1H MRSI Indications of Elevated Brain Choline in Childhood-Onset Schizophrenia

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Introduction: [1]H MRS finds low NAA, NAA/Cr, and NAA/Cho and/or high Cho and Cr in several brain regions in adult schizophrenia. The rarer and more severe childhood-onset schizophrenia is less studied with MRS[2-3,5]. Auer *et al.*[1] maintain that elevated Cho supports the "membrane hypothesis" of schizophrenia and suggest that earlier onset occurs in patients with more severe phospholipid disturbances. This implies that Cho should be elevated in one or more brain regions in childhood-onset schizophrenia. We investigated this possibility.

Methods: 11 DSM-IV childhood-onset schizophrenics (12.3 ± 3.8 yr; 4 ♀; all but 2 medicated) were compared to 20 healthy controls (11.7 ± 2.9 yr; 10 ♀). Whole-brain MRI (axial FSE: TR/TE = 3000/13 ms; sagittal SPGR: TR/TE = 24/9 ms) and water-suppressed multislice [1]H MRSI (IR: TR/TI/TE = 2300/170/272 ms; 10x10x12 mm^3 voxels) were acquired at 1.5 T (GE). [1]H MRSI was collected from 3 contiguous axial slices (basal ganglia, ventricular, supraventricular) broadly sampling cortex, white-matter, and subcortex. After FT, each subject's [1]H MRSI volume underwent spatial filtering, 2.0-Hz apodization, and automated baseline fitting; voxels with lipid signals exceeding NAA, with NAA SNR < 2.0, with linewidth > 10.0 Hz, or with other artifact were excluded manually. Individual [1]H MRSI voxels were interrogated from (left and right): superior and inferior anterior cingulate; frontal, parietal, and occipital cortices; caudate head and body, putamen, thalamus; and frontal and parietal white matter, sites implicated in schizophrenia. Structures were identified from FSE PD images coregistered to MRSI. Voxel tissue composition was obtained from coregistered SPGR T1 MRI segmented into gray matter, white matter, and CSF. Voxels were sought with ≥ 75% cortical gray matter; ≥ 75% white matter, or ≥ 50% subcortical gray matter, according to site. There were no significant between-group differences in gray- or white-matter content at any site. Signal intensities for NAA, Cr, and Cho were adjusted for transmitter and receiver gains, normalized to MRI PD intensity, and corrected for voxel CSF, yielding absolute metabolite levels (uncorrected for T1, T2) in Institutional Units (IU). Data were processed blind to subject identity. Repeated-measures ANCOVA was performed for NAA, Cr, and Cho for each left-right structure pair with hemisphere as within-subjects factor, group as between-subjects factor, and age and sex as covariates. For significant interactions *post-hoc* comparisons were made with one-way ANOVA. Criterion for significance was $P < 0.05$. Bonferroni correction was not applied in this exploratory study with *a priori* hypotheses.

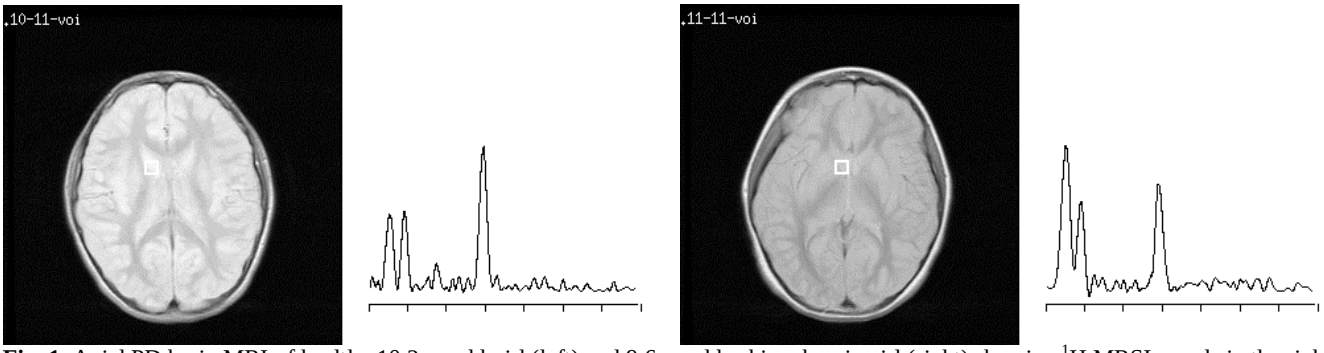

Fig. 1. Axial PD brain MRI of healthy 10.2-yr-old girl (left) and 9.6-yr-old schizophrenic girl (right) showing [1]H MRSI voxels in the right caudate head and corresponding spectra. Note elevated Cho and Cr relative to NAA in patient.

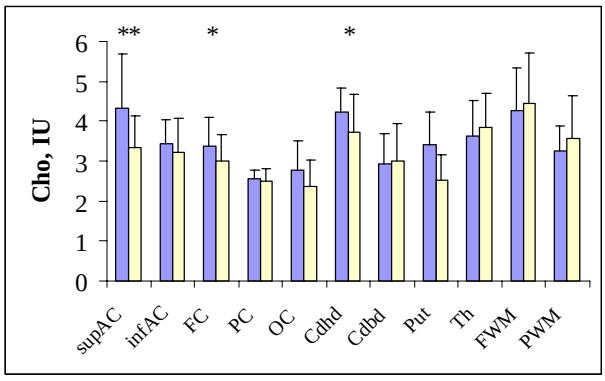

Fig. 2. Absolute Cho (left-right group means ± SD) at all brain sites in childhood-onset schizophrenics (dark) and healthy age-matched controls (light). *p < 0.05,**p < 0.01 (ANCOVA). Note elevated Cho at 3 sites in patients.

Results: Fig. 1 shows elevated Cho and (less so) Cr and lower NAA in a sample schizophrenic spectrum. In superior anterior cingulate, Cr was 14.3 % higher ($F(1,21) = 5.0$, $p = 0.04$) in patients than in controls. Cho (Fig. 2) was higher in patients in superior anterior cingulate (30.3 %; $F(1,21) = 9.6$, $p = 0.006$), frontal cortex (13.3 %; $F(1,15) = 6.3$, $p = 0.02$), and caudate head (13.5 %; $F(1,23) = 5.2$, $p = 0.03$). Thalamic NAA was lower in male patients than in female patients ($F = 19.5$; df = 1,10; $p = 0.002$) or in male controls ($F(1,16) = 5.8$, $p = 0.03$).

Discussion: This long-TE [1]H MRSI study finds above-normal Cr (superior anterior cingulate) and Cho (superior anterior cingulate, frontal cortex, caudate head) and (in males) diminished thalamic NAA in childhood-onset schizophrenics. These regions also exhibit structural and metabolic abnormalities in adult schizophrenia, suggesting similarity of neurodysfunction in the two disorders. The Cho results support the notion[1] that elevated Cho should be evident in schizophrenics with younger age-of-onset. Insofar as Cho represents membrane metabolism, these results support the membrane hypothesis of schizophrenia. Elevated Cr may reflect altered cellular energetics accompanying putative membrane disturbances. Reduced thalamic NAA is consistent with prior findings in adult schizophrenia[4] and suggests neuronal dysfunction. Limitations include low number of subjects and medication of most patients. **References:** 1. Auer et al. **Schiz Res 52**,87-99 (2001). 2. Bertolino et al. **Am J Psychiatry 155**,1376-1383 (1998). 3. Brooks et al. **Biol Psychiatry 43**,263-269 (1998). 4. Deicken et al. **Am J Psychiatry 157**,644-647 (2000). 5. Thomas et al. **JMRI 8**,841-846 (1998).