Correlations of Cerebral Metabolite Levels with Cognition in Children with Pervasive Developmental Disorder: A Preliminary ^{1}H 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, language and stereotypic behavior. 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 ^{1}H MRS studies have shown decreased cerebral levels of N-acetylaspartate (NAA) (1-3), as well as increased levels of myo-inositol (mI) (3) in individuals with autism. In this preliminary study of a group of children with PDD, proton MR spectra were collected from brain regions implicated in pathogenesis of PDD as shown in pathologic and functional studies (4-6). To determine if metabolic abnormalities in these brain regions are related to cognitive dysfunctions in children with PDD, the metabolite levels were correlated with the results of neuropsychological tests.

Methods

The PDD subjects (6 male and 2 female; age range: 8-16 yrs, mean ± SD: 11 ± 2 yrs) were diagnosed based on clinical criteria, including six children with PDD-NOS, one with AD and one with AS. Consent and parental permission were obtained prior to MR and cognitive examinations. These subjects were free of medication at the time of this study. The neuropsychological tests (7) including Rey complex figure test and recognition trial (Rey), Benton facial and visual recognition tests, 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 ^{1}H MRS measurements, routine T_1- and T_2-weighted images were obtained covering the whole brain in all three orthogonal directions. T_2-weighted coronal images were used as scouts for single-voxel ^{1}H MRS data acquisition with a PRESS sequence, TE = 40 ms, TR = 2000 ms, and 128 scan averages. The proton spectra were collected from left hippocampus-amygdala (LHA) (1.6x1.6x1.6 cm^3) (Fig. 1a), right hippocampus-amygdala (RHA) (1.6x1.6x1.6 cm^3) (Fig. 1b), and cerebellum (2.0x2.0x2.0 cm^3) (Fig. 1c) regions. According to pathologic (4), PET (5), and functional MRI (6) studies, these areas exhibit abnormalities in PDD.

The raw spectral data were processed using 3 Hz line broadening, Fourier transformation, and phase and baseline corrections. Resonance peaks of NAA, total creatine (Cr), choline-containing compounds (Cho), and 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.

The relationships between metabolite ratios and scores of cognitive tests were assessed using Pearson correlations.

Results

As we have previously reported (3), NAA/Cr is significantly ($p < 0.05$) decreased in the LHA and RHA regions, but not in the cerebellum area, while mI/Cr is significantly ($p < 0.05$) increased in all three brain regions in children with PDD compared to age- and sex-matched healthy controls.

In correlation with cognitive performance of the eight PDD subjects after controlling for age, NAA/Cr in the LHA region was found to be inversely related (Fig. 2) to scores of Rey immediate recall test (Rey_Imm) which measures perceptual memory, while mI/Cr in the RHA region was found to be positively associated (Fig. 3) with scores of performance IQ test (IQ_P) which measures perceptual intelligence. Though not statistically significant, the trends of similar correlations between LHA/RHA NAA/Cr and mI/Cr ratios and scores of other individual cognitive tests were quite strong (absolute r values ranging from 0.45 to 0.60). There were no significant correlations or trends found between cerebellum metabolite ratios and cognitive functions.

Discussion

In this preliminary study, significant correlations were found between cognitive performances and metabolic abnormalities in the LHA and RHA brain regions where pathologic and functional deficits were revealed in children with PDD (4-6). NAA is the neuronal marker, while mI is the glial marker (8). The decrease in NAA levels may be resulted from the process contributing to volume displacement of NAA-rich cells, 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 (9). This study shows that the noninvasive approach of ^{1}H MRS may provide important information in the endeavor to understand the underlying neuropathology of PDD. We are currently expanding the study to a larger population of children with PDD to improve the significance level of correlation analysis, and to evaluate possible PDD subgroup differences in relations between metabolic abnormalities and cognitive dysfunctions.

References

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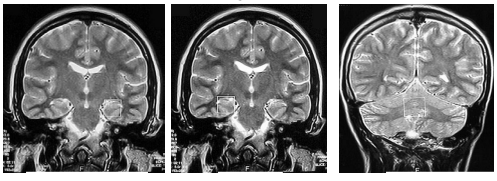

Fig. 1a **1b** **1c**

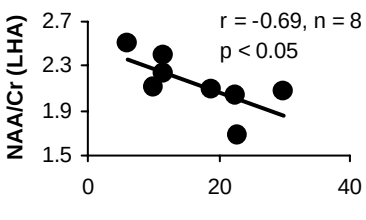

Fig. 2

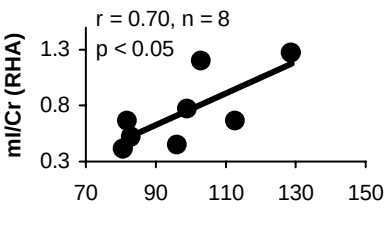

Fig. 3