



Research paper

Association of adult attention deficit hyperactivity disorder subtypes and response to methylphenidate HCL treatment: A magnetic resonance spectroscopy study

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HIGHLIGHTS

- The effects of MPH on NAA, Cho, and Cr are examined in different subtypes of ADHD.
- No significant change was determined in brain metabolite levels after MPH between the subtypes.
- Choline levels increased after MPH in striatum in combined type.

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ABSTRACT

The effects of methylphenidate (MPH) treatment on *N*-acetyl aspartate (NAA), choline and creatine are being examined in individuals with different subtypes of attention deficit hyperactivity disorder (ADHD). Sixty ADHD subjects were included into the study aging between 18 and 60 years. Levels of NAA, creatine and choline in anterior cingulate cortex, cerebellum, striatum and dorsolateral prefrontal cortex were measured with magnetic resonance spectroscopy. Then, 10 mg oral MPH was given to the subjects and the same metabolite levels were measured after an interval of 30 min. Distribution of the patients according to the ADHD subtypes was as follows: 21 of them (35.0%) were in the inattentive type, 11 of them (18.3%) were in the hyperactive type and 28 of them were (46.7%) in the combined type. Changes of brain metabolite levels after MPH were found not to be statistically significantly different between the subtypes. The increase of choline levels after MPH compared to the levels of choline before MPH in striatum in the combined type patients were statistically significant. No clear association was found between ADHD subtypes and changes of brain metabolites with use of MPH in adult ADHD.

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1. Introduction

Neuroimaging techniques have an important place to understand the structural and functional changes in attention deficit hyperactivity disorder (ADHD) related brain areas. Recent advances in these techniques also provide such further investigations on brain structures and functions in response to psychostimulant drug treatments. In structural neuroimaging studies; it was reported that there was reduction in brain regions including frontal lobe, cerebellum, corpus callosum, total and right brain and caudate nucleus

by volume [1]. In functional neuroimaging studies; the regional bloodstream and glucose metabolism were reported to decrease in prefrontal and cerebellar areas but to increase in parietooccipital cortex in resting state, and the symptoms to remit after psychostimulant drug treatment [2].

Magnetic resonance spectroscopy (MRS) is used in the differential diagnosis of diseases that have neurodegenerative activity. Since *N*-acetyl aspartate (NAA) is a marker of neuronal integrity, low NAA/ creatine (Cr) ratio is associated with neuronal loss or damage. Choline (Cho) reflects the membrane integrity and higher choline levels or Cho/Cr ratio results in higher cellular destruction, myelin destruction, gliosis and inflammation. Creatine is a relatively constant member of cellular energy metabolism [3].

In neuroimaging studies performed on patients with MRS in ADHD, it is reported that there were increases in the ratio of

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glutamate + glutamine/creatine (Glx/Cr) and in choline levels in anterior cingulate cortex (ACC) [4]. Jin et al. [5] found a decrease in the ratio of NAA/Cr and increase in the ratio of Cho/Cr and reported no significant changes in these ratios after single dose of methylphenidate (MPH). In a MRS study comparing the subtypes of adult ADHD, it was reported that there was a significant group difference in NAA concentration in the left dorsolateral prefrontal cortex (DLPFC) of patients with pure ADHD and that of healthy controls. Also, absolute concentration of NAA was reported to be significantly decreased only in the ADHD group. The authors speculated that since decrease of NAA reflects a state of neuronal dysfunction, these results indicated an evidence of subtle left prefrontal neuropathology in ADHD of adults [6]. Most of the neuroimaging studies supported impairment in frontostriatal-cerebellar circuit [7].

It was demonstrated that MPH effects the functions of fronto-striato-thalamic circuit, which is related with the pathophysiology of ADHD. It was reported that increased blood flow rate was determined in bilateral prefrontal, caudate and thalamic areas after MPH administration [2]. Methylphenidate is effective to provide sufficient attention via dopamine and serotonin system in neocortex and to filter unnecessary sensorial stimuli by normalising the excessive excitability in somatosensory cortex [2].

It is aimed to investigate the relation between ADHD subtypes and MPH treatment in adult ADHD patients and the changes in NAA, creatine and choline levels in ACC, cerebellum, striatum and DLPFC measured by MRS.

2. Materials and methods

Magnetic resonance spectroscopy studies were obtained and commented in Department of Radiodiagnostics, School of Medicine, Pamukkale University, Denizli. The protocol for the research project has been approved by Ethics Committee of Faculty of Medicine, Pamukkale University that conforms to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2000).

2.1. Subjects

A total of 60 patients between ages 18 and 60, meeting DSM-IV criteria for adult ADHD were admitted to the study. Written inform consent has been obtained from all the subjects. All patients were recruited from the research center and were of Turkish origin. Patients were evaluated with Wender–Utah rating scale (WURS) and adult attention deficit hyperactivity disorder diagnosis and evaluation scale. Patients, who scored 36 points or more on the WURS and answered at least 6 of the 9 questions as 2 or 3 points in the first and/or second parts of adult attention deficit hyperactivity disorder diagnosis and evaluation scale were diagnosed as ADHD.

The patients accompanying neurologic/chronic disease, mental retardation, psychotic disorder, psychiatric disorder due to organic reasons and who were illiterate were discarded from the study.

2.2. Instruments

2.2.1. Social demographic data form

A data sheet developed by the researchers for studying socio-demographic characteristics of study groups.

2.2.2. Wender–Utah rating scale (WURS)

This scale can be used to assess adults for attention deficit hyperactivity disorder with a subset of 25 questions associated with that diagnosis. WURS was developed by Ward and Wender in 1993 [8].

Turkish validity and reliability of WURS was established by Oncu and colleagues and the cut-off score point was 36 [9].

2.2.3. Adult ADD/ADHD DSM IV–based diagnostic screening and rating scale

Adult attention deficit hyperactivity disorder diagnosis and evaluation scale were developed by Turgay in 1995 [10]. It is a self assessment scale and patients can complete the questionnaire after being duly informed. When developing adult ADD/ADHD Scale, 18 symptoms of the diagnostic criteria in DSM-IV were reframed, so patients can understand them. The first part of this scale had 9 inattention questions and the second part had 9 hyperactivity/impulsivity questions. The third part of the scale consisted of the most frequently associated symptoms in ADHD that were not in DSM-IV ADHD diagnostic criteria. Turkish validity and reliability was established by Gunay et al. [11].

2.3. Magnetic resonance spectroscopy (MRS)

The study was performed by 1.5 Tesla magnetic resonance device (GE Medical System, Milwaukee, WI, USA) with using a standart head coil. Magnetic resonance protocol was as follows: horizontal plane, 10 mm thickness, TR/TE: 3000/88.2, FOV: 10, Matrix: 512 × 512, Next:1. T2 weighted fast spin echo (FSE) sequences were obtained by using aforementioned parameters. MRS was performed by using single voxel (1H-voxel) technique that were placed in each ACC, striatum, cerebellum, and DLPFC areas. Volume of interest (VOI) was placed on the related areas manually and visually with surely aware of containing the related brain tissue and on predominantly determined areas. Chemical shift selective pulse (CHESS) process was used to inhibit water derived signals. Following CHESS, point-resolved spectroscopy (PRESS) technique was used (TR/TE: 3000–35). Consequently, short-time TE spectrums were obtained from the VOI of ACC, striatum, cerebellum and DLPFC areas and the metabolite ratios obtained by “General Electric Software Spectral Analysis Programme” were evaluated.

¹H MRS analysis were performed by an expert radiologist and NAA, Cho, Cr values were measured at the ACC, striatum, cerebellum and DLPFC areas. Oral MPH (10 mg) was given to the patients and NAA, Cho, Cr values were measured again after an interval of 30 min.

2.3.1. Statistical analysis

SPSS (statistical package for social sciences) version 16.0 for Windows computing program was used for statistical analysis of the data. Kolmogorov–Smirnov test was used for normality. Two-way ANOVA for repeated measures test was performed to compare the effects of MPH on brain metabolite levels between the subtypes of ADHD. A *p* value of <0.05 was accepted statistically significant. To determine the effects of MPH on brain metabolite levels in each subtype, the study group was divided into three groups according to the subtypes of ADHD. So far, a *p* value of <0.017 (0.05/3) was accepted statistically significant. For each subtype, the change in brain metabolite levels after MPH was analyzed by paired *t* test.

3. Results

Mean age of the patients was 28.98 ± 7.66 (18–59) and 12 (20.0%) of them were female (ADHD subtypes: 6 inattentive type, 6 combined type) and 48 (80.0%) of them were male (ADHD subtypes: 15 inattentive type, 11 hyperactive type, 22 combined type). Distribution of the patients according to the ADHD subtypes was as follows: 21 of them (35.0%) were in the inattentive type, 11 of them (18.3%) were in the hyperactive type and 28 of them were (46.7%) in the combined type.

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