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Heavy Metal and Thiol/Disulfide in Children with Attention-Deficit and Hyperactivity Disorder

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ABSTRACT

Background: In the etiology of attention-deficit and hyperactivity disorder (ADHD), oxidative stress and heavy metal exposure are still controversial topics. In this study, our goal was to examine heavy metal levels and oxidative balance in newly diagnosed patients with ADHD and reveal whether heavy metal levels have an effect on the oxidation balance.

Methods: The study included 35 patients with newly diagnosed ADHD and 31 healthy control groups of similar age and gender. Participants' parents or caregivers completed a semi-structured questionnaire regarding their children's breastfeeding and prenatal and postnatal smoking exposures. The levels of heavy metals lead (Pb), mercury (Hg), and cadmium were measured with inductively coupled plasma optical emission spectroscopy, and a unique automated spectrophotometric approach was used to quantify serum total thiol, native thiol, and disulfide quantities and ratios.

Results: The rate of smoking during pregnancy was significantly higher in the ADHD group than in the control group ($P = .030$). Compared to the control group, the native and total thiol levels of children with ADHD were significantly higher ($P < .001$). Likewise, the ADHD group had significantly higher Hg levels compared to the control group ($P = .002$). Cadmium levels were substantially greater in the control group compared to the ADHD group ($P < .001$). However, there was no significant difference between Pb levels in the ADHD and the control group ($P = .844$).

Conclusion: Exposure to Hg and prenatal smoking may contribute to the development of ADHD in childhood. In response to oxidative stress, the young brains of children with ADHD may enhance their antioxidant levels.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is typically diagnosed in childhood and is characterized by inattention, hyperactivity, and impulsivity. Attention-deficit hyperactivity disorder is one of the most prevalent pediatric psychiatric disorders, with an estimated prevalence of greater than 5% worldwide. Similar to other intricate disorders, ADHD cannot be solely attributed to a single risk factor, as multiple genetic, pre-perinatal, and environmental factors play a role in its development. Furthermore, the inheritance pattern for most individuals affected by ADHD is multifactorial. Although studies suggest that these factors play a role in the development of ADHD, the precise degree to which each factor contributes remains uncertain.[1]

Pre-perinatal factors, including but not limited to delivery injuries, preterm birth, low birth weight, exposure to maternal smoking, drinking, and illicit drugs during pregnancy, and breastfeeding status, have been identified as potential risk factors for the development of ADHD.[2] Studies have indicated that an extended period of breastfeeding is linked to enhanced cognitive development, and children who are breastfed for a longer duration exhibit a reduced likelihood of developing ADHD.[3] There is a well-established link between maternal smoking during pregnancy and ADHD in the offspring. It is unclear to what extent this reflects causal intrauterine effects versus unmeasured confounding.[1]

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Heavy metals found in the environment are suspected of playing a role in the onset of neurodevelopmental disorders such as ADHD. Due to the rapid cell division, high energy demand, and lack of a fully developed blood-brain barrier, previous research has shown that fetal and childhood brains are especially susceptible to toxic substances, including heavy metals. Following exposure to heavy metals in the environment, this susceptibility may make an individual more likely to develop ADHD and other neurodevelopmental problems. Lead (Pb), mercury (Hg), and cadmium (Cd) are only a few of the compounds that have been linked to neurotoxicity and are regarded as potential factors in the development of neurodevelopmental disorders such as ADHD. These heavy metals can accumulate in the body over time, leading to toxic effects on the nervous system and brain.

The eating of manufactured foods that include high fructose corn syrup, seafood, or dental amalgams is the primary way in which we are likely to be exposed to the harmful element Hg. The majority of reviewed studies describe Hg as a neurotoxic substance, but evidence is still lacking for ADHD development.[4] According to the findings of Dufault and colleagues, eating foods that include high fructose corn syrup may cause Hg levels to rise, which might result in a zinc shortage and alterations in brain function.[5] The association between Hg exposure and autism development is more precise, as stated in a recent meta-analysis.[6]

Lead is a well-known neurotoxic substance that has drawn attention globally. Most recent studies have shown a relationship between even low levels of Pb and medically diagnosed ADHD.[7] In addition, Pb exposure is recognized as a risk factor for ADHD in professional medical literature.[7] Researchers revealed that both prenatal and postnatal Pb exposure may lead to neurodevelopmental disorders and low intellectual capacity. Because of these health concerns, Pb from gasoline, paints, and other equipment has been dramatically reduced in many countries.

Regarding whether there is a correlation between Cd exposure and ADHD, researchers have reached divergent conclusions. Cadmium is a neurotoxic substance whose precise mechanism for inducing cognitive dysfunction remains unknown. Cadmium has been hypothesized to disrupt synaptic transmission, bind to calmodulin, or cause an oxidative imbalance.[8,9]

MAIN POINTS

- The study aimed to determine heavy metal levels and thiol/disulfide levels in children with attention-deficit hyperactivity disorder (ADHD).
- Mercury levels and prenatal smoking were significantly higher in ADHD patients compared to the control group.
- The ADHD group had significantly higher native and total thiol levels, suggesting a possible oxidative stress response in children.

It is believed that an imbalance in the oxidative system plays a significant role in the etiology of a number of neurological and mental conditions.[10] Imbalances in the thiol/disulfide balance have been observed in psychiatric disorders such as post-traumatic stress disorder and obsessive-compulsive disorder.[11,12] Patients with ADHD have normal levels of antioxidant production, but their response to oxidative stress is inadequate, resulting in oxidative damage, according to a meta-analysis of different parameters examined across all age categories.[10] The literature on oxidative status in ADHD is still contradictory.[10,13-17]

Thiols are a category of chemical compounds that contain a sulfhydryl (-SH) group. This group is susceptible to oxidation, which leads to disulfide bond formation. This process is readily reversible and in a constant state of flux. The dynamic balance of thiol and disulfide has essential functions in defending against oxidation, detoxifying, transmitting signals, facilitating apoptosis, controlling enzyme actions and transcription factors, and managing cellular communication processes.[18] When the equilibrium of thiol/ disulfide homeostasis leans toward disulfide creation, the balance tilts in favor of oxidation. Imbalanced thiol/disulfide homeostasis is believed to contribute to the mechanisms underlying various inflammatory conditions. To date, 5 studies have examined thiol/disulfide homeostasis in ADHD patients.[19-23] Among these, 4 focused on children and adolescents with ADHD.

This is the first study to examine the relationship between heavy metal levels and thiol/disulfide balance among children with ADHD.

MATERIAL AND METHODS

Participants

This research was conducted at the Child and Adolescent Psychiatric Clinic and Pediatrics Clinic. It was a cross-sectional study. In the research, there were a total of 35 newly diagnosed ADHD children ranging in age from 6 to 17 years as well as 31 healthy children of the same age and gender. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition was used in every kid's evaluation, which was performed by the same child psychiatrist. None of the patients suffering from ADHD had yet begun taking any medication. To rule out the possibility of additional mental disorders, the current and lifetime versions of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children were used. In addition, the teachers and parents filled out the Conner's Teacher Rating Scale and the Conner's Parent Rating Scale, respectively. The Wechsler Intelligence Scale for Children-Revised was completed by all of the participants in order to determine their respective intelligence quotient (IQ) levels. A survey

covering sociodemographic information, prenatal history, breastfeeding duration, parents' education levels, and parents' smoking status was completed. Due to the possibility of affecting the oxidant balance, approximately 80 patients with IQs below 80 or those with other autoimmune, neurological, neuropsychiatric, or metabolic diseases and using any medication were excluded from the study. Financial support was provided by the Sakarya University Research Committee, Project Number 2016-40-02-001. The study received approval from the Human Ethics Committee of Sakarya University (Approval No: 16214662/050.01.04/49). All participants involved in this study signed informed consent forms after gaining full knowledge of the research.

Sample Collection

Both the disease group and the control group had samples of their blood drawn in the morning. These blood samples consisted of a 3 mL whole blood specimen collected in an ethylenediaminetetraacetic acid (EDTA) vacutainer tube for heavy metal testing, 2 mL of blood in a plain tube for serum separation, and 3 mL of blood in a tube with a gel separator. These blood samples were placed in separate tubes and analyzed separately. After being centrifuged at a speed of 1500 rpm for a duration of 10 minutes, serum samples were separated, and then they were kept at a temperature of −80°C until they were ready to be analyzed.

Measurement of Heavy Metals

Each sample's contents were placed in individual mineralization tubes. After spending the night in 10% HNO_3, the plastic and glass containers were given a thorough rinsing with distilled deionized water (Milli-Q (Millipore, Bedford, MA, U.S.A.) 18.2 MΩ/cm) after being soaked in the solution overnight. High-purity analytical grade reagents were employed for heavy metal analysis in this study. Standard solutions (1000 μg/mL) for each heavy metal were utilized with inductively coupled plasma optical emission spectroscopy (ICP-OES) (Spectro Analytical Instruments, Kleve, Germany), with the methods procured from Merck. Deionized water (Millipore, Darmstadt, Germany) was consistently used for the serial dilution of standards throughout the research. The ICP-OES method was utilized so that the presence of heavy metals such as Cd, Hg, and Pb could be ascertained.

Measurement of Thiol/Disulfide Homeostasis

After being separated by centrifugation from the venous blood samples, the serum was then chilled to −80°C. Erel and Neşelioğlu's unique automated method for measuring serum thiol/disulfide levels was run on an automated clinical chemistry analyzer (Roche, cobas 501, Mannheim, Germany). Direct measurements were taken of both the native thiol levels (-SH) and the total thiol levels (-SH+-S-S-).[18]

Statistical Analysis

The Statistical Package for the Social Sciences software program, version 22.0 (IBM SPSS Corp.; Armonk, NY, USA), was utilized in order to carry out the analysis of the collected data. Frequencies and percentages represented the descriptive statistics for categorical variables. The Kolmogorov-Smirnov test was used to determine whether the distribution was normal or non-normal. Normal distributed data were reported as mean with SD, and non-normal data were reported as median with maximum and minimum values. The chi-square and Fisher's exact tests were utilized in the analysis of the categorical data, whereas the nonparametric Mann-Whitney *U*-test as well as the Student's *t*-test were utilized in the comparison of the various quantitative data. A value of $P < .05$ was regarded as statistically significant. In order to assess the significance of bivariate relations, Spearman correlation coefficients were computed.

RESULTS

The study examined 66 participants with a mean age of 10.8 (± 2.8) years, of whom 86.40% (n = 57) were boys and 13.60% (n = 9) were girls in the ADHD group. The control group had the same age and gender distribution as the patient group ($P = .857$, $P = 1.000$, Table 1). There were no significant differences in family income level or parents' education level between the 2 groups ($P = .712$, $P = .439$). The duration of breastfeeding was similar in both groups ($P = 0.311$), but the rate of smoking during pregnancy was significantly higher in the ADHD group than in the control group ($P = .036$, Table 1). There were no significant differences in blood Pb levels between the ADHD and control groups ($P = .844$). However, the average blood Hg levels were significantly higher in the ADHD group than in the control group ($P = .002$). The mean blood Cd levels of the control group were substantially greater than those of the ADHD group ($P < .001$, Table 2). There was

Table 1. Gender, Age, Breastfeeding, and Smoking Exposure Rates of ADHD and Control Group

	ADHD (n = 35)	Control (n = 31)	*P*
Mean age ± SD (years)	10.7 ± 3	10.9 ± 2.7	.857
Sex (n), female/male (%)	5/30 (14.2/85.7)	4/27 (12.9/87.0)	1.000
Breastfeeding (median, months)	14.5	18	.311
Maternal smoking, n (%)	14 (40)	11 (35.50)	.706
Paternal smoking, n (%)	23 (65.70)	23 (74.20)	.454
Smoking during pregnancy, n (%)	9 (25.70)	2 (6.40)	**.036**

Pearson χ^2 test, independent *t*-test. The significance level was taken as $P < .050$
ADHD, attention-deficit hyperactivity disorder.

Table 2. Comparison of Blood Heavy Metals Lead, Mercury, and Cadmium Levels Between ADHD and Control Groups

	ADHD (n=35)	Control (n=31)	*P*
Lead, µgdL [median minimum-maximum)	3.74 (2.9-5.6)	3.74 (3.2-5)	.844
Mercury, µgr/dL [median (minimum-maximum)	(0.9 (0.2-2.1)	0.4 (0.2-4.2)	**.002**
Cadmium, µg/dL [median (minimum-maximum)	0.4 (0.1-0.9)	0.9 (0.2-4.2)	**< .001**

Mann-Whitney *U*-test. The significance level was taken as $P < .050$
ADHD, attention-deficit hyperactivity disorder.

no significant association found between current parental smoking status and blood Cd levels (mother and father, $P = .709$ and $P = .829$, respectively). Table 3 demonstrated that the mean native and total thiol levels in the ADHD group were significantly higher than those in the control group ($P < .001$ and $P < .001$, respectively). Although the difference was not statistically significant, the ADHD group exhibited higher disulfide levels than the control group ($P = .234$). There were no significant differences between the 2 groups in terms of native thiol/total thiol ratios, disulfide/total thiol ratios, or disulfide/native thiol ratios ($P = .712$, $P = .714$, and $P = .685$, respectively). The correlation analysis did not reveal any significant associations between oxidative stress parameters and heavy metal levels in children with ADHD. Further information regarding the correlation analysis is provided in Table 4.

DISCUSSION

There are a relatively small number of research projects that have been conducted on the combined impact of heavy metal levels in children with ADHD. The correlation

Table 3. Comparison of Plasma Oxidative Stress Parameters Between Patients and Controls

	ADHD (n=35)	Control (n=31)	*P*
Total thiol, µmol/L (mean ± SD)	466.5 ± 86.6	383.6 ± 72.6	$P^a < .001$
Native thiol, µmol/L (mean ± SD)	426.5 ± 83.6	350.4 ± 66.6	**$P^a < .001$**
Disulfide, µmol/L (mean ± SD)	20.3 ± 6.3	16.5 ± 7.6	$P^a = .234$
Native thiol/total thiol, % (mean ± SD)	91.2 ± 3	91.5 ± 3.5	$P^a = .712$
Disulfide/total thiol, % (mean ± SD)	4.3 ± 1.5	4.2 ± 1.2	$P^a = .714$
Disulfide/native thiol, % [median (minimum-maximum)	4.5 (1.57-10.7)	4.4 (1.16-13.4)	$P^b = .685$

ADHD, attention-deficit hyperactivity disorder.
[a]*P*: Student's *t*-test.
[b]*P*: Mann-Whitney U-test.

Table 4. Correlation Between Plasma Oxidative Stress Parameters and Heavy Metal Levels Among ADHD Patients

		TT	SS	SS/SH	SS/TT	SH/TT
Pb	Rho	0.181	0.314	0.221	0.221	−0.221
	P	.314	.066	.216	.216	.216
Hg	Rho	0.053	−0.017	−0.228	−0.228	0.228
	P	.769	.924	.202	.202	.202
Cd	Rho	−0.015	0034	0.169	0.169	−0.169
	P	.934	.845	.347	.347	.347

ADHD, attention-deficit hyperactivity disorder; Cd, cadmium; Hg, mercury; Pb, lead; rho, Spearman's correlation coefficient; SH, native thiol; SS, disulfide; TT, total thiol.

between Hg levels and ADHD remains a subject of ongoing scientific debate. According to the findings of certain studies, children who suffer from ADHD have higher postnatal blood Hg contents.[24] In our research, we discovered a statistically significant relationship between even low levels of Hg and clinically diagnosed ADHD in children and adolescents. Contrary to other studies where Hg levels were 2-3 µg/dL, in our study, both ADHD and control Hg levels were lower than 1 µg/dL, but there was a statistically significant difference. Furthermore, certain genetic factors have been proposed for genetic susceptibility to the disease, and gene-environment interactions can increase the risk. There may be specific genetic factors that heighten our patients' susceptibility to even low levels of Hg, which could play a crucial role in ADHD development. Woods et al showed that exposure to Hg in amalgam may lead to various neurodevelopmental disorders in children with some genetic polymorphisms, supporting our hypothesis.[25]

Recent research has changed the previous belief that only higher blood Pb levels (>10 µg /dL) are neurotoxic. It is now understood that even lower levels of Pb (<5 µg/dL) may contribute to neurodevelopmental disruptions.[8,26-29] In our study, we did not observe a connection between blood Pb levels and clinically diagnosed ADHD in children, which is in line with the findings of some researchers.[30] A large meta-analysis by Goodlad et al[7] uncovered a link between ADHD symptoms and Pb exposure in children and adolescents. The Center for Disease Control has lowered the recommended blood Pb level of concern to 3.5 µg/dL. In our study, the results for both the control and ADHD groups were approximately 3.8 ± 0.5 µg/dL. Current data suggest that there is no safe threshold for blood Pb levels. Since ADHD is a multifactorial disorder, Pb exposure may be one of the factors that contribute to its development. However, by investigating these cases prospectively and evaluating their responses to Pb exposure in a larger patient population, we may obtain scientifically credible results.

Cadmium is a carcinogenic heavy metal, but its neurotoxicity has not been clearly established. Only a few studies have looked at the connection between Cd levels and ADHD, and the majority of them did not find any significant association.[26,31] Interestingly, our study found significantly higher levels of Cd in the control group compared to the ADHD group. Cadmium has been studied in various fields of psychiatry and has been shown to cause neuropsychiatric outcomes such as depression, schizophrenia, and anxiety.[32] Remarkably, it has been demonstrated that it is elevated in depressive cases but low in manic cases.[32] Similarly, Ciesielski et al[33] found lower urinary Cd levels in ADHD patients. They suggested that higher levels of Cd may lead to decreased activity levels, which could make an ADHD diagnosis less likely. Cadmium exposure has been linked to a range of neurocognitive dysfunctions that may potentially interfere with the diagnosis of ADHD. Therefore, in studies investigating the relationship between Cd exposure and ADHD, it is important to consider and control for these potential competing risks. Blood Cd levels are better indicators of recent Cd exposure, while urinary Cd levels are better for overall body burden. Consequently, there could be other factors that increase blood Cd levels in the control group that we were unable to identify. Clearly, more research with larger populations and both blood and urinary Cd levels is needed to evaluate the association between Cd and ADHD in children. Thus, the higher concentrations of Cd in the control group were unexpected and should be interpreted cautiously.

Another significant concern is maternal smoking during pregnancy, which is often cited as a prenatal risk factor associated with higher rates of ADHD. We discovered a statistically significant higher rate of smoking during pregnancy among mothers of ADHD patients compared to the control group. According to a review article, the odds ratio suggests over a 2-fold increase in the risk of an ADHD diagnosis for individuals whose mothers smoked during pregnancy.[34] Our study was cross-sectional and had a small sample size. As a result, our findings do not provide robust statistical evidence to assert that smoking during pregnancy causes ADHD development in children.

There is a limited amount of research in the literature on the involvement of oxidants and antioxidants in patients with ADHD, with most studies focusing on adults and yielding conflicting results. To mitigate the influence of other factors that could affect the oxidative/antioxidant balance, we selected a sample of children who were newly diagnosed, were not taking any medication, and had no chronic illnesses or active infections.

According to Joseph et al's[10] meta-analysis, patients diagnosed with ADHD exhibit typical levels of antioxidant production. However, their ability to respond to oxidative stress is inadequate, resulting in oxidative damage. It should be noted that the meta-analysis included both adult and pediatric patients and examined various oxidant and antioxidant markers. As the study population consisted primarily of adults, it is possible that in individuals with ADHD, the balance between oxidants and antioxidants becomes skewed toward oxidants in response to oxidative stress. The authors noted that various markers were used in different studies, making it challenging to compare results. As such, longitudinal studies involving larger populations may help identify new biological markers associated with childhood ADHD.

In contrast, Oztop et al[21] observed higher levels of thiol in children with ADHD, although this difference was statistically insignificant. The authors speculated that this increase in antioxidants may be a response to the disease process induced by oxidation. There are 5 published studies that investigate thiol levels in ADHD patients. One of these is performed on adults. In this study, Kurhan et al[20] discovered high disulfide, low thiol, and balance shifting toward oxidation in the adult ADHD group. However, it is known that aging, environmental pollution, smoking, and alcohol consumption increase oxidative capacity and that adults are more likely than children to be exposed to these factors. Similarly to our study, Avcil et al[19] found elevated total and native thiol levels in children with ADHD. This elevation was interpreted as a response to the oxidation caused by the disease. Oztop et al,[21] on the other hand, observed an increase in thiol in the ADHD group, which was not statistically significant, but they did not investigate disulfide levels to compare. Öğütlü et al[23] discovered that individuals with ADHD had low levels of total, native thiol, and disulfide, with the balance shifting toward oxidation.

Another important aspect of ADHD is its treatment, and recent studies have explored the potential benefits of antioxidant therapy. Guney et al[22] conducted a study measuring various oxidative stress indicators as well as antioxidant enzymes, including total antioxidant status, total oxidative status of plasma, paraoxonase, stimulated paraoxonase, arylesterase, and thiols, in children and adolescents with ADHD. The participants received methylphenidate treatment for 12 weeks, and the same parameters were measured again post-treatment. The researchers found that post-treatment thiol levels rose. Guney et al[22] suggested that methylphenidate treatment may restore the oxidative balance in patients with ADHD by enhancing antioxidant defense mechanisms. The detection of elevated levels of thiol in a number of studies conducted in children's age groups lends credence to the findings of our investigation. In this context, it can be assumed that children's levels of antioxidant thiols rise in response to the oxidation caused by the disease.

We hypothesized that heavy metal exposure, including Pb, Hg, and Cd, may increase oxidant levels in pediatric patients with ADHD, potentially contributing to the disease process. However, our correlation analysis did not reveal any statistically significant associations between oxidative stress parameters and heavy metal levels in children with

ADHD. It is known that heavy metals such as Hg can cross the blood-brain barrier, leading to increased oxidative stress in the brain, reduced neuronal plasticity, and impaired learning.[5] This is the first study to investigate the association between dynamic thiol/disulfide homeostasis and heavy metal exposure, so we were unable to compare our results to those of other studies. We found that the mean blood Hg levels in our sample were lower than in other studies, which may explain why Hg levels lower than 1 μg/dL did not induce a significant oxidative imbalance in thiol/disulfide levels.

Our study is limited by the fact that it was conducted on a small number of patients. The strength of our study is that it is the first to examine heavy metal levels and oxidative balance simultaneously in newly diagnosed ADHD patients who have not yet been treated with medication.

In summary, our study suggests that high blood Hg levels and smoking by the mother during pregnancy may relate to an increased risk of clinically diagnosed ADHD in children and adolescents. Although we did not observe significant imbalances in dynamic thiol/disulfide homeostasis, the increase in oxidative disulfide levels may trigger an increase in antioxidant thiols in the brains of individuals with childhood and adolescent ADHD, serving as a potential biochemical marker for diagnosis. Furthermore, different heavy metals may lead to neurotoxicity via distinct pathways. Overall, the study provides valuable insights into the potential role of heavy metals and thiol/disulfide levels in ADHD and suggests avenues for future research.

Ethics Committee Approval: This study was approved by Ethics Committee of Sakarya University (Approval No: 16214662/050.01.04/49, Date: February 8, 2016).

Informed Consent: Informed consent was obtained from the participants who agreed to take part in the study.

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