Original Article

Lead as a Risk Factor for Attention Deficit Hyperactivity Disorder (ADHD) in Children.

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ABSTRACT

Background: Attention Deficit Hyperactivity Disorder (ADHD) is considered one of the most common childhood psychiatric disorders. The worldwide prevalence is approximately 5%. In Egypt, exposure of children to heavy metal is considered one of the risk factors lead to ADHD. The aim of this study was to investigate the potential association between lead exposure and ADHD in children and find the association between the level of exposure to lead and degree of ADHD symptoms. **Method:** Case control study was done by random selection of children from outpatient Clinic at Assiut University Hospital of Children. Data were collected by a questionnaire to evaluate environmental exposure to lead and blood analysis for this heavy metal level. **Results:** Lead level in ADHD children was significantly higher than control (20.88± 7.47 ug/dl versus 16.13 ± 7.91 ug/dl). While there is no significant difference between lead level and degree of symptoms among the ADHA children. **In conclusion,** there is a significant association between ADHD in the examined sample of children and exposure to lead especially through water contamination with lead. Lead level is significant for reflecting exposure to lead.

Key words: Lead - ADHD - heavy metal

1. INTRODUCTION

One of the most common psychiatric disorders in children is (ADHD) Attention deficit hyperactivity disorder. It has many bases such as neurobiological, neurochemicals, and genetic (Singh et al.,2015). It is a lifelong debilitating disorder with many social skill difficulties (Klein et al.,2015). It is well known that ADHD in children of school-age, is a serious disorder that can be safely and effectively remediated when early diagnosed and treated (Rappley,2005).Worldwide prevalence of ADHD in school age children is calculated to be about 5% (Polanczyk et al.,2007). Many factors can affect the occurrence of this problem including geographical and demographic factors (Simon et al.,2009). The ratio of boys to girls with ADHD is between 3:1 and 9:1 in clinical samples. Part of the gender difference may be due to referral bias related to symptoms of disruptive behavior, since boys have both more hyperactive/impulsive and conduct/oppositional symptoms than girls(Genro et al.,2012).

Lead (Pb), mercury (Hg), and cadmium (Cd) are heavy metals naturally found in the environment and are also widely proliferated in the environment through human activity(Kim et al.,2013). Lead (Pb) is an environmental toxicant with no known biological function. Lead is often used in industrial settings worldwide and can be found in many aspects of daily lives, such as drinking water, food packaging products, dietary supplements، and even ceramics (Meyer et al.,2008). It has been used in various commercial products, such as gasoline and paint, in order to enhance the economic and functional benefits of such products throughout the world. Paint and leaded gasoline were banned due to increase level of lead. However, old houses are still painted with leaded paint. The main source of lead in environment is that which emitted

from the leaded gasoline (Toscano and Guilarte,2005).

Water-soluble lead is differing from other sources of lead. It can affect the development if taken by children or pregnant mothers. Water- soluble lead can be absorbed by children in high percentage 40-50% with oral dose if compared to the amount absorbed by adult 3-10% (Hanna Attisha et al.,2016). Symptoms of ADHD as inattention, hyperactivity and irritability may appear in children even at low lead exposure. With high level of lead in blood, children symptoms may be in the form of decreased intelligence, delayed growth, hearing loss and short-term memory. At higher levels, it can lead to brain damage which is permanent and even death (Flora et al.,2012). Many studies have shown the harmful effects of higher blood lead levels (BLL) (>10 µg/dL), however a growing body of evidence is showing adverse effects at lower BLLs (e.g., ≤ 5 µg/dL), suggesting no threshold of developmental neurotoxicity(Kim et al.,2013).

This work aims to investigate the potential association between lead exposure and ADHD in children and to find the association between the level of exposure to lead and degree of ADHD symptoms.

2. MATERIALS, SUBJECTS AND METHOD

This study is a case control study. It was conducted in the period from 1st of January 2017 to 31st of December 2017. It was done at Assiut University Children's Hospital covering whole Assiut governorate and Clinical toxicology and forensic chemistry lab - Faculty of Medicine- Assiut University.

2.1 Materials:

- Chemicals: Nitric acid 65% El nasr co. for chemicals, hydrogen peroxide El nasr co. for chemicals, and double distilled water.
- Instruments: Graphite tube Atomizer (GTA 120) - Aligent technologies.

2.2 Subjects:

One hundred enrolled children were classified into two groups after ADHD diagnosis: group I (ADHD children) and group II (Controls):

a. Group I (ADHD children):

Seventy children of both sexes were diagnosed to have ADHD by pediatricians and psychologist at psychiatric clinic of Assiut University Children's Hospital by using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. The age of children ranged from 4-12 years. They were selected randomly.

DSM IV criteria includes, persistent pattern of hyperactivity-impulsivity and/or inattention that interferes with development or functioning. Several hyperactive-impulsive or inattentive symptoms present before age 12 years. Several hyperactive-impulsive or inattentive symptoms present in more than one setting (e.g. at school, work, home, with relatives or friends; and in other activities). Evidence that the symptoms decreases or interfere with the quality of academic, occupational or social functioning. Symptoms do not occur during course of any other psychotic disorder, and cannot be related to other mental disorder (e.g. mood disorder, dissociative disorder, anxiety disorder, etc…).

According to ADHD-SC4, children are classified into severe, moderate or low scoring for each scale.

- **Inclusion criteria:**

Children in the age group from 4 to 12 years, medically diagnosed as ADHD, not having any other chronic disease (Zaky et al.,2015).

- **Exclusion criteria:**

Children with active smoking, presence of any other chronic illness, or association of ADHD and other neurodevelopment disorders (Zaky et al.,2015).

b. Group II (controls/non-ADHD children)

Thirty children matching for age and sex with children in the 1st group. Neither of them was diagnosed to have ADHD. They were selected randomly from children visiting clinics for any other cause other than ADHD.

2.3 Ethical considerations:

This study was done after the approval of Ethical Committee, Faculty of Medicine, Assiut University. Informed consent was obtained from all parents of the participated children in the study. Confidentiality of the data was maintained.

2.4 Method:

Full medical history was taken from enrolled parents (the mothers) for children younger than 10 years or from studied children who

were older than 10 years in both groups. This history includes the following items, Personal history (Age, sex, residency especially those live near smoking areas or factories). A questionnaire was answered by household respondent (living in house older than 1978, any history of lead toxicity in the family, type of water in the house, history of pica, living near lead factory, parents' occupation, history of lead poisoning among those who live in the same locality) according to (Yassa,2014).

2.4.1 Blood sampling:

Two ml whole blood sample were collected in a vacutainer tube contain heparin (heparinized, lead-free, "green-top" blood collection tubes); blood samples can be stable for 3 days in 4°C.

Digestion was done by one ml blood in nitric acid (HNO_3) and hydrogen peroxide (H_2O_2) (2:1). Hot plate temperature was increased to 250◦C and continued until volume is 1 ml for blood remained (2–3 h)(Yassa,2014).

Lead level was measured using Graphite Tube Atomizer.

2.5 Statistical analysis:

The collected data were reviewed and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± standard deviation SD or median (range) while nominal data was expressed in form of frequency (percentage). Chi²-test was used to compare the nominal data of different groups in the study while student t-test was used to compare mean of different two groups and ANOVA test for more than two groups. *P* value was significant if < 0.05 and highly significant if <0.001.

3. RESULTS

One hundred children were included in the study and were divided into two groups, (group I) the studied group, includes 70 children with ADHD and the (group II) control group, includes 30 healthy children.

Table (1) shows the demographic data of both groups. The mean age of ADHD children was 6.52 ± 1.60 years and the majority (67.1%) of them were 6 years old or less while the mean age of control group was 6.70 ± 1.87 years also, the majority (46.7%) of them were 6 years old or less.

Fifty-eight (82.9%) of children with ADHD were males and only 12 (17.1%) of them were females while 25 (83.3%) of the control group were males and 5 (16.7%) were females **(Figure 1)**. Majority of mothers were homemakers (70% in case of ADHD group and 83.3% in case of control group) while 47.1% of fathers of ADHD group and 50% of fathers of control children were employed **(Table 1).**

As regarding age, sex, fathers, and mothers' jobs, there were no significant differences between both groups (*P* > 0.05) but it was noticed that males are significantly higher among ADHD group in comparison to females **(Table 1).**

Table 1: Demographic data of studied groups.

Variables	ADHD group (n= 70)	Control group (n =30)	*P* value
Age (years)			
4- ≤ 6 years	47 (67.1%)	14 (46.7%)	0.62
6- 9 years	18 (25.7%)	13 (43.3%)	
9-12 years	5 (7.1%)	3 (10%)	
Sex			
Male	58 (82.9%)	25 (83.3%)	0.61
Female	12 (17.1%)	5 (16.7%)	
Mother's job			
Housewife	49 (70%)	19 (63.3%)	0.33
Employed	21 (30%)	11 (36.7%)	
Father's job			
Farmer	28 (40%)	14 (46.7%)	0.34
Employed	33 (47.1%)	15 (50%)	
Worker	9 (12.9%)	1 (3.3%)	

Data was expressed in form of frequency (percentage) using Chi²-test. n=number of subjects.

Figure (2) shows that most of the children was diagnosed at age of 6 years old (44.3%) followed by age of 5 years old (18.6%) and age of 7 years old (15.7%).

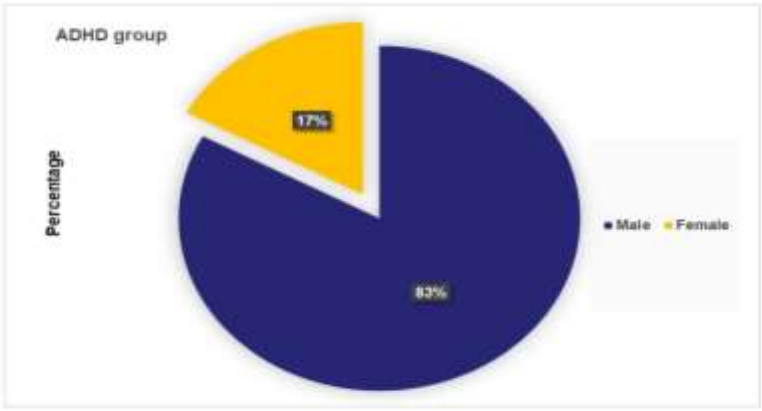

Figure 1: Sex distribution of ADHD group.

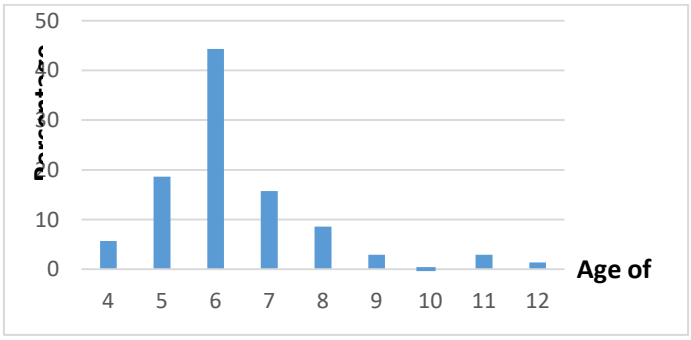

Figure 2: Age of ADHD in children of the first group.

Table (2) and figures (3-5) show that exposure to smoking presented in 62 (88.6%) of children with ADHD and presented in 14 (46.7%) of control group. As regarding number of relatives who are smokers, 56 (80%), 1 (1.4%) and 5 (7.1%)of children with ADHD had one, two and three relatives respectively while all of exposed children (14

child) in the control group had only one relative. Exposure to cigarette smoking, waterpipe and both presented in 53 (75.7%), 5 (7.1%) and 4 (5.7%) of children with ADHD respectively while 11 (36.6%) of control group exposed to cigarette smoking and 3 (10%) of them exposed to water pipe smoking.

Table 2: Grades of the ADHD symptoms based on age of the children at psychiatric clinic of Assiut University Children's Hospital.

Grades of ADHD symptoms	Age groups (years)						
	4-≤ 6 years (n= 47)		6- 9 years (n= 18)		> 9 years (n= 5)		P_1value
	n.	%	n.	%	n.	%	
Inattention							
Mild	1	2.1	1	5.6	0	0	0.23
Moderate	34	72.3	10	55.6	2	40	
Severe	12	25.3	7	38.9	3	60	
P_2 value	**0.01***		**0.02***		**0.02***		
Hyperactivity /impulsivity							
Moderate	9	19.1	5	27.8	1	20	0.28
Severe	38	80.9	13	72.2	4	80	
P_2 value	**0.01***		**0.03***		**< 0.011***		
Oppositional Defiant							
Mild	1	2.1	1	5.6	0	0	0.09*
Moderate	14	29.8	5	27.8	0	0	
Severe	32	68.1	12	66.7	5	100	
P_2 value	**0.02**		**0.04**		**< 0.001**		

Data was expressed in form of frequency (percentage) using ANOVA. *P* value was significant if < 0.05 and highly significant if < 0.001 (P_1 compared between grades of the disease with different age groups, P_2 compared different grades at the same age group). n=number of subjects

Mean time of smoking exposure (hours/day) was significantly higher in the ADHD group (3.40 ± 1.53) in comparison to the control group (2.57 ± 0.93; *P*= 0.04). Also; Mean years of smoking exposure was significantly higher in the ADHD group (6.18 ± 1.55) in comparison to the control group (5.07 ± 1.77; *P* value was 0.01).

Exposure to passive smoking during pregnancy was recorded in 8 (11.4%) of those with ADHD and in 8 (26.7%) of the control group.

Only exposure to smoking and duration of exposure (both hours/day and year) were significantly higher in those with ADHD group in comparison to the control group.

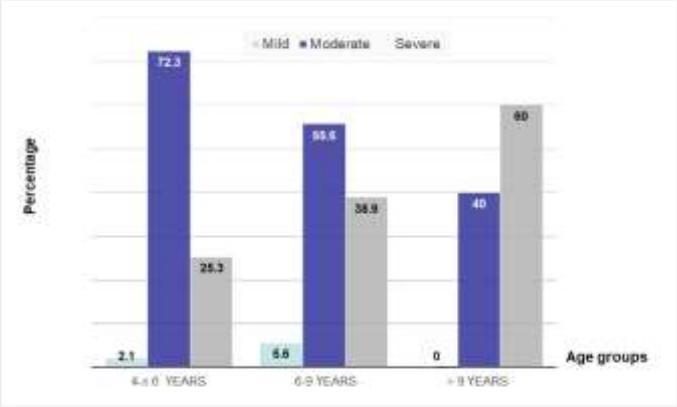

Figure 3: Grades of Inattention in the first group based on age group.

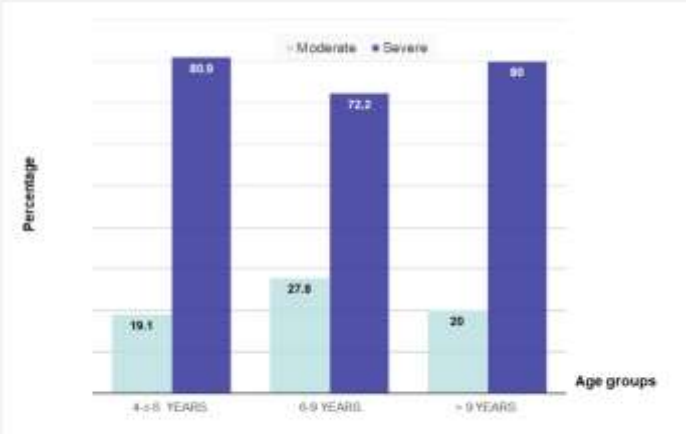

Figure 4: Grades of Hyperactivity in the first group based on age group.

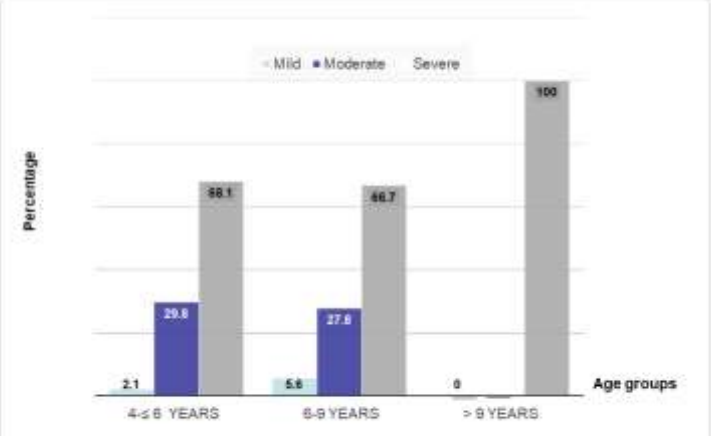

Figure 5: Grades of Oppositional Defiant in the first group based on age group.

Table (3) shows majority of males' children (70.7%) had moderate inattention while majority of females' children (58.3%) had severe inattention. Majority of both sexes (82.8% of males and 58.3% of females) had severe hyperactivity also; majority of both sexes (70% of males and 75% of females) had oppositional defiant.

Grades of ADHD symptoms had no significant differences between both sexes. Moderate inattention was significantly frequent in males and sever inattention was frequently in females. Severe hyperactivity was significantly high in males (p value < 0.001). While oppositional defiant was significantly high among both sexes.

Table 3: Grades of the ADHD symptoms based on gender of the children.

Grades of ADHD symptoms	Sex of children				P_1 value
	Male (n= 58)		Female (n= 12)		
	No.	%	No.	%	
Inattention					
Mild	2	3.4	0	0	0.34
Moderate	41	70.7	5	41.7	
Severe	15	25.9	7	58.3	
P_2 value	**0.04**		**0.02**		
Hyperactivity					
Moderate	10	17.2	5	41.7	0.39
Severe	48	82.8	7	58.3	
P_2 value	**< 0.001**		**0.01**		
Oppositional Defiant					
Mild	2	3.3	0	0	0.11
Moderate	16	26.7	3	25	
Severe	42	70	9	75	
P_2 value	**0.02**		**0.02**		

Data was expressed in form of frequency (percentage) using ANOVA. *P* value was significant if < 0.05 and highly significant if < 0.001 (*P*1 compared between different grades in both sexes and *P*2 compared between different grades at the same sex)

Table (4) and figure (6) show that lead level was highly significant in the ADHD group compared to the control group (20.88 ± 7.47 versus 16.13 ± 7.91 µg/dL).

Table 4: Blood Lead level in the studied groups (ADHD and Control groups).

Variables	ADHD group(n= 70)	Control group (n= 30)	*P* value
Blood Lead level (µg/dL)	20.88 ± 7.47	16.13 ± 7.91	**0.00**

Data was expressed in form of mean ±(SD) using T-test. P value was highly significant < 0.001. ADHD, Attention Deficit Hyperactivity Disorder.

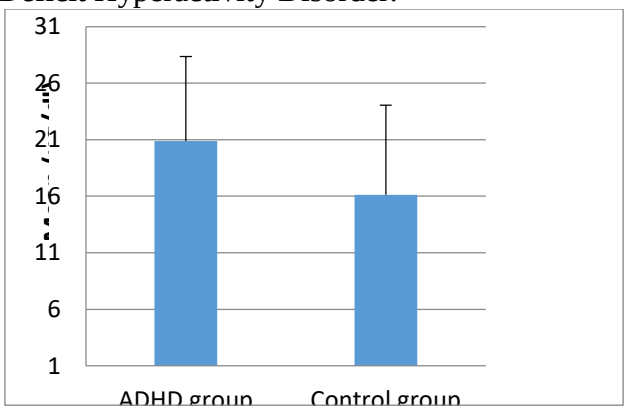

Figure 6: Blood Lead level in both studied groups (ADHD and Control groups) at psychiatric clinic of Assiut University Children's Hospital.

Table (5) and figure (7) show insignificant difference in blood lead levels between the ADHD and Control groups based on environmental exposure with exception to the use of filtered water that was significantly associated with lower lead level in the control group than ADHD group.

Table 5: Blood Lead Level in both studied groups at psychiatric clinic of Assiut University Children's Hospital in relation to different risk factors of lead exposure.

Exposure to lead	ADHD group (n= 70)	Control group (n= 30)	*P* value
Live in \ regularly visit a house/building peeling or chipping paint	22.75 ± 7.09	24.53 ± 7.40	0.69
Recent renovation or remodeling	20.88 ± 7.47	19.13 ± 7.91	0.11
Living near smoking area	21.43 ± 6.04	20.12 ± 5.67	0.54
Use of filtered water	22.21± 5.33	15.08 ± 4.56	**0.03**

Data was expressed in form of mean ± standard deviation(SD) using T-test. *P* value was significant if < 0.05. ADHD, Attention Deficit Hyperactivity Disorder

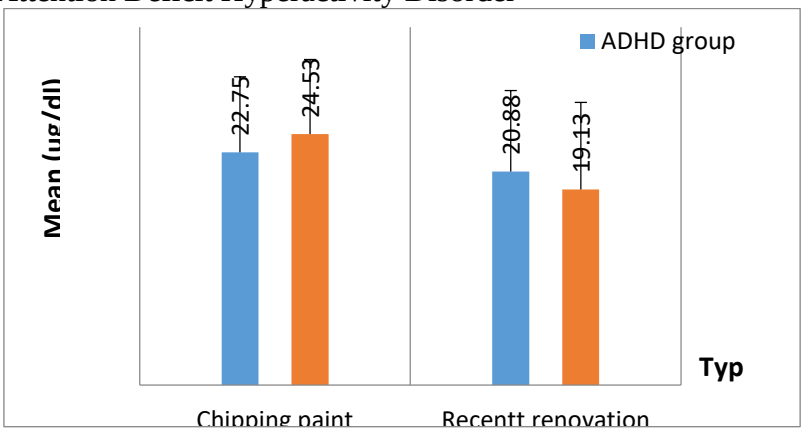

Figure 7: Lead level in the studied groups (ADHD and control) at psychiatric clinic of Assiut University Children's Hospital based on type of housing

Table (6) and figure (8) show that lead level was insignificantly higher in ADHD children with frequent pica behavior than other ADHD children.

Table 6: Mean blood lead level in the ADHD group based on pica behavior:

	With pica (n= 8)	Without pica (n= 62)	*P* value
Mean BLL(µg/dL)	24.95 ± 10.73	20.35 ± 6.89	0.10

Data was expressed in form of mean ± standard deviation (SD) using T-test.

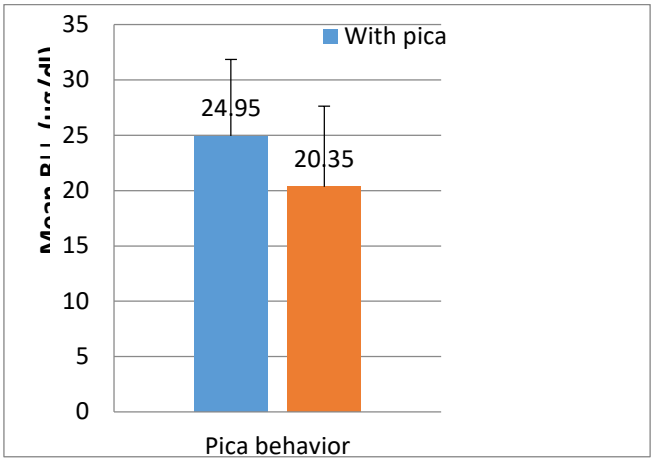

Figure 8: Mean blood lead level in the ADHD group based on pica behavior.

Table (7) and figure (9) show that lead level had insignificant differences between different grades of ADHD symptoms.

Table 7: Mean blood lead level in the ADHD group at psychiatric clinic of Assiut University Children's Hospital based on grades of ADHD symptoms.

Grades of symptoms of ADHd	Mean Blood lead level/ symptom		
	Inattention	Hyperactivity	Oppositional Defiant
Low	15.50 ± 8.98	-----	26.25 ± 12.23
Moderate	21.80 ± 7.29	25.02 ± 8.5	20.82 ± 7.85
Severe	19.43 ± 7.67	19.75 ± 6.81	20.68 ± 7.26
P value	0.21	0.93	0.59

Data was expressed in form of mean ± standard deviation (SD) using ANOVA. *P* value was significant if < 0.05. ADHD, Attention Deficit Hyperactivity Disorder.

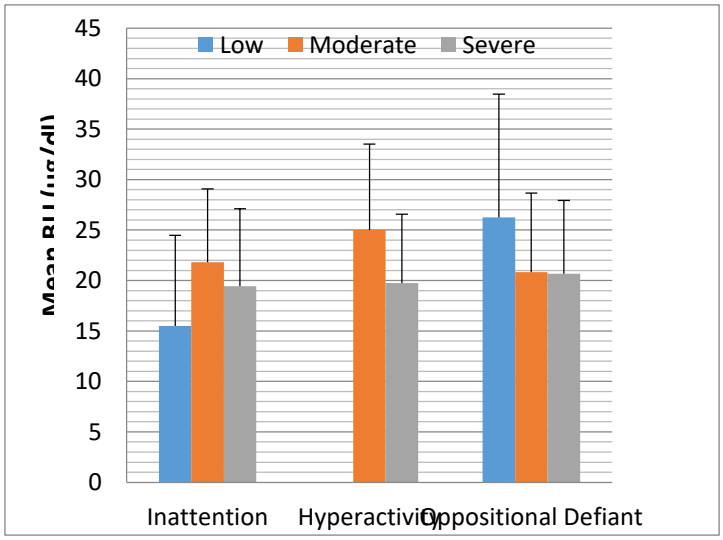

Figure 9: Mean blood lead level in the studied ADHD group based on grades of ADHD symptoms.

Figure (10) shows distribution of BLL among ADHD children. About 94% of ADHD children have BLL exceeding the accepted level (10 µg/dL).

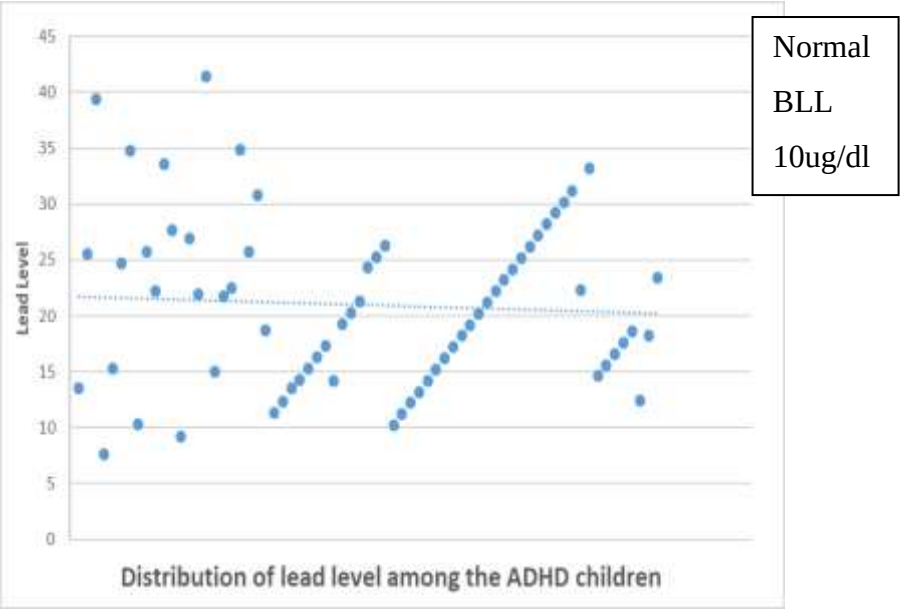

Figure 10: distribution of BLL among ADHD children.

4.DISCUSSION

In this study, the authors tried to answer the question about the relation between lead as a heavy metal exposure and the occurrence of ADHD. The present study showed that the commonest age of the children with ADHD was six years old (67. 1%). As regarding age there was no significant difference between ADHD and control groups as all children in both groups were at age group 4-12 years old**.**

Male children were more affected by ADHD than females (82.9% and 17.1% respectively). This agreed with (Nussbaum,2012) who found that ADHD in children is 2–9 times more common in males than females. (Bakare,2012) also agreed with the present study, regarding sex distribution of ADHD. It has been suggested that ADHD may be underdiagnosed in females due to the less overt nature of inattentive symptoms, as well as possible diagnostic overshadowing from anxiety, eating or depressive disorders(Martin et al.,2018).In contrast (Höök et al.,2006) found that both sexes were equally affected using Child Behaviour Checklist (CBCL).

Mean age of diagnosis of ADHD in this study was 6.52 ± 1.6 years, which is due to that age, is the school age. This result was in accordance with (Kessler et al.,2007) who stated that impulse control disorders have the earliest age of onset distributions, with median age of onset across countries of 7–9 years for attention-deficit/hyperactivity disorder (ADHD).

Moderate inattention was significantly frequent in children below 9 years old while severe inattention was significantly frequent in those above 9 years old. In all age groups, severe hyperactivity and oppositional defiant were significantly frequent.

As regarding symptoms there were insignificant differences between both sexes but females usually presented by inattention which is agreed with (Nussbaum,2012) who stated that compared to males with ADHD, females with ADHD have been presented with inattentive symptoms more than other symptoms.

This study showed that Lead level was significantly higher in ADHD group compared to the control**.** This result was in concordance with studies that associate blood lead levels with medically diagnosed ADHD in children (Nigg et al.,2008 and Wang et al.,2008 and Nigg et al.,2010). Many studies have shown the harmful effects of higher blood lead levels (BLL) (>10 µg/dL), however a growing body of evidence is showing adverse effects at lower BLLs (e.g., ≤5 µg/dL), suggesting no threshold of

developmental neurotoxicity(Kim et al.,2013).

Lead level was statistically insignificant between the ADHD and control groups based on environmental exposure with exception of the use of filtered water that was significantly associated with lower lead level in the control group than ADHD group. This result could be explained by that the changes in water sources, water infrastructures, and changes in treatment of the water with disinfectant. In addition to that, lead leaches into drinking water via lead-based plumbing or lead particles that detach from degrading plumbing components(Triantafyllidou et al.,2014). Lead was banned in plumbing material in 1986, but older homes may still contain lead service lines, lead solder, lead connections, or other lead-based plumbing materials(Hanna Attisha et al.,2016).

Lead level was insignificantly higher in children with frequent pica behavior than other children which disagreed with (Lavoie and Bailey,2004). They reported that ingestion of the house dust due to paint, which contains lead, on walls in the older properties and chalking of paints from toys, and woodwork becomes the major pathway to lead. Also, (Thihalolipavan et al.,2013) stated that in pregnant women poisoned with lead, pica was associated with higher peak blood lead levels (BLLs).

It was noticed that lead level had insignificant differences between different grades of ADHD symptoms. This result is agreed with (Huang et al.,2016) who noticed that there is an association between lead and symptoms of ADHD when blood lead was ≤ 5 µg/dl. However, this association was decreased when levels were > 5 µg/dL, which may explain why behavior problems are not often correlated with lead exposure. This explain the lack of a clear dose–response relation at higher levels of lead. Goodlad et al.,(2013) described that there was a small to medium association between inattention symptoms and hyperactivity symptoms and lead exposure. In contrast to (Nicolescu et al.,2010) who reported that the main elements of ADHD were associated with low environmental blood lead concentrations (even below 10 µg/dl).

5.CONCLUSION

In conclusion, there is a significant association between lead exposure and the occurrence of ADHD in the studied sample of Egyptian children.

All symptoms like inattention, hyperactivity, impulsivity and oppositional defiant can be aggravated with lead exposure.

6.RECOMMENDATIONS

From the current study, it is recommended to:

- Minimize the dissolved lead in water by using filters removing the heavy metals from it.
- Improve the awareness of the community about the lead exposure and its complication in children and adult.

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الرصاص كعامل خطورة للاصابة بمرض قصور الانتباه وفرط الحركة في الاطفال

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يعتبر اضطراب قصور الانتباه وفرط الحركة احد اشهر الاضطرابات النفسية في الاطفال. وينتشر عالميا بنسبة ٥% تقريبا. في مصر يعتبر تعرض الاطفال للمعادن الثقيلة احد عوامل الخطورة للاصابة بقصور الانتباه وفرط الحركة. **الهدف من هذه الدراسة:** استقصاء احتمالية العلاقة بين التعرض للرصاص والاصابة باضطراب قصور الانتباه وفرط الحركة في الاطفال وكذلك العلاقة بين مستوي التعرض للرصاص واعراض الاضطراب. **الطريقة:** دراسة مقارنة عن طريق الاختيار العشوائي للاطفال من العيادات الخارجية لمستشفي الاطفال الجامعي باسيوط.وتم جمع المعلومات عن طريق استبيان لتقييم التعرض البيئي للرصاص وكذلك قياس مستوي ذلك العنصر في الدم. **النتائج**: مستوي الرصاص في دم الاطفال المصابة باضطراب قصور الانتباه وفرط الحركة اعلي من باقي الاطفال بشكل مؤثر. بينما لاتوجد علاقة مؤثرة بين مستوي الرصاص في الدم واعراض اضطراب قصور الانتباه وفرط الحركة في الاطفال. الخلاصة: هناك علاقة بارزة اضطراب قصور الانتباه وفرط الحركة في العينة المختارة من الاطفال والتعرض للرصاص خاصة من خلال تلوث المياه بالرصاص . مستوي الرصاص في الدم يعكس مدي التعرض للرصاص .
التوصيات: تقليل التعرض للرصاص في مياه الشرب عن طريق استخدام فلتر المياه وزيادة وعي المجتمع بأضرار التعرض للرصاص للأطفال والبالغين.