Original article / *Araştırma*

Might BPA and phthalates have a role in etiopathogenesis of ADHD?

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ABSTRACT

Objective: *Although the etiology ofattention deficit hyperactivity disorder (ADHD) is unknown, it is thought that endocrine disruptors may be involved in the etiopathogenesis. The aim of this study was to investigate the relationship between ADHD development and exposure to mono-(2-ethylhexyl) phthalate (MEHP), di-(2-ethylhexyl) phthalate (DEHP), and bisphenol A (BPA).* ***Methods:*** *The study included 44 children who were diagnosed with ADHD according to DSM IV-TR diagnostic criteria and 51 healthy children as controls. In all subjects, serum MEHP, DEHP, and BPA were measured by using high performance liquid chromatography (HPLC).* ***Results:*** *Serum MEHP and BPA levels were found to be significantly higher in the ADHD group (0.47±0.22 µg/ml, 1.48±0.28 ng/ml) than the controls (0.31±0.13 µg/ml, 0.91±0.23 ng/ml). There was no difference in the level of DEHP between the ADHD group and healthy controls (2.17±0.69 µg/ml, 2.26±0.56 µg/ml).* ***Conclusion:*** *Our results could be accepted as an evidence to support an association between BPA, MEHPlevels and ADHD. However, further studies are needed to clarify the linkage between ADHD and endocrine disruptors.* ***(Anatolian Journal of Psychiatry 2018; 19(3):300-306)***

Keywords: *ADHD, children, bisphenol A, phthalates, etiology.*

DEHB etiyopatogenezinde BPA ve fitalatların rolü olabilir mi?

ÖZ

Amaç: *Dikkat eksikliği hiperaktivite bozukluğunun (DEHB) etiyolojisi tam olarak bilinmemekle birlikte, etiyopatogenezinde endokrin bozucuların rol oynadığı düşünülmektedir. Bu çalışmanın amacı, ADHD gelişimi ile mono- (2-etilheksil) fitalat (MEHP), di- (2-etilheksil) fitalat (DEHP) ve bisfenol A'ya (BPA) maruz kalma arasındaki ilişkiyi araştırmaktır.* ***Yöntem:*** *Çalışmaya, DSM-IV-TR tanı ölçütlerine göre DEHB tanısı konan 44 çocuk ve kontrol grubu olarak 51 sağlıklı çocuk alındı. Tüm olgularda, serum MEHP, DEHP ve BPA, yüksek performanslı sıvı kromatografisi (HPLC) kullanılarak ölçüldü.* ***Bulgular:*** *Serum MEHP ve BPA düzeyleri DEHB grubunda (0.474±0.223 µg/ml, 1.485±0.285 ng/ml) kontrole (0.311±0.134 µg/ml, 906±0.232 ng/ml) göre istatistiksel olarak anlamlı yüksek bulundu. DEHP düzeyleri açısından her iki grup karşılaştırıldığında aralarında anlamlı fark bulunmadı (2.168±0.694 µg/ml, 2.262±0.565 µg/ml).* ***Sonuç:*** *Çalışmamızın sonuçları MEHP ve BPA düzeyleri ile DEHB arasındaki ilişki olduğunu destekler nitelikte kabul edilebilir. Bununla birlikte, DEHB ve endokrin bozucular arasındaki bağlantıyı açıklığa kavuşturmak için daha ileri çalışmalara gerek vardır.* ***(Anadolu Psikiyatri Derg 2018; 19(3):300-306)***

Anahtar sözcükler: *DEHB, çocuk, bisfenol A, fitalat, etyoloji*

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Received: October, 10th 2017, Accepted: December, 11th 2017, doi: 10.5455/apd.280093

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood, which manifests with symptoms of attention and cognitive deficits, hyperactivity and impulsivity.[1] ADHD is becoming an important health concern with a nearly 30% increase inprevelanceduring the last decade worldwide.[2]

Although it is known that ADHD is a heterogeneous disorder involving multiple causes and risk factors, its etiology hasnot yet been fully elucidated. In recent years, a significant increase in the incidence of ADHD has emphasized the need to investigate the factors that may be involved in ADHD etiology. In general, the majority of hypotheses related to ADHD etiology focus on brain dysfunction, neurological, genetic, psychosocial and environmental factors.[3]

It is known that bisphenol A (BPA) and phthalates are endocrine disruptors which have harmful effects on human health. BPA is an important chemical endocrine disruptor which is often encountered during daily life. People are exposed to it requently due to its use in the production of polyvinyl chloride (PVC) plastics, paint and plastic film lining the inner surface of beverage tins, compact discs, and feeding bottles.[4] Phthalates are industrial compounds belonging to phthalic acid esters that are commonly used to give transparency, elasticity, and strength to plastics in personal care products and to soften plastics in toys, household items such as food containers, and medical devices.[5] Phthalates are not chemically bound to the plastics, and in fact disperse into the environment easily, leading to exposure via inhalation, and dermal contact, resulting in widespread exposure.[5,6] Di- (2-ethylhexyl) phthalate (DEHP) is one kind of phthalate which is used in medical products such as intravenous tubes, bags, catheters, nasogastric tubes, and intubation tubes. Mono-(2-ethylhexyl) phthalate (MEHP) is known to be one of the most toxic metabolites of DEHP.[5-7]

The potential role of exposure to environmental chemicals on the risk of developing child behavioral problems and ADHD has been investigated in certain studies. It has been suggested that BPA may alter the course of normal neurodevelopment.[8] Exposure to BPA has been associated with ADHD behaviours, such as externalizing problems, hyperactivity, weaker emotional control, and impaired behavioural inhibition.[9] In an important study, associations between BAP exposure and higher ADHD scores and inattentiveness were observed.[10] In another study, it was reported that ADHD was more common among formula-fed infants in the 2007 sample but not in the 2011/12 sample, where exposure to BPA was markedly reduced.[11]

It is thought that phthalates can play a major role in the etiopathogenesis of ADHD and other neuropsychiatric disorders.[12,13] However, limited human analyses have investigated relationships between phthalate metabolites with attention deficit disorder orADHD symptoms among children. The studies have shown that phythalates may cause neurodegenerative diseases and impaired cognitive functioning by mechanisms of inflammation and lipid metabolism.[14] Exposure to low levels of phthalates resulted in loss of midbrain dopaminergic nuclei and aberrations in the dopamine system which play a major role in the pathophysiology of ADHD.[15] It has been reported that DEHP inhibited cell proliferation and promoted cell differentiation in animal studies.[16] Also, a cross-sectional study of 1493 children suggestedthat increase of DEHP metabolite raised the risk of ADHD.[17] In addition, it has been found that MEHP concentrations were related to child attention problems, aggressive behaviors, and externalizingbehaviors,and the authors suggested that child exposure tophthalates may contribute to ADHD, ODD, and externalizing and internalizing behavior problems.[18]

Additionally, it is known that the brains of young children are sensitive to environmental chemicals much more significantly than those of adults,[19] therefore it is important to examine the relationship between endocrine disrupting environmental chemicals, such as BPA, DEHP and MEHP, and brain development. In the present study, we investigated the relationship between ADHD and exposure to MEHP, DEHP, and BPA.

METHODS

Study population

The study included 44 children with ADHD without comorbidity and 51 healthy, volunteer children who presented to the Child Psychiatry Department of Erciyes University Medical School between May 2012 and May 2014. The assessments were made by a multidisciplinary team (comprised of an experienced child psychiatrist, social pediatric specialist and a pediatric neurologist) and included clinical history and physical, neurological and psychiatric examina-

tions. None of the subjects had neurologic, genetic, metabolic, or psychiatric disorders. Also, both the ADHD and control groups were carefully screened for signs of infection and subjects with acute illness were excluded.

The ADHD diagnoses were made according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR)[1] and the Turkish version of Kiddie Schedule for Affective Disorders and Schizophrenia of School-Age Children–Present and Lifetime Version.[20,21] The severity of ADHD was assessed using the short form of the Conners Parent Rating Scale (CPRS).[22] The patients received a diagnosis of ADHD for the first time and medical treatment was not initiated. The study was approved by the Erciyes University Ethics Committee. In addition, written informed consent was obtained from the parents of the children who participated in the study.

Laboratory analyses

For serum MEHP, DEHP, and BPA levels measurement, venous blood samples were obtained under sterile conditions in the morning and after fasting for at least eight hours. Samples were numbered and centrifuged at +4°C 1500 rpm. The plasma was separated and the obtained samples were stored at -70°C until analysis. All laboratory evaluations were performed at the Metabolism Laboratory of Erciyes University Medical School. Plastic products were avoided during blood sampling and analysis in order to prevent contamination.

BPA measurements: BPA concentrations were determined by using HPLC (Hewlett Packard Agilent 1100 Series, Vienna, Austria) with an auto-sampler using the following UV detector settings: an excitation wavelength of 227 nm and an emission wavelength of 331 nm. A Spherisorb C18 ODS2 column was used (250 mm x 4.6 mm I.D., 5 µm, USA) where mobile phase A (70%) consisted of acetonitrile and mobile phase B (30%) consisted of water. The chromatographic analysis was performed at 25ºC with a flow rate of 1 mL/min and injection volume of 20 µl. For serum extraction, 100 µl of 0.01 mol/l ammonium acetate buffer (pH 4.5) and 4 ml mixed solvent of n-hexane and diethyl ether (70:30, v/v) were added to 500 µl serum. The samples were centrifuged and the organic layer was evaporated to dryness under nitrogen stream. The samples were dissolved in 100 µl of HPLC grade acetonitrile for injection to HPLC for the analysis.

The retention time for BPA was 4.5 minutes. Recovery studies were performed on blank samples and the average recoveries were found to be 91±0.1% on 20 occasions. Between-run precisions were 5.98±0.09% coefficient of variation (CV) for BPA. Within-day precisions were 4.78±0.52% CV for BPA. The concentrations of BPA in the samples were calculated by using the calibration curve of the peak area prepared for BPA standards. The detection limit was set to 0.5 ng/ml. BPA (purity of 99.9%) was purchased from Sigma-Aldrich Co. (St Louis, MO, USA). Acetonitrile (HPLC grade) and all other analytical grade reagents were obtained from Sigma Aldrich Co. (St Louis, MO, USA) and Merck Co. (Darmstadt, Germany).

MEHP and DEHP measurements: MEHP and DEHP concentrations were determined by using highperformance liquid chromatography (HPLC) (Hewlett Packard Agilent 1100 Series, Vienna, Austria) with an auto sampler using a UV detector (230 nm). A Spherisorb C18 ODS2 column was also used (250 mmx4.6 mm I.D., 5 µm, Waters, Milford, MA, USA). Separations were performed at room temperature. The mobile phase was orthophosphoric acid 0.1% (acetonitrile (90:10, vol/vol)), and the flow rate was 1 mL/min. For serum extraction, 400 mL of Na OH 1N, 100 mL of 50% H3PO4 and 600 mL of acetonitrile were added to a serum sample of 200 mL. After each addition, the sample was shaken by vortex for 30 s. After centrifugation for 10 min at 3500 rpm, the supernatant was separated and the residue was again extracted with 600 mL of acetonitrile. After another centrifugation using same parameters, the supernatants collected were evaporated, reconstituted with 400 mL of mobile phase and injected into the chromategraph. The injection volume was 100 µL. Stock solutions containing DEHP or MEHP (2000 ppm) were prepared by dissolving a weighed amount of substance in acetonitrile. Standard solutions were prepared by dilution of the above stock solutions with mobile phase at varying concentrations ranging from 0.05 to 5.0 ppm. The concentrations of DEHP and MEHP in the samples were calculated using the calibration curve of peak area prepared according to DEHP and MEHP standards. The detection limits were set as 0.05 ppm for DEHP and 1 ppm for MEHP.

The retention times for MEHP and DEHP were 5.2 minutes and 20.7 minutes, respectively. Recovery studies were performed on blank samples of serum spiked with levels of 7.5 ppm of DEHP and 1.25 ppm of MEHP, and the average recoveries were found to be (mean±SD)

92±1.12% for DEHP and 99±1.10% for MEHP on 20 occasions. Between-run precisions were 6.44±0.12% coefficient of variation (CV) for DEHP and 8.03±1.05% CV for MEHP. Within-day precisions were 8.75±0.43% CV for DEHP and 4.83±0.21% for MEHP. DEHP and MEHP were purchased from Merck Co. (Hohenbrunn, Germany) and Cambridge Isotope Laboratories, Inc. (Andover, MA, USA), respectively.

Acetonitrile (HPLC grade) and all other analytical-grade reagents were purchased from Sigma-Aldrich Co. (St Louis, MO, USA).

Statistical analysis

The study data were analyzed with the IBM SPSS Statistics 21.0 and SigmaStat 3.5 statistical software packages. The variables were expressed as number (n), percentage (%), mean and standard deviation. The Shapiro-Wilk test was used to evaluate whether the data were normally distributed. General linear models were used for the comparison of intergroups and repeated measurements. In all, comparisons were adjusted by gender. The Pearson correlation test and Spearman correlation test were used to determine the correlations among the variables. Statistical significance was set at $p<0.05$.

RESULTS

The mean age was 8.56±3.55 years in the ADHD group which consisted of 13 girls and 31 boys. The mean age was 8.39±2.46 years in the control group which consisted of 17 girls and 34 boys (Table 1). No significant difference was found between patients and healthy children in terms of age (p=0.47) and gender (p=0.21). Regarding subtypes, 22 (50.0%) of the ADHD cases were predominantly combined and 14 (31.8%) were inattentive.

Serum MEHP and BPA levels were found to be significantly higher in the ADHD group (0.474±0.223 µg/ml, 1.485±0.285 ng/ml) when compared to healthy controls (0.311±0.134 µg/ml, 906±0.232 ng/ml). There was no difference in level of DEHP between the ADHD group and healthy controls (Table 2). When data was compared according to the general linear model, gender did not affect the serum MEHP, DEHP and BPA levels.

Table 1. General characteristics of groups

Features	ADHD group	Control group
Age (mean±SD)	8.56±3.55	8.39±2.46
Gender	31 boys, 13 girls	34 boys, 17 girls
Residence	32 urban, 12 rural	35 urban, 16 rural

ADHD: Attention deficit hyperactivity disorder

In the ADHD group, no significant correlation was detected between the severity of ADHD and phthalates while a positive correlation was detected between the severity of ADHD and BPA (r=0.447, p=0.027).

DISCUSSION

The associations between ADHD and endocrine disruptors are uncertain, but several mechanisms of adverse neurodevelopmental outcomes in humans exposed to BPA and phthalates have been observed. Experimental studies with animals indicated that gestational BPA exposure disrupts normal neurodevelopment, affecting aggression, anxiety, exploration, and spatial memory.[23,24] BPA exposure also induces prefrontal and hippocampal spin synapse loss in rodents which may result in cognitive dysfunction.[25] The animal literature suggests that exposure to BPA affects the development of the forebrain dopaminergic system via binding to estrogen dependent dopaminergic receptors that are important for regulation of behavioral impulses.[26] Exposure to BPA was associated

Table 2. Comparison of mean serum MEHP, DEHP and BPA levels between both groups

	ADHD group (n=44)	Control group (n=51)	p
MEHP (µg/ml)	0.47±0.22	0.31±0.134	<0.05
DEHP (µg/ml)	2.17±0.69	2.26±0.565	0.06
BPA (ng/ml)	1.48±0.28	0.91±0.232	<0.001

(Mono-(2-ethylhexyl)-phthalate (MEHP), di-(2-ethylhexyl)-phthalate (DEHP), and bisphenol A (BPA) Adjustment for multiple comparisons: Bonferroni, statistical significance was set at p<0.05 p value, adjusted by gender: not affected by gender, partial eta-squared: respectively, 0.408, 0.394, 0.402)

with ADHD behaviours like externalizing problems and anxiety, hyperactivity, weaker emotional control, and impaired behavioural inhibition.[9] However, there have been few studies assessing the association between childhood BPA exposure and meeting diagnostic criteria for ADHD.[27] The majority of prior studies of childhood BPA exposure have focused on children younger than eight years of age.[28] Higher urinary BPA concentrations were associated with ADHD in children; especially in boys.[29] Some research suggest that phythalates can cause aberrations in the dopamine system and this can lead to ADHD.[30-32] It has been shown that phthalates cause hyperactivity in animals similar to the clinical syndrome of ADHD found in children and possibly through effects on the dopamine system in rats.[33,34] Phthalates could disturb dopamine receptor D2, tyrosine hydroxylase and homeostasis of calcium-dependent neurotransmitters, resulting indecreased release of dopamine in experimental studies.[35]

Also, there are studies which suggest that exposure to phthalates is associated with ADHD and ADHD behaviours, specifically conduct problems and concentration or orientation.[36-38] In our study, we found serum BPA and MEHP levels were higher in the ADHD group when compared to healthy controls. The high level of BPA and MEHP in the ADHD group may be related to those dopamine hypotheses. BPA and phthalates, particularly MEHP, have effects on midbrain dopaminergic neurons, which are implicated in ADHD.[26,39]

In our study, we found no differences between serum DEHP levels in the ADHD group when compared to healthy controls. But, in one study, exposures to DEHP metabolites were associated with ADHD in children between the ages of 8 and 11.[38] Also, in a recent cross-sectional study, stronger associations were observed between DEHP metabolites and co-occurring ADHD and learning disabilities in girls compared to boys.[40]

As an interesting result, we found a positive correlation between the severity of ADHD and BPA while no significant correlation was detected between the severity of ADHD and phthalates including DEHP. It is known that both phthalates and BPA are considered endocrine modulating chemicals: phthalates are believed to function as antiandrogens, while BPA may act as an estrogen, anti-estrogen, androgen, or anti-androgen.[41,42] This result could be interpreted as increased BPA levels in ADHD affecting neuronal connectivity, synaptic function, and dendritic length by effects on estrogen and androjen. Also, this result could be accepted in line with the suggestion that BPA acts via estrogen receptors to alter dopamine signaling, leading to hyperactivity and attention deficits in humans.[43]

Studies have reported that higher postnatal BPA was associated with increased behaviors of internalizing and externalizing scores in only girls, or in only boys.[27,44] Studies which assess the effects of phthalates exposure on children's neurodevelopment reported that boys are higher at risk for neurodevelopmental disorders.[45] In contrast to the literature, our study found no significant effects of gender on endocrine disruptors in either group.

This study has some limitations which include its small sample size and lack of comprehensive questioning regarding the severity of environmental toxins during the antenatal and post-natal period. Time and severity of exposure to BPA which may result in ADHD, need to be explored in large populations to better understand the etiology of ADHD.

In conclusion, to better understand the etiology of ADHD and the effects of BPA, MEHP and DEHP on neurodevelopment, further investigation by multifactorial anaylysis in large populations is needed.

Authors' contributions: *D.B.Ö.: conceived and designed, performed the investigation, literature review, analyzed the data, wrote the paper; E.D.: conceived and designed, performed the investigation, literature review, wrote the paper; S.Ö.: conceived and designed, performed the investigation, literature review, wrote the paper; M.K.: conceived and designed, analyzed the data; F.K.: conceived and designed, performed the investigation; H.P.: conceived and designed, performed the investigation.*

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