Ch is an indicator of demyelination (22, 23). Metabolite ratios from normal-appearing regions in the same

---

**TABLE 2: Correlation coefficients between neuropsychological data and MR spectroscopic metabolite ratios from abnormal and normal-appearing brain regions on MR images**

<table>
<thead>
<tr>
<th></th>
<th>NAA/Cr</th>
<th>NAA/Ch</th>
<th>Ch/Cr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal posterior regions (n = 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance IQ</td>
<td>0.90</td>
<td>0.91</td>
<td>−0.76</td>
</tr>
<tr>
<td>P value</td>
<td>.0001</td>
<td>&lt;.0001</td>
<td>.009</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>0.94</td>
<td>0.94</td>
<td>−0.67</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>.05</td>
</tr>
<tr>
<td>Mazes</td>
<td>0.76</td>
<td>0.77</td>
<td>−0.54</td>
</tr>
<tr>
<td>P value</td>
<td>.005</td>
<td>.004</td>
<td>.09</td>
</tr>
<tr>
<td>Normal-appearing anterior regions (n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction time</td>
<td>0.96</td>
<td>0.90</td>
<td>−0.56</td>
</tr>
<tr>
<td>P value</td>
<td>.007</td>
<td>.04</td>
<td>.4</td>
</tr>
<tr>
<td>Omission errors</td>
<td>NC</td>
<td>0.58</td>
<td>−0.90</td>
</tr>
<tr>
<td>P value</td>
<td>.4</td>
<td>.04</td>
<td></td>
</tr>
</tbody>
</table>

Note.—NC indicates no correlation.
patients also exhibit these patterns, and they are significantly different from those found in control subjects. The mean values are between those of the control subjects and those of the abnormal regions, indicating that the metabolic changes due to the disease are in progress before any change in intensity is seen on T2-weighted MR images. Monitoring of these normal-appearing regions by MR spectroscopy may be helpful in early diagnosis.

A comparison of MR spectroscopic metabolite ratios of normal-appearing regions with neuropsychological data helps to confirm that MR spectroscopic changes may herald the onset of disease before abnormalities are apparent on MR images. MR spectroscopic data from patients with posterior demyelination correlated well with performance IQ scores. In examining the subtests, we found that picture arrangement, which measures visual sequential ability and attention to visual detail, correlated highly with all three metabolite ratios from abnormal regions. Scores on the mazes subtest, a measure of visual processing and organization, also correlated with NAA/Cr and NAA/Ch ratios. No correlation was found with the measure of attention, thought to represent functions of the anterior brain region. The metabolite ratios from the normal-appearing anterior regions in these patients also showed significant correlation with measures of reaction time and vigilance. Thus, anterior region abnormalities, although normal-appearing on MR images, may be detected by MR spectroscopy. Too few patients with normal-appearing posterior regions were available for a detailed analysis.

Neuropsychological testing with the performance IQ test can be done in all patients over 3 years of age; however, measurement of attention on the TOVA can be done only in children over 6 years of age. Furthermore, loss of vision, a common occurrence in ALD, precludes the use of either test. Development of an auditory TOVA and a measure for preschool children will enable us to gather data on the full range of patients in the future.

In summary, we have shown that metabolite ratios from regions that appear normal at MR imaging can show abnormalities at proton MR spectroscopy. Thus, metabolic changes may precede morphological changes that manifest later as hyperintense areas on T2-weighted MR images. In addition, significant correlations between MR spectroscopic metabolite ratios and neuropsychological measures were found, indicating that such normal-appearing regions are involved by ALD.

Acknowledgments

We thank the nurses and technicians of the MR imaging division of the Department of Radiology, University of Minnesota, for their excellent help in providing patient care and assistance.

References


17. Wechsler D. *Wechsler Preschool and Primary Scale of Intelligence Revised.* San Antonio, Tex: The Psychological Corporation; 1989


**NOTICE**

Beginning January 1, 1998, new manuscripts and correspondence should be sent to the following address:

*American Journal of Neuroradiology*
2210 Midwest Rd, Suite 207
Oak Brook, IL 60521