SERUM MANGANESE LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVE DISORDER

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Abstract

Background: ADHD is one of the most common neurodevelopmental and psychiatric disorders of childhood. Manganese is an essential micronutrient, however exposure to high doses of manganese either by ingestion or inhalation produces several adverse effects in humans.

Objective: To assess whether serum manganese levels are high in children with ADHD.

Methods: The present study is a case-control study that was conducted on forty patients and twenty controls from 1st September 2016 to end of December 2017. The ADHD patients were treatment-naïve. Both case and control groups were assessed by history taking, Child Behavior

Checklist, Attention Deficit Hyperactivity Disorder rating scale (SC4),Stanford Binet $5^{th}$ edition and had their blood sample taken to measure serum Manganese levels using measured with Inductively Coupled Plasma- Mass Spectrometry.

Results: Higher mean manganese level among ADHD cases (5.5±1) compared to controls (4.1± 0.6) respectively and the difference is highly significant statistically (P<0.001)

Conclusion: We speculate that our observed relationship between ADHD diagnosis and higher Mn levels may be part of an ‘‘environmental etiology of dopamine deficits (ADHD)’’. Exposure to low/moderate but biologically relevant levels of Mn might interfere with optimal levels of dopamine in predisposed subjects leading to ADHD.

Keywords: Attention Deficit Hyperactivity Disorder, Manganese, Dopamine, Dopamine Transporter, children.

قياس المنغنيز في مصل الدم فى الأطفال الذين يعانون اضطراب نقص الانتباه و فرط النشاط

المقدمة:

اضطراب نقص الانتباه وفرط النشاط هو اضطراب النمو العصبي التي يحددها نمط مستمر من الغفلة و / أو فرط النشاط والاندفاع الذي يتداخل مع عمل أو التنمية، ظهرت عليه أعراض في مكانين أو أكثر (على سبيل المثال في المنزل أو المدرسة أو العمل؛ مع الأصدقاء أو أقارب، في

أنشطة أخرى).ازداد اضطراب نقص الانتباه وفرط الحركة في الانتشار خلال السنوات القليلة الماضية، مما أدى إلى زيادة الوعي وحث العديد من الباحثين للبحث عن العوامل البيئية ومراقبة دور المواد السامة المختلفة في الاضطرابات العصبية النمائية بما في ذلك نقص الانتباه وفرط الحركة. على الرغم من المنجنيز هو معدن أساسي في الجرعات الملائمة، قد ارتبط التعرض المفرط والمزمن لجرعات عالية بالسمية العصبية، مؤدية إلى السلوكية العصبية التي تنطوي على الوظائف الحركية والمعرفية فضلا عن المشاكل النفسية ويشمل التسمم نظام الدوبامين حيث أشارت دراسات حديثة أن المنغنيز يتراكم في الخلايا العصبية للدوبامين مما يؤدى لإنخفاض مستوياته فى المخ . وقد تم أيضا ربط اضطراب نقص الانتباه وفرط الحركة إلى اختلال وظائف الدوبامين حيث أن نظام الدوبامين هو الموقع الرئيسي لعمل علاج اضطراب نقص الانتباه وفرط النشاط الدوائي.

الهدف من الدراسة

١- تقييم مستويات المنغنيز في مصل الدم في الأطفال الذين يعانون من اضطراب نقص الانتباه فرط النشاط الحركى

٢- المقارنة بين مستويات المصل المنغنيز وشدة الأعراض والتواكب المرضي في الأطفال الذين يعانون من اضطراب نقص الانتباه وفرط الحركة

منهجية الدراسة:

نوع الدراسة: دراسة حالات وشواهد

المرضى: أجريت هذه الدراسة على اربعين طفلا من المصابين بفرط الحركة وتشتت الانتباه وعشرين طفل طبيعي من الجنسين الذين يترددوا على عيادة الطب النفسي بمركز ذوي الاحتياجات الخاصة، جامعة عين شمس.

تم اخذ التاريخ الطبي الشامل ، فحص اكلينيكي شامل، وعمل القياسات النفسية( مقياس مستوى الذكاء Stanford Binet 5th Edition ، مقياس فرط الحركة وتشتت الانتباه ADHD rating scale- SC4،

مقياس Child Behavior Checklist، وصاحب عينة دم لتحديد مستوى المنغنيز في مصل الدم

النتائج:_ مستويات المنغنيز في مصل الدم أعلى في الاطفال المصابين بفرط حركة وتشتت الانتباه عن

أقرانهم الطبيعيين.

الخلاصة: وجود_علاقة بين اضطراب فرط الحركة وتشتت الانتباه ومستوى المنغنيزالعالي في مصل الدم يمكن ان يعتبر سبب بيئي يؤدي لاضطراب مستويات الدوبامين.

الكلمات المفتاحية: فرط حركة/ناقص انتباه – منغنيز – دوبامين– ناقل الدوبامين

## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, has symptoms presenting in two or more settings (e.g. at home, school, or work; with friends or relatives; in other activities) and negatively impacts directly on social, academic or occupational functioning. ADHD is considered one of the most common psychiatric disorders of childhood and adolescence; it has a global prevalence of about 5% (American Psychiatric Association, DSM5, 2013).

Even though the exact etiology of ADHD is still unknown, what is believed to predict the existence of ADHD is family history of the disorder, comorbid psychiatric disorders and psychosocial adversities .Dysregulation of the catecholaminergic system in ADHD patients has been suggested by evidence based neurochemical, imaging and genetic studies (Biederman, 2005).

ADHD has increased in prevalence over the past several years, leading to increased awareness and urging many researchers to look for environmental factors & observe the role of different toxicants in neurodevelopmental disorders including ADHD (Wasserman et al., 2006)

Essential nutrients, such as trace minerals including manganese (Mn), iron, zinc, iodine, selenium, copper, fluoride, and chromium, have been associated with changes in neuronal function therefore their excess or deficiency could lead to adverse effects on behavior and learning (Hubbs et al.,2005). Specifically, manganese is essential to human beings, it is needed by children to support normal brain growth and development as well as nerve function.

The main exposure to manganese is from industrial emissions, fuel combustion and by ingestion of manganese containing food, water and nutritional supplements (Farias et al., 2010), people who consume soy milk, whole-grain cereals, green leafy vegetables and nuts (manganese rich ), as well as heavy tea drinkers may have a higher intake of Mn than the average person (WHO, 1973). Specifically children receive excess exposure to manganese postnatally through two major sources: auto exhaust ( because manganese is used as an octane enhancer in gasoline ) and soy based infant formula the latter may contain 200-300 meg/liter ( 50 times the levels in breast milk )

Although Mn is an essential metal at low doses, excessive and chronic exposure to high doses has been associated with neurotoxicity (Wasserman et al., 2006), where high levels of exposure show an extrapyramidal syndrome similar to parkinsonism (Manganism) characterized by gait dysfunction with propensity to fall backward, postural instability, bradykinesia, rigidity, micrographia masked facies speech disturbance and muscle tremors. Lower levels of exposure may produce neurobehavioral deficits involving motor and cognitive functions as well as Psychological problems (Levy & Nassetta, 2003)

Intoxication involves the dopaminergic system where recent studies have suggested that manganese accumulates in dopaminergic neurons via presynaptic dopamine transporter (DAT) decreasing dopamine levels ( Farias et al., 2010 ). ADHD has been also linked to impaired dopaminergic function where dopaminergic system is the primary site of action of pharmacological ADHD treatments.

## AIM OF THE STUDY:

The aim of this research is to assess serum manganese levels in children with attention deficit hyperactive disorder and correlate between serum manganese levels, severity of symptoms and comorbidities in children with attention deficit hyperactivity disorder.

## Subjects and Methods

The present study is a case-control to highlight the correlation between serum Mn levels and ADHD in children under study.

A) Subjects:

The present study was conducted on forty patients who attended the child psychiatry of center of special needs, Faculty of Postgraduate Childhood Studies, Ain Shams University from 1st September 2016 to end of December 2017. By the standardized psychiatric evaluation they were diagnosed as ADHD according to DSM V.

(i)Choice of the study sample:

Inclusion Criteria:

In this study, forty participants were selected by purposeful sampling and were contacted by the researcher and the concerned team. The sample consists of patients whose:

- Age: 6-11 years
- Gender: Both sexes
- IQ scores: 90-110
- ADHD treatment: Treatment naïve patients.

Exclusion Criteria:

- Children with IQ less than 90
- Age less than 6 years
- ADHD treated with methylphenidate.
- ADHD with any other neurodevelopmental disorder
- ADHD with any other chronic disease
- Non-consenting subjects or care-givers

(ii) Choice of the control group:

Twenty participants who were randomly selected from apparently healthy children attending the pediatrics clinic from 1st September 2016 to end of december 2017 matched cases in age, sex residence and IQ

Ethical Aspects :

Approval of the study by the Ethical Scientific Research Committee, Institute Of Postgraduate Childhood Studies (IPGCS, 2014) in the form of informed written consent from the caregiver and ascent from the child him/herself.

B) All children in this study were subjected to:

1. Full history taking: including age, gender, residence as well as full medical, nutritional and Psychiatric history.

2. Full medical examination.

3. Psychological Assessment:

- Stanford–Binet Intelligence Scales: is an individually administered intelligence test that was revised from the original Binet-Simon Scale by Lewis M. Terman, a psychologist at Stanford University. The Stanford–Binet Intelligence Scale is now in its fifth edition (SB5) and was released in 2003. It is a cognitive ability and intelligence test that is used to diagnose developmental or intellectual deficiencies in young children. The test measures five weighted factors and consists of both verbal and nonverbal subtests. The five factors being tested are knowledge, quantitative reasoning, visual-spatial processing, working memory, and fluid reasoning (Gale, 2003)

- Child Behavior Checklist (CBCL) of Achenbach (1991), Achenbach and Rescorla (2001). It is a behavior checklist for children from 1.5 to 18 years of age, it's a rating scale filled out by parents, teachers or the child himself to assess various aspects of psychopathology in childhood & adolescence, these instruments are designed to provide standardized description of functioning.

The behavioral profiles of children in the study as reported by caregivers of both the study and control groups, were recorded on eight syndrome subscales: (Internalizing subscales ) "Anxious/ Depressed" "Withdrawn/ Depressed" " Somatic complaints",
( Externalizing subscales ) "Aggressive behavior", "Rule-breaking behavior" and other subscales "Social problems" " Thought problems" " Attention problems" and finally all scales are represented in Total problem scores (Asenbach, 1991a ).

- Attention Deficit Hyperactivity Disorder Rating scale IV (ADHD-SC4) Arabic version (Gomaa and Zeinab, 2002): It is completed by parents to evaluate patients with ADHD, assessing severity of the following: Inattention, Hyperactivity/Impulsivity, peer conflict and oppositional defiant disorder (ODD).

4. Laboratory investigations :

A 5 CC sample of venous blood will be obtained from each child and transferred to a metal free test tube with no additives. After clotting the blood samples will be centrifuged and the serum will be separated in an acid washed plastic screw capped vial using approved guidelines and kept at −20 °C for atomic absorption spectrometry, Normal manganese level in serum measured with Inductively Coupled Plasma– Mass Spectrometry (ICP–MS) ranges from 0 to 2 ug/L (Wu, 2006). In literature it was suggested that the upper limit of serum manganese reference range could be raised to 2.9ug/L (Muniz et al., 2001)

## Results

Table (1): Comparison between ADHD cases and controls as regards the mean Manganese level in serum

Manganese level in serum (ug/L)

| | Mean (ug/L) | ± SD | t–test | P–Value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Cases N=40 | 5.55 | 1.0 | 5.5 | 0.000** |
| Control N=20 | 4.11 | 0.6 | | |

** $P<0.01$ highly significant

This table shows a higher mean manganese level among cases of ADHD 5.55 compared to 4.11 among controls and the difference is highly significant statistically.

Table (2): Comparison between cases and controls as regards cut off value 5 ug/L serum Manganese level.

Manganese level in serum (ug/L)

| | <5 No. % | >= 5 No. % | $X^2$ | P-Value |
|---|---|---|---|---|
| Cases N=40 | 15 37.5 | 25 62.5 | 12.0 | 0.001 |

| | | | | |
|---|---|---|---|---|
| | | | | ** |
| Control<br><br>N=20 | 17 85.0 | 3<br><br>15.0 | | |

** P<0.01 highly significant

This table shows a higher percentage of high manganese in serum among cases 62.5% compared to 15% among controls and the difference is highly significant statistically.

Table (3): Pearson Correlation coefficient between ADHD SC4 T scores and Manganese level in serum

| | |
|---|---|
| ADHD SC4 | Manganese level in serum |

| | |
|---|---|
| | (ug/L) |
| Attention score | r= −0.173<br>P=0.2 |
| Hyperactivity,<br>impulsivity | r=0.747<br>P=0.000** |
| Combined score | r=0.446<br>P=0.004 ** |
| Peer conflict score | r=0.810<br>P=0.000** |
| ODD score | r=0.879<br>P=0.004 ** |

** $P<0.01$ highly significant

This table shows no significant correlation between attention score among cases the manganese level in serum. On the other hand it shows a highly significant positive correlation between hyperactivity impulsivity scores among cases and the manganese level in serum, it also shows highly significant positive correlation between combined score among cases and the manganese level in serum, a highly significant positive correlation between peer conflict score among cases and the manganese level in serum and a highly significant positive correlation between ODD score among cases and the manganese level in serum as well.

## Discussion:

The present study examined the association between levels of Mn in serum and ADHD symptoms in children. First, we found that treatment-Naïve children with ADHD were found to have higher serum Mn levels than controls. Second we found positive and strong associations between serum Mn levels and externalizing symptoms, hyperactive and aggressive behaviors. In this study, no measurement of serum Mn was below the upper limit of reference range in both cases and controls, with mean Mn serum levels in cases 4.2ug/L and in controls 5.8ug/L. Interestingly, 62.5% of cases had serum Mn levels higher than 5ug/L while only 15% of controls have serum Mn levels higher than 5ug/L.

While neurotoxic effects of high level Mn exposure have been clearly documented, little is known about exposure to subtoxic Mn levels. Toxicological studies have shown that children exposed to subtoxic levels of Mn may exhibit symptoms of ADHD. Compared with adults, children absorb and accumulate more manganese and it is to be noted that in infants, manganese easily gains access to the brain. Findings of high serum manganese levels in children with ADHD are consistent with prior studies that suggested that the exposure to subtoxic levels of Mn, could be linked to the etiology of ADHD (Pihl and Parkes, 1977; Collip et al., 1983; Farias et al., 2010; Yousef et al., 2011; Lucchini et al., 2012; Shin et al., 2013)

Farias et al. (2010) performed a study in a Brazilian city where he assessed a group of children with ADHD and matched control children without psychopathology who attended the public schools in a southern Brazilian city and found that ADHD children who were not currently taking any medications had significantly elevated levels of serum Mn than those of controls.

Similarly Yousef et al. (2011) found that higher manganese blood levels were associated with ADHD. In another study in a Korean city by Shin et al. (2013), the association between hair Mn and ADHD symptoms in children was examined; a significant association was evident between Mn levels and the presence of ADHD.

On the contrary a study was done in Valcamonica, a valley in the pre-Alps where ferroalloy plants had been operating for about a century until 2001, and the Garda Lake, a tourist area with limited industrial activity. Subjects were recruited from junior high schools (total 20 schools) of the local public school district with average age of 12.9 years old, no association was found between hair/ blood manganese concentrations and attention deficit hyperactivity or behavioral scores (Lucchini et al., 2012).

Earlier studies have discussed the fact that higher peripheral Mn levels could be linked to ADHD based on the associated attention problems(Pihl and Parkes, 1977) and hyperactive behaviors (Collip et al., 1983) noted in those subjected to subtoxic Mn levels when compared with controls.

Interestingly, in the present study there was a positive and strong association between hyperactivity/impulsivity scores and high Mn levels in serum of ADHD children, but on the other hand, no significant association is observed between attention scores and Mn serum levels in ADHD children.

Excess Mn has also been associated with hyperactivity and other behavior disorders in children (Bouchard et al., 2007; Ericson et al., 2007). A pilot study performed by Bouchard et al. (2007) in Quebec (Canada) where naturally occurring high Mn levels in water were present in the public water system, showed that children living in the houses connected to water wells with higher Mn levels displayed higher concentrations of Mn in their hair and hair Mn was associated with increased hyperactive and oppositional behaviors displayed by those children. Those relations remained significant after adjustment for income, age, and sex.

A study was performed by Ericson et al. (2007), where prenatal manganese exposure was linked to childhood behavioral disinhibition. Findings suggested that prenatal accretion of Mn, as reflected in tooth enamel deposits dating to the 20th gestational week, is significantly associated with childhood behavioral outcomes. Children with higher levels of prenatal manganese showed higher scores on hyperactivity subscales. These findings were also consistent with experimental evidence from prenatally exposed rats to Mn, showing increased hyperactivity (Pappas et al., 1997). This agrees with a study performed by Mora et al. (2015) on American-Mexican children, where higher postnatal dentine Mn levels were associated with more frequent maternal reports of behavioral problems at seven years in cross-sectional analyses of boys and girls combined including hyperactivity.

On the contrary, Farias et al. (2010) found higher serum Mn levels to be associated with predominantly inattentive ADHD children. Similarly, Bhang et al. (2013) found that attention scores could be affected by high Mn blood levels in Korean children. Oulhote et al. (2014) also reported that high levels of hair Mn were associated with poorer performance in attention, memory and motor functions.

The mechanism by which Mn causes neurotoxicity is not entirely known. Studies have shown that once Mn crosses the blood–brain barrier, either by diffusion or active transport, Once inside neurons, Mn can promote autooxidation of dopamine, leading to the production of reactive dopamine quinones (Shen and Dryhurst 1998). Furthermore, it has been shown that

Mn interferes with mitochondrial adenosine triphophate (ATP) biosynthesis. Although Mn is heterogeneously distributed in the brain, it has a tendency to accumulate in DA-rich cortical and subcortical areas, particularly in the basal ganglia (Guilarte et al., 2006). Since Mn toxicity produces adverse motor effects that resemble Parkinson's disease, the dopaminergic system has been the focus of intensive research. Of particular interest, studies have indicated that DAT is a substrate for Mn (Ingersoll et al., 1999).

It has been suggested that Mn decreases DAT binding site availability. PET studies on cynomolgus macaques chronically exposed to Mn showed a dramatic decrease in the capacity of striatal dopamine release after an amphetamine challenge (Guilarte et al., 2006). However, the majority of the studies have examined the effects of high levels of acute or chronic exposure to Mn (10–150 ug/L); thus, little is known about exposure to lower subtoxic levels (Aschner et al.. 2007). The normal blood concentration of Mn has been estimated to be in the range of 0.8 and 2.1 ug/L (Wu, 2006). Here, we showed that subtoxic concentrations of Mn (3.8–7.5ug/L), lower than that observed in patients exhibiting parkinsonian symptoms, may be associated with ADHD.

## Limitations of the study:

Mn concentrations were measured in serum only. Although serum Mn has been shown to be a good indicator of recent exposure, additional measures, such as Mn presence in hair, could provide an index of chronic exposure.

## Conclusion

The relationship between ADHD diagnosis and higher Mn levels may be part of an ‘‘environmental etiology of dopamine deficits (ADHD)’’, where small but biologically relevant levels of Mn may interfere with maintenance of optimal levels of DA in predisposed subjects. It may also be clinically relevant to prescribe reduced ingestion of Mn–rich food, such as rice and soy–derived products, in children who have a familial predisposition to develop ADHD.

## Recommendations:

1- The above data suggests that further studies of Mn levels in children with ADHD should be replicated in a larger, randomized, and double-blind controlled study.

2- It will be of interest to assess whether or not the observations presented here may represent an interaction between genetic vulnerability and environmental risk factors, particularly with regard to the effect of Mn on the dopaminergic system.

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