Proton magnetic resonance spectroscopy in developmentally delayed young boys with or without autism

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Summary: Objective: The aim of the present study is to investigate whether brain metabolism of boys with autism spectrum disorder (ASD) is altered compared to boys with a developmental delay without autism if corrected for patient age and developmental level. Study design: 25 boys with ASD (with or without concurrent mental retardation) and 12 boys without ASD with mental retardation or language disorder underwent proton magnetic resonance spectroscopy. All analyses were performed with chronological age and developmental level as independent variables. Results: No metabolic differences were found between boys with ASD and without ASD. Conclusions: Our findings do not replicate previous reports of differences in NAA, Cho and Cr levels in ASD.

Keywords: Autism spectrum disorder, developmental delay, MRS (or proton) magnetic resonance spectroscopy

Introduction

Autism is a pervasive developmental disorder characterized by a triad of social deficits, language and communication problems and a pattern of stereotyped, repetitive and restricted behaviors and interests (American Psychiatric Association, 1994). It is a clinically heterogeneous condition that has a broad range of severity and is frequently associated with concomitant learning disability.

Imaging of patients with autism offers valuable information on anatomy and function (Akshoomoff et al., 2002; Cody et al., 2002). At present, several magnetic resonance spectroscopy (MRS) studies in patients with autism in the age range of 2–32 years) have been performed. In general, a trend of decreased N-acetylaspartate (NAA) concentrations, decreased NAA/choline (NAA/Cho) or decreased NAA/creatinine (NAA/Cr) ratios was found (Friedman et al., 2003; Filippi et al., 2002; O’Neill et al., 2002). Still, interpretation of MRS data in autism studies is complicated. In addition to differences in absolute and relative metabolic concentrations between studies, regions of interest vary widely (Rumsey and Ernst, 2000; Sokol et al., 2002; Yurgelun-Todd and Renshaw, 2000). Otsuka et al. found lower NAA levels in the amygdala-hippocampal region (Otsuka et al., 1999) whereas others made similar observations in the cerebellum (Chugani et al., 1999) or parietal cortex (Hashimoto et al., 1997). More important, in general it is difficult to elucidate which cerebral metabolic changes are related to autism itself. Approximately three-quarter of the patients with autism also suffers from learning disabilities, which in itself may give rise to metabolic abnormalities (Volkmar and Pauls, 2003). Therefore, when comparing a group of (retarded) autistic children with a group of normal developing children (Hashimoto et al., 1995; O’Neill et al., 2002), autism itself as well as mental retardation may underlie metabolic differences. Except for a study of patients with Asperger syndrome (Murphy et al., 2002), none of the MRS studies in this field used a correction for mental retardation. Moreover, the effects of age dependency on metabolic concentrations are often underestimated. Developmental studies have shown that the concentration of NAA, creatine (Cr), and glutamine and glutamate (Glx)
increases with brain development, whereas the concentration of choline (Cho) and myo-inositol (mI) decreases with brain development (Bhakoo and Pearce, 2000; Friedman et al., 2003; Moore, 1998; Kreis et al., 1993). In this respect, it is important to keep the age range of both patient and (age matched) control group as small as possible. Even then, including age as an independent covariate in data analysis seems obligatory.

The overall purpose of the present study is to replicate the previously reported abnormalities in our group of boys with autism spectrum disorders (ASD) and a control group of boys with a developmental delay without ASD. The aim was to determine these possible metabolic cerebral changes in the amygdala-hippocampal region and in the frontal subcortical white matter. All participants were between the ages of 1 year 9 months and 6 years 7 months. To correct for the effects of age and developmental level, all analyses were performed with chronological age and developmental level as independent variables.

Material and methods

37 children participated. Participants were recruited from referrals to the Department of Child and Adolescent Psychiatry of University Medical Center Utrecht. Diagnosis was made by a team of board certified child psychiatrists (EvD, JB, HvE) according to DSM-IV criteria (American Psychiatric Association, 1994). Children younger than 42 months at the time of scanning had a final diagnosis when they reached 42 months. The diagnosis was confirmed by Autism Diagnostic Interview Revised (Lord et al., 1994) and the Autism Diagnostic Observation Schedule G (Lord et al., 1989) diagnoses.

When a child was diagnosed with autism (A) or PDD-NOS with or without concurrent developmental retardation; mental retardation (MR) (without an autism spectrum diagnosis); or language disorder (LD), parents were offered the possibility of MRI and MRS. Patients were included if a) they were 18 months to 7 years of age, b) were diagnosed with an autism spectrum disorder, a language disorder or mental retardation, and c) had no contraindication for MRI. For all four groups, children having significant motor or sensory impairment (e.g., blindness, deafness), major physical abnormalities, history of serious head injury, identifiable neurologic disorder or metal implants such as prostheses were excluded. Patients were scanned under full anesthesia with sevoflurane. The study design was approved by the Medical Ethical Review Board of the University Medical Center Utrecht. All parents gave written informed consent.

Children were administered the Mullen Scales of Development (Mullen, 1995) to measure the developmental level. Several children were at the floor of the standardized scores. It was decided, therefore, to convert raw scores to a developmental level in order to allow us to look more closely at the functioning of the more impaired children. Four subtests were used; visual receptive, fine motor, receptive language, and expressive language. The developmental level was calculated as Mean Age Equivalent of the four subtests/Chronological Age × 100. For some children the Mullen was found to be too difficult. For 7 patients with A and one patient with PDD-NOS the Psychoeducational Profile – Revised (Schopler et al., 1994) was used to assess the developmental level. For 5 children either the Griffith (1986) (in one case with PDD-NOS), the Dutch Snijders-Oomen niet-verbale intelligentietest (Tellegen et al., 1996) (for one patient with LD and one with A) or the Kaufman Assessment Battery for Children

| Table 1. Descriptives of the patients |
|-----------------|---|---|---|---|
|                | A  | PDD-NOS | MR  | LD  |
| N               | 17 | 8       | 4   | 8   |
| Age in months   | 43 (SD 7) | 45 (SD 15) | 40 (SD 8) | 39 (SD 14) |
| Developmental quotient (SD) | 44 (SD 8) | 80 (SD 13) | 67 (SD 10) | 86 (SD 8) |

Fig. 1. The VOI in the frontal subcortical white matter

Fig. 2. The VOI in the amygdala-hippocampal complex