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# SERUM MANGANESE LEVELS IN CHILDREN WITH ATTENTION DEFICIT HYPERACTIVE DISORDER

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَقُلْ اَعْمَلُوا فَسَيَرَى  
اللَّهُ عَمَلَكُمْ وَرَسُولُهُ  
وَالْمُؤْمِنُونَ

صدق الله العظيم

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# List of Abbreviations

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Abb.	Full term
5-HIAA.....	5-Hydroxyindoleacetic acid
ADHD SC4.....	Attention Deficit Hyperactivity Disorder Scale IV
ADHD.....	Attention Deficit Hyperactivity Disorder
ATSDR .....	Agency for Toxic Substances and Disease Registry
BBB .....	Blood Brain Barrier
CBCL.....	Child Behavior Checklist
CD.....	Conduct Disorder
CNS .....	Central Nervous System
DA .....	Dopamine
DAT.....	Dopamine Transporter
DSM .....	Diagnostic Statistical Manual
DZ.....	Dizygotic
Fe .....	Iron
FSH.....	Follicular Stimulating Hormone
GABA.....	Gamma-aminobutyric acid
ICP-MS .....	Inductively Coupled Plasma- Mass Spectrometry
IQ.....	Intelligence Quotient
LH.....	Luteinizing Hormone
Mn.....	Manganese
MPH .....	Methylphenidate
MZ.....	Monozygotic
NE.....	Norepinephrine
ODD .....	Oppositional Defiant Disorder
PET .....	Positron Emission Tomography
SB5 .....	Stanford Binet Intelligence Scale Fifth edition

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## List of Abbreviations (Cont.)

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Abb.	Full term
SPECT.....	Single-photon emission computed tomography
SPSS .....	Statistical Package for Social Science
Tf .....	Transferrin
TfR.....	Transferrin Receptor
WHO.....	World Health Organization

# 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:** Assess serum manganese levels in children with Attention Deficit Hyperactivity Disorder and correlate between serum manganese levels, severity of symptoms and comorbidities in children with Attention Deficit Hyperactivity Disorder.

**Methods:** The present study is a case-control study that was conducted on forty patients and twenty controls from 1<sup>st</sup> 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<sup>th</sup> 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 ( $5.5 \pm 1$ ) compared to controls ( $4.1 \pm 0.6$ ) respectively and the difference is highly significant statistically ( $P < 0.001$ ).

**Conclusion:** High serum manganese levels in children could predispose to and/or aggravate ADHD symptoms and many children could be at risk of neurological and behavioral consequences of low/moderate manganese exposure.

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

## INTRODUCTION

**A**ttention-deficit/ hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders of childhood & adolescence (*Polanczyk et al., 2007*). ADHD results in impairing symptoms of inattention, hyperactivity and impulsivity, it affects about 8% of school aged children worldwide (*Polanczyk et al., 2007*) and about 5% of college students and adults worldwide (*Kessler et al., 2006*). Children with ADHD are at higher risk for academic problems, school dropouts, anxiety, depression, antisocial behaviors and substance abuse (*Fredriksen et al., 2014*). Many cases of ADHD persist into adulthood accompanied with increased risk of being unemployed and having reduced income (*Altszuler et al., 2016*).

Although the exact etiology of ADHD remains unknown, various lines of evidence based on neurochemical, imaging and genetic studies point towards the dysregulation of catecholaminergic systems in ADHD (*Leo and Gaintdinov, 2013*). Neurochemical studies showed that stimulant medications like methylphenidate (MPH) that are used for treatment of ADHD block the dopamine transporter (DAT) and also enhance the release of dopamine (DA) & norepinephrine (*Engert and Pruessner, 2008*). Positron emission topography (PET) studies also showed that therapeutic oral doses of (MPH) have strong binding affinity to (DAT) (*Volkow et al., 2009*).

ADHD is highly heritable with estimated range of 60%-90% (*Smalley, 1997; Faraone et al., 2005; Thapar et al., 2013*). Genetic studies have yielded mixed results using both candidate gene analysis as well as linkage and genome-wide association studies, with the majority of risk still unexplained (*Farias et al., 2010*).

In spite of the possible variations in sample size & diagnostic criteria used, the existing evidence suggests that other factors may also play a role in the development of ADHD symptomatology, including environmental risk factors (*Froelich et al., 2011*).

Necessary nutrients, such as trace minerals including manganese (Mn), iron, iodine, zinc, copper, selenium, Chromium and fluoride, are associated with changes in neuronal functioning possibly leading to adverse effects specifically on learning and behavior (*Hubbs-Tait et al., 2005*).

Manganese is a naturally occurring element that constitutes 0.1% of the earth's crust and it's present in low levels in water, food and air (*ATSDR, 2012*). The main exposure to manganese is by eating food or Mn-containing nutritional supplements (*Farias et al., 2010*). Vegetarians who eat foods rich in manganese such as green leafy vegetables, whole grain cereals and nuts as well as heavy tea drinkers may have higher intake of manganese than the average person (*WHO, 1973; ATSDR, 2012*). Additionally people who smoke

tobacco or inhale second hand smoke are also exposed to higher levels of manganese (*ATSDR, 2012*).

Manganese is neurotoxic at high concentrations (*Aschner et al., 2007*). Manganese neurotoxicity is characterized by alterations of dopamine neurobiology of the brain. The dopamine transporter is affected by high Mn levels (*Erikson et al., 2007*). ADHD has also been linked to impairment in dopaminergic functioning, therefore high manganese levels in children with ADHD reflects a similar neurotoxic effect (*Tran et al., 2002*).

## AIM OF THE STUDY

**T**his study aims to investigate serum levels of toxic manganese and their association with ADHD in school aged children in Cairo and correlate between serum manganese levels, severity of symptoms in children with ADHD.

## Chapter 1

# ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

It's a common place for children specially preschoolers to be active, energetic, flit from one activity to another as they explore the surrounding environment and act without much forethought, responding on impulse to events occurring around them with their emotional reactions readily apparent, but when children persistently display levels of activity and inattention, that are far in excess of their age or when their self-regulation lags far behind expectations for their developmental level, they are no longer expressing the “Joie de vivre” that characterizes childhood.

These children who are now diagnosed as having ADHD have impairments concerning their familial, social, cognitive, academic and eventually occupational domains of major life activities (*APA, 2013*).

ADHD is considered one of the most well studied childhood disorders of our time.

### **Historical overview of ADHD**

In literature, describing individuals having serious problems with inattention, hyperactivity dates back to William