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Plasma Leptin, Adiponectin, Neuropeptide Y Levels in Drug Naive Children With ADHD

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Abstract

Objective: ADHD is one of the most common childhood psychiatric disorders. Research indicates that there is some link between obesity/overweight and ADHD, though the mechanism of this association remains uncertain. It is the aim of the present study to explore the association between ADHD, obesity, and plasma leptin, neuropeptide Y (NPY), and adiponectin levels. **Method:** Thirty-six patients diagnosed with ADHD were included in the study. The control group consisted of 40 healthy children and adolescents who had similar age and gender features with the patient group. Plasma leptin, adiponectin, NPY levels were measured, and body mass index (BMI), weight for height, and standard deviation scores (SDS) of height, weight, and BMI were calculated. **Results:** No significant difference was found between patients and healthy children in terms of BMI and BMI percentile. Participants were classified into three groups according to their weight to height values. There was no significant difference between the two groups, but 10% of the control group and 30.6% of the ADHD group were classified as overweight, which was 3 times higher than the control group. The adiponectin plasma level was significantly lower and leptin/adiponectin (L/A) ratio was significantly higher in the ADHD group. There was no significant difference between serum NPY levels. In the ADHD group, the mean leptin plasma level was high, but was not statistically significant. **Conclusion:** We think that a low adiponectin level and high L/A ratio may be the underlying mechanism of the obesity in ADHD patients. *(J. of Att. Dis. 2018; 22(9) 896-900)*

Keywords

leptin, adiponectin, NPY, attention deficit hyperactivity

Introduction

ADHD is one of the most common childhood psychiatric disorders, with an estimated worldwide prevalence of about 5% among school-aged children (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). According to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; *DSM-IV*; American Psychiatric Association, 1994), ADHD is characterized by a pattern of pervasive, impairing, and developmentally inappropriate symptoms of inattention and/or impulsivity-hyperactivity. ADHD is associated with impairments in emotional, social, familial, academic, and behavioral functioning (DuPaul, McGoey, Eckert, & VanBrakle, 2001).

It is well known that ADHD is often associated with other disorders, which contributes to the functional impairment of the patient. Commonly reported psychiatric comorbid disorders include oppositional defiant disorder, conduct disorder, anxiety disorder, depressive disorders, and speech and learning disorders (Biederman & Farone, 2005). However, sleep/alertness disturbances and eating disorders associated with ADHD have been quite overlooked in researches as well as in clinical practice. However, increasing empirically based evidence has suggested a significant association between ADHD and abnormal feeding behaviors (Cortese, Bernardina, & Mouren, 2007; Güngör, Celiloglu, Raif, Ozcan, & Selimoglu, 2013; Holtkamp et al., 2004; Stulz et al., 2013). In a recent review, all included clinical studies reported a higher than average body weight in participants with ADHD (Cortese et al., 2008). Although research suggests that there is a possible link between obesity/overweight and ADHD, the mechanism of this association remains uncertain (Cortese et al., 2008; Elmquist & Scherer, 2012; Holtkamp et al., 2004).

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Several peptides such as leptin, adiponectin, and neuropeptide Y (NPY) are involved in the regulation of food intake and energy expenditure (Ahima, Qi, & Singhal, 2006). These are the major molecules that influence appetite and weight gain; however, their behavior in the case of obesity/overweight in ADHD is not clear. The aim of the present study is to explore the association between ADHD and obesity and to observe plasma leptin, NPY, and adiponectin levels in those children.

Method

Thirty-six patients diagnosed with ADHD (between the ages of 6 and 13 years) in the Child and Adolescent Psychiatry Department, Inonu University Faculty of Medicine, between February and April 2013 were included in the study. The control group consisted of 40 healthy children and adolescents who had similar age and gender features with the patient group. The study was approved by the Inonu University Ethics Committee. In addition, written informed consents were obtained from the parents of the children who participated in the study.

Diagnosis was made by two experienced child and adolescent psychiatrists using *DSM-IV* criteria and the Turkish version of Kiddie Schedule for Affective Disorders and Schizophrenia of School-Age Children–Present and Lifetime Version (K-SADS-PL; Gökler, 2004). The K-SADS-PL is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology according to *DSM-IV* for psychiatric disorders in school-aged children and adolescents (Kaufman et al., 1997).

The patients received a diagnosis of ADHD for the first time and medical treatment was not initiated. According to the psychiatric examination, all patients had normal intelligence (Wechsler Intelligence Scale for Children, Revised Form [WISC-R]).

Children using drugs that might affect appetite, who had exercise programs, who had chronic diseases, and who were on any diet were excluded.

Age, height, and weight of the cases were recorded. Body mass index (BMI), weight for height (WFH), and standard deviation scores (SDS) of height, weight, and BMI were calculated for all patients enrolled in the study. BMI percentile curves established for Turkish children were used for the evaluation, and cutoffs used were as follows: (a) malnutrition, <5th percentile; (b) normal, ≥5th but ≤85th percentile; (c) overweight, 85th to 95th percentile; and (d) obesity, ≥95th percentile (Neyzi et al., 2006).

For plasma leptin, adiponectin, and NPY levels measurement, venous blood samples were obtained under sterile conditions in the morning and after fasting for at least 8 hr. Samples were numbered and centrifuged at +4 °C 3,500 rpm. The plasma part of the blood was separated, the obtained samples were stored in polypropylene plastic tubes at −80 °C until analysis.

The following kits were used: Leptin, DIAsource ImmunoAssays S.A; NPY, Phoenix; Adiponectin, BioSource company's commercial kits were studied in the Basic RadimImmunoassay Operator (BRIO); and RadimSpA, Pomezia, Italy brand device using the Enzyme-Linked ImmunoSorbent Assay (ELISA) method. In accordance with the manufacturer's instructions, analysis results were expressed in μg/mL for adiponectin and ng/dL for leptin and NPY.

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SPSS 17. 0 was used for statistical analyses. The Mann-Whitney *U* test and Pearson's correlation test were used for assessment of the relationship between different parameters. The relationship between BMI and leptin, adiponectin, and NPY levels in both ADHD and control group was evaluated with Spearman's rank correlation test. The level of significance for this study was $p < .05$.

Results

Overall, data from 36 patients (drug naive) and 40 healthy children were analyzed. Regarding subtypes, 11 (30.6%) of the ADHD cases were predominantly inattentive and 25 (69.4%) were combined. Of patients, 29 (80.6 %) were boys and 7 (19.4 %) were girls, and the mean age was 9.3 ± 1.78 years. No significant difference was found between patients and healthy children in terms of age ($p = .247$) and gender ($p = .410$; Table 1).

With regard to BMI percentiles, in the control group, 35 (87.5%) patients were normal, 1 (2.5%) was overweight/obese, and 4 (10%) patients were underweight. In the ADHD group, according to BMI percentiles, 27 (75%) patients were normal, 5 (13.9%) patients were overweight/obese, and 4 (11.1%) were underweight. No significant difference was found between the two groups in terms of weight, height, and BMI SDS (Table 1).

Furthermore, when children were evaluated according to the BMI percentiles and WFH scores, no statistical significance was found, though 10% of the control group and 30.6% of the ADHD group were classified as overweight, which was 3 times higher than the control group (Table 2).

Plasma adiponectin level was significantly lower ($p = .003$) and leptin/adiponectin (L/A) ratio was significantly higher ($p = .009$) in the ADHD group compared with healthy children. There was no significant difference between serum NPY levels in the ADHD group versus the healthy children group ($p = .225$). In the ADHD group, the mean leptin plasma level was higher, but was not statistically significant (Table 3).

When relationship between BMI and leptin, adiponectin, and NPY levels in both ADHD and control group was evaluated, it was found out that there was positive correlation between BMI and leptin level in both groups (Table 4).

Table 1. Means and Standard Deviations for Variables Used in Analysis of the Two Groups.

	Controls (n = 40) $M \pm SD$	ADHD (n = 36) $M \pm SD$	p
Age (years)	8.87 ± 2.13	9.30 ± 1.78	.247
Gender (%)			
Male	29	29	.410
Female	11	7	
Weight SDS	−0.06 ± 1.01	0.16 ± 1.19	.409
Height SDS	−0.13 ± 1.01	−0.20 ± 1.34	.763
BMI SDS	0.03 ± 1.15	0.39 ± 1.48	.238
Weight for height	97.40 ± 11.99	102.52 ± 17.99	.204

Note. SDS = standard deviation scores; BMI = body mass index.

Table 2. Nutritional Status of the Patients and Healthy Children According to Weight for Height Ratios.

Weight for height value	<89 (malnutrition) n (%)	90 to 110 (normal) n (%)	>110 (overweight) n (%)
ADHD	8 (22.2)	17 (47.2)	11 (30.6)
Control	10 (25)	26 (65)	4 (10)
Total	18 (23.7)	43 (56.6)	15 (19.7)

Note. p = .075.

Table 3. Serum Leptin, Adiponectin, NPY Levels, and L/A Ratio of the Two Groups.

	Control	ADHD	p
Leptin	3.35 ± 3.84	5.97 ± 7.18	.110
Adiponectin	16.42 ± 8.78	10.77 ± 6.05	.003
NPY	493.80 ± 205.00	565.40 ± 245.03	.225
L/A	0.23 ± 0.24	0.81 ± 1.19	.009

Note. NPY = neuropeptide Y; L/A ratio = leptin/adiponectin ratio.

Table 4. Relationship Between BMI and Leptin in ADHD and Control Group According to the Spearman's Rank Correlation Test.

	Leptin (r)	p
BMI		
ADHD	.708	.0001
Control	.509	.001

Note. r = correlation confident; BMI = body mass index.

Discussion

Recent studies suggest an association between ADHD and obesity. Moreover, available studies show that individuals with ADHD have higher-than-average BMI z scores and/or a significantly higher prevalence of obesity compared with participants without ADHD. Three mechanisms underlying the association between ADHD and obesity have proposed that (a) it is possible that obesity and/or factors associated with it (such as sleep-disordered breathing) manifest as ADHD-like symptoms; (b) ADHD and obesity share common biological dysfunctions, involving the dopaminergic and, possibly, other systems (e.g., brain-derived neurotropic factor, melanocortin-4-receptor); and (c) the impulsivity and inattention of ADHD contributes to obesity (Cortese & Morcillo Peñalver, 2010; Cortese & Vincenzi, 2012).

Holtkamp et al. (2004) studied 97 inpatient and outpatient boys with ADHD and found that, the mean BMI *SD* of the ADHD patients was significantly higher than the age-adapted reference values. The proportion of obese (7.2%) and overweight (19.6%) participants was significantly higher than the estimated prevalence. Hubel, Jass, Marcus, and Laessle (2006) obtained significant differences in the BMI SDS and basal metabolic rate between the ADHD and the control group, but not between the ADHD subgroups. Also, Lam and Yang (2007) obtained results suggesting that adolescents who exhibit a higher tendency toward ADHD are more likely to be overweight or obese. In our recent study (Güngör et al., 2013), we found that the frequency of malnutrition and overweight/obesity is higher among the ADHD group compared with control group, suggesting that ADHD is a risk factor for development of eating disorders due to behavioral problems such as irregular eating habits. Biederman et al. (2003) compared weight and height in a sample of 140 ADHD girls and 122 female controls aged between 6 and 17 years and reported that the age and height corrected weight index of the ADHD participants was

greater than average, but there was no significant difference between the two groups. All these studies suggest a positive association between ADHD and overweight/obesity.

However, some studies reported that ADHD does not have any effect on overweight or obesity. Dubnov-Raz, Perry, and Berger (2001) reported that the prevalence of overweight and obesity was lower in 6- to 16-year-old 275 ADHD cases without neurological comorbidity after a 17-month follow-up when compared with a control group, and the national and regional prevalence for the same age group.

Feeding induces a release of melatonin, secretin, cholecystokinin, leptin, ghrelin, vasoactive intestinal peptide, gastrin-releasing peptide, somatostatin, and NPY (El-Sherif, Tesoriero, Hogan, & Wierasko, 2003). There are few publications regarding the pathogenesis of association between ADHD and weight gain. Proposed mechanisms include increased leptin and NPY levels and a decrease in plasma levels of adiponectin.

Leptin is a hormone produced by adipocytes, which provides signals to specific regions of the hypothalamus to control energy homeostasis and, it also regulates the development and function of feeding circuits, and influences hippocampal-dependent learning and memory as well. Moreover, leptin-induced alterations in neuronal excitability have been implicated in the regulation of food intake, reward behavior, and anticonvulsant effect (Bouret & Simerly, 2004). Reda and El-Hadidy (2011) and Flier (2004) reported a positive correlation between BMI and serum leptin hormone levels. An earlier study by Jequier (2002) reported that sex is an important factor in determining plasma leptin, with women having markedly higher leptin concentrations than men for any degree of fat mass. This contradicted our results, as there was no significant correlation between sex, BMI, and serum leptin. In our study, there was no significant difference in leptin plasma levels between the two groups. NPY is a potent appetite-enhancing hormone. NPY has both a central and peripheral effect on the regulation of the appetite. NPY reduces glucose uptake in muscle tissue and stimulates insulin-dependent glucose uptake in adipose tissue (Spitzweg, & Heufelder, 1997). Leptin plays an important role in the control of food intake and energy balance and reduces appetite and nourishment through the central inhibition of NPY secretion (Schwartz, Woods, Porte, Seeley, & Baskin, 2000).

Adiponectin is an appetite-reducing hormone synthesized in fat tissue. In the case of obesity, adiponectin level decreases; however, weight loss causes increase in plasma adiponectin levels (Yang et al., 2001). Diamond, Cuthbertson, Hanna, and Eichler (2004) reported that L/A ratio might be a more sensitive indicator for obesity compared with leptin and adiponectin separately. In addition, Li et al. (2009), stated that an increase in the plasma adiponectin level and a decrease in the L/A ratio causes loss of appetite. Based on these results, we can affirm that a decrease in the adiponectin plasma level and an increase in the L/A ratio might be related to an increase in appetite and weight gain. The results of our study supported this theory. We thought that an increase in leptin and NPY plasma levels and a decrease in the adiponectin plasma level might be the underlying mechanism of the obesity in ADHD patients. A low adiponectin level and high L/A ratio in the ADHD group supported our hypothesis. Also positive correlation between BMI and leptin levels in both groups is noteworthy.

It is important, however, to emphasize that the links between ADHD and obesity could also be mediated by many other factors not examined in this study. A limitation of this study is the small sample size.

Conclusion

As a result of this study, we think that a low adiponectin level and high L/A ratio may be the underlying mechanism of the obesity in ADHD patients. Although the literature on overweight, obesity, and ADHD has been growing every day, there is little attempt to examine the association between overweight/obesity and ADHD. Future research should further investigate the casual link between obesity and ADHD and explore potential common neurobiological alterations.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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