Assessing the Effect of Comorbidity in Attention-Deficit/Hyperactivity Disorder (ADHD) Using In vivo ^{31}P Spectroscopy

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental behavioral disorders. ADHD is first diagnosed in children with symptoms of inattention, hyperactivity and impulsivity. In a preliminary *in vivo* phosphorus (^{31}P) spectroscopy study [a noninvasive technique that can directly assess the metabolism of membrane phospholipids (MPL) and high-energy phosphates in multiple brain regions], we have shown deficits in MPL precursor levels in the basal ganglia (BG) and prefrontal (PF) regions of children with ADHD compared to healthy control subjects [1]. The purpose of this study is to assess the effect of comorbid oppositional defiant disorder (ODD) and/or conduct disorder (CD) on MPL deficits. We hypothesized greater MPL deficits in ADHD subjects with greater severity in behavioral symptomatology.

SUBJECTS AND METHODS

Twenty-five children with DSM-IV ADHD [all males; mean age 8.8±1.5 yrs; 6.3-11.9 yrs; 16 stimulant-naïve (nADHD) and 9 treated-ADHD (tADHD) subjects; 15 with the combined type and 10 with the predominantly inattentive type], and 22 healthy control subjects (HC; all males; mean age 9.2±2.1 yrs; 6.4-12.1 yrs) participated in this study. There were 13 ADHD subjects who had a comorbid ODD and/or CD diagnoses (coADHD).

A doubly tuned transmit/receive volume head coil was used to acquire the multi-voxel ^{31}P spectroscopy data on a GE LX 1.5 T whole body MR imager. Based on sagittal scout images, the CSI slice was positioned parallel with the anterio commissure-posterior commisssure line to include the right and left PF and BG regions. A single slice selective excitation RF pulse followed by phase encoding pulses to spatially encode the two dimensions within the axial slice (termed FIDCSI on a GE system) was used to acquire the ^{31}P CSI data. The experimental parameters for the FIDCSI sequence are: FOV= 240x360 mm^2, slice thickness= 30 mm, 8x8 phase encoding steps (nominal voxel volume= 40.5 cm^3), TR= 2,000 ms, complex data points= 1,024, spectral-bandwidth= 5.0 kHz, pre-acquisition delay= 1.7ms, and NEX= 16. The FIDCSI sequence in the ^{1}H mode was used to shim on the axial slice priori to the ^{31}P measurement.

To optimize the right and left voxel positions for the PF and BG regions, the 8x8 CSI grid was shifted accordingly prior to the IFT. The remaining post-processing and quantification steps were 100% automated. With a 5Hz Gaussian apodization, the ^{31}P resonances, phosphomonoester (PME), phosphodiester (PDE), phosphocreatine (PCr), adenosine triphosphate (γ-, α- and β-ATP), and inorganic orthophosphate (Pi), were modeled in the time domain with Gaussian damped sinusoids and by omitting the first 3.2ms of the FID using the Marquardt-Levenberg algorithm. Additionally, the relatively broad peaks underlying the PDE resonances [PME(i-τ_c)+PDE(i-τ_c)], which are due to less mobile molecules with PDE and PME moieties (e.g., synaptic/transport vesicles and micelles, and phosphorylated proteins), were quantified by taking the difference between the total modeled amplitude when omitting 3.2ms and 0.2ms of the FID [2]. This approach ensured that the quantified PME and PDE primarily reflected the freely mobile MPL precursors [PME(s-τ_c)] and breakdown products [PDE(s-τ_c)], respectively [2].

A generalized linear regression model (SAS Institute Inc., PROC GENMOD) with subject group, age and hemisphere as the main effect terms was used to test bilateral group differences in each region. A second model with an additional subject group-by-age interaction term was used for only the two-group comparisons.

RESULTS

The tADHD subjects were significantly older than the nADHD subjects (p=0.0035); however, age was not significant between the ADHD subjects with or without comorbidity.

Total ADHD subjects vs HC: The PME(s-τ_c) levels were significantly lower in the PF (p=0.0065) and BG (p=0.027) of ADHD subjects compared to HC subjects. There also was a significant age-by-group interaction (p=0.0021) with lower PF PME(s-τ_c) levels in the older ADHD subjects (Figure 1).

coADHD, ADHD and HC: The PME(s-τ_c) levels were lower in the PF (p=0.0010) and BG (p=0.0009) of coADHD subjects compared to HC subjects, as well as being significantly lower in the BG of coADHD compared to the ADHD with no comorbidity (p=0.023).

Clinical correlations: Including all subjects, the ODD and externalizing t-scores (as part of the Child Behahavior Checklist assessment) inversly correlated with the BG PME(s-τ_c) levels [r=-0.38 and p=0.0007; r=-0.40 and p=0.0003 (Figure 2)].

DISCUSSION AND CONCLUSIONS

Overall, there is a significant deficit in the MPL precursor levels in the PF of relatively older ADHD children and in the BG across the ADHD children suggesting decreased synthesis of MPL due to reduced membrane mass or content, which is consistent with an underdevelopment of neuronal processes and synapses in ADHD. Also, the marked reduction in BG MPL precursor levels in the coADHD subjects compared to both HC and the ADHD subgroup without any comorbidity along with the clinical correlations suggest greater MPL deficits with increasing ODD symptomatology and externalizing behavior in ADHD children. These MPL precursor deficits reflect a potential valuable marker of behavioral symptomatology among ADHD children.

1. Stanley JA, Kipp H, Greisenegger K, et al (2005) ISMRM:1200.
2. Stanley, JA and Pettegrew, JW (2001) Magn Reson. Med., 45, 390-396.

Figure 1.

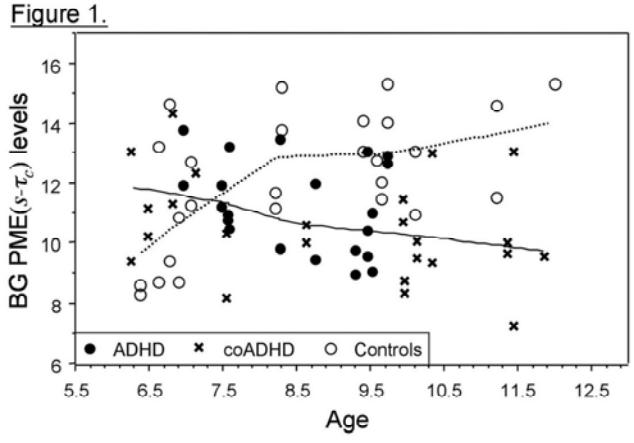

Figure 2.