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SERUM ZINC LEVEL AMONG CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER

By

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ABSTRACT

Background: Zinc deficiency causes abnormal dopaminergic neurotransmission and may contribute to the physiopathology of attention-deficit/hyperactivity disorder (ADHD). Attention-deficit hyperactivity disorder is an early-onset, clinically heterogenous disorder of inattention, hyperactivity, and impulsiveness. The diagnosis and treatment of attention-deficit hyperactivity disorder continues to raise controversy, and, there is also an increase in treatment options. Therefore, we aim to assess serum zinc level among children with ADHD.

Methods: This was a case control cross sectional study, in which 100 ADHD children were recruited from Bab Elsharya outpatient pediatric psychiatry clinic and compared with 40 healthy control children in the period between May 2017 and May 2018. Serum zinc level was assessed with atomic absorption in both groups.

Psychometric procedure: The Arabic version of Conners' Parent Rating Scale-Revised-Long version, and social score were used to calculate social standards of families.

Results: The mean serum zinc levels were lower in the children with ADHD (mean \pm SD, 75 \pm 19 ug/dL) than in the controls (mean \pm SD, 112 \pm 15 ug/dL; P < .001). Serum zinc levels were less than (<70 ug/dL) in 69% of children with ADHD and 22% of controls (P < .001). There was no statistically significant difference between zinc deficient cases and non-zinc deficient cases as regards conners scale and its subscales (inattention, hyperactivity, impulsivity, ADHD index and DSM V total ADHD), however it was nearly near significance in impulsivity.

Conclusion: This study brings additional information about the role of zinc in the etiology of ADHD. The study indicated that ADHD patients has significant decrease in serum zinc level in comparison to the controls, however there was no significant correlation between serum zinc level and symptoms of ADHD, mostly due to the multi-factorial nature of its etiology.

Recommendations: serum zinc level should become a routine measurement in ADHD children which might benefit from a therapeutic trial with zinc supplementation.

Furthur studies are required to assess the effectiveness of zinc administration in the management of ADHD children.

Key words: attention-deficit hyperactivity disorder, socioeconomic standard, serum zinc level.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a serious, high-incidence disorder that impairs academic learning, disrupts social and peer relations, and can greatly disturb functioning within the home and at school. characterized ADHD is bv inappropriate of symptoms impulsivity, inattention. and overactivity, according to DSM criteria (American Psychiatric Association, 1994).

Although many studies have been carried out regarding the aetiology of ADHD, no definite cause of the illness has yet been determined. Both animal and human study suggest that involvement of zinc deficiency plays a major role in hyperactivity (Golub et al., 1996).

Human zinc deficiency syndrome leads to concentration impairment and jitters (Agget and Harries, 1979), and can delay cognitive development (Black, 1998).

Some investigators have reported that zinc was found to be significantly deficient in ADHD

compared to controls (Bekaroglu et al., 1996); (Kozielec et al., 1994).

In spite of the good response of many patients with ADHD to stimulant drugs, a substantial percent do not respond to or develop significant side effects from stimulants. For this reason, new investigations have been initiated for ADHD treatment.

PATIENT AND METHODS

This studv included 100 Egyptian children diagnosed with ADHD according to diagnostic and statistical manual of mental disorders, fifth edition. 2013. (DSM V) criteria. All of them were selected by simple random method from Bab Elsharya outpatient pediatric psychiatry clinic during the period from May 2017 to May 2018. Forty healthy control children were selected by simple random method from normal children of the same age . All the patients ranged with age from 4 to 14 years, both sexes were included.

Inclusion criteria:

- Age: (4-14 yrs.) old.
- Sex: both gender (Male & Female)
- DSM V diagnostic criteria of ADHD (American Psychiatric Association, 2013).

Exclusion criteria:

- Mental retardation.
- Presence of other medical conditions as chronic illness, hearing or vision impairment, medications side effects which may result in hyperactivity and impaired sleep rhythm.

The control group was chosen from normal children of the same age .both the patient and the control group had the same educational and socioeconomic level as well as the same genetic background. All patients had retardation (MR) mental (IO below 70 as assessed by the Stanford Binet test), organic etiology. Children with congenital disorders, any chronic medical illness, or those receiving medical treatment for systemic disorders were excluded from the study.

METHOD OF STUDY

Semi structural interview:

A specially designed semi structural interview obtained from the Al-Azhar pediatric psychiatric sheet was used to determine demographic data, personal history (prenatal, natal, and childhood history), past history, family history, and mental state examination. The diagnosis was made according to the DSM-V criteria (American Psychiatric Association, 2013).

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The Arabic version of Conners' Parent Rating Scale-Revised-Long version (El-Sheikh et al., 2002)

developed This was bv (Conners et al., 1997), translated by (El-Sheikh et al., 2002), and validated by use in many subsequent researches. It is a paper-and-pencil screening questionnaire designed to be completed by parents to help determine whether children between the ages of 3 and 17 years might have ADHD. It consists of 80 questions, to be answered by parents, each followed by four choices: 0 (not at all), 1 (just a little), 2 (pretty much), or 3 (very much).

The following subscales are provided after scoring the test: Oppositional, cognitive problems/Inattention,

hyperactivity, anxious-shy, perfectionism, social problems, psychosomatic, Conners' ADHD index, Conners' global index restless/impulsive, Conners' global index emotional lability, Conners' global index total, DSM-V inattentive, DSM-V hyperactiveimpulsive, DSM-V total.

Social score to calculate social standards of families (Fahmy and El-Sherbini, 1983)

This is the type of social score correlate the social to used with standard the knowledge attitudes and practices of certain with certain groups health problems related to culture. The model is modified by certain additions of some social indices include the presence that or absence of audiovisual aids of information inside houses. Thus, the indices used were education of father. education of the the mother, per-capita income of family members, crowding index, sanitation in general, family size, and information tools in the house. The total score summed is 37. A total score of 20-25 indicates a low social standard. A middle social standard is determined by a total score of 26-30, whereas high social standard needs total score of 31-37 (Fahmy and El-Sherbini, 1983).

Laboratory assessment:

We take 5ml of the blood sample from children then centrifugation was done for serum separation then collected sample stored at -20° C until analysis.

Principle:

absorption Atomic spectroscopy a form of is quantitative analysis can measure the concentration of certain elements in a sample depending upon how much of a specific wavelength is absorbed. depend on that certain elements absorb certain wavelengths, and this level of absorption is characteristic of each element. Also, electrons in atoms can only exist in particular energy levels and when an electron moves to a higher energy level, electromagnetic radiation of a particular frequency is absorbed. the element being tested must be known because a wavelength must be emitted which is specific to the element being tested, as certain elements only absorb certain wavelengths (Smith and Hieftje, 1983).

Serum Zinc by Flame Atomic Absorption Spectrometer:

Serum Zn level determination had been carried out using Varian Flame Atomic Absorption Spectrometer 220 as described by (Smith and Hieftje, 1983), the wavelengths used for Zn determination and the optimum working ranges were as follow: Wavelength (nm) Optimum working range (mg/L) Zinc213.9

0.01 - 2. Sample volume was introduced continuously after serum sample dilution with distilled water (750 ML of serum + 3 ml of distilled water). (Normal serum zinc level is 0.70-1.20 microgram/ml).

Statistical analysis:

- Student T Test was used to assess the statistical significance of the difference between two study group means.
- The Spearman ρ method was used to test the correlation between numerical variables.
- Data were analyzed using SPSS win statistical package version 17 (SPSS Inc., Chicago, Illinois, USA). Numerical data

were expressed as mean and SD or median, and range as appropriate. Qualitative data were expressed as frequency and percentage.

- Comparison of categorical variables between the study group and their siblings was carried out using the McNemar test.
- For quantitative data, comparison between two groups was carried out using the Mann-Whitney U-test (nonparametric t-test). Different scores between the study group and their siblings were compared. A Pvalue less than 0.05 was considered significant.

RESULTS

The sample included 100 children with ADHD (mean age 8.1 \pm 2.2 years); 40 of healthy normal children were included as a control

group (mean age 7.8 ± 2.7 years). 88% of the cases were males and 12% were females.

	Patients "n=100"		Control "n-40"		Р
Age Range(years) Mean± S.D.	4-14 8.1 ± 2.2		4-14 7.8 ± 2.7		0.28
Sex	0.0	0.00/	26	0.00/	1.00
Male	88	88%	36	90%	1.00
Female	12	12%	4	10%	0.497
Maternal age of					
conception		•••	10		
Range		-33.0		0-33.0	
Mean		.22		5.98	0.727
S.D.	±3	.82	±	3.52	
Number of sibling					
Range	1.0-5.0		1.0-5.0		
Mean		89	2.95		0.137
S.D.	±0.86		± 0.88		
Family history of 1 st					
&2 nd degree relatives:		•		1	
Hyperactivity	14	14%	4	10%	0.37
Autism	7	7%	2	5%	0.387
Epilepsy	2	2%	0	0.0%	0.509
MR	3	3%	0	0.0%	0.682
Mother occupation					
Not working	67	67%	31	77.5	0.621
Working	33	33%	9	22.5	0.512
Perinatal asphyxia					
-ve	85	85%	40	100%	0.621
+ve	15	15%	0	0%	0.512
Language&social					
Delay	2	2%	0	0.0%	0.621
Socioeconomic status					
Low	12	12%	7	17.5%	2.05
Moderate	54	54%	24	60%	0.512
Average	34	34%	9	22.5%	0.358

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in india gouinal of i ca	101.22	110.2	119110, 2012

This table shows that there was no statistically significant difference between the two studied groups as regards demographic characteristics.

Table (2): Comparison between	patients and controls as regards deficient
serum zinc	

		Groups					
Zn		Patients		Controls		Total	
		Ν	%	Ν	%	Ν	%
	w cut off (70ug/dl)	69	69%	9	22.5%	78	55.7%
	ve cut off (70ug/dl)	31	31%	31	77.5%	62	44.3%
,	Total	100	100%	40	100%	140	100%
Chi-	X^2	25.03					
square	P-value	0.0001*					

This table shows that there was a highly significant difference between cases and controls as regards serum zinc level.

 Table (3): Correlation between zinc-deficient and non-zinc-deficient cases as regards conners sub-scales

	Zinc-deficient cases (n=69)		Non-zinc-o cases (n		
Variable	Mean	SD	Mean	SD	P value
Conners scale: Oppositional	65.38	9.39	65.56	12.34	0.698
Conners scale: Inattention	75.38	8.27	71.74	9.69	0.412
Conners scale: Hyperactivity	75.46	15.11	70.85	10.83	0.107
Conners scale: Impulsivity	76.46	14.69	67.41	12.55	0.068
Conners scale: ADHD index	72.31	8.81	69.78	10.86	0.211
Conners scale: DSM total ADHD index	75.00	11.12	71.04	10.00	0.21

This table shows that there was no statistically significant difference between zinc deficient cases and non-zinc deficient cases as regards

DISCUSSION

ADHD is а behavioral syndrome of childhood characterized bv inattention. hyperactivity and impulsivity (McArdle, 2004). It's a chronic, debilitating psychiatric illness that co-occurs with other often common psychiatric problems. Although empirical evidence supports pharmacological and behavioral treatments; side effects and concerns regarding safety and fears about long-term use of these drugs all contribute to families searching for alternative methods of treating the symptoms of ADHD (Rucklidge, 2009).

Zinc has been recognized as an essential element for plant and animal for over 60 years (**Prasad et al., 2003**). It is the second most abundant trace element in the human body, and the total content is approximately two grams in adult person (Aggett and Comerford, 1995).

Zinc is an important cofactor for metabolism relevant to neurotransmitters, prostaglandins, and melatonin. And indirectly affects dopamine metabolism. It is necessary for 100 different conners scale and its sub-scales however it was nearly near significance in impulsivity.

metalloenzymes and metalenzyme complexes (Toren et al., 1996).

It contributes to the structure and function of the brain (Black 1998). One biochemical and physiological role receiving increasing attention is zinc ion release during neuronal activity (Li et al, 2003).

Approximately 15% of the brain's zinc can be found in synaptic vesicles (Lopez-Garcia et al., 2001). Because these ions exhibit numerous effects on ligand-gated, voltage-dependent ion channels in vitro, zinc ions likely modulate synaptic transmission, though this is not directly confirmed (Li et al., 2003). Zinc can also affect the brain indirectly, because it is needed for cell membrane stabilization, indirect antioxidant functions. proper hormonal metabolism, and cellular energy release (Prasad 1993 and Powell, 2000).

These functions have been shown to be affected by somewhat moderate zinc deficiencies in humans and experimental animals (Prasad 1993; Powell, 2000; Devine et al., 1998 and Licastro et al., 1992).

Several data suggest that the marginal zinc deficiency may be more concentrated in the ADHD population-or, stated conversely, that the ADHD population may have a higher prevalence of marginal zinc deficiency (Halas and Sandstead, 1975; Sandstead et al., 1977 and Golub et al., 1996).

In our study The zinc deficient patients were found to be 69 (69%)(abnormal cases) and the normal zinc level cases were found to be 31(31%) cases (normal cases).while the zinc deficient controls were found to be 9(22.5%) and the normal zinc level controls were found to be 31 (77.5%).

There are several data suggest that the zinc deficieny play an important role in pathogenesis of magnetic Higher ADHD. (MRI) Resonance image resonance of glutamate neurons ADHD children observed in (Courvoisie al.. 2004)et combined with achelatable zinc the synapses of these pool in neurones may suggest higher zinc turnover in this disorder and possibly higher zinc requirement with subsequent deficiency of zinc in ADHD (Colvin et al., 2000).

Low serum status of both zinc and copper might have resulted from low dietry intake of those trace mineral (Hotz et al., 2003). Our results could be also explained by the fact that Zinc has a critical role in the function of several structural, regulatory and catalytic proteins (Fierke, 2000 and Hambidge, 2000).

It is present in the brain bound to proteins and is important for its structure and function (Sandstead, 1986 and Pfeiffer & Braverman, 1997).

Extensive work has been done on animals to examine the role of zinc deficiency on brain function and cognitive development. The exact mechanisms are not clear but its presence in high synaptic concentrations in the vesicles of the special 'zinc containing' neurons in the forebrain (Hesse, 1979; Howell et al.. 1984; Frederickson & Danscher. 1990 and Frederickson 2000) et al. together with its function in biochemical processes like myelination and release of neurotransmitters like g-amino butyric acid [GABA] (Ben-Ari 1991) and Cherubini, and glutamate, indicates that it may be a key modulator of neuronal excitability. There is also some evidence to suggest that zinc

deficiency results in lowered levels of long v-3 and v- 6 chains possibly causing impaired fatty acid metabolism in the neurons (Wauben et al., 1999).

Moreover. it seems to he important for neurogenesis, neuronal migration and synaptogenesis and its deficiency could interfere with neurotransmission and subsequent neurophysio-logical development (Dvergsten, 1984; Colvin et al., 2000 and Fredrickson et al. 2000).

In addition, zinc is involved in the metabolism of thyroid hormones, receptor function and transport of other hormones that could influence the central nervous system (Morley et al., 1980).

Our results could be compared to those obtained by **(Kozielec et al., 1994)** in Poland reported serum zinc significantly (p <0.001) deficient in ADHD children, compared to controls.

(Bekarogluet al., 1996) in Turkey reported mean serum zinc of $60.6 \pm 9.9 \text{ mcg/dL}$ in 33 boys and 15 girls with ADHD, compared to $105.8 \pm 13.2 \text{ mcg/dL}$ in healthy volunteers (30 boys and 15 girls) (Toren et al., 1996), in Israel, reported significantly lower serum zinc levels and more variance in 39 boys and 4 girls 6– 16 years of age with ADHD than in a control group of 28 agematched healthy controls; 30% of ADHD subjects were below the control range.

In another Polish study. 1998) (Starobrat-Hermelin, found a high rate of magnesium, zinc, iron, copper, and calcium deficiencies in 116 children with ADHD on the basis of serum, red cell, and hair analyses. Hair zinc lower in ADHD with was comorbid oppositional-defiant or conducts disorder than in ADHD alone or with anxiety.

(Arnold et al., 1990) reported that 118 children with Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised (DSMIII-R) ADHD had 30% lower 24-hour urine zinc than 7 normal controls, suggesting either lower dietary intake or poorer absorption rather than zincwasting metabolism.

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مستوى الزنك في مصل الدم لدى الأطفال الذين يعانون من المنتوى النباه

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أقسام *طب الأطفال **قسم الباثولوجيا كلية الطب - جامعة الأزهر

يعتبر مرض فرط الحركة وقلة الانتباه أحد المتلازمات السلوكية للأطفال حيث يعاني الطفل من فرط في النشاط الحركي وسمات الغفلة والاندفاع ، إنه يعتبر من الأمراض النفسية المزمنة التي يمكن حدوثها مع غيرها من الأمراض النفسية ، وبالرغم من وجود العلاج الطبي والنفسي لهذا المرض. فإن هناك كثير من الأبحاث المستمرة لإيجاد طرق أخرى لعلاج هذا المرض لتفادي الأعراض الجانبية للعلاج الطبي .

إن استخدام العلاج المكمل والبديل بدأ يتزايد في الآونة الأخيرة حيث وجد أن من 60-65٪ من الآباء للأطفال الذين لديهم أطفال يعانون من فرط الحركة يستخدمون العلاج البديل لتفادي الأعراض الجانبية للأدوية المستخدمة في علاج فرط الحركة حيث أصبح العلاج الغذائي هو البديل ومن أهم خصائص علاج فرط الحركة وقلة الانتباه.

إن نقص الزنك يؤدي إلى اختلال الانتقال العصبي الدوباميني وبالتالي من الممكن أن يساهم في الفيسيولوجيا المرضية لاضطراب فرط الحركة وقلة الانتباه.

الهدف من الرسالة: قياس مستوى الزنك في مصل الدم في الأطفال مرضى فرط الحركة المصحوب بقلة الانتباه.

الجزء العملي: العينة والأدوات:

المجموعة الأولى:

(100 طفل مصري) تم تشخيصهم كمرضى فرط حركة مصحوبا بنقص الانتباه وفقا للدليل التشخيصي والإحصائي للجمعية الأمريكية للطب النفسي الصورة الخامسة وقد SERUM ZINC LEVEL AMONG CHILDREN WITH ATTENTION DEFICIT HYPERACTIVITY DISORDER Muhammad abdel-Aziz Ibrahim Karam, Mohsen Taha Elkeiy, Ibrahim Ahmed Shobair, Kamel Soliman Hammad

تم اختيار هم من عيادة الأطفال للأمراض النفسية والعصبية في مستشفى باب الشعرية الجامعي يتراوح عمر هم من 4-14 سنة الجنسين (ذكور و إناث) ولا يعانون من أي مسببات عضوية للمرض أو أي مرض مزمن ، ولا يتناولون علاج دوائي لأي أمراض مزمنة.

المجموعة الثانية: (مجموعة ضابطة):

40 طفلا مقابلين للمرضى من الجنسين يتراوح عمر هم من 4-14 سنة وبنفس معايير استبعاد المرض وعلى ألا يكون لديهم تاريخ مرضي سواء كان نفسيا أو سابقة لكشف نفسي.

الأدوات:

لكلا المجموعتين تم عمل الآتي:

1- أخذ تاريخ مرضي كامل وتم توقيع كشف طبي عليهم.

2- خضع جميع الأطفال للاختبارات الآتية:

- مقياس كونورز لتغيير سلوك الطفل "تقدير الوالدين" الصورة المطولة المراجعة لمعرفة مدى حدة المرض ولتأكيد التشخيص الإكلينيكي.

- قياس المستوى الاجتماعي لعائلات الأطفال المصابين بمرض مزمن باستخدام مقياس فهمي والشربيني 1986.

- تم أخذ عينات دم لجميع الأطفال لعمل تحليل مستوى الزنك في مصل الدم.

النتائج:

توصلت الدر اسة إلى النتائج الآتية:

- أغلب العينة من الذكور (88%) بينما (90%) من العينة الضابطة من الذكور.

- وجد أن 68 حالة تعاني من نقص مستوى الزنك في مصل الدم بينما 32 حالة لا يعانون من هذا النقص.

- تمت مقارنة الحالات التي تعاني من نقص الزنك والحالات التي لا تعاني منه بالنسبة لمقياس كونورز تقدير الوالدين وقد وجد أنه لا يوجد فرق إحصائي واضح بين الحالات التي تعاني من نقص الزنك والحالات التي لا تعاني منه وإن هناك فرق إحصائي شبه معتبر بالنسبة لمقياس الإندفاعية.

هذه النتائج تشير إلى أن الزنك قد يلعب دوراً هاماً في مرض فرط الحركة كما أن علاج الأطفال المصابين بإعطاء الزنك قد يؤثر بالإيجاب على أعراض هذا المرض.