Age-dependence and Clinical Correlates of Brain Metabolism in Rett Syndrome

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Introduction

Rett Syndrome (RTT) is a neurodevelopmental X-linked disease that affects primarily girls. Clinically, these children are normal at birth and then develop progressive autistic-like behavior, neurodevelopmental delay, with loss of motor skills[1]. Methyl-CpG binding protein-2 (MeCP2) gene, located in chromosome Xq28, is the underlying abnormality in over 80% of the patients. All ethnic groups are affected[1]. MRI shows microcephaly[2], and previous proton MR spectroscopy (MRS) studies have shown mild reductions in N-acetyl aspartate (NAA) levels, particularly in the frontal lobe[2-5]. However, the relationship of these spectroscopic changes to neurological involvement has not been previously investigated in detail. The purpose of the current study was therefore to evaluate the relationship between brain metabolites, age and clinical characteristics in RTT patients.

Materials and Methods

Thirty-five girls diagnosed with RTT (age range 1.1 to 13.9 years, mean age 6.5 years) were examined. Clinical diagnosis was made by established clinical criteria. All subjects showed mutation in MeCP2 gene. The study was approved by local IRB and parental consent was obtained for all subjects. Eight controls (who were unaffected siblings of patients and normal volunteers) with mean age of 10.5 years and age range of 6.4 to 14.7 years were also examined.

During the MRI and MRS exams, all patients were sedated with chloral hydrate (80-100 mg/kg). Normal controls were not sedated. MRI and proton MRS were performed in a 1.5T Intera scanner (Philips, Best, The Netherlands) with protocols including sagittal and axial T1 weighted images, axial double-echo T2, axial Fluid Attenuated Inversion Recovery (FLAIR) and volumetric T1-weighted (3D- FFE). Single voxel MRS was performed in the left frontal white matter, utilizing a Point Resolved Spectroscopy (PRESS) sequence (TR/TE=1500/30 msec), with an 8 ml voxel size (2.0 x 2.0 x 2.0 cm^3). Spectra were recorded with water suppression (number of scans=128) and without water suppression (number of scans=8).

All spectra were analyzed with the LCModel, to obtain ratios relative to creatine (Cr) of the following metabolites: NAA, myo-inositol (mI), glutamate (Glu) and choline (Cho).

Regression analysis was used to evaluate age-related differences in metabolite levels. ANOVA was applied to examine the effect of clinical findings (seizures, hyperventilation and gait abnormalities) on metabolite ratios in RTT compared to controls. Fisher's LSD method was used for post-hoc analyses. Significance level was set to $p<0.05$.

Results

NAA/Cr decreased by 33% and mI/Cr increased by 195% over the examined age range (14 years) in RTT (both $p<0.01$), while both NAA/Cr and mI/Cr were stable in controls (Figure 1). On average, the only group difference between RTT and controls detected were a 74% higher mI/Cr ratio in RTT. There were trends for higher Glu/Cr ($p=0.065$) and lower NAA/Cr ratios in RTT patients compared to controls. The effect of presence or absence of seizures on metabolite ratios is presented in the Table - NAA/Cr was lower in patients who had seizures than those who did not. No effect of gait abnormalities or hyperventilation status on metabolite ratios was observed.

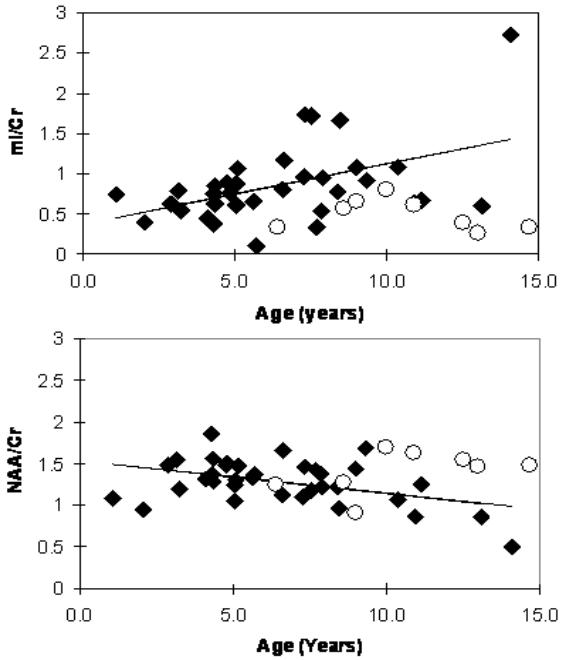

Figure 1 – Age dependence of mI/Cr and NAA/Cr in RTT (diamonds) and controls (circles). In RTT, mI/Cr increased (slope 0.07 $year^{-1}$) and NAA/Cr decreased (slope -0.039 $year^{-1}$) with age (both $p<0.01$) while mI/Cr and NAA/Cr were stable in controls

		Metabolite ratios (mean ± SD)				N
		Cho/Cr	Glu/Cr	mI/Cr	NAA/Cr	
Seizures:	present	0.27 ± 0.06	1.05 ± 0.46	0.94 ± 0.56‡	1.15 ± 0.28*‡	13
	absent	0.32 ± 0.08	1.26 ± 0.31	0.79 ± 0.38‡	1.36 ± 0.20	22
Average ratios:	patients	0.30 ± 0.08	1.20 ± 0.41	0.87 ± 0.49‡	1.28 ± 0.27	35
	controls	0.28 ± 0.08	1.09 ± 0.17	0.50 ± 0.19	1.41 ± 0.25	8

Post-hoc: *$p<0.05$ (Seizures present vs. absent), ‡ $p<0.05$ (RTT vs. controls).

Discussion

The age-related decrease in NAA/Cr and increase in mI/Cr are novel findings suggestive of progressive axonal damage with accompanying gliosis in patients with RTT. These results, which show a progressive change in metabolite ratios, do not, however, correlate with the "clinical plateau" that is commonly observed in RTT[3]. The trend for higher Glu levels, and previously detected increased glucose utilization in the frontal lobe by PET, is suggestive of increased glutamate-glutamine cycling at the synapses and astrocytes in RTT[2]. Lower NAA/Cr in patients with seizures may be consistent with seizure-related axonal loss or dysfunction in RTT.

In summary, this study, which includes the largest number of RTT patients studied by MRS to date, indicates that MRS may be a valuable tool for the understanding of the pathophysiology of RTT, and its relationship to neurological involvement. In the future, MRS may also have a role in therapeutic monitoring in RTT.

References

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