Cerebral Metabolic Abnormalities and Correlations with Cognition in Children with Pervasive Developmental Disorder: A Preliminary Proton MRS Study

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Introduction

Individuals with a disorder in the autistic spectrum or a Pervasive Developmental Disorder (PDD) are a heterogeneous group of patients with early childhood onset of deficits in social interaction, verbal and non-verbal communication, and adaptive behaviors and interests. They are believed to be an etiologically heterogeneous group of patients with differing severity and patterns of developmental delays. The underlying neuropathology is unclear. The autistic spectrum largely consists of three disorders: autistic disorder (AD), Asperger’s syndrome (AS) and PDD-not otherwise specified (PDD-NOS). Previous 1H MRS studies (1-4) have shown decreased levels of N-acetylaspartate (NAA) in different brain regions of individuals with autism. In this preliminary study of a group of children with three PDD subtypes, proton MR spectra were collected from brain regions implicated in pathogenesis of PDD as shown in pathologic and functional studies (5-7). The goal was to compare metabolic levels in these brain regions between the PDD group and the control group, between the PDD subgroups, and to investigate if metabolic abnormalities are related to values of intelligence in children with PDD.

Methods

The PDD subjects (10 male and 3 female; age range: 7-16 yrs, mean ± SD: 11 ± 2 yrs) were diagnosed based on clinical criteria, including seven children with PDD-NOS, one with AD and five with AS. Consent and parental permission were obtained prior to MR and cognitive examinations of the PDD and control subjects (4 male and 4 female; age range: 7-17 yrs, mean ± SD: 10 ± 3 yrs). These subjects were free of medication at the time of this study. The neuropsychological tests (8) (including Rey complex figure test and recognition trial (Rey), Benton facial and visual recognition tests, and Stroop color and word tests) and Wechsler abbreviated scale of intelligence (IQ tests), were administered within a week of the MR scans.

The MR data were acquired using a 1.5T scanner (Philips; Marconi Edge) with the body coil as the transmitter and the head coil as the receiver. Prior to 1H MRS measurements, baseline T1- and T2-weighted images were obtained covering the whole brain in all three orthogonal directions. T2-weighted coronal images were used as scouts for single-voxel 1H MRS data acquisition with a PRESS sequence, TE = 40 ms, TR = 2000 ms, and 128 scan averages. The proton spectra were collected from left hippocampal-amygdala (LHA) (1.6x1.6x1.6 cm3) (Fig. 1a), right hippocampus-amygdala (RHA) (1.6x1.6x1.6 cm3) (Fig. 1b), and cerebellum (2.0x2.0x2.0 cm3) (Fig. 1c) regions. According to pathologic (5), PET (6), and functional MRI (7) studies, these areas exhibit abnormalities in PDD.

The raw spectral data were processed using 3 Hz broadening, Fourier transformation, and phase and baseline corrections. Resonance peaks of NAA, total creatine (Cr), choline-containing compounds (Cho), and myo-inositol (mI) were identified and fitted using a nonlinear-least-squares fitting procedure with a Levenberg-Marquardt algorithm. Peak area ratios over Cr resonance were calculated and used as measures of metabolite ratios. Non-parametric Wilcoxon test was used to compare the metabolite ratios between the groups. The relationships between metabolite ratios and scores of cognitive tests were assessed using Pearson correlations.

Results

No apparent anatomic abnormalities were observed on MR images of the brain in the PDD group compared to the control group. The metabolite ratios over Cr are tabulated in the Table. NAA/Cr was significantly decreased in the LHA and RHA regions, but not in the cerebellum area, while mI/Cr was significantly increased in all three brain regions in children with PDD compared to healthy controls. Cho/Cr was significantly elevated in the LHA and cerebellum regions of the PDD subjects. In comparison of PDD subgroup differences, the LHA Cho/Cr was significantly (p < 0.01) higher in the PDD-NOS group compared to the AS group which had similar values to those of the controls.

Table Metabolite Ratios in Children with PDD (N = 13) and Healthy Controls (N = 8)

<table>
<thead>
<tr>
<th></th>
<th>LHA</th>
<th>RHA</th>
<th>Cerebellum</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NAA/Cr</td>
<td>1.99 ± 0.19*</td>
<td>2.34 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>0.79 ± 0.20*</td>
<td>0.59 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>mI/Cr</td>
<td>0.87 ± 0.21*</td>
<td>0.51 ± 0.13</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.76 ± 0.45</td>
<td>0.62 ± 0.10</td>
<td>0.55 ± 0.11*</td>
</tr>
</tbody>
</table>

mean ± SD; *: mean in PDD group differs significantly from the control group (p < 0.05).

In correlation with cognitive performance of the PDD subjects after controlling for age, Cho/Cr in the LHA region was found to be inversely related (Fig. 2) to scores of Benton Visual Form Discrimination (BVFD) test which measures ability to make fine visual discrimination, while mI/Cr (Fig. 3) and NAA/Cr in the RHA region was found to be positively associated with scores of performance IQ (IQ_P) test which measures perceptual intelligence.

Discussion

In this preliminary study, significant metabolic abnormalities, as well as significant correlations between metabolic abnormalities and cognitive performances were found in brain regions where pathologic and functional deficits were revealed in children with PDD (5-7). NAA is the neuronal marker, while mI is the glial marker (9). The decrease in NAA levels may be resulted from neuronal loss/dysfunction, or the existence of immature neurons, while the increase in mI levels may stem from proliferation of myelinating and non-myelinating glial cells. Myelination is suggested to improve cognitive performance based on observed faster stimulus inspection times in high-IQ individuals (10). Children with AS usually demonstrate normal language development. Significantly higher LHA Cho/Cr in the PDD-NOS group compared to the AS group suggests that LHA Cho/Cr may be a marker of language development. This study shows that the combined approach of 1H MRS and neuropsychological measurements may provide important information in understanding the underlying neuropathology of PDD.

References


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