Proton MR Spectroscopic Imaging in Cryptogenic Developmental Delay

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Introduction. Developmental delay (DD) refers to the delayed acquisition of cognitive, motor and adaptive functions in children. In some cases it represents the first sign of future mental retardation. The prevalence of DD is estimated between 1 and 15%. Although most severe form of DD are associated with structural or genetic pathologies, often an etiology cannot be found for the mildest forms, which are also often associated with normal MRI findings [1]. Recent studies using single voxel spectrosopy have demonstrated localized abnormalities in metabolite ratios in DD subjects [2]. The purpose of this study was to investigate whether cryptogenic DD with normal MRI is associated with metabolic abnormalities which could be detected by by proton MR spectroscopic imaging (MRSI) of the brain.

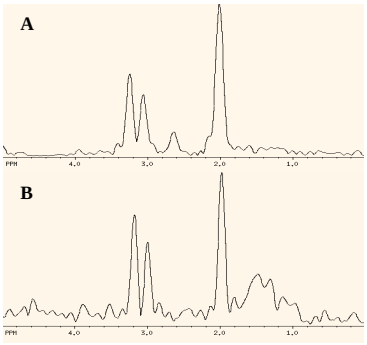


Fig. 1: Spectra from parietal grey matter of a 3.38-year-old control subject (A) and a 3.75-year-old subject with developmental delay (B). Both spectra have been scaled to NAA

Methods. *Subjects.* We reviewed MRI and MRSI of 40 children with a diagnosis of DD. To have a diagnosis of cryptogenic DD, patients had to have normal MRI and no other pathological findings. Inclusion criteria were also the availability of good quality MRSI data and age above 2 years. Based on these criteria, we included 7 subjects (mean age: 7.08 years; sdev: 2.6). The control group was composed of 7 healthy subjects (mean age: 7.67 years; sdev: 3.48), who were selected based on best matching age and sex from a group of children recruited as controls for other two different MRSI research projects [see published data in:3]. *MRI and MRSI*. Each subject underwent a standard brain MRI. MRSI was performed using a spin-echo (SE) sequence with two-dimensional phase-encoding and outer-volume saturation pulses for lipid suppression [4]. Three or four 15-mm thick slices were recorded parallel to the anterior - posterior commissure (TR/TE 2300 /272 msec; FOV 240 mm) with either a 32x24 or a 32x32 matrix. *Selection of Brain Regions and MRSI Data Pprocessing*. Spectra were evaluated from nine brain regions encompassing gray matter, white matter and basal ganglia: putamen (1), thalamus (2), deep premotor/motor white matter (3), posterior prefrontal cortex (4), inferior parietal cortex (5), deep parietal white matter (6); medial premotor cortex (7), motor cortex (8) and dorsal parietal cortex (9). Only voxels that appeared completely encompassed by the boundaries of the anatomic regions of interest (ROIs) were included. MRSI data sets were processed as described previously [5]. Signals of total choline (Cho), total creatine (Cr), and *N*-acetyl aspartate (NAA) (Fig. 1) were fitted to a Gaussian line shape using a simplex routine [5]. The ratios of NAA/Cho, NAA/Cr, and Cho/Cr were calculated. *Statistical analysis*. Due to the small sample size we used non-parametric tests (SPSS 8.0 for Windows) to explore the relation between metabolite ratios and three factors: group (DD or control), brain region and hemisphere side. The effect of age within each group was tested with regression analysis.

Results. The group factor was found to be significant for all three metabolite ratios (NAA/Cr and NAA/Cho: df = 1, $p < .001$; Cho/Cr: df =1, $p < .05$). Post-hoc analysis (Mann-Whitney) revealed significantly ($p < .001$) lower NAA/Cr ratio in each brain region of the DD group compared to the control group (Fig. 2). A similar pattern was found for the NAA/Cho ratio that, compared to the control group, was significantly ($p < .05$) lower in all brain regions of the DD group, except for the dorsal parietal cortex ($p < .06$) and the motor cortex ($p < .08$) where only a trend in the same direction was found. The parietal grey matter, the thalamus and the putamen were the only brain regions where Cho/Cr ratio was significantly ($p < .005$) different between the two groups, with lower ratios associated with the DD group.

Fig. 2

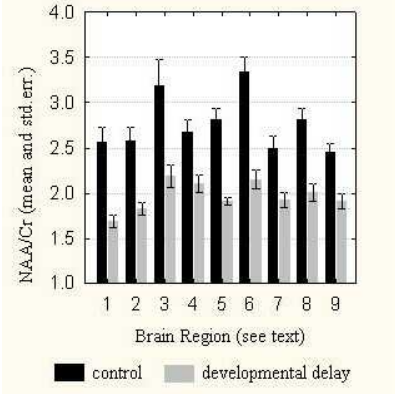
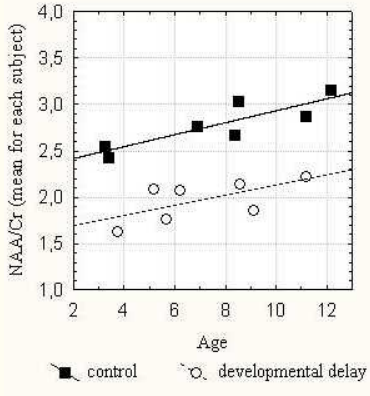


Fig. 3



Similar differences in the regional distribution of metabolite ratios were found within both groups: NAA/Cho ratio was higher in prefrontal, parietal, and motor cortex; the Cho/Cr ratio was higher in the thalamus and in the frontal and parietal white matter; the NAA/Cr ratio was higher in the frontal and parietal white matter.

A regression analysis revealed that within each group there was an overall significant ($p < .005$) positive linear relation between both NAA/Cho and NAA/Cr (Fig. 3) ratios and age. Only the DD group showed a significant ($P < .001$) negative realtion between Cho/Cr ratio and age.

Discussion. Consistent with a previous single voxel study [2] , the NAA/Cr ratio was lower in DD than in controls. MRSI suggests that these changes are widespread and not specific to any brain region, involving both white and grey matter. Since NAA/Cho is low at birth and increases over the first few years of age [6], these results suggest that children with functional DD also have delayed maturation of brain metabolism. Although the limited sample size does not allow strong general conclusion, we suggest that spectroscopic imaging could be useful in the diagnosis of DD. Further, possibly longitudinal, studies are required to determine if metabolite ratios are correlated with clinical outcome, and/or helpful for the early identification of children at risk for possible mental retardation.

References.

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