

Original Research Article

Blood heavy metal levels in children with attention deficit hyperactivity disorder: an unsolved enigma

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ABSTRACT

Background: The role of heavy metals in the etio-pathogenesis of attention deficit hyperactivity disorder (ADHD) is a burning enigma. The available studies with discordant results are from different geographical localities with different monitoring, regulations and sociocultural backgrounds. The differential association of heavy metals with ADHD severity and phenotypes has not been adequately examined. Also, there are concerns about laboratory quality control. Therefore, the present case control study was formulated.

Methods: Thirty children with ADHD diagnosed by DSM IV criteria and thirty group age matched controls were enrolled. Detailed perinatal, past, developmental and possible exposure history to various heavy metals was taken. Severity of ADHD was assessed using ConnersTM Parent reporting questionnaire. Blood level of metals was estimated by inductively coupled plasma- atomic emission spectroscopy (ICP-AES).

Results: The mean blood lead, mercury, cadmium, arsenic, zinc were comparable in children with ADHD and group age matched controls. The mean blood lead, mercury and cadmium levels in study population was higher than found in studies from developed countries. Elevated arsenic, mercury and cadmium were found in both cases and controls. Blood zinc correlated significantly with inattention T score and blood mercury with hyperactivity-impulsivity T score of Conners parent rating scale. Blood cadmium was present in greater proportion of predominant hyperactive-impulsive type patients.

Conclusions: Zinc deficiency correlates with inattention; cadmium and mercury toxicity correlate with hyperactivity. Mean blood levels of heavy metals is elevated in a substantial proportion of study population. So, there is an urgent need for sensitization and environmental control.

Keywords: Attention deficit hyperactivity disorder, Cadmium, Lead, Mercury, Zinc

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurobehavioral disorder that is believed to result from an interplay of environmental influences with inheritable factors. Amongst environmental factors, the possible contribution of heavy metals seems logical as cellular

enzyme systems are disrupted by heavy metals and there is environmental ubiquity of various heavy metals.

However, in the currently available literature, there are discordant results of association of heavy metals especially lead with ADHD. Moreover, studies with discordant results are from different geographical localities with different environments, monitoring and regulations and socioeconomic backgrounds.

The role of metals like arsenic, cadmium and zinc has also not been adequately studied. Also, there are concerns about laboratory quality control and assurance. Moreover, differential association of heavy metals with ADHD severity and phenotypes has not been adequately examined.^{1,2}

Therefore, the present study has been formulated to fill this knowledge gap and compare the mean blood level of heavy metals in children ADHD (aged 6-12 years) with group age matched controls using standardized, validated tools and instruments. An attempt was also made to compare exposure history to the blood levels of heavy metals and differential association of heavy metal levels with ADHD severity.

METHODS

Participants

The study center was a tertiary care research, training and referral institute. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1964. The study was a case control study where participants were enrolled after obtaining Institutional ethics committee clearance and written informed consent. The flow of patients in the study is depicted in Figure 1.

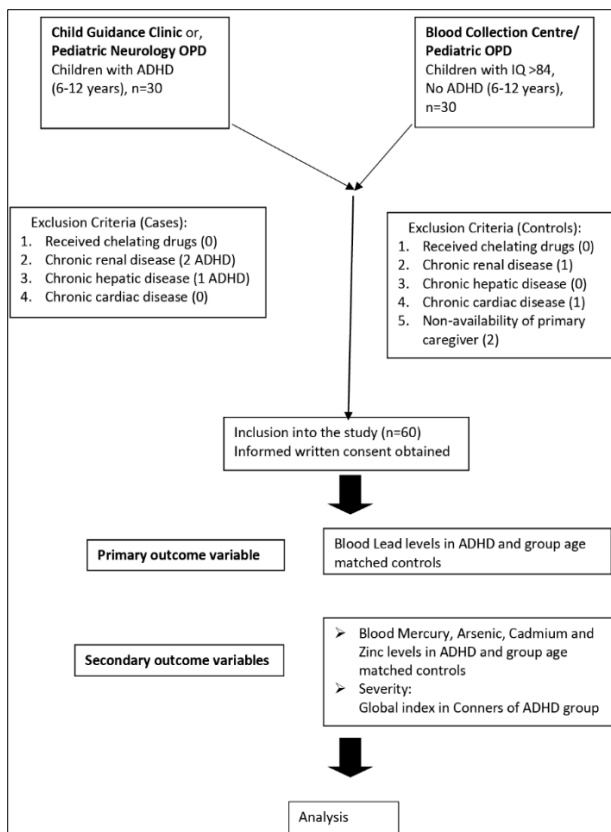


Figure 1: Study flow diagram.

Inclusion criteria

The study subjects fulfilled all the following criteria:

- Group A (N=30): attention deficit hyperactivity disorder (ADHD): 6-12 year old children who met DSM IV criteria for ADHD
- Group B: Controls (N=30): 6-12 year old children with age appropriate development (DQ>84) without features of ADHD. They were enrolled from the children attending the blood collection center attached to Pediatrics ward for investigation of fever (n=22), or those attending pediatrics OPD for investigation of non-neurological co-morbidities [constipation/ poor growth: (n=5); recurrent diarrhea (n=3)]. Healthy controls were not chosen in view of ethical concern of drawing blood sample.

Exclusion criteria for case or controls

Use of any chelating drug in the past or evidence of chronic systemic illness: like chronic renal disease, cardiac disease or hepatic disease.

Sample size and outcome variables

From a previous study, difference in mean blood lead between ADHD and controls=0.37µg%, standard deviation of mean blood lead=0.67, effect size: $E/S=0.37/0.67=0.5.3$ Considering 2-sided alpha- 0.05, 80% power, sample was 64 in each group. Sample taken due to feasibility purposes was 30 children with ADHD and 30 controls.

Blood lead level in children with ADHD and controls was taken as primary outcome variable. The secondary outcome variables included blood mercury, arsenic, cadmium and zinc levels in ADHD and controls and severity of ADHD as judged by Global score and subdomain T scores of ConnersTM Parent reporting questionnaire.

Definitions and study tools used in the study

DSM IV criteria were used to make a diagnosis of ADHD. Based on DSM IV criteria, three types of ADHD are identified: ADHD, combined type, ADHD, predominantly inattentive type or ADHD, predominantly hyperactive-impulsive type.⁴

Severity of ADHD was scored using Conners TM Parent reporting questionnaire by the clinical psychologist using Conners 3rd Edition (Conner 3TM, 2008).⁵ Global index of ADHD, problems in executive functioning, learning problems, aggression, peer/family relations, conduct disorder and oppositional defiant disorder were also assessed using the same. Positive impression, negative impression and inconsistency index were applied to evaluate validity of rating.

In the group of controls, the intelligence of the children was measured by the cognitive sub test of the Developmental Profile 3 that was used to calculate the equivalent DQ standard score as per the guidelines. Detailed perinatal, past, developmental and possible exposure history to various heavy metals was taken from parents of each child.

Exposure history

This was elicited to find out possible environmental factors that may have contributed to elevated levels of heavy metals in blood of subjects, if any. The presence of power plants, small scale industries using coal, battery manufacturing plants, cement industry that may contribute to lead or cadmium environmental pollution were considered significant, if they were within 1km of residence. History of use of enamel paint at home (source of lead) in last one year, use of maternal dental amalgams containing mercury before or during pregnancy, presence of dental amalgams in the child, average (median number) of fish servings (believed to concentrate heavy metals) per month were assessed. Other possible sources of lead, cadmium, zinc and arsenic including use of surma, pica, ground water, traditional medicines were also taken. Insecticide exposure was considered if child resided in a rural locality with frequent visits to the farm. Thiomersal is a preservative in few vaccines and contains mercury. The maximum cumulative was calculated from the immunization history and using the values previously assessed.⁶ Antibiotic use is known to almost completely inhibit excretion of mercury in rats due to alteration of gut flora. Thus, higher use of oral antibiotics in the children is proposed to result in their reduced ability to excrete mercury.⁷ So, average antibiotic usage in infancy was calculated by multiplying average number of episodes of illness with the average number of days of antibiotic days for each child.

Blood investigation

Whole blood venous samples, 1ml from each participant were collected in commercially available heparinized polypropylene tubes for blood lead (Pb), mercury (Hg), zinc (Zn), cadmium (Cd), arsenic (As) estimation with ICP-AES (induction coupled plasma atomic emission spectrophotometer)

Sample collection and reagents

A total of 60 samples were collected, coded and analysed from the study participants; 30 each from children with ADHD and controls. Samples were promptly labelled and stored at -80°C till digestion. Closed-multimode-microwave was used for complete digestion or dissolution of blood samples using high temperature, pressure and 70% nitric acid as a digestion reagent. For calibration curves, the standard solution mixture was diluted step-wise with 5% nitric acid and solutions for five points including the blank test solution was prepared.

Three replicates were prepared for each analyte concentration. The limit of detection (LOD) was determined based on 3 times of standard deviation running a matrix blank.

Operating and acquisition parameters

ICP-AES, fitted with a cross flow nebulizer and a quartz spray chamber was used with the conditions: forward power of 1.0kW; vacuum pressure of 1.8×10^{-6} ; nebulizer flow rate of 0.84L/min; dual detector and sweep/reading of 3, reading/replicate of 3, dwell time of 5 seconds and integration time of 10 seconds. Standard addition method was used in the experiment. The precision was established by triplicate runs involving different operators for the same batch of samples.

RESULTS

Baseline demographics and exposure history

The median age of the ADHD group was comparable with that of group age matched controls ($p=0.15$).

However, the gender ratio was skewed in ADHD group with all children enrolled being males. The mean severity of ADHD as depicted by global index was 90, shown in Table 1. There was no significant difference in exposure history in the two groups.

Medical and Treatment history of children with different subtypes of ADHD and controls

In the three subtypes of ADHD, there was no significant difference in the antenatal or perinatal risk factors or comorbidities like epilepsy or sleep problems. In the control group, one child had pregnancy induced hypertension in the mother as an antenatal risk factor. No other risk factors or co-morbidity was present. Majority of children were on antiepileptic drugs for comorbid epilepsy and on combination of drugs and behavioral therapy.

No child was on any chelators, hematinic or zinc supplementation. No control was on any long-term medications. Conners 3TM parent reporting questionnaire was used to determine the severity of ADHD in different subdomains and associated comorbidities. There was a high frequency of associated learning problems, executive functioning, aggression, inter-personal peer relationships, conduct disorder and oppositional defiant disorder.

Comparison of blood heavy metal analysis in children with ADHD and controls

Table 2 shows geometric mean and median blood level of lead, mercury, arsenic, zinc and cadmium in both group B and D were comparable.

Table 1: Characteristics of children with ADHD versus controls.

Characteristic	ADHD (N=30)	Controls (N=30)
Age, Mean±SD	93.9±20.6	100.9±19.4
Median (range)	86.5 (73-125)	97 (73-144)
M:F	30:0	18:12
Severity score Mean±SD (95% C.I.)	Conners 3 Global Index 90 (63-90)	-

Age is described in months; SD- standard deviation; N- numbers.

Table 2: Comparison of blood heavy metal analysis in children with ADHD and controls.

Heavy Metal	ADHD (N=30)	Control (N=30)	p-value
Blood lead (ppb) median (range)	57.7 (0-115.8)	57.8 (22.4-84.9)	0.81
Geometric mean (95% C.I.)	59.3 (52.7-66.7)	58.1 (53.4-63.1)	
Blood cadmium (ppb) median (range)	17.9 (0-37)	18.2 (0-27)	0.44
Geometric mean (95% C.I.)	9.2 (5.0-17.1)	11.5 (7.2-18.2)	
Blood zinc (ppb) median (range)	878.2 (492-4089.0)	746.0 (453.6- 4409)	0.68
Geometric mean (95% C.I.)	904.5 (766.2-1067.9)	890.6 (736.9-1076.4)	
Blood arsenic (ppb) median (range)	1.1 (0.0-5.8)	6.8 (0.0-5.6)	0.43
Geometric mean (95% C.I.)	1.3 (0.7-2.3)	1.0 (0.6-1.9)	
Blood mercury (ppb) median (range)	6.5 (0.4-223.9)	6.9 (1-114.8)	0.65
Geometric mean (95% C.I.)	7.3 (4.4-12.0)	9.4 (6.0-14.6)	

Ppb- parts per billion; CI- confidence interval; N-numbers.

Table 3: Correlation of global index of ADHD and subdomain T scores of ADHD with blood heavy metal levels.

Blood heavy metal (ppb)	Spearman rho (p-value)										
	Global index	Inattention T score	Hyperactivity impulsivity T score	Learning problem T score	Executive functioning T score	Aggression T score	Peer relation T score	DSM IV AN	DSM IV AH	Conduct T score	ODC T score
Cadmium	0.01 (0.92)	-0.07 (0.97)	-0.06 (0.71)	0.15 (0.44)	-0.01 (0.92)	0.12 (0.52)	0.03 (0.85)	0.15 (0.41)	-0.09 (0.64)	0.03 (0.85)	0.09 (0.63)
Lead	0.12 (0.52)	0.25 (0.17)	0.01 (0.96)	0.33 (0.07)	0.11 (0.56)	0.26 (0.16)	0.21 (0.28)	0.28 (0.13)	0.17 (0.19)	0.01 (0.97)	0.33 (0.08)
Zinc	0.13 (0.49)	0.40 (0.03)*	0.02 (0.92)	0.31 (0.09)	0.13 (0.48)	-0.08 (0.66)	0.12 (0.51)	0.32 (0.08)	0.04 (0.85)	0.01 (0.99)	0.13 (0.46)
Arsenic	0.04 (0.80)	0.17 (0.36)	0.09 (0.63)	0.22 (0.33)	.05 (0.79)	0.07 (0.70)	0.02 (0.91)	0.15 (0.41)	0.01 (0.98)	0.07 (0.72)	0.02 (0.880)
Mercury	0.05 (0.79)	-0.01 (0.98)	0.39 (0.03)*	0.01 (0.05)	0.01 (0.99)	0.03 (0.84)	0.10 (0.57)	0.01 (0.94)	0.01 (0.94)	0.05 (0.80)	-0.01 (0.93)

Table 4: Blood heavy metal analysis in different subtypes of ADHD.

Heavy metal	Total (N=30) n (%)	Combined type (N=17) n	Predominant Inattentive (N=5) n	Predominant hyperactive impulsive (N=8) n	p-value
Elevated blood cadmium (>10ppb)	19 (63.3)	7	4	8	0.01*
Elevated blood Lead (>100ppb)	1 (3.3)	0	1	0	0.17
Change in Zinc					
Elevated blood zinc (>1300ppb)	3 (10)	2	0	1	0.71
Deficient blood zinc (<1000ppb)	17 (56.7)	9	2	6	0.26
Normal blood zinc (1001-1300ppb)	10 (33.3)	6	3	1	-
Elevated blood arsenic (>5ppb)	11 (36.7)	5	3	3	0.45
Elevated blood mercury (>10ppb)	5 (16.7)	3	1	1	0.92

p-value<0.05; ppb- parts per billion; N, n- numbers.

Heavy metals and ADHD severity

Table 3 shows blood zinc correlated significantly with inattention T score and blood mercury with hyperactivity-impulsivity T score.

None of the blood heavy metal level correlated significantly with global index.

However, on comparison of elevated levels of heavy metals above the level of concern with different subtypes of ADHD revealed that elevated blood cadmium was present significantly more frequently in predominant hyperactive-impulsive type patients ($p=0.01$).

However, no such association was observed with other heavy metals as shown in Table 4.

Frequency of elevated/deficient blood heavy metal levels

Table 5 shows that both zinc deficiency and elevated blood zinc levels were more prevalent in control group. No significant difference was observed for other heavy metals.

Table 5: Frequency of elevated/ deficient blood heavy metal levels in children with ADHD versus group age matched controls (age range 6-12 years).

Metal	ADHD (N=30) n (%)	Controls (N=30) n (%)	p-value
Elevated blood cadmium (>10ppb)	19 (63.33)	23 (76.67)	0.26
Elevated blood lead (>100ppb)	1 (3.33)	0	0.31
Elevated blood zinc (>1300ppb)	3 (10.0)	6 (20)	0.02*
Deficient blood zinc (<10ppb)	17 (56.67)	22 (73.33)	0.02*
Elevated blood arsenic (>5ppb)	11 (36.7)	7 (23.33)	0.26
Elevated blood mercury (>1000ppb)	5 (16.67)	8 (26.67)	0.38

DISCUSSION

All the children with ADHD enrolled were males. This was significantly different from gender ratio of 3:2 (male:female) in the control group. However, in a previous study, gender of the child did not predict ADHD.³ This difference may be explained by less healthcare seeking behavior for female children prevalent in Indian society.⁸

Primary outcome: lead and ADHD

In contrast to the previous studies, the geometric mean as well as the median blood lead level in both children with ADHD and controls was comparable.^{3,9} In fact, the geometric mean blood lead levels in ADHD and control groups in the present study are comparable to national population averages. This is evidenced by the fact that the geometric mean lead level in ADHD group in the present study is $5.9\mu\text{g}\%$. Similarly, in a recent study from

Amritsar, Punjab, India, where blood zinc, cadmium, lead and copper were analysed in children aged 3 months-6 years residing in different parts of the city, the geometric mean lead levels ranged from $2-12.6\mu\text{g}\%$. This depended on vicinity to industrial area.¹⁰

Also, mean blood lead levels of $11.4\pm 5.3\mu\text{g}\%$ was seen in 756 children 3-7 years of age attending pre and elementary school in Chennai, India.¹¹

On the contrary, mean blood lead levels in children with ADHD found in CHEER (children health and environmental research) study in Korea and USA were lower with a geometric mean of $1.8\mu\text{g}\%$ and mean blood lead level of $1.03\pm 0.04\mu\text{g}\%$ respectively.^{3,12} This discrepancy may be commensurate with the lower national averages of blood heavy metals in the developed countries secondary to stringent pollution control measures.

The reason for increased mean blood lead level may be understood in light of previous studies. It is well documented that a small increase in lead levels in air can result in higher blood lead concentration. There is an estimated increase in blood lead of $15-30\mu\text{g}/\text{L}$ with increase in air lead by $1\mu\text{g}/\text{m}^3$.¹³

Surprisingly, even the geometric mean of dust lead loadings for floor and interior windowsill samples were $19.9\mu\text{g}/\text{feet}$ and $75.5\mu\text{g}/\text{feet}$ respectively in a previous study from Delhi in India as compared to US levels of $1.1\mu\text{g}/\text{feet}$ and $9.4\mu\text{g}/\text{feet}$ respectively.¹⁴ Moreover, in another study, 84% enamel paints tested, intended for residential use in India, exceeded the regulatory level ($<600\text{ppm}$) and reached up to $140,000\text{ppm}$.¹⁵ Eventually, the normal hand to mouth activity of young children may be a pathway for transmission as it is known to effectively transfer lead laden dust from the environment into the body.¹⁶

Thus, the findings of the present study are of paramount importance and there is a need to sensitize health care providers and also public health officials need to give attention to possible heavy metal poisoning in Indian children.

In the present study, there was no difference in exposure history of coal combustion, power plants and cement industry, pica and ground water use amongst children with ADHD and controls. However, vehicular and air pollution could not be quantified.

Secondary outcomes: other heavy metals and ADHD

In the present study, average blood cadmium, zinc, arsenic and mercury levels in two groups of ADHD and age-matched controls were comparable.

Geometric mean blood mercury in the ADHD group was 7.3ppb (median 6.5ppb) and in the control group was

9.4ppb (median 6.9ppb) which is higher than geometric mean of 2.99ppb in children less than 7 years and 2.78ppb in more than 7 years of age in children with ADHD in CHEER study group.¹²

There is paucity of studies on mean blood cadmium and arsenic levels in children with ADHD. However, blood cadmium geometric mean levels were found to be 0.01-0.11 in different residential areas in the study from Punjab, India.¹⁰ The higher levels seen in the present study could be due to differences in geographical distribution and needs to be substantiated by larger studies.

Moreover, elevated blood cadmium (>10ppb) was found to be significantly associated with predominant hyperactive-impulsive phenotype ($p=0.01$). In contrast, in a recent study where urine samples were obtained to measure the levels of few heavy metals in children with ADHD and controls, the ADHD-Inattention phenotype patients demonstrated the highest cadmium levels ($p=0.034$).¹⁷ However another study did not find statistically significant effects of cadmium on children's behavior using ADHD rating scale.¹⁸ A study from Spain observed a dose-response relationship between urinary arsenic levels and inattention and impulsivity scores.¹⁹ In India, chronic arsenic poisoning has been documented in few locations with source being contaminated drinking water.²⁰ A recent meta-analysis concluded that although a 50% increase of arsenic levels in urine would be associated with a 0.4 decrease in the intelligence quotient (IQ) of children aged 5-15 years, it was not associated with ADHD.²¹

Thus, the findings of present study raise a concern that mean blood levels of heavy metals is elevated in a substantial proportion of study population including both children with ADHD and controls.

Zinc deficiency was highly prevalent in both children with ADHD as well as controls as shown in Table 5. This highlights poor nutritional status regarding minerals prevalent in India. This may be related to poor intake of zinc rich foods as well as phytate rich Indian diet that interferes with zinc absorption.²²

Blood heavy metals and ADHD phenotype

Most ADHD research has focused on the combined phenotype or has not differentiated between three phenotypes of ADHD namely combined, predominantly hyperactive and predominantly inattentive.¹ There is a felt need to investigate whether exposure to a chemical or metal is differentially associated with specific ADHD phenotype.²

In the present study, elevated blood cadmium (>10ppb) was found to be significantly associated with predominant hyperactive-impulsive phenotype ($p=0.01$) shown in Table 4.

Moreover, correlation of Conners subdomain T scores with blood heavy metals in the present study, also revealed correlation of blood mercury with hyperactivity impulsivity T score (spearman $\rho=0.39$, $p=0.03$). Blood zinc was also correlated with Conners inattention T score (spearman $\rho=0.40$, $p=0.03$) as shown in Table 3.

This is similar to a previous study, where 48 children aged 5-10 years with ADHD were enrolled. Serum zinc levels correlated at $r=-0.45$ ($p=0.004$) with parent teacher rated inattention even after controlling for gender, age, income and diagnostic subtypes. But correlation with parent-teacher rated hyperactivity-impulsivity was insignificant.²³

Strengths of the study

To the authors' best knowledge, it is the first study for its kind from India. It yields useful information for healthcare programs targeting pollution control measures as in India, there is scarcity of data on exposure assessment of toxic trace metals for children.

Methodologically, confirmation of diagnosis in valid age ranges was done using standard validated diagnostic and statistical manual IV (DSM IV) tool and collection of detailed data on possible sources of heavy metals was done. Blood levels of heavy metals were estimated by ICP-AES which is fast and effective and using standardized laboratory results done by double checking 10% of sent samples to NIN (National Institute of Nutrition, Hyderabad, Andhra Pradesh, India).

Exposure to environmental heavy metals from house dust, air pollution could not be accounted for and exposure history may be subject to recall bias.

Other possible confounders like parental psychopathology, maternal education and socioeconomic status was not adjusted for. Lastly, the controls were not truly healthy controls like school going children as subjecting such children to unnecessary blood sampling raises ethical concerns.

CONCLUSION

Blood mercury, lead, zinc, arsenic and cadmium did not show significant association with diagnosis of ADHD. The increased mean blood arsenic, mercury and cadmium level and zinc deficiency was prevalent in both children with ADHD as well as controls. However, differential association of hyperactive-impulsive phenotype was observed with elevated blood cadmium and blood mercury; and of inattention phenotype with blood zinc levels.

Recommendations

Heavy metals interfere with many biological processes. The fact that both children with ADHD and controls had

increased mean blood levels of heavy metals, it raises concern about waste and environmental management. There is a need for more stringent environmental laws and implementation for the sustainable development.

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