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Short-TE proton magnetic resonance spectroscopy investigation in adolescents with attention-deficit hyperactivity disorder

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ABSTRACT

In this study, short echo time ^{1}H-magnetic resonance spectroscopy (MRS) was applied for quantification of neurometabolites using the LC Model algorithm in Taiwanese adolescents with attention-deficit hyperactivity disorder (ADHD). Proton magnetic resonance spectra were acquired bilaterally on the prefrontal area (part of the anterior cingulate gyrus and part of the medial frontal gyrus) in 15 adolescents with ADHD (average age of 13.88 years) and 22 controls (average age of 14.85 years). Absolute metabolite levels and ratios relative to creatine plus phosphocreatine (Cr + PCr) were obtained to be compared between groups. Results showed that adolescents with ADHD had significantly lower mean right prefrontal levels of Cr + PCr as compared with the controls. No significant differences between groups were noted in the remainder of the prefrontal metabolites. As for the group comparison of relative ratios, the *N*-acetylaspartate/Cr + PCr ratio was significantly higher in the right prefrontal regions of ADHD adolescents. This finding provides evidence of a right prefrontal neurochemical alteration in ADHD adolescents, which is consistent with current ADHD theory of prefrontal neuropathology with developmental mechanism. In addition, it highlights the importance of the method in interpretation of MRS findings in the context of ADHD.

1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder in children with a worldwide prevalence reported to be 5.2% (Polanczyk et al., 2007). It is defined by persistent, developmentally inappropriate, cross-situational, impaired levels of inattention, impulsiveness and hyperactivity (American Psychiatric Association, 2000). Deficits in ADHD are hypothesized to be due to the impairment of fronto-striatal–cerebellar networks, which are found to be abnormal in children with ADHD in neuroimaging studies (Durston, 2003; Seidman et al., 2005; Konrad et al., 2006). Meta-analysis of structural imaging studies of ADHD reported the most frequently replicated findings as smaller volumes of the total brain, the right frontal cortex and white matter, the cerebellum and striatal subcortical structures (Durston, 2003; Konrad et al., 2006; Seidman et al., 2005; Valera et al., 2007).

Neurochemically, dysregulation of dopamine and norepinephrine systems plays the central role in the pathophysiology model of ADHD. This is initially suggested by the action of drugs for the disorder, which increase the synaptic availability of these neurotransmitters, and by animals showing that lesions in dopamine pathways create animal models of ADHD (Biederman and Faraone, 2005). In this regard, proton magnetic resonance spectroscopy (^{1}H-MRS) has been considered to be a suitable tool in investigating the neuropathology of ADHD because it allows the reliable and noninvasive in vivo measurement of neurometabolites, such as *N*-acetylaspartate (NAA), the glutamatergic resonance (glutamate and glutamine or GLu + GLn), creatine plus phosphocreatine (Cr + PCr), choline compounds (glycerophosphorylcholine and phosphorylcholine, GPC + PC) and myo-inositol (Ins). A recent meta-analysis reviewed 16 MRS studies of ADHD (Perlov et al., 2008) and revealed significant changes of choline compounds in left striatum (effect size: 0.66) and right frontal lobes (effect size: 0.52) of ADHD children as compared with normal children.

ADHD begins in childhood and may persist into adult life in a substantial subgroup. However, most of the available MRS studies of ADHD were focused on childhood, and only two studies reporting neurometabolites ratios addressed subjects with average age in the adolescent range (Jin et al., 2001; Sun et al., 2005) . In these two studies, single-voxel ^{1}H-MRS was applied to investigate the basal ganglia of adolescents with ADHD, yielding a decreased NAA/Cr ratio in bilateral striatum (Jin et al., 2001) and right lenticular nucleus (Sun et al., 2005). Given that not all the children with ADHD will be clinically affected as adolescents, one could speculate that adolescents/adult patients with ADHD represent a distinct subpopulation, possibly with a different neurobiological or environmental underpinning. Hence, scientific investigations of neurochemical substrates for ADHD beyond childhood are needed to determine the nature of

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neurobiological alterations. In a recent study of 31 psychostimulant-naïve children (age range 6.1–10 years) using in vivo ^{31}P spectroscopy methods, Stanley et al. reported a group × age interaction in the prefrontal cortex (PFC) and inferior parietal region, with relatively older psychostimulant-naive ADHD children showing significantly lower PFC and higher inferior parietal membrane phospholipids precursor levels (Stanley et al., 2008). This finding would provide support for a developmental mechanism targeting a bottom-up dysfunction of the basal ganglia impairing the fine-tuning of prefrontal function so that PFC alterations were not apparent until the onset of fine-tuning processes in the PFC of children with ADHD.

In this study, we applied short echo time ^{1}H-MRS for quantification of neurometabolites of the prefrontal area in ADHD adolescents and compared their spectra with healthy adolescents. The method of single-voxel spectroscopy allowed us to obtain both ratios and absolute levels of neurometabolites in a defined region of interest. Based on previous studies, we hypothesized that in ADHD adolescents, alterations in neurometabolites would be observed in the prefrontal areas as these subjects have already reached adolescence.

Table 1
Treatment characteristics of ADHD subject.

Participants ($N=15$)	Mean ± S.D. or %
Mean age at diagnosis (years)	9.88 ± 3.24
Mean age starting medication (years)	10.92 ± 2.64
Subtype	
Combined	$N=9$ (60%)
Inattentive	$N=6$ (40%)
Any comorbidity	$N=10$ (66.7%)
Oppositional defiant disorder/conduct disorder	$N=6$ (40%)
Mood/anxiety disorder	$N=3$ (20%)
Learning disability	$N=5$ (33.3%)
Current medication	
Methylphenidate only (mg/day) $N=11$	31.4 mg/day
Bupropion only (mg/day) $N=1$	300 mg/day
No medication for more than 6 months $N=3$	
Previous medication exposure duration (weeks)	
Methylphenidate only ($N=12$)	79.3 ± 57.27
Methylphenidate plus others ($N=1$)	21 weeks
Medication naive ($N=2$)	

2. Methods

2.1. Subjects

The case group was recruited through the outpatient service of the Department of Psychiatry, Kaohsiung Medical University Hospital. The control group was recruited from the community. Male and female subjects between 12 and 18 years of age were recruited. The diagnosis was ascertained through a semi-structured clinical interview, the Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children- Epidemiologic Version (Puig-Antich and Chambers, 1978), by a child psychiatrist. The case group met the DSM-IV diagnostic criteria for ADHD (inattentive, hyperactive/impulsive or combined subtype), while the control adolescents were ascertained to be free of any axis I diagnoses by the same individual who decided whether potential subjects for the ADHD group met DSM-IV criteria. The study subjects consisted of 37 adolescents: 15 ADHD adolescents (13 boys, 2 girls with average age of 13.88 years, range: 12.10–16.75 years) and 22 control adolescents (14 boys, 8 girls with average age of 14.85 years, range: 12.0–16.9 years). All the ADHD adolescents received the complete Wechsler Intelligence Scale for Children-III (Wechsler, 1991) to obtain full intelligence quotients (IQ). The control adolescents were given the Information (fund of factual knowledge), Similarities (verbal reasoning), and Block design (nonverbal reasoning) subtests to provide the age-corrected estimate of IQ (EIQ). The EIQ obtained from this abbreviated version is reported to be highly correlated with IQ (Sattler, 1992). For entry into this study, all participants were required to have an IQ above 80. There were no group differences in IQ between ADHD cases and controls (average IQ for the case group: 101.15 ± 11.37; average IQ score for the control group: 103.34 ± 9.08; P = 0.562). Sixteen ADHD adolescents were receiving medication treatment during the period of the study. The disease and treatment characteristics of the ADHD subjects are reported in Table 1. Both the subjects and their parents gave written informed consents after a full explanation of the procedure of the study. This study was approved by both the Institutional Review Boards of Kaohsiung Medical University and Veterans General Hospital-Kaohsiung.

2.2. MRS acquisition and analysis

All MRS studies were performed on a 1.5 T MR system (General Electric, Milwaukee, WI) with a conventional single-voxel MR spectroscopy protocol (PRESS, echo time, 35 ms; repetition time, 1600 ms; 128 data averages).Two spectra were acquired from right and left prefrontal areas (part of the anterior cingulate gyrus and part of the medial frontal gyrus) for each subject according to the pre-scanned axial 3D T1 MR images (Fig. 1A) with voxel size of 8 cc ($20\times20\times20$ mm^3) by default. After global shimming, the signal intensity over the voxel was shimmed to achieve a typical full width at a half maximum (FWHM) of 4–8 Hz in the examination. Water-unsuppressed spectra were acquired automatically before applying the water-suppression sequence, which is provided with the GE scanner as a conventional protocol. Compounds that can be identified using proton MRS include the neuronal marker *N*-acetylaspartate (NAA), the glutamatergic resonance (Glu + Gln), creatine/phosphocreatine (Cr + PCr), glycerophosphorylcholine and phosphorylcholine (GPC + PC) and myo-inositol (Ins). MRS data files were subsequently analyzed by LCModel 6.1 fitting program as shown in Fig. 1(B). The LC Model method analyzes in vivo spectra as a linear combination of model in vitro spectra from individual metabolite solutions (Provencher, 1993; Provencher, 2001) Absolute levels in institutional units were obtained by using internal water signal as the concentration reference standard with partial volume correction. To ensure that differences in tissue concentration did not account for metabolite differences between subject groups, the tissue composition of each ^{1}H-MRS voxel was analyzed using an in-house program to determine the percentage of gray and white matter and CSF compositions in the voxel of interest. The segmentation algorithm was based on the method proposed by Herndon et al. (1998) with 3D T1 MR images. All segmented results were reviewed by experienced radiologists and, if necessary, adjusted manually to ensure the accuracy of the partial volume correction. A partial volume correction for the metabolite levels was performed on the basis of methods published earlier (Ernst et al., 1993; Kreis et al., 1993). Cramér-Rao lower bounds (S.D.% or CRLB) were calculated by the LCModel to evaluate the quantitative result of absolute levels. Only those levels of CRLB (i.e. S.D.%) less than 20% were considered reliable and were included for further statistical analysis.

2.3. Statistical analysis

Analysis of ^{1}H-MRS metabolites was carried out using SPSS for Window Version 13.0 (SPSS Inc., Chicago, IL). Group differences in absolute metabolites levels were tested with analysis of covariance (ANCOVA) with differences of voxel gray matter ratio, voxel white matter ratio, and age and gender controlled as covariants. Furthermore, metabolite ratios to Cr/PCr were calculated, respectively, for NAA, Myo-inositol, GPC + PC and GLu + Gln. These relative values were also compared between groups by ANCOVA with the above-mentioned parameters as covariates. A level of $P<0.05$ was used as the criterion of statistical significance.