Original Article

Relationship between Antioxidant Status and Attention Deficit Hyperactivity Disorder Among Children

Abstract

Background: Attention deficit hyperactivity disorder (ADHD) is one of the prevalent neuropsychiatric disorders in childhood. In general, diagnoses of ADHD include inattention, hyperactivity, and impulsivity. Recent studies have reported increased oxidative stress in psychiatric disorders such as ADHD, but the results are conflicting. This research aimed to study the relationship between antioxidant status and ADHD in children of 6–13 years old. **Methods:** From schools, 32 ADHD students whose diseases were diagnosed by child and adolescence psychiatrist based on Diagnostic and Statistical Manual of Mental Disorders-IV index were recruited; moreover, 32 healthy subjects, which according to the medical history questionnaire of psychiatric disorder had not had chronic disease, were selected. Total antioxidant capacity (TAC), catalase (CAT), glutathione (GSH), and malondiadehyde (MDA) were measured. General information, health history, and medication history were collected. All participants completed a 168-item food frequency questionnaire. Dietary intakes of antioxidants were obtained through this questionnaire. **Results:** There was no significant difference between mean of energy intake and Zn, Se, vitamin E, C, and β-carotene as antioxidants between the two groups. The mean of serum TAC, GSH level, and CAT level in the patients were significantly lower than the healthy group ($P < 0.001$), but the mean of MDA was not significantly different between the two groups ($P = 0.18$). **Conclusions:** The result of this study indicates that, in ADHD, the serum levels of GSH, CAT, and TAC decrease; the level of antioxidant in the serum has been compromised to fight oxidative stress. More perspective studies with large sample sizes are essential to confirm these findings.

Keywords: *Antioxidant, attention deficit hyperactivity disorder, children, oxidative stress*

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Introduction

Attention deficit hyperactivity disorder (ADHD) is the most common behavioral disorder and one of the prevalent neuropsychiatric disorders in childhood.[1-3] ADHD is diagnosed almost in all patients before the age of 16, and this disease continues to adolescence in about 60% of patients and improves between the ages of 12 and 20.[4-6]

ADHD is a general problem worldwide and in children has led to an increase in public health concerns.[7,8] The global prevalence of ADHD in children and adolescents has been reported from 5% to 10% and that in Iranian school-age children is 9.7%.[9,10] ADHD is more common in boys, and the proportion of this disorder varies from 2 to 9 times in boys to girls.[11,12] The main symptoms of ADHD based on Diagnostic and Statistical Manual of Mental Disorders-IV criteria include a sustained pattern: (1) attention deficit, (2) hyperactivity, and (3) impulsivity (incidence of sudden behaviors without thinking) is disproportionate to age.[13-15] Children with ADHD may also experience more negative social events and have less social skills. These patients have symptoms of motor function, disturbance in family relationships, and peers. Educational failure, weakness of self-esteem, depression, aggression, anxiety, learning disability, antisocial behavior, and occupational problems are the symptoms of this disorder.[5,6,16,17] The cause of ADHD is still unclear although biochemical, genetic, psychological, environmental factors, neurochemical, and neuroanatomical disorders are involved in the etiology of ADHD.[9,18] Certain areas of the brain that are connected with attention have a defect in neuronal transmission.[19] Researchers believe that biomedical factors such

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as changes in the catecholamine's signal, deficiency, imbalance, or inefficiency of neurotransmitters, which includes dopamine, serotonin, and noradrenaline, and the slowness of the inhibitory activity of the brain play a role in the development of ADHD.[5,20,21] Dietary factors such as lack of micronutrients (zinc, copper, and omega-3) and nutritional behaviors may contribute to the development of ADHD.[10,22]

More research on ADHD focused on genetic factors and less concentrated on mechanisms and other factors involved in it. One of these factors is oxidative metabolism.[23] Several studies have shown that neuronal damage by oxidants plays an important role in the pathophysiology of mental disorders. In various studies, the relationship between ADHD and oxidative stress has been investigated.[24,25] Free radicals such as superoxide and radical hydroxyl ions (OH^-), which are called reactive oxygen species (ROSs), may be produced excessively during the natural processes of metabolism. Despite the very short half-life, these compounds have a strong tendency to combine with fats, proteins, and DNA in nervous and non-neuronal cells.[23,26] ROS reacted with the proteins in the membranes to prevent the normal intake of enzymes and neurotransmitters. Furthermore, it is associated with the death of neurons in many neurological disorders such as psychiatric disorders.[27,28] Cells and biological fluid contain enzymes and nonenzymatic antioxidants that act together to protect cells from oxidative damage and prevent the formation of radicals.[29] After the adipose tissue, the organ that has the highest fat content is the brain.[30] This tissue has the most sensitivity to oxidative stress than other tissues due to its high content of peroxidizable long-chain fatty acid, high mitochondrial activity, relatively low antioxidant content, and high glucose uptake, which is a process with high free radical production.[31–33]

Few studies have been conducted on relation between ADHD and antioxidants. Based on the results of previous studies on the theory of oxidative stress and its destructive role in the nervous system, the present study compares the possible changes in oxidative and antioxidant parameters in ADHD children with healthy individuals.

Methods

This case–control study, which was conducted in Isfahan province, Iran, was carried out from October 2016 to January 2017.

The exclusion criteria in this study for the subjects include the use of antioxidant supplements, multivitamins, minerals, and omega-3s over the past 1 year, and smoking and lack of co-operation of the participants in the study or their families with project executive. In addition, patients who had taken another medicine apart from Ritalin were excluded from the study. Written consent was obtained from all subjects, and the stages of the plan were explained to all the subjects. After at least 8 h of fasting and physical inactivity, all participants were taken venous blood samples. Antioxidant parameters including total antioxidant capacity (TAC), catalase (CAT), glutathione (GSH), and malondiadehyde (MDA) were measured in this study. The venous blood samples were then centrifuged for about 10 min with 3000 rpm. The serum was isolated at 80°C until the time of analysis. General information, health history, and medication history were collected using demographic questionnaire. Height in standing position without shoes with the precision of 0.5 cm and weight with light clothing without shoes were measured at a precision of 100 g. Information about physical activity was obtained through Baecke physical activity questionnaire. Validity and reliability of this questionnaire have already been validated.[34] To evaluate the dietary intakes of antioxidants (Vitamin E, C, Se, Zn, and β-carotene), all participants completed a 168-item food frequency questionnaire (FFQ) whose validity and reliability were confirmed.[35] The subjects were asked to indicate the frequency of their intake of any food in relation to its amount over the past year. The quantities listed for each food product were converted to gram per day according to the household measures. Analysis of FFQ data was performed using N4 nutritional software. Serum levels of MDA were measured by the spectrophotometric method using reagent thiobarbituric acid.[36] The CAT activity was measured by the spectrophotometric method based on the rate of reduction of optical absorption of hydrogen peroxide (H2O2).[37] Ellman (DTNB) was used as a reagent to measure GSH.[38] The TAC of the serum was measured by Rise *et al.*'s method.[39]

Statistical analysis

Data were analyzed by independent *t*-test and Pearson's correlation coefficient. The level of significance in all tests is considered 0.05. SPSS v. 22 software was used to analyze the statistical measurements. Descriptive analysis was used to describe the demographic data and clinical data of the research samples.

Result

In this study, 36 patients and 32 healthy people were selected. Demographical values of patients and control groups are shown in Table 1. In the patient group, 35 patients (97.2%) used Ritalin, but in the healthy group, no one had a history of Ritalin intake. Independent *t*-test showed that there was no significant difference between the two groups in mean of age, weight, height, BMI, leisure time points, and sports score.

As shown in Table 2, the mean of TAC, GSH, and CAT levels in the patients was significantly lower than the healthy group ($P < 0.001$), but the mean of MDA was not significantly different between the two groups ($P = 0.18$).

Table 3 shows that there was no statistically significant difference in Zn, Se, vitamin E, vitamin C, β-carotene, and energy, which includes carbohydrate (CHO), fat, and protein (Pro) intake, between the two groups.

Table 1: Demographical values of the ADHD and control groups

Variables	Patients' group (*n*=36) mean±SD	Healthy group (*n*=32) mean±SD	*P*
Age (year)	9.4±1.6	9.5±1.9	0.68
Weight (kg)	30.9±5.9	35.1±12.3	0.07
BMI (kg/m^2)	16.9±2.5	17.8±3.8	0.25
Leisure time score	2.72±0.73	2.52±0.43	0.53
Sports score	2.93±0.79	2.95±0.74	0.97

ADHD=Attention deficit hyperactivity disorder, SD=Standard deviation, BMI=Body mass index

Table 2: Comparison of the oxidative stress parameters among ADHD and control groups

Parameters	Patients' group	Healthy group	*P*
TAC (mg/dL)	53.5±31.1	141.02±57.3	<0.001
GSH (nmol/L)	13.7±2.5	18.9±4.3	<0.001
CAT (U/mL)	16.4±5.9	22.1±6.2	<0.001
MDA (nmol/L)	201.8±36.8	190±28.3	0.18

TAC=Total antioxidant capacity, GSH=Glutathione, CAT=Catalase, MDA=Malondialdehyde

Table 3: Comparison of dietary antioxidants and energy intake in ADHD and control groups

Variables	Patients' group	Healthy group	*P*
Vitamin E (mg)	8.72±3.94	8.92±6.08	0.87
Vitamin C (mg)	176.9±88.6	194.5±68.04	0.37
Se (mcg)	0.102±0.054	0.101±0.060	0.98
Zn (mg)	9.7±4.8	10.5±6.7	0.58
β-carotene (mcg)	902.1±725.1	1126.7±1091.7	0.31
Energy intake (kcal)	2104.6±130.5	2153.2±181.2	0.50
CHO intake (percent of calorie)	53.13±10.18	47.74±12.29	0.061
Fat intake (percent of calorie)	30.69±9.98	35.70±14.79	0.117
Pro intake (percent of calorie)	14.04±3.44	12.39±4.29	0.095

Se=Selenium, Zn=Zinc, CHO=Carbohydrate, Pro=Protein

Pearson's correlation coefficient showed that there was no significant relationship between dietary antioxidant levels (vitamin E, C, Se, Zn, and β-carotene) with serum antioxidants and MDA in the healthy and patient groups ($P > 0.05$) [Table 4].

GSH level and TAC were not significantly correlated with any dietary antioxidants ($P > 0.05$) [Table 4].

Discussion

The aim of this study was to measure the levels of serum and dietary antioxidants intake, and MDA is used as an oxidant marker in ADHD patients in comparison with healthy people. The results showed that in the case group the serum levels of GSH, CAT, and TAC decrease, but the mean of MDA was not significantly different between the two groups. In addition, there was no statistically significant differences in Zn, Se, vitamin E, vitamin C, β-carotene, and energy, which includes carbohydrate (CHO), fat, and protein (Pro) intake, between the two groups. In the study of Karababa *et al.*, the relationship between total antioxidant status and ADHD was not observed.[24] In Karababa *et al.*'s study, however, the measurement of oxidation parameters and age group was different from this study. The findings of Hatice Sezen, regarding the overall antioxidant status, was consistent with this study results.[40] TAC is one of the important indicators of oxidative stress,[41] as it determines the synergistic effect of different antioxidant compounds in the sample. However, TAC does not evaluate all the antioxidant components and the important role of enzymes such as SOD, CAT, and GPX; consequently, the data should be interpreted with caution.[42] In this study, reducing the antioxidant capacity in the patient group is likely to contribute to the progression of ADHD by strengthening the mechanism that increases the levels of oxidant.[9] Another finding of this study is that CAT levels were significantly lower in children with ADHD than in the control group. On the other hand, V. Kanak Celik *et al.* did not see the relationship between CAT levels and ADHD. The study included children who had ADHD recently diagnosed. Probably, at the beginning of the disease, antioxidant enzymes against oxidative stress have created a high potential protection.[29]

Table 4: Pearson correlation coefficients between dietary antioxidants level with the oxidative stress parameters in the patient and healthy groups

Variables	CAT		GSH		TAC		MDA	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Vitamin E	−0.054	0.66	−0.021	0.86	0.102	0.40	0.07	0.57
Vitamin C	−0.054	0.66	0.016	0.89	0.120	0.32	−0.112	0.36
Se	−0.084	0.63	−0.037	0.83	−0.181	0.29	−0.102	0.55
Zn	−0.115	0.50	−0.118	0.49	−0.153	0.37	−0.146	0.40
β-carotene	−0.134	0.27	0.110	0.37	0.013	0.91	−0.025	0.83

CAT=Catalase, GSH=Glutathione, TAC=Total antioxidant capacity, MDA=Malondialdehyde, Se=Selenium, Zn=Zinc

The serum GSH level in this study was significantly lower in the patients than in the control group; any human study for GSH levels in children with ADHD was not found. The results of Douglas Teixeira Leffa *et al.*'s study indicate that the brain GSH is not different from those of ADHD and healthy mice.[43] The findings of this study show that although the mean antioxidant markers in ADHD patients were significantly lower than the healthy group, there was no significant difference in serum MDA between the two groups. A study by Dimem Oztop reported a decrease in the MDA level in ADHD patients; in this study, oxidative stress may be reduced due to hypodopaminergic conditions.[27]

On the other hand, the reason for this contradiction with his study may be due to the geographical locations and the gender groups. On the other hand, recent studies have reported an increase in oxidative stress in adults with ADHD. However, a similar increase in children in this study was not observed in children. In the study of Muhmut Bulut *et al.*, which was conducted on adults with ADHD, the results showed that the serum levels of MDA were higher in patients than in healthy subjects. Differences in the findings may be due to the fact that children are less exposed to environmental risk factors that increase oxidative stress such as toxin, psychological stress, smoking, and alcohol.[44,45] In addition, when only one oxidant parameter such as MDA is measured, it may be possible that the reduction or not change of the parameters is observed. Despite the actual increase in the oxidation state.[9] On the other hand, the lack of difference in this oxidant parameter may be related to the consumption of Ritalin by patients. Previous studies have shown that methylphenidate treatment in children with ADHD may have protective effect on oxidative stress.[18] Long-term exposure to oxidative toxin in adults,[45] measuring only one oxidative stress marker or the protective effect of Ritalin[18] are some of the important factors that can cause this difference in these findings. The most important limitation of our study is the small sample size, and few oxidative stress markers were detected.

Conclusions

The result of this study indicates that, in ADHD, the serum levels of GSH, CAT, and TAC decrease; and the level of antioxidant in the serum has been compromised to fight oxidative stress. Although this study aims to identify the antioxidant agents with ADHD, the findings may help to prevent or treat ADHD. However, more perspective studies with large sample sizes are essential to confirm these findings.

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Conflict of interest

There are no conflicts of interest.

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