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Relationship between Serum Iron Level and Zinc Level with Attention Deficit Hyperactivity Disorder in Children

Norhan Zakaria Hassanien El-Saadany*[1], Mohamed Fawzy Abdel-Fattah[1], Ahmed Galal Siam[1], Nilly Raafat Abdel-Fattah[2]
Departments of [1]Pediatrics and [2]Psychiatry, Faculty of Medicine, Zagazig University, Egypt
***Corresponding Author:** Norhan Zakaria Hassanien El-Saadany, **E-Mail:** ahmed.ibrahim198780@gmail.com

ABSTRACT

Background: ADHD (Attention Deficit/Hyperactivity Disorder) is the most frequent pediatric mental disorder. Zinc and iron are the most commonly investigated elements in children with ADHD.

Objective: The aim of the current work was to discuss the role of iron and zinc in the brain development and the possible lowered serum levels of these elements in patients with ADHD to prevent and control some of ADHD symptoms.

Patients and Methods: 42 children, aged from 4 to 14 years were included in this study as their parents complained from inattention, excess activity, or difficulties in school achievement of their children. All children included in the study were subjected to Full detailed medical history, clinical examination including physical examination, neurological examination, and laboratory investigations.

Results: There was statistical significance decrease in both Fe and Zn among cases compare to control group. In addition, there were statistical significance increases in frequency of low Fe and Zn level among cases group compared to control group. The levels of Fe and Zn had statistically significant –ve relationships with the ratings given by both parents and teachers. A statistically significant link between Zn and Fe levels was also found. There were statistical significance increase in frequency of ADHD C and PH and sever ADHD among cases had low Zn level compare to cases had normal level.

Conclusion: It could be concluded that both zinc and iron serum levels were found to have a significant correlation with parent-reported hyperactivity symptoms, suggesting that patients with low levels of iron and zinc may be at greater risk of developing ADHD symptoms.

Keywords: Iron, Zinc, Attention Deficit Hyperactivity Disorder,

INTRODUCTION

Hyperactivity/impulsivity and inattentiveness are two of the most prevalent symptoms of Attention Deficit Hyperactivity Disorder (ADHD), the most common pediatric mental illness **(1)**. Neuroimaging studies and the effects of pharmacotherapeutic treatment suggest that dopaminergic neuronal growth in the prefrontal cortex and subcortical regions may play a role **(2)**.

However, a number of studies have shown that both genetics and the environment play a crucial role in the development of the symptoms. Environmental (non-genetic) factors may have a role in the development of attention deficit hyperactivity disorder **(3)**.

In youngsters with attention deficit hyperactivity disorder, zinc and iron are frequently examined. Neurotransmitters (such as dopamine, melatonin, and prostaglandins) are all dependent on zinc for their metabolism **(4)**.

It is uncertain how zinc may be linked to ADHD symptoms, although it serves as a cofactor for more than 300 enzymes and has a role in the creation of prostaglandins and neurotransmitters in the human body **(5)**. Inattention, one of the hallmarks of ADHD, is one of the hallmarks of zinc insufficiency. Number of case-controlled studies have shown that children diagnosed with ADHD had lower zinc levels than their peers **(6)**.

Iron is another extensively studied element in children with ADHD, which is a cofactor for tyrosine hydroxylase, the enzyme of monoamine synthesis and thus is critical for dopamine and norepinephrine production. **Bener *et al.* (7)** after controlling for age, gender, and other characteristics, it was observed that children with ADHD had low serum iron levels **(7)**.

Other research has shown that iron deficiency raises the likelihood of mental health issues, ADHD, and other developmental problems **(8)**.

Cheatham (9) discovered that iron deficiency worsened the symptoms of attention deficit hyperactivity disorder. Further studies suggested that iron supplementation could help alleviate the symptoms of ADHD.

The goal of this work was to discuss the role of iron and zinc in the brain development and the possible lowered serum levels of these elements in patients with ADHD to prevent and control some of ADHD symptom.

PATIENTS AND METHODS

This case control trial study included a total of 42 patients with ADHD and 42 healthy children as controls, selected from Psychiatric Outpatient Clinics and the Pediatric Outpatient Clinic, Zagazig University Hospitals. Patients were 30 boys (71%), and 12 girls (29%) with ADHD aged between 6 and 14 years.

Ethical Consideration:

This study was ethically approved by Zagazig University's Research Ethics Committee. Written informed consent of all the participants' parents was obtained and submitted them to Zagazig University (ZU-IRB#6756). The study protocol conformed to

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the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Inclusion criteria: Age:

6-14 years, **Sex:** Both sexes are included, and they had never been examined for psychiatric illnesses or treated with psychopharmacological medicine before this treatment. All patients were newly diagnosed. The standard classification of mental disorders (DSM-V) criteria was used to make the diagnosis.

Exclusion criteria:

The exclusion criteria were chronic medical problems requiring medical treatment, such as asthma, epilepsy, etc., and all children having a history of mental illness, brain abnormalities, epilepsy, drug misuse or mental retardation were ruled out of the study.

A complete medical history, including any existing or past illnesses, pregnancies, children, and their development, as well as any relatives with a history of this or a comparable condition or treatment, must be provided. Pregnancy, labor and delivery, and neonatal problems are more common in children with ADHD than in healthy controls, suggesting that the environment may have a role. Such early brain trauma during critical times of development may have long-lasting repercussions on cognition and behavior, it is thought **[10].** Neonatal of complications may be a risk factor with a putative causal link to the development ADHD. Low birth weight (LBW) (≤ 2500 g) as a neonatal risk factor was almost exclusively associated with ADHD **[11, 12].**

This included both physical examination and psychometric evaluation by a certified psychologist for both patients and controls.

Family socioeconomic scale (SES): Modified form of Fahmy and El-Sherbini scale **[13].**

DSM-5 classifies ADHD in three presentations: Predominantly inattentive presentation, predominantly hyperactive-impulsive presentation, and predominately Combined Presentation

A systematic interview with 18 questions about DSM-5 ADHD symptoms was used to conduct the ADHD assessment (one question for each symptom).

Samples of children's venous blood were collected. In the lab, samples were maintained on ice and aliquoted before being analysed. Atomic absorption spectroscopy was used to assess zinc and iron levels in whole blood serum. The concentration of zinc in the blood was measured three times and the coefficient of variance was less than 5%.

Statistical analysis

The independent t-test (t) and the Mann-Whitney (MW) tests were employed to compare parametric and non-parametric data respectively on SPSS version 23, in the analysis of the differences between the groups. When there was a difference between two groups of non-parametric data, Proportions were compared using the Chi-square test (X^2). Diagnostic and prognostic utility in newborn sepsis were evaluated using Receiver Operating Characteristics (ROC) analysis. Cut-off points and their associated values. P value 0.05 was considered statistically significant (S). It was judged highly significant (HS) when the P value was 0.001 and non-significant (NS) when the P value was >0.05.

RESULTS

There were no statistically significant differences between the studied groups as regard age and sex distribution **(Table 1).**

Table (1): Analysis of the analyzed groups' socio-demographic characteristics:

Variable		**Cases (n=42)**		**Control (n=42)**		**MW**	**P**
Age: (years)	Mean ± SD Median Range	7.63 ± 2.63 7 4 - 16		7.57 ± 2.19 7.5 4 - 11		0.43	0.67 NS
Variable		**No**	**%**	**No**	**%**	**χ^2**	**p**
Sex:	Female Male	12 30	28.6 71.4	16 26	38.1 61.9	0.86	0.36 NS

52.4% had ADHD C, 21.4% had PH, 26.2% had PI according to DSM5 symptoms scale, and 64.3% were moderate according to severity. Finally 80.9% had associated symptoms **(Table 2).**

Table (2): Clinical data of ADHD among cases group:

Variable		No	%
DSM 5 symptom scale:	ADHD C	22	52.4
	ADHD PH	9	21.4
	ADHD PI	11	26.2
Severity:	Moderate	27	64.3
	Sever	15	35.7
Associated symptoms:	No	8	19
	Anxiety	13	30.9
	Bipolar	2	4.8
	ODD	3	7.1
	Learning disability	15	35.7
	Conduct disorders	1	2.4

Table (3) showed that there was statistical significance decrease in both Fe and Zn among cases compare to control group. In addition, there were statistical significance increases in frequency of low Fe and Zn level among cases group compared to control group.

Table (3): Serum Iron Level and Zinc Level among the studied groups:

Variable		Cases (n=42)		Control (n=42)		MW	P
Fe: (mcg/dL)	Mean ± SD	60.60 ± 5.94		96.94 ± 13.29		**6.04**	**<0.001 ****
Zn: (µg/dl)	Mean ± SD	64.55 ±4.24		95.19 ± 14.68		**4.33**	**<0.001 ****
Variable		**No**	**%**	**No**	**%**	χ^2	**p**
Fe: (mcg/dL)	Low	26	61.9	0	0	34.81	<0.001 **
	Normal	16	38.1	42	100		
Zn: (µg/dl)	< 50	25	59.5	0	0	**37**.66	<0.001 **
	50 – 120	16	38.1	42	100		
	>120	1	2.4	0	0		

Table (4) was shown that the levels of Fe and Zn had statistically significant –ve relationships with the ratings given by both parents and teachers. A statistically significant link between Zn and Fe levels was also found.

Table (4): Correlation between Iron and Zinc level and some variables among the cases group:

Variable	Fe (n=42)		Zn (n=42)	
	r	**P**	**r**	**P**
Age (years)	-0.07	0.66 NS	0.13	0.42 NS
Number of siblings	-0.03	0.89 NS	0.11	0.49 NS
Order of birth	-0.09	0.57 NS	0.03	0.88 NS
Onset (years)	-0.30	0.06 NS	-0.10	0.53 NS
Duration (years)	0.13	0.40 NS	0.25	0.11 NS
Parents rating scale	**-0.37**	**0.02***	**-0.31**	**0.04***
Teachers rating scale	**-0.33**	**0.03***	**-0.30**	**0.04***
Serum Zn	**0.78**	**<0.001****	**---**	**---**

Table (5) shows there were statistical significance increases in frequency of male sex among cases low Fe level compared to cases had normal Fe level.

Table (5): Relation between Fe level and sex, history and risk factor among cases group:

Variable		Low (n=26)		Normal (n=16)		χ^2	P
		No	%	No	%		
Sex	Female (n=12) Male (n=30)	3 23	25 76.7	9 7	75 23.3	**9.7**	**0.002** ******
Family history	No (n=30) Yes (n=12)	18 8	60 66.7	12 4	40 33.3	0.16	0.69 NS
Consanguinity	No (n=25) Yes (n=17)	15 11	60 64.7	10 6	40 35.3	0.10	0.76 NS
Maternal smoking	No (n=38) Yes (n=4)	23 3	60.5 75	15 1	39.5 25	0.32	0.57 NS
Maternal education	Illiterate (n=11) 1ry (n=7) 2nry (n=3) Intermediate(n=16) University (n=5)	8 3 0 12 3	72.7 42.9 0 75 60	3 4 3 4 2	27.3 57.1 100 25 40	7.67	0.10 NS
Parents relationship	Not living together (n=11) Bad (n=7) Not bad (n=7) Not Good (n=6) Good (n=11)	7 4 5 4 6	63.6 57.1 71.4 66.7 54.5	4 3 2 2 5	36.4 42.9 28.6 33.3 45.5	0.66	0.96 NS
Dietary habits	No (n=36) Yes (n=6)	22 4	61.1 66.7	14 2	38.9 33.3	0.07	0.80 NS

There were statistical significance increase in frequency of sever ADHD cases and associated symptoms among cases had low Fe level compared to cases had normal **(Table 6).**

Table (6): Relation between Fe level and clinical data among cases group:

Variable		Low (n=26)		Normal (n=16)		χ^2	P
		No	%	No	%		
DSM 5 symptom scale:	ADHD C (n=22) ADHD PH (n=9) ADHD PI (n=11)	14 7 5	63.6 77.8 45.5	8 2 6	36.4 22.2 54.5	2.25	0.32 NS
Severity:	Moderate (n=27) Sever (n=15)	13 13	48.1 86.7	14 2	51.9 13.3	**6.07**	**0.01***
Associated symptoms	No (n=32) Yes (n=10)	17 9	53.1 90	15 1	46.9 10	**4.39**	**0.04***

There was no statistical significance relation between Zn level and sex, history and risk factor among cases group **(Table 7).**

Table (7): Relation between Zn level and sex, history and risk factor among cases:

Variable		Low (n=25)		Normal (n=17)		χ²	P
		No	%	No	%		
Sex	Female (n=12) Male (n=30)	5 20	41.7 66.7	7 10	58.3 33.3	2.22	0.14 NS
Family history	No (n=30) Yes (n=12)	17 8	56.7 66.7	13 4	43.3 33.3	0.36	0.55 NS
Consanguinity	No (n=25) Yes (n=17)	15 10	60 58.8	10 7	40 41.2	0.01	0.94 NS
Maternal smoking	No (n=38) Yes (n=4)	21 4	55.3 100	17 0	44.7 0	3.01	0.08 NS
Maternal education	Illiterate (n=11) 1ry (n=7) 2nry (n=3) Intermediate(n=16) University (n=5)	9 4 0 9 3	81.8 57.1 0 56.3 60	2 3 3 7 2	18.2 42.9 100 43.8 40	6.77	0.15 NS
Parents relationship	Not living together (n=11) Bad (n=7) Not bad (n=7) Not Good (n=6) Good (n=11)	7 6 4 3 5	63.6 85.7 57.1 50 45.5	4 1 3 3 6	36.4 14.3 42.9 50 54.5	3.22	0.52 NS
Dietary habits	No (n=36) Yes (n=6)	21 4	58.3 66.7	15 2	41.7 33.3	0.15	0.70 NS

There were statistical significance increase in frequency of ADHD C and PH and sever ADHD among cases had low Zn level compare to cases had normal level **(Table 8).**

Table (8): Relation between Zn level and clinical data among cases group:

Variable		Low (n=25)		Normal (n=17)		χ²	P
		No	%	No	%		
DSM 5 symptom scale:	ADHD C (n=22) ADHD PH (n=9) ADHD PI (n=11)	15 7 3	68.2 77.8 27.3	7 2 8	31.8 22.2 72.7	**6.68**	**0.04***
Severity:	Moderate (n=27) Sever (n=15)	12 13	44.4 86.7	15 2	55.6 13.3	**7.14**	**0.008 ****
Associated symptoms	No (n=32) Yes (n=10)	17 8	53.1 80	15 2	46.9 20	2.28	0.13 NS

DISCUSSION

One of the most common psychiatric disorders, attention-deficit/hyperactivity disorder (ADHD) is characterized by problems with attention and/or overactivity as well as impaired social, intellectual and adaptive functioning. Environmental and other reversible risk factors have been identified in ADHD even though evidence suggests it is mostly a family disorder [(14)]. Substances ingested prior to conception are among them, as heavy metals and chemicals, as well as food and other dietary and lifestyle factors.

ADHD is not only a prevalent cause of mental health consultations in children, but it may also contribute to academic failure, school dropout and a low sense of self-worth if it is not identified and treated early. In older teenagers, those with ADHD are more likely to engage in delinquency and substance addiction if they are left untreated [(15)].

Trace elements have been studied in the past few years to see whether they might provide light on the etiology of ADHD. Studies focusing on the link between zinc and iron and attention deficit hyperactivity disorder stand out [(16)].

This case control study was conducted to find association between serum iron and zinc deficiency and attention deficit hyperactivity disorder in children, where 42 children were divided according to DSM 5 criteria into: ADHD C (combined) that presents 52.4%, ADHD PH (predominantly hyperactive) that presents 21.4%, and ADHD PI (predominantly inattentive) that presents 26.8%.

The results were nearly agreed with the study done by **Hergüner and Hergüner** [(17)] who reported that the frequency of ADHD inattentive, hyperactive and combined type was 36.1%, 3%, 60.9% respectively.

In our study, the age of the study sample ranged from 4-14 years with a mean of 7.63±2.63 years. This was the age group selected for the study to be able to apply DSM-5 criteria, as the symptoms must begin before age 12. Moreover, 14 years was the upper age limit for children in the Psychiatric outpatient clinics located in Zagazig university hospital where the study sample was taken.

Children were of both sexes. Males accounted for 71.4%of the study sample and females for 28.6%, so the male to female ratio was ~2.5: 1, which is consistent with sex differences reported in the literature for patients with ADHD.

This agree with a study that made by **Alharaiwil *et al.*** [(18)] found a link between ADHD and male sex. According to this study conducted in Arab countries, men outnumber women by a ratio of 1.61:1 to 2.5:1.

In our study, there was statistical significance decrease (P<0.01) in Zn among cases compare to control group. Regarding zinc levels, 59.5% of the cases (n=25) were below the laboratory reference range, which was 50-120 µg/dl, denoting prevalent zinc deficiency among children with ADHD in the study sample.

These results are in line with data from previous studies made by **Ghanizadeh and Berk** [(19)] suggesting that many children with ADHD have lower than average zinc levels.

An overall meta-analysis made by **Arnold *et al.*** [(20)] also suggests a significant association between low zinc levels and a diagnosis of ADHD.

Yang *et al.* [(21)] stated that children with ADHD have lower zinc levels than typical children in the four most commonly examined elements (Cu, Zn, Fe, and Mg), according to a study.

In our study there was statistically significant (P<0.05) increase in frequency of ADHD C (combined type) & PH (predominantly hyperactive type) and sever ADHD among cases had low Zn level compared to cases had normal level.

A lack of iron during a child's formative years might impair brain and behavioral development by serving as a cofactor in the production of essential neurotransmitters like dopamine, nor-epinephrine, and serotonin [(22)].

In our study, there was statistical significance decrease in serum iron among cases compare to control group.

A study made by **Konofal *et al.*** [(23)] stated that iron deficiency, which has previously been linked to cognitive impairment, learning impairments, and psychomotor instability, should be evaluated in the context of central dopaminergic dysfunction in the context of ADHD symptoms.

The longitudinal study by **Corapci *et al.*** [(24)] chronic iron insufficiency in infancy predicted externalizing issues at the ages of 5 and 11–14 in 185 healthy Costa Rican children. Children with ADHD had significantly lower levels of concurrent serum ferritin than children without the disorder, according to the case-control study conducted by **Juneja *et al.*** [(25)] in India, but no link could be found between ferritin levels and parent or teacher assessments of inattention or hyperactivity.

In contrast to the previous research, a cross-sectional study of Brazilian youngsters by **Menegassi *et al.*** [(26)] and a pilot study of youngsters in Vancouver by **Kiddie *et al.*** [(27)] despite the fact that both investigations were constrained by small sample sizes (N=62 and N=43, respectively), no correlation was found between current iron status and ADHD or associated symptoms.

Most recent investigation by **Wang *et al.*** [(28)] are not in agreement with us because they found no significant difference in blood iron levels between ADHD and control groups.

CONCLUSION

It could be concluded that both zinc and iron serum levels were found to have a significant correlation with parent-reported hyperactivity symptoms, suggesting that patients with low levels in these minerals may be more likely to suffer from ADHD symptoms.

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